LITERATURE REVIEW ON PELLET FORMULATIONS

1. Pellets containing propranolol hydrochloride were coated with ethylcellulose powder to achieve extended release. The film forming ability of ethylcellulose powder and the effect of formulation factors (plasticizer type and concentration) and curing conditions (curing temperature and time) were investigated. Extended drug release could be obtained with coating level of 15%. Because of its high glass transition temperature, ethylcellulose coated pellets showed unchanged drug release profiles upon storage at room temperature for 3 years (Nantharat Pearnchob, et al. 2003).

2. The release of water soluble substrates from aquacoat coated pellets was through water filled channels. The release rate from the pellets was dependent on the substrate solubility and the osmotic pressure of the external dissolution medium. The release rate from the coated pellets initially was zero order and changed to first order when there was no solid substrate left in the pellets. The release rate of theophilline was increased by incorporation of a more water soluble substrate diphenhydramine, in the pellets (Russell Nesbitt, et al. 1994).

3. The drug release mechanisms in pellets coated with aqueous ethylcellulose dispersion, providing long term stable drug release profiles and containing different types of starter cores was investigated. The systems were thoroughly characterized using mechanical analysis. All experimental results indicated that diltiazem HCl release from pellets coated with ethylcellulose containing small amounts of poly(vinyl alcohol)-poly(ethylene glycol) graft copolymer is primarily
controlled by drug diffusion through the intact polymeric membranes, irrespective of the type of starter core (Muschert et al., 2009).

4. Studies were conducted to determine the mechanism of drug release from pellets coated with an ethyl cellulose based pseudolatex widely accepted for use as a sustained release coating for pharmaceuticals. These results indicated that while the plasticizer is important in terms of forming a continuous film, diffusion through plasticizer channels is unlikely to make a significant contribution to the overall release rate. Release was also studied as a function of the osmotic pressure in the medium (Ozturk et al., 1990).

5. The effects of PVP based additives on the drug release properties of ethylcellulose coated pellets were evaluated. Incorporation of cross-linked molecular-composite polyvinylpyrrolidone (MCPVP) and N-vinyl-2-pyrrolidone and vinyl acetate co-polymer (PV/VA) to form a composite ethylcellulose pellet coat was found to enhance drug release markedly, even at a low additive concentration of 10%. The release-enhancing effect of PVP increased with increasing molecular weight (Ong et al., 2009).

6. The diclofenac sodium pellets were coated with cow ghee composition. Pellets with good surface morphology and smooth texture were produced as a result of hot melt coating with ghee and ethyl cellulose. The diclofenac sodium pellets showed sustained release of drug for 8hrs with cumulative percent release of 99.8 ± 2.5%. By means of hot melt coating using cow ghee and ethyl cellulose, sustained-release pellets containing diclofenac sodium were successfully prepared. (Sakarkar et al., 2009).
7. Multiparticulate formulation comprising pellets with a multilayer of pectin and ethyl cellulose on non pareil seeds by powder layering technology was carried out. The pellets were prepared to target ketoprofen in colon based on the microbial enzyme dependent drug release mechanism. The transit behavior and scintigraphy image clearly indicates that the formulation can delay the drug release prior to colon. In albino rabbit, the coated pellets released drug in the colon indicating that the site specificity has been achieved with pectin and ethyl cellulose (Subhabrota et al, 2011).

8. The drug release mechanisms from aqueous ethylcellulose-coated pellets containing different types of drugs like theophylline, paracetamol, metoprolol succinate, diltiazem HCl and metoprolol tartrate was evaluated. Drug release was found to be controlled by diffusion through the intact polymeric membranes, irrespective of the drug solubility and type of core formulation. The ethylcellulose coating was dominant for the control of drug release, minimizing potential effects of the type of pellet core and nature of the surrounding bulk fluid (Muschert et al, 2009).

9. The effects of the parameters on the spheronization and the nature of the wetting liquid on the properties of matrix pellets prepared by extrusion and spheronization were studied. Ethylcellulose was used as a matrix former and atenolol as a model drug. It was concluded that significant effects were exerted not only by the operational parameters, but also by the nature of the liquid. The breaking hardness and the dissolution revealed that the ethanol in the liquid
caused changes in the wettability of the components and consequently in the matrix structure (Elnazeer et al., 2010).

10. Pancreatin pellets, placebo pellets and tablets containing vitamin B2 were coated with various aqueous and organic enteric polymers, HPMCAS, HP, Eudragit L 100-55, Eudragit L 30 D-55, CAP, CAT, CMEC and PVAP, comparatively investigated and tested for storage stability. The coated vitamin B2 tablets with Eudragit L 100-55, Opadry enteric (PVAP) and Aqoat (HPMCAS) proved to be quite stable aqueous enteric coatings, whereas cellulose acetate phthalate CAP or cellulose acetate trimellitate CAT coatings as ammonia-neutralized aqueous solution or as water-based pseudolatex Aquateric were unstable when stored under stress conditions (Thoma et al., 1999).

11. The novel soft pellets were designed to ensure rapid disintegration of the tablets when in contact with water. The deformability and disintegration properties of these pellets were controlled using olive oil. Hard pellets, produced by extrusion / spheronisation, were optimized and characterized and were film coated. Granulation / spheronisation was the preferred method of manufacture of the soft pellets and lower percentages of olive oil were found to be more beneficial to the disintegration properties of the compacts (Jan Pick et al., 2010).

12. Four commercial grades of microcrystalline cellulose were compared for extrusion spheronization. Model mixes containing Avicel PH 101 with different proportions of fillers like lactose and dicalcium phosphate dihydrate (DCPD) were also compared to observe the influence of these fillers on the pellet properties. Pellets containing dicalcium phosphate dihydrate showed the best flow properties
owing to their greater circularity and a high density. Among the Avicel grades
pellets of Avicel PH 302, showed the best flow properties (Sinha et al, 2005).

13. The feasibility of producing solid self-emulsifying pellets using the
extrusion/spheronization technique. The release kinetics and the
microenvironment of the pellets during the release process were assessed using
electron spin resonance (ESR) spectroscopy. The ESR results showed that the
hydrophobic spin probe was localized mainly in the lipid environment all over the
release time. Furthermore, the formulation was capable of accelerating the

14. The influence of non-active ingredients in the manufacture of pellets on in vitro
dissolution rate and on bioavailability of hydrochlorothiazide has been studied. In
vitro drug release from the different pellet formulations were retarded in
comparison to a conventional tablet formulation and was dependent on the
nature of the non-active ingredient and, for the microcrystalline cellulose-
carboxymethylcellulose sodium blend (Herman et al, 1988).

15. Sustained release pellets of ketorolac tromethamine were prepared and
evaluated. The method involves a simple microencapsulation technique using
Eudragit RL and Eudragit RS and nonpareil seeds as carrier. The proposed
formulation provided sustained ketorolac tromethamine release over 12 h and
exhibited good physical and chemical stability. The pellets are recommended to
be stored at conditions not exceeding 25 °C and 60% RH to maintain a proper
extended-release profile (Mohamed et al, 2008).
16. The effects of spheronizer speed, spheronization time and amount of water content, on physical properties and appearance of pellets was studied. A $2^3$ factorial design was used to study the effect of significant factors and their interactions in the response. The selected process variables were studied and their influence on usable yield, sphericity, density and moisture content was determined. Good sphericity and smooth surface were obtained with higher spheronizer speeds (Shikha et.al, 2011).

17. The present study aims to develop self microemulsifying drug delivery systems (SMEDDS) in sustained-release pellets of puerarin to enhance the oral bioavailability of puerarin. The performances of puerarin–SMEDDS including oils, emulsifiers, and co-emulsifiers were evaluated. The absolute bioavailability of the puerarin–SMEDDS sustained-release pellets was enhanced by approximately 2.6 fold compared with that of the puerarin tablet. The results revealed that the puerarin–SMEDDS pellets had a sustained release effect, and could remarkably improve the oral bioavailability of puerarin (Yi Zhang et.al, 2012).

18. The influence of the formulation and operating conditions on pellet preparation by the pan technique. The effect of initial core weight on the physical parameters of pellets as well as to conduct stability study was also the goal of this study. For this domperidone maleate was selected as the model drug. The results showed that the system is efficient for the production of highly stable formulations. This study also showed the good performance of the conventional coating pan system in obtaining instant release domperidone pellets prepared by the powder layering technique (Golam et. al, 2010).
19. The present study was concerned with the feasibility of formulating ranitidine into pellets with a range of alternative excipients in place of microcrystalline cellulose (MCC) by extrusion–spheronization. A direct relationship was observed between the concentration of MCC in the formulation and the properties of the pellets. In general, the higher the concentration of MCC, the rounder, stronger, and less friable the pellets. However, even pellets without MCC were also successfully prepared with a superior size distribution and shape over those with MCC (Abdul et. al, 1999).

20. The oral controlled release matrix pellets of water insoluble drug Propafenone Hydrochloride (PHC) were prepared and evaluated using blend of sodium alginate (SA) and glyceryl palmito stearate (GPS) as matrix polymers, methyl crystalline cellulose (MCC) as spheronizer enhancer, sodium lauryl sulphate (SLS) as pore forming agent. The drug loaded pellets were stable, compatible, as confirmed by DSC and FTIR studies. XRD patterns revealed the crystalline nature of pure PHC. Loose surface crystal study indicated that crystalline PHC was observed in all formulation (Gowda et. Al, 2012).

21. Scanning electron microscopy was used to visualize the pellet morphology and drug release mechanism during dissolution testing for ketoprofen sustained release pellets. In vivo evaluations of the extended release pellets in rats indicated a significant increase in the time to reach maximum concentration (t$_{max}$) and extent of absorption (AUC$_{0-\infty}$) compared to the ketoprofen immediate release tablet blend dispersed and dosed. In conclusion, extended release pellets of
ketoprofen could perform therapeutically better than conventional dosage forms, leading to improved efficacy for a prolonged period (Raveendra Pai et al. 2011).

**PAST STUDIES ON DILTIAZEM HYDROCHLORIDE**

22. The studies were undertaken to evaluate the effect of pH of dissolution media on the release profile of three drug molecules with diversified physicochemical properties. Matrix tablets of diclofenac sodium, theophylline and diltiazem HCl were prepared by using ethyl cellulose as the matrix forming agent (Mohiuddin et al., 2005).

23. The aim of this study was to prepare and evaluate controlled release tablets of Diltiazem by a wet granulation method using Ethyl cellulose and Ethylene vinyl acetate as a retardant and chloroform (solvent for the polymer) as granulating fluid. The polymers were used at 2, 5 and 10 % concentrations in the formulae. Diltiazem release from the matrix tablets was slow and spread over a period of 12 h depending on the type of the polymer and its concentration (Satyanarayana et al., 2011).

24. The deformation mechanism of pharmaceutical powders, used in formulating directly compressed matrix tablets, affects the characteristics of the formed tablets. Three polymers of different deformation mechanisms were tested for their impact on diltiazem directly compressed tablets namely Kollidon ® SR (KL SR, plastic deformation), ethylcellulose (EC, elastic deformation) and Carnauba wax (CW, brittle deformation) at different compression forces (Ibrahim et al., 2010).
The results showed that all the polymers used in this study could slow down the release of diltiazem HCl from the matrices prepared. This effect, except for HPMC, generally increased proportionately with the amount of polymer. HPMC imparted the best control over drug release and could sustain it for approximately 6 hr. All the matrices prepared had a burst release initially; however, it was minimum with HPMC containing formulations (Hadi et al, 2005).

The existence of a possible interaction between diltiazem HCl and the polymers was investigated by using DSC and XRD. The DSC curves and XRD patterns indicated that there was no interaction between diltiazem and the polymers (Turk et al, 2009).

The results of dissolution studies indicated that formulation with drug to polymer ratio 1:1.25 was found to be most successful as it exhibits drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio (Modi et al, 2010).

Diltiazem HCl was chosen because of its high water solubility. Tablets containing the drug were prepared by direct compression method using different matrix ratios of ethyl cellulose (EC) and hydroxypropyl methylcellulose (HPMC). The formulations were evaluated in vitro for their dissolution characteristics over a period of 8 h. Drug release was analyzed according to various release kinetic models (Enayatifard et al, 2009).

The effect of ethyl cellulose on the release of diltiazem hydrochloride was found to be predominant in barrier coating system than that of the matrix system. In the matrix system the drug comes to dissolution media easily and water soluble
additives form channel very fast. The kinetic study of the drug was performed and it was revealed that the release of drug from pellets appeared to follow zero order kinetics (Golam et al, 2007).

30. The selected model dependent methods studied by analyzing the dissolution data using kinetic equation like the zero order, the first order, Higuchi square root, and K-peppas equations. The analysis of kinetic equations data that it follows first order kinetics and the release mechanism involves anomalous transport (Jagadeesh et al, 2011).

31. Microparticles were prepared by non-solvent addition phase separation method and characterized by micromeritics, scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), x-ray diffraction (XRD), dissolution test and thermal analysis (Murtaza et al, 2010).

32. The most widely used multiparticulate system in pharmaceutical industries is Dry Powder Layering Technique. Powder layering involves the deposition of successive layers of dry powder(s) and excipients on preformed nuclei or cores with the help of binding liquids. The prepared multiparticles were evaluated for friability, drug content uniformity, density and percentage yield (Subhabrota et al, 2010).

33. It was observed that the concentrations of polymers directly affected the drug release profile. Eudragit RLPO and ethyl cellulose showed effects opposite to each other on drug release. Mathematical models were generated for each response parameters to predict their values at selected levels of formulation variables (Mathure et al, 2011).
34. The drug containing pellets were further coated to achieve the required release profile. The different coating formulations adopted in this research work were based on polymeric coatings of ethyl cellulose (EC), hydroxypropyl methyl cellulose (HPMC) and Eudragit S-100. The coating system was further modified based on the principle of microporous membrane drug delivery using a soluble salt, such as sodium lauryl sulphate (SLS), as a leachable pore forming agent, which forms micropores on coming into contact with gastrointestinal medium (Gowdaa et al, 2007).

35. Diltiazem hydrochloride was incorporated into the biocompatible and biopolymer blends of chitosan (CH) and micro crystalline cellulose (MCC) matrix pellets using pelletization technique. Solid, free flowing matrix pellets and yields up to 97.5 %. More than 98 % of the isolated pellets were of particle size range 1037 to 1146 nm. The obtained matrix pellets having smooth surfaces, with free flowing and good packing properties. Scanning electron microscope (SEM) confirmed their spherical structures (Rajesh et al, 2011).

36. In vitro release studies showed retardation of drug release from the coated pellets of diltiazem HCl. The DSC thermogram revealed no interaction between the polymer and drug in the formulation. The SEM data shows no change in the surface topography after 20 min curing (Vinayak kadam et al, 2011).
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37. Controlled release microparticles of verapamil hydrochloride were prepared with the ultrasonic spray congealing technique using waxes and evaluated for in vitro drug release. The results indicated that by selecting the type and the amount of the carriers, microparticles with a spherical shape and good encapsulation efficiency were prepared. These microparticles showed zero order release for 8 h (Nadia et al., 2003).

38. Verapamil hydrochloride was formulated as extended release pellets. The pellets were prepared by extrusion spheronization technique and evaluated for in vitro release. The prepared verapamil pellets were evaluated for the influence of organic acids on drug release. The dissolution rate of the drug from pellets containing fumaric acid was high at elevated pH, which may be due to creation of micro environmental pH inside the pellet core (Kumud Kumar et al., 2003).

39. Sustained release microcapsules of verapamil hydrochloride were prepared using various polymers by emulsification method. The prepared microcapsules were evaluated for flow behavior, drug entrapment efficiency, in vitro dissolution studies, in vivo studies and stability studies. The results revealed that the drug release from the microcapsules was found to be following non fickian diffusion. In vivo results for pharmacokinetic parameters revealed that $t_{\text{max}}$ of reference and test formulations were almost same (Farhana et al., 2010).

40. A study was performed to determine whether verapamil hydrochloride administered in extended-release pellet-filled capsules is bioequivalent to the same formulation administered by sprinkling the contents of the capsules onto
Thirty-two healthy subjects participated in the randomized, two-way crossover study. There were no significant differences between the AUC0-48, AUC0-\(\alpha\), C\(_{\text{max}}\), t\(_{\text{max}}\), and k for the two methods of dose administration. For verapamil the differences for all variables were less than 5%, and for norverapamil the differences were less than 4% for all variables except t\(_{\text{max}}\) (9.5%) (Kozloski et al, 1992).

41. A method of compression of floating pellets with verapamil hydrochloride in a dose of 40 mg was performed. Kollicoat SR 30 D was selected for coating. In experiments three plasticizers were examined—propylene glycol, triethyl citrate and dibuthyl sebecate. Pellets were prepared by wet granulation of powder mixture, spheronization of the granulated mass and coating of the cores with a sustained release film. The best formulation was evaluated taking into account the effect of compression force an tablet hardness and friability, and pellet agglomeration and flotation. Tablet cross-section photographs were taken confirming necessary coating film thickness preventing their deformation caused by compressing into tablets (Wiesław et al, 2005).

42. A multiple-unit, extended drug delivery system for prolong release of verapamil HCl through out the day was evaluated. In this work organic acids such as fumaric & malic acid were added to the drug–polymer system as a pH-adjuster inside the pellet core for the maintenance of constant acidic micro-environment inside the core of dosage form. pH-independent drug release was achieved from pellets consisting of organic acid in their core when coated with selected pH-
independent coating polymers like ethylcellulose, hydroxypropylmethyl cellulose and Eudragit polymers (Kumud Padhee et al, 2010).

43. Film coated pellets were prepared using two strategies to enhance drug release at high pH values. Firstly, pellets were coated with Eudragit RS / hydroxypropyl methylcellulose acetate succinate mixtures in proportions of 10:1 and 10:3, respectively. Dissolution profiles of samples tested in pH 1.2 for 12 hr were compared with those using the pH change method (pH 1.2 for first 1.5 hr, pH raised to 6.8 for remaining 10.5 hr) using the area under the dissolution curve, the dissolution half-life (t50%), and the amount of drug released in 3 hr values. Both strategies enhanced drug release into neutral medium although the strategy using HMAS in the film was more effective (Munday 2003).

44. The effect of Eudragit RS 30D, talc on verapamil hydrochloride dissolution and mechanical properties of beads coated with drug-layered matrices was evaluated. Beads were coated in a fluidized-bed coating unit. Surface morphology and mechanical properties were evaluated by surface profilometry and texture analysis, respectively. The release of verapamil from the beads was influenced by matrix components. Increasing the level of both talc and Eudragit decreased the percent drug released. It was concluded that beads could be efficiently coated with drug-layered matrices (Yasser et al, 2008).

45. Verapamil hydrochloride pellets were prepared in fluid-bed coater. An optimum condition was established by orthogonal test for preparing verapamil hydrochloride pellets, and the release of pellets was studied in vitro. The optimum condition was that 5%PVP was used as adhesives, and the
temperature in fluid-bed coater was 28°C. The release stability of pellets was good, drugs can be released completely within 30 minutes (WU Xiao et al, 2003).