2 LITERATURE REVIEW

1) Sirisha V K et al., (2012) discussed advantages of pellets in tablet form over pellets in capsule. The pellets compressed to pellets called as multi unit particulate system (MUPS) tablet. MUPS tablets are tamper proof and better stability than capsules. It is easy to swallow, cheaper than capsules, didn't lost modified release property on splitting which made flexible dosage form and easily passed through upper GIT so no risk of dose dumping hence less intersubject variability . Manufacturing of MUPS tablets is a challenging task like pellets has electrostatic charges leads to uneven distribution in blend, changes the release profile after compression, during compression coated pellets fused which resist the tablet to disintegrate.

There are two types of MUPS tablets. One is matrix MUPS tablets in which drug is mixed with polymer and entrapped the drug while second is MUPS reservoir tablets in which pellets coated with drug followed by polymer to control the drug release. There are four stages involved in compression of pellets - Deformation of coating layer, densification of polymeric coat, fragmentation and attrition of pellets. The deformation depends on composition of pellets and extragranular excipients used for compaction.

2) Dashevskya A et al., (2004), developed pellets with various aqueous polymer and compressed to tablet. The polymers were Kollicoat SR 30D, Kollicoat EMM 30D, Kollicoat MAE 30 DP. The drug loaded pellets of propranolol HCl coated with Aquacoat ECD 30, and triethyl citrate (25% w/w) and compressed. The release was increased with compression force increased and more pellets damage due to compression. The film of Aquacoat® ECD 30 with plasticizer was brittle and weak and has low elongation and puncture strength. Kollicoat® SR 30D not required plasticizer. Drug release was similar with Kollicoat® SR 30D coated without a plasticizer pellets like Aquacoat pellets after compression. At 10% TEC in Kollicoat SR 30D showed same drug release profiles at varied compression forces due to mechanical properties improved. Drug release increased with 1:1 ratio or pellets to Kollidon CL-M while release decreased with Kollidon VA 64.

In conclusion, Kollicoat® SR 30 D was the best suitable polymer to avoid rupture of pellets during compression and no effect on dissolution compared with pellets while
Aquacoat® ECD 30 has tendency to rupture the pellets and altered the dissolution profile. In Kollicoat® SR 30 D, film flexibility improved by addition on 10% w/w of TEC and compression had no impact on drug release.

3. Bashaiwoldu A B et al., (2011) studied the impact of compression of coated pellets on tablets properties and release behaviour. Paracetamol was model drug and pellets were manufactured by extrusion-spheronization method. Paracetamol, MCC, MCC LM and GMS in various proportion granulated with Water, ethanol and glycerol in various ratios. Film coating performed in bottom spray FBC using Surelease (Ethylcellulose dispersion). Surelease was heated to 60°C prior coating start. Three different weight gain samples were removed i.e. 10, 20 and 55%. Pellets were compressed at desired compression force. Pellets of with and without coated analyzed for dissolution in water at 100 rpm and SEM to study the fracture surface of pellets. The use of Avicel LM grade in pelletization found more brittle pellets. In summarized, the compressibility of pellets is depend on excipients nature and binder. Deformation of pellets depends on compressibility and shear strength of pellets.

4) Abbaspour M R et al., (2008) developed SR oro-dispersible tablets of ibuprofen from pelletization technology. The study was conducted with 4:1 ratio of Eudragit RS30D : Eudragit RL 30D and various concentrations of TEC. The coating was performed in FBC at outlet temperature of 25–35 °C for 250-300 micron coat thickness. The coated pellets were cured at 40°C for 24 hour. A two factors at three levels design was selected where quantity of Avicel, ratio of PVP XL/ PEG were the factors while hardness and disintegration time were the dependent variables (responses). The levels of percentage of Avicel and ratios of PVP XL/PEG were studied at 20-50-80% and 0/1-1/1-1/0 ratio. Tablets containing various percentage of pellet and filler blend were prepared with maximum compression force of 5, 10, and 15 kN and at fix compression speed. The tablets were testing using USP I/ pH 7.2 phosphate buffer/100rpm.

As coating level increased, drug release decreased significantly. In the case of 5% coating release of ibuprofen was up to 24 h was achieved, while 10% and 15% coating showed slow drug release about 40-50% up to 24 h. Disintegrating effect of MCC was dominant when ratio of PVP XL to PEG was high while when ratio was low, effect of MCC was less. Hence MCC had major role in disintegration time.
Tablet disintegration time, friability and hardness increased when pellets content changed from 60 to 80%. The hardness increase by using granular filler. Curing to pellets had no effect on pellets elasticity and yield point. Sustained release profile up to 24 h was achieved by 5% coating level.

5) Pagariya T P et al., (2013) prepared SR pellets has floating nature of Alfuzosin HCl. He used microcrystalline sphere for the for study and applied three coats - Alfuzosin HCl coat, sodium bicarbonate and Hydroxypropoxy methylcellulose (E5 LV) - Sodium bicarbonate as effervescent layer and Kollicoat SR 30D to entrapped the carbon dioxide gas. Two factors at three level design was selected for research. Hydroxypropoxy methylcellulose to Sodium bicarbonate ratio and polymer, Kollicoat SR 30D were selected as formulation factors. The formulation prepared at level of 1:4, 1:1, and 2:1 ratio of Hydroxypropoxy methylcellulose to Sodium bicarbonate ratio and 10%, 20% and 30% levels of Kollicoat SR 30D. Drug loading performed on MCC spheres with Alfuzosin HCl and polyethylene glycol 6000 in water using fluidized bed coated. Second layer coated at 12% w/w level and third layer with Kollicoat SR 30D and 10% triethyl citrate of Kollicoat SR 30D as per level in experimental design. The responses were selected as time required to float and drug release at 10 hours. The pellets were evaluated for SEM, floating study, drug release study and stability studies. From the study it was concluded that floating ability of pellets depended on level of Hydroxypropoxy methylcellulose to Sodium bicarbonate ratio and Kollicoat SR 30D level. The pellets floated in 5 minutes and remained floated for next 10 hours. The optimum formulation contained 1:4 ratio of Hydroxypropoxy methylcellulose to Sodium bicarbonate, 10 percentage of Kollicoat SR 30D and results found 4 minute 16 seconds time required to float and 92.85% of release in 10 hours.

6) Wagnera K G et al., (2000) developed MUPS tablet of delayed release bisacodyl pellets, He used Eudragit FS 30D as enteric coating polymer. The drug loaded pellets were prepared by bisacodyl, binder as Eudragit L30D, talc (as anti-tacking agent) and triethyl citrate (as plasticizer) coating on 850-1000 micron placebo pellets in FBC. The delayed release coated using Eudragit FS 30D along with glyceryl monostearate, TEC and Tween 80. Four pellets formulation were prepared in combination of 12.5 and 25% of Eudragit FS 30D and 5 and 10% of TEC. The lubricated blend contained
enteric coated pellets, Avicel PH 101, MCC granules, Kollidon CL, talc, Aerosil and magnesium stearate in various percentage. The percentage of pellets varied 60% and 70%. The lubricated pellets blend compressed using 10 mm FFBE punch tooling using tablet press at various turret speed i.e. 26, 50, 75 an 100 rpm and compression force at 10, 15 and 20 kN. The uniform pellets distribution was observed using Avicel formulation at all turret speed while using MCC granules poor variation was observed at high speed. The dissolution study was performed as per USP monograph. Stage I dissolution was carried out in simulated gastric fluid for 2 hours where drug release should be less than 10% and stage II dissolution was performed in buffer pH 7.2 for 45 min where drug release should not less than 80%. The tablets also evaluated for disintegration time, hardness and content uniformity. Elasticity of Eudragit FS30D was 50% with 5% of TEC while 6 fold increased when TEC percentage increase to 10%. Only sufficient TEC percentage in polymer would not increased the film elasticity however thickness of polymeric layer contributing to increase the elasticity. In conclusion, Avicel PH 101 was the best filler for MUPS formulations. Eudragit FS 30D was the best enteric coating polymer for delayed release formulation required drug release in the large intestine. Eudragit FS 30D also has good elasticity at low percentage of TEC compared to other enteric coating polymer. At 70% of pellets level, pellets ruptured during compression and failed in stage I dissolution. However at 60% of pellets level, tablet passed all physical and chemical tests.

7) Chamsai B et al., (2013) prepared idomethacin fast disintegrating pellets using MCC to improve dissolution. Indomethacin has poor water solubility hence issue of poor dissolution. Only MCC would not improve the dissolution hence various solubility enhancers and disintegrant used. Pellets were prepared by extrusion-spheronization technology. Granulation was prepared by indomethacin, MCC at various ratio (from 50-80% w/w), and croscarmellose sodium (0-10% w/w) and granulated by polysorbate (0-10% w/w), polyethylene glycol 400 (0-10% w/w), purified water and ethanol. The extrudes were prepared using .5mm screen and pellets were prepared using extruder at 500 rpm plate speed for 3 min. The pellets were characterized for disintegration test, friability, dissolution, morphology, mechanical strength and specific surface area. The dissolution test performed in 0.1N HCl in disintegration apparatus with 500 micron mesh cloth at the tube using 100mg pellets. The aseptic ratio of pellets found 1.04-1.07 when concentration of PEG 400 and
Tween 80 was 10% w/w. Porous pellets prepared due to PEG 400 and Tween 80 while due to croscarmellose sodium cavities formed in the pellets. Pellets only with MCC not disintegrated in 30 min while pellets with PEG 400 or Tween 80 disintegrated in 90 sec. Combination of PEG 400 and Tween 80 in pellets reduced the disintegration time to 20 sec. Pellets manufactured using croscarmellose sodium, PEG 400 and Tween 80 showed the disintegration time to 5 sec. The mechanical strength of those pellets also less compared to other pellets and finer particles formed during disintegration test and dissolution test which enhanced the dissolution.

8) Tunón A et al., (2003) studied the impact of excipients on compaction of reservoir pellets. Salicylic acid (SA) was selected as a model drug. SA and MCC mixed in mixer and granulating using various proportion of water to ethanol ratio (25:75 to 100:0) and various granulation liquid to powder ratio (0.8:1 to 1.1:1). The wet mass immediately passed through the extruder using 1.2mm screen. The pellets were dried at ambient temperature for 3 days and coated with ethanolic solution of ethylcellulose. The coated pellets were lubricated with MCC (2% w/w of pellets) and magnesium stearate (0.5% w/w of pellets). The blend was compressed using tablet press and 11.3mm FFBE punch tooling. Due to compression, extensive densification and deformation of pellets occurred which retarded the drug release. The mode of deformation was critical for pellets for the change in drug release due to compression. Small particles acts as protective while large particles affected negative on drug release. Structural changes was happened in coating due to compression which changed the drug release profile.

9) Naikwade S R et al., (2009) prepared piroxicam enteric coated pellets by polymer matrix and polymer coating method. The evaluated three polymers i.e. Eudragit L100, HPMC phthalate and CAP. The ratio of MCC and DCP was evaluate and 100:0 ratio was finalized. In extrusion spheronization method, MCC (4 times of piroxicam) and piroxicam was granulated using PVP (5% w/w). The wet mass pass through extruder and spheronised at 1400 rpm for 4 min. In matrix pelletization method, piroxicam granulated with polymer using IPA and extruded followed by spheronised at 1400 rpm for 4 min. In coated approached pellets, uncoated pellets coated with Eudragit L100 (5-8-10%), HPMC phthalate (5-11-15%) and CAP (5-10-15%). The formulation contained 2:3 ratio of drug to polymer showed satisfactory
release in acidic media however failed in pH 6.8 buffer which was not complied USP. When sodium lauryl sulphate, and croscarmellose sodium pregelatinized starch added in same formulation, dissolution passed in both acidic and pH 6.8 buffer media. Total 10% and 8% coat of Hydroxypropoxy methylcellulose phthalate and Eudragit L100 required respectively for controlled drug release in pH 6.8 buffer. Piroxicam enteric coated pellets successfully manufactured by both the method i.e. polymer matrix and polymer coating, however polymer coated had less friability.

10) Beckert T E *et al.,* (1998) prepared disintegrating tablet from bisacodyl enteric coated pellets. The pellets were prepared by bottom spray FBC process. The bisacodyl dispersed with Eudragit L30D-55 and 10% of TEC in water and coated on sugar spheres. Tablets were compressed using different extragranular excipients. Avicel granules were prepared by using Kollidon 30 as binder in planetary mixer. Dicalcium phosphate granules prepared by anhydrous dicalcium phosphate lubricated with magnesium stearate. Blend of bisacodyl pellets (in various percentage), 4% w/w of Kollidon CL, extragranular excipients (or placebo granules) followed by magnesium stearate was prepared. In 10% w/w pellet formulation RSD of tablet weight was not within limit due to segregation occurred due to fine powder. In 30% w/w pellets formulation segregation noticed when pellets mixed with fine or coarse diluent compressed to tablets however with larger mean particle size of diluent better uniformity observed. In 50% w/w pellets formulation good mass uniformity was observed with granules or coarse excipients. In 70% w/w pellets formulation unstable tablet was prepared with DCP granules due to low binding property of dried granules however only mixture with Avicel Ph 101 showed high RSD. Avicel PH 102 was the good excipient for preventing the segregation due to ability to fill the void space between pellets.

11) Mehta S *et al.,* (2012) developed starch based multiparticulate tablets to study effect of various disintegrants on tablets parameters. Pellets were manufactured by extrusion-spheronization technology. A four factors at 2 levels design was applied where % of starch pellets, conc of extragranular disintegrant (4-8), compaction force (5-15kN) and type of extragranular disintegrants were the factors and physical parameters of tablet were the responses. Total 33 experiments were performed. The wet mass for extrusion prepared in mixer of dry mix of lactose, MCC, disintegrants
(8%) and PVP K30 (4%) as binder. The wet mass passed through extruder. The fraction of 710-1000 micron collected for next step. The granules of excipients was prepared using lactose (33.5%), MCC (54.5%) and disintegrant (8%) any from three taken in design experiments, in mixer using PVP K30 (4%) as binder. Granulated the dry mix in 15 min and dried. The fraction of 710-1000 micron granules same as starch pellets were taken. The starch pellets and excipient granules along with silicon dioxide, extragranular disintegrant as per design and SSF were mixed in blender. the granules and pellets were characterized for friability image analysis, porosity and bulked and tapped density. The tablets were compressed at tablet press using 17.1 X 8.2 mm oblong punch tooling.

The results explained that lower percentage of starch pellets and higher compaction force leads to lower friability (<1%), lesser disintegration time (<3 min) and high value of hardness. Granules prepared using polyplasdone had low friability and low porosity while tablets containing polyplasdone were hard.

12) Tunon A et al., (2003) studied the impact of intergranular porosity on reservoir pellets drug release behaviour on compaction. Salicylic acid (SA) used as model drug for study. The pellets of SA prepared by extrusion spheronization method by taking 1:9 ratio of SA: MCC. The pellets were prepared on spheronizer at plate speed 800 rpm for 3 min. The fraction of 710-1000 micron pellets were collected for coating. various types of pellets were manufacture using 100:0,50:50 and 25:75 proportion of water and ethanol, and 1:1, 0.9:1 and 0.9:1 proportion of granulation liquid and powder. The pellets were characterized for specific surface area, porosity, bulked density and drug release. Sustained release coating was applied of 5% ethanolic solution of ethylcelluose for 10-15% weight gain. The EC coated pellets blend compressed at 500mg tablet weight. Pellets from tablets separated by gently shaking tablets in petri dish and these pellets were characterized for thickness, porosity, drug release, shape and surface area. From the results, it was revealed that coating has not affected compression nature. Due to pellets compaction, porosity of pellets affected and deformation magnitude which impacted drug release at minor level. In pellets with low porosity, effect of compaction of release was showed however less impacted the deformation degree and densification. It would be concluded that pellets porosity is the prominent factor and should consider during design of formulation to optimized
the drug release and robust formulation. Coating only contributed in deformation and densification of pellets.

13) AlHusban F et al., (2011) developed oro-dispersible multiunit particulate system of omeprazole by lyophilized technology. He used readymade enteric coated omeprazole pellets (8.5% w/w). The central composite design (CCD) was applied for systematic study. Concentration of gelatin, alanine and carrageenan used as formulation variables (factors) while hardness, disintegration time, pH and viscosity were responses. The lyophilized tablets were prepared by dissolving gelatin at 40°C then carrageenan added for clear solution and then add alanine. The dried tablet characterized for viscosity, pH, disintegration time, mechanical properties, density, drug content and drug release. The viscosity and disintegration time were impacted due to interaction between carrageenan and gelatin due to hydration which formed complex of strong strength which governed the viscosity and resisted the tablet to disintegrate. Hence carrageenan and gelatin, and interaction of both were the potential factors. Alanine and gelatin concentration increased hardness of tablet increased. The target kept for optimized formulation was minimum disintegration time, maximum viscosity and hardness.

14) Shimizu T et al., (2003a) developed fast disintegration tablet (FDT) of lansoprazole and optimized the polymer concentration to reduced cleavage of pellets during compression. They prepared drug loaded pellets by suspension loading method. In drug load, along with lansoprazole, lactose-MCC pellets, magnesium carbonate, low substituted HPC, HPC used. Seal coating of HPMC applied on drug loaded pellets. Enteric coating contained Eudragit L30D-55 as enteric coating polymer, Eudragit NE30D as flexibility of enteric polymer, TEC and talc or glyceryl monostearate (GMS). The ratio was studied as 10:0, 9:1, 8:2 and 5:5 ratio and varied the concentration of TEC as 10, 15, 20 and 30%. In enteric coating talc was replaced with GMS due inorganic nature of talc which damaged the enteric coating at higher concentration. So concentration of GMS also optimized in the range of 3-5% of TEC. The lansoprazole FDT was prepared from the blend of enteric coated pellets, L-HPC LH-33, mannitol, MCC, crospovidone and magnesium stearate. The optimum film flexibility of enteric coat was achieved by 9:1 ratio of Eudragit L30D-55 to Eudragit
NE30D and by 20% of TEC addition. As concentration of TEC increase above 20%, agglomerates formation increased. At 20% TEC level and 5% of GMS, less agglomerates formation reduced.

15) Shimizu T et al., (2003b) optimized ratio of Eudragit L30D-55 to Eudragit NE30D and TEC concentration but TEC found incompatible with lansoprazole and bitter taste hence other plasticizer i.e. PEG 6000 was used. They developed enteric coated lansoprazole pellets by seven layers - 1) Lactose-MCC pellets, 2) Drug coat, 3) Barrier coat, 4) first enteric coat, 5) second enteric coat, 6) third enteric coat, and 7) cushion coat. The concentration PEG 6000 varied from 15 to 30mg in first and third enteric coat. The 30mg of PEG 6000 in first and third enteric coat had same flexibility that of enteric coat without first and third coat and with TEC.

In conclusion, TEC contributed to increased the flexibility of Eudragit L30D-55. However bitter taste overcome by repacing TEC with PEG 6000. They used PEG 6000 in first and third enteric coat and found stable formulation. So final formulation had seven layers.

16) Shimizu T et al., (2003c) developed optimized lansoprazole FDT by studying various percentages of pellets in tablet and adding suitable excipients helped for better mouth taste. The three levels of enteric coated pellets were studied i.e. 37.5%,47.4% and 64.3% w/w. They also used new grade of low substituted HPC i.e. LH-33 has less percentage of hydroxypropoxyl group (i.e. 5.0-6.9%) and has no rough texture. It used as binder and disintegrant. The 47.4% w/w concentration of enteric coated pellets was finalized because of that concentration of pellets tablets had good strength, disintegration less than 30 sec in mouth and passed dissolution criteria.

17) Tan X et al., (2015) summarized factors involved in development of multiunit particulate system (MUPS) tablets. Formulation factors are pellets core, composition of core, porosity, PSD of core, in coating covered polymers, plasticizers and coating thickness and in extragranular part covered tabletting excipients. Pellets core should have good elasticity and toughness. Due to deformation degree increased of MCC containing pellets core distance between pellets decreased and which improved the tablet hardness. Low porosity pellets has less space to restructured after compaction and ruptured the functional coat leads to change the drug release. However, high
porosity pellets absorbed the compaction shocks and restructured internally and functional coat remained unchanged. Coating polymer selected based on the target of drug release. For enteric coating formulation, Eudragit L30D-550is the best polymer but it is brittle in nature so additional polymer like Eudragit NE30D required to increase the flexibility of coating. Triethyl citrate is the best plasticizer for Eudragit L30D-55 and other Eudragit polymers. In some cases PEG 6000 and polysorbate 80 also used as plasticizer. Thickness contributing major role to avoid rupture of pellets during compression along with film elasticity enhancer and plasticizer. Tabletting excipients also called as cushioning excipients used to avoid cleavage of pellets during compression. The excipients are such a that mean PSD and bulked density matched with pellets.

In technological factors, coating parameters and tableting parameters involved. polymers like ethylcellulose required curing due high Tg value. If improper film formed of ethylcellulose based coated pellets, it changed the drug release profile. Process parameters like spray rate, atomization air pressure and air volume decide the quality of pellets. Tablets parameters like main compression force and turret speed are the major variables affect on drug release and content uniformity respectively.

18) Rujivipat S et al., (2012) studied the effect of high humidity exposure to pellets which compressed to tablet. In study, various enteric coating polymer used like Eudragit L30D-55, Eudragit S100, AQQAT AS-MF and CAP. The drug loaded pellets was performed in FBC using PEG 4000, HPMC and ethanol. The enteric coating performed using Eudragit L0D-55 and 20% of TEC in FBC and 10,20 and 30%weight gain pellets samples collected. The pellets were exposed to 0% RH, 52% RH, 75% RH and 84% RH, 95% RH and 100% RH for 3-24 hour and 1 month. Moisture content calculated of before and after exposed pellets. Tablet compressed of exposed and non-exposed pellets blended with Avicel PH 200 and magnesium stearate. The tablet compressed using 10 mm FFBE punch tooling at 15kN compression force. The dissolution of tablet performed in 0.1N HCl followed by pH 6.8 buffer.

Moisture exposure had less impact on other enteric coating polymer on mechanical properties while Eudragit L30D-55 had significant impacted. Elongation of Eudragit L30D-55 was 3% at dried state which changed to 140% due to moisture exposed.
Pellets exposed at 84% RH has comparable drug profile that of uncompress and compressed pellets but tableting properties improved like tablet crushing strength and deformation. When pellets exposed to 75% to 84% RH, Tg decreased significantly below compression temperature. In conclusion, pellets compression characteristics can be improved through plasticization of pellets where brittle coat formed due to brittle polymers like Eudragit L30D-55.

19) Nikowitz K et al., (2011) prepared diltiazem pellets by layered technology. The drug loaded pellets prepared in Wurster. Diltiazem HCl and Kollidon 25 solution in the ratio of 5:3 of 40% solid content loaded on Cellent 500 seeds. Functional coating did with Acryl-EZE dispersion. The samples was removed of different weight gain. The pellets were characterized for thickness, SEM and drug release. The dissolution performed in USP I/1000ml simulated gastric fluid/100 rpm/2 hr followed by USP I/1000ml pH 6.8 buffer/100 rpm/90 min. The gastric resistance was observed at 13% weight gain and about 30 micron coat thickness of Arcyl-EZE which very less quantity required than Eudragit based coating. In conclusion, Acryl-EZE was suitable delayed release polymer for pellets without using additional ingredients.

20) Debunne A et al., (2004) studied the impact of formulation variables and process variables on in vivo study and tablet parameters. Piroxicam was the model drug for study. The drug pellets were prepared using piroxicam, MCC, Sodium CMC. The pellets were coated with Eudragit L30D-55 and Eudragit FS 30D in various ratios i.e. 100:0, 70:30, 60:40 and 40:60. The pellets mixed with cushioning pellets and Kollidon CL ingredients and compressed using 12 mm FFBE punch tooling at compression force 10-30 kN. The D-optimal design was applied where Eudragit L30D-55 to and Eudragit FS 30D ratio, % weight gain, Piroxicam to cushioning waxy pellets ratio and compression force were factors while hardness, disintegration time, friability and dissolution in 0.1N HCl were the responses.

In conclusion, waxy cushioning pellets protected the enteric coated pellets of piroxicam during compaction without impact of film thickness or flexibility. The tablet administered to dogs and tested for 72 hours and found that pellets and tablets delayed the onset action of piroxicam in plasma but extend was same as immediate release formulation. hence disintegration time of tablet not affected the onset action of piroxicam.
21) Pai R et al., (2012) developed matrix MUPS tablet of Sertraline HCl by extrusion spheronization technology. They used various polymers for study i.e. Eudragit L30D-55, Eudragit NM 30D, Aquacoat ECD and Sodium Alginate. Sertraline HCl, MCC and HPC (wherever required) mixed in RMG and granulate using polymer dispersion. Prepared spherionised at 850 rpm for 415 sec. The wet pellets dried at 50°C inlet temperature and taken fraction of 20 mesh and 40 mesh sieves. The sized pellets mixed with MCC, PEG 6000, crospovidone and magnesium stearate. The pellets were compressed at tablet press with compression force of 2-6 kN and hardness in the range of 80-240N. The tablet were characterized for hardness, disintegration test, dissolution and content uniformity. The pellets content was studied from 30-40% and found no impact on dissolution. But tablets containing 60% and more pellets contained failed for disintegration test. Avicel PH 102 used in extragranular to improve the blend flow but it failed in acceptance value. Avicel PH 102 replaced with Avicel PH 101 or milled Avicel PH 102 and found reduced acceptance value within range. The pellets wet mass passed through 1.0, 1.2 and 1.5mm aperture screen of extruder. The pellets were dried and blended with extragranular excipients. The tablets of different pellets size had no impact on dissolution but as pellets size increased, acceptance value also increased due to pellets segregation in blend.

22) Riis T et al., (2007) developed mini matrix tablets of extended release application of weakly acidic drug and poorly soluble. Polyvinyl acetate/polyvinylpyrrolidone used as a matrix former. Addition of sodium citrate and sodium carbonate (water-soluble salts of weak acids) not helped to reached pH-independent 8-PN release. Magnesium hydroxide and magnesium oxide (water insoluble salts of a strong base) improved the drug release at pH 1.0 up to 10 hours.

23) Pan X et al., (2010) developed novel compaction technique to prepared MUPS tablet. Doxycycline HCl selected as model drug. The drug loading was performed in FBC with PVP K30 as binder in water. The drug loaded pellets with HPMC E3 as barrier coat. Seal coated pellets coated with Eudragit L30D and Eudragit FS30D in the ratio of 1:2 with 5% of talc and 5% of GMS of 20% w/w solid content. The product temperature was maintained at 30°C. The 250-300 micron fraction was selected for next step. The enteric coated pellets were coated with MCC, PVPP,
mannitol, lactose, starch 1500 and sodium alginate using 5% w/w of PVPK30 in 1N HCl in centrifugal granulation with control binder spray and powder feed. The pellets were dried at 40°C/24 h in oven. Fraction of 300-420 micron were used for further study. The cushioning granules were prepared from MCC and PVPP in the ratio of 9:1 in granulator using 10% of PVP K30 as binder. The fraction of 250-300 micron used to prepared tablet of original pellet and fraction of 300-420 micron were collected for tablets of pellets containing granules. The ingredient of cushion granules were used for granulation by FBC and fraction of 250-300 micron and 300-420 micron was collected.

Due to granulation of pellets, surface of coated pellets changes and made pellets rough which increased the flow and flow properties close to cushioning granules. Content uniformity and weight variation of tablets manufactured by pellets containing granules was lower than tablets manufactured by coated pellets.

24) Lin X et al., (2011) used novel cushioning agent to reduced the coated pellets cleavage during compaction. The lactose (Pharmatose 80) was milled in jet mill at 0.4Mpa pressure and at 5,000 and 18,000 rpm of wheel to collect micronized lactose (ML) particles in the mean range of 2 and 10 micron respectively. The polymers were HPMC E3, HPC EF and PVP K17 used at various levels. The saturated dispersion spray dried at 160°C inlet temperature. The spray dried material characterized for particle size distribution, X-ray diffraction, flowability, density, compressibility, SEM and moisture content. The drug loaded pellets were prepared by Chlorpheniramine maleate (CPM), HPMC and Plasdone C-15 dispersion. The pellets blend content 50%. The blend compressed using 15 mm FFBF punch tooling at 5kN compression force. The tablets were characterized for dissolution, disintegration and hardness. Micronized lactose effectively protected pellets coated with ethylcellulose. Spray dried lactose slightly reduced cushioning effect. HPC was found most effective to reduced the yield pressure, improved the compressibility and cushioning effect. In all cased, 15% polymer needed for improvement.

25) Lecomte F et al., (2004) studied plasticizers were triethyl citrate (TEC) and dibutyl sebacate (DBS). The propranolol HCl used as model drug. The drug loaded pellets coated with ethylcellulose and Eudragit RL in the ratio of 100:0, 75:25, 50:50, 25:75 and 0:100 w/w. The film coatings characterized for water uptake, mechanical
resistance and weight loss behavior to understand the mass transport mechanisms. It was revealed that drug release depend on typed of plasticizer nature of the plasticizer played important role on drug release mechanisms. TEC easily leached out and reduced the film mechanical resistance and crack formed also significantly increased the water uptake. However, in DBS has less affinity for Eudragit RL and high for ethylcellulose resulting uniform redistribution of plasticizer in polymeric system and change the release profile. That effect could overcome by cured the pellets at appropriated condition and proper coating dispersion preparation technique.

26) Kambayashi A et al., (2014) studied the biorelevant media dissolution of diclofenac capsules (Diclo-Puren, commercially available pellets in capsule formulation) which is poorly soluble to understand the pharmacokinetic profile. The pellets exposed in 250 ml FaSSGF medium at 75 paddle rpm for 30 min. The pre-exposed pellets used for FaSSIF-V2.

27) Schmid W et al., (2009) studied on various alginate grades and their impact on the tabletting properties. The study involved total seven grades of alginate i.e. two potassium alginate grades and five sodium alginate grades. The grades had different ratio of guluronic acid and mannnuronic acid and main aim was to study the impact of these acid ratio on tablet compaction. Bisacodyl was the model drug. Dry mix of bisacodyl, MCC and lactose granulated with water in granulator and extrude though extruder 0.6 mm screen aperture. The extrude pass through spheronizer and dry the pellets. The fraction of 425 micron and 630 micron were collected and performed enteric coating of Eudragit L30D-55, GMS, polysorbate 80 and polyethylene glycol dispersion on sized pellets. The fraction of 500 micron and 630 micron pellets were collected. The blend of enteric coated pellets (40% w/w) with different alginate grades were prepared. The tablet compressed at tablet press. The tablets and pellets from tablet were characterized for dissolution test, SEM, hardness. The compression behaviour of sodium alginates depended on composition of alginate. The higher elasticity of material was more suitable for tabletting compared to plastic material.

28) Johansson B et al., (2001) studied impact of MCC granules and pellets on compression. The 3 porosity type of MCC granules were prepared of same fraction. The pellets were prepared by extrusion-spheronization method. The compression
behaviour was studied for retrieved pellets/granules. Mostly complete permanent deformation was observed in tablets.

29) Hamedelniel E I et al., (2011) developed matrix pellets of Atenolol by extrusion-spheronization to increased the bioavailability. It was concluded that water or combination with other solvents were sufficient for the preparation of pellets from the mixture of ethylcellulose, MCC and Atenolol. Ethanol used in wetting liquid decreased the dissolution but reduced the breaking strengths of coated pellets. To increase the bioavailability of Atenolol form pellets, alkalizing components i.e. anhydrous Na2HPO4 and Na3PO4 used. Na3PO4 was the best alkalizing agent for satisfactory shape parameters. At highest amount water level in wetting agent resulted compact nature pellets, smooth surface and desired hardness achieved. MCC formed gel-like structure and the water-soluble Na3PO4 gone through rapid recrystallization, resulted strong solid bond form with other particles. alkalizing component increase the pH by giving the microenvironment and hence increased dissolution.

30) Mota J et al., (2010) investigated impact of various on reservoir pellets. Paracetamol is sparingly soluble and release from was independent of type of core either sugar or MCC spheres, paracetamol diffused through coating. Freely soluble drug and charged propranolol HCl release affected by type of core. The release was faster with MCC spheres due to swelling of core which is not in sugar spheres. Very soluble drug and charged metoprolol tartrate has release from coated MCC and sugar spheres found identical. The drying effect on release of MCC and sugar spheres was studied. Core dried at various temperature from 40° to 60°C. Drying of core had affect of release profile for pellets coated some polymer but Kollicoat SR 30 D and non aqueous ethylcellulose coated pellets was unaffected.

31) Gutsche S et al., (2010) innovated new pelletization technique using biopolymers. Ionotropic gelation method was used for encapsulation of verapamil model drug. Dripped the drug in sodium alginate solution in CaCl2 solution to get spherical beads of high encapsulation efficiency and high drug load. During drying, pellets shrieked and approximately 10% drug loss due to dehydration. prevented by using magnesium chloride to the medium of gelation to made uniform polymer
structure which prevent drug loss. However, pellets prepared had low hardness and this was the disadvantage over extrusion-spheronization technology.

32) Pašić M et al., (2008) studied to improved the stability of lansoprazole enteric coated pellets. Pellets were developed by suspension/solution loading and direct pelletization in rotor technology. Suspension/solution loading method found lengthier than direct pelletization so direct pelletization method finalized for preparation of lansoprazole pellets. Sugar core found better than MCC core based on lower porosity and good shelf life of sugar core. Barrier coat was applied to drug loaded pellets. The 20% w/w weight gain of enteric coating polymer was stable compared to other higher weight gain pellets. Lansoprazole has better solubility in higher pH so microalkaline environment provided to lansoprazole in drug coat which improved the stability of pellets.

Direct pelletization involved spray rate, rotor speed and inlet-air humidity were process variables. Based on the experimental design results it was cleared that high spray rate with lower rotor speed had a positive effect on pellets size. Optimum formulation process parameters had spray rate 10 rpm, rotor speed 50% and 16% w/w drug load to get 911 micron pellet size.

33) Kan S et al., (2014) developed enteric coated pellets based on QbD approach. The wet mass for extrusion prepared from naproxen, PVP, MCC, GranuLac 200, Sodium CMC and polysorbate 80 by granulation with water. The wet mass passed through extruder followed by spheronizer. Dried pellets screened through 24 and 30 mesh and 24-30 mesh fraction used for further study. Naproxen loaded pellets coated with Eudragit L30D-55, TEC, Polysorbate 80 and GMS. The pellets were coated in Wurster. The pellets were characterized for dissolution in simulated gastric fluid for 2 hrs at 50 rpm followed by pH .8 phosphate buffer for 45 min at 50 rpm. The fish bone diagram covered formulation variable, process variables, people variables, equipment variables and environment variables and enteric coated pellets CQAs. The FMEA, risk assessment tool was applied to decided to more potent variables. The Plackette Burman design was applied for selective formulation and process variables, those were TEC percentage, GMS percentage, spray rate, atomizing pressure, batch size, coating solid content and coating weight gain, curing time while acid resistance and drug cumulative release were the responses. Total 12 experiment performed and
interpreted the results and found coating solid content, TEC percentage and GMS percentage had potential impact on independent variables. The Box-Behnken design was applied for coating solid content, TEC percentage and GMS percentage factors. Total 15 experiments were performed. The results were interpreted and design space was created from software giving not more than 10% limit to acid medium dissolution and not less than 80% limit to pH 6.8 buffer medium dissolution. Based on software feed data control strategy defined.

34) **Bendas E R et al., (2010)** developed novel technique for compaction of coated pellets to tablets to achieved release profile same for compressed tablets and pellets before compression. Mesalamine has absorption window in colonic region. The drug pellets were manufactured by extrusion-spheronization method. The lubricated blend for compression contained enteric coated pellets or additional gelatin coated pellets, Explotab and stearic acid. When additional coating of gelatin was applied then only 5% of Eudragit L100-55 weight gain required. Additional gelatin coating provided additional protective coat to enteric coated pellets to absorb the shocks of compression force during tablet preparation. The dissolution profile matched of uncompressed pellets and pellets compressed to tablet. The release of mesalamine capsule in acidic media was 0.3% and after extended for next 1 h in pH 6.0 release was 0.37% and 89% drug release was observed in pH 7.2.

35) **Xu M et al., (2015)** developed dissolution method to study profile if individual pellets. For this study USP apparatus 7 was used to perform dissolution of single pellet by DoE approach. The drug loaded pellets of metformin prepared from mixture of drug, MCC and lactose followed by ethyl cellulose coat in various weight gain i.e. 8 and 10% w/w. The dissolution of pellets performed in apparatus 1 and 2 however pellets were floated and confounded drug release profile was occurred. Hence, actual drug release from single pellet couldn't characterized in apparatus I and II. So there was limitations of apparatus 1 and 2 for dissolution of single pellet while dissolution in apparatus 7 found accurate and precise for different weight gain. The dip interval and speed of apparatus 7 (reciprocating holder) were critical operational variables which affected on release profile of sustained release individual pellet. The dissolution of single pellet was successfully performed in USP apparatus 7 (reciprocating holder) without odd observations like floating and agglomerates.
36) Sagale L et al., (2015) prepared celecoxib delayed release pellets using calcium alginate. Drug dissolved in self-emulsifying phase in calcium alginate pellets. The target was to dissolve the drug above pH 7 means in in vivo in colonic region. The impact of formulation and process variables were studied. Microscope images explained the pellets were dried and spherical. DSC study explained the absent of crystalline form drug. The swelling behaviour of pellets was independent on formulation and process variables rather swelling was pH sensitive. All formulation showed complete release in pH 7.4 and decreased the release in lower pH. At pH 7.4, the rate and extend of drug release reduced considerably as concentration of cross-linking agent increased.

37) Štefanič M et al., (2014) predicted the in vivo performance of lansoprazole delayed release pellets in fasted condition using USP dissolution apparatus 4 (flow-through cell). During dissolution, flow rate of biorelevant medium maintained low and low volume to mimic in vivo condition. Additional rotating magnetic stirrer fitted in silicon tube to give physical stress and movement of pellets. The increase in residence time of pellets in acidic environment had less impact on release rate however to total drug release of test formulation was significantly reduced due to degradation in acidic medium. Physical pressure on pellets was there due to rotating stirrer which compensated with low flow rate. The proper modification in dissolution apparatus mimic the gastric kinetics and prediction of in vivo drug release. It is possible to use more biorelevant media and modify conditions accordingly by adjusting flow rate and medium volume.

38) Wulff R et al., (2014) investigated the impact of combination of Eudragit RL and Eudragit L 100-55 on release profile of theophylline pellets. The pellets were coated with various ratios of polymer in organic or aqueous dispersion. Due to difference in pH value, difference in release was observed which was confirmed form results of experiments. From the results of design of experiments revealed that effect of coating level on release in acidic medium and blend ration has impacted on dissolution in pH 6.8 phosphate buffer. Dissolution in different pH medium showed release profile was depended on ratio of Eudragit L100-55 to Eudragit RL due to interaction of functional group occurred and ionization happened.
39) Roy P et al., (2009) reviewed the current approaches for pulsatile drug delivery (PDD). Multiparticulate system suitability for PDD discussed. In the human body many bioactive substances are regulated at specific site and time. To mimic the living system function chronotherapeutic concept, PDD interest increasing. The chronotherapeutic release could be achieved by single and multi unit system. Multi unit systems has many advantages over single unit like no dose dumping risk, gastric emptying is predictable, increased bioavailability, less intra and inter subject variability and flexible release pattern.

40) Patel HP et al., (2011) prepared multiple unit particle system of ramipril to improve stability and improve bioavailability. The aim was to overcome degradation of ramipril and conversion to thermal sensitive impurity diacid. The formulation contained ramipril polymer coated pellets, Hydrochlorothiazide and suitable excipients showed improved dissolution and impurities reduced to 2% which was significantly reduced compared with conventional impurities 15%.

41) Mallipeddi R et al., (2014) developed pellets by extrusion-spheronization using ethylcellulose of fine PSD. The result of design of experiments showed the impact of MCC, water, polyethylene oxide and speed of spheronization and spheronization time for pellets. Yield of pellets, shape, size, drug release, morphology and friability had been studied. The particle size of ethylcellulose had no impact on release profile.

42) Wang J et al., (2014) developed sustained release pellets of tamsulosin HCl by 2 membrane method. Drug loading performed by using centrifugal granulator and 2 membrane coating by FBP coating respectively. Pellets characterization was performed for physical appearance, drug release at various pH medias, SEM and DSC. The pellets were coated with first layer of Eudragit® L30D55 and Eudragit® NE30D in the ratio of 1:18 and up to 11 percentage of coating level. Second layer contained Eudragit® L30D55 and coating level was 0.8%. The dissolution profile was comparable with reference product in all multimedia and f2 found above 50. DSC results ensured compatibility of drug with excipients and SEM study revealed the differences in pellets surface with reference pellets.
43) Xu M et al, (2014) developed bio-adhesive pellets targeted for colon of 5-ASA. The pellets manufactured using polymer Carbopol and HPC. The pellets coated with aqueous dispersion of ethylcellulose as waterproof coat and outer coat of Eudragit® S100 for colon targeted release. The pellets administered to rats to study efficiency of pellets. The MCC (Avicel PH 301) was found best suitable excipient for pellets core. Drug release study performed in artificially prepared gastric fluid of pH 1.0 for 2 hours followed by release in phosphate buffer of pH 6.0 for hours followed by buffer pH 7.4 for 20 hours which mimic the colonic conditions. The ratio of HPC to Carbopol (CP940) was optimized to 1:1 for best bio-adhesion. Surelease level optimized to 16 to 20% and Eudragit® S100 level was finalized to 28%.

44) Abbas M et al., (2014) increased the solubility of famotidine which has variable bioavailability due to lower solubility in water. The solubility enhanced by solid dispersion using Pluronic F-127 and Gelucire 50/13. The drug to excipient reaction were studied by DSC and found no interaction even with high concentration of polymer upto 5 times. The pellets were prepared from 3:1 ratio of Pluronic F-127 to Gelucire 50/13 and pellets formed were spherical confirmed by SEM images. Dissolution study confirmed that solid dispersion increased the solubility compared to plain drug.

45) Li Z et al., (2014) developed floating pellets of matrix core and has good floating ability. The pellets manufactured using HPMC in drug and seal coating layer and Eudragit® NE 30D in sustained release coat. The matrix core was made up with ethylcellulose and mannitol. The finalized formulation showed drug release up to 12 hours and floated up to 10 hours without any lag time.

46) Kolter K et al., (2013) used aqueous dispersion of Polyvinyl acetate marketed under trade name of Kollicoat® SR 30 D. It is pH independent permeability, high flexibility and withstand mechanical stress without affection controlled release behaviour. It has MFT i.e. 18°C of plain polymer and after curing treatment pellets. It has pH independent drug release. Triethyl citrate is best suitable plasticizer with Kollicoat® SR 30D and 10% of plasticizer increased the film flexibility significantly which was suitable for compaction of pellets.
47) Hosseini A et al., (2013) developed ethylcellulose extended release pellets free from segregation and compress to tablet. Propranolol HCl used as model drug. The ethylcellulose coated pellets mixed with cushioning excipients from regular use like MCC, sorbitol and lactose. These excipient form layer on ethylcellulose coated pellets and absorbed the pressure applied during compression also overcome the segregation issue. MCC and croscarmellose sodium acted to reduced the disintegration time. Due to compression pellets ruptured and dissolution increased. Due to glidant between croscarmellose coat and cushion layer reduced the drug release significantly due to reduction in compression impact.

48) Wang Y et al., (2013) prepared stable and robust diclofenac pellets prepared by extrusion–spheronization technology. Main excipient was used as MCC. Short term stress stability was performed form upto 10 days at high RH and temperature and 2 main impurities found out of limit. Diclofenac was incompatible with MCC hence stabilizer was introduced to control degradation of diclofenac. The alkalizer, NaOH in 1.5% w/w concentration used in formulation and found that even with incorporation of MCC which has tendency to absorb the water however due to NaOH, degradation control significantly and robust pellets formed.

49) Hou Y et al., (2013) studied the release mechanism of different types of drugs coated with Surelease. Propafenone HCl used as model drug. It was found that drug release was faster when pellets was uncured. After curing, drug migrated from seal coat in to the Surelease coat due to reaction with ammonia present in dispersion. The migration of drug was confirmed by SEM study. In coating process, ammonia evaporated and combined with drug has cationic nature and form coalescence of polymeric film. Ammonia decomposed due to curing and interacted with polymer coat coalescence which increased the drug release. This decomposition was overcome by faster evaporation of ammonia and reduced ionization of drug.

50) Han X et al., (2013) prepared diltiazem HCl pellets extrusion–spheronization technology. The pellets coated with ethylcellulose and methacrylic acid polymer for sustained release profile. The dissolution profile of ethylcellulose and Eudragit® NE30D coated pellets had comparable dissolution profile with marketed pellets on capsules. The in vivo study performed in dog and found bioequivalent test product.
51) Ravella V N et al., (2012) developed sustained release pellets of aceclofenac. The pellets were coated with ethylcellulose and HPMC E5 for sustained release profile. The ratio of ethylcellulose and HPMC E5 was optimized. Dissolution was performed in pH 6.8 phosphate buffer.

52) Shendge R S et al., (2013) developed colon targeted microspheres of budesonide. The microspheres prepared by spray drying method using natural polysaccharides. Chitosan used as a natural polymer for along with glutaraldehyde which helped in cross linking between budesonide and Chitosan. Optimized microspheres shoed about 0% release in first 5 hours and 80% release in fecal media prepared from rat body.

53) Nikowitz K et al., (2013) developed diltiazem HCl pellets by solution layering method. The pellets were characterized for DSC, TG and XRD studies. Diltiazem HCl used in both form i.e. amorphous and crystalline form to investigate the migration of drug. From the results it was found that amorphous formed drug migrated in coating layer while crystalline form drug remained in pellet and nor migrated.

54) Hamdani J et al., (2002) studied melt granulation where solvent 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.

55) Cheboyina S 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.
56) Chatlapalli R et al., (1998) found that HPMC and HEC posses more tapped and bulk density than MCC, hence are good candidates for extrusion and spheronation 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 was generated. Same way excessive quantity of liquid will form bigger pellets having higher size distribution.

57) Bukovec P 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 450C. 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.

58) Musko Zs 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 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 fell 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 -200C 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.

59) Christopher R Y et al., (2012) 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 45minutes 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.

60) Sadeghi F 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 E 15 was inserted and finally solution of talc in water is adjoined 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, metoclopramide hydrochloride was slowly released from uncoated pellets. It depends up on manufacturing condition applied during coating the drug coated pellets by surelease polymer.

61) Bialleck S et al., (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.

62) Fu J 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.

63) Bodea A et al, (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.

64) Amighi K 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.

65) Kadam V D et al., (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 out puts.

67) Ghosh B 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.

68) Cui Y 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.

69) Pandey S et al., (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.

70) Chhipa P 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.

71) Rahman M A 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.

72) 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 Hixon-crowl rule.

73) Kleinebudde T R et al., (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.

74) Cheboyina S 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.

75) Zhou F 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 68-720C. 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 nonsmokers 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.

76) 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.

77) Jia J 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 -200C 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.

78) Yamanaka K 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 1month 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.

79) Zhao X et al., (2010) manufactured the nicotinic acid pellets by extrusion and spherization 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 400 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.

80) Voincovich D 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 heart 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 gastro intestinal 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 tmax and this results was also be proved true by the obtained value of t1/2. 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.
81) Santos H et al., (2005) formulated the two verities of pellets consisting of ibuprofen and diclofenac by utilizing extrusion and spheronization 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 1 hour. 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.

82) Hamdani J 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 bicarbonate 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 bicarbonate this combination made the pellets more water loving. 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.

83) Berhane N H 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.

84) Gunder W 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.

85) Nevsten P 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 compare 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.

86) Schilling S U 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 1720C and experiences the thermal degradation over 1800C. 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 140C. 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.

87) Sousa J J 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 to 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 1000 rotation 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 350°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.
88) Moschwitzer J 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 850µm 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 L30D55enteric 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 400C 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.

89) Krause J et al., (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 100C 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 600C 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 700C 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 150°C and under the binder’s melting point and also temperature nearer to 80°C was not sufficient for the formulation having appropriate shape. In present situation temperature of spheronizer must be 100°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 320°C.

90) Chatchawalsaisini J et al., (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 glyceryl monostearate may be get melted but in present method the process was completed in just 30to 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 glyceryl monostearate were found to be having small in diameter as compared to pellets containing glyceryl monostearate. It was noted that incorporation of glyceryl 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 glyceryl 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 glyceryl monostearate not affects the process of dissolution.

91) Kramar A et al., (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.
92) Leopold C S et al., (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 CO2 and ammonia was done from ammonium salt by heating at 650C 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.

93) Sadeghi F 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.

94) Singh S K 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.

95) Hiorth M et al., (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.
96) Siepmann J 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.

97) Bodmeier R et al., (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 ethylcellulose 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 700 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.

98) Grassi M 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.

99) Schmidt P C 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.

100) Damle A V et al., (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 500C 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 600C. The same results were obtained when pellets were coated with ethyl cellulose film
101) Levine S P et al., (2012) presented application of PlasACRYL T20 in functional coating. PlasACRYL T20 contained triethyl citrate and 20% solid content. It acts as anti-adherent and plasticizer. Methacrylic acid polymers have high Tg so they required high percentage of plasticizer and due to more plasticizers, agglomerates formed so talc used. But talc required 20-50% of polymer which has tendency to settle down and block the coating guns. PlasACRYL T20 contained glyceryl monostearate (GMS) acts as anti-tacking agent and only 5% of polymer is enough to avoid agglomerates formation and has not settling tendency and reduced processing time.

102) Levine S P et al., (2008) introduced the concept of GMS as alternative for talc for faster coating process. They prepared placebo pellets by coating of ethylcellulose (Aquacoat ECD) with 10% of TEC and 10% of GMS in different trials to study the impact. At 15 g/min spray rate, 15.1% agglomerates formed in talc based coating while 1.07% agglomerates formed in GMS based coating. At 20 g/min spray rate, 75.1% agglomerates formed in talc based coating and 5.7% agglomerates formed in GMS based coating. In conclusion, GMS based coating significantly reduced the agglomerates formation at high spray rate.

103) Honda Y et al., (2010) presented new type of microcrystalline cellulose grade has high degree of compaction suitable for high dose tablet product and vitamin tablet to maintain lower tablet weight. Ceolus KG-1000 has bulked density 0.12 g/ml which is lowest compared to existed MCC grades. Ceolus KG-1000 has high L/D value. Particles of Ceolus arrange perpendicularly upon compression so contact area increase of MCC.