

**Controlled release drug delivery system of cardiovascular drug**Rajesh Asija^{1*}, Sangeeta Asija¹, Arvind Mehta¹¹Department of pharmaceuticals, Maharishi Arvind institute of pharmacy, Mansarovar, Jaipur-302020, Rajasthan, India**Received 21 September 2014; Accepted 29 September 2014****ABSTRACT**

Conventional medication systems that require multi-dose therapy are with problems. With a view to overcome these problems, the current trend in pharmaceutical research is to design and develop new formulations, thereby enhancing the therapeutic efficacy of existing drugs. Controlled release (CR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into systemic circulation at a predetermined rate. The choice of drug to be delivered, clinical needs, and drug pharmacokinetics are some of the important considerations in the development of controlled release formulation, in additions to the relation between the rates of drug release from the delivery system to the maximum achievable rate of drug absorption into the systemic circulation. By gaining, a premonation and reproduce bioactive agent release rate for an extended period of time, controlled release formulation can achieve optimum, long time efficacy, minimised toxicity and therapeutic potent responses. Controlled release pellets are manufactured either to deliver the bioactive agent at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended time period. Since these results have been achieved through the application of a functional coating materials at times the core pellets themselves have been modified to provide the desired effect.

Key words: Controlled release, Novel approach, Pellets**INTRODUCTION:**

Although a variety of dosage forms have been developed for the preparation of oral controlled release formulations, they generally fall into two categories: single unit dosage forms and multiple (multiparticulate) dosage forms^{1,5,18}.

Single unit dosage forms:

Single unit dosage forms are defined as oral dosage forms that consist of single units, with each unit containing one dose of the drug and intended to be administered at a single time. There are several dosage forms that have been developed for controlled release of various bioactive materials, and of which monolithic matrix-based tablets is the most common used for controlled drug delivery. Advantages associated with such dosage forms include high drug loading, simple and cost-effective manufacturing operations, the availability of a wide variety of excipients and polymers for controlling drug release and the possibility of using different mechanisms for drug release control (such as diffusion controlled, swelling controlled, erosion controlled or a combination of all of these). Single unit dosage forms that have been used for controlled drug delivery include controlled drug

release from polymer membrane-coated tablets formulations with osmogens^{2,6,8,9,12,15,16}.

Multiple unit dosage forms:

The concept of multiple unit dosage form was initially introduced in the early 1950s. 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 different units, each shows some desired property. These quality units serve the overall desired controlled release of the dose. These multiple units are also referred to as pellets, spherical granules or spheroids. Historically, the term **pellets** has been used by a number of industries to describe a variety of agglomerates produced from diverse raw materials, using different forms of manufacturing equipment. These mass include fertilizers, animal foods, iron ores, and pharmaceutical dosage units and thus do not only differ in composition but also encompass different sizes and shapes. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherically or semi-spherically units, referred to

as pellets⁴. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. These pellets usually range from 0.5-1.5 mm and in applications may be large as 3mm^{3,4,10,11,20}.

NEED AND OBJECTIVES OF WORK:

Isosorbide mononitrate (1, 4:3, 6-dianhydro-D-glucitol) is one of the hexitol classes of bicyclic heterocycles derived from simple sugars, which in recently years has attracted increasing interest, particularly as regards its biological action. This increased importance particularly of certain analogues of isosorbide is attributable to the reactivity of the hydroxyl groups, relative to the ring juncture, outer at the 2-position and inner at the 5-position^{13,14}.

Isosorbide-5-mononitrate is currently the most commercially important analogue of isosorbide, which is an vasodilator used in cardiac treatment eg. treating angina.

At present there are many oral formulations of Isosorbide mononitrate that are available in the market e.g. Imdur 60mg, 120mg, Ismo 20mg, Monoket 20mg etc. Recently, Isosorbide mononitrate (30mg SR) pellets was launched in the market i.e. Monoisodril. However there is vacuum of formulations of Isosorbide mononitrate pellet preparations in growing market for antianginals¹⁷.

Hence the present work was aimed at an objective to formulate Isosorbide mononitrate pellets with a view to achieve:

- Extended Symptomatic relief.
- To maintain the plasma concentration for considerable period by controlling the release.
- Reduction in frequency of dosing can be reduced and thus improving patient compliance.
- To design stable pellets of Isosorbide mononitrate that will effectively release drug by different pelletization techniques.
- To study the effects of polymers on release profile of Isosorbide mononitrate formulation.
- To arrive at better formulation based on comparison amongst the studied ones.
- To evaluate and characterize the prepared optimized formulation.

RATIONALE FOR PELLETIZATION:

Pellets are of great interest to the pharmaceutical industry for a variety of reasons. Pelletized products offer flexibility in dosage form design and development also utilized to better safety and efficacy of bioactive agents.

However, the most important factor responsible for the proliferation of pelletized products is the popularity of controlled release technology in the delivery of drugs. When pellets contains the active ingredient are administered in vivo in the form of disintegrating tablets, capsules or suspensions, they offer significant therapeutic advantages over single unit dosage forms. Because pellets disperse freely in the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering drug bioavailability. Pellets also reduce variations in gastric emptying rates and overall transit times. Thus, intra – and inter – subject variability of plasma profiles, which are common with single unit dosage regimens, are minimized. Another advantage of pellets over single-unit dosage forms is that high local concentrations of bioactive agents, which may be inherently irritating or anesthetic, should be avoided. When formulate in modified release dosage forms, pellets are less prone to dose dumping than the reservoir type, single unit dosage formulations.

Controlled release pellets are manufactured either to deliver the bioactive agent at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. When these results have been traditionally achieved through the application of a functional coating material, at times the kernel pellets themselves have been modified to provide the desired effect^{19,21,22}.

Advantages of pelletization:

1. Pellets provide an ideal shape for application of film coating.
2. High local concentration of bioactive agents can be avoided
3. Pellets reduce variation in gastric emptying time.
4. They also provide tremendous flexibility in development of oral dosage form.
5. It allows combined delivery of two or more bioactive agents that may not be compatible, at same site or at different site in gastrointestinal tract.
6. It also permit combination of pellets of different release rates of same drug in single dosage form.
7. It is not difficult to obtain uniform and reproducible fill weights in capsules.
8. Pellets can also be made attractive due to various shades of color that can be imparted.

TECHNIQUES OF PELLETTIZATION

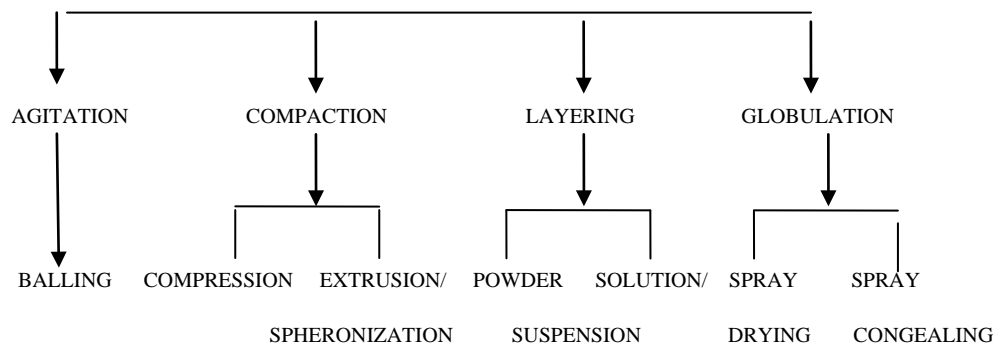


Figure 1: Classification of pelletization processes.

THEORY OF PELLET FORMATION AND GROWTH:

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 presupposed related to the mechanism of formation and growth of pellets. Some theories are derived from experimental results while others are confined to visual observations. As the conventional granulation, the rapidly studied, most classified pelletization method, which involve a rotary drum, a pan or a vessel, has divided into three consecutive steps: nucleation, transition and ball growth. However, based on the experiments carried on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer.

Nucleation is a common stage in all pelletization/granulation processes and occurs whenever a powder is wetted by liquid. The primary particles are attract together to form three-phase air-water-liquid nuclei and are attached together by liquid bridges which are pendulous in nature. The bonding strength is improved by reduction of particle size. The sizes of the primary particles, moisture content, viscosity of the binding particles, the wettability of the substrate and the processing states, such as tumbling and drying rates, affect the size, the rate and the extent of nuclear formation. Both the mass and number of core in the system change as a event of time, that is significant feature of nucleation.

Nucleation is followed by a transition stage, and growth mechanisms affecting the transition region are coalescence and layering. Coalescence is defined as the formation of large-sized particles by random collision of well formed core, and mechanism needs little excess moisture on the nuclear surface. Although the number

of core is progressively decreased, the total lot of the system persists unchanged during this step. Layering is a slow process and involves the successive addition of fragments and fines on an already formed nucleus., Number of particles remains the same in layering step, but total mass in system is increases due to increasing particle size as a function of time.

The fragments or fine particles can be formed by particle size reduction that occurs due to attrition, breakage and shatter. Large pellets pick up the fines and the fragments that are produced through size reduction. Production of fines and subsequent coalescence and layering continues until the number of favorable collisions declines fast, thereby conduct to a reduction in rate of growth of the pellets. At this point the third stage, the ball growth area is reached. In the ball growth phase the main mechanism affecting the slow growth of agglomeration is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction. This situation does not result in a change in the total number or mass of the particles. The particles, however, undergo a continuous change in size as long as the conditions that lead to the transfer of material exist.

One of significant properties of pellets is their ability to withstand the mechanical forces that act on them during the manufacturing process and subsequent conditioning and or coating and handling of the pellets. Due to insufficient mechanical strength, they may break completely or erode down in size attributed to frictional forces. It is absolutely essential; therefore, the pellets possess sufficient strength to overcome any appreciable abrasion during agitation. Thus, it is essential that fundamental mechanisms of pellet formation and growth are clearly understood in order to judiciously select and optimize any pelletization process. Various theories that

attempt to explain these mechanisms have been postulated. Some of these theories are supported by experimental results, while others are interferences relying on visual observations²³.

COATING EQUIPMENT:

Conventional coating pan:

Coating pans have been used in pharmaceutical coating operations since the early 19th century when they were used extensively for sugar coating. There are three types of coating equipment used to apply polymeric materials: perforated coating pans, conventional coating pans and fluidized beds. The conventional coating pan system consists of a round coating pan that rotates on an inclined axis. Tablets in the coating pan slide due to pan rotation. Heat is passed across the surface of the tumbling tablets and exhaust air is withdrawn. The conventional coating pan was generally used in the sugar coating process, where syrup is ladled onto the substrates. Water soluble polymeric film coating, however, requires more quick solvent evaporation and the drying efficiency of conventional coating pans was improved by adding perforations. These perforations allow air to be forced through the tablet bed. As with conventional coating systems, pan rotation results the solid cores to continually move during the coating process. The application region is the area in the pan where the atomized polymer is sprayed onto the substrate exterior. Tablets must form multiple passes through the application area to form the film. Baffles contribute to the tumbling action of the tablets and facilitate uniform film coverage in the perforated coating pans.

Blythe described the first pelletization process in the coating pan in a patent issued in 1956. Although McAinsh and Rowe described the use of a side-vented pan for pellets coating in a patent issued in 1979, most pelletization processes today rely on the same basic equipment used in the 19th century. Conventional coating pans are used extensively in pelletization processes for several reasons. Coating pans are less expensive than most other types of pelletization equipment. They are also extremely versatile in that both layering and pellet coating. Coating pans are available in a wide variety of shapes and sizes. Pear, hexagonal, angular, spherical, elliptical, and donut-shaped. Pellet movement is best described as cascading, with maximum turbulence in the centre of the load²⁰. Conventional coating pans, however, have significant limitation as pelletisation equipment. The degree of mixing is very poor, and the drying is not efficient. Mixing is a function of the pan like, incline angle, the baffle arrangement, and rotational speed of

pan itself. These data optimized to provide uniform drying and sufficient particle movement to eliminate the potential formation of dead spots during the operation and to maximize yield. For instance, during pelletization elliptical pans tend to have fewer stagnant spot than do cylindrical pans and, consequently the equipment of choice. Reducing the tilt angle can also minimize formation of dead spots. If the rotational speed of the pan is too slow, segregation may occur owing to percolation and induce the preferential layering of the drug onto larger particles.

Theophylline pellets were prepared by powder layering processes using the tangential rotary granulator.

The basic components of coating pan are rotating pan, air supply system, spray system, powder addition system and sir-exhaust system.

The variables in a coating pan process- powder application rate, solution spray rate, load size, spray atomization, pan speed, spray gun position, bed temperature, inlet temperature, exhaust airflow, rolling time.

As pan rotates, the nonpareils or starter seeds tumble in a cascading fashion. Initially, the nonpareils are wetted by applying (usually by spraying) an adhesive solution. As the wet seeds reach the front end of pan, powder is added to them in the vortex. A baffle inserted into the rolling bed enhances the vortex action, which intensifies the mixing and shear, so that the adhesion of the powder to the wetted seeds can be improved. After the wet seeds pick up powder, they are directed back into the upward moving bed and the entire process is repeated.

Variables in a coating pan process :

- Load size
- Spray rate and powder application rate
- Pan speed
- Spray gun position
- Spray atomization
- Rolling time
- Inlet and bed temperatures

Load size:

An optimum load size must be established for both the initial and final drug loading stages. As layering continues, the pellets increase in size, thereby increasing the load. As the load approaches the maximum capacity, the layering efficiency is reduced. When the load is large, it is more difficult to control the powder application during the final phase of the drug loading. This result in either too dry or too wet conditions in the pan and ultimately affects the physical characteristics of the pellets.

Spray rate and powder application rate:

Spray rate and powder application rate are considered to be the most critical variables in the drug loading process. Adding the powder too slowly leads to a wet bed and pellet agglomerates. Adding the powder too speedily results in a dry bed with excessive loss of powder through exhaust system powder caking on walls of pan, and formation of seedless drug agglomerates of various sizes. Pellets layered in a "dry" bed often have a rough surface. Pellets layered in wet bed often have smoother surfaces, but batch will have increased amount of agglomerates.

Pan speed:

It is also an important variable that has a significant effect on optimizing the process. If the rotating speed is too low, agglomeration is more likely to occur due to less pellet turnover. Increasing the pan speed will allow an increase in spray rates due to an increased pellet movement, which prevents pellet aggregation^{25,26}.

Spray gun position²¹:

The best mixing and adhesion between the pellets and drug powder occur in the vortex. A spray gun that is too close to the bed results in localized over wetting and pellet agglomeration. In general, the proper distance between the spray gun and bed is 8-11 inches, depending on the nozzle combinations and air pressure used. As pellets grow, it is necessary to adjust the gun position to maintain a proper distance throughout the layering process.

Spray atomization:

The airless spray system is the most commonly used spray system during drug powder layering in the pan. The advantage of airless spray system is that it avoids the high air velocity that tends to fluidize the pellets excessively during application. The important consideration in powder layering is to wet the pellets in such a manner that drug can adhere during a simultaneous powder application. In powder-layering process, a relatively coarse spray is required.

Rolling time:

Rolling time is defined as the time the pan rotates after completion of the layering process. During the rolling, the solvents within the pellets evaporate and the surface of the pellets is shaped. Therefore, a proper rolling time for each product needs to be established^{27,28}.

Inlet and bed temperatures:

A proper supply of hot air must be applied to maintain the desired bed temperature. Hot air may be blown directly into the pan to warm up the bed. Another way to adjust the bed temperature is to install a partial cover on the top of the pan. When hot air is blown onto the outer shell of the pan, the heat is then transferred to the bed.

This approach is advantageous because more uniform bed temperatures can be achieved and concentrated heat in a single area is eliminated.

If a solvent system is used, an adequate exhaust system is necessary to ensure removal of solvent^{29,30}.

CONCLUSION:

Although Isosorbide mononitrate is one of the emerging molecules in case of angina it is usually given orally with dosage regimen depending on patient, site of action and need. To get symptomatic relief, fast healing and also patient compliance, controlled release of isosorbide mononitrate is desirable. Hence, in the present work an attempt has been made to prepare controlled release formulation of Isosorbide mononitrate using different techniques of pelletization. Three different techniques that is drug solution layering on non pareils, pelletization from drug matrix by conventional coating pan and pelletization by extrusion of drug matrix were used.

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