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Review Article

Different Aspects of Pellets Formulation and their Evaluation

Amit M. Gupta*, Umesh D. Shivhare and Pravin B. Suruse
Sharad Pawar College of Pharmacy, Wanadongri, Hingna road, Nagpur- 441 110 (M.S), India.

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Abstract

The mechanism of drug release from coated pellets is widely accepted for use as a sustained release drug delivery system. Plasticizer-free sustain release coatings were too brittle and ruptured during compression. The possible mechanism for drug release includes solution/diffusion through the continuous polymer phase or plasticizer channels, diffusion through aqueous pores and osmotically driven release through aqueous pores. To distinguish between these mechanisms, the release rate was studied as a function of coating thickness, plasticizer content and osmotic pressure in the dissolution medium. This treatment led to the formation of multiple layers of drug particles around an inert core resulting in the production of pellets that can further be coated by different polymers to obtain modified release formulations.

1. INTRODUCTION

Extrusion-spheronization technology has been adopted by most of the pharmaceutical industries for production of pellets, Factors that mostly influence pellet production have been studied and found to be reformulation parameters, irrespective of the solid dosage form, influence both the process and the quality of the final product[1].

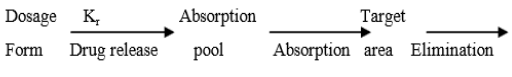
In particular, the morphology of pellets and total structure can change with any variation in formulation or in materials properties, affecting quality parameters such as porosity and surface roughness. These properties are considered to have a great influence on coating, flow and packing during capsule filling or tabletting. Porosity and pore structure can also provide relevant information for predicting the disintegration, dissolution, adsorption and diffusion behavior of drugs. Recent studies have shown that porosity parameters, such as pore size distribution, total pore surface area, mean pore diameter and pore shape of pellets formulated with an insoluble drug, correlate with drug release. Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes and also can be blended to deliver incompatible bioactive agents simultaneously and to provide different release profiles at the same or different sites in the gastrointestinal tract. In addition, pellets, taken orally, disperse freely in the GI tract, maximize drug absorption, minimize local irritation of the mucosa by certain irritant drugs, and reduce inter and intra patient variability. Pellets are spherical agglomerated powders and can be prepared by various processes. Pelletization techniques widely used in pharmaceutical industries are direct pelletization, extrusion spheronization and layering. Direct pelletization technique using fluidized bed equipment has many advantages such as one-unit process with short processing time. The layering technique is the process in which drug in powder solution or suspension form is layered onto seed materials.[2,3]

Corresponding Author:
Mr. Amit M. Gupta
Sharad Pawar College of Pharmacy,
Wanadongri, Hingna road,
Nagpur- 441 110 (M.S), India
Email: amitmgupta31@gmail.com

2. SUSTAINED RELEASE SYSTEM

The concept of sustained release formulations was developed to eliminate the need for multiple dosage regimens, particularly for those drugs requiring reasonably constant blood levels over a long period of time. In addition, it also has been adopted for those drugs that need to be administered in high doses, but where too rapid a release is likely to cause undesirable side effects.

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and respiratory dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of orally administered forms, however, this period is measured in h and critically depends on the residence time of the dosage form in the GI tract. A conventional dosage form includes solutions, suspensions, capsules, tablets, emulsions, aerosols, foams, ointments and suspensions. These dosage forms can be considered to release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme:



..... (01)

The absorption pool represents a solution of the drug at the site of absorption, Kr, Ka and Ke first order rate-constant for drug release, absorption and overall elimination respectively.

Non-immediate release delivery systems may be divided in to four categories:

1. Delayed release
2. Sustained release
   A. Controlled release
   B. Prolonged release
3. Site specific release
4. Receptor release

3. DELAYED RELEASE SYSTEMS

Delayed release systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets, capsules and enteric-coated tablets where timed release is achieved by barrier coating. A delayed release dosage form does not produce or maintain uniform blood level within the therapeutic range that achieves slow release of drug over an extended period of time. This system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled release system.

A. Controlled release
B. Prolonged release
C. Conventional release

Site specific and receptor release refer to targeting of a drug delivery directly to a certain biological location. In these cases of site-specific release, the target is adjacent to or in the diseased organ or tissue for receptor release. The target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery. Release rate and dose consideration although it is not necessary or desirable to maintain a constant level of drug in the blood or target tissue for all therapeutic cases, this is the ideal goal of a sustained release delivery system.[4,5]

3. BIOLOGICAL PROPERTIES

Absorption

The rate, extent and uniformity of absorption of a drug are important factors when considering its formulation into a sustained release drug delivery system. Since the rate limiting step of sustained release drug delivery system is it's release from rather than absorption of the drug relative to its release is essential if the system is to be successful. The extent and uniformity of the absorption of a drug as reflected by its bioavailability and the fraction of the total dose absorbed may be quite low for a variety of reasons like poor water solubility, smaller partition coefficient, acid hydrolysis and metabolism or site specific absorption.

Distribution

Parameters which are used to describe the distribution characteristics of a drug which are its apparent volume of distribution and the ratio of drug concentration in tissue to that in plasma at the steady state, the so called T/P ratio. For the drugs, which follow one compartment, the apparent volume of distribution is

$$V = \text{dose} / C_0 \quad \text{..... (02)}$$

Where,

C_0 = initial drug concentration

In case of two-compartment model, it has been shown that the apparent volume of distribution at steady state gives the best estimate of total volume of drug distribution:

$$V_{ss} = (1+ K_{12}/K_{21})\ V1 \quad \text{..... (03)}$$

Where

V1 = volume of central compartment

K_{12} and k_{21} = rate constants

V_{ss} = drug concentration at steady state.

Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained release system for that drug. There are two factors, which are associated with the metabolism of drugs. One is the ability of drug to induce or inhibit enzyme synthesis: this may result in a fluctuating drug blood levels with chronic dosing. The other is hepatic or first pass effect.

Elimination and biological half-life

The rate of elimination of a drug is described quantitatively by its biological half-life (t ½). A drug with shorter half-life requires frequent dosing, whereas for drug having longer half-life does not need to develop sustained release. Drugs having an intermediate half-life are suitable candidates for sustained release dosage form. Side effects and safety considerations: The most widely used measure of the margin of safety of a drug is its therapeutic index, TI, defined in following equation

$$TI = TD_{50} / ED_{50} \quad \text{..... (04)}$$

Where,

TD_{50} = median toxic dose

ED_{50} = median effective dose

Larger the values of TI indicates drug is safe. Drugs with small values of TI usually are poor candidates for formulation into sustained release products.

Advantages of sustained release dosage form

- Avoid patient compliance problem
- Employ less total drug
- Minimize or eliminate local side effect
- Minimize or eliminate systemic side effect
- Obtain less potentiation or reduction in drug activity with chronic use
- Minimize drug accumulation with chronic dosing
- Improve efficiency in treatment
- Cure or control conditions more promptly
- Reduced fluctuations of drug level
- Improve bioavailability of some drug
- Dosing frequency is reduced
- Dose size is reduced
- Safety margins of high – potency drugs can be increased

Disadvantages of sustained release dosage form

- Prompt termination is not possible
- Less flexibility in adjusting dosage regimen
- Costlier
- Poor in vivo in vitro correlation
- Less systemic availability6,7

5. PELLETIZATION TECHNIQUES

The term pellet has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials, using different pieces of manufacturing equipment. In the pharmaceutical industry, pellets can be defined as small, free flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. The term also has been used to describe small rods with aspect ratios of close to unity. Pellets offer a high degree of flexibility in the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes and also can be blended to deliver incompatible bioactive agents simultaneously and to provide different release profiles at the same or different sites in the GT tract.[8,9]

Enormous advantages of multiparticulate systems over single-unit oral dosage forms, extensive research has focused recently on refining and optimizing existing pelletization techniques as well as on the development of novel manufacturing approaches that use innovative formulations and processing equipment. Pellets provide a solid dosage form with several advantages.[10]

Various techniques of pelletization

A. Powder layering technique
B. Solution / suspension layering technique
C. Extrusion- spheronization technique
D. Balling / spherical agglomeration
E. Spray congealing / drying
F. Cryopelletization
G. Melt spheronization

A. Powder Layering: Various steps involved in this technique are as follows:

1. Sifting/milling
2. Loading of non pareil seeds
3. Drug coating
4. Drying
5. Sizing
6. Functional coating
7. Encapsulation

Converting powders to pellets can be achieved by a variety of techniques. Layering a suspension or solution of drug onto a seed material can result in pellets that are uniform in size distribution and generally possess very good surface morphology. These characteristics are especially desirable when the pellets will

subsequently be coated for some type of controlled release for 24 h. This method involves the disposition of successive layers of solutions and/or suspensions of drug substances and binder on starter seeds, which may be inert materials or granules of the same drug. In principle, the factors that control coating processes apply to solution or suspension layering and as a result, require basically the same processing equipments. In the initial stages, the drug particles are bound to the starter seeds and subsequently to the forming pellets with the help of liquid bridges originated from the sprayed liquid. These liquid bridges are eventually replaced by solid bridges derived either from a binder in the application medium or from any other material, including the drug substances, that is soluble in the liquid. Successive layering of the drug and binder solution continues until the desired pellet size is reached. Throughout the process, it is extremely important to deliver the powder accurately at a predetermined rate and in a manner that maintains equilibrium between the binder liquid application rate and the powder delivery rate. If the powder delivery rate is not maintained at predetermined equilibrium levels, over wetting or dust generation may occur and neither the quality nor the yield of the product can be maximized. Towards the end of the layering process, it is likely that fines may be generated owing to potential inter particle and wall-to-particle friction and appears in the final product thereby lowering the yield. The problem can be overcome if the application medium is sprayed on the cascading pellets at the end of the layering process to increase the moisture level at the pellet surface and facilate layering of the fines onto the pellets. The equipments like tangentianal spray equipment, centrifugal fluid bed granulator, rotary granulator are used for this purpose.[11]

B. Solution / suspension layering technique

Various steps involved in this technique are as follows:

1. Mixing/milling
2. Loading of non pareil seeds
3. Drug coating
4. Drying
5. Sizing
6. Functional coating
7. Encapsulation

This method involves the deposition of successive layers of solution and/or suspensions of drug substances and binders on starter seeds, which may be inert materials or crystals/granules of the same drug. The factors that control coating processes apply to solution or suspension layering and require basically the same processing equipment. Consequently, conventional coating pan, fluid bed granulator and wruster coaters have been used successfully to manufacture pellets. The wruster coating process which was invented about 30 years ago, had evolved through elaborate design modifications and refinement into ideal equipment for the manufacture of pellets by solution/suspension layering. The high drying efficiency inherent in fluid bed equipment, coupled with the innovative and efficient design features of the Wruster process, has allowed the machines to hold center stage in pharmaceutical processing technology. The disadvantage of the Wruster process is the inaccessibility of the nozzle. If the nozzles are clogged at any time during the layering process, the operation has to be interrupted and the spray guns must be removed for cleaning. The problem can be alleviated by screening the formulation or by using a spray gun with a bigger nozzle. Another aspect of the process that is challenging when multiple nozzles are used is the potential overlap of adjacent spray zones. Although the position of the nozzle is fixed, the spray zone overlap can be minimized using the air cap at the end of the spray gun.

During processing, all the components of the formulations are first dissolved or suspended in an appropriate quantity of application medium to provide a formulation with the desired viscosity and is then sprayed onto the product bed. The sprayed droplets immediately impinge on the started seeds and spread evenly on the surface, provided the drying conditions and fluid dynamics are favourable. This is followed by a drying phase that renders dissolved materials to precipitate and form solid bridges that would hold the formulation components tighter as successive layers on the started seeds. The process continues until the desired quantity of drug substance and thus target potency of the pellets is achieved. Ideally, no new nuclei are formed, and the particle population remains the same. However, the sizes of the pellets increase as a function of time, and as a result, the total mass of the system also increases. Optimization of process variables is difficult for the successful development of a palletized product.[12]

Although it is possible to manufacture pellets from a formulation that does not contain binders, almost invariably, the layers of drug applied tend to delaminate or break off from the cores in the later stages of the layering process or in the subsequent drying step. Therefore, binders are consistently used during this process to impart strength to the pellets. They are usually low-molecular-weight polymers that are compatible with the drug substance.

C. Extrusion and spheronization

Various steps involved in this technique are as follows:

Sifting/milling
Mixing/binding
Extrusion
Spheronization
Drying
Sizing
Coating
Encapsulation

This is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying and screening. The first step is dry mixing of the drug and excipients in suitable mixers followed by wet granulation, in which the powder is converted in to a plastic mass that, can be easily extruded. The extruded strands are transferred into a Spheronizer, where they are instantaneously broken into short cylindrical rods on contact with the rotating friction plate and pushed outward and up the stationary wall of the processing chamber by centrifugal force. Finally, owing to gravity, the particles fall back to the friction plate, and the cycle is repeated until the desired sphericity is achieved. The technology is unique in that it is not only suitable for manufacture of pellets high drug loading but it also can be used to produce extended-release pellets in certain situations in a single step and thus can obviate the need for subsequent film coating. Extrusion – spheronization is a multistep process involving a number of unit operations and equipment. However, the most critical pieces of processing equipment that, in effect, dictate the outcome of overall process are the extruders and spheronizer.[13]

A variety of extruders, which differ in design features and operational principles are currently on the market and can be classified as screw-fed extruders, gravity-fed extruders, and ram extruders. Screw-fed extruders have screws that rotate along the horizontal axis and hence transport the material horizontally. They may be axial or radial screw extruders. Axial extruders, which have a die plate that is positioned axially, consist of a feeding zone, a compression zone and an extrusion zone. The product temperature is controlled during extrusion by jacketed barrels. In radial extruders, the transport zone is short and the material is extruded radically through screens mounted around the horizontal axis of the screws.

Gravity-fed extruders include the rotary cylinder and rotary gear extruders which differ primarily in the design of the two counter-rotating cylinders. In the rotary-cylinders extruder, one of the two counter-rotating cylinders is hollow and perforated, whereas the other cylinder is solid and cats as a pressure roller. In the so-called rotary-gear extruder, there are two hollow counter-rotating gear cylinders with counter bored holes. In ram extruders, a piston displaces and forces the material through a die at the end. Ram extruders are preferred during formulation development they are designed to allow for measurement of the rheological properties of formulation. In an extrusion – spheronization process, formulation components such as filler, lubricants and pH modifiers play a critical role in producing pellets with the desired attributes. The granulated mass must be plastic and sufficiently cohesive and self lubricating during extrusion. During the spheronization step, it is essential that the extrudates break at appropriate length and have sufficient surface moisture to enhance formation of uniform spherical pellets.[14]

D. Spray drying and spray congealing

Both are known as globulation processes involve atomization of hot melts, solutions or suspensions to generate spherical particles of pellets. The droplet size in batch is kept small to maximize the rate of evaporation or congealing and particle size of the pellets produced is usually small. During spray drying, drug entities in solution or suspension are sprayed with or without excipients, into a

hot air stream to generate dry and highly spherical particles. As the atomized droplets come in contact with hot air evaporation of the application medium is initiated.
This drying process continues through a series of stages whereby the viscosity of the droplets constantly increases until finally almost the entire application medium is driven off and solid particles are formed. Generally spray-dried pellets tend to be porous.

E. Cryopelltization
This is the process whereby droplets of liquid formulations are converted into solid spherical particles or pellets by using liquid nitrogen as fixing medium. The technology which was initially developed for lyophilization of viscous bacterial suspension can be used to produce drug-loaded pellets in liquid nitrogen at 160ºC. The procedure permits instantaneous and uniform freezing of the processed material owing to the rapid heat transfer that occurs between the droplets and thus the large surface area facilate the drying process. The amount of liquid nitrogen required for manufacturing a given quantity depends on the solids content and temperature of the solution or suspension being processed. It is usually between 3 and 5 kg per kilogram of finished pellets.

F. Melt spheronization
It is a process whereby a drug substance and excipients are converted into a molten or semi molten state and subsequently shaped using appropriate equipment to provide solid spheres or pellets. The drug is blended with the excipients, polymers and waxes and extruded at predetermined temp. The extrusion temp must be high enough to melt at least one of the components. The extrudates is cut into uniform cylindrical segments with a cutter and then they are spheronized resulting pellets are dried.[15,16]

Role of disintegrating agent
Disintegrants are agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule "slugs' into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. The emphasis on the availability of drug highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behavior. Number of factors affects the disintegration behavior of tablets. The disintegrants have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet. The stronger the binder, the more effective must be the disintegrating agents in order for the tablet to release its medication. Ideally, it should cause the tablet to disrupt not only into the granules from which it was compressed but also into powder particles from which the granulation was prepared. Disintegrants are an essential component to tablet formulations. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling, wicking and deformation are the mechanisms of disintegrant action. A disintegrant used in granulated formulation processes can be more effective if used both "intragranularly" and "extragranularly" thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution. However, the portion of disintegrant added intragranularly (in wet granulation processes) is usually not as effective as that added extragranularly due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrant. Since a compaction process does not involve its exposure to wetting and drying, the disintegrant used intragranularly tends to retain good disintegration activity. There are three methods of incorporating disintegrating agents into the tablet:

a. Internal Addition (Intragranular)
b. External Addition (Extragranular)
c. Partly Internal and External

In a direct compression process, drug is blended with a variety of excipients, subsequently lubricated and directly compressed into a tablet. A disintegrant used in this type of formulation simply has to break the tablet apart to expose the drug substance for dissolution. Most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and disintegrating tablets that are swallowed but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth. Most prior studies have focused on the function related properties of superdisintegrants with special emphasis on correlating these functional properties to disintegrant efficiency and drug release rate. Water penetration rate and rate of disintegration force development are generally positively related to disintegrant efficiency in nonsoluble matrices. However, such a positive correlation is not always observed between tablet disintegration time and drug dissolution rate.[17,18]

6. CHARACTERIZATION OF PELLETS [19-26]

Crushing strength
Strength testing was performed in 20 pellets of each formulation with an available radial force apparatus.

Density and porosity
Densities were derived as follows: An exact quantity ' M ' of pellets was taken and was placed into a measuring cylinder. Volume ' V ' occupied by the pellets was noted without disturbing the cylinder and bulk density was calculated using the following equation

$$\text{Bulk density}\,(P_b) = \frac{M}{V} \quad \text{..... (05)}$$

The tapping method was used to determine the tapped density in which the cylinder containing known amount (M) of pellets was subjected to a fixed number of taps (approximately 100) until the bed of pellets had reached the minimum. The final volume after tapping 'V_o ' was recorded and the tap density was calculated by the following equation:

$$\text{Tapped density}\,(P_p) = \frac{M}{V_o} \quad \text{..... (06)}$$

Angle of repose, Hausner ratio and Carr index (% compressibility index) were determined to predict flowability. A higher Hausner ratio indicates greater cohesion between pellets while a high Carr index is indicative of the tendency to form bridges. Angle of repose of the pellets is the maximum angle possible between the surface of the pile of pellets and the horizontal plane was obtained by fixed funnel method using the formula:

$$\text{Angle of repose}(\theta) = \tan^{-1}\left(\frac{2h}{d}\right) \quad \text{..... (07)}$$

Where, h is height and d is the diameter of the microsphere pile that is on a paper after making the microspheres flow from the glass funnel.

Hausner ration and Carr's index
Hausner ration and Carr's index were calculated using the formulae:

$$\text{Carr index or \% compressibility index or C} = \left[1 - \frac{V_o}{V}\right] \times 100$$

$$\text{Hausner ratio} = \frac{100}{100 + C} \quad \text{..... (08)}$$

Here, V and V_o are the volumes of the sample before and after the standard tapping respectively and C is Carr index.

***In vitro* dissolution studies**
Dissolution was conducted in a USP (Method 1, rotating basket) apparatus, at a speed of 100 rpm, in 900 ml of dissolution media (phosphate buffer at pH 7.2 ±0.05), maintained at 37 ± 0.5°C, using an automated assembly UV spectrophotometer.

Stability study of sustained release pellets
Stability study of pellets was performed as at room temperature, 40°C/75% RH & 30°C/70% RH for three months. The physical properties of pellets as well as the *In vitro* release profile of the drug was found to be a function of the different storage conditions as well as the physico-chemical nature of the polymers.

Physical properties of pellets

Shape and size of the pellets

Two hundred pellets were randomly chosen from each batch to be analyzed. The pellets were placed on the nonshiny black surface of the microscope (black–white contrast plate) serving as the background. Therefore 15–20 photos were taken of each batch, and the images produced were analyzed. In this study, the pellet size and shape were characterized by roundness, aspect ratio (AR) and Feret diameter. Roundness (C) was calculated using the following formula:

$$C = \frac{p^2}{4 \times \pi \times A} \quad \text{..... (09)}$$

Where, p is the perimeter and A is the area of the pellet.

AR is the ratio of the maximum Feret diameter. In these cases the value for an ideal sphere is 1. The more the value differs from 1, the more the object differs from a perfect round particle. The values presented for each type of pellet are the average and standard deviation (SD) calculated from the measurement of 200 individual pellets.

Tensile strength of the pellets

Twenty pellets of each batch were measured with a texture analyzer operating with a 5-kg load cell. Single pellets were placed onto a flat steel plate. A cylindric punch of 5 mm diameter was moved from the top with a speed of 0.1 mm/s towards the pellet. The crushing load (F) and the diameter (d) of each individual pellet were recorded during the test. The surface tensile strength was calculated using Eq.

$$\sigma_f(s) = \frac{1.6 \times F}{\pi \times d^2}. \quad \text{.....(10)}$$

The average of 20 values was reported as the tensile strength for each batch.

7. CONCLUSION

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product reduction in the frequency of administration to prolong duration of effective blood levels reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection. Second it should deliver the active entity directly to the site of action minimizing the side effects.

REFERENCES

1. Dashevsky A., K. Kolter and R. Bodmeier, 2004. Compression of pellets coated with various aqueous polymer dispersions. International Journal of Pharmaceutics, 279, 19–26.
2. Kai Pan, Xing Tang and Jianhong Yang, 2009. Preparation of sustained release pellets of poorly soluble drugs by cogrinding and extrusion-spheronisation. Asian Journal of Pharmaceutical Sciences, 4 (2), 106-114.
3. Carla Martins Lopes, José M. Sousa Lobo, João F. Pinto and Paulo C. Costa, 2007. Compressed Matrix Core Tablet as a Quick/Slow Dual-Component Delivery System Containing Ibuprofen. AAPS PharmSci. Tech., 8 (3), 76.
4. A.G. Ozturk, S.S. Ozturk, B.O. Palsson, T.A. Wheatley and J.B. Dressman, 1990. Mechanism of release from pellets coated with an ethylcellulose- based film. Journal of Controlled Release, 14, 203-213.
5. Gautam Singhvi and Mahaveer Singh, 2011. Review: In-Vitro drug release characterization models. International Journal of Pharmaceutical Studies and Research, II (I), 77-84.
6. Mangesh E. Bhad, Shajahan Abdul, Sunil B. Jaiswal, Anil V. Chandewar, Jayesh M. Jain and Dinesh M. Sakarkar, 2010. MUPS Tablets – A Brief Review. International Journal of PharmTech Research, 2(1), 847-855.
7. Vishal Sachdeva, Md. Shoaib Alam, Ramesh Kumar and Mahesh Kumar Kataria, 2013. Oral multiunit pellet extended release dosage form: A review. International Current Pharmaceutical Journal, 2(10), 177-184.
8. Claudio Nastruzzi, Rita Cortesi, Elisabetta Esposito, Alberto Genovesi, Alessandro Spadoni,Carlo Vecchio, Enea Menegatti, 2000. Influence of formulation and process parameters on pellet production by powder layering technique. AAPS Pharm. Sci. Tech, 1 (2) article 9.
9. Lourdes Ochoa, Manuela Igartua, Rosa Ma, Hernández, Alicia R. Gascón and José Luis Pedraz, 2005. Preparation of sustained release hydrophilic matrices by melt granulation in a high-shear mixer. J Pharm Pharmaceut Sci, 8(2), 132-140.
10. Raveendra Pai, Kanchan Kohli and Birendra Shrivastava, 2012. Compression and evaluation of extended release matrix pellets prepared by the extrusion/spheronization process into disintegrating tablets. Brazilian Journal of Pharmaceutical Sciences, 48(1), 117-129.
11. Jamila Hamdani, Andre´ J. Moe¨s and Karim Amighi, 2002. Development and evaluation of prolonged release pellets obtained by the melt pelletization process. International Journal of Pharmaceutics, 245, 167- 177.
12. Vinayak D Kadam and Surendra G Gattani, 2009. Effect of Curing Time on pH and Time Dependant Coated Pellets. International Journal of Health Research, 2(1), 75-81.
13. F. Podczeck, P.E. Knight and J.M. Newton, 2008. The evaluation of modified microcrystalline cellulose for the preparation of pellets with high drug loading by extrusion/spheronization. International Journal of Pharmaceutics, 350, 145–154.
14. Srujan Reddy, Palash Das, Harika Das and Arpita Ghosh, 2011. MUPS (Multiple Unit Pellet System) Tablets - A Brief Review. Journal of Pharmaceutical and Biomedical Sci., 12(02), 1-5.
15. Nikolett Kállai, Oliver Luhn, Judit Dredán, Kristóf Kovács, Miléna Lengyel and István Antal, 2010. Evaluation of drug release from coated pellets based on isomalt, sugar and microcrystalline cellulose inert cores. AAPS Pharm. Sci.Tech., 1(1), 383-391.
16. Guanhao Ye, Siling Wang, Paul Wan Sia Heng, Ling Chen and Chao Wang, 2007. Development and optimization of solid dispersion containing pellets of Itraconazole prepared by high shear pelletization. International Journal of Pharmaceutics, 337, 80–87.
17. Mohit Mangal, Sunil Thakral, Manish Goswami and Pankaj Ghai, 2012. Superdisintegrants: An updated review. International Journal of Pharmacy and Pharmaceutical Science Research, 2(2), 26-35.
18. T.S. Nithiyananthan, V. Shankarananth, K.K. Rajasekhar and G. Hareesh, 2009. Formulation and evaluation of Tamsulosin hydrochloride as sustain release matrix tablet. International Journal of Chem. Tech. Research, 1(4), 1278-1290.
19. C.P. Jain and P.S. Naruka, 2009. Formulation and evaluation of fast dissolving tablets of Valsartan. International Journal of Pharmacy and Pharmaceutical Sciences. 1(1), 219- 226.
20. Dhirendra Kumar, Vivek Dave, Shaila Lewis, Brajesh Parmar, Kavita R. Gajbhiye, Sarvesh Paliwal, 2010. Design and evaluation of sustained-release matrix once daily formulation of Stavudine. International Journal of Drug Delivery, 2, 125-134.
21. Gihan Nabil Fetih, 2010. Formulation and characterization of Gelucire pellets for sustain release of Ibuprofen. Bull. Pharm. Sci., Assiut University, 33(2), 217-224.
22. Golam Kibria, KM Ariful Islam and Reza-Ul Jalil, 2009. Stability studies of Ambroxol Hydrochloride sustain release pellets coated with acrylic polymer. Pak. J. Pharm. Sci., 22(1), 36-43.
23. V. S. N. Murthy Dwibhashyam and J. Vijayaratana, 2008. Key formulation variables in tableting of coated pellets. Indian Journal of Pharmaceutical Sciences, 70 (5), 555-564.
24. Jaber Emami, Mona Tajeddin and Fatemeh Ahmadi, 2008. Preparation and *In vitro* evaluation of sustained-release matrix tablets of Flutamide using synthetic and naturally

occurring polymers. Iranian Journal of Pharmaceutical Research, 7 (4), 247-257.

25. Phutane P, Shidhaye S, Lotlikar V, Ghule A, Sutar S and Kadam V, 2010. *In vitro* evaluation of novel sustained release microspheres of Glipizide prepared by the emulsion solvent diffusion-evaporation method. J Young Pharmacists, 2, 35-41.

26. Subal Chandra Basak, Kesevan Senthil Kumar and Murugesan Ramalingam, 2008. Design and release characteristics of sustained release tablet containing Metformin HCl. Brazilian Journal of Pharmaceutical Sciences, 44(3), 477- 483.