INTRODUCTION

1.1 PREAMBLE

The pellets are dosage forms which deliver the drugs safely to the body and in pelletization technique materials are changed to spherical shapes which flow easily. Pharmaceutical companies are now applying pelletization technique for changing powders into pellets which flow smoothly. Basically pellets are agglomerates obtained from different starting materials by using varying parts of production equipments. Agglomerates consist of animal feeds, fertilizers and pharmaceutical unit preparations.\(^1\)

Pellets are explained as different types of geometrically shape agglomerates were obtained from different raw ingredients by applying special operations. Pelletization is defined as an agglomeration process which transforms excipients, fine powder or granules into semi-spherical, spherical easily flowing small units called as pellets. Size of pellets is lies in limit of 0.5-1.5 mm. The processing method will decides the size of pellets to be prepared.

Pelletization is the famous well defined technique practiced by the formulator scientists from so many years. Different pelletization techniques now used in pharmaceutical industries are conventional pan coating, fluid bed technology, centrifugation and extrusion-spheronization. Methods mentioned above have some drawbacks such as pan coating technique which is mostly applied because of its low charge of installation but required trained personnel and consumes time with less product yield\(^2\). The fluid bed apparatus formed the more spherical pellets but it is very intricate with more production charges\(^3\).
Presently in pharmaceutical industry extrusion and spheronization is utilized to form the cheap pellets with high speed, but its purchasing budget is very high and cannot bear by small scale units \(^4,5,6,7\). So these are the limitations which motivate the researcher to develop a method to overcome these issues. Images of pellets are depicted in Figure 1 was taken by stereomicroscope of Intel play.

**Advantages of Pellets**

1. Pellets are flexible to design and formulate in dosage form with enhanced safety and efficiency of biological preparations.
2. Pellets are used in the supply of drugs by controlled released technique.
3. Pellets give excellent therapeutic benefit on single unit formulation when given in capsule, disintegrating tablet or suspension forms \(^1\).
4. Pellets disseminate easily in GIT with complete absorption of drug and less side toxicities, less variations in peak plasma.\(^1\)
5. Pellets lower the fluctuations in transit time and gastric emptying rate \(^8\).
6. Pellets reduced within and among subject variances of plasma profile.
7. Pellets prevent the higher localized concentration of medicament.
8. Pellets are less liable to dose dumping \(^9\).
9. Pellets can sustained the drug over prolonged time and deliver drug at particular site within GIT.
10. Pellets permit the combined administration of two or more drugs at different or same site inside GIT which may not be or may be compatible.
11. Pellets allowed administration of same drug having varying release profile in single dosage preparation.

Pellets possess an excellent shape for film coating because of less surface area to volume ratio.

**Mechanism of Pellets Formation and Growth**

For the formation and growth of good quality pellets process conditioning acts substantially. Initially primary particles tied together due to physical forces and then pelletization procedure started\(^{10}\).

1) **Binding Forces**
Physical forces determine the hardness of pellets to a large degree which bind the primary particles with each other. Attrition, capillary and interfacial are the few different binding forces which gives idea about strength of agglomerates and pellets.

2) Elementary Growth Mechanical

This theory of pellets was suggested on the basis of experimental evidences. In this theory the starting step is nucleation. After this step the name of next step is coalescence. Coalescence operation is in connection with the abrasion transfer. The ending step of the theory is layering. All these steps has impacts on the preparation and growing of pellets throughout manufacturing.

3) Nucleation and Coalescence

Nucleation consists of growth process where starting particles are unit to produce water, solid and air nuclei system. A significant aspect of nucleation is that here quantity of nuclei and mass in the system alter as a part of time. The entire system not alters in coalescence but quantity of nuclei is progressively decreases.

4) Layering

Layering is reported as growth process in which sequential application of material has been done on prior made nuclei. Particles quantity stays the same but consistently there is improvement in particle sizes as a part of time which leads to overall improvement in entire system mass.

5) Abrasion Transfer

Movement of particles from one to other particles, in any direction takes place in abrasion transfer. It is evident hence full quantity of particles mass not resulted in alterations in this position.

6) Size Reduction

It has three steps indirectly affecting on elementary growth mechanism specially layering and to some degree coalescence. Good formulated particles pass through size reduction because of attrition and shattering. Fine and broken pieces formed then moves to surviving nuclei and take part in growing mechanism especially by layering. Particles having good surface plasticity they may combine to give bigger particles on collision.

Formulation Excipients

As pellets are taken orally, the excipients utilized for the pellets manufacturing are the identical to the oral solid dosage forms. The formulation additives used are discussed as follow.
1) Fillers

Fillers are the materials which are insoluble or soluble in water and used in pellet manufacturing specially to increase bulk. Filler should be selected on the basis of pellets properties. Fillers has wide role on the rate and release of medicament from pellets. Fillers should be pharmacologically and physicochemically inert because these two parameters affect largely its selection. Fillers are utilized in concentration from 1% to 99%. Binders are nothing but adhesive substance added in to pellets manufacturing for binding powder and to hold pellets unity.

If filler is the core material of pellet formula then the characteristics which are present within the fillers are automatically came within the pellets and become the pellets features. Hence few times it was observed that amount of fillers present in the formula majorly help in availability of drug through the pellets by taking over the other diluents functioning. Physicochemical properties of fillers and its inert are the two important points which must be consider while selecting the fillers. Many types of filler are well matched with so many drugs and do not showed any incompatibility. The fillers which get affected by change in pH must be use with great care in combination with highly basic or acidic drugs. Starch is hydrolyzed in presence of highly acidic drugs. It is necessary that all fillers selected for preparation must be chemically inert. The role of fillers gets vital when the quantity of fillers use with respect to drug is more. Optimal stability of pellets is depends on fillers physicochemical stability. Apart from adding bulk to the formulation fillers are added in preparation depending up on few requirements by the manufacturer. If bulk density of the medicine is much less then in that case calcium sulfate is added to the preparation for improving final pellets bulk density. In a same way fillers may be used to reduce the pellets density. Starch, sucrose, lactose and MCC are few frequently used examples of fillers.

2) Binders

Binders are adhesive type of substances which are added in preparation of pellets for binding the material and for upholding the integrity of pellets. Binders are the key ingredient of pellets manufacturing. Binders are also chosen for pellets manufacturing on the basis of drugs physicochemical ability and formulation processing. Binders might be used in dry state or in liquefied form but more effective as compare to dry blending if added in solution. When employed in solution form then binders have to completely dissolve in aqueous or non aqueous solution. The aqueous system is generally favored for pelletization. Hence maximum binders used now a days are aqueous soluble consisting of synthetic or natural polymers and sugar. Binders vary in binding
capability and solubility properties therefore choice of ideal binder for the pellets preparation is done by screening method. The physicochemical characteristics of the active and formulation process are the main considerable parameters which have an effect while selecting the binder. The binder is generally applied in wet massing technique of granulation or extrusion process as a liquid. In the starting of process there is formation of liquid bridges which retain the particles with each other. Later on, after evaporation of solvent the binder get hard and function as key force of bonding among the particles. Binders are generally employed in range from 2 to 10 percent w/w. for those substances having poor cohesive property more quantity of binder is needed. In spite of which binder is utilized in pelletization technique the quantity of binder must be standardized so that pellets remain stable with other required features in them. Hence choice of an ideal binder with its quantity is an important step which must be done more cautiously. Gelatin, sucrose and HPMC are the examples of binders.

3) Separating agents
These are the ingredients which accumulate on the surface and help to sort out the pellets in to discrete units in pelletization procedure. Surface charges were formed on outer boundaries of pellets during formulation may resulted in aggregation. Agglomeration also happened due to extent of wetting of pellet surface paired with local amount of binding agent. Such kind of problems can be easily handled by the addition of separating agent within the formulation or in between processing. At the time of suspension or solution layering process adsorbent material kaolin is incorporated to the preparation for decreasing stickiness which finally leads to agglomeration. Separating agents are commonly required when the binder solution is more viscous and sticky in nature. The way of addition of these agents differ on the basis f process employed. Separating agent either sprinkled as dry fine powder or it might be added in binder suspension or solution on revolving pellets bed. The quantity of these agents added depends up on the formulation process and preparation type.

For protecting the sticking of pellets to the boundaries of spheronizer and plate the separating agents are employed by dusting in spheronization process in dry state on to the moving bed of pellets. In spheronization process the humidity which transfers to the outside of pellets will get adsorbed by the separating agents.

4) Lubricants
Lubricants are materials which are added in pellet manufacturing to decrease the friction coefficient within particles or within the surfaces of formulating instrument and the particles. Lubricants consist of solids and liquids with different chemical and physical features. Solid type of lubricant should coat the pellets and possess less shear strength for showing its effect. Lubricant which are liquid in nature should develop consistent coat over the pellets outer layer. This formulated coat should tolerate enlarged pressure during process of pelletization. Many solvents cannot be used as lubricant because they possess very less film strength. Lubricants vary in physicochemical features hence having different performances. Efficacy of lubricants decided by the coating thickness prepared among the two layers in lubrication process. Rotary machines having great speed are employed during pelletization operation and hence lubricants are exceptionally required. But in extrusion and spheronization processes lubricants are added for production of quality pellets. The value and utilization of lubricants in compression operation is significantly mentioned in to the literature. If more quantity of lubricant is get added during spheronization process then pellets will not rotate and only plate rotate. Hence the amount of lubricant need to be added cautiously calculated tremendous pellets movement resulting in spherical and smooth pellets. Glycerine, mineral oil, magnesium stearate and propylene glycol are the examples of lubricants.

5) Surfactants
The rational for using these agents in pellets preparation is similar for which they are employed in other preparation. These are the ingredients use to meliorate the wetting property and improve rate of dissolution of less soluble drugs. During pelletization process pellets growth rely on the bridges formed by the liquid responsible for keeping primary particles with each other. Hence it is essential that solvent must wet these particles properly. Surfactants are incorporated to enhance the wetting by decreasing the interfacial tension among the drug and solvent. Unluckily decrease in interfacial tension has reverse effect on the strength of bond developed among the particles. Pellets are break easily or sometimes fines may be generated. In pellets production addition of surfactant must not be done unless and until it is most necessary to add them. Sodium lauryl sulfate and polysorbate are the examples of surfactants.

6) pH Adjusters
Micro environment of drug molecules are effected by pH adjusters. The drugs which are unstable in acidic portion of GIT are safeguards by applying enteric coat of film on their outer surfaces.
The buffers are incorporated to the main preparation for keeping the pH in most favorable condition and which help in stability of drug. Buffer is also incorporated into the preparation of drug whose solubility is affected by alteration in pH for improving rate of dissolution of drug. The release of drug from the pellets are controlled by membrane and drug release is totally depends up on its solubility. In preparation of pellets with less soluble or greatly soluble drugs issues concerning with solubility are generally arises. Higher sticking with too much binding is detected in pelletization of compound having great water solubility by using spheroidization operation. Hence buffers are incorporated in manufacturing of pellets for adjusting drug solubility to suit the specific operation. Phosphates and citrates are the examples of the pH adjusters.

7) Glidants
In powder layering process flow property has a unique character. Flow characteristics of cohesive materials are enhanced by the glidants having hydrophobic or hydrophilic properties. The glidants functions by decreasing frictions among the particles. Broadly hydrophobic glidants are efficient to a greater extent for hydrophilic materials and hydrophobic glidants are added to increase flow property of hydrophilic powders. For attaining the good flow of material extra step in operation is added like wet or dry granulation in formulation procedure. In compression procedure it is most essential that the material flow constantly up to the die from hopper with proper speed so as to form the pellets with same content of drug and weight. In powder layering procedure flow property is an ideal parameter because for regulating concurrent addition of binder solution the procedure needed well organized feeding of powder rate. It is very important that the powder will not remain stay to the wall of hopper and develop bridges. If possible the flow of material could be achieved by using gravitational force instead of any other mechanical tool like vibration. In manufacturing of pellets the required flow rate cannot be attained till the incorporation of agent called as glidants which help in improving the flow of materials. Starch, talc and magnesium stearate are the examples of glidants.

8) Spheronization Enhancers
These are the materials which assist in preparation of spherical shape pellets especially in balling and spheroidization process. These materials give plasticity and binding properties to the pellets which are necessary for pellets durability and unity. Microcrystalline cellulose and carboxymethyl cellulose are the examples of spheroidization enhancer. In spheroidization process
The rigid extrudates not having plasticity produces more amounts of fines same way plastic extrudates not having rigidity produce agglomerates and finally gives rise to round shape large ball. Hence there is need to maintain equilibrium among the plasticity and rigidity. Microcrystalline cellulose acts as a spheronization enhancer and it is high topic of research and help to develop spherical shape pellets. The quantity of MCC in pellets preparation appropriate for spheronization is calculated by chemical and physical features of drug and other ingredients.

9) Disintegrants

These are the materials which encourages the disruption of pellets with help of liquid. The motto is to improve drug dissolution by providing bigger surface area to the dissolving fluid. Hence, binder are use to hold the dosage form and role of disintegrants is to get over it. If powerful binders are added in preparation of pellets then there effect must be overcome by adding the effective disintegrants in preparation of immediate release dosage form. The disintegrants must possess the significant swelling and absorptive characteristics so as to prevail over the binder effect. So many disintegrants have these characteristics and hence they are generally water insoluble. The fact is also essential to recognize that the disintegrants absorbed the more quantity of water and hence cause the negative effect to the pellets. Deterioration of drug could be observed if pellets contain the medicine which is susceptible to moisture on its storage. Porosity is also important factor in disintegration of pellets. The extent of porosity in a pellet may differ on the basis of formulation features and manufacturing process. Diffusion of solvent within the pellets is depends up on pellets porosity. Pellets with more porosity will naturally disintegrate first and removal of drug is speedy as compare to pellets with low porosity. In manufacturing of pellets if disintegrants are present with more quantity of soluble ingredients then the working of disintegrants is prevented because of formation of sticky liquid by the soluble ingredients which arrest the solvent diffusion inside the pellets.

In spheronization and compaction process disintegrants are broadly utilized because high pressure is employed to the preparation to form high density pellets. When fast dissolution of drug is required then the disintegrants used must be more effective which overcome the compaction forces and binder effect. Crospovidone and alginates are the few examples of disintegrants.

10) Release modifiers
The actual intention behind the pelletization technique is to prepare spherical shape core containing drug which will be consequently consist of functionally active film. Pellets core having different release rate can also be produce by using single stage. It can be accomplished by adding the compound which will improve the removal of drug when pellets are with the dissolution fluid. These ingredients have broad pharmaceutical use. As these agents differ in physicochemical features the pellets are prepared with diverse rate of release of medicament. Commonly substances having less molecular weight, soluble in water and surfactants might be added in the preparation for improving the rate of drug. Whereas hydrophobic and hydrophilic materials and polymers which are insoluble in water are added in preparation of pellets for delay the rate of release of medicament. On the basis of chemical and physical features of drug and release modifier removal of drug may be takes place either by single or multiple systems. Preparation of pellets in one step with the required release profile is appealing but this method cannot be preferred as so many trials have to be done for standardizing the procedure and formulation. Also this method is not economical and time consuming. Simple approach towards the modification of release of medicament is by applying the coat to the surfaces of pellets.

**Different Pelletization Process**

Spray drying and spray congealing are the two different methods of globulation. In spray drying medicament is sprayed in suspension or solution form may or may not be with other excipients to form dry mini ball shaped circular particles. This method is applied for the formulation of pellets which are controlled release. Spray drying method was in existence since years for so many reasons in pharmaceutical companies.

In spray congealing drug is melted and dispersed in heated melted waxes or gums and then sprayed in chamber of air whose temperature is less than melting point of ongoing preparation so as to give proper operational state resulting in pellets which are spherical and congealed. Based on chemical and physical properties of ingredients and different formulation variability, controlled or immediate release nature pellets will be formed.

In compression process the stuff of drug and materials are compressed at certain pressure to form pellets having specified size and shape. The formed pellets are such a small that they can be easily added in to the desired capsules. Different production and technical variabilities occurred during manufacturing of pellets are same as that of happened in formulation of tablets. Actually pellets obtained by compression technique are mini tablets which are about spherical shape.
In balling method of pelletization fine separated particles are changed to circular small particles with the application of suitable amount of liquid by nonstop rolling movement.

**Sustained Drug Delivery System**

In this system slow removal of drug is attained over a long period and in the beginning drug was made obtainable for the body in quantity to have the expected pharmacological effect. It is novel technology and with consequent finding and research in this field proved rich with numerous findings. Sustained action, controlled release, sustained release, timed release, prolonged action, depot dosage form and extended action are the different terms utilize to designate it. The main intension is to attain prolonged effect by slow but continuous removal of drug to a longer time after taking a unit dose. On the basis of stay time in gastro intestinal tract the oral sustained released dosage forms produces pharmacological effects for several hours 12, 13. By prescribing sustained release drugs doctors are now obtaining various desired therapeutic benefits. Patient’s abidance is more as drug administration frequency is less and drug is more conveniently administer. Blood level oscillations of numerous dosing produced by the conventional dosage form is overcome by the sustained released dosage forms because more regular and uniform blood level is achieved through it.

In patients having sensitive nature the chances of systemic and local effects are greatly cut down and the safe margin of drug with more potency is improved. Sustained release dosage forms offers, improved reliability, higher availability with minimum dosing 14, 15. There is variation among sustained and controlled release preparations. Controlled release preparation are completely follows the zero order release style, means removal of drug takes place with time regardless of quantity of drug.

![Figure 2: Release style of sustained and conventional medicaments](image-url)
In sustained release preparations the removal of drug takes place gradually up to a given time period. Fabrication of sustained release preparations which remove the medicine at constant speed is remained the all time task for the pharmaceutical companies. Although commercial benefits entertained by the companies after a huge expenses on research are increased in final product age and patent filling.

Drug should possess some desirable characteristic to be an ideal candidate for sustained release dosage form. Following are the ideal properties of drugs,

1. Drugs must have shorter half life as longer half life drugs are long acting.
2. Drug must get entered in body from larger surface of GIT, as absorption takes place throughout the GIT.
3. Drug should possess good solubility feature.
4. Drugs having fewer doses are ideal candidate to be selected for sustained release dosage from.

The release of medicine in a same manner up to a longer time period was occurred in sustained drug delivery system hence decrease in the rate of dosing. It was also observed that there is minimal drug variation within the blood. This system keeps the plasma level of drug in a therapeutic range. There are few physicochemical properties of drug which must be consider before going to formulation of sustained release preparations. The molecular weight of the selected drug candidate must be less than 1000 Daltons with more apparent partition coefficient value. Half life of drug may be present in a range of 2-8 hour with more than 75% absolute bioavailability. The drug must show higher intrinsic absorption rate as compare to rate of release. The release of the medicine could not be get affected by the presence of enzyme and pH.

**Factors Influencing the Choice of Sustained Release Dosage Form**

Drug having half life in between 2 to 8 hours are thought to be an ideal and appropriate for designing sustained release dosage forms as it decrease the quantity of dosing. So as to achieve sustained effect for drug with very less half life may needed excessive quantity of drug in each dosage form. Drug distribution inside the tissues is an important parameter in complete drug removal kinetics. As it decrease the quantity of available drug and a limiting step for drug concentration in extra vascular tissues and blood. The drugs which get metabolized prior to absorption in intestine or lumen demonstrated less bioavailability from sustained release formulations. For traditional dosage form 500 to 1000mg dose is thought to be optimal and the
same dose may be consider correct in designing of sustained release preparations. Additional important parameter is the safety margin of drugs. Drugs are generally weak bases or acids and in aqueous medium drugs should get dissolve around administration spot and then distribute to absorbing membrane for better absorption. Drug bioavailability is greatly affected by partition coefficient. Due to lipophilic characteristic of biological membrane drug transfer through the membrane greatly control by drug partition coefficient. Drugs with less partition coefficient property are not selected in sustained release preparation.

**Classification**

Sustained release drug delivery is basically categorized in to six major classes. The first type is diffusion sustained consisting of two sub categories i.e. matrix and reservoir. The second type is dissolution sustained again having two sub types as described earlier. The next types are based on osmotic pressure and ion exchange techniques. The fifth type is preparations which are independent of pH. The last types of preparations are those having alteration in their densities and behave as sustained release.

**PROBLEM ON HAND**

The term arthritis is come from Greek words i.e. Arthro means joint and itis means inflammation. It causes inflammation to either one or few joints and is basically joint disorder. Around 100 types of arthritis are identified nowadays but famous general type is osteoarthritis. It is an autoimmune type of illness in which immune system of body gets puzzle and start harming the body itself. Patients suffering from arthritis are mostly complaint about having joints pain. Many times pain is unvarying and localized to involving joint. Damages and depreciation occur to joints because of disease and muscle deformation resulted finally in firm and fatigue joints. The general signs of all kinds of arthritis are different levels of pain followed by joint swelling and painful stiffness or sometimes continue intense pain feel round the joint. Different organs in the body are also get affected by arthritic disease like rheumatoid and lupus with various signs like difficulty in walking, feeling of depleted strength, insomnia and problem in joint moving. The general reason behind disability in America is arthritis. Approximate 20 million arthritic patients facing serious problems in their daily work of life. Around 400000 patients are now present only in UK and about 12000 new cases are identified each year. As compare to males,
women are getting more infected by this disease. The maximum age is thought to be 70 at which both sexes develop rheumatoid arthritis but this disease can affect persons of any age group. Because of arthritis it becomes very hard for patients to remain physically fit and many more restricted at home bound, resulting in obesity, depression, increased cholesterol and chances of heart disease. The basic goal behind therapy must include protection and lessening of joint impairment with decrease in its functional failure. Special measure should be taken to reduce the joint pain with progress in quality of life.

Osteoarthritis is the general type of arthritis affecting body joints like feet, hands, knee and hip. There is less pain initially at the time of movement but shortly persistent pain develops also at resting position. The pain keep away individual from performing minor activities. Osteoarthritis specially has effect on weight supporting and holding joints like, pelvis and spine. After 65 years of age about 30% women may be susceptible to osteoarthritis. Inactive lifestyle, over weight and joint injury are probable elements behind osteoarthritis. It is a non curable disease but can be stop to turn to worsen state. Strengthening of joints and muscles by physical therapy is much useful. Tension on joints may also be decrease by weight loss therapy. In far progressive state of disease patient may opt for surgery. Replacing of joints may support to patients in many cases suffering from osteoarthritis.

Patient’s own immunity initiates attack on tissue of body in rheumatoid arthritis. The attack is not up to joints but it also goes to other portions of body. Cartilages and joints are very badly damage in rheumatoid arthritis affecting finger joints, elbows and knees resulting finally in deformity, if treatment is not given. It takes place in age group of 20 years and over. If disease is identified in early stages and proper therapy is given then many patients can be cure and can live a normal good quality life. NSAIDs are choice of drugs to be used as first line treatment in rheumatoid arthritis. If COX2 inhibitors and NSAIDs are not giving desired control on disease, then there is need to examine the biological drug or disease modifying treatment.

Care and medication of patient must be done on the basis of patient’s choice. Persons suffering from rheumatoid arthritis must be given chance to take judgment regarding the medication and care in relationship with their doctors. If persons not possess the judgment taking capability then doctors pursue the instructions as given by department. Proper discussion among the health caring team and patient is necessary. It is also necessary to take the advice of expert if the disease is influencing joints of feet and hands. The case is also forwarded to expert if many joints
are involved and if there is gap of three months from the start of signs to take medical opinion. Weight is the significant factor which must be control if arthritis is detected. Excess weight places the higher load on the joints. Proper control on weight is more beneficial than taking any extra food. Going for surgery is one of the important decision taken mutually between patient and doctor if joint is seriously damaged and not working properly. Medicines used to treat the disease will lessen the defense system of body and there may be of chances of getting infected by pneumonia. Hence antibiotic may be prescribed or may be hospitalized to the patient if infection is more severe.

Equally these two groups of medicines are use to control the signs of disease i.e. rheumatoid arthritis. Analgesic is highly prescribed medicine for the disease but it’s over prescription is debatable topic. Previously NSAIDs were used as first line therapy but presently NSAIDs are missed the position because of so many toxicities induces by them. These medicines may be prescribed with proton pump inhibitors. To overcome joint pain and rigidity less quantity of corticosteroids like prednisone may be prescribed. DMARDs means disease modifying antirheumatic drug is diverse group of medicines brought collectively for the management of rheumatoid arthritis.

These drugs decrease the soreness and swelling of joints. These drugs also cause the improvement in joint functioning and control the damage of joints. Methotrexate is the leading drug of this class. Leflunomide and sulfasalazine are also prescribed for the rheumatoid arthritis. DMARDs are given jointly and so many combinations are established successful. This category of drug showed good results but they required more time (6-12 weeks) to show the therapeutic effect. Toxicities related to DMARDs are nausea and toxicity of lungs. Biological agents are also used for the management of rheumatoid arthritis either alone or jointly.
The leading biological agent in use is TNF. These medicines stop the proteins like cytokines which are responsible for joint impairment and inflammation. These agents are administered as infusion or injected beneath the skin. Arthritic patients are more susceptible to death because of cardiovascular and infectious disease. People should stop smoking at the public places as it is a cause for rheumatoid arthritis. Smoking ban is the primary protection from this disease.

**OBJECTIVE OF PROJECT**

Arthritis is basically a joint disorder and statistically more than 1% of world population is now suffering from it. For the rheumatoid arthritis treatment combined drugs are administered comprising of disease modifying anti rheumatic drug (DMARD) with NSAIDs or steroids. Gastritis, peptic ulcer and bleeding are common problems when NSAIDs administered orally for an extended time period. DMARDs are given jointly and so many combinations are established successful. This category of drug showed good results but they required more time (6-12 weeks) to show the therapeutic effect. Toxicities related to DMARDs are nausea and toxicity of lungs. Biological agents are also used for the management of rheumatoid arthritis either alone or jointly. The leading biological agent in use is TNF. These medicines stop the proteins like cytokines which are responsible for joint impairment and inflammation. These agents are administered as infusion or injected beneath the skin. Arthritic patients are more susceptible to death because of cardiovascular and infectious disease. Thus there is demand to formulate the dosage form which is economical and bears distinctive qualities over existing dosage forms like
less dose, decrease gastric irritation and free unavailable drug. Pellets are said to posses numerous therapeutic benefits as compare to existing single unit dosage forms. Pellets are spread homogenously in GIT and hence produce enhance drug absorption with less peak plasma variation, decrease dose dumping, dose frequency and GIT irritation. Pelletized products are more safe and effective with improved patient compliance. Various finding proved that sustained released dosage forms of certain drugs showed good therapeutic performance than conventional dosage forms.

Scientists are now putting efforts to convert the presently used pharmaceutical dosage forms in pelletized forms so as to achieve better bioavailability. Hence, it can be anticipated that pelletized products will enjoyed dominance over all pharmaceutical dosage forms. There is need to focus on short thorough treatment which elevate the disease than long term costly treatment. Lastly, arthritis can be control if it is detected initially and if proper treatment is taken. Many people are leaving good and normal life only after proper medicines, surgery, exercise and joint prevention methods.

In present study efforts have been done to formulate the pellets of NSAIDs drugs (celecoxib, etoricoxib, aceclofenac) so as to release the drug with sustained rate used in treatment of arthritis.

**SCOPE OF PROJECT**

Arthritis is an autoimmune type of illness in which immune system of body gets puzzle and start harming the body itself. Patients suffering from arthritis are mostly complaint about having joints pain. Many times pain is unvarying and localized to involving joint. Damages and depreciation occur to joints because of disease and muscle deformation resulted finally in firm and fatigue joints. The general signs of all kinds of arthritis are different levels of pain followed by joint swelling and painful stiffness or sometimes continue intense pain feel round the joint. Different organs in the body are also get affected by arthritic disease like rheumatoid and lupus with various signs like difficulty in walking, feeling of depleted strength, insomnia and problem in joint moving. The general reason behind disability in America is arthritis. Drug therapy tries to lessen the signs of disease. Reducing the pain and development of disease are the main concerns for the rheumatic patients. Radiological development gets halt or slow down because of disease modification. If disease is identified in early stages and proper therapy is given then many patients can be cure and can live a normal good quality life. NSAIDs are choice of drugs to be
used as first line treatment in rheumatoid arthritis. As described previously approximately 20 million arthritic patients are now facing serious problems in their daily work of life. Around 400000 patients are now present only in UK and about 12000 new cases are identified each year. As compare to males, women are getting more infected by this disease. The maximum age is thought to be 70 at which both sexes develop rheumatoid arthritis but this disease can affect persons of any age group.

Thus there is demand to formulate the dosage form which is economical and bears distinctive qualities over existing dosage forms like less dose, decrease gastric irritation and free unavailable drug. Pellets are said to posses numerous therapeutic benefits as compare to existing single unit dosage forms. Pellets are spread homogenously in GIT and hence produce enhance drug absorption with less peak plasma variation, decrease dose dumping, dose frequency and GIT irritation. Pelletized products are more safe and effective with improved patient compliance. Various finding proved that sustained released dosage forms of certain drugs showed good therapeutic performance than conventional dosage forms.

Scientists are now putting efforts to convert the presently used pharmaceutical dosage forms in pelletized forms so as to achieve better bioavailability. Arthritis can be control if it is detected initially and if proper treatment is taken. Many people are leaving good and normal life only after proper medicines. In present study efforts have been done to formulate the pellets of NSAIDs drugs (celecoxib, etoricoxib, aceclofenac) so as to release the drug with sustained rate used in treatment of arthritis. All the three drugs selected for the study were sustained the rate of release for the period 12 hr when optimized quantity of eudragit RL 100 was used. It was also viewed that increased in quantity of eudragit RL 100 decreased the quantity of liberation of medicament. To an extent it was desirable but if the quantity of eudragit RL 100 enhanced more than required limit then it retarded the liberation of medicament through the system. First order release rate obtained from the pellets by using eudragit RL 100 as a sustaining agent and dibutyl phthalate as a plasticizer in proportionate quantity.

It was concluded that OD dose of capsule containing sustained release pellets of medicament for the treatment of arthritis was successfully prepared by the method utilized in this work. It was also gained that in current study the method used was inexpensive and for the industrial purpose it could be scale up.
1.2 ORGANIZATION
In this portion, the information is provided about the project work. Initially the name and address is given where the actual work was performed. After this information the later pages contains the detail information on the product which were formulated during the work. The pages also have detail information on various processes which were used during formulation of the pellets. Some advance industrial processes is also added. Lastly very short profile on medicaments is given which contains information about the nature and properties of medicament.

WHERE WORK IS CARRIED OUT
The present research work was carried out in the pharmaceutics laboratory of department of pharmaceutics of Dr. Vedprakash Patil pharmacy college, Georai tanda, paithan road, Aurangabad, Maharashtra.

PRODUCTS
In current piece of research work attempts have been done to formulate the pellets of NSAIDs drugs so as to release the medicaments with sustained rate used in treatment of arthritis. All the three drugs selected for the study were found to sustain the rate of release for the period 12 hr when optimized quantity of eudragit RL 100 was used. Following three products were separately formed at the end of work.
1) The capsule containing the sustained release pellets of etoricoxib medicament. Each capsule has individual weight of 520mg after filling of medicament, lubricant and diluent.
2) The capsule containing the sustained release pellets of celecoxib medicament. Each capsule depicted individual weight of 540mg after filling of medicament, lubricant and diluent.
3) The capsule has the sustained release pellets of aceclofenac. Each capsule has individual weight of 540mg after filling of medicament, lubricant and diluent.

PROCESSESS
Coating pans
In pharmaceutical coating procedures coating pans have been utilized from 19\textsuperscript{th} century. Conventional coating pans are cheap than other pelletization machines but there less prices are takeover by the deficiency in processing control, higher operating time, less product yield and increased labor budget The major drawback of coating pan is unavailability of operation control.
Though efforts have been put forth in regards of automation of the instrument, the pelletization procedure stay tough to develop and tedious to validate.

![Figure 5: Standard coating pan](image)

Although several advancement have been done in tablet coating operation in pans, still sugar coating stay more as an art. In sugar coating procedure variability from batch to batch is considerable but in pelletization duplicability is vital and must assured. The coating pan consists of air supply, spray and powder addition systems. Initially drug was added in dried form on nonpareil seeds then development of pellets was takes place. Initially the nonpareil seeds were
coated with drug and then outer layer of polymer coating was applied. These are the steps behind pelletization by coating pans.

**Rotating pan**
Different shape and size of pan are now come in market like spherical, hexangular, rounded having diameter 6-90 inch. Jacket may be provided to the pan depending up on desire. Suppliers are now fabricating pan as per customer description. Pellets motion in a pan can be better explained like cascading, higher turbulency at the middle of weight. Dead points were generates at the forward or backward of the pan. Decreasing angle of tilt $45^\circ$ to $25^\circ$ will decrease the dead spots formation. Mixing operation in a pan can be improve by making pan inside surface rough means initially pan boundaries are sprayed by coating liquid and later drug powder is sprinkled. Dusting powder used may be inert, depending upon procedure followed. Improvement in mixing operation is observed when baffle of different shape and size utilized.

**Air supply arrangement**
Drying and exhaust air facility is normally present in coating pans. The air flow is not sufficient for whole pan as air supplying lines are present near to the opening of pan. In coating operation hot air is also utilized which help organic solvent to get evaporate. Generally hot air is applied in between spray gaps so as to dry to the pellets. The air supplying pipes brought near to the bed for efficient drying. Pellets may be dry in FBD or oven so as to reduce remained moisture contain. Dry air is not required in uninterrupted ongoing pelletization operation if proper balance is kept in between solvent and dry powder application rate. It was observed that low dust is formed in layering of drug procedure when drying air is not in use. Exhaust air is a critical and exhaust should protect the removal of solvent and dust from the pan. The exhaust must be located on topper third of pan. Exhaust air flow speed has straight impact on moisture content of bed and same effect on rate of spray and application of powder. Exhaust air system also put impact on dissolution of controlled release pellets may be due to surface characteristics. Hence rate of exhaust flow must always be placed at 450-650 CFM. The exhaust flow must be double than drying air rate.

**Spray system**
Air spray or air less spray technique is employed for spraying coating solvent in a pan. In air spray system vigorous air is added to the flowing liquid within the nozzle or external to nozzle
top. 10-100 psi pressure is required within the nozzle. In airless method liquid is allowed to pass at a very great pressure within the nozzle opening. It is the nozzle opening size and shape which decide the pattern of spray and droplet size of coating liquid. In laboratory air spray system is selected for use because of their better accuracy at slow rate of spray. As uniformity is observed in spraying form air less technique is famous in production and can be easily operates. Because of various design of nozzle different spraying varieties are available. Flat spraying variety is mostly selected in pan coating so as to enlarge area of coating. Many guns pattern may be employed some time in formulation. Single or double gun commonly utilized in pan. The gun must be placed in such a way that spray gets enforced straight downward without break on revolving bed of pellets. A gap of 9-12 inches is considered as optimal from spray to bed. Spraying angle must be set in such a fashion to reduce the turbulency in a bed. At the time of drug layering place of gun must be interchanged so as to have similar overall distance in coating procedure. Pellets gets over wet when spray came very near to bed resulting in jumbled collection of pellets. If the gun is positioned at higher distance spray get dry, mostly in air spray method. Various pumps are used by the companies to transport the coating solvent to the spray gun. Pump transfer the solvent to either individual pump or many pumps joined in a group. Pump are furnished with hand operated buttons, timer or advanced computer based control systems.

**Powder delivery arrangement**

Accurate quantity of drug and powder must be added in pellets formulation is a critical part of production process. Feeders which can add the powder to the pan at the speed of 1g to 10kg in a single minute are now came to the market. Two types of feeders are available, weigh and volume type. Exact quantity of powder volume per minute is transfer by the volumetric feeders. Movement of powder takes place from hopper to auger is due to acting gravitational force and machine vibration. Feeding quantity in a hopper depends up on frequency of rotation and diameter of screw present in auger. Calibration of hopper must be done ahead of every use so as to achieve required feed speed. Weigh feeder work on the principle of quantity of powder weight reduced in delivery of it. In weigh feeder microprocessor is fitted which check the quantity delivered and automatically set the feeding rate. Powder is added to pan through auger. No matter which kind of feeder is applied for adding material to the pan but more important is addition of glidants like silicon dioxide so as to avoid bridging phenomenon. Care should be
taken to control dust. It can be achieved by adding powder in vortex which appeared at the opening of pan.

**Operational qualities**
1. Application of drug on non pariel seeds means layering of drug.
2. Initial preparation of granules of drug or components and the final formation of pellets.
3. Sprinkling of drug solvent on dummy nonpareil seeds.
4. Final external coating of controlled release coat.

**Modified pans**
Because of properties high air flow and better bed tumbling modified pans are proving more effective as compare to conventional coating pan but it never means that modified pans take over the coating pan for pelletization techniques.

In pelletization application of modified pans are less than regular coating pans. Vents and baffles present within the modified pans forbid the addition of powder in a pan and coating duration is similar as in regular coating pan. Erosion of coat is also one of the big issue of concern.

These pans are accessible in a size of 0.6kg-1400kg. Size of 6000 kg pan is also available but in candy factories. Automatic cleaning, product release, reverse air flow pattern are the prominent characteristics of these pans. Burst proof and microprocessor added pan are come in the market. All these special features are installed in to the pans to satisfy the GMP demands by the pharmaceutical companies.

**Few newer types of equipments**

1) **Pellegrini pan**
It is an angular shaped pan which moves on its horizontal line. Two ways of air handling methods are present in it. Heated filter air is flow in from pan back side to the bed and escaped through two immersion swords. Four different sizes of pan are now in market especially for pharmaceutical companies.

2) **Accela cota**
It is an angularly shaped pan which rotates on its horizontal line. It consists of perforations on the periphery of pan and this is the only distinct difference in between pellegrini and accela cota. In
this pan heated air is flow inside the pan from upper sides which is flow through the bed and finally removes from perforated drum. Pan consists of 2-6 baffles as rely on its size.

3) **Hi coater**
In Hi coater machine four perforations are design rather than perforated outer boundaries as in Accela Cota. This is only the signified difference in between Accela cota and Hi cota pans. The perforated lines are joined with air supplying tubes.

4) **Driacoater**
It is polygonally shaped machine similar to that of Hi coater. Heated air blown in from upward or downward of drum and escaped from same way. The 0.25 mm screen hides the perforations present in a pan.

5) **Dumoulin coater**
These pans are most recently designed, having perforations similar to accela cota. Heated air is blown inside from upper or lower side of the pan and escape from upper side of pan. Few pans have 4 mm of perforations but pan with 2 mm perforation is also obtainable. The pan has feature of distribution arrangement for coating liquid and powder.

**Extrusion and Spheronization**

This equipment is used for the manufacturing of pellets at commercial level in pharmaceutical companies. In this machine a high pressure was applied to a mass so that it runs in the opening having specified diameter. As length is sole variable quantity because of cross divisional geometry of opening. The product length might deviate on nature of material and extrusion technique applied. Different verities of extrusion apparatus utilized are sieve and basket, drum and roll extruder.

**Extrusion**

It is a technique in which pressure is put on a mass so that it propels from definite opening. On the basis of physical features of the substance, extrusion type the length of extrudate may change.

1) **Screw extruder**
Screw extruder consists of screw for applying essential pressure on the material so that it flows from homogenous hole and forms homogenous extrudates. The machine mainly consist of three parts feed, transport and compression zones respectively. In feed zone the material is charged to the machine. Hopper is attached to the machine for allowing smooth flow of substance in to the
area where screws are situated. In few machines design, there is special arrangement at this point for adding solvent in powder so that powder turns to moisten state. Screws present in the transport area forward the material to the compression zone. Screw developing industries are developing single or twin type screw designs. Extruder of twin shaped are preferred because it cause low bridging in feed area and shows better conveying of material to the extrusion area. Also it forms the extrudates which are lightly denser. With twin shaped screw extruder enhanced capability for each screw is obtain. Air which is present among the agglomerates is pulled out from compression area. In compression zone vents are designed in few extruders for removing discharged gases. Vacuum can be attached to vent which help in removing of gases present in the system because of which there is enhanced product standard as well as functioning of extruder. Care must be taken to close the vacuum source in such a fashion which stops the flow of material with the air going outside the machine. Depending up on need of compression design of screw differ. When less compression is required uniformly gap screw flights are used but when more compression is required then nearer screw flights are applied.

![Screw extruder](image)

**Figure 7: Screw extruder**

2) **Sieve and basket extruder**

Sieve extruder consists of chamber in which material is added to be extruded and at the bottom it has screen or plate. The revolving wing present inside the machine forces the damp mass to pass through the screen to form extrudates of little or longer sizes on the basis of moisture quantity. Sieve extruder is also use for the formulation of granules to form the tablets.
Basket extruder is same as that of sieve extruder with exception of screen which is fitted on the side of wall. The formulated extrudates come outside the machine in horizontal form as pressure is applied on them from vertical openings.

3) Roll Extruder
This extruder is also called as pellets mill in which material is added among the roller and ring shape die. The damp mass is passed through the die. Roller extruder has three types of designs. In type I design the ring shape die will revolve round the single or more than one roller. In type II type of design the roller are constructed exterior to ring die. The powder is added to the extruder by using hopper with the help of screw to the space among die and roller. Roller and die revolve opposite to each other. Type III design consist of rollers which are present on upper side and rotate with horizontal, fixed die plate.

4) Ram Extruder
This extruder is used in pharmaceutical industry from a very long time. Piston present within the cylinder compresses the material to go from a definite opening. On return of stroke the material filled in to the chamber. Due to compression of mass the formation of extrudate occurs. Piston length and frequency are the main formulation variable to be controlled.

Spheronizing Machines
Spheronization is an old concept and travels the many stages of development. The old name was marumerizer i.e. round maker. Marumerizer word is yet used to explain the method. The spherical shape posses many benefits on the other forms and one major benefit is very easy for coating. In spheronization the formulated cylindrical forms extrudates are breaks down in particles having similar length and then progressively changed to spherical forms. This equipment is utilized for making materials in spherical shape. It posses uprightly empty cylinder and horizontally moving rubbing plate present at the center. Friction plate available in two forms i.e. grid and cross hatch shape. Manufacturing procedure comprises the addition of fixed quantity of cylindrical form extrudate in the revolving plate. The extrudates are cut off in to same length particles instantly by the collisions with particles, wall and rotating disk. In this mechanical energy by revolving plate is transferred to kinetic energy to form a mechanical fluidized bed.
More treatment causes the extrudates to change into spherical shapes. This shaping procedure is similar to deformation of plastic\textsuperscript{29}. Different types of assisting instruments may also be used for making process fast and which will help the particles to become round shape easily. When there is more amount of moisture within the extrudate is observed in that case powder feeder is used. Addition of powder will soak the moisture if any and will reduce the process of particle sticking and agglomeration. Hence powder must be selected as an ingredient of formulation or may be added in to the process of coating. It is necessary that powder must be compatible with the formulation. Jacket may be provided outside the instrument which will increase the interior temperature and removed the moisture. If the product get destroy by the increased temperature of the process then cooling the outside boundaries will defiantly help to solve the problem.

In air supported spheronizer dried air is added below the plate to overcome the moistures present on particles surface. Because of it particles fall freely towards one another and help to produce fluidization. At this point of stage now spheronizer is behaving as mixer or granulator. The solvent may be added at this stage of fluidization. Higher agitation of powder with binding liquid is required to get uniform coherent damp mass. Air assisted spheronizer is same to that of fluid bed granulator. Air filtration technology is essential when using air based spheronizer. Pretreatment on air is also being done for controlling humidity. Heating and cooling are the other methods of pretreatment performed on air for making it suitable for use.

**DRUGS PROFILE**

1) **Etoricoxib**

*Figure 8: Spheronizer*
It is selective (COX2) cyclooxygenase-2 enzyme inhibitor which inhibits isoform 2 of COX2. It brings down the prostaglandins synthesis from arachidonic acid. Etoricoxib is prescribed in psoriatic arthritis, rheumatoid arthritis, gout, osteoarthritis, acute pain. It has molecular weight 358.842, molecular formula C_{18}H_{15}ClN_{2}O_{2}S and meting point is 134-135°C respectively. Etoricoxib is soluble in ethanol, methanol and dose is about 60 mg OD in osteoarthritis and 90 mg OD in rheumatoid arthritis for adults\(^{30,31}\).

When taken orally it is speedily absorbed with nearly 100% bioavailability and 92% protein binding property. Metabolism of etoricoxib is takes place in liver by enzyme CYP3A4 to 6-hydroxymethyletoricoxib and etoricoxib 1'-n'-oxide metabolites. The 70% of it discharged by urine and by fecal matter only 20% and it has 22 hours of plasma half life\(^32\). Adverse drug reaction produced by etoricoxib are hypersensitivity reactions, nervousness, headache, ischemic cardiac events, insomnia, hypertension, taste change, chest pain and blood disorders. Prostaglandin is present all over the body and shows impression on tissues and organs. Prostaglandin causes pain in body. Formation of endoperoxidase was stop by action of etoricoxib which selectively block COX2 enzyme and synthesis of prostaglandin is stop.

2) Celecoxib

Celecoxib comes under the class of NSAIDs which is selectively COX2 inhibitor and diaryl substitute chemically. Celecoxib has formula C_{17}H_{14}F_{3}N_{3}O_{2}S, molecular weight 381.38 and melting point 157-158°C with 97% protein binding. It is metabolized in liver by CYP2C9 enzyme and excreted in urine. Adult dose is ranges from 100-200mg OD or BD. After taking orally celecoxib achieve peak plasma concentration in about 3 Hrs. Peak plasma level were slow down for 1-2 hr with step up of 10-20% area under the curve when celecoxib was administered with meal having high fat content. When dose over than 200 mg given in fasting then there is promotionally low increase was observed in AUC and C max because of less drug solubility in water media. The drug is metabolized by CYP2C9 enzyme and its inactive metabolites namely alcohol, glucuronide and carboxylic acid are found in plasma. If radio marked single celecoxib is given orally then 57% dose was eliminated in feces and 27% in urine. Drug has 11 hr of half life with 500ml/min apparent plasma concentration\(^{33}\). Celecoxib showed substantial decrease in joint pain, swelling and tenderness and used in juvenile rheumatoid arthritis, ankylosing spondylitis, analgesia and dysmenorrhea. Celecoxib may cause ulceration, hepatic failure, liver necrosis, impaired renal function, toxic epidermal necrolysis, anemia and puncture of intestine and
stomach which may be dangerous. This drug can’t be given to patient having known hypersensitivity, urticaria and allergic type of reactions.\textsuperscript{34,35}

3) **Aceclofenac**

It is derived from phenylacetic acid having analgesic and anti-inflammatory actions and reduces the different types of pains. Inflammatory mediators were gets affected by aceclofenac. It reduces the pain in osteoarthritis of knee and increases its function ability. In rheumatoid arthritis aceclofenac decreases joint inflammation, morning stiffness and level of pain. In ankylosing spondylitis it enhances the spinal mobility. Aceclofenac is also been used in gynecological and dental pains. Aceclofenac has chemical formula C\textsubscript{16}H\textsubscript{13}Cl\textsubscript{2}NO\textsubscript{4}, melting point 149-153 \textdegree C and molecular weight 354.2. When taken orally it quickly gets absorbed and shows 100% bioavailability with 99.7% protein bound and diffuses into synovial fluid.\textsuperscript{36,37} Aceclofenac works inside cyclooxygenase pathway. By suppressing arachidonic acid, aceclofenac competitively bound to cyclo oxygenase \textit{in vitro} and \textit{in vivo} resulting in reduced production of PGF\textsubscript{2}, PGE\textsubscript{2} and prostacycline by stopping formation of prostaglandins. The drug is good tolerated and less frequently may cause abdominal pain, dyspepsia, vertigo, diarrhea, dermatitis and pruritus. Aceclofenac is not prescribed to patient suffering from duodenal or peptic ulcer, hepatic or renal failure and to pregnant lady. Aceclofenac may also elevate digoxin and lithium plasma concentration and suppress the diuretics drug action.\textsuperscript{38,39,40}

1.3 PROBLEM/ HYPOTHESIS

In present research work the selected hypothesis is that “whether the eudragit RL 100 and eudragit RS 100 will help in sustaining the selected medicament for the treatment of arthritis.” Based on this hypothesis a thorough literature will be conduct to know about the different characteristics of polymers and drugs. The formulation table will be finalized and it is predicted that 12-15 batches will be formulated. The drugs will check for their solubility in the organic solutions. The solublized medicament will be separately externally coated on to the non pariel seeds. In the solution of medicament the eudragit RS 100 will be added. Final coat of eudragit RL 100 will be employed manually by using coating pan and gun. Different batches will be formulated in which medicament and eudragit RS 100 quantity will keep same but eudragit RL 100 quantity will differ. The \textit{in vitro} dissolution study will be carried out to obtain the best formulation.
Pellets are spread homogenously in GIT and hence produce enhance drug absorption with less peak plasma variation, decrease dose dumping, dose frequency and GIT irritation. Pelletized products are more safe and effective with improved patient compliance. Various finding proved that sustained released dosage forms of certain drugs showed good therapeutic performance than traditional dosage forms.

Formulation scientists are now putting efforts to convert the presently used pharmaceutical dosage forms in pelletized forms so as to achieve better bioavailability. Arthritis can be control if it is detected initially and if proper treatment is taken. Many people are leaving good and normal life only after proper medicines.

**INTRODUCTION**

Before considering pellets as carrier for transferring drug to the body the various manufacturing parameters must be checked ahead of production to be done. There are various manufacturing considerations that must be meets before formulation when pellets are used as a media for transferring drug. Pellets formulation required costly methods or highly sophisticated and specialized machines. Unluckily in few cases, the pelletization processing is costly and time consuming. Sometimes production of a batch needed hours or days to get finished which hike up the production cost. Reversely, to obtained production in less time it becomes compulsory to install highly efficient machines which required high share of capital investment. Rotor granulator, Spheronizers and extruders come under this class. Another important issue which strongly affects the successful formulation of pellets is coating to freshly prepared pellets containing medicament. Any tablet coating machine possibly is used for coating of pellets but advanced and especial coating machines are needed for good appearance and for extending release of drug. Hence availability of required coating machines must be checked ahead of pellets formulation. As the coated pellets are better represents from their external look and shape hence drug pellets having surface properties optimal is chosen for coating. Lastly, pellets are enclosed within proper hard gelatin capsule size or may be compressed to form tablets. Regardless of method of pelletization used all the formulated pellets are not same in sizes and express a very limited mesh fraction. Coating is given to all pellets to have desired release rates. Some time pellets also mixed with other drug pellets so as to form combine pellet product. For setting required potency placebo pellets are mixed with drug pellets. Achieving content uniformity may be a serious concern if segregation is happened. When vibration is given to
pellets it resulted in segregation. It happened due to variations in density and size of pellets. The key factors behind segregations are surface morphology and static electricity. At the time of blending process the interparticle friction causes static electricity to develop resulting in segregation of particles. If irregular surface pellets are mixed with smooth surface pellets then in this case it is not possible to obtained uniform mixing. The above discussed technical trouble can be solved by adding less quantity of separating agent ex. Magnesium stearate, talc. Segregation happening because of variation in density and size can be corrected by using narrow mesh which selects the same density pellets and reject the over sizes pellets. It is not hard to manufacture the pellets of same density but quite hard to make the placebo and drug pellets of similar densities. Another valuable parameter which is not straightly concerned with segregation but decides the overall successfulness of enclosed pelletized product is content of drug in a single pellet. If drug content is found much greater in pellet then it becomes tough to achieve uniformity of content in final product, particularly with potent drugs. Low potency in product was also observed if pellets were not filled properly. It is advisable to add inert bulk pellets with potent pellets and quantity of potent medicament should be kept very less and filled in selected size capsule.

**DESCRIPTION**

**Fluid bed equipments**

This machine has been in used in Pharmaceutical companies from last 30 years. Inlet air handlings exhaust air, spray and product discharge systems are the different parts of this equipment.

These different parts are very much advanced and hence difficult for maintenance and handling but give a high quality product. Therefore this equipment now becomes intact part of pharmaceutical and food manufacturing plants. The air goes inside the equipment by air handler to the product preparing area of instrument. In many cases escape air filter is present in this section of instrument to remove the product from air, ahead of its movement through duct to exhausting machine which deliver to environment. A fluid bed machines need control on them.

**Air handling**

In fluid bed machine action will be done on processing air to more or few extent as required by the method. This system is constructed to have a better check on humidity and temperature of ongoing procedure so as to have enhanced duplicability among batches.

**Air flow**
Flow of air in fluid bed equipment is achieved generally by suction process. Hence minor errors which may be present within the duct not lead to removal of dust in building. Same way solvent fumes pollution in plant will not happened if organic solutions are employed. This style is highly harmonious with explosion prevention techniques. As many fluid bed equipments may get burst hence safety air duct must be must supplied with it which releases the discharge freely to air. Explosion relief wing present within the system can easily identify small increased in pressure inside the equipment. When air is coming through pressure supply instead of suction supply then in this case there is no need to install this system. Lastly, due to suction system processing air and product fluidization property is handled properly.

**Air conditioning**

**Simple air handler**
It consists of prefilter as well heat exchanger. Steam heat exchanger of average pressure size is present in maximum fluid bed equipments. In this kind of equipments control of temperature is lies in range of ± 2-3°Celsius. In pharmaceutical companies HEPA filtration is needed and such kind of demanded filtered air is produced by air handling systems.

**Bypass and face system**
This is a more novel approach for the steam valve modulation required for check over temperature. It consists of dampers which allow mixing of bypass air flow with the air flow which is blowing on heat exchanger. The heat exchanger unit is always put on switch on mode and temperature is governed by combing bypass air with hot air. Benefit behind this kind of style is that temperature can be adjusted very fastly as required by operator which holds firmly the set temperature.

**Dehumidification**
This is another important part of complicated air handler unit. In this section air humidness is corrected to required degree. The present moisture within the air can be removed by process of condensation by allowing air to flow on cool coils. The final condensate is gathered and moved out from the machine so as to protect it from enter again by flowing air.
**Humidification**

It is observed that in warm and cool weather humidity of air might be less as received by dehumidifier coils hence humidification part is essential in unit. After joining humidifier with dehumidifier perfect control is obtained at dew point of flowing air. Humidification can be achieved by injecting steam. When humidification is needed then heater is also equipped with the system so as to make air warm and could carry required moisture.

**Bypass loop**

It is specially designed parameter which conditioned the air and permits the processing air to get bypass the formulation till it arrives at desired humidness and temperature. This factor is important in those products which get affected by slight change in temperature and humidity. The addition of such kind of devices will surely increase the cost of the instrument and production but gives similar conditioned processed air throughout the year, no matter which season is going outside the plant.

**Air handler position**

Where should air handler present is a matter of discussion. It can be joined straight away to process part of machine and be placed in processing area. The ideal benefit of this kind of design is that air handler is in close connection with the formulation and permits less loss of heat within air handler and part of machine where formulation is going on. Drawback of this kind of design is increase in surface area of machine which has to be cleared in process. Another problem with
this arrangement is that heat is produces in operation which increase heat burden on air condition of room.

Air handler may be located in the machines room present inside the building or may be placed outdoor on ceiling of plant. It may be designed on outside yard of the plant. If installation is planned outside the building then proper covering to the coils must be given so as to provide protection from atmosphere and heat loss from the coils.

As air handling system are not capable to bear the high pressure produced during explosion therefore this system must be separated from product developing part of instrument by the use of safety device which provide safety in explosion.

DETAILS

1) Fluid bed dryer

When product is dried by using fluid bed dryer it has to go through three different stages. Initially at the start of dying process the material starts to heat up to wet bulb temperature from ambient temperature. There is constant temperature until when all the moisture of the material get decrease to critical point. At this stage there is no extra free water is available on granules surface and then temperature start to begin from here onwards. Product processing part of the instrument comprised of container which keeps the material which is yet not be fluidized. It consists of expansion area where the material is fluidized and filters to remove the boarded particles of material present in flowing air.
As the intention behind using fluidized bed dryer is to decrease the moisture contain of the material with good efficacy. It is essential that expansion area for fluidization should not be much more. Equilibrium should be maintain in providing plenty of processing air to make the material completely fluidized and providing enough air to remove moisture correctly. Because of drying of material a huge amount of fines get catch in to air filters hence expansion area must be of such a length requiring less cleaning in preparation of batch.

In fluid bed dryer the product container is made up of steep wall and quality to exchange the lower screen of open area. Proper and identical fluidization is controlled by open area of lower screen, which is may be differs in between products. So as to gather the sample, the sampling point is to be provided with the product container. Possibly observation window may be provided so as to have check on product movement in between formulations.

The addition of agitator and delumping device or different small instruments may be done depending upon need of product. Because of these instruments capital of equipments get rise and such kind of instruments also needed timely cleaning and their maintenance. It is not necessary that because of addition of such instruments better fluidization of the material will takes place.

Consistency plays a big role in selecting agitators. Few materials needed much more force of agitator but some will not required high force.

2) Fluid bed granulator

This equipment is needed few design changes as described earlier for FBD. It is mandatory to enlarge the expansion area up to 50% to the length of expansion area of fluid bed dryer. The important difference from FBD design is that nozzles for liquid spraying are present in expansion chamber of fluid bed granulator. Liquid which is used for binding purpose is constantly sprayed out through nozzles in a controlled manner so as to form pellets or granules from fluidized powder. Narrow and deep size product container is used in fluid bed granulator as compare to fluid bed dryer in which distinctive product container is utilized. Because of this well controlled material movement is takes place with noticeably below on the periphery and moderately on upward movement of material in the centre part of the container.
Many windows are provided in container to have look and to observe the particles movement. Window designed in expansion chamber permits the viewers to have a complete full look of expansion area. In process of granulation use of temperature sensing instrument is beneficial for checking the temperature of the processing material.

3) **Fluid bed top spray coater**

It is not the method of preference for pellets production. In top spraying the solvent is applied on pellets or particles which are in fluidized state. The machine design is same as that of fluid bed granulator yet there are few important changes in design of this machine. The design of this machine is consist of lower plenum on bottom side then product container is above to it. Above container there is expansion chamber and finally on to the top of machine there is filter housing. The nozzles used for spraying the liquid are situated below to the expansion area and liquid is sprayed on to the particles which are in moving with a very high speed. Due to application of solvent by this method it causes material to become less wet and reduces material particles clinging with each other.

Figure 11: Fluid bed granulator
If material is fluidized with greater speed in top spray coater needed higher expansion area in a design. Length of expansion area is as much as twice the length of fluid bed dryer. The design of expansion area is exchanged from spherical cylindrical to conical shape. Due to this kind of design particles speed reduce when they travel in upward direction.

Lastly, a big design variation among the fluid bed dryer and coater is present in filters and way of its cleaning. In fluid bed dryer single piece filter is applied and for cleaning to the filter blowing of air in machine has to shut down and required shaking of filter so as to remove trapped particles.

While in coating procedure fluidization of particle is not disturbed and coaters are supplied with many filters. For cleaning purpose flowing of air is shutdown through single filter selected for cleaning and that particular filter is cleaned without disturbing another filters and fluidization process is not stop.

4) Fluid bed bottom spray coater (Wurster coater)

This Wurster machine is in used from last 18 years for coating as a bottom spray. It is cylindrical in design having cylindrical shaped division inside it having diameter of about one half in compare to external cylinder. There is a plate at the bottom with perforations. Minor size holes are present at the periphery of the plate and bigger size perforations are located in to the centre of the plate. The nozzles which used for application of liquid is situated in mid of perforated plate and cylindrical shaped partition is present over to it so that the particles movement will takes place exterior to the partition with good speed. Because of such kind of design a very controlled
flow of material in upper direction from partition to expansion chamber takes place. When quantity of number of batches is improved on a production level the quantity of inside partitions is also required to be increased with improvement in external cylinder boundaries. For such kind of design maximum seven partitions can be added. Mainly there is three different types of design are present to handle the particles of different size.

**Type I**

For tablet coating purpose Wurster coater possess less expansion area on upward side generally not more than 300-400mm over the partition. Filters are not essential and mainly not required because of recycling of dust over the outer layer of tablet may reduce the coating quality. For coating of tablet Wurster coater must be in cylindrical shape and inside partitions must be in cylindrical style. The quantity of open space in a plate must be changeable because the amount of air blowing inside the partition against the air blowing outer to the partition required adjustment on the basis of tablets characteristics like density and size etc. Because of only this reason level of partition over perforated plate require adjustment.

![Figure13: Coating from bottom](image)

**Type II**

This style of Wurster coater is used for small size pellets. The expansion area over the partition required to be enlarged so as to have good expansion of pellets in a fluidized state. The expansion area shape is turned to conical form from cylindrical from so as to decrease the
velocity of particles. A very thin size mesh is fixed in an orifice plate so as to hold the material in Wurster area. Adjustment of window can be done so as to observe the product movement in expansion chamber. Use of temperature monitoring device for checking the ongoing product temperature also be done with facility of sampling port. As this method of coating from bottom is utilized when more quantity of solvent or drug layering is to be employed on material hence it is essential to do adjustment for height of partition in processing.

**Type III**

Expansion area having more height is used when material of small particle size is to be process. Expansion area with enlarged height is essential so as decrease the moving particles velocity. Side angle of expansion area needed care during operation. Fast motion of fluidized material is taken place reverse in Wurster area because of steep angle. For achieving nonstop fluidization of material it is essential to implant filters. Potentiality to put partition height proper is much vital as partition remains in a state of movement near to bottom screen and do not disturb the particles flow. When we want to coat a very small powder in that case particularly constructed partition are used. The instrument is cylindrical shaped but it gets widen at its bottom in conical form to give the more space at the partition bottom for the materials required to be carried to partition and to coating area.

**Centrifugal Equipment**

In the beginning this machine was used as granulating apparatus but later on it utilized in other pharmaceutical applications too. Centrifugal equipment is the most recent and modern machine for manufacturing the pellets and posses many benefits to the other existing methods of pelletization. These advantages are easy operation and automation with less production cost. But purchasing and installation price is more than other equipments like coating pan. By efficient solvent coating and powder layering with proper drying in this machine will help in decreasing the economy of production and time as well. The concept of automation of production machine is a recent one and will needed extra skillful personnel to reach the set goals. Automation of centrifugal machine right now will not be useful as manual handling is quite practical.
Centrifugal apparatus have same parts as used in fluid bed equipment i.e. product and expansion areas, air handling and filtration systems. At the time of manufacturing three forces like gravitational, fluidized air and centrifugal works on product. Spray method is the unique feature of machine. The guns are dipped in the product and solution is sprinkled to the moving pellets means solvent is coated in parallel path of product movement\(^{14}\). The machine design helps to explain about repeat and competency of process. This equipment allows the straight addition of powder to the bed of material which is another feature of this machine from fluid bed system. Due to all these contributing characteristics the centrifugal machine gives a more pellets revenue, use of dry air, accurate spraying of solvent and powder with least loss than other methods.

1) CF Granulator
The CF granulator is an open machine and not allows the complete fluidization of material. The main parts of the CF granulators are solvent spraying, material processing area, and air supply method and powder delivery apparatus. The manufacturing chamber consists of fixed stator of cylindrical shape with revolving rotor. Depending up on requirement the baffles may be attached to rotor. A temperature monitoring device put just over the rotor for checking the temperature of bed. Cover is provided on to the surface of stator for reducing the filth deposition throughout production. Through the permanent outlet channel the formulated product is removed from processing area towards the stator by using centrifugal force. While discharging the material air pressure of slit and rotor pace possibly enhanced.
2) **Glatt Rotor Granulator**

Glatt rotor granulator consists of fixed cylindrical boundaries in product chamber and revolving disc at the bottom and this configuration is same as CF granulator. The size and length of disc is simply change manually or automatically. Efforts to be taken to add waffle plate at the surface of disc plate for improving pellets motion. The coating solvent is sprinkled in tangential manner on the material bed. The gun should completely dip in moving material during layering procedure.

3) **Rotor Processor**

The material processing area consists of revolving disc having partial holes at the boundaries and on exterior side is cylindrical chamber. In starting steps of pelletization the wall is in fixed state till solvent spraying and powder layering produces the spheres. After manufacturing of spheres the walls of rotor processor rise up and permit the spheres to go in the fluidization area. The spheres go to bowl after their fluidization. The cycle is replicated till formation of dry pellets. Speed of disc and height are changeable. Powder feeder in rotor processor is present at the top and feed tube help to convey it by using gravity. By exit port the formulated pellets were removed using centrifugal force to container.

4) **Spira a Flow**

Fluidization of the material is achieved by inside air pressure, coming from perforations in a disc and clearance among the stator and rotor. The dampers manage the amount of air supply separately for these two areas. Efforts should be done for the addition of mixer blades which move with great speed and protect the lump formation in granulation step. To the expansion area the material is added by using gravity from a port. The product is removed from exit port using centrifugal force. Binding liquid can be added to the material bed using gear pump. This instrument cannot be utilized for powder layering procedure hence needed extra changes in it. Expansion area of this instrument is looks like conical. Facility of window is also provided in this area for observing particles movement.

**Suspension and Solution Layering**

Nonpareil seeds can be layered by drug suspension or solution to produce pellets having similar size distribution property and excellent morphology of surfaces. From last many years traditional coating pan are used in pharmaceutical industries for pelletizing purpose.

Conventional coating pans are available in various shapes and sizes, consisting baffles to improve the material movement and blending. The walls of pans are constructed with tough
metals. For evaporation of coating solvent inside the bed the heated air is allow to blow and a duct is constructed at the opening of pan for removing the air. Coating solvent can be sprayed either by one or many spraying nozzles. Evaporation of the solvent during coating is a big issue of concern need to be solved. The pharmaceutical industries are now migrating towards the aqueous coating than organic solvent coating. Efforts are now put forth for the development of system which dries effectively.

The fluid bed unit is well match for the production of pellets using layering technique and any kind of solvent is coat by it. Top spraying method generally used for layering but rotary tangential spray and bottom spray are also the methods of choice. The traditional top spray coater is gradually developed from fluidized bed dryer and utilize in pharmaceutical companies from last ten years. The material is placed in the product container which does not have baffles and air get distribute uniformly through the plate, present at the bottom. Material is being fluidized by the air and nozzles spray and the coating solvent spray on the fluidized particles. The particles move to expansion area from spray area. The material is come back to product chamber and the cycle is being repeated.

The next air suspension method is bottom spray method. The famous design used for bottom coating is called as Wurster method. Rotary fluidized bed is a modern technique use for the formulation of greater potency pellets. The material container is cylindrical shape without baffles area having disc of adjustable speed at its bottom. While manufacturing spiraling helix pattern is gets generated because of grouping of three types of forces like gravity, centrifugal and velocity of fluidized air.

**HISTORY**

Certain pharmaceutical companies have installed successfully the pelletization technology to formulate pellets of considerable size and shape. In 1950 pharmaceutical company wishes to sustained the release of drug about desired time period. Conventional pills were started to produce having extended drug release pattern. Different pills with various release patterns in preset concentration were mixed and presented in capsule of hard gelatin. The drawback was quantity of pills to be filled in capsule and period of drug release can’t be prolonged more than few hours. Production of pellets was also tedious and required skilled men power. As the manufacturing machines were became more advanced and tablet machines were introduce which can produce thousands tablets in a minute. Enormous steps were done to overcome the
production time length and improvement in technology which resulted in manufacturing of mini tablets which can be filled in capsule but this apprentice could not solve the size restriction which was experienced at the time of formulation of sustained release pills. High research work done to develop such a technique which can sustain the pelletized products over a time being period.

An important discovery was made in 1949 when a scientist recognized the possibility of candy seeds (tiny sugar pieces) can be done in sustained release preparation and go ahead with the formulation of small drug pellets which can filled in capsules.

In 1951 a research paper was published covering all information on production of seeds. It explained about use of coating pan and application of powder and binding solution on granule of sugar till circular seeds of expected size can be achieved. Although the process was time consuming but still it started a new epoch for the pelletization technology.

In 1964 spray congealing technology was came which produces the sustained release pellets (0.25-2.0mm). In this method slurry was formed between the active drug and molten lipid which was atomized in to the chamber of gas so as to formed circular pellets. In same period Marumerizer was launched by Japan with high production capability in small time. Because of advancement in drug delivery system the active part of pellets in design of dosage form and formulation was also same way increased. Day by day pharmaceutical companies are making themselves accord with the technological development coming in to the field of pelletization. The orientation will be anticipated in coming future also.

**CRITICALITY**

Blending of material inside the pan will take place because of pan shape, angle, speed and baffles design. For the preparation of sustained release pellets film thickness is important. Pellets were stick to inside area of pan if there is higher air speed in exhaust duct. Single or many nozzle patterns may be employed on the basis of need of bed area to be coated. Pans are also available in different sizes from 1kilogram to 400 kilograms.

Traditional top spraying is least used technique for pelletization and layering purpose. The unpreventable spray drying and spontaneous fluidization style creates major problems to technicians practicing this method. Again the characteristic of coated film employed after the layering is conditional to formulation.
Processing variable related to Wurster method are height of partition and design of plate orifice. The partition is put on at the height of 2 cm or smaller than that over the orifice plate when dealing with small batch having less quantity of material. Wurster method can be easily scale up only if few important aspects must be considered. The big problem arises at time of transfer of formula from laboratory to pilot plant. Wurster present in lab consist of nozzle which can spray at the rate of 200ml in a minute but Wurster in production consist of bigger size nozzle which spray at the speed of 1000ml in a single minute.

Processing variable related to rotor method basically include the design of material container. At first size of batch is calculated and during processing it is essential that nozzles must be dipped inside the bed in initial steps of layering. If nozzle is obtruded from the material bed then drying of spray will takes place which gives sub standard quality in final pellets. Few important variables rely on pellets size are rate of spraying, temperature and volume of air. To a large degree the speed of fine particles going from the coating area is calculated by disc radial velocity. Radial velocity is present in between 3-8 m/sec nevertheless of disc diameter. The speed of coating and blending is insufficient if the radial velocity found to be below 3m/sec. on the other hand if radial velocity is much greater than material bed experiences the abrasion. Material has to face greater quantity of mechanical stress as compare to other methods and it is one of the major demerits of rotor method. To reduce the pellets breaking baffles must be removed from the disc. It is essential that disc must be sooth and employed only for purpose of improving the pellets movement.
LITERATURE REVIEW

1. Youness Karrout, et al., 2009, was formulated and coated the pellets with special polymers and delivered the medicament to the specific site of the colon. By utilizing extrusion and spheronization techniques loading of drug on to the pellets cores were done. Granulator was used to mix the powder and purified water was incorporated to it till formation of uniform wet mass occurred. Three types of various experimental units were needed to check the release of medicament in the GIT. Hence initially, removal of drug was investigated in to the starting portion of GIT then examined in to the complete GIT having fecal material. Lastly the dissolution study comprised of checking of drug release in to the GIT but containing fecal material. In vitro release of medicament through pellets was performed using agitating flask kept at 37°C. Although at 20% coating concentration removal of medicament was considerable and 20% release of medicament was recorded in 11 hours of study. It must be noted that these findings were achieved with the dissolution fluid not containing enzymes. It was not exactly coincides with the in vivo conditions. It was also observed that effect of enzymes on to the polymeric film was nil. For reducing the rate of medicament release through the pellets the quantity of ethylcellulose in to the film was improved. The rate of medicament release substantially reduced after reducing polymer ratio. However in all the situations the rate of medicament release reduced proportionally with improving level of coating. Around 15 to 20 percent level of coating with ethylcellulose to nutriose mixture in proportion of 4:1 and 5:1 was observed satisfactorily for totally restraining the release of medicament. There was negligible response was seen if pepsin and pancreatin was incorporated to the dissolution medium independent of quantity of polymer and level of coating.

For purpose of comparison removal of medicament was also checked in contact with dissolution fluids simulating the situations in initial portion of gastro intestinal tract and then exposed to the culture media in absence of feces of patient. Significantly no rapid improvement in to the rate of drug release was detected in 12 hours of study. The main bacterium present in to the samples of feces was to be recognized and another medium was prepared which simulate the situation inside the colon. It was lastly concluded that removal pattern of 5-aminosalicylic acid efficaciously depressed by exposing to medium copying the
situations as in starting part of gastrointestinal tract regardless of enzymes and agitation speed. But release order is get improved and removal of drug was observed in a timely regulated style because of meeting of pellets with fecal matter of patient suffering from bowel inflammation.

2. **Anette Pauli Bruns, et al., 2010**, formulated the matrix sustained release pellets in single step with the help of fluidized bed equipment in which binder used was microcrystalline wax and matrix forming material was talc. The model medicament used was theophylline. Primary substances were characterized by laser diffraction technique. Sieve analysis of microcrystalline was done. Pycnometer was used for examination of density. For the determination of melt density around five gram of microcrystalline was taken and shifted to the measuring cylinder of 10ml. Water bath was used for the application of heat and wax starts to melt at 60\(^0\)C. This volume was used for the measurement of density. DSC technique was employed for the measurement of microcrystalline wax peak temperature of melting and melting range. Around three gram of sample was selected and kept in aluminium pan having an aperture. At the rate of heating 10\(^0\)C in a minute scanning was done in the middle of 20\(^0\)C and 90\(^0\)C. For the calibration standard indium was employed. For getting higher sustained release rate the quantity of binder was not enough for the process and hence extra matrix polymers was required to be added. These matrix material are non meltable in nature and are not soluble in to the dissolution fluids. These substances have particle size very fine and talc was selected for this reason. All the prepared formulations have size of 500 grams containing microcrystalline wax and powder blend of drug and talc. The experiment consists of utilization of fluid bed granulator not having spraying nozzle system. For the purpose of SEM study complete and broken agglomerates were taken. With the help of liquid nitrogen the selected agglomerates were rapidly frozen and then were broke. After breaking images were taken by microscope. With the help of sputter coater machine sputtering of agglomerates with the gold was performed prior to microscopy. At the beginning of study it was observed that smooth pellets with circular in shapes were produced with easy and small experiment. For the immersion and layering procedures it was essential that particle size of binder must be greater as compare to added solid materials particle size hence resulting in formation of hollow pellets. When drug have more median size of particle and binder have less median particle size then development of more quantity
of fines will take place with less quantity of pellets. When theophylline with less median size of particle was utilized then formation of pellets having smooth surface with less quantity of fines was occurred. The quantity of binder may be added in limit of 12% to 28% of total formula and was approved quantity as per the literature survey. Decrease in quantity of binder less than this causes huge quantity of fines development. If quantity was improved higher to this limit then formation of lumps was taken place and melted binder was gets adhere on to the wall of granulator and bottom sieve. Processing parameters have negligible impact on the product development. The value of crush resistance lies in the middle of 0.16N to 0.53N. Matrix stability governs the value of crush resistance. The solid particles are properly connected by large quantity of binder and hence more crush resistance was examined in spite of small thickness of layer round the pellet. It was also noted that porosity was not affected by the particle size of pellet.

3. **Manjanna K.M, et al., 2009,** concluded that, gellan, scleroglucan are exopolysaccharides hydrogels possibly used biosubstances in different developed dosage forms. Various cross linking substances are the source for hydrogels which are suited for personation and release modification of different formulation.

4. **Nisar-ur- Rahman, Umeruqiatulain, 2008,** compared the order of absorption and degree of bioavailability of theophylline and designated sample as test and reference. They found no variation in their absorption when *in vivo* absorption pattern was checked. It was concluded that two unlike drugs have negligible effect on theophylline bioavailability. The content of drug for the tablet and capsule can be obtained by triturating them individually in a mortar to form fine particles. During dissolution study of both the dosage form very slight variation was identified. In ten hours of dissolution study higher than 90% medicament was liberated. HPLC was utilized for examining the samples of plasma. In vivo work was conducted on to the 12 physically fit adult volunteers who do not smoke and having weight between 50-65 kg. It was necessary to take written permission from them and inform them about the study. Urine and blood examinations were performed on to the volunteers for knowing about their health status.

5. **Jamila Hamdani, et al, 2002,** said that in melt granulation process solvent was not used and granulation was achieved by incorporation of binder which softens at less temperature and this melted binder works as a binding solvent for the process of granulation. Wax, PEG and
fatty acids are the examples of binders which melt on application of heat. In melt pelletization process the drying step was cut off and hence it proved to be energy and time saving process. Also extend drug removal could be achieved in melt pelletization technique without application of final coat on to the pellets surfaces. Melt pelletization is a good option for those materials which are not suitable with water. In present piece of investigation by applying melt pelletization method controlled release pellets of phenylephrine hydrochloride was obtained with the help of laboratory grade instrument i.e. high shear mixer. In this study speed of impeller and impact of jacket temperature on to the pellets was examined. It was observed that pellets having small size distribution can be obtained at impeller and chopper speeds of 800 and 4000 rotations per minutes respectively. This method was also utilized for the formulation of sustained release pellets of low solubility drugs as ketoprofen and ciprofloxacin. If mixture of compritol and precirol in proper concentration was used then extend release pellets can be formed in less span of time for water soluble medicament.

6. Sreekhar Cheboyina, et al, 2008, formulated the pellets of wax matrix by freeze pelletization method containing medicament with different water solubility. In the present work of research for the development of pellet equipment was constructed in house having glass tubes of borosilicate grade. The plan precirol was taken and was melted and with the help of syringe and needle the molten liquid was inserted inside the column from bottom side manually. The apparatus consist of glycerol solution. The injected drops travel in upward direction and were removed from the top of the equipment in solid state. By using deionized water the pellets were properly washed 3 times. After that the pellets were kept for drying at twenty five degree celsius for 1 day. In freeze pelletization technique the role of suspending agent is important because it maintain the drug in dispersed state in suspension of wax. Hence the ideal suspending agent was silica gel for all the carriers. For the formulation of melted wax the theophylline was added in a melted wax having silica gel as suspending agent. Melted matrix wax about ten gram was formed and inserted in to the column with the help of needle and syringe in droplet form. The product was gained from upper side of equipment and deionized water was used for washing of them. The wetted pellets were dried at twenty five degree celsius.

It was noted that if the solution with more viscosity was employed then there was no impact of temperature on the shape of pellets. It was found that improving in quantity of silica gel
will resulted in improvement in the suspension stability. In case of 10% silica gel the suspension was more stable but very viscous and cannot pass from needle of 22 G. Hence optimal quantity of silica gel was selected to be just 5%. The rate of medicament release was affected by the amount of silica gel. Therefore in all preparations of wax matrix 5% quantity was set as constant. It was observed during the study that enhancement in loading of medicament enhances the size of pellet. During DSC study it was seen that dissolution of theophylline in to the matrix wax was occurred due to increase in temperature limit till melting point of drug was arrived. Crystals of theophylline was also seen inside the matrix of GMS in micro images of pellets if medicament was largely loaded. Finally it was concluded that freeze pelletization is a modern and easy method of pellet production for the formulation of matrix wax based pellets.

7. Ramarao Chatlapalli, Bhagwan D. Rohera, 1998, found that HPMC and HEC posses more tapped and bulk density than MCC, hence are good candidates for extrusion and spheronization techniques. But, MCC has more compressibility property resulting in pellets having more tapped and bulk density than HEC and HPMC. Characterization of the pharmaceutical materials is the highly significant because it has a vital role in product development. Examination of moisture content revealed that MCC, HEC and HPMC polymers are same with very slight differences. The results of tapped and bulk densities showed less variation among the batches. Bulk and tapped densities of the MCC is less than HEC and HPMC. The value of compressibility was more for the MCC as compare to other two cellulosic excipients. It was also stated that the MCC has less flow property than HPMC and HEC. It was found that MCC has greater compressibility than HEC and HPMC. It was seen that if the particle size is small then it produces the system having greater surface area and hence more quantity of fluid is needed for the wetting the powder. Liquid must be properly mixed and distributed so as to form the denser extrudates. If moisture content of the extrudates is low then pellets will break and high amount of fines wad generated. Same way excessive quantity of liquid will form bigger pellets having higher size distribution.

8. P. Bukovec, et al, 2009, found that macrogolglycerides are the binders of less viscosity and hence pelletization work remains under controlled but when binder having higher viscosity was used then it becomes tough to control the operation. Hence, in second case use of heating jacket and cold inlet air was done to have effective temperature control. It was stated that the
thermoplastic pelletization technique was employed for the formulation of fastly release medicament which consist of the binders having less melting point. High shear mixer was utilized for the production of matrix pellets. The equipment was consists of double jacket for cooling and heating purpose. Impeller was also implanted inside the equipment with three blade facility for effective mixing. So many trials were taken on the machine before optimizing the formulation components. The excipients were blended in a plastic bag by the hands for the formulation of pellets. The material was added to the high shear mixer which was previously heated to the $45^\circ\text{C}$. Friction generated during particle mixing and jacketed wall of the equipment provides the necessary heat for melting the binder. After completion of process of pelletization the freshly prepared pellets were kept at room temperature and pass from sieve of 2.4mm size. Pellets size distribution study was performed by putting the pellets on the vibrating sieves. Optical microscope was employed for the examination of surface and shape of the pellets. The drawback of high shear mixer is that it will not supply the heat uniformly to the complete vessel. Setting of correct temperature before the experiment is essential point to be considered because it has direct influence on the production and pellet size distribution. The two important parts of manufacturing process was apparently observed. The granulation was the first part of the process in which the torque rise rapidly and then attained the highest value. Pelletization was the second part of the process. It was seen that initially the torque came down and then rises gradually. If blending time increased up to the six minutes then the yield was more but higher increase in blending time influences the yield. Shorting of mixing time affect the process due to insufficient time remain for the binder to get melt. To obtain the appropriate size of particles sufficient time must be given for the mixing so that temperature of the product increased a very little over the binder melting temperature.

9. **Zs. Musko, et al, 2001**, evaluated the impact of coating materials on in vivo and in vitro release of medicament through the pellets. The coating polymer utilized for the coating of pellets was Eudragit L. For the formulation of pellets the cores were added in to the centrifugal granulator. The instrument was rotated with the speed of 200 revolutions in a minute. The coating of pellets was done by the strea one fluid bed equipment. During in vitro study the non coated pellets were disintegrated in five minutes. After the five minutes the curve of dissolution came down. It was observed that the rate of dissolution was slow and
quantity of medicament released was gradually felled off. For the in vivo study healthy white rabbits of New Zealand weighing between 2.5 to 3 kg were selected. To them oral administration of 200 mg theophylline pellets in a capsule were given. The rabbits were kept away from food for twelve hours before the start of the study. Direct administration of capsule was done in to the esophagus of the animal and samples of blood were taken through the vein present in ear after the pre decided time intervals. TDX centrifuge was utilized for the further processing on the samples. The collected plasma was kept at -20°C for performing additional tests on it. In second and fourth hours of study no major differences were noted. Plasma concentration of theophylline was declined in third hour of study and significant declined in concentration of plasma was to be observed in fourth and twelfth hours of study. Pellets having coating of Eudragit L showed the highest quantity of medicament in a blood after the six hours of study. Finally it can be summarized that the authors prepared Eudragit L coated and uncoated pellets with differences in film coating. Rabbits were used to study in vivo release of medicament. TDX analyzer was used to measure serum concentration of medicament.

10. Christopher R. Young, et al, 2002, stated that the hot melt extrusion technique was employed in pharmaceutical companies for the manufacturing of sustained release tablet or granules. In this method the utilization of solvents and water is avoided and it consists of few manufacturing stages to formulate the product. The formulation steps are easy, effective and nonstop. In present research work circular shape pellets were formulated by employing HME technique and medicament releasing features of the pellets in a controlled way was observed. For the manufacturing of pellets the theophylline and other active excipients were properly mixed and then melt extruded. With the help of traditional spheronizer the extrudates were spheronized at the increased temperature. The role of MCC in to the powder mixture was to overcome the sticking. PEG 8000 help the in the process and acts as a plasticizer. It was revealed through the SEM study that the beads have variations in their morphological characters and it happened due to timing of spheronization. Those beads which remain 45 minutes in spheronization process showed similarity in their morphology. Medicament was released from the beads by diffusion controlled method. Different formulation excipients and extrudates were evaluated by thermal analysis to check whether they are appropriate for the HME technique. It was observed that porosity play a significant role in liberation of
medicament form the sustained release melts extruded pellets. At the pH 6.8 release of theophylline was enhanced as at this pH dissolution of polymers begins. Lastly it was summarized that the authors were manufactured the controlled release pellets which are matrix using spheronization and HME techniques. Matrix pellets prepared from melt extruded showed drug removal as diffusion controlled.

11. Hanan F. Kakish, et al, 2002, formed the diclofenac sodium and diltiazem HCl modified release preparations. Drugs were added to ethylene vinyl acetate polymer and formation of non uniform level of drugs distribution in matrix polymer was obtained by using phase separation method. Diltiazem HCl was loaded up to 81% and diclofenac up to 76% in matrix polymer in successful manner. Microspheres were detected in 1.6-2 mm diameter. For the manufacturing of drug loaded polymer microspheres ethylene vinyl acetate was incorporated in to the methylene chloride. After it medicaments were suspended in to the prepared solution so as to form the homogenous suspension. This suspension was then transferred through the pump in drop by drop to the absolute ethanol solvent having temperature at -70°C leading to the formation of circular shaped droplets. Kept it aside for one night at room temperature and microspheres were collected and dried up to five hours. For calculating the amount of medicament loaded on the microspheres the spectrophotometers was utilized. The formulated microspheres were flow easily and do not stick with each other. The SEM study was conducted to examine the untreated and treated diltiazem and diclofenac sodium beads. This study was conducted on to the beads before and after the in vitro dissolution study. The images of SEM study revealed that the surfaces of untreated and treated beads are relatively same before the dissolution study and large quantity of asymmetrical deep pores were found on the surface on untreated beads after the dissolution. The treated beads showed the tiny and identical pores on the surface. Hence it was proved that freeze drying and extraction techniques have impact on surface morphology of the beads and also influenced the distribution of medicament inside the beads. At the beginning of the study release behavior of medicament through the untreated beads was higher and then came down slowly by the passage of time.

12. Fatemeh Sadeghi, et al, 2003, investigated that the removal of diclofenac sodium and metoclopramide hydrochloride through ethylcellulose film of varying concentration and found that there exist a variation in drug release rates in prepared diclofenac sodium and
metoclopramide pellets. Accela cota pan was used to coat the metoclopramide drug on the nonpareil seeds. Pore mesh was fixed to the inside portion of pan to protect the pellets to go outside the pan. For the preparation of coating solution calculated quantity of HPMC was added to the previously warm water and cold water was included in it. This solution was then set to stand for 2 hours. In another beaker metoclopramide hydrochloride was added to water and in it HPMC E15 was inserted and finally solution of talc in water is adjointed to it. For the preparation of suspension of diclofenac sodium the medicament was added to water and passed through 105 micrometer sieve. Add liquid of HPMC E15 to it. Finally solution of talc in water was inserted to the formulating suspension. Additional coating of HPMC E5 was applied on to the prepared pellets to achieve extra 2% weight.

Accela cota machine was utilized for the coating of pellets with surelease. Pharmaceutical evaluations were done on to the manufactured batches of the pellets. Dissolution work was performed by using USP-I apparatus.

It was found that pellets shape and its surface area have impact on to the removal of medicaments. Because of layering the mean size of pellets was improved. Pellets size distribution must be control so as to reduce the differences among coating thickness. Quantity of bigger sizes particles are more in case of metoclopramide pellets but large pellets were found to be of uniform size after layering as present before layering. Surface property of pellets also has impact on removal characteristic of drug. When uniform coating was employed on the drug carrying pellets then pellets with smooth surface showed the less removal of drug as compare to pellets having rough surfaces. SEM also proved that surface features of both the drug loaded pellets are same. When a coating of surelease was applied in concentration of 4% and 8% then release behavior of drug in case of metoclopramide hydrochloride was faster than diclofenac sodium pellets. Metoclopramide hydrochloride may be slowly removed from the pellets because there may be chances of reaction among coating film and drug. Because of formation of precipitate among the ammonium oleate and metoclopramide hydrochloride having low solubility, etoclopramide hydrochloride was slowly released from uncoated pellets. It depends up on manufacturing condition applied during coating the drug coated pellets by surelease polymer.

13. Sebastian Bialleck, Hubert Rein, 2011, found that polymer and their size has profound effect on drug release profile. Pellets carrying effervescent sodium bicarbonate can be used to
have pH relying drug removal pattern. Erosion was the mechanism behind drug removal from corn starch waxy pellets and it was not depends on chemical nature of medicament.

14. Fu Jijun, et al, 2011, formulated the diclofenac potassium sustained matrix pellets with low quantity of carbomer 974P and found that it showed same effects in vivo as marketed voltaren formulation. It was also observed that formulation showing same action in vitro might vary in vivo due to variations in rate of drug release in vivo. The final coating on the outside of pellets was applied by using the fluidized bed coater containing Eudragit grade of sustained release polymers. It was evident while dissolution study that after coming in touch with the dissolution fluid the pellets having immediate release profile were fastly disintegrated. It was revealed that structure of matrix was quickly breaks because diclofenac potassium was solublized within the water and matrix has less inhibiting property. If the quantity of release modifying substances were enhanced then it affects the circular shape of the pellets. It was also known that performance of matrix pellets was quite superior as compare coated pellets and hence proved that matrix formulations are the better options to administer the diclofenac potassium in sustained release form to achieve maximum bioavailability regardless of formulation expenses and process. Partial absorption of medicament was taken place from the matrix preparation because of less transit time in small intestine and stoppage of release of medicament inside the colon part due to low solubility.

15. Adrian Bodea, Sorin E. Leucuta, 1997, formulated the sustained release propranolol HCl pellets by utilizing the coating pan and applied coat of Eudragit RS on it having determined rate of release. As propranolol poses less half life it will be a choice of drug to be sustained for the management of angina and elevated blood pressure. Factorial designing is an optimization method in development of sustained release preparations having good features related with the removal of medicament. In present study identification of formulation related variables will be done which have influence on drug removal features. There was optimization of removal of drug in relation to manufacturing variables by utilizing response surface graph and useful equations. The recorded drug release readings were added in to the computer application MSFIT. For the preparation of pellets the sucrose which was earlier passed through sieve was added to the pan and dispersion of Eudragit NE30D was applied on it. Powder blend consisting of propranolol, polyvinylpyrrolidone and lactose will be dusted on it. The prepared pellets were coated finally by Eudragit using classical coating pan.
Dissolution study was conducted by using basket type USP XXIII equipment. It was also evident from the study that when more coating will be applied to the pellets it takes more time to get dissolve and vice versa. For enhancing the mechanical features of coating layer plasticizers are incorporated to the formula. If PEG 6000 is added in coating composition then speedy removal of drug was observed which leads to generation of extra pores within the film. The dissolution data supports the selection of proper polymer: plasticizer proportion and quantity of coating solvent dispersion might be vital for the action of sustained release pellets. Finally it was concluded that selection of suitable polymer and plasticizer ratio and quantity of coating solvent to be applied on to the surface of the pellets are vital issues to be addressed in formulation of sustained release dosage form.

16. K. Amighi, *et al*, 1998, said that usage of pellets must be urged in sustained release form carrying slowly dissolving or poor soluble medicaments because of their pharmaceutical benefits and good releasing property as compare to other dosage forms. The authors also proved that dissolution property and solubility of the medicament in dissolution study was largely depends on the pH of the fluid. In recent research work sustained release formulations has been done which liberate the entire active in nonstop manner during passing from GIT. The technique employed for the manufacturing of sustained released pellets was extrusion and spheronization. Coating of sustained release film was achieved by using the Eudragit L30D55 and NE 30D materials in varying concentration.

17. Vinayak D Kadam, Surendra G Gattani, 2009, prepared that pellets containing the theophylline pellets as a drug of choice. The solution containing the binder and medicament was coated on the beads with the help of fluidized bed coater. The suspension was sprayed from the bottom side of the instrument. The solution containing the combination of Eudragit and TEC as a plasticizer was coated by using the same equipment discussed before. As per the SEM finding all the pellets have even and smooth morphology. DSC study showed no interaction among the material and medicament. Those pellets which were uncured depicted quick liberation of medicament from them. Enhancing in time of curing and temperature was reduced the release of medicament. It was also observed that pellets coated with Eudragit RL100 and Eudragit S100 showed curing phenomena. Pellets showed drug stability with another used ingredients. Desired lag phase will be obtained by acting with curing time and
medicament was released with an estimated release rate. Thus, it is desirable to fix the curing time to have well and consistent outputs.

18. Mohammad Reza Avadi, et al, 2004, demonstrated that supply of medicine to the colon either in localized or systemic form is a matter of research from several decades. In present research work chitosan beads of theophylline drug was formulated and given in capsule dosage form so that medicament was supply to the colon. Some formulation related parameters were also to be identified. At the beginning of the study chitosan was characterized and then evaluation of molecular weight was done. For the manufacturing of chitosan beads the chitosan was incorporated in to the 1% solution of acetic acid and at the room temperature stirring was continue up to the twenty minutes. The medicament theophylline was then incorporated in it to form the mixture. With the help of syringe the prepared mixture containing chitosan and theophylline was added in drop wise to the solution of aqueous tripolyphosphate. The freshly formulated beads were kept in solution of tripolyphosphate for additional 15 min. Filter paper was utilized for the separation of beads from the solution and then double washed with water. The beads were then charged to the freeze dryer for drying purpose. Capsule of size 1 was used for filling about 500mg beads per capsule. It was then coated with the solution containing TEC and Eudragit RS 100 by using pan. Eight batches were prepared. Particle size examination was done by selecting 100 beads and their diameter was calculated with the help of micrometer for each formulation. Drug loading was calculated by crushing the beads and then adding it in the solution of hydrochloric acid of 1.2 pH. Spectrophotometer was employed to know the drug loading at 272nm. USP basket apparatus was utilized for calculating the liberation of medicament through the beads packed in capsules having coat of enteric coated material. All the beads were found to be circular in shape after freeze drying. In scanning electron microscopy it was revealed that all the beads possess the smooth surface. Shrinking of beads was not occurred due to freeze drying technique. It was proved that formulation of beads and their shape were control by the chitosan viscosity. Batch F8 depicted highest loading of drug i.e. 40.15%. It was also observed that those beads which were dried by air depicted less drug entrapment as compare to freeze dried beads. Shrinking of beads was occurred in case of air dried beads. It was showed that reduction in temperature and saturation of outer phase by tripolyphosphate
and theophylline could have profound effect on system characteristics. Finding suggested that all variable should be addressed while preparing such kind of system.

19. Fatemeh Atyabi, et al, 2004, formulated the microcapsules having dual layers for the inhibition of quick gelatin dissolution. For the conveying of medicament to the colon gelatin is proved to be a good natural material. To the core of gelatin an external layer of ethyl cellulose coat was employed. After drying all the microspheres were viewed by microscope as circular and evenly distributed. At reduced pH range the micro particles were safe. When stored in neutral or acidic fluids no alteration in morphological features was detected. All the batches showed the good entrapment of medicament and similar results were also found after their coating. Microspheres intake more quantity of water inside them therefore liberation of medicament was rapid and whole medicament was released in six hours. When water penetrates inside the microspheres swelling of gelatin was takes place leading to dissolution of medicament. The dissolved medicament was then diffused through hydrogels of gelatin. Hence for controlling the rate of medicament release absorption of water must be controlled. Swelling of gelatin microspheres occurred quickly leading to the generation of blockage of gel. It was concluded that by combining polysaccharides and hydrophobic polymer advance drug delivery could be formulated which deliver the medicament to the colon.

20. Margret Chandira, et al, 2009, stated that in gastro retentive drug delivery system the dosage form is keep on hold for higher time period and hence ultimately enhancement in bioavailability of drug was obtained. Diltiazem hydrochloride is largely prescribed in angina pectoris and high B.P. In the beginning of the study the authors were plotted the calibration curve for the drug. The drug absorbance was measured at 236.80 wave length by utilizing UV spectrophotometer having double beam. The role of lactose was as a diluent and sodium carbonate gives brightness to the tablets. 30% medicament was added in all batches and tablet weight was kept in a range so that every tablet must carry 90% drug. By using punches of 9mm diameter the powder was directly compressed and weight was set at 300mg for each tablet. Before compressing the tablet the evaluations were done on blend comprising of tapped and bulk density determination. Flow characteristic of powder and compressibility index was also checked. After the manufacturing of tablet the regular test performed on them to check tablet thickness, harness, swelling, content uniformity and friability. In vitro evaluation was also done on tablets. The repose angle for the powder before going to
compression was detected in level of 21°-25°. Compressibility value was examined in 9.38-
15.94 range. When observed microscopically tablet showed smooth and circular in shape.
Tablets were passes the friability and hardness tests. All the prepared tablets posses the
uniform weights with minor deviation limit. In swelling study it was examined that the
polymer absorbed the water and swell leading to development of gel at the boundaries of the
tablets. Batch F6 was made by using ethyl cellulose and two HPMC grades of polymers
showed greatest swelling value. In present research work floating tablet of diltiazem have
been made which stay within the stomach and remove the entire medicament in acidic
medium. Further, IR study showed that there was no incompatibility among the used
polymers and active medicament. The tablets also cleared the stability study and externally
tablet looks better. Finally batch F6 was declared as optimized one among all the prepared
batches.

21. Rajani Shettigar, A.V. Damale, 1994, found that sodium CMC get swell with filler after
coming in contact with dissolution media and formation of gel takes place around every
pellet which assists in slow removal of medicament till end of dissolution process without
pellets breaking.

22. Bijaya Ghosh, et al, 1999, concluded that if less quantity of ethyl cellulose was used in
formulation then drug was removed by diffusion controlled mechanism and transfer to zero
order release with addition of ethyl cellulose. Orally administered sustained preparation of
diltiazem hydrochloride was successfully prepared by using ethyl cellulose and stearic acid in
proportion. For the formulation of nonpareil seeds the very warm syrup was sprayed on the
sucrose particles which are present inside the revolving pan. Those seeds having size in
between 450 to 500 micron meter were selected for medicament loading purpose. Initially the
medicament was incorporated in the hot stearic acid and kept for cooling. To obtain the
freely moving particles the mixture was then pass from the sieve no. 44. Beads of sucrose
were added in to the pan revolving with speed of 32 rotations in a minute. To it solution of
PVP was incorporated. Particle of medicament having stearic acid coating were then added.
The procedure was continued till the loading of medicament has been done. Lastly, solution
of ethyl cellulose in combination with diethyl phthalate was coated on the pellets. For
obtaining the better quality of coated pellets the coating procedure was performed for twenty
seconds and then pellets were permitted to dry for two minutes. Spectrophotometer was
utilized for calculating the content of medicament present in the pellets. As the pellets are spherical they possess the appreciable flow characteristics and can be easily packed inside the hard shell of capsules. It was observed that enhancing the coating thickness will enhance the release behavior of medicament from the system. Complete release of medicament was not achieved in all the formulations and this phenomenon was enhanced by improving the quantity of ethyl cellulose.

It was summarized that ethyl cellulose and stearic acid can be used in proper combination to obtain the sustained release system containing the diltiazem HCl.

23. **Yue Cui, et al, 2008,** formulated the sustained release pellets containing ofloxacin as a drug of choice. The prepared pellets showed enhanced rate of release of medicament along with better absorption of medicament. For the manufacturing of pellets centrifugal granulator of laboratory grade was employed. Microcrystalline cellulose was utilized for the preparation of nonpareil seeds. The nonpareil seeds were added in the centrifugal granulator and blend of excipients and medicament previously passed through 120 mesh screen was incorporated to it. Layering of drug and excipients were taken place with concurrent water spraying on the surface of pellets. When feeder gets empty and complete powder was added put the plate revolved for additional four minutes so that pellets gets polished. It was found that ofloxacin solubility was pH dependent. In alkaline media it is less and in acidic fluid it is more. Therefore it is must to have restrained over its release in acidic fluid. For this purpose Eudragit L30D55 was employed. It was seen that when dissolution study was conducted for the uncoated pellets then complete removal of medicament was occurred in lower than 60 minutes and ofloxacin was removed through the uncoated pellets in just only 20 minutes. Hence there was high demand to coat the ofloxacin pellets.

During dissolution study loss of physical intactness was seen in dissolution fluid having pH 7.4. It was happened because of Eudragit L30D55 gets dissolved in the liquid and inability of Eudragit NE30D to hold the pellets firmly. It may be concluded that the medicament was gradually removed in to the stomach through the pellets and when pellets arrived at intestine the remaining medicament was also gets released in less time. Hence a better option for the absorption of complete dose of medicament within the blood with improved bioavailability. If preparation contains the sodium then it will not react with the drug ofloxacin. It was also noted that if sodium chloride was incorporated in the preparation of pellet having coating of
Eudragit RS then the drug was gradually released and it may be due to reaction among coating film and chloride. Osmotic pressure was not responsible behind the release of drug through sustained release system. Ofloxacin tablet having gastro retentive features formulated by the Indian pharmaceutical industry exhibited same release profile to that of sustained release ofloxacin pellets in acidic media during in vitro study. Finally authors were proved that due to coating of ofloxacin pellets by Eudragit L30D55 and Eudragit NE30D coating agents having DEP as plasticizer pellets showed sustained effect in dissolution fluid in 8:1 proportion.

24. Pandey Shivanand, Rathanand Mahalaxmi, 2009, formulated the pellets by using conventional coating pan in which mixture of polymer and medicament was deposited on to the surface of nonpareil seeds with the help of binding fluid. Preformulation work was carried out in accordance with the B.P. 99.7% pure medicament was found in assay performed by the titration technique. After the FTIR examination study it was revealed that polymer and medicament were compatible with each other. Friability study showed that all the formulated pellets possess the adequate mechanical strength and passes the test. The pellets were chosen for stability work as per ICH instructions for 2 months. After 2 months all variables were in limit. Batch F7 recorded slight increase in vitro removal of drug in comparison study with the marketed formulation.

25. Pankaj Chhipa, et al, 2009, said that it was the polymer type and coating parameters like coating degree which governed the drug removal from pellets. Structure of film was influenced by coating polymer type and hence affecting release mechanism of drug. Fluidized bed coater was used for the application of binder and drug solution on the surface of beads. After the layering of the medicaments on the beads the pellets were dried at the suitable temperature limit.

26. Md. Akhlaquer Rahman, et al, 2010, found that if 1% of citric acid was added within the core of pellet it causes the remarkable release of drug in simulated gastric media. Micro environmental pH of pellet was suppressed by citric acid and in initial 2 hours of dissolution process it was observed that there was reduction in quantity of drug discharge in 0.1N HCl. Trial batches have been prepared to form the circular pellets having less friability with smooth surface. During study it was found that MCC was significant excipients in process of spheronization. When air get in touch with sodium para amino salicylate then it converts to
brownish colour and hence need to incorporate antioxidant like sodium metabisulphite. Formation of spherical pellets depends also on the binder concentration and time of spheronization. Coating of cellulose acetate phthalate on the pellets will protect the medicament to get degrade in to the GIT fluid and also inhibit the irritation property of medicament. It was concluded that for the enhancement of surface features corn starch was added.

27. Mothilal M, et al, 2010, formulated the pellets having sustained release profile by using ethyl cellulose material of 50 and 7 cps. The fluid bed coater was utilized for the coating of binder and medicament solution on to the surface of nonpareil seeds. After the process of drying the same equipment was employed for the coating of sustained release material on to the medicament loaded pellets. During FTIR examination no material and medicament interaction was seen. All the pellets exhibited a good flow characteristic when examined by repose angle method. SEM study showed that homogenous and even film was applied on the pellets. Finally it was concluded that Wurster technique could be used to formulate ambroxol HCl pellets by the using polymers EC 50 cps and EC 7cps. Kinetic study showed that it complies like non fickian first order release. Removal of drug might because of erosion as it follows Hixoncrowl rule.

28. Thies R, Kleinebudde, 2000, formulated the pellets by using small quantity of binder in range of 1.1%-14.1%. By reducing impeller speed and improvement in rate of granule growth can be adjusted with enhancement in binder quantity. Identical pellets with spherical in shape were formed after determined time.

29. Dushendra J. Chetty, Cassim M.Dangor, 1994, found that coat of polymer thickness play inversely proportional role in releasing medicament from formulated pellets. If membrane was thick then more time was required for dissolution fluid to penetrate and hence causing delay in drug removal.

30. Biswanath S.A. et al, 1990, presented that size distribution of prepared micro pellets were affected by speed of stirring and polymer drug combination. Polymer drug combination and mini pellets size governed the theophylline release.

31. Sreekhar Cheboyina, et al, 2004, presented that hydrophobic solid can be used to formulate immediate release pellets and combined hydrophobic and hydrophilic materials can be used
to formulate the sustained released pellets. Drugs solubility in matrix control the physical state of drug in career media.

32. F. Zhou, et al, 1998, concluded that starch derivatives and microcrystalline waxes can be used in formulation of pellets and bioavailability from it can be altered by changing quantity and type of both the polymers. The bioavailability of two preparations were checked which are sustained release in nature. Two preparation 15% waxy maltodextrin and 60% ibuprofen were prepared but the binder quantity was diverging in both preparations. In same study in vivo study has been performed on pellets which are immediate release in nature containing Lunacera P 30%, corn starch which is dried in drum 40% and lastly ibuprofen 30%. High shear mixer of jacketed type of laboratory grade was used for the formulation of the pellets. Batches F2 and F1 are sustained release in nature as proved by the in vitro study but F2 preparation remove the active at a faster speed than F1. It happened so because of Lunacera M which was added in F1 batch pellets have melting point in between 68-72°C. As depicted by the figure given in to the research paper batch F3 of pellets was not said as sustained release matrix pellets because in just only 45 minutes of dissolution study about 90% of active medicament was gets released. On the basis of in vivo data it was said that bioavailability of pellets preparation could be changed by altering the quantity and type of starch derivatives and microcrystalline waxes. Starch and wax may be used in designing of delivery system with immediate or sustained release profiles. The research also comprised of HPC and chromatography checking. In vivo study of ibuprofen was well accepted by the volunteers. While one person has objected of having weak pain in abdominal region after administering F1 batch dose in the beginning of study but in further study there was no such complained from any subject participated in study. All the selected volunteers were male non smokers and 18-40 years old. Written approval was taken from all the subjects before performing study on them. Initially physical checkup was done on all the subjects followed by electrocardiogram and urine and blood examinations.

33. Zhou, et al. 1996, demonstrated that melt pelletization can be utilized for the matrix pellets manufacturing containing mixture of starch derivatives and microcrystalline waxes. High shear mixer was utilized for the mixing of starch and medicament and melted was added to it. The wet mass was constantly mixed up till the formation of pellets. The speed of chopper and impeller may be altered during the process of mixing so as to form the pellets having fine
particle size distribution. Matrix pellets were easy to prepare and less time required for the manufacturing as compare the coated pellets. The preparations having ibuprofen and dried corn starch were not behaved like the matrix pellets and in just 60 minutes of study eighty percent of medicament was removed. It was observed that by using starch and wax suitable matrix pellets were formed which could released the medicament up to the set time period. This system could be prepared by using wax having appropriate quantity and quality in combination with starch. Rate of release of medicament was reduced by enhancing the concentration of wax. The preparation in which waxy maltodextrin was added showed the release of 95% ibuprofen medicament in forty eight hours of dissolution study and it was the slowest release among all the formulated batches. Removal of medicament was taken place through pores and diffusion of matrix.

34. Junting Jia, et al, 2011, compared the pharmacodynamic, pharmacokinetic and in vitro release parameter of sustained release preparation with immediate release pellets containing atenolol as a model drug. For this study young rat weighing about 200g each of male sex have been selected and were kept on standard situation of 12 hours of day/night sequence and allowed free movements to food up to one week. Extrusion spheronization technique was used for the formulation of immediate release pellets containing atenolol sustained release pellets and same compound was formulated by utilizing small glatt fluidizing bed apparatus consisting surelease and HPMC Es. The above both formulations are finally loaded in a hard gelatin capsules of size 5. Dissolution study was performed by using university made Chp method I. The withdrawn sample was checked at the 274nm. At the beginning the 10 rats were chosen and equally distributed in two sets and 16mg per kg dose of drug was given to the rats orally later anesthesia (ether) was given to them. Sample of blood was collected by using special capillary. The samples were centrifuged for 2minutes and at 1000 rotation per minute. Finally put at -20°C up to next examinations were performed on it. The removal of drug from sustained release pellets was gradually slow and only 90percent active was removed in 24hrs of study but in case of immediate release pellets of same drug about 90percent of active get removed in just 5 hours of study. It was also found that tolerance was caused due to sustained atenolol pellets and it may happened because of more amount of catecholamines which gives week input and hence less stimulation of compensatory responses.
35. **P.K. Bhoyar, D.M. Biyani, 2010,** found that 92% of drug get removed in 7 hour from prepared indione 244 resinate tablets when HPMC (K100M) was used in 8-10% level. If 12% polymer used then drug removal was not affected. As indione 244 resinate has greater particle size hence its tablet was dissolved speedy in dissolution fluid. If the quantity of resin was enhanced then more quantity of medicament get adsorbed on the resin present in solution but same way reduction in content of medicament was to be noted. At the temperature $60^0C$ the highest quantity of medicament was to be loaded on to the resin. The batch B6 sustained the medicament up to the ten hours and was declared as optimized.

36. **M.R. Bhalekar, et al, 2007,** formulated resinates of drug verapamil by utilizing indione resins. For the formation of resinates solution of medicament in a water was incorporated to the resin and stirring was done with the help of magnetic stirrer. As drug was not properly sustained because of resinates thus resinates were added in pellets by use of technique extrusion spheronization to get planned release profile. It was found that maximum drug loading was observed at pH 3.5 having resin drug 1:1 concentration. At various pH ranges the loading of medicament was different and at pH 3.5 it was found to be highest. It was also noticed that if temperature was enhanced then it resulted in enhancement in loading of medicament to a limit. At temperature $45^0C$ the highest medicament was loaded. If during the process more quantity of ionized molecule of medicament was present then it resulted in higher loading of medicament.

37. **P.M. Dandagi, et al, 2005,** prepared the mixed salbutamol and theophylline sustained matrix tablets by wet granulation technique. SEM study revealed that batch FH3 showed better swelling property. Drug released was observed by erosion and diffusion. The prepared granules showed good flow characteristics. The FH3 formulation was selected as an ideal one due to in vitro dissolution findings. It released the medicaments up to the twelve hours in dissolution study. The SEM study revealed that surface of tablet have porous and smooth surface. During dissolution study the tablet showed formation of gel in three hours and total swelling was occurred in 8 hours of study. After stability study on the selected batch during pharmaceutical evaluation no considerable remark was noted in to the tablets. FTIR results were also as per the expectations.

38. **Kenta Yamanaka, et al, 1997,** in this research the pharmacodynamic and pharmacokinetic parameters of sustained release imidapril pellets were examined against osmotic pump
present in rat having hypertension. The pellets were formulated by using melt pressing method. Imidapril pellet was inserted below the skin and back side of rat having hypertension by using sodium pentobarbital anesthesia. Imidapril osmotic pump having medicament in solution form was also inserted to in similar manner as that of previous one. The pump was removed after 1 month by applying anesthesia. Radioimmunoassay technique was utilized to examine plasma concentration of the drug. For checking in vitro removal of active compound the tube with cap was used having phosphate buffer agitated with 60 hits in a minutes for 1 month in bathshaker. Removed samples were examined by UV spectrophotometer. Removal of imidapril through pellet follow the zero order kinetic for 1 month and the drug was solely gets removed in 1 month in case of pellet. The release behavior of osmotic was also same to the pellet released. The drug plasma concentration was improved and reached to constant state in 4 week and vanished in 5 week of study. The osmotic pump was also behaved in same manner to that of pellet. It was also observed that drug plasma concentration was much less when it was subcutaneously given in osmotic or pellet form and hence imidapril changed to imidaprilate because of hydrolysis. As per the figure mentioned in research article in vivo removal of imidapril through the system follows the zero order kinetic up to 4 weekend and drugs gets solely removed in 4 weeks and the in vivo removal pattern of drug was almost same to in vitro removal pattern. Regarding osmotic pump this in vivo and in vitro drug removal pattern was also very similar. These finding hence proved that removal and absorption of imidapril through osmotic pump or pellet below the skin occurred in hypertensive rat in a very same way like in vitro drug removal pattern. Lastly it can be stated that pharmacodynamic and pharmacokinetic features of pellet were almost same to osmotic pump after subcutaneous implantation. If imidapril was given in pellets form then it would prove a very beneficial system which up hold the drug plasma concentration for a sustained period of time.

39. Xingna Zhao, etal, 2010, manufactured the nicotinic acid pellets by extrusion and spheronization technique and further applied double coating of ethylcellulose so as to obtain sustained release rate and magnesium oxide was crushed with simvastatin to form immediate release pellets. In present work eudragit NE30 D and ethylcellulose were applied as sustained release agents. The microcrystalline cellulose and nicotinic acid were blended and allowed to pass from 80#. In preset formula HPMC E5 play role as a binder. The damp mass then passes
from extruder. The formulated extrudates were then exposed to spheronizer. Hot air oven was used for drying purpose.

It has been observed that removal of drug from pellets which are coated by the polymers was controlled by the thickness of the coat and concentration of PVPk30 and ethylcellulose. When the ratio exceeds breaking of pellets was observed. If pellets were coated only by ethylcellulose then suitable release profile will not be achieved. By using 1.5% ethylcellulose suitable release of nicotinic acid was achieved and then further sub coating of Eudragit NE20D with 1% concentration was done. When pellets were kept at elevated temperature of $40^0$ C with relative humidity of 75% the removal of drug was poor. Simvastatin was not a stable molecule and it gets degrade hence it required to incorporate the stabilizing material like magnesium oxide. In present formulation there was a big difference for the dose among simvastatin and nicotinic acid. With the help of HPLC 99.13% simvastatin content was determined. Finally it can be concluded that it was an important procedure in formulation of pellets carrying multiple drugs by using fluidized bed coater particularly a huge dissimilarity among the doses of medicaments was present.

40. D. Voincovich, et al., 2000, prepared theophylline sustained release pellets by using lactose and stearic acid. The powder from which granules were formulated consists of 20% of both stearic acid and lactose and theophylline was added 60%. The formulated granules were checked for scanning electron microscopy, size distribution characteristics, XPS and porosity determination. In vivo and in vitro were the further tests done on the preparation. Mercury porosimetry was used for determining the porosity of pellets. To have the better results of porosity the pellets which are having pore size more than 50 micro meters was not selected within the study. For in vitro dissolution testing USP XIII apparatus (basket type) was utilized which revolve with 100 rotations per minute having temperature of 37±0.1 degree Celsius. For in vivo testing four healthy subjects equally from both sex having 27-40 years old were chosen. It was necessary that subjects do not have any renal or hart related problems. The dissolution study said that drug removal was depends on the pellets size. The fastest removal of theophylline drug to the dissolution liquid was done by evaluating the theophylline on the outer surface of pellets and XPS study will help to prove it. The gastrointestinal fluid has varying pH range and it will not merely affect the removal of drug through the pellets. The system follows the zero order release kinetics. For the determination
of in vivo finding a capsule of 300 mg theophylline was given to the volunteers which showed increased value of $t_{\max}$ and this results was also be proved true by the obtained value of $t_{1/2}$.

During study researchers were strongly feel that the quantity of subjects selected in the study were less and also there was vast difference among them. By keeping in mind these drawbacks the researchers will suggest that the quantity of volunteers chosen for the study must be increased so as to formulate sustained release OD dose of theophylline. In present piece of investigation melt pelletization method was utilized to prepare the pellets with the aid of high shear mixer. The discussed method produces the sustained release pellets of theophylline in a just one step. The anhydrous lactose was taken as filler and stearic acid gets melted and acts as a binder.

41. Helton Santos, et al, 2005, formulated the two verities of pellets consisting of ibuprofen and diclofenac by utilizing extrusion and spheroidization method. In this study xanthan gum was used in formulation of pellets and pellets were checked for compression, drug removal and compaction properties. Xanthan gum is heteropolysaccharide with high molecular weight gum having broad application as stabilizing ingredient in topical or orally administered preparations. With the help of single punch tablet machine the prepared pellets were compressed to form the tablets and further evaluations were made on the tablets. The formulated pellets were found to be smooth as revealed by SEM study. Xanthan gum pellets which are made by using diclofenac sodium are found to be higher spherical than those xanthan gum pellets which are made by ibuprofen pellets. After going through 3D and 2D images of the tablet it was seen that shapes of pellets were gets alter because of force of compression. The pellets lose their actual round shape and converted in similar direction of pressure employed on them. Ibuprofen pellets are found to be more breakable, less porous and cannot be deformed easily in comparison with diclofenac pellets. Tensile strength for xanthan gum pellets consisting of diclofenac was noted much more in comparison with ibuprofen pellets. Immediate release of drug was found for both the medicaments in dissolution study. In dissolution study the entire diclofenac drug was gets released in only 30 minutes from pellets and ibuprofen was gets released about 60% in 1hour. In between the test the pellets soaked the more amount of water and showed higher swelling and hence removed the complete medicament because of breaking of swelled pellets. Same kinds of results were
obtained for the tablets made by pellets. It was also found that diclofenac sodium was slowly releases from the tablets consisting of pellets and in 24 hour of dissolution study only 70% actives gets removed. Laser profilometry can be used to study the pellets compaction.

42. J. Hamdani, et al, 2006, formulated the pellets which float with the help of high shear mixer by utilizing melt pelletization technique. Two verities of pellets i.e. non-floating and floating were formulated. Only those pellets which were present in between 1250-2000 micro meters were selected for the floating in vitro study. For in vitro testing of pellets USP24 No. II dissolution equipment paddle type was used. For in vivo study nine volunteers of 23-45 years old were selected having male sex. Spectrofluorimetric technique was used to identify the amount of riboflavin present in urine sample. Resultant weight values given by the floating riboflavin pellets were positive because of their floating capacity due to addition of tartaric acid and sodium bi carbonate but non floating pellets of drug showed resultant weight values as negative. From the findings of counting test it was revealed that after eight hours of study 70%-80% of pellets were in floating state in case of floating riboflavin pellets but in case of non floating pellets no one pellets float after 30 minutes. Floating riboflavin pellets were go down after eight hours of study was mainly because of complete removal of carbon dioxide through the pellets and less generation floating forces by the preparation itself. For checking in vivo floating capacity of the pellets the amount of riboflavin present in urine was examined. It is necessary that floating pellets must acts similar to non floating pellets in case of in vitro dissolution study. As the floating pellets consist of tartaric acid and sodium bi carbonate this combination made the pellets more water loving than non floating pellets. The dissolution rate of floating pellets was observed to be higher than non floating pellets. Non-floating and floating pellets of riboflavin was given to the male healthy subjects orally under fasting and feed state. Urine examination was done to check the riboflavin pellets floating capacity. Riboflavin was less absorbed from the initial portion of small intestine and hence absorption of riboflavin was depends on its floating characteristics. Removal of riboflavin in to the urine was more in case of floating pellets as compare to non floating pellets in both fasting and fed situations. Hence it can be summarized that floating pellets of drug were float in vivo. One can extend the gastric retention of pellets by administering them after the food.

43. T. Raja Sekharan, et al, 2009, formulated the controlled release theophylline matrix tablets by utilizing the xanthan gum. Wet granulation technique was used in preparation of granules.
Xanthan gum and theophylline and lactose were mixed together and a damp mass was developed with the addition of already prepared solution of PVP K30 in isopropyl alcohol. The role of lactose and PVP K30 was as filler and binder respectively. Sieve no 16 was used to formulate the granules and then dried and after that again pass it from sieve no.16. Preformulation evaluations were done on the granules. Magnesium stearate works as antiadherent and glidant. Pharmaceutical evaluations were done on the prepared tablets. Formulated granules displayed good flow characteristics. For checking the tablet hardness Monsanto hardness apparatus was used and noted in between 4-7 kg/cm². All the tablets were cleared the friability test. Drug content for all batches were found in between 95-97%. As per the results of FTIR findings there was no difference found among the peaks of pure theophylline and theophylline preparation. Same result was found in case of xanthan gum. Dissolution study was conducted on the formulated matrix tablets for about 10 hours by using disso 2000 equipment which was of paddle type and batch F6 demonstrated 73% drug release. This drug removal by F6 formulation was proved to be prolonged release in nature in comparison with another prepared formulation. Hardness of tablet and quantity of polymer added in to the preparation governs the drug release pattern. Finally, from the present study it was confirmed that quantity of polymer and hardness of tablet could affect the release of medicament through the matrix system.

44. Margret Chandira, et al, 2009, pointed out that enormous attempt has been done to formulate the dosage form which will remain in to the GIT to give better absorption of medicaments. Famotidine is largely used medicine now days for the management of gastric and intestinal ulcer. In present research work famotidine floating tablets were prepared and evaluation has been done to check its suitability as ideal preparation. For the formulation of tablets the less density polymers were used which enhanced the gastric retention of tablet resulting in release of medicament for extended time period. Xanthan gums, HPMC grade of polymers were employed to function as sustained release agents. Different processing and preparation related parameters which have direct impact on the release behavior of drug were also been observed. Direct compression method has been employed for formulation of tablets having different concentration of xanthan gum, HPMC K100M and HPMC K4M. The dose of famotidine was set at 40mg per tablet. Melting point examination on pure drug has been carried out and it was observed in between 162⁰ to 164⁰C. As per the solubility data in the
water the drug gets dissolved and in ether and ethanol not dissolved. The surface of tablets was smooth with free from fractures. The prepared tablets possess the friability lower than 1 percent and sufficient hardness to overcomes the mechanical shocks experienced while transportation and handling of it. All the tablets were successful in content uniformity and weight variation examinations. Famotidine tablets consist of polymers which swell after coming in contact with liquid media and formation and removal of carbon dioxide was taken place. Because of removal of carbon dioxide the density of tablets was decrease. This phenomenon will help the tablets for keeping in floating form. For achieving better floating performance of the tablet within the stomach the tablet must have low density in comparison with content of GIT. After immersing the tablet at temperature 37°C in solution of hydrochloric acid of 0.1N the tablets were stay float and not disintegrated. Swelling study indicated that as the time elapse the polymer swell and take more amount of water inside it. Due to swelling and hydration of polymer there was development of gel at the boundaries of tablet. After some time this layer get dispersed and new surface starts to swell and process was continue which keep the dosage form intact.

45. Nahor Haddish Berhane, et al, 2006, found that if the pellets were not uniformly coated then thickness of coat governs the release of drug in vivo and hence this factor must be consider while designing the formulation. In this work a model was build up in which pellets were coated with ion exchange material which leads to non equality in thickness of applied coat. Resin and drug complex was developed and finally applied the coating of polymer kollicoat SR 30D. Dextromethorphan was the choice of drug for the present study. The coating was done in varying concentration. The researchers design a model which gives idea about the release of medicament from the system coated with ion exchange resin.

46. W. Gunder, et al, 1995, was used the HPMC as coating agent which form the pore across the membrane and releases the medicaments in controlled fashion as per the demand by the body. Dibutyl sebacate was employed as plasticizer. For the manufacturing of pellets coating fluidized bed instrument was used. Initially the formulated pellets were checked for thickness of coat and later on drug release was determined by DAB paddle instrument. The theophylline pellets were coated in different concentration ranging from 10% to 25%. In the starting the release of drug was speculated speedy because of presence of HPMC but only in 2 hours lower than 5% medicament was liberated. Later on the drug release pattern follows
the similar path. Therefore it can be summarized that removal of medicament occurs in two styles. In first style the existing pores were filled with water and diffusion of medicaments will occurred on the basis of its solubility either in unionized or ionized form. After passing of 2 hours time period the pores gets shut down and will not permit the further diffusion of drug. As per second style removal of drug occurred because of diffusion and distribution of drug which was present in undissociated state. Once again the diffusion of medicament through pores was totally stop. It was important to know the required quantity of HPMC at which release of medicaments occur for extended time period. The amount detected for HPMC was in from 25-30%. Enhanced removal of drug was observed in this limit of HPMC. It was also observed that at concentration of 30% HPMC the release of medicament was slow at the beginning. If 40% HPMC was used then the release of medicament was not takes place through membrane but it was gets disintegrated. In case of ethyl cellulose the two phase release style of medicament was achieved only at 10% HPMC concentration in pH range of 9 because of presence of carboxylic group in the coating polymer. If more concentration of HPMC was utilized the removal of medicament will takes place by single phase style. If we go on increasing the concentration of HPMC the coat does not have the controlling power over the release of medicament. At 40% concentration of HPMC cracks were observed inside the membrane. The cracks can be examined easily by macroscopically. In just 10 minutes of time around 50% medicament was released and uncoated pellets of theophylline will needed just 3 minutes for the complete dissolution. It was also studied in the present research paper that the pH of system determines the release of medicament. At pH 5.9 the removal of medicament from the pellets coated with 30% HPMC was slow but removal of medicament was speed up at pH 9. When sustained or controlled release dosage from pass through GIT it experiences the change of pH. In stomach there was acidic pH but in intestine the dosage form exposed to basic pH. After 1 hour of observation etofylline pellets which were previously coated with 30% HPMC in pH 4.4 it was again check at pH 9 for 7 hours. In 1 hour of study both the curves were same and no considerable improvement was marked at pH 9 as compare to pH 4.4.

47. Pernilla Nevsten, et al, 2005, used the XEDS and SEM techniques to explain the release behavior of drug and different non predictable deviations in the release of medicament from the pellets. It was observed that pellets having rough surface showed greater release of
medicament as compared to smooth surface pellets in two hours of study. Hence it was clearly confirmed that pellets shape have an effect on drug release property. Three different types of pellets were selected for the study. Pellet A was designated for spherical shape pellet. Pellet B and C are assigned for the dumbbell and twin shape pellets respectively. Pellets of type A showed two forms of release. In first type drug was released slowly and uniform film of polymer was observed having minor cracks on the surface. Other type of pellets showed speedy release of medicaments. The quantities of second type of pellets were of only 10%. Above described study was performed by SEM. The pellets having dumbbell shape (B) follows the same pattern of drug release as describe earlier for A form but with higher rate of speed at the intermediary point was observed. At the portion of neck there was thin film gets deposited during coating operation. Hence such kind of fast release was attained only because of this reason. Holes present at the neck portion allowed to see the ingredients present inside it. It was tough job to manufacture the pellets having C type shape i.e. twin form pellets because during manufacturing pellets breaks up in two different units. It was examined that strain produce at the time of manufacturing and release of medicament cause film rupture at the point where two different pellets were connected with one another. Breaking of coated film occur in many styles and one can easily observed the inside active ingredient from the point where rupturing of film has been taken place. Same way if rupturing of film occurred at the time of coating then formation of portion taken place having thinner non uniform film. Hence for the type C pellets the mechanism of drug release could not be explained simply. Ruptures were found in the coated film of polymer for those pellets which showed speedy release of drug and only minor cracks were seen on pellets surface exhibiting slower release of medicament. When ethyl cellulose was used for coating of pellets then release of medicament occurred from the cracks. Cracks might be developed because of fragile and very weak coated film. Hydrodynamic pressure leads to core swelling was also resulted in cracking of film. In present research work the release behavior of pellets coated with 10% polymer has showed defect in film and immediate removal of medicament taken place at high speed.

48. Sandra U Schilling, et al, 2010, were identified the different characteristics of pellets formulated by hot melt extrusion technique. Pellets prepared by melt extrusion technique were strong if compressed directly to multiparticulate monolithic forms because of their
excessive mechanical strength and also release behavior of drug was not depends on the film intactness. For extrusion purpose the powder mixture was made by the pre blending of plasticizers (acetyltributyl citrate, triethyl citrate) and polymer followed by mixing with the medicament. It was observed that polymers like Eudragit L100 and S100 which are not plasticized shown increased glass transition temperature of above 172°C and experiences the thermal degradation over 180°C. Mixtures which were formulated by polymethacrylates were require higher temperature for extrusion so as to effectively decrease the torque and yield melt viscosities which was lower adequately to permit the easy passage of strands of polymer from the die. Eudragit L100-55 could not form the extrudates because melted mass was very viscous to pass from the die of 500 micrometer size. All the prepared batches exhibited starting burst phenomenon in dissolution study followed by higher release of medicament after passing 15 minutes and then release the drug in sustained form in remaining period of time in acidic media. In acidic media the pellets having TEC plasticizer showed more burst phenomenon and higher rate of drug diffusion but pellets prepared with polymethacrylates removed greater than 20% medicament in two hours. So as to decrease the matrix permeability ATBC plasticizer was added instead of TEC. The removal of medicament in acidic media was decreased to 14.84% but yet not pass the USP criteria 10% or fewer than of it in two hours of study. Pellets prepared from the polymethacrylic showed higher sustained release behavior and released 61.15% drug coated with Eudragit L100 and 66.56% drug coated with Eudragit S100 coated pellets in 2 hours of study. Eudragit S100 also showed better processibility if added with more quantity of plasticizer and best thermal stability than blend of polymer. Rate of drug removal from the sustained release or melt extruded pellet could be linked with polymer to drug proportion and diffusion controlled and burst release were speed up by improving the quantity of medicament. For knowing the drug loading effect extrusion has been done of enteric pellets with the drug theophylline in concentration of 10%-40% by using Eudragit S100 as matrix film former and TEC (40%) as a plasticizer. When quantity of plasticizer was improved up to 40% it was observed that improvement in the permeability of matrix polymer in both the medium of dissolution study and also extrusion were taken place at less temperature i.e. at 140°C. During dissolution study improvement in pellets porosity has been observed as plasticizers which are soluble acts as pore formers while leaking through the matrix. When TEC or
ATBC plasticizers are used in preparation of pellets then rate of release of drug was less. It was due to minor leaching of plasticizer while dissolution study and diffusion of medicaments from pores were taken place. It was also found that non plasticized pellets formulated at elevated temperature and plasticized matrix pellets formulated at less temperature showed same drug release features. SEM revealed that the formulated pellets have smooth texture and no pores on the surface.

49. J.J. Sousa, et al, 1996, studied the various options where water was utilized as a main ingredient and in what quantity it must be added to obtained wet mass. In spheronization process the extrudates were cut off in smaller sections and by using force turned them to spherical shape pellets. Preliminary study was also done to check the suitable conditions for uniform and smooth coating.

The factorial method was used to know the impact of aqueous phase in pellets features. Three types of factors were selected for the study. In first factor the quantity of water needed for the purpose of mixing was set at three different levels. In second factor the time period among the formation of mass and extrusion and just before the process of extrusion and further the product were stored in seal container for 12 hours were checked. In the third and last factorial study consist of process of drying and the product was dried by using fluid bed dryer and oven. For the formulation of pellets the dry powder was taken and weighed accurately and then mixing was performed for 10 minutes by using planetary mixer. The quantity of water needed for every powder was incorporated in it and again mixed up to 10 minutes by using same planetary mixer. After the formation of wet mass as per the experimental plan few formulations were extruded instantly and few were stored up to 12 hours in properly sealed plastic container before there extrusion. All the formulations were passed through die having 1mm diameter and 4 mm length by using ram extruder. Spheronizer consisting of radial plate was utilized which rotate at the speed of 1000rotation per minutes. The spheronizing process was continued up to 10 minutes till the formation of spherical shape pellets. After this step selected formulations were dried by using tray oven up to 24 hours and fluid bed dryer up to 30 minutes at temperature of 35\(^0\)C. Ethyl cellulose latex coating was done on all the formulations. Surelease was also used to achieve weight gain about 10%. Every cycle required normally 15 minutes. For calculating the actual drug content the pellets were crushed and mixture was added to the water. Later on sieve analysis, porosity and density
were performed on pellets. With the help of tablet strength tester crushing strength of pellets were determined by selecting around 20 pellets from every formulation. Thermogravimetric analysis technique was used to examine the residual water inside the pellets after their drying. DSC, dissolution study and SEM are the further studies performed on the pellets. Those pellets which were dried by using the fluid bed dryer not that much tough as compare to those pellets dried by using oven tray. Finally it could be said that the water which was stay inside the pellets was remain in a free state might be escape due to evaporation. It was also stated that more the quantity of water utilized more was the specific area formed because of insoluble fillers which were added to the preparation starts to swell. Though the readings of porosity of various pellets were same the surface area examination revealed that there were foremost structural differences in the pellets.

The function of water in formulation of pellet by extrusion and spheronization method affects the physical parameters of prepared pellets and drug release behavior through the pharmaceutical dosage forms. In present work correlation among the particle size distribution and quantity of water was also explained. However structure, shape and surface area were linked with quantity and process of drying. Porosity and density were depends on the characteristics of raw materials. The strength was affected by lag time and quantity of water added among massing stage and extrusion process. Different release rates were obtained for all the formulations independent of thickness of coated film as it was a constant factor of the study. It was concluded that preparation and formulation condition are of utmost valuable for the preformulation work of sustained release preparations manufactured by extrusion and spheronization. Water must be believed to be as a key formulation component instead of an inert constituent of wet massing and extrusion process.

50. Jan Moschwitzer, Rainer H. Muller, et al, 2006, prepared the nanosuspension of mucoadhesive type using weakly soluble medicament formulated by higher pressure technique of homogenization with the help of fluid bed processor. In present piece of work the weakly soluble hydrocortisone acetate medicament in mucoadhesive nanosuspension form was applied as layering dispersion by using fluid bed processor.

The formulation of dispersion for layering was required manufacturing of two preparations A and B. For the manufacturing of preparation A chitosan and poloxamer 188 were added to the Millipore water. The particle size was examined by the photon correlation spectroscopy.
Layering of the dispersion of preparation A and B were done on the nonpareil seeds having the diameter in the range from 710 µm to 850 µm by utilizing fluidized bed coater having spray nozzle from bottom and Wurster column. After drug layering on the nonpareil seeds the next step was to determine the content of medicament. Consequently Eudragit L30D55 enteric polymer was applied from top on to the surface of layered pellets by utilizing similar equipment used before. The final coating was 10% and 20%. After application of the final enteric coat on to the pellets they were dried by using oven at 40°C for 24 hours so that complete enteric film was formed. X-ray diffraction technique was employed to examine crystalline nature of original drug, preparation A and B and then the medium of dispersion.

With the help of ESEM of grade XL 30 the surface characteristic of coated and non coated pellets was determined. This equipment was also utilized to measure the exact thickness of various coating layers applied on the pellets. In this research work the smallest size of particle was arrived after twenty cycles of homogenization. Laser diffractrometry was used to check the micronized suspension size. Lastly it can be said that the need for improved velocity of dissolution of weakly soluble medicament and enhanced saturation solubility could be obtained by homogenization with high pressure. About 20 cycles of homogenization were essential to obtain the suspension having particle size distribution in narrow limit and particles of nanometer size.

So as to achieve the controlled release of medicament in the region of colon and intestine Eudragit L30D55 polymer was utilized. Below the layer of coating a tiny layer of medicament having drug in nanocrystals form and also nonpareil seeds were present. Because of less loading of medicament about 1% the layer holding drug was very fine. This method has two big advantages as compare to matrix dosage forms. The process of layering was easy and fast and consists of utilization of similar machines essential for coating procedure. Second advantage was that no limitation for drug loading. By enhancing layering level enhancement in drug loading could be done. HPLC technique determined the actual drug content in to the sample. From the preparation A about 99% drug was fastly released and 88% drug was released from preparation B. To decrease the quantity of released medicament in acidic medium below 10% the enteric coating must be done up to 20%. Therefore the preparation accomplishes the conditions for delayed release system and 7.9% and 9.6% medicaments were released from preparation A and B respectively in acidic media.
In regard of preparation A if enteric coating level was improved then it will not have any impact on total quantity of drug release and approximately all 93% drug was released in 10 hours of study. The removal of medicament through preparation B was not complete and only 76% was released. When dissolution behavior of preparation A and B was compared then it was found that total drug was released with improved dissolution velocity.

51. Julia Krause, Markus Thommes, Jorg Breitkreutz, 2009, utilized the lipid as a binder which was harmless substitute aid in extrusion process for the production of pellets. In present research work immediate release pellets were prepared by adding lipid binder having cold property by means of solvent free extrusion spheronization method. In this technique the temperature was reduced to $10^0\text{C}$ less then lipid melting point. This method was beneficial for binders and those substances which destroyed by heat because high temperature affects their morphology and stability. Wet extrudate of 300 grams were taken and put in spheronizer at 1000 rotations per minute for 5 minutes. Fluid bed dryer was utilized for drying purpose at $60^0\text{C}$ for 10 minutes. 3 samples were separately collected from every batch prepared with wet extrusion process for calculating the water content in extrudate. Drying was done for 24 hours at $70^0\text{C}$ by using vacuum oven to the collected samples. Extrudates water was determined on the basis of dry mass. With the help of stereomicroscope image analysis was performed. Beginning studies carried out for dissolution purpose demonstrated that there was no considerable impact speed of basket on behavior of dissolution. The absorbance was determined at 273nm for examining the quantity of sodium benzoate drug within a dissolution fluid. Initial findings confirmed that the aids which were added in extrusion stage not have any effect for the absorption of medicament at 273nm. Content of sodium benzoate in carrageenan and MCC extrudates was evaluated by the HPLC technique. It was observed that the extrusion aids were not melted during the operation. The drug material was binds with the binder only after their softening or melting and melting of excipients were not taken place. The crucial step during preparation containing lipids was process of spheronization. For optimizing the factors affecting spheronization process which gives spherical shape pellets the preparation containing the witocan and sodium benzoate was to be spheronized at various temperature limits at various time periods with altered rate of rotations. Temperature greater than $15^0\text{C}$ and under the binder’s melting point and also temperature nearer to $8^0\text{C}$ was not sufficient for the formulation having appropriate shape. In
present situation temperature of spheronizer must be $10^0\text{C}$ beneath the witocan melting point showed the perfect results. As a feature of quality different parameters were assigned for the characterization of pellets shape. Aspect ratio was mostly utilized parameter. For the pellets value of average aspect ratio was equal or less than 1.2 was thought to be adequate. If aspect ratio was more than this value then consider as not sufficient. However it was confirmed that benzoic acid was better than sodium benzoate with regard to narrow shape and size distribution and also produces spherical pellets. Benzoic acid was found to be not suitable because it has more vapour pressure. After wet extrudates formation the required drying and partial vaporization of benzoic acid was occurred leading to generation of sponge shapes design. But pellets containing lipid as a binder not formed the circular shape pellets. Uniformity of content was also not attained in case of benzoic acid and hence was disqualified for the further studies.

Phosphate buffer and purified water were used as a media for the release of sodium benzoate medicament. In both the liquids of dissolution similar release pattern was obtained. The rapid release of medicament occurred because of more loading of drug about 80% and sodium benzoate was easily solublized within the water. All the preparations of lipid pellets must be stored at accelerated state for four weeks at $32^0\text{C}$.

52. Jittima Chatchawalsaisini, Fridrun Podczeck, J.Michael Newton, 2005, formulated the pellets with extrusion and spheronization methods using four drugs, and MCC, glyceryl monostearate as ingredients. By using planetary mixer the dry powder was mixed for five minutes. While mixing the adequate amount of liquid binder was gradually incorporated and allowed to mix for ten minutes. In every formulation four concentration of binder was employed. The exact higher and inferior range of binder was decided on the basis of trial and error basis. By using coffee grinder the material was grinded till it was passed from sieve of 250µm size. Extrusion has been done on formulated wet mass by ram extruder. Spheronization was the next step to be performed after it.

If glyceryl monostearate was not added to the preparation having indomethacin then during the extrusion process higher force of extrusion was observed. It was also marked that in extrusion process there might be chances of water migration which affect the various level of water in various extrudates portion. The final formulated extrudate posses the sufficient consistency and capacity of spheronization was restrain. For examining the irregularities on
the surface profilometer was employed. In extrusion process the mass was forced to pass from the small opening causing development of shear forces. Due to these forces glycercyl mono stearate may be get melted but in present method the process was completed in just 30 to 40 seconds and more amount of water was present inside preparation. It was not seen that the extrudates came out with higher temperature than wet mass present inside the extrudates. Pellets not containing the glycercyl monostearate were found to be having small in diameter as compared to pellets containing glycercyl monostearate. It was noted that incorporation of glycercyl monostearate to the formulation was not affect the mechanism of spheronization process. It was found that pellets porosity was reduced by enhancing the quantity of water in the formulation. If glycercyl monostearate was added 30% in diclofenac sodium formulation then it was seen that porosity was enhanced by enhancing the quantity of water. The important point of finding was that glycercyl monostearate not affects the process of dissolution.

53. **A. Kramar , S. Turk, F.Vrecer, 2003**, were formulated the pellets of diclofenac sodium having sustained release profile. In present piece of investigation impact of 3 parameters related with the preparation were examined on the release of medicament. On the surface of the nonpareil seeds solution of diclofenac and binder were applied with the help of fluidized bed coater. For the preparation of suspension of coating the polymers Eudragit RL, Eudragit RS were used. About 1500 gram of drug loaded pellets was shifted to fluidized bed coater who coats the previously prepared suspension from the bottom of the apparatus. Rate of medicament release in acidic liquid was less and not depend on the thickness and composition of coated film. It was seen that improvement in rate of release of medicament through the pellets was occurred by reducing quantity of plasticizer.

54. **Claudia S. Leopold, Yassin Farag 2011**, demonstrated that shellac is the better film forming agent obtained from animal source. For the formulation of coating solution the shellac was properly grinded and was added in to the solvent ammonium bicarbonate at fifty degree temperature. Shellac film was not properly dissolved due to more quantity of ammonium salt. Evaporation of CO$_2$ and ammonia was done from ammonium salt by heating at 65°C temperature. The process was continued till constant pH was attained at 7.5. Immediate release pellets of theophylline were subcoated using fluid bed coater. Another layer of shellac coating was applied using the similar equipment. Shellac is the acidic
substance and in acidic pH range was not get dissolved. When *in vitro* study was conducted in acidic fluid for 120 minutes only 4% medicament was observed to be released from all the formulated batches. In current research study the utilization of calcium was done to obtain the reverse effect i.e. sustained release effect. When calcium ion reacts with shellac development of insoluble salt was occurred. Hence calcium ions were administered in to the substance used for subcoating. When shellac film was swelled the dissolution liquid moves inside the pellet and subcoating of calcium chloride was gets dissolved. Reaction among shellac coating and released calcium ion was takes place resulting in the formation of calcium shellac precipitate. This precipitate causes the reduction in swelling of film and works as a barrier producing the sustained release effect. The FTIR finding proved the no interaction was detected among the used materials and drug.

55. F. Sadeghi, *et al*, 2008, prepared the ibuprofen tablet of sustained release profile which when orally taken dispersed in to the sustained release pellets without losing the pellet core intactness.

It was seen that if triethyl citrate was utilized as plasticizer then film elongation was enhanced and reduction in stress while breaking was noted. If 20% TEC was incorporated in the formulation then this quantity was thought to be the exact one as a plasticizer. It was observed in dissolution test that improving the level of coating up to 10% was considerably reduces the speed of medicament released and an additional improvement in the level of coating up to 15% has the negligible delaying effect. It was observed that if 5% level of coating was done on the surface of sustained release ibuprofen pellets then it released the medicament up the 24 hours. Because of applied compaction pressure there were alterations in structure of coated film and hence medicament release through the system was affected. The filler of choice employed in manufacturing of tablets from pellets should protect the pellets to come in contact with each other and play a role of cushion in compression. It was seen that if PEG was incorporated then formations of tablet taken place which was easily break and gradually disintegrated. It was not possible with only 100% pellets to form the tablets because during ejection stage disaggregation of pellets was occurred. Reduction in the rate of release of medicament was noted by improving the force of compaction. It was also observed that improvement in force of compression leads to enhancement in disintegration
time and hardness of the tablet but reduction in friability was also noted. If the quantity of the pellets in the tablets were enhanced up the 60% then reduction in disintegration time and hardness was observed with enhanced friability of the tablets.

56. Jiptkate, Amol, R, 2011, used the HPMC, MCC and ethylcellulose polymer for the development of sustained release citicoline tablets. Through this study authors tried to know the mechanism of release of medicament and also the role of HPMC in controlled or sustained release preparations. Wet granulation technique was employed for the preparation of tablets. During compatibility study it was detected that no interaction was occurred among the used polymers and medicament. When less quantity of polymers was utilized in formulation then release of medicament was directly affected and vice a versa. After performing the stability study the prepared batches passes the test. Due to MCC and HPMC polymers generation of thick gel was happened and for the medicament it serve as a diffusion rout and controlled release behavior of the medicament was observed. HPMC was identified as a polymer which controls the rate of release of medicament through the system.

57. Shailes K. Singh, et al, 1995, were examined the controlled release features of methylmethacrylate and ethylacrylate latex on the ibuprofen pellets. On the surface of nonpareil seeds drug was applied more than sixty percent loading of medicament. For the antiadherent purpose talc was incorporated in to the formula which overcomes the particle sticking during process of coating. With the help of fluidized bed coated the medicament suspension was applied on the nonpareil seeds. The main intension behind the seal coat was to coat the layers on the surface of pellets before giving the final coat of controlled release to protect medicament layer from abrasion and to reduce the medicament leaking to the latex. Finally it was said that latex gave the sufficient release of ibuprofen anionic medicament.

58. K. Amighi, et al, 2008, were formulated sustained release granules of levodopa by utilizing melt granulation technique and then minitablets were developed after direct compressing the granules. Tablet machine having single punch was employed for the development of minitablets. The granules were added by the hands in to the die cavity of machine. Fluidized bed coater having spray at the lower side of machine was used. For the formulation of sustained release floating minitablets the optimization was done for the rate of release of medicament and floating feature from the dosage form. In recent research work the produced gas was hold by the film of polymer which was flexible and could sustain the medicament
release profile. For the development of floating dosage form the selection of coating agent was done on the basis of its water permeability so that effervescent process was quickly occurred and dosage form start to float. The applied coating film must also not permit the escape of carbon dioxide to achieve the floating but the film must efficiently not permeable for the medicament to achieve desired level of sustained release behavior.

59. Paola Mura, et al, 2008, were observed that metformin hydrochloride medicament having small half life and lesser bioavailability and these parameters motivated the authors to develop the sustained release system of it. In present work of research the matrix tablets was formulated by using direct compression technique having jointly metformin hydrochloride along with triacetyl βcyclodextrin. The system was developed in such a way that it must released the 40% medicament as a starting dose inside the gastric media in first two hour of its administration and then after the passage of three hours around 90% medicament was get released. DSC examination was done to check the any possibility of interaction among the polymers and medicament and no incompatibility were observed. The dissolution data showed that mixture containing the Eudragit L100-55 and HPMC in combination were higher beneficial instead of using them alone for controlling the release of medicament. Finally it was concluded that mixture of drugs dispersed in the polymer matrix of chitosan and eudragit was attain the set objective of the study by releasing 30% of medicament in gastric fluid in first two hour and then in third hour of study 90% of medicament was removed in jejunal media.

60. Mariaanne Hiorth, Terje Skoien, Sverre Arne Sande, 2010, formulated the pellets having chitosan and calcium inside the core of pellet and then another coating was applied consisting of alginate and pectin having chitosan and calcium combination. For the formulation of solution of polymer to the measured quantity of water chitosan and pectin was incorporated. The dosage form was prepared to convey the medicament up the colon part. When low chitosan and higher alginate amounts were taken then it was resulted in smooth pellets surface. In case of calcium pellets the removal of medicament was follow the sustained release path and in four hours of study just 46% of medicament was released. The present work demonstrated that calcium pellets which were having coating of alginate and chitosan were most efficiently delivered the medicament to the colon portion. So many findings
proved that polysaccharide and chitosan are jointly slow down the release of medicament from the system.

61. **J. Siepmann, et al, 2006**, formulated the matrix pellets of lipid containing theophylline medicament and later on *in vitro* evaluation has been done on them to check the impact of different manufacturing factors. The pellets were manufactured by two techniques i.e. extrusion spheronization and melt solidification. The extrudates were formed by using extruder of piston type which were quickly spheronized and dried. It was seen that when size of beads was reduced reduction in loading of medicament was occurred causing reduction in encapsulation effectiveness. It was observed that rate of release of medicament was specifically more in the beginning of the study and goes down as the time passes. Removal of medicament through the pellets formulated by the melt solidification technique follows diffusion controlled mechanism. The release of theophylline from the system was also impacted by the temperature of drying of pellet.

62. **Ian G. Tucker, Aleksandra Krajacic, 2003**, investigated the phenomenon of dumping of dose in matrix tablets which were weakly formed and it was governed by the tablet gastric residence time. Inside the stomach the tablets may be stay differently either in minutes or hours based on the presence of food in the stomach. It was previously proved that nonstop administration of food all over the day may cause hindrance in gastric emptying and sometimes require ten hours for emptying the tablet. Peristaltic movement has the important role in gastric emptying it was higher in morning but recorded slower in afternoon session. If treatment was given to the tablets and granules then it impacts the mechanical features and the release profile of the tablets. The coated film depicted alterations in mechanical characteristics and rate of release of medicament through it on storage. The degree of mechanical variability of the polymeric film largely depends on the environmental and formulation parameters. It was noted that granules compactibility was improved due to higher quantity of tiny pores and porous structure inside the granules. It was observed that granules treatment, timing along with the quantity of polymer added affects the rate of release of medicament.

63. **Roland Bodmeier, 1997**, stated that due to compaction force formation of single unit tablets was occurred from the multiple unit dosage form. In present review work the various parameters which would influence the process of compaction and functioning of coated pellet
were analyzed. It was observed that when ethyl cellulose was used as a coating polymer for the pellets at the time of compaction of pellets coating layer was injured and no sustained release effect was achieved. This observation was shocking but it was well known that ethyl cellulose possess weak mechanical traits. When coating of surelease was applied on the surface of microcrystalline cellulose pellets then speedy release of medicament was taken place but when same pellets were not coated with the same polymer then release of medicament was observed to be slower. Due to more compression force the fewer drugs was released and less compression force gives higher amount of medicament release. To overcome the damage caused to the pellets coated with ethyl cellulose due to compression the pellets were kept for 1 day at 70°C in an oven for creating obstacles in release of medicament. Flexible and appropriate film was formed when acrylic polymer were used for coating purpose. When Eudragit L30D 55 was used for the coating purpose and subsequent compression of the coated pellets leads to damage of film. It was observed that compact formed by using powder blend showed enhanced tensile strength if quantity of MCC was enhanced however the beads formed by using spheronization and extrusion techniques depicted the negative results. If pellets were formed by using MCC and compacted and was observed through SEM then it was seen that all the pellets have similar look and size as that of present in actual pellets before compression. Hence it could be concluded that MCC pellets were not break down due to force of compression and maintain their intactness. If the pellets were lubricated then the prepared tablets showed less tensile strength in comparison with the tablet formulated from the pellets which are not lubricated. During process of compaction the applied film of polymer must remain unbreakable so as to remove the medicament for longer period of time. Those polymers which are unable to bear the high pressure during compaction are not the ideal candidates in formulation of compacted pellets. Hence polymers used in coating purpose must possess the sufficient flexibility so that it could not be get ruptured.

64. Ehab A. Hosny, et al, 1997, formulated the diclofenac sodium beads by using two different preparations. Dispersion of medicament and CMC was drop on the aluminium chloride solution. The generated pellets were circular in shape. The quantity and quality of polymer decides the size and shape of pellets. It was observed that if more quantity of sodium alginate was used then formulated beads were irregular in shape having less friability. If quantity of
sodium alginate was reduced then typical shape beads were obtained having friability lower than one percent. It was seen that large quantity of sodium carboxymethyl cellulose forms the spherical and regular beads and when less quantity was used the results were not up to the mark. The particle diameter of aluminum carboxymethyl cellulose was found to be more because viscosity of solution of sodium carboxymethyl cellulose was more. Content of drug in all the formulations were found to be similar which proved that quantity of polymer added has no impact on the medicament. Comparative in vitro dissolution study was conducted with the marketed preparation to examine the impact of polymer quantity and quality on the release of medicament from the system. The rate of removal of diclofenac sodium through the beads of aluminum carboxymethyl cellulose was slow because they disintegrate slowly. Only 72% diclofenac sodium was released in ten hours of dissolution study of marketed voltaren tablet and it was recorded the very less released quantity.

65. M. Grassi, et al, 2008, suggested that the co extrusion technique is advance process of melt extrusion having so many plus points on the melt extrusion method. In co extrusion technique concurrent extrusion has been done on two or more than two ingredients so as to form the extrudates having multi layered. The shape of formulated extrudates was decided by the die. In co extrusion technique two in compatible medicaments can be given in two separate layers. The outer layer may provide the coat to the inside layer and protect the medicament or may sustained the release of medicament of inside layer. In recent study by employing melt extrusion technique formation of extrudates of cylindrical shapes has been done which could sustain the medicament. The formulated co extrudates consist of two matrix layer of inner one and outer one. The inside layer possess the hydrophilic nature and outside layer possess the lipophilic nature. Rapid removal of medicament was occurred through hydrophilic layer and sustained release of medicament was observed from hydrophobic layer.

66. Peter C. Schmidt, et al, 1996, demonstrated that coated pellets could be compressed to form the tablets which will disintegrate quickly. If the pellet containing magnesium stearate and Eudragit NE 30D was premixed then it decreases the matrix formation capacity of the pellets after the process of compression. The release of medicament bisacodyl after the two hour in dissolution study was not depends on the applied compression force. After the examination it was observed that not a single ingredient was affects the release of medicament due to
compression. Coated film was get ruptured and it was the major reason behind the pellets damage. If tough material was come in touch with the pellets then it leads to pellet deformation during compression. If quantity of pellet was enhanced in the tablets then it produces pellet deformation within the tablet. If less crushing strength was recorded in the pellet then film may be ruptured. When Eudragit L30D55 was used for the application of film then the generated film was much fragile leading to damage of coated film. This problem could not be solved by increasing the quantity of coating solution twice. It was concluded that the release of active in acidic fluid was occurred due to pellets deformation at the time of compression which cause rupturing of film. It was necessary that pellets must possess the more crushing strength and polymer formed the film of higher thickness around the pellets. The ingredients must absorb the compaction forces. The application of elastic film on the pellets further help to overcome the deformation of pellet and minimizes the rupturing of film. Quality and thickness of applied polymeric film were the most significant factors. Enteric coated pellets were compressed to form the disintegrating tablets which were released only 10% of medicaments in two hours of dissolution study.

67. M.F. Saettone, et al, 1995, stated that plasticizer was incorporated in the coating solution of polymer to enhance mechanical property of the coated film. For the manufacturing of the pellets the mixer granulator was employed consisting of spray for the addition of binding liquid. The coating solution was shaken properly so that plasticizer was distributed homogeneously in the solution. The coating solution consists of mixture of ethyl cellulose or acrylic polymer and different plasticizer in their various proportions. If the plasticizer quantity was increased then there was reduction in release rate of medicament was observed. It was proved through the present study that the selection of suitable plasticizer and polymer combination with their proper concentration in an important step in achieving sustained release rate of the medicament. It was concluded that quantity and type of plasticizer have impact on the release of medicament.

68. A.V. Damle, R. Shettigar, 1995, manufactured the pellets of controlled release profile containing isoxsuprine HCl. Lactose and avicel PH 101 were utilized in to the formulation as key ingredients. Passed the medicament and ingredients from sieve 80 and then proper weighing and blending was done. Water was used for binding purpose and then extrusion and spheronization was carried out. Drying was done for two hours at 50°C in hot air oven.
Pharmaceutical evaluations were done on the prepared pellets. The polymer which was not soluble in to the water was employed for coating purpose so as to achieve sustained release behavior. During in vitro study it was seen that the medicament was liberate in 45 minutes and hence demanding the application of film on the pellets surface to slow down the release. So many materials has been check to slow down the release of medicament but Eudragit RS 100 and ethyl cellulose showed the better results. Dibutyl phthalate was in corporate as a plasticizer in the preparation. When the formulations having coating of Eudragit RS 100 were examined for accelerated stability study then the results were in favor of authors expectations that no alteration was observed in release behavior of medicament. The alteration in release of medicament was seen only in formulation kept at 60°C. The same results were obtained when pellets were coated with ethyl cellulose film.