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Review on: -"Multiparticulate System"AEmerging Trend In Drug Delivery System

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ABSTRACT-
The development of pharmaceuticals is increasingly centred on delivery strategies that maximise therapeutic benefits while reducing adverse effects. Multiparticulate drug delivery systems appear to be particularly well-suited for producing controlled and delayed release oral formulations with less chance of dose dumping, according to recent developments. Biopharmaceutical benefits are provided by these oral multiparticulate drug delivery methods in terms of consistent and even distribution and transit inside the gastrointestinal tract. The process of pelletization is a revolutionary drug delivery technique that helps create a site-specific drug delivery system by turning tiny powder particles into pellets. Pellets can be prepared using a variety of methods. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future pharmaceutical development.

INTRODUCTION

Multiparticulate Drug Delivery Systems (MDDS)

The notion of multiple unit dosage form was initially presented in the early 1950's. Due to their special qualities and the flexibility inherent in their production, these forms are crucial to the design of solid dosage form procedures. These dosage forms can be characterised as oral formulations made up of several tiny, distinct units, each displaying specific desired properties. When combined, these feature units provide the dose the overall, desired regulated release. Other names for these numerous units include pellets, spherical granules, and spheroids. Pelletization is a process of agglomeration that creates small, free-flowing, spherical or semi-spherical units known as pellets from fine powders or granules of bulk medicines and excipients. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. These pellets usually range in size from 0.5-1.5mm and in applications may be as large as 3mm.

Multiparticulate drug delivery systems (MDDS), which are primarily administered orally, are made up of numerous small, distinct components with various properties. Subunits such granules, beads, microspheres, pellets, spheroids, and Minitab serve as its foundation. Compared to monolithic devices, these subunits have a number of advantages (non-divided shapes). Drug compounds are broken down into several subunits in MDDS, which are usually made up of hundreds of spherical particles with a diameter of between 0.05 and 2.00 mm. These subunits are crushed into tablets, put into sachets, or encapsulated in order to give or recommend a whole dose1. Because multicomponent MDDS demonstrates distinct mechanisms of action, and it is also possible to formulate it. minimises the dosages of separate drugs, has a restricted number of adverse effects, and has an additive or synergistic impact. Though it is expensive than monotherapies in short term, it reduces treatment failure rate, lower case fatality ratios and reduction in development of resistance for creation of new products in long term therapy2. Pellets are collections of finely ground excipients and/or bulk medicament granules. Small, freely flowing, spherical or semi-spherical solid units make up these particles, which are often meant to be taken orally.

ADVANTAGES OF MULTIPARTICULATES (PELLETS)

The use of pellets as a medium for medication administration at controlled rate has recently gained substantial interest. Although there are other ways to produce pellets, the drug-layering process is currently the most used. As listed below, multiparticulates offer a variety of advantages.

1. avoiding the dumping of doses
2. Faster stomach emptying

Because multiarticulate are small enough to pass through the pylorus during the digestive phase, performance is less dependent on nutritional status.

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4. Displays a high degree of dispersion and enhanced repeatability of transit time in the gastrointestinal tract.
5. More widely dispersed and unlikely to irritate nearby areas.
6. Increased compliance, comfort, and stability for the patient
7. Develop a distinctive releasing pattern.
8. Expand patent protection, market the product internationally, and defeat rivals. Pellets offer more sophisticated drug-delivery systems as they provide greater advantages over other single unit drugdelivery systems.
a) Process Benefits: For flexible and consistent drug-polymer coating, several types of particles with defined less-porous surfaces, spherical shapes, and low surface area to volume ratios are ideal as subunits.
b) Benefits of Formulation: Compared to single units, pellets provide considerable therapeutic advantages by providing greater flexibility in the design and formulation of the active component into oral dosage forms such tablets, capsules, and solutions 4, 5. Every subunit in the fluid bed coating process is endowed with the distinctive drug release capabilities by the functional coating that is typically applied. Drugs designed as coated pellets that can be compressed into tablets or packed into capsules have a higher advantage in controlled-release, gastro-resistant, prolonged release, or site-specific drug administration. They can be combined to deliver even incompatible bioactive agents simultaneously or particles with distinct release profiles at the same site or at multiple sites within the gastrointestinal tract. They can also be divided into appropriate dose strengths without changing the formulation or method. The safety and efficacy of the formulation is higher than that of other dosage forms.
c) Therapeutic benefits include: minimising local irritation of the gastric mucosa caused by certain irritant drugs due to the small amount of drug available in a single pellet; reducing the risk of dose dumping; increasing the safety and efficacy of a drug; minimising peak plasma fluctuations; minimising potential side effects with improved drug bioavailability; and minimising oral drug administration. 7; reduces inter- and intra-patient variability; provides decreased variance in gastric emptying rate and transit time, which is less dependent on the condition of nutrition. 5; more suited for creating formulations including medications that are sensitive to acid, such as Erythromycin 8. As the advantages of pellets over single units became clear, the pharmaceutical industry as a whole started to devote resources to conduct research in pelletization technology, whenever possible, acquire advanced equipment suitable for the manufacture of pellets
Disadvantages:
1. Low drug loading
2. Proportionally higher need for excipients
3. Lack of manufacturing reproducibility and efficacy
4. Large number of process variables
5. Multiple formulation steps
6. Higher cost of production
7. Need of advanced technology
8. Trained/skilled personal needed for manufacturing.

Because of its high bulk density, the volume per dose is high in accordance with single units. Given the increased specific surface area per dosage, a greater quantity of coating should be applied. Pellet preparation is a difficult and time-consuming procedure. Despite these realities, pelletization technology is becoming more and more popular in the production of pharmaceutical products because to its advantages in patient compliance, safety, and efficacy.

Pelletization Techniques Pellet growth and creation can happen in several ways, depending on the procedure and equipment used. However, the basic growth mechanisms and bonding forces can account for the underlying phenomena that describe the systematic creation of pellets during the various pelletization processes. Recent research has concentrated on developing new manufacturing strategies that make use of cutting-edge formulations and processing machinery, as well as on improving and enhancing the pelletization processes currently in use. This is because multiparticulate systems offer significant advantages over single-unit oral dosage forms. The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering, and extrusion–spheronization8,9

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Fig.– Classification OfPelletizationTechniques

A. Balling, also known as spherical agglomeration, is a Pelletization process in which powders are continuously rolled or tumbled into spherical particles once a suitable amount of liquid is added. You can add the liquid either before or after the agitation phase. Balling has been done in horizontal drums over the years. tumble blenders, inclined dish pelletizers, and pelletizers; rotary fluid-bed granulators are a more recent technology Drug layering Pelletization by layering involves the deposition of successive layers of drug entities from solution, suspension or dry powder on preformed nuclei, which may be crystals or granules of the same material or inert starter seeds. The initial materials required for the preparation of pellets by the layering process are the inert starter seeds over which the powdered drug(s) is (are) layered and the possible coating applied. Non-pareils have been widely used as initial substrates in the preparation of pellets by the layering process. However, sucrose, the main component of non- pareils, has some well-known drawbacks like harmful effects on diabetics and potential carcinogenicity. Most recently, microcrystalline cellulose (MCC) has been tested as a substrate for drug layering.

B. Layering of Powder Regardless of the drug's solubility in the binding liquid, complete dissolution does not happen in powder layering liquids due to poor saturation. Powder is usually added after a binder solution has been sprayed onto the nuclei. The majority of the nuclei fall into the revolving disc pan, gather powder particles, and create layers of tiny particles that cling to the nuclei and one another thanks to capillary forces created in the liquid phase. More powder is layered on the nuclei as more bonding occurs and liquid is sprayed, continuing until the required particle sizes are reached. The binder and other dissolved materials crystallise out after drying, partially replacing the liquid bridges with solid ones.Figure shows the principal of powder layering.

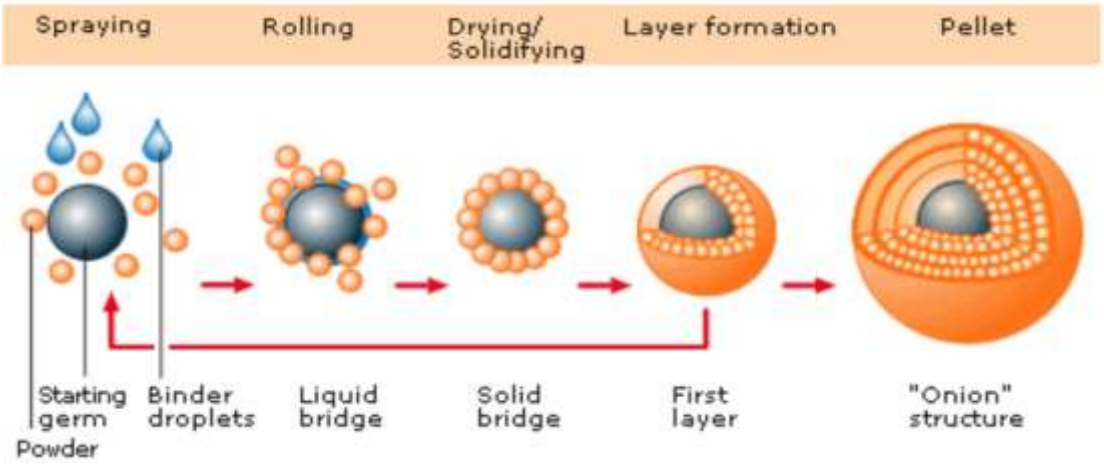

Fig: Principle Of Solution / Suspension Layering

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C. Layering of Suspension and Solution The suspension and solution stacking process's guiding principle: Solution and suspension layering entail the deposition of successive layers of solutions and suspensions of pharmacological compounds, respectively, on beginning seeds that may be inert materials or crystals or granules of the same medication. The variables that govern coating processes can, in theory, also govern solution or suspension layers. All of the formulation's ingredients dissolve or suspend in the application medium during solution or suspension layering, which establishes the liquid's viscosity and solid content. As the solution or suspension is sprayed onto the product bed, the droplets impinge on the starter seeds or cores and spread evenly on the surface, provided that the drying conditions and fluid dynamics are favorable. This is followed by the drying phase which allows dissolved materials to crystallize and formsolid bridges between the core and initial layer of the drug substance as well as among the successive layers of drug substance. The process continues until the desired layers of drug and hence the target potency of the pellets is achieved. The rate of particle growth is rather slow due to the incremental addition of the dissolved or suspended drug. In this process, though the particle population remains the same, the size of the pellets increases as a function of time and, as a result, the total mass of the system increases. Figure 3 shows the principal of solution or suspension layering.

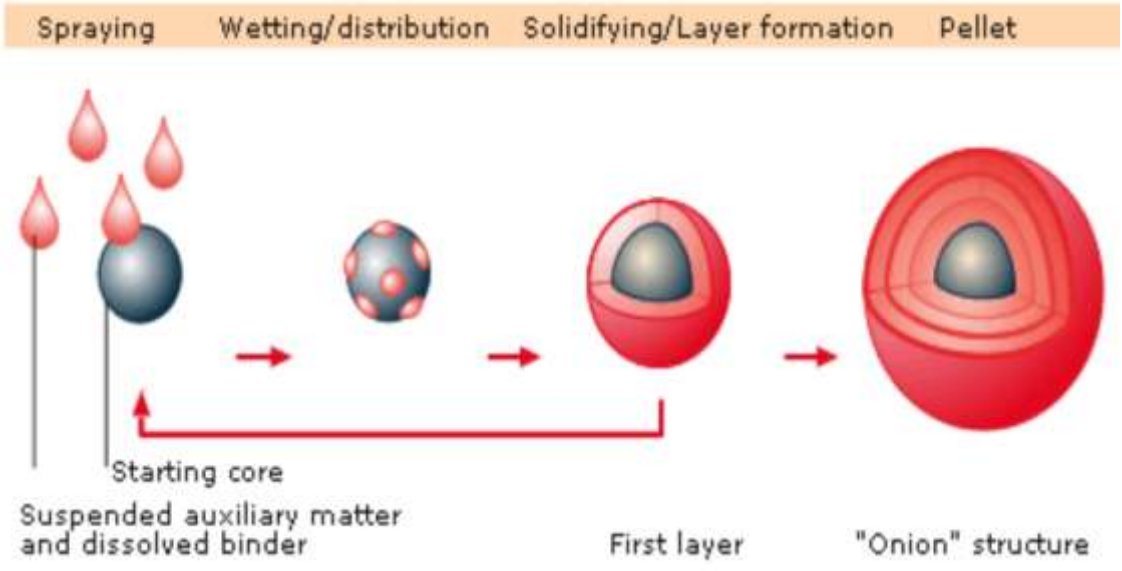

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Fig Principle OfSolution / Suspension Layering

APPLICATION	EQUIPMENT
Drying	Top spray
Spray granulation/drying	Top spray, bottom/Wurster, rotor
Pelletizing	
Solution/suspension layering	Top spray, bottom/Wurster, rotor
Dry powder layering	Rotor
Direct pelletization	Rotor
Coating (fine particles/pellets)	
Organic solvent	Top spray, bottom/Wurster, rotor
Water based	Top spray, bottom/Wurster, rotor
Hot melt	Top spray, bottom/Wurster, rotor

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Characterization of Pellets:

Pellets undergo an evaluation process based on specific quality metrics that indicate how well-suited and durable the material is for different tasks such as filling, handling, and transportation. The most often assessed physical attributes are:

1. Simple and affordable sieve analysis is used to measure the size and distribution of pellets; microscopy techniques include laser diffraction and scanning electron microscopy (SEM) 33, 34. This pellet property influences coating and medication release rate. An other technique for figuring up pellet size is to estimate fret diameter using data from four distinct angles. A normal distribution fit the size data the best in all of the scenarios.
2. Shape influences flow of pellets during coating, filling into capsules and dies. The most common method of analysis is by ring gap analyzer; scanning electron microscopy (SEM) for qualitative and quantitative analysis 35. Visual inspection of pellets by microscope and stereomicroscope also determines shape of pellets.Another method to determine spherical shape (sphericity) is by taking optimum size pellets, stained with dye solution in a petri dish and dried on a hot air oven. Each pellet is recorded for two-dimensional image i.e., length and width using camera lucida fixed to an optical microscope and circulatory factor(s) was calculated using the equation S = P2 / (12.56 * A); where A is the area (cm2)and P is the perimeter(cm) of circular tracing. Circularity, another parameter to determine shape is calculated as 4πA/P2, where A is projection area and P is projection perimeter.
3. Surface area has an effect on drug release and results in batch-to-batch variability. To ensure the production of consistent shape pellets, surface area is analyzed by particle size distribution, gas adsorption (BET methodBrunauer, Emmett & Teller) and air permeability method 35. Surface roughness is analyzed by fractal geometry of particle obtained by microscopy with image analysis and SEM. This property influences flow and packing of pellets 35.
4. Porosity influences rate of drug release from the pellets by affecting the capillary action of the dissolved drug; analysed qualitatively by scanning electron microscopy and quantitatively by mercury porosimetry 36. The sample is introduced into the chamber, degassed, and then completely covered with mercury. Pressure is applied and the volume of mercury that penetrates into the pores is recorded. Pore radius is given by Washburn equation: R = 2 g [cos q] / P; Where g = 480 ergs/cm3, q= 140o, r = pore radius, p = mercury-intrusion pressure.
5. Tap density and bulk density have an impact on the final product's potency, cause segregation during mixing, and cause batch-to-batch variations. A pycnometer or an automated tapper can be used to estimate bulk density, which is determined by dividing weight by the occupied volume (37, 38, 39, 40).
6. True density indicates extent of densification or compactness. Air- comparison pycnometer, helium pycnometer or solvent displacement method are different methods of analysis.
7. Friability and hardness help to withstand subsequent coating and high attrition during coating. Roche friabilator, Erwekafriabilator, Pharma Test friabilator are different equipment used. The % friability of pellets should be less than 0.08% 41, 42. Relative hardness of the pellets is determined by using Kaul pellet hardness tester.
8. Tensile strength is determined by using tensile apparatus with a 5 kg load cell. The radius of pellets is recorded and these pellets were strained continuously until failure occurs. Further load is recorded. The tensile strength is calculated by applying the value for the failure load (F) and the radius of the pellets (R) by the formula $\sigma f(s) = 0.4F/\pi R2$.
9. Flowability is determined by angle of repose. If Θ40°- poor flow ability.
10. In-vitro Dissolution Testing most commonly is by USP I (basket) and USP II (paddle) apparatus

Mechanism of Drug Release from Pellets:

The mechanism of drug release from pellets can occur in the following ways:

1. Erosion: Some coatings are designed to erode gradually with time, thereby releasing the drug contained within the particle.

2. Osmosis: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

3. Diffusion: On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and

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the drug solutions diffuse across the release coat to the exterior. Three different release mechanisms were identified from pellet dosage forms coated with polymers insoluble in GIT through diffusion.

1. Diffusion of solution through the continuous plasticized polymer phase; assumes that the polymer forms a phase in which the plasticizer and other additives are homogeneously dispersed. The diffusion of a solute molecule within an amorphous polymer phase is an activated process involving the cooperative movements of the penetrant (drug) and the polymer chain segments around it. It is by this stepwise process that hindered molecular diffusion occurs. The frequency with which a diffusion step occurs depends on the size and shape of the drug, tightness of the bonds between adjacent polymer chains and the stiffness of the polymer chain. Further below its glass transition temperature (Tg), less permeable is the polymer. Plasticizers lower the Tg, increase free volume and increase diffusivity. Accordingly, this mechanism is dominant in continuous film, flexible polymers which lacks pores. Overall permeability of the polymer to the drug will depend on the ability of the drug to partition into the polymer as well as its ability to diffuse through the polymer
2. Solution/diffusion through plasticizer channels; occurs when the plasticizer is not uniformly distributed in the coating polymer and its content is high. The plasticizer takes the form of a continuous phase in the form of patched channels. Diffusivity in the plasticizer will generally be lower than in water since plasticizers tend to be relatively viscous
3. Diffusion through aqueous pores intervenes when a continuous, but inhomogeneous coating layer is punctuated with pores. This mechanism is more likely to be operative for the coatings formed from aqueous dispersions and when the pellets come in contact with an aqueous medium. These pores fill with solution thus facilitating the diffusion of the drug. During the coating and curing processes, the pseudolatex particles often do not fuse completely, thereby creating a porous coating. The pores may be of 1µm size and the release mechanism is illustrated in Figure.

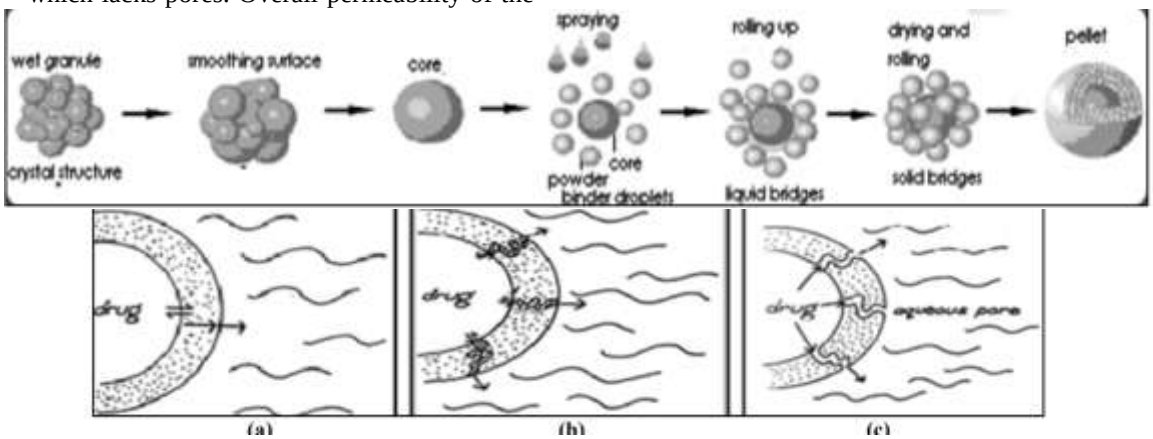

Fig: Mechanism Of Pellet Formation

The recent market for novel drug delivery system has continued to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into a new delivery system, thus providing numerous therapeutic and commercial advantages. Pelletization lays the scope for different oral immediate or controlled delivery system. Due to its simple design, greater flexibility, efficiency of producing spherical pellets and fast processing; it has found a special place in the pharmaceutical industry.

REFERENCES

[1]. Shaji J, Chadawar V and Talwalkar P: Multiparticulate Drug Delivery System. The Indian Pharmacist. 2007;6(60):21-28.

[2]. Dashora K, Saraf S and Saraf S. Development of sustained release multicomponent microparticulate system of Diclofenac sodium and Tizanidine hydrochloride. Int J Pharm Sci and nanotechnology. 2008; 1:98-105.

[3]. Roy P and Shahiwala A. Review: Multiparticulate formulation approach to pulsatile drug delivery: Current

perspectives. J Cont Rel. 2009; 134:74–80.

[4]. Gibaldi M. Biopharmaceutics and clinical pharmacokinetics. Lea and Febiger, Philadelphia, Third Edition 1984.

[5]. Palsson BO, Wheatley TA and Dressman JB. Mechanism of release from pellets coated with an ethylcellulose based film J Cont Rel.1990;14:203-213.

[6]. Ghebre-Sellassie: Pellets: A General Overview. Pharmaceutical Pelletization Technology, Marcel Dekker, First Edition 1989.

[7]. Melia C, Washington N and Wilson GC. Multiparticulate Controlled Release Oral Dosage Forms. Scottish Academic Press Ltd., First Edition 1994.

[8]. Claudio N, Rita C, Elisabetta E, Alberto G, Alessandro S, Carlo V and Enea M. Influence of the formulation and process parameters on pellet production by powder layering technique. AAPS Pharm SciTech. 2000;1(2):1-12.

[9]. Kaynak MS, Kas SH and Oner L. Formulation of controlled release Glipizide pellets using pan coating method. Hacettepe Univ. Journal of Faculty of Pharmacy. 2005;93-106.

[10]. Newton A, Podczeck F, Alderborn G and Chopra R. The influence of pellet shape and surface properties on the drug release from uncoated and coated pellets. Int. J. Pharm. 2002;239(1):171-178.

[11]. Thoma K and Ziegler I: The pH independent release of fenoldopam from pellets with insoluble film coats. Eur J Pharm and Biopharm. 1998;46(1):105-113.

[12]. Gandhi BR, Badgujar BP and Kasliwal AV. Development and In-vitro evaluation of multiparticulate system using novel coating material for controlled drug delivery system. Int J Pharm Pharm Sci. 2011;3(3):96-99.

[13]. Maryadele J, O'Neil, Ann Smith, Patricia E, Heckelman and Susan B: The Merck Index. White House Station, NJ: Merck Research Laboratories, Thirteenth Edition 2001.

[14]. Sweetman SC: Martindale-The complete drug reference. London: Pharmaceutical Press, Thirty-fourth Edition 2002.

[15]. Langtry HD and Benfield P. Zolpidem: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential. Drugs. 1990; 40:291-313. 1

[16]. Thoma K and Ziegler I. The pH independent release of fenoldopam from pellets with insoluble film coats. Eur J Pharm and Biopharm. 1998;46(1):105-113.

[17]. Shivkumar HN, Desai BG and Sarasija S. Design and evaluation of pH sensitive multi-particulate systems for chronotherapeutic delivery of diltiazem hydrochloride. Ind J Pharm Sci. 2006; 68(6):781-787.

[18]. Handa AK, Kerudi AV and Bhalla HL. Development and evaluation of ethylcellulose coated controlled release pellets. Ind J Pharm Sci. 2000;62(2):147-153.

[19]. Jose S, Dhanya K, Cinu TA and Aleykutti NA. Multiparticulate system for colon targeted delivery of ondansetron. Ind J Pha Sci. 2010; 58-64.

[20]. Padhee K, Chowdhary KA, Pattnaik S, Sahoo SK and Pathak N. Design and development of Multiple-Unit, Extended-release drug delivery system of Verapamil HCL by Pelletization Technique. International Journal of Drug Development and Research. 2011; 3(3):118-25