

A REVIEW ON EXTENDED RELEASE DRUG DELIVERY SYSTEM AND MULTIPARTICULATE SYSTEM

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ABSTRACT

Recently, extended release pharmaceutical products become a very useful tool in medical practice, offering a wide range of actual and perceived advantages to the patients. Oral drug delivery is the most preferred route for the various drug molecules among all other routes of drug delivery, because easy of administration which lead to better patient compliance. So, oral extended release drug delivery system becomes a very promising approach for those drugs that are given orally but having the shorter half-life and high dosing frequency.

Key words: Extended Release, Oral route, Therapeutic concentration, Pellet, Dosage form.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

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, diabetes or hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

There are certain considerations for the preparation of extended release formulations: If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active is not directly related to its blood levels, If the absorption of the drug involves an active transport and If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design.

Drawbacks of Conventional Dosage Form

Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.

The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

Advantages of Extended Release Delivery System.

- 1) The extended release formulations reduce dosing frequency of drugs.
- 2) The extended release formulations may maintain therapeutic concentrations.
- 3) Reduce the toxicity by slowing drug absorption.
- 4) The use of these formulations avoids the high blood concentration.
- 5) Extended release formulations have the potential to improve the patient compliance and convenience.
- 6) Minimize the local and systemic side effects.
- 7) Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- 8) Improvement in treatment efficacy.
- 9) Minimize drug accumulation with chronic dosing.
- 10) Improve the bioavailability of some drugs.

Disadvantages of Extended Release Delivery System

- 1) Extended release formulation contains a higher drug load and thus any loss of integrity of the release characteristics of the dosage form.
- 2) The larger size of extended release products may cause difficulties in ingestion or transit through gut.
- 3) The release rates are affected by various factors such as food and the rate of transit through the gut.
- 4) Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- 5) High cost of preparation.
- 6) Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

Rationale of Extended Drug Delivery

The main objective to formulate an API in an extended drug delivery system is related to its pharmacokinetics parameters. An appropriate formulation can make the absorption, distribution, metabolism and elimination (ADME) profile of a drug much more favourable. This change of the ADME can have a profound impact on many aspects of the clinical use of the drug from patient compliance and convenience to its very efficacy, tolerance and safety parameters.

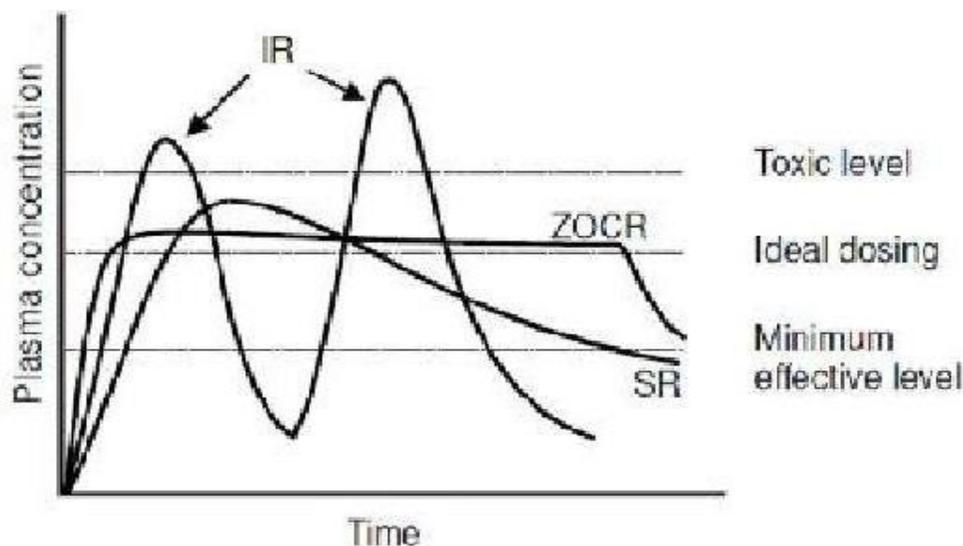


Figure 1: Plasma Concentrations

Pellets

Pelletization is an agglomeration process, that converts fine powder blend of drug(s) and excipients into small, free flowing, spherical units, referred to as pellets.

Rationale of extended release pellets

Pellets provide the development scientist with a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes, and can also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within the gastrointestinal tract.

Advantages of extended release pellets

- 1) To Reduce dosing frequency of drugs.
- 2) Maintain therapeutic concentrations.
- 3) Reduce the toxicity by slowing drug absorption.
- 4) The use of pellets avoids the high blood concentration.
- 5) Extended release formulations have the potential to improve the patient compliance and convenience.
- 6) Reduce the local and systemic side effects.
- 7) Increase the stability by protecting the drug from hydrolysis.

DRUG PROPERTIES OF EXTENDED RELEASE FORMULATIONS

During design of extended release delivery systems, variables such as the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug, are considered of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug. These properties are classified as:

(a) Physicochemical properties

(b) Biological properties

These properties have the greatest effect on the behaviour of the drug in the delivery system and in the body. There is no clear cut distinction between these two categories since the biological properties of a drug are a

function of its physicochemical properties. By definition, physicochemical properties are those that can be determined from in vitro experiments and biological properties will be those that result from typical Pharmacokinetic studies of the absorption, distribution, metabolism, and excretion (ADME) characteristics of a drug and those resulting from pharmacological studies.

Physicochemical Properties

- a) Dose Size
- b) Aqueous Solubility and pKa
- c) Partition Coefficient
- d) Drug Stability
- e) Molecular Size and Diffusivity
- f) Drug Protein Binding

Biological Properties

- a) Absorption
- b) Distribution
- c) Metabolism
- d) Elimination of biological half life.

Approaches to Achieve Extended Release Drug Delivery

The purpose of designing ER dosage form is to develop a reliable formulation that has all the advantages of immediate release dosage form and yet devoid of the dose dumping. Various techniques have been used in the formulation of ER products. In general, extended formulations can be divided into different categories based on the mechanism of drug release.

- 1) Dissolution Controlled Release
- 2) Diffusion Controlled Release
- 3) Ion Exchange Resins Controlled Release
- 4) Swelling Controlled Release.

1) Dissolution Controlled Release

This type of controlled release involves two processes, the detachment of drug molecules from the surface of their solid structure to the adjacent liquid interface, followed by their diffusion from the interface into the bulk liquid medium. The rate of dissolution and the amount dissolved per unit of time from this system can be calculated using Noyes-Whitney equation which relates the rate of dissolution of solids to the properties of the solid and the dissolution medium, and the relation is given by:

$$dW$$

$$DA (C_s - C) = dtL$$

dW/dt is the rate of dissolution;

A is the surface area of the solidification;

C is the concentration of the solid in the bulk dissolution medium;

C_s is the concentration of solid in the diffusion layer surrounding the solid;

D is the diffusion coefficient and

L is the diffusion layer thickness.

2) Diffusion Controlled Release

In this type of controlled release system, the active ingredient diffuses through the polymeric material. These are mainly classified as reservoir and matrix systems.

Reservoir System

Cellulose derivatives are commonly used in the reservoir systems. It consists of a core and membrane of the diffusion barrier. The active ingredient diffuses from the reservoir through the coating membrane.

For a reservoir system where the drug depot is surrounded by a polymeric hydrogel membrane, Fick's first law of diffusion can be used to describe drug release through the membrane.

Matrix System

In this review article greater emphasis is given for matrix controlled release for design of extended release tablets. A matrix system consists of active and inactive ingredients that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral extended release technology and the popularity of the matrix systems can be attributed to several factors. The release from matrix type formulations is governed by Fick's first law of diffusion.

3) Ion Exchange Resins Controlled Release

Ion exchange resins are cross-linked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrant, because of their swelling ability. It forms irreversible complex with ionizable drugs upon prolonged exposure of the drug to the resin. A resin bound-drug is removed when appropriate ions are in contact with ion-exchanged groups.

4) Swelling Controlled Release

Swelling controlled systems are based upon swelling of ER polymer. Due to the viscoelastic properties of the polymers, which are enhanced by the presence of cross-linked network, anomalous penetrate transport can be observed. This behavior is bound by pure Fickian diffusion and case II transport. Therefore, transport can be reduced to three driving forces. The penetrate concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release.

Advantages of Matrix System

Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipments. Secondly, development cost and time associated with the matrix system generally are viewed as variables, and no additional capital investment is required. Lastly, a matrix system is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.

Disadvantages of Matrix System

As with any technology, matrix systems come with certain limitations. First, matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles, more complex matrix based technologies such as layered tablets are required.

Types of Matrix System

The matrix system can be divided into two categories depending on the types of polymeric materials.

1) Hydrophobic Matrix System

2) Hydrophilic Matrix System

Hydrophobic Matrix System.

This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system is the release mechanism, and the corresponding

release characteristic can be described by Higuchi equation known as square root of time release kinetic. The square root of time release profile is expected with a porous monolith, where the release from such system is proportional to the drug loading. In addition, hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development. With the growing needs for optimization of therapy, matrix systems providing programmable rates of delivery have become more important. Constant rate delivery always has been one of the primary targets of controlled release system especially for drug with narrow therapeutic index.

Hydrophilic Matrix System

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell when in contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since matrix swelling lengthens the diffusion path. It has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release.

For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms.

TYPES OF MULTIPARICULATE SYSTEM

A) Matrix Systems

In matrix systems a polymer: drug solution or dispersion is granulated with excipients to form pellets or sprayed onto pellets in order to achieve extended drug release. The drug homogeneously distributed within the polymer is dissolved, dispersed or dissolved and dispersed. These systems present several advantages as follows,

Easy manufacture and low cost (1 step process),

Lower risk of dose dumping and

The Possibility of improve the aqueous drug solubility.

Drug-polymer interactions can occur and bring benefits in terms of mechanical properties such plasticizing effect. The main disadvantages include fast initial release and incomplete release in a defined time. The latter could be avoided by coating sugar cores with different polymer: drug ratios, in which the drug was more concentrated in deeper layers of the matrix and so counteracting for the increased diffusion pathway. In addition, matrix systems were found suitable to control drug release of a highly soluble drug.

Matrix solutions, matrix dispersions and drug release mechanisms

In matrix systems, the drug and polymer are dissolved or dispersed in a common solvent and upon solvent evaporation, a solid solution (drug dissolved in the polymer) or a solid dispersion (drug dispersed in the polymer) or a combination of both is obtained. If the initial drug concentration is below drug solubility in the polymer, drug is dissolved and drug release is mainly extended by drug diffusivity in the polymer.

B) Reservoir Coated Systems

A reservoir coated system consists of a drug layered core surrounded by a polymer. The major advantages of this system rely in the fact that very high drug loadings can be used and variable drug release profiles can be obtained, by just varying the type of polymeric membrane.

Aqueous coating and organic coating

Pellets can be coated with an aqueous polymeric dispersion or an organic solution in order to achieve extended drug release. Organic coatings present many disadvantages as the dependence of viscosity on molecular weight

and the concentration of polymer used. In contrast, aqueous polymer dispersions are characterized by low viscosity even at high solid contents, leading to a decrease in coating process time. Organic solutions present additional disadvantages like the presence of residual solvents in the coating that can create changes in film properties, environmental pollution and explosion hazards. As a result, the use of aqueous polymeric dispersions is preferred for pharmaceutical coatings. However, film formation mechanisms (aqueous versus organic) are very different. With organic polymer solutions, polymer macromolecules are dissolved and this can create a high viscosity solution. During solvent evaporation, an intermediate gel-like phase is formed. After complete solvent evaporation, a polymeric film is obtained. In contrast, film formation from aqueous dispersions is a more complex process. During drying of aqueous dispersions, polymer particles come into contact with each other in a closed packed order. The high interfacial surface tension between air and water leads to the formation of a layer of polymer spheres filled with water. The particle fusion or coalescence is then possible when the capillarity forces (air water interfacial tension) are strong enough. Usually the coating process is performed at sufficient high temperatures to guarantee softness of the discrete polymer particles. The softening is related to the glass transition temperature (T_g) of the polymer. A curing step (post coating thermal treatment) is carried out after coating process to assure complete film formation and avoid further gradual coalescence. The aqueous dispersions can have additional ingredients as surfactants that act as stabilizers during the production process. Other compounds as plasticizers and anti-tacking agents are used to enhance the coating process and film properties. Plasticizers are added to promote the polymer particle coalescence, softening the particles and reducing minimum film formation temperature (MFT). Film formation is related to glass transition temperature of the polymer or minimum film formation of the aqueous dispersion. The MFT is the minimum temperature above a continuous film is formed during drying under standardized conditions. Below this temperature the dry latex is opaque and powdery; however these conditions are different from drying during coating. Actually, water can decrease T_g of the some polymers (due to its plasticizing effect) and in this case the MFT is lower than the T_g of the polymer. T_g and MFT shows a linear relationship between different polymer/plasticizer concentrations.



Figure 2: Spheronization Process

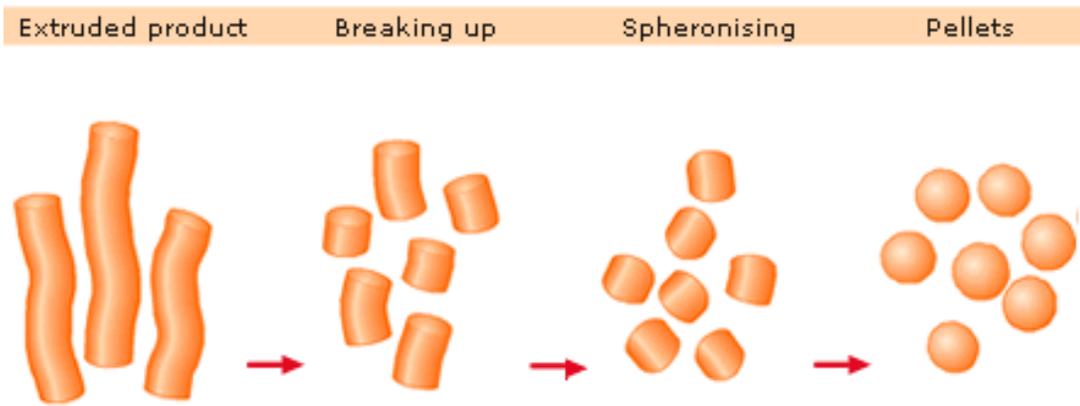


Figure 3: Extrusion Spheronization Technique

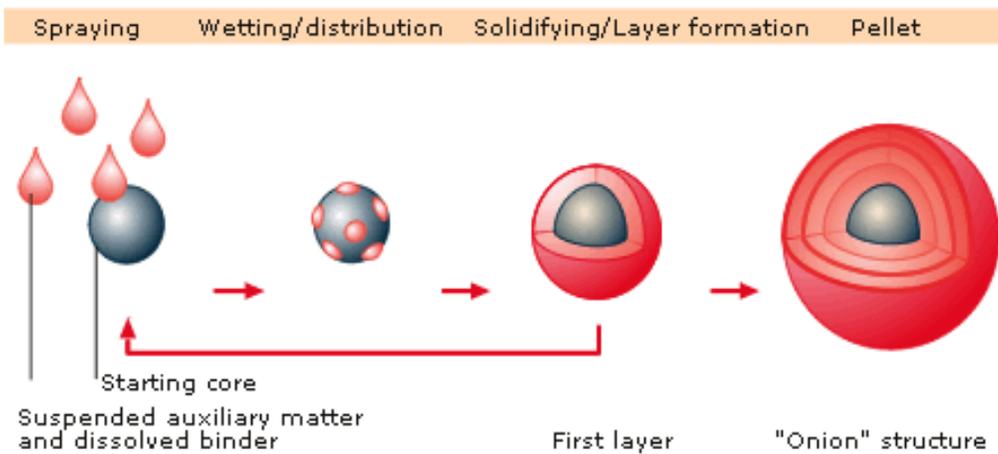


Figure 4: Drug Layering technique

❖ **Preparation of the coated pellets:**

Table 1: Drug loading on sugar pellets

Sr.No.	Ingredients(gms)	T1	T2	T3	T4	T5	T6
1	Sugar pellets (25-30#)	50	50	50	50	50	50
2	API USP	1.25	1.25	1.25	1.25	1.25	1.25
3	HPMC E5LV USP	2	4	2	-	4	4
4	Low substituted HPC E5LV	2	2	4	4	2	-
5	PVP K30	4	2	2	2	-	2
6	SLS AR	0.2	0.2	0.2	0.2	0.2	0.2
7	Talc	1.00	1.25	1.50	1.75	2.00	1.75
8	Isopropyl alcohol AR	20	20	20	20	20	20
9	0.1N HCL	60	60	60	60	60	60

Drug Release Mechanisms

The mechanism controlling drug release from reservoir coated pellets is often a complex process and it depends on coating type and thickness, drug type and core type. One of the mechanisms is diffusion through the

continuous polymer film surrounding the drug loaded core. Firstly, water penetrates through the coating until reaches the pellet core. After- wards, drug is dissolved and released. The drug is released due to the concentration gradient inside the pellet (C_i) versus outside the pellet. In the case of perfect sink conditions the amount of drug released (dM) within a certain time period (dt) can be calculated as follows (according to Fick's law of diffusion):

$$dM/dt = D_m \cdot A \cdot K \cdot C_i / d$$

D_m is the apparent diffusion coefficient of the drug in the polymeric film, A the surface available for diffusion, K the partition coefficient of the drug (aqueous phase – polymeric phase), and d denotes the thickness of the film coating. Unfortunately, Fick's Law (which was only ever intended to describe diffusion in binary mixtures) cannot be extended to drug release from reservoir pellets that easily. The diffusivity for example is assumed to be constant in homogeneous, intact polymer films. However, in reality many polymers swell upon contact with medium which is known to gradually increase the diffusivity over time. In addition most polymers contain crystalline regions in which drug diffusion is negligible.

Drug diffusion in the amorphous regions of polymers has been described by the so-called 'jump-and-run'-model. It was proposed that the amorphous segments in polymers contain homogeneous, semi-crystalline structures of polymer molecules which are aligned in parallel. Permeates like the diffusing drug 'run' along the tube between parallel polymer chains until reaching a 'dead-end' (a crystalline region or a point of high chain entanglement). There they are forced to 'jump' from one tube to the next, pushing and bending the polymer chains apart. Drug release can occur through water filled pores. These pores can be due to leaching of water soluble compounds into the release medium or due to cracks formed by high hydrostatic pressure generated inside these systems upon water uptake. Drug release can be described as follows:

$$dM/dt = D_p \cdot A \cdot C_i / d$$

Where D_p is the diffusion coefficient of the drug in the aqueous phase present in the channels and pores, ϵ the volume fraction of the pores, τ the tortuosity of the channels. Another possible mechanism controlling drug release from coated pellets is due to osmotic effects. For this mechanism to occur an osmotic active core should be surrounded by semi permeable membrane and a difference in osmotic pressure between the inner and outer side of the membrane.

Osmotically driven release depends on the porosity of the polymeric membrane and the osmotic pressure of the sugar core and the drug. Upon water uptake, drug is pushed out via pores in the coating. Drug release can be described as follows:

$$dV/dt = A \cdot \Delta \pi / l$$

Where dV/dt denotes the water flow, A the membrane surface area, l the membrane thickness, θ the permeability of the polymeric membrane, and $\Delta \pi$ the difference in osmotic pressure (neglecting the counteracting hydrostatic pressure). The overall drug release rate from coated pellets may be governed by one of the above mechanism or a combination of them. Parameters as core and coating swelling also contributes to the drug release rate. The type of drug can strongly affect the resulting drug release rates. Ibuprofen diffused through the coating (due to high solubility in the polymer) while chlorpheniramine maleate diffused through micro-channels in Aquacoat coated pellets, resulting from osmotic pressure developed by the core. Drug release rate can be affected by changes in surface area (during dissolution study) of the pellets. The coating level also changes the mechanism of drug release. At low coating levels, drug release occurred through pores in the coating, while at high coating levels drug release rate was extended by diffusion through the coating. Consequently the mechanism controlling drug release at higher coating levels was not just dependent on drug solubility but also on the polymer/dissolution medium partitioning coefficient of the drug.

Drug release mechanism from ethyl cellulose coatings with pore formers was investigated by several researchers. At lower pore former (HPMC) contents, drug release occurred through osmotic pumping, but above a certain value diffusion also contributed to overall drug release. Addition of small amounts of polyvinyl alcohol polyethylene glycol graft copolymer to ethylcellulose coatings was found to control drug release from coated

pellets irrespective of the drug solubility and type of core formulation. The mechanism controlling drug release was shown to be diffusion through intact polymeric membranes.

The glass transition temperature of the polymer also affects the drug release mechanism. With water soluble plasticizers, the polymer was in glassy state after plasticizer migration and drug diffused through water filled pores. With water insoluble plasticizers, the polymer was in the rubbery state and a two phase release mechanism was found. In the first phase drug was released through pores created by leaching of HPMC and in the second phase pore shrinking occurred leading to a decrease of free volume in the polymer chains.

The type of coating technique (organic versus aqueous) was found to contribute to drug release mechanism in different ways. Drug release mechanism from coating with blends of a water-insoluble (ethylcellulose) and an enteric polymer (ethylcellulose: methacrylic acid ethylacrylate copolymer, Eudragit L) occurred by diffusion through the intact polymeric films and/or waterfilled cracks. However, lower hydrostatic pressures were necessary to induce crack formation within aqueous coatings. Organic coatings were mechanically strong with high degree of polymer-polymer interpenetration and thus higher hydrostatic pressure was required to induce crack formation.

The polymer particle size affects the film coating structure and properties. Blends of aqueous dispersions of a water-insoluble and an enteric polymer, ethylcellulose and Hydroxypropyl methyl cellulose acetate succinate (HPMCAS) and Eudragit L were used as coating materials to control theophylline release from matrix pellets. Drug releases were similar for both types of blends in 0.1 M HCl, but significant differences were observed in phosphate buffer pH 7.4. Eudragit L particles are smaller than HPMC particles (nano. vs. micrometer size range) and more effectively hinder the formation of a continuous and mechanically stable ethylcellulose network. Ethyl cellulose structures remaining upon HPMC leaching are mechanically stronger and drug release is extended by diffusion through the polymeric remnants. In contrast, ethylcellulose structures remaining after enteric polymer leaching at high pH are mechanically much weaker in the case of Eudragit L. Upon exposure to phosphate buffer, water-filled cracks are formed, through which the drug rapidly diffuses out.

Storage Stability

Although the curing step is performed in order to complete film formation, drug release rate was reported to decrease especially under elevated humidity. This was mainly attributed to further gradual polymer coalescence, leading to denser films and decreased permeability for water and drug. Changes in drug release profiles were also observed with high glass transition temperature polymers. Faster drug release may be caused by brittle films or the formation of micro-ruptures in the film coat during storage. Thermal humidity curing was found to help to enhance coalesce of polymeric films, however presence of high levels of humidity during storage can destabilize films, originating changes in drug release rate over time.

FORMULATION METHODS

Extrusion Spheronization Process

The concept of multiparticulate dosage forms introduced in the 1950's with the increasing use of multiparticulate extended release (CR) oral dosage forms, in recent times there has been a rise in interest in the methods of preparing these dosage forms. A method that has gained increased usage over the past few years is that of extrusion and spheronization. It has extensively as a potential technique and also as a future method of choice for preparation of multiparticulate CR dosage forms. This is a multi-step process involving dry mixing, wet granulation, extrusion, spheronization, drying and screening. The first step is dry mixing of the drug and excipients in a suitable mixer followed by wet granulation, in which the powder is converted into a plastic mass that is easily extruded. The extruded strands transferred into a spheronizer, where they are instantaneously broken into short spherical 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 friction plate, and the cycles repeated until the desired sphericity achieved. Extrusion-spheronization is a multistep process involving a number of unit operations and equipment. However, the most critical part of processing equipment dictates the outcome of overall quality of pellets.

Extrusion

Shaping of the wet mass into long rods is called as extrusion. A variety of extruders, which differ in design features and working principles, are currently on market and can be classified as screw-fed extruder, gravity-fed

extruder and ram extruder. Screw-fed extruder have screws that rotate along the horizontal axis and hence transport the materials horizontally, they may axial or radial screw extruders. The product temperature extended during extrusion by jacketed barrels. In radial extruders, the transport zone is short, and the material extruded radially through screens mounted around the horizontal axis of the screws. Gravity-fed extruders include the rotating cylinder and rotating gear extruders, which differ primarily in the design of two counter-rotating cylinders. In the rotating cylinder extruder, one of the two counter rotating cylinders is hollow and perforated, whereas the other cylinder is solid and acts as a pressure roller. In ram extruders, piston displaces and forces the materials through a die at the end. Ram extruders preferred during formulation development they 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 desired attributes. The granulated mass must 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 the formulation of uniform spherical pellets. Excipients play an important role during extrusion spheronization than during with other pelletization process. They facilitate extrusion and determine the sphericity of the wet pellets, impart strength and integrity of the pellets. Microcrystalline cellulose (MCC) is the most commonly used excipient in extrusion spheronization it leads to the formation of round spheres with desirable characteristics.

Spheronization

During the third phase of extrusion spheronization process the extrudates dumped on to the spinning plate of the spheroniser, call the friction plate, where the extrudate broken up into smaller cylinders with a length equal to their diameter, those plastic cylinders rounded due to frictional forces. In the spheronization process different stages are distinguished depending on the shape of the particles, i.e.; starting from a cylinder over a cylinder with rounded edges, dumbbells and elliptical particles to eventually perfect spheres. Another pellet forming mechanism might exist. In this mechanism twisting of a cylinder occurs after the formation of cylinders with rounded edges, finally resulting in the breaking of the cylinder into two distinct parts. Both parts have round and flat side. Due to rotational and frictional forces involved in the spheronization process the edges of the flat side fold together like a flower forming the cavity observed in certain pellets. The spheronization of a product usually takes 2-10 minutes. A rotational speed of friction plate in the range between 200 and 400 RPM would be satisfactory to get highly spherical pellet. This statement is in a sharp contrast with most reports indicating the use of spheronization speeds exceeding 400 RPM. This contradiction is explained by the fact that not the absolute speed is important but the speed in combination with the diameter of the friction plate. From those two parameters the plate peripheral velocity is calculated and this data should be compared instead of absolute rotational speed of the friction plate.

Layering Process

Layering processes involve loading solid inert cores with drugs and/or excipients. Inert cores, placed in a suitable vessel such as a coating pan or a fluid bed, may be layered according to different methods. Some methods consist of spraying onto the cores a solution/suspension containing both drug and binding agent. Others are based on layering the drug directly in powdery form where drug loading occurs by gravity and adhesion is ensured by a liquid binder sprayed into the cores.

The layering process is particularly suitable for production of small drug loaded units, multiples of which are placed into capsules for patient delivery. In the case of spherical inert cores such as nonpareils, the layering techniques from solution/suspensions produce homogeneous drug loaded particles, which retain an approximately spherical shape. They are therefore particularly suitable for successively film coating to build up the particle with the aim of providing a desired drug release profile.

Powder layering involves the deposition of successive layers of dry powder of drug or excipients or both on performed nuclei or cores with the help of a binding liquid. Because powder layering involves the simultaneous application of the liquid and dry powder, it generally requires specialized equipment. Pieces of equipment revolutionized powder layering processing as a pelletizing techniques are- tangential spray or centrifugal fluid bed granulators. In case of tangential spray the rotating disk and fluidization air provides proper mixing. With a double wall centrifugal granulator, the process is carried out in the open and closed position. With powder layering, the inner wall is closed so that simultaneous application of liquid and powder could proceed until the

pellets have reached the desired size. The inner wall is then raised, and the spheres enter the drying zone. The pellets are lifted by the fluidization air up and over the inner wall back in to forming zone. The cycle is repeated until the desired residual moisture level in the pellets is achieved.

Mechanism of fluidized bed coating process

The fluidized bed process widely use in the pharmaceutical industry powder coating and pellets coating. The fluidized bed containers available in the size that 100-500g to 800 Kg batch size can run. The process is used commercially for particles coating from less than 100 μm to tablets. The coating chamber of fluidized bed (Wurster) is typically slightly conical, and houses a cylindrical partition that in about half the diameter of the bottom of the coating region. At the bottom region, air distribution plates (ADP) also know as orifice plate accommodated. ADP divided in to two regions. The open area of the plate that is under the Wurster column is more permeable to allow volume and air velocity transport parallel to air flow. As inle tair accelerate upward, particles pass a spray nozzle that is mounted in the center of this up bed ADP. The nozzle is a binary type - one port of nozzle for liquid while other for atomized air at predecided volume and pressure. The spray pattern is in a solid cone of droplets, with a spray angle approximately 30–50° called as coating zone. Down bed is region outside the partition. The ADP selected based on size and density of material used. The air flow in the down bed region keep material in suspended form and drawn horizontally into the gap at the base of the partition. The height of column controls the rate of substrate flow horizontally into the coating zone. During coating in progress, mass increased gradually so height of column increased to achieve desire pellets flow. Above the product container is the expansion area, which is typically conical to allow for decreasing air and particle velocity. All fluidized-bed techniques are known for high rates of heat and mass transfer, and the Wurster process is very effective in this regard. Highly water-soluble materials can be coated using water based applications without concern for concentration. Droplets applied to the surface spread, and form a continuous film and rapidly dry. After a initial coat has been applied, increased the spray rates. Films formed from organic solvents base coating has high in quality, because the formed droplets impinge on the substrate very quickly, minimizing the potential for spray drying of the film

Evaluation Parameter of Extended Release Pellets

- 1) Micrometric Properties
- 2) Morphological Properties
- 3) Drug Content
- 4) In-vitro Dissolution

1 Micrometric Properties

The results obtained for micromeritic properties of drug loaded spheres are shown in Table 2. The angle of repose near to the 20 shows excellent flow and for hausner ratio around 1 show good flow properties^{14, 15, 16}. The results obtained for micromeritic characteristics of active substance loaded pellets showed good to excellent flow behavior.

Table 2: Micromeritic properties of drug loaded pellets

Formulation batches	Bulk density(gm/ml)	Angle of repose	Hausner ratio	Drug content(%)
T1	0.813± 0.124	23.540±0.325	1.02±0.254	98.59±0.24
T2	0.798±0.247	18.37±0.412	1.07±0.264	96.74±0.15
T3	0.853±0.217	21.09±0.428	1.05±0.213	97.15±0.31
T4	0.809±0.301	20.17±0.364	1.0±30.398	102.53±0. 31
T5	0.782±0.103	23.93±0.256	1.05±0.512	100.39±0.14
T6	0.793±0.264	24.15±0.259	1.06±0.368	98.74±0.30

*Mean±S.D. (n=3)

2) Morphological Properties

The morphology of non pareils was checked by SEM. The view of pellets showed a spherical structure with rough surface morphology. After coating of non pareils, smooth surface of pellets was observed. SEM study at X100 as well as X60 magnifications revealed that the active substance layered spheres are dense with wrinkled, rough and porous circumference which is due to gradual loss of aqueous material during active substance layering process from the surface of spheres.

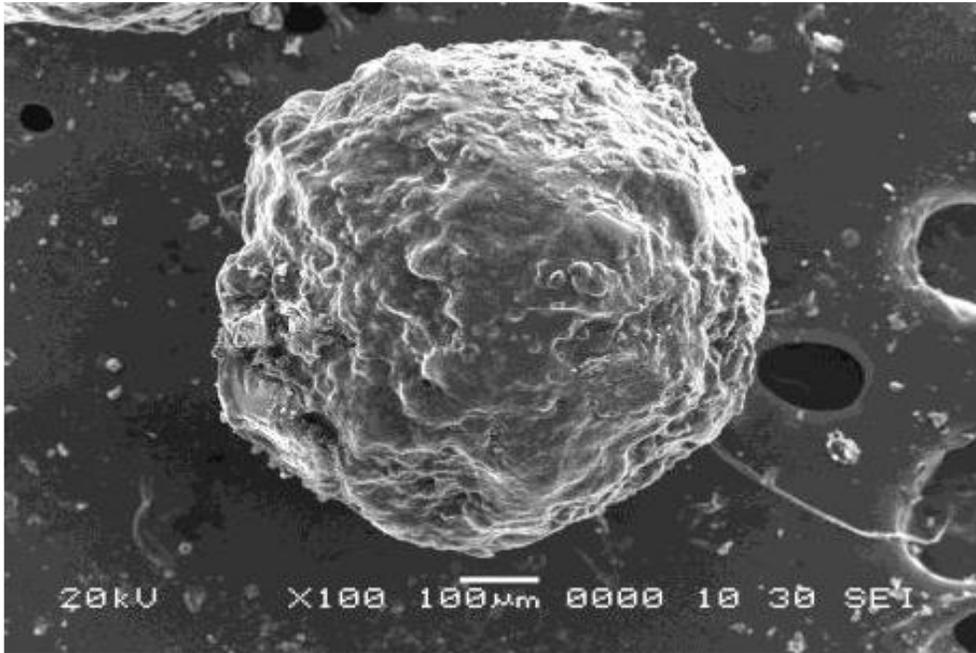


Figure 5: SEM photograph of drug loaded pellets.

3) Drug Content

The drug content of Batches T1 to T6 is shown in Table no 1. The active substance content of drug loaded pellets was found to be 96.00 % -105 % for T1 –T6 which was within the limits (Std. limits-95% - 105%)

4) In-vitro Dissolution

The release pattern of the drug loaded pellets is given in Figure. *In vitro* release trials were performed to check the release of active substance from drug coated spheres. The releasing profile of batches T1 to T6 was noted to vary due to changes in the quantity of HPMC 5 Cps, lower substituted HPC and PVP K30. The batches T1-T3 gives the minimum active material release due to combination of PVP K30 with lower substituted HPC and HPMC 5 cps; while the composition T4-T6 gives the better release pattern as compare to T1-T3. From the figure 11, it was shown that, the combination of low substituted HPC, HPMC 5cps and PVP K30 lowers the active substance release while combination of PVP K30 either with lower substituted HPC or HPMC 5cps gives better active substance release. Based on active substance release pattern, the composition T6 was chosen for further sub-coating batches.

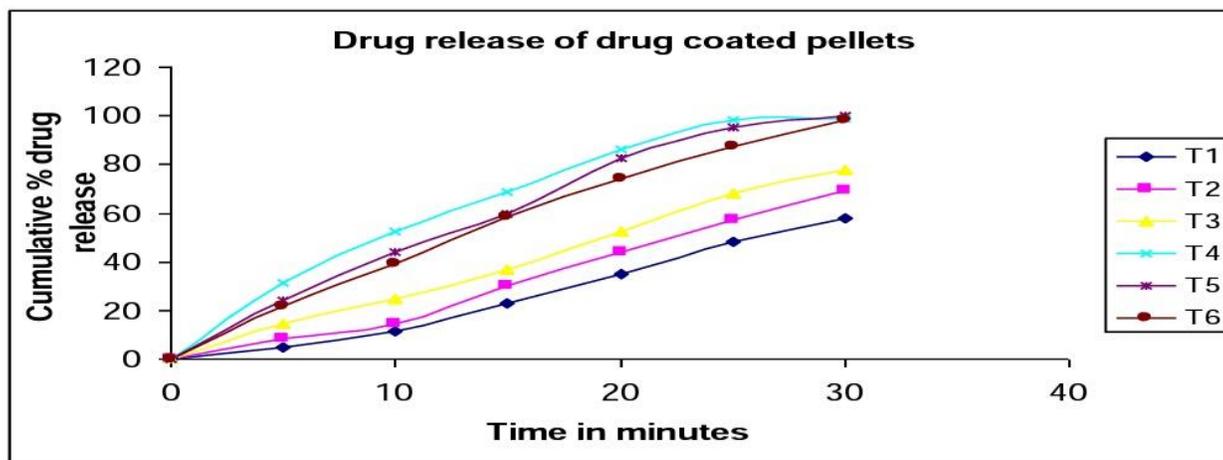


Figure 6: Drug release of drug loaded pellets

CONCLUSION

A number of drugs are now marketed in a variety of different extended release products. However, only those, which result in a significant reduction in dose frequency or reduction in dose related toxicity, are likely to improve therapeutic outcomes. The market for extended release drug delivery has come a long way and will continue to grow. We Concluded that Pellets are for pharmaceutical purposes and are produced primarily for the purpose of oral extended-release dosage forms having extended release properties or the capability of site-specific drug delivery. For such purposes, coated pellets are administered in the form of hard gelatin capsules. As drug-delivery systems extended release pellets become more sophisticated, the role of pellets in the design and development of dosage forms is increasing. Formulation of drugs in multiple-unit dosage forms, such as extended release coated pellets filled in capsules, offers flexibility as to target-release properties. The safety and efficacy of the formulation is higher than that of other dosage forms. *In vitro* release trials were evaluated in response to check release of drug from the drug coated spheres. The release pattern of batches T1 to T6 was observed to vary due to variation in the concentration of HPMC 5cps, low substituted HPC and PVP K30. The trials T1-T3 showed the slow drug release due to combination of PVP K30 with low substituted HPC and HPMC 5cps; while the formulation T4-T6 showed the good release behavior as compare to T1-T3. From the figure 11 it was found that, the combination of HPMC 5cps, low substituted HPC and PVP K30 decreases the drug release while combination of PVP K30 either with low substituted HPC or HPMC 5cps shows better drug release. Based on drug release study, the formulation T6 was selected for further sub-coating trials.

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