1.0 INTRODUCTION

1.1 EXTENDED RELEASE (ER) DOSAGE FORM

Extended release (ER) dosage form is defined as those modified release dosage forms which are making the drug bioavailable upto extended time after an administration which helps to reduce dosing frequency than that of a conventional type i.e. immediate release (IR) dosage form.

This can be divided into two types viz.:
A) SINGLE UNIT DOSAGE FORMS (e.g. tablets) and
B) MULTIPLE UNIT DOSAGE FORMS or MULTIPARTICULATE PELLET SYSTEMS.

The systems can be further subdivided into two concepts regarding to the design of dosage forms: (i) Matrix systems and (ii) Reservoir systems.

A) SINGLE UNIT DOSAGE FORMS

(i) Matrix systems

Matrix systems consist of drug dispersed homogenously throughout a continuous phase of polymer or lipid. These devices can be prepared either by the compacting drug with polymer or by solubilising the drug, resulted in the molecularly dispersed drug. The drug transport often results from a combination of several mechanisms included dissolution, diffusion, swelling and erosion.

a. Water-soluble matrix formers

Water-soluble or hydrophilic matrices are a well known type of ER oral dosage forms

Popular polymer for this system is hydroxypropyl methylcellulose (HPMC) a hydrophilic carrier material, several others includes (i) cellulose derivatives: hydroxypropyl cellulose (HPC), carboxymethylcellulose sodium (NaCMC), (ii) natural polymers: sodium alginate, carrageenan, chitosan and (iii) synthetic polymers: polymerized acrylic acid (Carbopol), polyvinyl alcohol (PVA), polyethylene oxide (PEO). It has been suggested, however, that the term ‘swellable matrices’ is more appropriate as it better explains the characteristic of the systems

b. Water-insoluble matrix formers

This system includes

(i) lipid-base excipients: white wax, carnauba wax, glyceryl stearates, hydrogenated vegetable oil, paraffin etc.

(ii) polymer-based excipients: ethylcellulose (EC), cellulose acetate.
These systems have a greater physical stability and less variable drug release with the lower incidence of ‘dose dumping’ in presence of food, comparatively than water soluble matrix systems.

(ii) Reservoir systems
Reservoir systems are mainly characterized by a drug core surround drug layer around core covered by release-rate controlling one or more polymers. Following are the popular reservoir systems.

a. Coated tablets
In this system tablet made up of the mixture of active drug and other excipients, which are layered with water impenetrable polymers solution. When these tablets exposed to aqueous media, the surrounded coating is transformed into a partially permeable membrane through which the drug releases throughout the system.

b. Osmotic pump systems
It is a special type of the reservoir systems, where the drug release is controlled dynamically by an incorporated osmotic agent in the active drug core. The rigid surrounding semi-permeable membrane consists for example of cellulose acetate. The drug is released through an orifice which is mechanically drilled in the membrane.

B) MULTIUNITPARTICULATE SYSTEMS
Advantages of multiparticulate systems over the single unit ones as below:

i. Can be swallowed easily compared to large size capsules.

ii. Can administer divided dose as a multiple-units without changing controlled release properties.

iii. Incorporation of large dose of drug than that of capsules.

iv. Cost effective than capsules with respect to large scale.

v. Conventional tabletting capacities required.

vi. Greater stability of formulation that are incompatible with gelatin.

vii. Formulation of orodispersible base that can be used as a reconstitution agent which helps to form a swallowable suspension without changing drug release properties.

viii. Cannot tampered product easily.

(i) Matrix systems
The matrix type of multiparticulate systems can be prepared by several techniques such as extrusion/spheronisation spherical crystal agglomeration and melt-solidification. Although, the production of multiparticulate matrix systems is considered to be easier than that of the reservoir systems, their extent of retardation is limited because of pellet geometry.

(ii) Reservoir systems
Coated pellets as a mean to control drug delivery are widely used in the pharmaceutical industry, although the development and optimisation of the systems are rather complex. Numerous aspects of the system performance have been investigated, for instance, the influence of formulation and coating technique, the effect of drug solubility and core material the use of polymer blends on drug release rate.

1.2 MULTIPLE UNIT DOSAGE FORMS
In the past three decades, multiple unit drug delivery systems like e.g. pellets have gained increasing attention due to numerous advantages. One reason may be commercial benefits.
like extended patent protection and market expansion. However, more important are their formulation advantages and therapeutically benefits. Due to their multitude, pellets of different, potentially noncompatible drugs or pellets with unlike drug release profiles can be combined in just one final dosage form, thus allowing a greater flexibility during formulation development. The spherical shape, narrow size distribution and excellent flow properties of pellets result in uniform and reproducible application of drug and polymer layers as well as accurate volumetric dosing on tablet presses or capsule filling machines.

In vitro and in vivo formulation profile from pellets is controlled by a multitude of particles rather than just one device as in case of single units, e.g. coated tablets. This reduces the variability in release profiles and prevents dose dumping. The gastric residence time of pellets is shorter and more predictable compared to single units. And pellets spread more homogeneously throughout the GI-tract, thus causing less local irritations of the mucosa and potentially leading to higher bioavailability. Also coated single units can not be divided by any means, whereas the pellets can be re-obtained easily by opening the capsule or dispersing the tablet in water. This allows easier swallowing for children and elders or even administration via naso-gastric feeding tubes.

1.2.1 Different designs of coated multiple units

The term ‘pelletization’ originally described the agglomeration of fine powders of drugs and excipients into round spheres which were described as pellets. However, the potential of sugar seeds (so called nonpareils) as starter cores for the formulation of layered / coated pellet dosage forms has been recognized as early as 1949. Various designs have since been developed for coated pellets. Matrix pellets via extrusion and spheronization with microcrystalline cellulose (MCC), lactose or blends of the two can be used for formulation of high dose of drug. This technique allows sufficiently high drug loading levels. However, these matrix pellets alone would disintegrate quickly in contact with medium and thus requires an outer polymer film coating which can control the drug release. Potent low dose drugs, on the other hand, can be formulated easier by spraying them onto inert starter cores in fluidized bed equipment. The polymer which determines the release rate can be applied with the drug from the same solution or dispersion, yielding so called matrix-coated pellets. However, this approach has several disadvantages like higher risk of drug-polymer interactions, fast initial release and incomplete release. Therefore a separate polymer
coating step, subsequent to the drug layering, is more common. The term ‘reservoir pellets’ typically refers to the latter system.

Figure No. 2. Diagramatic presentation of: a) Matrix pellets, b) Polymer and drug coated pellets and c) Reservoir pellets (black: drug; grey: release-controlling polymer; white: other excipients)
1.3 Release from reservoir pellets

In contact with aqueous medium, release from reservoir pellets follows a typical sequence of events. First media is taken up into the pellet; soluble components (mainly drug, binder and sucrose starter cores) are dissolved and then released from the pellet across the barrier of the polymer coating. However, the precise mechanism of this release is highly complex and determined by a variety of pellet properties. For pellets coated with an insoluble film, different ‘passage ways’ have been described. Following concentration gradients, the drug diffuses either through a) The intact coating, b) Through channels made by plasticizers or pore formers or c) Through medium filled channels / pores. d) Osmotically driven release.

Figure No. 3. Diagramatic representation of typical release mechanisms of coated pellets
(for reasons of simplicity, channels / pores / cracks are depicted interconnected and without any tortuosity)

Diffusion through intact polymer is often described quantitatively by applying Fick’s Law to coated systems:

$$\frac{dm}{dt} = \frac{D \cdot A \cdot c_s}{h}$$
Assuming perfect sink conditions (conc. in medium $\approx 0$) and steady state, the

Herein Drug diffusion in this case of amorphous state is well explained with the help of ‘jump-and-run’-model. Whereas drug was diffused thoroughly carried with the tube between parallel polymer chains awaiting towards ‘dead-end’. This probable phenomenon enforced to ‘jump’ to another polymer chains.

![Jump and Run Model](image)

**Figure No. 4. Jump and Run Model**

Naturally, this requires energy and thus determines the frequency of such ‘jumps’ and in consequence the apparent diffusivity. Even if the proposed parallel alignment of polymer chains in the amorphous segments seems somewhat unlikely and a more random structure is assumed; these ‘jumps’ between the chains will nonetheless be necessary for diffusion. Increased chain mobility, e.g. due to hydration of the polymer, use of plasticizers or elevated temperatures, will facilitate ‘jumps’ by increasing the free volume within dense polymer films and thus increase diffusivity. Fick’s Law further does not consider potential swelling of pellets (which changes surface area A and coating thickness h) or interactions between medium, drug and polymer during diffusion e.g. ionic interactions between charged drugs and polymers or counter-diffusive processes: ‘medium in’ versus ‘drug out’. Especially cores containing osmotically active substances induce a pronounced medium influx which could result in swelling of pellets as well as counter-act the outwards diffusion of the drug.

Diffusion through plasticizer channels, although theoretically possible, was not reported in the literature. In addition, plasticizers are often used in amounts which are not expected to form a continuous, interconnected plasticizer phase. However, diffusion through medium
filled pores / cracks is a rather common release mechanism. Such pores are either the product of the coating process or they form in situ during release. Factors which potentially cause formation of porous membranes during the application of the coating are e.g. poor film formation or spray drying of the polymer, the use of non-solvents in the applied polymer solution as well as the evaporation of plasticizers. In contact with medium, pores can be formed in situ by either leaching and / or cracking. Pore formers like water-soluble sorbitol or urea are easily dissolved and leached from the film. But also water soluble polymers like polyethylene glycol, polyvinylpyrrolidone, polyvinylalcohol, hydroxypropyl-methylcellulose, hydroxypropylcellulose are commonly applied as pore formers. Naturally, water-soluble plasticizers like triethylcitrate can also act like a pore former when they are leached from the coating. Diffusion through plasticizer channels, although theoretically possible, was not reported in the literature as it may be the possibility that most drugs exhibit a higher solubility in aqueous media than in plasticizer. In addition, plasticizers are often used in amounts which are not expected to form a continuous, interconnected plasticizer phase. However, diffusion through medium filled pores / cracks is a rather common release mechanism. Such pores are either the product of the coating process or they form in situ during release. Factors which potentially cause formation of porous membranes during the application of the coating are e.g. poor film formation or spray drying of the polymer, the use of non-solvents in the applied polymer solution as well as the evaporation of plasticizers. In contact with medium, pores can be formed in situ by either leaching and / or cracking. Pore formers like water-soluble sorbitol or urea are easily dissolved and leached from the film.
1.4 Formulation of reservoir pellets

1.4.1 Coating equipment

Due to their small size, pellets are layered in fluidized bed equipments in order to achieve homogeneous distribution of the coating formulation and avoid formation of agglomerates. The fluidizing air serves several functions: movement of the pellets, separating them from each other and adjusting the required product temperature. However, the drawback of this large airflow is a higher risk of spray drying during drug layering or polymer coating processes. In fluidized-bed-coating, different processing modes are differentiated by the spraying direction and the principle of air distribution in the processing chamber: top spray, bottom spray, Wurster or rotor coating. Due to the shorter distance between spray nozzle and product, polymer losses due to spray drying are less pronounced in bottom spray coaters compared to top spray coaters. Bottom spray coaters equipped with Wurster inserts, which concentrate the particle flow close to the nozzle, can reduce spray drying further. Rotogranulators are also used for pellet coating and yield comparable coating efficiencies to Wurster-coating when the nozzle position is tangential to the particle flow. Since fluidized bed coaters are equipped with pneumatic binary nozzles, both solutions and suspensions of drugs / polymers can be sprayed with a low risk of nozzle clogging. Still, the viscosity of solutions or the solids content of suspensions should be adjusted to the nozzle diameter, in order to further reduce clogging. All processes have in common essential coating steps: (i) the formation of suitable droplets from the coating, (ii) contact and adhesion of the droplets onto the particles’ surface and subsequently (iii) spreading and coalescence.

1.4.2 Drug layering

Layering is a term commonly describing the application of active pharmaceutical ingredients to multiparticulate starter cores. This can be done from either drug solution or drug suspension. A drawback of aqueous drug solutions is the partial dissolution of soluble starter cores like sucrose nonpareils during the layering process. This can reduce the yield of properly layered pellets by increased agglomerates formation (‘doubles’, ‘triples’) or by increased attrition or breakage of the drug cores. Pure organic drug solutions on the other hand may evaporate rapidly. In one report this led to very uneven, pockmarked core surfaces which rendered the subsequent extended release coating impossible. Another limiting factor for drug solutions is usually their viscosity which can cause stickiness. The resulting agglomeration of pellets can be minimized or diminished by dilution or lower spray rates. However, if drug contents of only 10% in solution lead to high viscosities already, suspension
layering is usually the more economic technique. For suspension layering the use of low-viscosity binders like hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC) or polyvinylpyrrolidone (PVP) is highly recommended in order to improve drug adherence to the starter cores and to prevent sedimentation of drug powder in the tubing. However, binders can also be necessary for solution layering to prevent cracking, attrition and delaminating of recrystallized and brittle drug layers.

1.4.3 Polymer coating
Since many polymers used for controlled drug release are water-insoluble, they were traditionally applied from organic solutions. The disadvantages of this process are explosion / flammability hazards, environmental considerations, risk of residual solvents in the polymer film and the higher viscosity of polymer solutions. As an alternative aqueous dispersions of the polymers have been developed, offering low viscosities even at higher molecular weight or solids content. However, the mechanism of film formation on the substrate differs strongly between organic and aqueous coating. Film formation from organic solution is a simple consequence of solvent evaporation: the solution droplets containing discrete polymer molecules coalesce to a fluid-layer on the substrate surface and gradually solidify to a dense, closed film due to the transition solution → sol → gel → film. Naturally, the same sequence occurs for water-soluble polymers when applied from aqueous solutions. Plasticizers are mixed with polymer solutions depending upon its requirement so as to reduce the brittleness of the final film on the dosage form.
With dispersions in the case of aqueous media, (so called lattices), polymer is not applied in the form of molecules but as colloidal particles, each containing hundreds of polymer molecules. During the evaporation of the aqueous continuous phase, the dispersed particles are gradually concentrated and ordered into a close packed, rhombohedral lattice on the substrate surface. Once in contact with each other, the particles are immobilized. This results in the deformation and coagulation of the polymer particles due to capillary forces (Brown theory) and polymer-water interfacial tension (Dillon-Matheson-Bradford theory). To ensure sufficient coalescence, the solid polymer particles often need to be softened by use of plasticizers in the dispersion and by elevated temperatures during the coating process. Plasticizers reduce the intermolecular forces and thus cohesion inside polymer particles which makes them softer and lowers the MFT i.e. Minimum Film Forming temperature as well as $T_g$ (glass transit temp.) of the polymer. Films applied from aqueous dispersions are usually more porous and exhibit lower tensile strength. Also water soluble drugs may penetrate in the polymer film during aqueous coating processes, thus causing a further
increase in porosity once this drug are leached from the coating. Interactions between ionisable drugs with the anionic surfactants in lattices can also lead to higher porosity of the film. This explains why usually higher amounts of polymer are required for aqueous dispersions in order to achieve comparable coating performance.

**1.4.3.1 Coated pellets stability during storage**

Storage stable systems coated from aqueous dispersions are mainly obtained by curing steps at elevated temperature and / or humidity subsequent to the coating or by incorporating small amounts of soluble or enteric polymers in the water-insoluble coat. In contrast, organically coated drug delivery systems are mostly considered storage stable. Since the polymer is applied in its molecularly dispersed form, very dense films can be obtained without the risk of further gradual coalescence. However, storage effects cannot be ruled out totally for organic coatings. The rather dense structure of organic films can trap volatile solvents easily which then can cause films mechanical properties upon gradual solvent evaporation during storage. Organic solvents are also more prone to spray-drying during the coating process due to their high volatility. This can create porous, organic coatings which are likely subjected to the same storage effects as aqueous coatings.

**1.4.3.2 Thoughts on the coating thickness**

In the majority of studies, the coating is applied on a weight base. This is an easy approach which does not require any characterization of the cores before the coating. However, it may yield coatings of different thickness for different pellets since it does not consider the surface area of a batch. As soon as size and / or density of the drug cores change, the thickness of a weight-based coating will change. The reason is simply that any amount of polymer is always applied to a surface area not a weight. With regard to pellets it is vital to keep in mind that the batch surface area is depending on the surface area of a single pellet and the number of pellets in a given batch weight. Therefore not only the size but also the density (hence the weight) of a single pellet are important. The density differences of pharmaceutical multiparticulates may appear negligible. However, the practical relevance has been reported before. Despite compensating increasing drug loadings with decreasing sizes of starter cores, in order to get drug cores of the exact same size, the authors obtained different coating thicknesses when all batches were coated with the same amount of polymer. The reason was the lower density of the drug layer compared to the starter core. Thus, differences in batch surface area can be expected for different drugs, different drug loading levels, different layering techniques (e.g. solution vs. suspension) or different starter cores. The density of
The densities of starter cores made of microcrystalline cellulose from two suppliers as $1.513 \pm 0.001 \, \text{mg/cm}^3$ and $1.363 \pm 0.001 \, \text{mg/cm}^3$ for Celphere® and Cellets®, respectively. Hence, whenever comparing pellets which are based on different drug cores, the coating should be applied based on the batch surface area (e.g. estimated from single pellet weight and size) rather than its weight.

### 1.4.3.3 The Curing Treatment

Though coating process was completed even with 10°C-20°C over MFT (Minimum Film Formation), thermal cure is essential to inclusive polymer particle coalescence. During this process, the polymer chains movability became higher subsequently this consequences into hastening of latex adherence.

Such thermal treatment i.e. The Curing can be generally done in hot air oven or in FBES following the coating process instantly. Very stumpy thermal treatment could results into partial film formation, on the contrary very thermal treatment could results into unnecessary tacky and sticking with agglomerates of the pellets. thermal treatment (curing) step able to be executed at numerous temperatures or dissimilar times with varying humidity range. These are found to be very important factors that can affect the drug discharge rate.

### 1.4.4 Process parameters

Coating process includes several phases occurring at the same time, like atomization of the spray liquid and droplet formation, contact and distributing on the substrate surface, evaporation of liquid and sticking of particles and film formation. The critical process parameters for application of aqueous dispersions include:

1) Fluidization air volume, affecting the movement of the pellets;
2) Fluidization air temperature, important for the vanishing of the solvent and the softening of the latex particles;
3) Solids content of the dispersion, too high solid contents may cause strong variations on batch reproducibility;
4) Spray rate, important parameter since a low spray rate leads to porous films due to partial drying on surface of pellets and film formation is comparable to spray drying. Too high spray rates lead to problems as sticking and agglomeration of pellets. The atomization air pressure affects the droplet size of the coating formulation
5) Atomization air pressure influences the droplet size and spraying pattern. The characteristics of substract, as density, diameter and stickiness should also be taken in consideration for the coating process.

6) Bed temperature should be above 10-20°C of the Minimum Film Formation Temperature of the polymer dispersion in order to achieve sufficient water evaporation and complete film formation. The product temperature can be adjusted by varying the inlet air temperature. Very less temperatures results into imperfect coalescence and very elevated temperatures results into originating very fast water evaporation on the pellet surface, leading to spray loss. Faster drug release rates can be a result of insufficient time necessary for the capillary forces to achieve complete coalescence. Tackiness problems can occur at high coating temperatures as a result of interaction of drug and spray dispersion ingredients. Instability of coated dosage forms can also result of inappropriate conditions during coating process. The causes for instability can be exposure to humidity, light, higher temperatures and interaction between coating and core materials.

9,13,15,25,31,38,49,65,72,75,78,79,82.

1.5 Excipients for extended release reservoir pellets

1.5.1 Polymers

1.5.1.1 Ethylcellulose (EC)

Ethylcellulose is a semi-synthetic, water-immisible, pH-independent polymer which is obtained from cellulose, a natural polymer of ~1000 β-anhydroglucose units.
Each of these glucose units contains three replaceable hydroxyl groups which are etherified with ethyl groups in a synthetic step. In commercially available EC grades, the Degree of Substitution ranges from 2.2 to 2.6 which explains the water-insolubility and pH-independency of this polymer. Viscosity and tensile strength increased at higher molecular weights, thus reducing the incidence of film cracking and decreasing drug release. However, with a glass transition temperature of ~133 °C (EC 10cP) films made from the pure polymer are very brittle and thus commonly require plasticizers.

1.5.1.2 Acrylates
These are ethylacrylate methylmethacrylate (2:1) copolymers i.e. Eudragit NE/ NM 30D

The main difference between both dispersions remains in the content and nature of emulsifier. Both aqueous dispersions have a solid content of 30% and a low MFT (5°C). Eudragit NE/ NM 30D films are highly flexible and do not need addition of a plasticizer. These films are insoluble in gastro-intestinal tract, show very low permeability and a pH independent swelling. For coating, anti-tacking agents are used to reduce the stickiness of the polymeric dispersion.

1.5.1.3 Celluloseacetate (CA)
Celluloseacetate is a semi-permeable polymer with high water permeability (~10 higher than EC (Ramakrishna and Mishra 2002)) and pronounced rigidity ($T_g$ ~190 °C, (Guo 1993)). Thus it is predominantly used in osmotic drug delivery systems but also as the release controlling membrane in reservoir type transdermal patches. The high rigidity of the polymer apparently stems from a high degree of chain entanglement and prevents deformation of the
outer coating of OCDDs during media uptake. Typical OCDDs are composed of an osmotically active core tablet (sodium chloride, sugar and / or highly soluble drugs) and a CA-top-coating. The coating can either contain a laser-drilled orifice for the convective transport of drug solutions or several pores which allow osmotic pumping. These pores can be formed during the coating process by using aqueous CA-dispersions or by adding small amounts of non-solvents like water to organic CA-solutions. Or they form in situ during the release by cracking or pore-former leaching. Various pore-formers have been applied to create micro-porous celluloseacetate membranes with even higher water permeability and hence shorter lag times: sorbitol, polyethylene glycol, urea, sucrose, propylene glycol, castor oil. However, when working with aqueous dispersions, the high rigidity of CA can only be overcome with unusually high amounts of plasticizers (100-320% based on polymer) or high process and curing temperatures (60-80 °C) which may be detrimental to the stability of some drugs. Thus, cellulose acetate films are best applied from organic solutions.

1.5.1.4 Polyvinylacetate (PVA)
Kollicoat SR 30 D has a solid content of 30% and contains of polyvinylacetate (27%), polyvinylpirrolidone (2.7%) and sodium laurylsulfate (0.3%) (BASF). If unplasticized, it has a MFT of 18°C and results in brittle films in dry state. Plasticizers are added to increase mechano behaviour of the final minimum film formation temperature confined on the kind and quantity of plasticizer included. Since Kollicoat SR 30 D has no charge or ionizable groups, it results in pH independent film coatings (BASF).

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\text{CH}_2 - \text{CH}_2
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In addition anti-tacking agents are also used to reduce the sticking tendency. It can be used for controlled release formulations or taste-masking when in combination with pore formers.

1.5.1.5 Additional additives
1.5.1.5.1 Plasticizers
When formulating a coating dispersion, the selection of plasticizer is very important. Plasticizers should remain in the films, and should not migrate or volatile and should not show incompatibility with the polymer. Contrary plasticizer with the aqueous dispersion can
lead to poor film formation and unstable formulations during storage resulting in tremendous changes on drug release. Plasticizers for film coating are excipients with high boiling point. They should be homogenously distributed and give flexibility and mechanical resistance to the polymeric film. Plasticizers also change other properties of film coatings like vapor transmission rates, moisture absorption and water penetration. If a hydrophilic plasticizer concentration increased then it may increase water diffusion in the polymer. Whereas hydrophobic plasticizers can close the pores in the film, causing less water uptake.

1.5.1.5.2 Pore formers
Drug release from aqueous polymeric coatings may be very low and require the addition of hydrophilic polymers to act as pore formers. The amount and type of hydrophilic polymer used is related with the desired release profiles. A variety of pore formers can be applied and hydroxypropyl methylcellulose (HPMC) is widely used. However addition of HPMC can lead to physical instability of coating dispersion. In order to circumvent this problem, water-soluble polyvinyl alcohol copolymer was can be incorporated to obtain the preferred drug release. Furthermore, drug release profiles were unchanged upon storage, if a curing step was performed before storage. In a recent study, PVP and PVA-PEG attach copolymer were added to Aquacoat ECD and Kollicoat SR30D.

1.5.1.5.3 Anti-tacking agents and pigments
Anti-tacking agents are necessary to reduce the tackiness of aqueous coatings. Often talc and glycercyl monosterate are used to prevent sticking of the coated pellets to each other and coating equipment walls and to improve coating performance. In order to reduce tackiness, much higher amount of talc is needed in comparison with glycercyl monosterate, due to higher effectiveness of glycercyl monosterate as anti-tacking agent. The addition of talc and glycercyl monosterate can decrease film flexibility, becoming more pronounced when the content increases. For light sensitive drugs, titanium dioxide can be used in film coating to improve stability of the drug.

1.5.2 Starter cores – Potential influences on drug release
Often sugar spheres (so called nonpareils, NP) are used as starter cores. They consist of an initial sucrose crystal which is then layered to various commercially available sizes with sucrose and starch. Alternatively, water-insoluble microcrystalline cellulose (MCC) starter cores can be used. They have been reported to offer higher abrasion resistance, lower agglomeration tendencies during aqueous drug layering and less interference by mechanical
stress during dissolution compared to sugar spheres. Just recently a third starter core made of isomalt was introduced to the market but data is still very limited. Starter cores are usually considered inert. However, recent reports indicate that the starter cores could affect the release from reservoir pellets. MCC starter cores are insoluble but adsorption of drugs to MCC (in the powder form) has been reported, which may slow down the release. In contrast sugar nonpareils dissolve and the major constituent (~75%) sucrose can be released, thus increasing the volume inside the pellets which can be filled by medium. This could be beneficial to the dissolution of drugs with poor solubilities. The strong osmotic activity of sucrose starter cores has also been suggested to cause faster and higher water uptake. Usually this results in increased tensile stress on the membrane, dilution of the drug concentration inside pellets and potentially the formation of a counter current to the outwards diffusion of drugs. After the sugar is released, the fluid filled spheres could show a higher sensitivity to mechanical stress. In addition, sucrose solutions could lead to changes in drug solubility and coating hydration.18,19,24,46,54,56,57,58,62,64,80.

1.6 Need for study:
1.6.1 Alzheimer’s disease (AD) disease is the the largest part of ordinary type of dementia. In progression with this delusive condition, symptoms like mystification, tetchiness and violence, displeasure, dilemma with speech and long-standing reminiscence failure. Generally medicines used to treat the alzheimer’s disease were as four are ACE inhibitors such as Rivastigmine, Tacrine, Donepezil And Galantamine and recently found Memantine (NMDAR) . ]

1.6.2 Galantamine is employed for the cure of mild to moderate Alzheimer’s disease and a range of further memory disease. Galantamine is a competitive and reversible cholinesterase inhibitor. It minimizes the exploit of AChE and consequently lean to enlarge the absorption of acetylcholine in the brain.

1.6.3 Current extended release formulation of galantamine hydrobromide in the market is in the form of capsule for extended release dosage form. Since it becomes uneasy to swallow such dosage form for elderly patients.
1.6.4 Hence, in the present proposed work, orodispersible tablet with an extended release profile was planned on the principles of multiunit particulate systems and orodispersible base. Also this could be used as reconstituted suspension with an extended release profile which can be easily palatable and consumable. Also it will easy for patient to carry and to administer such medication without water\textsuperscript{5,36,74,75}. 
1.7 REVIEW OF LITERATURE

1. **Abbaspour et al. (2007)** have employed thermal treating to prepare pellets prepared by Eudragit® RS PO and RL PO which subsequently used for compression i.e. tabletting. The mechanical test of these matrix pellets which contains ibuprofen as a drug, Eudragit® RS PO/RL PO, Povidone K30 and Avicel PH101 showed the brittle behavior. Subsequent of curing at 60°C, pellets for 24 hours showed a plastic deformation without any rupture.

2. **Amighi and Moes et al. (1996)** suggested that pellets of more plasticizer may reduce the curing effect but plasticizer content should be balanced to evade troubles such as sticking throughout coating process or to avoid agglomerisation during curing process.

3. **Aulton et al. (1994)** suggested that Pellet cores are also concern about the compression of coated pellets. Henceforth pellets seeds must behave elastic in nature, this will results into avoiding shape endurance during compression. Core should be enough strong & elastic that cannot be deformed during compression phase.

4. **Beckert and co-workers (1996)** had used pellets of inconsistent crushing capacities, and accomplished that the harder pellets were better candidate for multiunit particulate tablets as they can withstand less deformation and so that film coating cannot be ruptured easily. Also they proved that coating thickness is a key parameter in film integrity during compression. Higher the coating thickness results into higher mechanical strength of film that can resist damage of coating during compression.

5. **Beckert et al. (1998)** concluded about the blend with 30 % w/w pellets had performed ideal uniformity with extragranular ingreidens. Also blend containing 50 to 65 % w/w pellets of total weight of tablets showed uniform mixing. This was due to the arrangement of the pellets, which prohibited separation. Also they suggested that pellets to Excipient ratio is essential part in tabletting of the pellets to acquire acceptable content uniformity of tablets and also without rupturing the pellets so that desired drug release can be achieved.
6. **Berggren and Alderborn et al. (2001)** proved that the deformity due to relocating particulates inside the pellet, could be prohibited by the void space and volume in the pellets. Higher the pellet void space higher will be deformation of the pellets during compaction due to configuration of powerful bonding between granules. It could be solved by drying and inclusion of proper porous nature of interrelations of microcrystalline cellulose pellets.

7. **Bhattacharya and Wurster et al (2008)** studied that when increasing the curing time of eudragit coated ibuprofen pellets, decreases the drug release from pellets. This decreased drug dissolution rate was observed due to superior interfolding between drug and eudragit.

8. **Bodmeier and Paeratakul et al. (1994)** established about dispersion films of eudragit NE 30d was found to be very elastic in nature with high elongation value. Whereas Eudragit RS and RL30D containing plasticizer, based dispersions with cationic polymer having flexible films having lower elongation value.

9. **Bodmeier et al. (1997)** used the coprocessed tabletting approach for compaction of pellets which avoided the pellets to pellets contact and also acted as a cushion to provide them sufficient strength to avoid rupture phenomenon during compression cycle. Theses resulted into non friable disintegrating tablets at low hardness without compromising on drug release rate.

10. **Christensen and Bertelsen et al. (2008)** suggested that the coating process includes several phases occurring at the same time, like atomization of the spray liquid and droplet formation, contact and distribution over the surface of the substrate, evaporation of liquid and film formation.

11. **Dashevsky et al.(2004),** proved that Eudragit FS 30D can be used as ideal film forming flexible polymer for pellets that can be further compressed into tablets without compromising on drug release pattern. Using 10 % of plasticizer as triethyl citrate was found to be better choice during this study for the proper film formation.

12. **El-Mahdi and Deasy et al. (2000)** proved that coated Excipients by powder were more suitable tan that of pellets excipients, with respect to rupture of the reservoir pellets
during compression. But they also suggested that this phenomena decreases tablet disintegration.

13. **Hamed and Sakr et al. (2003)** showed that the curing step can lead to drug migration throughout coating of polymer, usually consequential in an increase in drug release. A seal coat was used in order to protect drug migration and stabilize drug release profiles.

14. **Haslam and co-workers et al. (1998)** proved that particulates bears a elevated capability to dandify outstanding to their porosity within pellets, and this could be possible alternative for deformation and densification of pellets during tableting.

15. **Iloañusi and Schwartz et al (1998); Pinto et al. (1997); Lundqvist et al. (1998); Vergote et al. (2002) and Nicklasson and Alderborn et al (1999)** suggested the inclusion of a waxy material like as glyceryl monostearate, PEG 6000, paraffinic wax, coating on pellet made matrix which changed and impoved compactivity and protection to the reservoir pellets.

16. **Iloañusi and Schwartz et al. (1998)** established that cellulose based blend with sift waxy excipients were found to be more compressible than that of the formulation lacking of wax. This may be due to higher concentrations of wax helps to transfer plastic deformation into predominant deformation mechanism, whereas formulations made without wax undergo higher elastic revival.

17. **Iloañusi and Schwartz et al. (1998)** showed that inclusion of elastic Excipients changes the ability of pellets to deform and compact, which do not impact on functional coating of the particulate system without compromising on drug release aspects.

18. **Johansson et al. (1995)** studied that Pellet porosity is one of the reason which can harshly affect on the compaction prototype and in that way lead to the polymer coat throughout compression.

19. **Johansson et al. (1998)** suggested that pellets size is on of the cause of deformation behavior of pellets during compaction, higher the particle size higher will be the degree of
deformation. Possible reason for this might be less force transmission within large particles, which resulted into more contact force within the particles.

20. **Kranz and Gutsche, (2009)**; showed that stable drug release profiles were obtained and attributed to the presence of more water trapped in these systems during film formation, facilitating particle coalescence.

21. **Lecomte et al. (2005)** showed that compression of pellets those were made with coating of fragile films like ethyl cellulose likely to cause deformation and thus crackening of the functional coating which may changes the drug release of the end product. Also he established study on various flexible coated pellets which can be used for compression into tablets with the help of suitable excipients.

22. **Lehmann et al. (1994)** revealed that that coating based on solvent are more flexible than that of made by aqueous coating and henceforth less affected by compaction.

23. **Liu and Williams et al. (2002) and Williams III and Liu et al. (2000)** used Controlled humidity in the curing process. Humidity accelerates the film formation process. Water smooth the progress of particle polymer coalescence and also it plays the role as plasticizers.

24. **Liu and Williams et al. (2002)** found that thermal humidity curing helps to enhance coalesce of polymeric films, whereas elevated humidity can weaken up films, which results into change in drug release pattern.

25. **Millili and Schwartz et al. (1990)** showed that the porosity of reservoir pellets affects the compaction behavior of it, and henceforth subsequently the drug release pattern. So proper control on pelletisation manufacturing can be helpful to avoid such problems.

26. **Muschert et al. (2009) and Siepmann et al. (2007)** showed that drug release profiles were unchanged upon storage, if a curing step was performed before storage for extended release pellets.
27. **Nicklasson and Alderborn et al. (1999)** studied that the inclusion of PEG as soft material had a less tendency to deform than that of when used with out of it with microcrystalline cellulose which showed harder particles, this results into rupture and deformation of the pellets during compression.

28. **Nicklasson et al. (1999)** suggested that more the drying rate, more will be porosity of the pellets, owing to less pellet densification which were more susceptible to deform.

29. **Parikh et al. (1993)** showed that very reduces temperature may results into imperfect coating thickness and this will results into uneven drug release pattern and very elevated temperature results originates very fast water evaporation on the pellet surface, leading to spray loss. Faster drug release rates can be a result of insufficient time necessary for the capillary forces to achieve complete coalescence.

30. **Petereit et al. (1995) and others** proved that anti-tacking agents are necessary to reduce the tackiness of aqueous coatings. Often talc and glyceryl monostearate are used to prevent sticking of the coated pellets to each other and to improve coating performance. In order to reduce tackiness, much higher amount of talc is needed in comparison with glyceryl monostearate, due to higher effectiveness of glyceryl monostearate as anti-tacking agent. The addition of talc and glyceryl monostearate can decrease film flexibility, becoming more pronounced when the content increases.

31. **Ragnarsson and co-workers et al. (1987)** suggested that compression of small particulates had less effect than that of bigger particulates during compression pattern. Also showed that pellet size was depended upon coating polymer to be used and also the properties exhibited by core and tabletting Excipients.

32. **Raymond and Ray et al. (1964)** suggested that the product temperature should be 10°C to 20°C above MFT of the polymer dispersion in order to achieve sufficient water evaporation and complete film formation.

33. **Salako and coworkers et al. (1998)** showed the effect of hard and soft pellets made by various materials. Pellets of microcrystalline cellulose had less brittle nature than that of
softer pellets made by GMS. This effect could be due to formation of coherent nature of deformable materials within the pellets.

34. **Schmid et al. (2000)** found that tackiness problems can occur at high coating temperatures as a result of interaction of drug and spray dispersion ingredients during pelletisation process.

35. **Schwartz et al. (1994)** recommended that altering components of uncoated pellets can change the compaction pattern of the formulation. This will include uneven size of pellets that will help to avoid the segregation of the coarser pellets during blending and during compression cycle in the turret of compression machine.

36. **Wagner and co-workers et al. (2000)** worked on the nature of microcrystalline cellulose (MCC) to be used as a tableting Excipient. He found that when compacting reservoir pellets, in vitro drug release was altered when used powder grade of microcrystalline cellulose whereas granules of MCC showed no effect on drug release. But also suggested to use MCC as a powder in the case of less flexible polymers.

37. **Wagner and co-workers et al. (2000)** studied on the proportionality of pellets and other Excipients. When used 70 % w/w pellets of tablet content, it showed rupture of the coating. So he suggested to use NMT 60 % w/w pellets of the tablet contains to fulfill drug release requirement.

38. **Wagner et al. (2000)** studied on various acrylic polymers and ethyl cellulose films. He found that films made up of acrylic polymers and PVA are more elastic in nature, thus ideal choice of the multiunit particulates tablet. Eudragit polymers were found to be forming very flexible film on pellets with respect to those had to be compressed into multinunit particulate tablets.