International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 123-129 www.ijprajournal.com ISSN: 2249-7781

A Brief Review on Multi Unit Pellet System

Varasala Divyasree
Centre for PharmaceuticalSciences,JNTUHUCESTH,Hyderabad, Telangana-500085,India
Corresponding Author: Dr. M. Sunitha Reddy,Dr. M. Ajithaand Dr.Gawaskar

Submitted: 11-03-2024 Accepted: 21-03-2024

ABSTRACT: In oral drug delivery modified release dosage forms (MRD) plays an important role in regulating the drug delivery to improve the quality of therapy. One excellent technique to formulate MRDs is multiple unit particle systems (MUPS), where the dosage form is distributed over multiple units rather than a single unit. This unique feature of MUPS makes them a suitable candidate for the delivery of different types of drug molecules for a variety of therapeutic purposes.Multiple Unit Pellet System (MUPS), is one of the more recent and challenging technologies that combine the advantages of both tablets and pellet -filled capsules in one dosage form.
KEYWORDS: Pellet, Multi particulate drug delivery system, Modified drug release.

I.INTRODUCTION

Multi-Unit Pellet System (MUPS):

Pellets are more advantages than regular single unit dosage forms like tablets & capsules because pellets disperse easily in GIT & increase drug absorption by reducing the regional exasperation of mucosa. Pellets also lessen the variability of inter-intra patients

Types of MUPS Formulations: In general, MUPS formulations can be classified into two categories

a) MUPS comprising of coated pellets ; pellets coated with polymer material using different pelletization techniques to achieve the desired release characteristics. These polymer-coated pellets were compacted into multiparticulate tablets either alone or with a mixture of inert excipients.

b) MUPS comprising of matrix pellets ; matrix pellets are particles which initially contain excipients that retard drug release by incorporation within the matrix of the pellet structure. This category is less frequently encountered in comparison to the compaction of polymer coated pellets.

Figure-1: MUPS- Multi unit pellets compressed to tablet

Tablets are indeed the most popular solid dosage form for oral administration. A relatively more recent approach that has come into existence is the one that combines the features of both controlled release tablets and modified release capsules in one dosage form, known as MUPS tablets.

ADVANTAGES OF MULTIPARTICULATES (PELLETS):

The use of pellets as a vehicle for drug delivery at controlled rate has recently received significant attention. Pellets can be prepared by many methods, the drug-layering technique is most widely used today. Multi particulates provide various advantages as given below,

1. Avoidance of the dose dumping
2. Gastric emptying is faster.
3. Performance is less dependent on nutritional state as multi particulates are sufficiently small and can be evacuated through pylorus during digestive phase.
4. Shows improved reproducibility of transit time and high degree of dispersion in digestive tract.
5. Better distributed and less likely to cause local irritation.
6. Improved stability, patient comfort and compliance.
7. Achieve unique release pattern.

DISADVANTAGES OF MUPS (PELLETS):

- Low drug loading
- Proportionally higher need for excipients
- Lack of manufacturing reproducibility and efficacy

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 123-129 www.ijprajournal.com ISSN: 2249-7781

- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained/skilled personal needed for manufacturing

APPLICATIONS:

1. Control release pellets for encapsulation.
2. Sustained release pellets.
3. Multi-particulate systems.
4. Multi-unit erosion matrix pellets.
5. Application of pellets for special tableting.
6. Application of pellets for Sachets having immediate release.

Rationale for Pellets:

Pellets are of great interest to the pharmaceutical industry for a variety of reasons. Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve safety and efficacy of bioactive agents. However, the single most important factor responsible for the proliferation of pelletized products is the popularity of controlled release technology in the delivery of drugs. When pellets containing the active ingredients are administered in the form of suspensions, capsules, or disintegrating tablets.

Techniques of Pelletization:

Depending on the type of equipment and process selected, pellet formation and growth may occur in number of ways.The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering, and extrusion–spheronization methods.

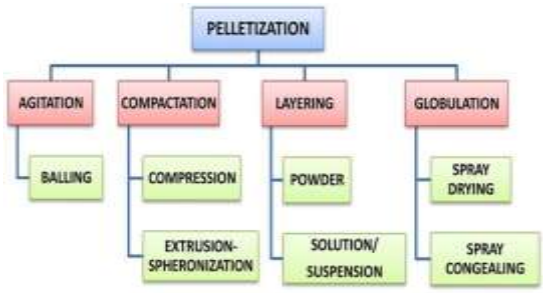

Figure-2: Classification of pelletization techniques

A.Balling:

Balling or Spherical agglomeration is a Pelletization process in which powders, upon addition of an appropriate quantity of liquid, are converted to spherical particles by a continuous rolling or tumbling action. The liquid may be added prior to or during the agitation stage Pelletizers, inclined dish pelletizers, and tumbling blenders; a more recent technology uses rotary fluid-bed granulators.

B. 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. Most recently, microcrystalline cellulose (MCC) has been tested as a substrate for drug layering.

C. Powder Layering:

In powder layering liquid saturation is low and irrespective of the solubility of the drug in the binding liquid, complete dissolution does not occur. Typically, a binder solution is first sprayed onto the nuclei, followed by the addition of powder. The most nuclei tumble in the rotating pan of disc, pick up powder particles, and form layers of small particles that adhere to each other and the nuclei by means of capillary forces developed in the liquid phase. As additional bonding, liquid is sprayed, layering of more powder on the nuclei continues until the desired pellet sizes are obtained. On drying, the binder and other dissolved substance crystallize out and the liquid bridges are partially replaced by solid bridges. On spraying with binder, fines may pick up moisture and enter a nucleate on phase.

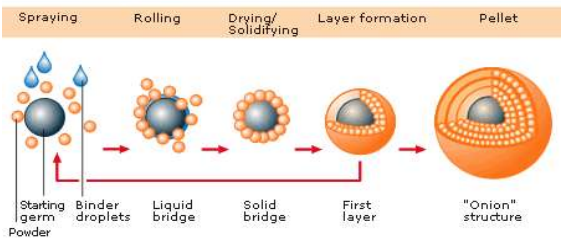

Figure-3: Principle of powder layering

D. Solution and Suspension Layering: Solution and suspension layering involve the deposition of successive layers of solutions and suspensions of drug substances, respectively, on starter seeds that may be inert materials or crystals or granules of the

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 123-129 www.ijprajournal.com ISSN: 2249-7781

same drug. In principle, the factors that control coating processes apply directly to solution or suspension layering. During solution or suspension layering, all the components of the formulation are dissolved or suspended in the application medium and hence determine the solids contents and the viscosity of the liquid sprayed. 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 favourable. This is followed by the drying phase which allows dissolved materials to crystallize and form solid 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 are 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.

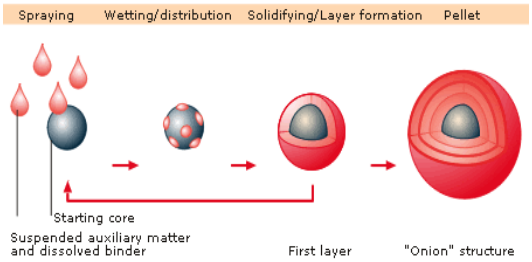

Figure-4: principle of solution/suspension layering

E. Spray Drying and Spray Congealing:

Spray drying and spray congealing, known as globulation processes, involve atomization of hot melts, solutions, or suspensions to generate spherical particles or pellets. During spray drying, drug entities in solution or suspension is 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 where 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.

During spray congealing, a drug substance is allowed to melt, disperse, or dissolve in hot melts of waxes, fatty acids, etc., and sprayed into an air chamber where the temperature is below the melting temperatures of the formulation components, to provide under appropriate processing conditions spherical congealed pellets.

F. Compaction:

Compaction is a form of pressure agglomeration in which drug particles or granules are forced together with or without formulation aids by a mechanical force to generate pellets of well-defined shapes and sizes. Compaction, as a general Pelletization process can be subdivided into compression and extrusion. Recently, however, melt Pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer.

G. Compression:

During first stage of compression, particles that are pre-treated through dry blending or wet granulation followed by drying, rearrange themselves to form a closely packed mass. At higher pressures, the particles are forced against each other even more and undergo elastic and plastic deformation, thereby increasing inter particle contact. Because particles approach each other closely enough, short range bonding forces like Van der Waals forces, electrostatic forces, and sorption layers become effective.

H. Extrusion:

Extrusion is another form of pressure agglomeration is not, by itself, a single pellet process. It is one of the three unit operations that constitute the bulk of the extrusion/spheronization process. During wet granulation, dry powder mixture is agglomerated with help of a binding liquid. The agglomerated are held together mainly by capillary forces. The granulation is then fed into the extruder to produce high-density extrudates. These extrudates are bonded together by capillary forces, solid bridges formed due to loss of moisture, mechanical interlocking, and, to some extent, molecular forces. These extrudates are finally converted to pellets on spheronization.

I. Spheronization:

Spheronization is not a relatively new technique. The early trade name was Marumerizer, which means “round maker.” Spheronization typically begins with damp extruded particles, granules from one of the extruders and the extruded, cylindrically shaped particles are broken into

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 123-129 www.ijprajournal.com ISSN: 2249-7781

uniform lengths almost instantaneously and are gradually transformed into spherical shapes.

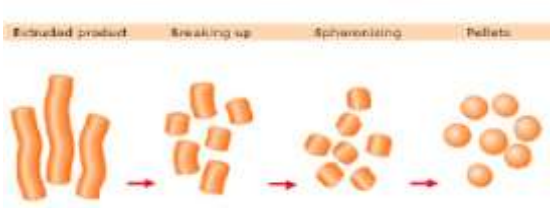

Figure-5: principle of extrusion and spheronization

TABLET PRESS FOR PREPARING MUPS:

Tablet press designed MUPS have a modification in the hopper, feed frame and forced feeders compared to normal tablet press. The hopper for feed consists of a butterfly valve to modulate the flow of blend to feed frame. The feed frame designed is continuous to ensure uniform clearance from the turret and prevent attrition/ segregation of pellets from extra-granular material and also crushing of coated pellets throughout the compression process, which is not possible with the regular rotary tablet press. The forced feeder used is gravity feeder, designed to prevent abrasion or grinding of pellets.

Four stages are considered in compression into MUPS includes Deformation of functional coating layer, Densification of polymeric coating layer, Fragmentation and Attrition of pellets.

II. STAGES IN COMPRESSION OF PELLETS TO MUPS

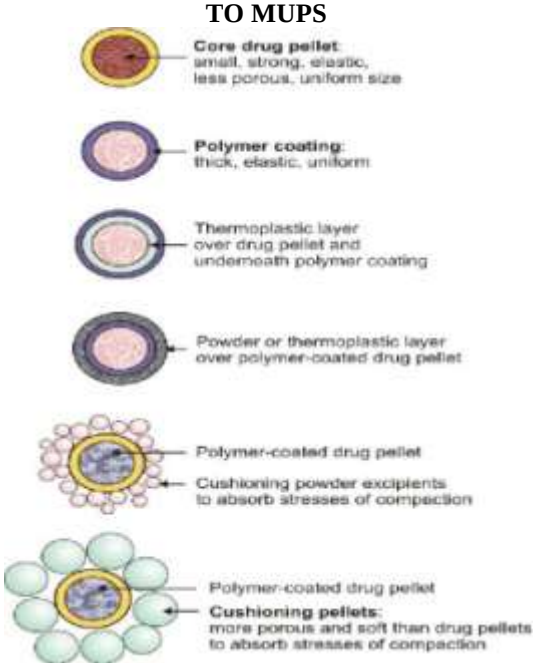

Figure-6: Schematic representation of various approaches to prepare MUPS of coated pellet formulations

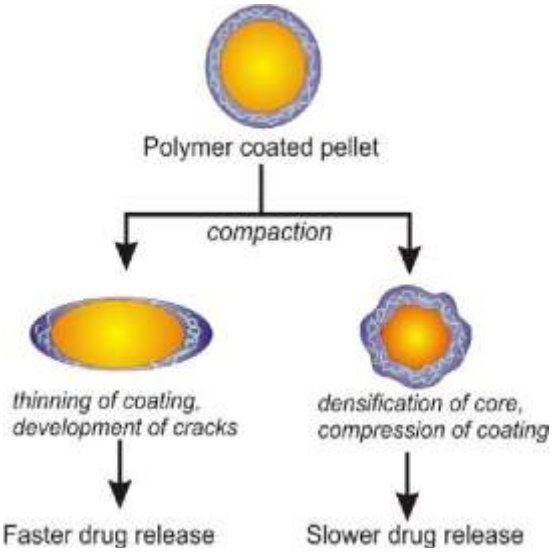

Figure-6:Impact of compaction on pellet deformation and drug release

Characterization of pellets:

1)Particle size analysis:

The particle sizes of the formed pellets are to be measured using an optical microscope with ocular and stage micrometer where the particle size distribution can be calculated. The 'Wesmox model' with a resolution of 45x may be used.

The particle size distribution study can also be done by 'Sieve Analysis' technique by using a set US standard sieve of different mesh size known as different sieve numbers such 14,16,18,22 and 44 with a pellet of the load of 10 gm. The sieve set is to be mechanically shaken for 10 min, total net weight of pellets retained on each sieve was determined and these values are used for calculating particle size distribution.

2)Micrometric properties:

a)The angle of repose :

Angle of repose is used to know the pellet flow property by using a fixed funnel method. The radius (r) of the pellet pile formed and height of the pellet pile (h) is determined. The angle of repose for the pellet sample is calculated using the formula:

$\theta = \tan^{-1}(h/r)$

Where 'r' is the radius of the pellet pile formed an 'h' is the height of the pellet pile.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 123-129 www.ijprajournal.com ISSN: 2249-7781

b)Carr's index :

It is a dimensionless parameter, which proves to be useful to the same degree as the angle of repose values for determining the flow property. Apparent bulk density was determined by pouring the bulk samples into a graduated cylinder. Tapped density can be determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapper apparatus (Electro lab tap density tester). Carr's index can be calculated by using the equation given below:

Carr's index=Tapped density-Bulk density/Tapped density

Hausner's ratio was measured by the ratio of tapped density to bulk density.

Hausner's ratio =Tapped density/Bulk density

c)Friability (F):

Friability test for pellets takes place by using known mass pellets particle size ranging from 1000 to 1410 µm as (WO) placed in an apparatus called as "Roche friabilator" where the procedure involved is a simplest one by maintaining 25 rpm for a time period of 4 min. After completion of the required time period, the pellets are removed from the apparatus in a sterilized manner and further subjected to know the weight of the pellets as finalweight or weight after 100 rotations i. e,4 min(W) of time and the friability was calculated by using the equation mentioned below:

$$\text{Friability\%} = [1 - W/W0] \times 100$$

Where, WO is the initial weight and W is the weight after100 rotations.

The friability test is performed on the formed pellets to ensure the ability of mechanical strength to withstand the property of strength where lower the friability value indicates good mechanical strength of the spheroids.

d)Pellet sphericity test:

The pellet size and spheroidal shape are determined by using an image analysis system. By using digital camera photomicrographs can be obtained where further analysis of the obtained pellet images is carried out by software (Digimizer, USA).

Therefore, characterization each individual pellet can be known by the aspect ratio (AR) and two-dimensional shape factor(eR). The equation for pellet sphericity is as follows:

$$eR = 2\pi r/Pm-(b/l)\ 2$$

Where 'r' is the radius, 'Pm' is the perimeter, 'l' is the length and 'b' is the width of the pellet.

e)Compatibility studies:

It plays important role in selecting the appropriate excipients for a particular drug and a particular formulation because the drug maintains its continuous contact with one or more excipients which directly or indirectly may affect the stability of drug or a formulation. These compatibility studies can be carried out by using FT-IR Spectrophotometer and Differential Scanning Calorimetry.

f)FTIR studies:

FTIR stands for Fourier transform infrared spectroscopic, where the analysis is used for pure drug and pellet grains using KBr pellet process on FTIR spectrometer. The drug is mixed with KBr and spectra are taken. FTIR spectrum of pure drug is compared with FTIR spectra of drug formulations. The disappearance of peaks or shifting of peaks in any of the spectra can be studied by using the apparatus named FTIR 8400-S, Shimadzu, Japan model.

Evaluation of pellets

1)Percentage yield :

Percentage yield determination is carried out to know the preparation procedure chosen for pellet formation is effective or not, and also to know the importance of the procedure used regarding safety and efficacy with lesser effort and greater benefit. Hence the quantity or the amount of active pharmaceutical ingredients, polymers, binding agent, anti-frictional agents, starch paste and other process parameters are the factors which play a major role in deciding the yield of the pellets during pelletization process. The formula for calculation of % yield of a pellet is written below:

% yield= weight of pellets/Weight of drug+weight of polymers×100

2)Loose surface crystal study (LSC):

A total amount of 200 mg of pellets are suspended in a beaker containing 100 ml of phosphate buffer (pH 7.4). The amount of drug present in the solution can be analyzed by spectrophotometrically at 265 nm.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 123-129 www.ijprajournal.com ISSN: 2249-7781

3)Determination of drug content:

Pellets drug content can be determined using UV/Visible spectrophotometer instrument were the prepared pellets are crushed into powder form. And the finely crushed sample of pellets equivalent to 100 mg of DPP is transferred to 100 ml volumetric flask which is diluted with 100 ml solvent which is particular for particular pellet particles and the absorbance value is noted at suitable wavelength, where initially before placing sample the background scan has to done and the drug content in pellet is determined using calibration curve.

4)Surface Morphology :

Scanning electron microscopy method is used to determine the surface morphology of formed pellets and also the cross-section pattern of pellets can be known.

5)Specific Surface Area:

Specific surface area totally depends upon the size and the shape of the pellet granules and if the coated pellets are available then a desirable surface area can be achieved.

6)In vitro drug release studies:

In vitro dissolution studies are carried out either by using paddle type or basket type apparatus using IP or USP model. According to the IP model, type 1 is a paddle and type 2 is basket apparatus and according to the USP model, type 1 is basket and type 2 is paddle . 900 ml of a solution which is suitable for the formulation is used as a dissolution medium. The paddles or basket is operated at a particular rpm based upon the drug, and the temperature has to be maintained at 37 °C±0.5 °C throughout the experiment.

TABLE 1: Marketed MUPS tablet formulations

Product	Company	Drug	Therapeutic Category	Formulation type
Theodur	Key	Theophylline	Antiasthamatic	Extended release
Losec MUPS	Astra Zeneca	Omeprazole magnesium	Antiulcer	Delayed release
Prevacid SoluTab	Takeda	Lansoprazole	Antiulcer	Delayed release orodispersible tablet
Toprol XL	Astra Zeneca	Metoprolol tartrate	Antihypertensive	Extended release

III.CONCLUSION

In present pharmaceutical trends MUPS drug delivery system provides more advantages including health care, medical, and business benefits. So it concludes that due to great supremacy of technological and biopharmaceuticals pelletization gained significance in the modern pharmaceutical sciences and predictable to play crucial roles as a carrier for control the release of drug. Many pharmaceutical industries expand the use of pellets in broad range as active pharmaceutical ingredients. Multi unit particulates system (MUPS) improves patient comfort and compliance.

Looking back on this project, the overall outcome of results to be observed. This can be evaluated by looking at how well our objectives were met. Our first objective is to control the engine valve of an engine, select a linear actuator that meets specifications, and construct an electronic control system, deal with the design aspect of our project and were all almost achieved. More specifically, next objective, the electronic control system we constructed is able to read engine speeds from 0 to 3600 rpm and vary the valve timing depending on engine speed and operator inputs. However, our final objective, to obtain gains in horsepower, torque, and efficiency of 2% was not met because of not setting up in an engine but theoretically it should be done. We are confident though that this objective of installing in an engine can be met if more time for testing and facilities is given. There is a lot we could say about the need for variable valve timing. This design is very realistic for the future of the automotive industry as well as our education.

REFERENCES

[1]. Chang R-K, Rudnic EM. Int J Pharm, 1991, 70: 261-70.Hedstrand AG. (Ed.). FASS 2002. LINFO, Stockholm, 2002, 853-54.

International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 123-129 www.ijprajournal.com ISSN: 2249-7781

[2]. Bhaskaran S, Lakshmi PK. Extrusion spheronization-a review. Int J PharmTech Res 2010;2:2429–33.
[3]. MirceaHirjau MD, Anca Cecilia Nicoara, MD VH. Pelletization techniques used in pharmaceutical fields. Pract Farm 2011;4:206–11.
[4]. Gupta AM, Shivhare UD, Suruse PB. International journal of pharmaceutical and different aspects of pellets formulation and their evaluation. Int J Pharm Phytopharm Res 2015;4:331–6.
[5]. Verma A. Pharmaceutical pellets: a versatile carrier for oral controlled delivery of drugs. Indian J Pharm Educ 2016;50:8–24.
[6]. Sachdeva V, Alam S, Kumar R, Kataria MK. Oral multiunit pellet extended release dosage form: a review. IntCurr Pharm J 2013;2:177–84.
[7]. Ravella VN, Nadendla RR, Kesari NC. Design and evaluation of sustained release pellets of aceclofenac. JOPR J Pharm Res 2013;6:525–31.
[8]. Bathool A, Gowda DV, Khan MS. Development and evaluation of porous membrane pellets of disopyramide phosphate for sustained release. Asian J Pharm 2012;12:107–15.
[9]. Karra N, Raju N. Formulation and evaluation of torsemide pellets for extended drug release by extrusion-spheronization method. Asian J Pharm 2018;12:5–6.
[10]. Kalyani C, Reddy KV, Rao EA, Kumari MP. Formulation and in vitro evaluation of metoprolol succinate extended release pellets. Br Biomed Bull 2013;1:73–82.
[11]. Gandhi R, Ashokraj Y, Kaul CL, Panchagnula R. Using extrusion–spheronization to develop controlled-release formulations of azithromycin. Pharmtech Com 2005;1:68–86.
[12]. 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.
[13]. 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.
[14]. 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.
[15]. MirceaHirjau MD, Anca Cecilia Nicoara, MD VH. Pelletization techniques used in pharmaceutical fields. Pract Farm 2011;4:206–11.
[16]. Gupta AM, Shivhare UD, Suruse PB. International journal of pharmaceutical and different aspects of pellets formulation and their evaluation. Int J Pharm Phytopharm Res 2015;4:331–6.
[17]. Verma A. Pharmaceutical pellets: a versatile carrier for oral controlled delivery of drugs. Indian J Pharm Educ 2016;50:8–24.
[18]. Sachdeva V, Alam S, Kumar R, Kataria MK. Oral multiunit pellet extended release dosage form: a review. IntCurr Pharm J 2013;2:177–84.
[19]. Ravella VN, Nadendla RR, Kesari NC. Design and evaluation of sustained release pellets of aceclofenac. JOPR J Pharm Res 2013;6:525–31.
[20]. Bathool A, Gowda DV, Khan MS. Development and evaluation of porous membrane pellets of disopyramide phosphate for sustained release. Asian J Pharm 2012;12:107–15.
[21]. Karra N, Raju N. Formulation and evaluation of torsemide pellets for extended drug release by extrusion-spheronization method. Asian J Pharm 2018;12:5–6.
[22]. Kalyani C, Reddy KV, Rao EA, Kumari MP. Formulation and in vitro evaluation of metoprolol succinate extended release pellets. Br Biomed Bull 2013;1:73–82.