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A Review on Extended Release Pellets

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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.

Keywords: 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.

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.

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.

Pellets

Palletization 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.

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/dt=

$$DA (Cs – C) = dtL$$

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;

Cs 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.

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.

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.

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.

Evaluation Parameter of Extended Release Pellets

1) Micrometric Properties

In this evaluation parameter determine the bulk density, angle of repose and flow behavior of pellets.

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.

3) Drug Content

The drug content of drug loaded pellets was determine within the limits (Std. limits-95% - 105%)

4) In-vitro Dissolution

In vitro release trials were performed to check the release of active substance from drug coated spheres.

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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