An overview on multiparticulate drug delivery system: Pellets

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ABSTRACT
Pellets can be defined as small, free flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and intended usually for oral administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and excipients using appropriate processing equipment. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today. Regardless of which manufacturing process is used, pellets have to meet the following requirements. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating. Pellets may have varied applications in varied industries. It just requires an innovative bend to use it to derive maximum profitability. The smooth surface & the uniform size of the pellets allow uniform coating not only for each pellet but also from batch to batch.

INTRODUCTION

MULTIPARTICULATE DRUG DELIVERY SYSTEMS (MDDS)
The concept of multiple unit dosage form was initially introduced in the early 1950’s. These forms play a major role in the design of solid dosage form processes because of their unique properties and the flexibility found in their manufacture. These forms can be defined as oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics. Together, these characteristics units provide the overall desired controlled release of the dose. These multiple units are also referred to as pellets, spherical granules or spheroids. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi-spherical units, referred to as pellets. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. These pellets usually range in size from 0.5-1.5 mm and in applications may be as large as 3 mm. Multiparticulate drug delivery systems (MDDS), mostly used for oral route, consist of multiplicity of small discrete units that exhibit different characteristics. It is based on subunits such as granules, beads, microspheres, pellets, spheroids and Minitab. These subunits show various advantages over monolithic devices (non-divided forms). In MDDS, drug substances are divided into number of subunits, typically consist of thousands of spherical particles having diameter of about 0.05-2.00 mm. To administer or to recommend total dose these subunits are compressed into a tablets or filled into a sachets or encapsulated. The formulation of multicomponent MDDS is also possible because it shows different mechanism of action, provides additive synergistic
effect, and reduces the doses of individual agents and limited side effects. Though it is costlier than monotherapies in short term, it reduces treatment failure rate, lower case fatality ratios and reduction in development of resistance for development of new products in long term therapy

RELEASE SYSTEMS
CONTROLLED DRUG DELIVERY SYSTEMS
Controlled drug delivery is delivery of drug at a rate or at a location determined by needs of body or disease state over a specified period of time. It also implies a “predictability & reproducibility” in the drug release kinetics, which means that the release of drug ingredient from a controlled delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another.

ADVANTAGES
1. Improved patience compliance and convenience due to less frequent drug administration.
2. Reduction in fluctuation in steady state and therefore better control of disease conditions and reduced intensity of local and systemic side effect.
3. Increased safety margin of high potency drugs due to better control of plasma levels.
4. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

DISADVANTAGES
1. Poor invitro – invivo correlations.
2. Possibility of dose dumping due to food, physiologic formulation variables or chewing or grinding of oral formulation by the patient and thus increased risk of toxicity
3. Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reaction.

SUSTAINED RELEASE DOSAGE FORMS
The aim of any drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration. In the recent years sustained release (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release, sustained action, prolonged action, extended action are the terms used to identify drug delivery system that are designed to achieve a prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

NEW DRUG DELIVERY SYSTEMS CAN BE OVER LOOKED AS
DELAYED RELEASE
Use repetitive, intermittent dosing of a drug from one or more immediate release units, incorporated into a single dosage form. e.g. - Repeat action tablets, enteric-coated tablets.

SUSTAINED RELEASE
They show release over extended period of time.

CONTROLLED RELEASE
Provides constant drug levels, with zero order kinetics

PROLONGED RELEASE
Provide extended release, but not necessarily constant drug levels. May not follow perfect zero order.

SITE-SPECIFIC AND RECEPTOR RELEASE
Targeting drug to the particular organ or tissue of the body. For receptor release, target is particular receptor for a drug within an organ or tissue.

CAPSULE
In the manufacture of pharmaceuticals, encapsulation refers to a range of techniques used to enclose medicines in a relatively stable shell known as a capsule, allowing them to, for example, be taken orally or be used as suppositories. The two main types of capsules are:

- Hard-shelled capsules, which are normally used for dry, powdered ingredients or miniature pellets (also called beads that are made by the process of Extrusion and Spheronization) - or mini tablets;
- Soft-shelled capsules, primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Both of these classes of capsules are made from aqueous solutions of gelling agents like:

- Animal protein mainly gelatin;
Plant polysaccharides or their derivatives like carrageenans and modified forms of starch and cellulose. Other ingredients can be added to the gelling agent solution like plasticizers such as glycerine and/or sorbitol to decrease the capsule's hardness, coloring agents, preservatives, disintegrates, lubricants and surface treatment.

TYPES OF MULTIPARTICULATE DRUG DELIVERY SYSTEMS
In order to get MPDDS, drug is distributed in small particles (0.05 to 0.2 mm) and then film coated to get desired drug release characteristics. Here is account of different types of MPDDS.

DRUG CRYSTALS
Drug Crystals, of appropriate size and shape can be coated directly with a modified release film coating.

IRREGULAR GRANULES
Granules used in preparation of tablets, can be film coated. Irregular shape and variation in particle size make it difficult to achieve uniform coating thickness around each particle.

SPHERONIZED GRANULES (PELLETS)
Sphere-shaped particles simplify the coating process. The production of spherical particles (pellets) is achieved by extruding the powdered mass, then cutting into small cylindrical particles and finally spheronizing these particles to spherical shape.

DRUG-LOADED NON-PAREILS (PELLETS)
Spherical particles about 1mm in diameter consisting primarily of sucrose and starch called “non-pareils” which are available in the market. Following techniques can be used to get drug loaded non-pareils.
- A powder-dosing technique involving alternate dosing of powder (containing drug Substance) and binder liquid onto the surface of the non-pareils until the required dose of the drug has been loaded.
- Spray application of drug, either suspended or dissolved in a suitable solvent (usually water) containing a polymer (such as hydroxyl propyl methyl cellulose or polyvinyl pyrrolidone) as a binder onto the surface of the non-pareils.

MINI TABLETS
Many of the other types of multiparticulates described suffer from two potential batch wise drawbacks, namely:
- Variation in particle size distribution
- Variation in particle shape and surface roughness.
Such variability can result in variable coating thickness and thus product performance. This problem can be overcome by using mini compressed tablets (size range of 1-2mm) produced using modification of traditional tableting processes.

MELT-SPRAY-CONGEAL MICROSPHERES
- Spherical, smooth, 50- to 300-μm particles, typically with embedded API, can be produced by a continuous spinning-disk process

PELLETS
Pellets can be defined as small, free flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and intended usually for oral administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and excipients using appropriate processing equipment. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today.
1. Regardless of which manufacturing process is used, pellets have to meet the following requirements. They should be near spherical and have a smooth surface; both considered optimum characteristics for subsequent film coating.
2. The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000mm.
3. The pellets should contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

SIGNIFICANCE OF PELLETS
Pellets may have varied applications in varied industries. It just requires an innovative bend to use it to derive maximum profitability. The smooth surface & the uniform size of the pellets allow uniform coating not only for each pellet but also from batch to batch.
The most important reason for the wide acceptance of multiple unit products is the rapid increase in popularity of oral controlled release dosage forms. Controlled release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function or through the formulation of matrix pellets to provide the desired effect. The advantage of multiple unit products as a controlled release dosage form is believed to be their behavior in vivo because of their advantageous dispersion pattern in the gastrointestinal tract and their special size characteristics.

THEORY OF PELLET FORMATION

In order to judiciously select and optimize any pelletization/granulation process, it is important to understand the fundamental mechanisms of granule formation and growth. Different theories have been postulated related to the mechanism of formation and growth of pellets. As the conventional granulation, the most thoroughly studied, most classified pelletization process, which involves a rotating drum, a pan or a disc, has been divided into three consecutive regions: nucleation, transition and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.

NUCLEATION

Nucleation is a stage of Pelletization process that occurs whenever a powder is wetted with solvent system. The primitive particles are drawn together to form three-phase air-water-liquid nuclei system which are held together by liquid bridges that are pendular in nature. The reduction of particle size will improve the bonding strength between them. Further the size, the rate and the extent of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates.

COALESCENCE

Nucleation is followed by a transition phase where the growth mechanisms affecting are coalescence and layering. Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei, this mechanism requires slightly excess moisture on the surface of the nuclei although the number of nuclei is progressively reduced even though the total mass of the system remains unchanged during this operation.

LAYERING

Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already formed nuclei. In the layering step, the number of particles remains constant while the total mass of the system increases due to increasing particle size as a function of time. The fragments or fine particles can be formed by particle size reduction the fines and the fragments produced through size reduction are taken up by larger pellets. Production of fines and subsequent coalescence and layering continues until the number of collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached.
BALL GROWTH
The main mechanism in the ball growth phase is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. This phase does not result in any change in the total number or mass of the particles. However, the particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist.

![Figure 2: Pellet growth mechanisms](image)

METHODS OF PREPARING PELLETS
Compaction and drug layering are the most widely used pelletization techniques in Pharmaceutical industry. Of the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletization methods such as globulation, balling and Compression are also used in development of pharmaceutical pellets although in a limited scale.

DIRECT PELLETIZING
In this process Pellets are manufactured directly from powder with a binder or solvent. Powder is mixed and moistened. A solvent or binder can also be added. The powder bed is set into a centrifugal motion. (Fluid Bed Pelletizing in the rotor). The impact and acceleration forces that occur in this process result in the formation of agglomerates, which become rounded out into uniform and dense pellets. The speed of rotation has a direct influence on the density and size of the pellets. The moist pellets are subsequently dried in the fluid bed. If required, the systems can be made inert for applications with organic solvents. Another alternative for direct pelletizing is Spray Granulation.

![Figure 3: Principle of Direct pelletizing technique](image)

POWDER LAYERING
Powder layering involves the deposition of successive layers of dry powders of drugs and Excipients on
preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders, hence it requires specialized equipment’s like Spherodizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked of by the wet mass of pellets that is being layered.

![Figure 4: Principle of powder layering process](image)

**SOLUTION / SUSPENSION LAYERING**
Solution/suspension layering involves the deposition of successive layers of solution or suspensions of drug substances and binder over the starter/non-pareil seeds, which is an inert material or crystals/granules of the same drug. In fact the coating process involved in general is applicable to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used.

**PELLETIZATION BY EXTRUSION AND SPHERONIZATION**
The process involves first making the extrudes from the powder material and then converting the extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc.). Beads as fine as 0.6mm can be made.

**OTHER PELLETIZATION METHODS**
Other pelletization methods such as globulation, cryo – pelletization, balling, and compression are also used, although a limited scale in the preparation of pharmaceutical pellets globulation or droplet formation consists two related processes, spray drying and spray congealing.

**SPRAY DRYING**
It is the process in which drugs in the suspension or solution without excipients are sprayed in to a hot stream to produce dry and more spherical particles. This process is commonly used for improving the dissolution rates; hence bioavailability of poorly soluble drugs.

**SPRAY CONGEALING**
It is the process in which a drug is allowed to melt, disperse or dissolve in hot melts of gums, waxes or fatty acids, and is sprayed into an air chamber where the temperature is kept below the melting point of the formulation components, to produce spherical congealed pellets. Both immediate and controlled release pellets can be prepared in this process depending on the physiochemical properties of the ingredients and other formulation variables.

**CRYOPELLETIZATION**
It is a process in which the liquid formulation is converted in to solid spherical particles or pellets in the
presence of liquid nitrogen as fixing medium. The shape depends up on the distance the droplet travel before contacting liquid nitrogen.

**COMPRESSION**
It is one type of compaction technique for preparing pellets. Compacting mixtures or blends of active ingredients and excipients under pressure prepare pellets of definite sizes and shapes. The formulation and process variables controlling the quality of pellets prepared are similar to those used in tablets manufacturing.

**BALLING**
It is the pelletization process in which pellets are formed by a continuous rolling and tumbling motion in pans, discs, drums or mixtures. The process consists of conversion of finely divided particles into spherical particles upon the addition of appropriate amounts of liquid.

**FREEZE PELLETIZATION**
In this technique, a molten-solid carrier/matrix is introduced as droplets into an inert column of liquid in which the molten solid is immiscible. The molten solid moves in the liquid column as droplets and solidifies into spherical pellets. The molten-solid droplets can move upward or downward in the liquid column depending on the droplets' density with respect to the liquid in the column. If the density of the molten-solid carrier/matrix is more than that of the liquid in the column, then the droplets are introduced from the top of the column and pellets solidify in the bottom portion of the column. Conversely, if the density of the molten-solid carrier/matrix is less than that of the liquid in the column, then the droplets are introduced from the bottom of the column and pellets solidify at the top portion of the column.

**PELLET COATING PROCESS**
The coating process for pellets is carried out primarily in order to modify the release of the drug from the pelletized drug delivery systems. Most of the coating processes use one of three general types of equipments.
1. The standard Coating pan
2. The Perforated Coating pan
3. The Fluidized bed coater

**CONVENTIONAL PAN SYSTEM**
**THE STANDARD COATING PAN**
The standard coating pan system consists of a circular metal pan mounted somewhat angularly on a stand, the pan is rotated on its horizontal axis by a motor, the hot air is directed into the pan and onto the bed surface, and is exhausted by means of ducts positioned through the front of the pan. Coating solutions are applied by spraying the material on the bed surface.

![Fig. No.5 Conventional coating pan](image)

**THE PERFORATED COATING PAN**
Perforated pan coaters are efficient drying systems with high coating capacity, and can be completely automated.
for both sugar coating and film coating processes. There are four different type of coaters available Acela-
Cota, Hi-Coater, Driacoater, Glatt coater. In all four of these perforated pan systems the coating solution is applied to the surface of the rotating bed of pellets through spraying nozzles that are positioned inside the drum.

**FLUID BED COATING**

The fluid-bed technology or air-suspension process is the potential tool to develop newer trends and implications in the sector of formulation development with maximum therapeutic efficacy. The technology is used for granulation/agglomeration, layering and coating of a wide range of particle size. In addition; the technique can be used for the drying process as well. The three patterns of the fluid-bed processes could be characterized by the position/location of the spray nozzle i.e. top spray, bottom spray or tangential spray. It is a batch or continuous operation or if the film is applied from a sprayed solution, suspension or hot melt. For this processing option the parameters have to be chosen to avoid agglomeration, i.e. liquid bridges between the air suspended particles. If spraying a solution or suspension the liquid only serves as a vehicle to deliver the coating material to the surface of the substrate. For hot melt coating the droplets must be small enough not to form solid bridges. The quality of the coating extensively depends on the statistical residence time of the particles in the coating zone.

**TOP SPRAY COATING PROCESS**

This is simplest process used for general coatings right up to enteric coating. With top spray coating in the fluid bed (batch and continuous), particles are fluidized in the flow of heated air, which is introduced into the product container via a base plate. The coating liquid is sprayed into the fluid bed from above against the air flow (countercurrent) by means of a nozzle. Drying takes place as the particles continue to move upwards in the air flow. Small droplets and a low viscosity of the spray medium ensure that the distribution is uniform. The product is continuously fed into one side of the machine and is transported onwards via the sieve bottom by means of the air flow. It can be used for taste masking, barrier coating, or functional coating. However, it is not a good choice for applications in which film quality (absence of pores) and uniformity of film thickness are important (e.g.,for sustained- or controlled-release dosage forms).
**BOTTOM SPRAY COATING PROCESS (WURSTER COATING)**

This process was developed by Dr. Dale Wurster in the late 1950s; the technique is well recognized for providing excellent coating uniformity and efficiency. The unique features of bottom-spraying are an air distribution plate and a partition that together organize fluidization of particles through the partition (coating zone). The nozzle is mounted at the bottom of the product container and is centered in the coating zone. The short distance between the coating materials and particles during the coating process minimizes spray-drying and contributes to high coating uniformity and coating efficiency. This processing option uses the energies and controls of the fluid bed to create a pneumatic mass transport inside a special insert, which consists of a perforated bottom screen with defined free areas. Most of the process air is channeled through the center via a tube, as such producing a venture effect, which sucks the product from outside the partition past the spray nozzle. Leaving the cylindrical partition and entering the conical expansion chamber the particle velocity is dramatically reduced, excess moisture is rapidly evaporated with the dry product returning again and again through the coating zone to receive more coating material. This uniform statistical residence time of all particles in the coating zone results in a very homogenous coating. Due to the high kinetic energy provided by the pneumatic mass flow moist particles are separated, as such allowing the individual coating of even very small particles. Due to the nozzle being positioned directly inside the product and concurrently spraying a premature viscosity change of the coating droplet is avoided. All this features result in the highest possible coating quality, which is imperatively required to produce reproducible drug delivery profiles.

**TANGENTIAL SPRAY COATING (ROTOR PELLET COATING)**

This technique is ideal for coatings with high solid content. The product is set into a spiral motion by means of a rotating base plate, which has air fed into the powder bed at its edge. The spray nozzle is arranged tangentially to the rotor disc and also sprays concurrently into the powder bed. Very thick film layers can be applied by means of the rotor method. The quality producing parameters are

- Uniform statistical residence time is warranted by defined rotor revolution speed
- The coating material is sprayed concurrently inside the rotating product
- The rolling motion of the particles provides an even higher separation force, as such preventing agglomeration.

However, this high kinetic energy makes it somewhat difficult to coat very small particles and is generally destructive for larger and non-spherical products. The benefits of this processing option are mainly for the layering and subsequent film coating of pellets. A significant advantage of tangential-spraying over the top spray or bottom-spray processes is the option of connecting a powder feeder to minimize exposure of compounds to water or solvent. This technique permits the production of pellets with high-dose loading of actives in a relatively short time. Tangential-spraying can be used to produce granules or pellets that require subsequent coating for controlled release. One drawback of tangential-spray coating is the potential for
strong mechanical forces during the process and not desirable during coating because they can cause substrates to break. Bottom-spray coating compared with the top-spray and tangential-spray coating processes. Analyzing the surface topography of the pellets through the scanning electron microscopy using all three fluid-bed processes; it was observed that for film coating (using aqueous and organic solvents), the bottom-spray process produced a smoother and more uniform coating compared with top-spraying.

![Figure 8: principle of a) Top b) Bottom c) Tangential spray coating](image)

**FACTOR AFFECTING PELLETIZATION TECHNIQUE**

**MOISTURE CONTENT**
It is one of the critical parameter for pellet growth in pelletization technique. Moisture in the wet mass bring cohesiveness to the powder so that the wet mass can be extracted and spheronize to give spherical shape. High moisture contents lead to agglomeration of pellets during the process of spheronization which is one of the technique of pelletization due to excess of water in the surface of pellets and low moisture content lead to generation of fines with large variation in size distribution.

**RHEOLOGICAL CHARACTERISTICS**
The Rheological condition of the wet mass determines the flow ability in extruder optimum Rheological condition leads to good flow ability in order to extrude the wet mass variation in rheology make improper and non-uniform extrusion.

**SOLUBILITY OF EXCIPIENTS AND DRUG IN GRANULATING FLUID**
A soluble drug get dissolve in a granulating liquid. Thus increasing the volume of liquid phase lead to over wetting of system of agglomeration of pellet sand increase in wetting liquid increases plasticity but induces sticky mass.

**COMPOSITION OF GRANULATING FLUID**
Besides water, alcohol, water / alcohol mixture, Ethyl Ether, Dilute Acetic Acid, Isopropyl alcohol is also used as a granulating liquid. According to researcher, a minimum of 5 % of granulation liquid have to be water in order to produce pellets be water in order to produce pellets containing Avicel pH (101) and theophylline .Some researchers used water and dilute acetic acid in different powder to liquid ratio and concluded that mass fraction can be increased up to 100% by using dilute acetic acid for granulation step in place of demineralized water. Aqueous polymer dispersion containing Eudragit, Hydroxy Propyl Methylcellulose (HPMC), Poly vinyl pyrrolodine (PVP) and Gelatin is used in the moistening liquid.

**PHYSICAL PROPERTIES OF STARTING MATERIAL**
Formulation variable such as type and content of starting material, type of filler and particle size of constituent have the effect on the pelletization process. Quality of pellets depends not only composition but also on different grades of the same product. The swelling property of material used in pelletization technique decides the release rate of the drug in pellets.

**SPEED OF THE SPHERONIZER**
The speed of the spheronizer affects the size, hardness, sphericity and density of pellets, high speed gives high sphericity, lower friability, smooth surface and higher crushing strength.
DRYING TECHNIQUE AND DRYING TEMPERATURE
It is important to get proper size, shape and flow of pellets and it must be reproducible and consistent in all the batches. Variation in pellet's size, shape and flow will lead to difference in physicochemical properties of final dosage form like weight variation, improper filling etc., which will further affect the therapeutic efficiency of the delivery system. Wider particle size distribution may lead to variation in the dose of drug delivery. Variation in shape may lead to variation in flow and compressibility.

EXTRUSION SCREEN
The quality of the extrudate / pellets is greatly influenced by the characteristics of the orifice of the screen. An increase in orifice dimension resulted in increased mean pellet size. The increase in orifice depth decreased with the presence of water at the extrudate surface, increasing the extrusion force, and then had a negative effect on granulometric distribution and on shape.

CHARACTERISATION OF PELLETS
SHAPE AND SURFACE ROUGHNESS
Shape and morphological features of pellets were observed by scanning electron microscopy (SEM). Surface and shape of the formulated pellets were observed to be varying depending on composition of polymer and plasticizer. The shape of the pellets was investigated by JEOL, JSM-6610LL, Scanning electron microscope, Japan and the images were shown in the fig.

ANGLE OF REPOSE
The angle of repose of nicardipine pellets was determined by the funnel method (Reposogram). The accurately weighed quantity of pellets was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the pellets. The pellets were allowed to flow through the funnel freely onto the surface. The diameter of the pellet cone was measured and angle of repose was calculated using the following equation.

\[
\text{Angle of repose (} \theta \text{)} = \tan^{-1} \left( \frac{h}{r} \right)
\]

Where h and r are the height and radius of the pellets cone, respectively

DETERMINATION OF BULK DENSITY AND TAPPED DENSITY
An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_b) was measured. Then the graduated cylinder was set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume was measured. The bulk density, and tapped density were calculated using the formulae

**Bulk density = Mass of the pellets/ Bulk volume**

**Tapped density = Mass of the pellets / Tapped volume**

Compressibility index (Car’s indices)

CARR’S COMPRESSIBILITY INDEX
Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fail. Table shows the relationship between compressibility index and flowability. It is calculated by using the formula,

\[
CI = \frac{\rho_{\text{tapped}}}{\rho_{\text{bulk}}} \times 100
\]

<table>
<thead>
<tr>
<th>CI</th>
<th>Flowability</th>
</tr>
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<tbody>
<tr>
<td>&lt; 15  %</td>
<td>shows good flow property</td>
</tr>
<tr>
<td>&gt; 15  %</td>
<td>shows poor flow property</td>
</tr>
<tr>
<td>&gt; 25  %</td>
<td>shows great potential problems</td>
</tr>
<tr>
<td>20 % - 40 %</td>
<td>shows reasonable flow property</td>
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</tbody>
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HAUSNER’S RATIO
Hausner’s ratio was measured by the ratio of tapped density to bulk density.

Hausner’s ratio = Tapped density/ Bulk density

FRIABILITY
The friability of pellets was determined by using USP friability tester. Friability of the pellet formulation was evaluated over 5g sample in Roche friabilator at 25rpm for 4min. Prior to and following the test, the weights of the formulation were accurately recorded and friability ratios were calculated with the given equation

\[
F = \frac{W_1 - W_2}{W_1} \times 100
\]

Where, \( W_1 \) = Initial weight of the formulation, \( W_2 \) = Final weight of the formulation

DRUG CONTENT
The nicardipine content of the pellet formulation was evaluated over accurately weighed 100mg pellets. The weighed quantity of pellets were transferred into 100ml volumetric flask and added up a little quantity of chloroform. The pellets were dissolved for 10min and the volume was made upto the mark with pH 6.8
phosphate buffer. This solution was filtered through whatmann filter paper. From this, 1ml of the filtrate was diluted to 10ml with pH 6.8 phosphate buffer. The UV absorbance of this solution was measured at 235nm. The content uniformity test was evaluated for the formulation by collecting samples from three different portions of the bulk and the results were expressed.

**IN VITRO RELEASE RATE STUDIES**
The in vitro dissolution study was carried out using USP type 1 dissolution apparatus. The study was carried out in 900 ml of phosphate buffer pH 6.8 at 50rpm. Capsules containing pellets equivalent to 200mg of nicardipine were taken for the dissolution study. The dissolution medium was kept in a thermostatically controlled water bath, maintained at 37 ± 0.5°C. The stirrer hood was lowered so that the lower end of the basket was 25 mm above the base of the beaker. At different time intervals, 5 ml sample was withdrawn and analyzed spectrophotometrically at 235 nm for drug release. At each time of withdrawal, 5 ml of fresh dissolution medium was replaced into the dissolution flask.

**REFERENCES**


[5]. P. Dipen kumar – Development of transdermal patches of nicardipine – an attempt to improve bioavailability - International Journal of Research in Pharmaceutical and Biomedical Sciences ISSN: 2229-3701


[15]. Pharmaceutical Dissolution Testing, Edited by Jennifer Dressman, Johannes Krämer, Germany; Published in 2005 by Taylor & Francis Group.