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AN OVERVIEW: SUSTAINED RELEASE MATRIX TECHNOLOGY

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ABSTRACT

Sustained release pharmaceutical products became a very useful tool in medical practice, offering a wide range of actual and perceived advantages to the patients. Sustained release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. Oral sustained release drug delivery medication will continue to account for the largest share of drug delivery systems. The sustained release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. This article contains the basic information regarding extended-release formulation and also the different types of the same**.**

Key Words:- Sustained release, Therapeutic concentration, Patient convenience and compliance.

INTRODUCTION

Drugs are rarely administered solely as pure chemical substances, but are almost given as formulated preparations. The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in the formulation.

Advantages of Tablets

The primary potential advantages of tablets are

They are the unit dosage forms, which offer the great capabilities of all oral dosage forms for the greatest dose precision and the least content variability. Before a drug substance can be successfully formulated into a dosage form, many factors must be considered. These factors can be broadly grouped in to 3 categories,

1. Biopharmaceutical considerations (Factors affecting absorption of drugs)
2. Drug related factors (Physical and Chemical properties of the drug)
3. Therapeutic considerations (Disease to be treated and Patient factors)

Among various orally administered dosage forms (tablets, capsules, syrup, solution etc…), the tablet dosage form is the most widely used.

Compressed tablets are defined as solid unit dosage forms made by compaction of the formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug product.

- The cost is lowest of all oral dosage forms.
- They are the lightest and most compact of all.
- They are in general the easiest and cheapest to packaging and shipment.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face. They may provide the greatest ease of swallowing with the least tendency for hang up above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products, such as enteric or delayed release products.

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- They are better suited to large scale production than with other unit oral dosage forms.
- They have the best combined properties of chemical, mechanical and microbiological stability of all the oral forms.

Disadvantages

In spite of all these advantages, tablets also possess some disadvantages. The disadvantages of tablets include the following

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting properties, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter tasting drugs, drug with obnoxious odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation / entrapment prior to compression / coating (. Lachmann L *et al*., 1976).

Classification of Tablets

1. Classification based on mode of administration
   i. Tablets to be swallowed
   ii. Chewable tablets
   iii. Tablets used in oral cavity
   - Buccal tablets
   - Sublingual tablets
   - Troches and lozenges
   - Dental cones
2. Tablets administered other than oral route
   i. Implants
   ii. Vaginal tablets / suppositories
   iii. Classification based on drug manufacturing process
   1. Standard compressed table
   2. Multiple compressed tablets
      - Compression – coated tablets
      - Layered tablets
3. Coated tablets
4. Molded tablets (Tablet triturates)

Classification based on drug release profile

- Fast Dissolving tablets
- Immediate Release tablets
- Controlled Release tablets (Sustained Release tablets)
- Delayed Release tablets (Enteric coated tablets)

Tablets used to prepare solutions

- Effervescent tablets
- Dispersible tablets (Aulton ME, Wells TI, 1988)

Sustained Drug Delivery System

The pharmaceutical industry provides a variety of dosage forms and dosage levels of particular drugs, thus enabling the physician control the onset and duration of drug therapy by altering the dose and / mode of administration. In some instances, control of drug therapy can be achieved by taking advantage of beneficial at drug interactions that affect drug disposition and elimination. Mixtures of drugs might be utilized potentate, synergize, or antagonize given drug actions. Alternatively, drug mixtures might be formulated in which the rate and / or extent of drug absorption is modified. Sustained release dosage form design embodies this approach to the control of drug action, i.e. through a process of either drug modification or dosage form modification, the absorption process, and subsequently drug action can be controlled (Gupta PK and Robinson JR, 1992).

Some therapeutic advantages of sustained release systems

1. Avoid patient compliance problems
2. Employ less total drug

i. Minimize or eliminate local side effects
ii. Minimize or eliminate systemic side effects
iii. Less potential or reduction in drug activity with chronic use
iv. Minimize drug accumulation with chronic dosing

3. Improved efficiency in treatment

i. Cure or control of condition more promptly
ii. Improved control of condition i.e. less fluctuation in drug level
iii. Special effects e.g. sustained release aspirin provides sufficient drug so that on awakening, the arthritic patient has symptomatic relief.

The disadvantages of sustained release formulations include the following

1. Administration of sustained release medication does not permit the prompt termination of therapy. Immediate changes in drug need during therapy, such as might be encountered in significant adverse effects are noted, can't be accommodated.
2. The physician has less flexibility in adjusting dosage regiments. This is fixed by the dosage form design.
3. Sustained release forms are designed on the basis of average drug biological half-lives. Disease states that alter drug disposition, significant patient variation are not accommodated.
4. Economic factors must also be assessed, since more costly processes equipments are involved in

manufacturing many sustained release dosage forms (Salsa *et al*., 1997; Wani MS *et al*., 2008).

DRUG PROPERTIES INFLUENCING A SUSTAINED RELEASE DOSAGE FORM

Physico-Chemical Properties

Dose Size

If oral product has a dose size greater than 0.5 gm, it is a poor candidate for a sustained release system, since addition of the sustaining dose and possibly the sustaining mechanism will, in most cases, generate a substantial volume product that will be unacceptably large.

Aqueous Solubility

Extremes in aqueous solubility are undesirable in the preparation of a sustained release product. For drug with low water solubility, they will be difficult to incorporate into a sustained release mechanism. The lower limit on solubility for such product has been reported to be 0.1 mg/ml. Drugs with greater water solubility are equally difficult to incorporate into a sustained release system.

pH

pH range would be another problem because of the variation in pH throughout the GI tract and hence variation in dissolution rate.

Partition coefficient

Drug that are very lipid soluble or very water-soluble (i.e.) extremes in partition coefficient, will demonstrate either low flux into the tissues or rapid flux followed by accumulation in the tissues. Both cases are undesirable for a sustained release system.

Drug Stability

Since most oral sustained release system by necessity, are designed to release their content over much of the length of the GI tract, drugs which are unstable in the environment of the intestine, might be difficult to formulate into prolonged release systems. Interestingly, placement of a labile drug in a sustained release dosage form often improves the bioavailability picture (Jantzen GM and Robinson JR, 1995; Altaf AS and Friend DR, 2003; Gwen MJ and Joseph RR, 1996).

Biological Properties

Absorption

Drug that slowly absorbed or absorbed with a variable absorption rate are poor candidates for a sustained release system. For oral dosage forms, the lower limit on the absorption rate constant is in the range of 0.25h-1 (assuming a GI transit time of 10-12h).

Distribution

Drugs with high apparent volumes of distribution, which turn influences the rate of elimination for the drug, are poor candidates.

Metabolism

Sustained release systems for drugs which extensively metabolized possible as long as the rate of metabolism is not too great nor the metabolism is variable with GI transit or other routes.

Duration of action

The biological half-life and hence the duration of action of drug obviously plays a major role in considering a drug for sustained release systems. Drugs with short half-lives and high doses impose a constraint because of the dose size needed and those with long half-lives are inherently sustained.

Therapeutic Drugs

Drug with a narrow therapeutic range require precise control over the blood levels of drugs, placing a constraint on sustained release dosage forms.

Before proceeding with the design of a sustained release form of an appropriate drug, the formulator should have an understanding of the pharmacokinetics of the drug, should be assured that pharmacologic effect and be correlated with drug blood levels, and should be knowledgeable about the therapeutic dosage range including the maximum effective and maximum safe doses.

Most sustained release forms are designed so that the administration of a single dosage unit provides the immediate release of an amount of drug that promptly produces the desired therapeutic effect and continual release of additional amounts of drug to maintain this level of effect over an extended period is usually 8-12 hours.

To maintain the constant level of drug in the system the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body (Leon Lechman *et al*., 1987).

Matrix Tablets

One of the least complicated approaches to the manufacture of sustained release dosage forms involvers the direct compression of blends of drug retardant materials and additives to form a tablet in

which drug is embedded in a matrix core of the retardant. Alternately, retardant drug blends may be granulated prior to compression.

There are three different types of matrix tablets , hydrophilic matrices, plastic matrices, and fat-wax materials, which can be differentiated by the matrix-building materials.

Hydrophilic matrix tablets

Sodium carboxy methyl cellulose, methylcellulose, hydroxyl propyI cellulose, hydroxyl ethyl cellulose, poly ethylene oxide, poly vinyl pyrolidone, polyvinyl acetate, carboxy poly ethylene, alginic acid, gelatin and natural gums and be used as matrix materials.

The matrix may be tableted by direct compression of the blend of active ingredient(s) and certain hydrophilic careers (or) form a wet granulation containing the drug and hydrophilic matrix materials.

The hydrophilic matrix requires water to activate the release mechanism. Upon immersion in water, the hydrophilic matrix quickly forms a gel around the tablet. Drug release is controlled by a gel diffusional barrier that is formed and / or tablet erosion (Kamboj S and Gupta GD, 2009).

Advantage Ease of manufacture and excellent uniformity of matrix tablets

Fat-wax matrix tablets

The primary constituents of a fat-wax matrix are fatty acids and / or fatty esters. The drug can be incorporated into fat-wax granulations by Spray congealing in air, blend congealing in an aqueous media with or Without the aid of surfactants and spray drying techniques. The mixture of active ingredients, waxy materials and fillers can be converted into granules by compacting with a roller compactor, heating in a suitable mixer such as fluidized bed and steam jacketed blender or granulating a with solution of waxy materials or other binders.

The drug embedded into a melt of fats and waxes is release by leaching and / or hydrolysis as well as dissolution of fats under the influence of enzymes and pH changes in the gastro intestinal tract. Fatty acids are more soluble in an alkaline rather than acidic medium. Fatty esters are more susceptible to alkaline catalyzed hydrolysis than to acid catalyzed hydrolysis. Polyethylene, ethyl cellulose and glyceryI esters of hydrogenated resins have been added to modify release pattern.

Plastic matrix tablets

Commonly used plastic matrix materials are polyvinyl chloride, polyethylene, vinyl acetate / vinyl chloride co-polymer, vinylidene chloride, / acrylonitryle co-polymer, acrylate/ methyl methacrylate co-polymer, ethyl cellulose, cellulose acetate and polystyrene.

Plastic matrix tablets can be easily prepared by direct compression of drug with plastic materials provided the plastic material can be comminuted or granulated to desired particle size to facilitate mixing with drug particle.

In order to granulate for compression into tablet embedding process may be accomplished by

i. The solid drug, and the plastic powder can be mixed and kneaded with a solution of the same plastic material or other binding agent in an organic solvent and then granulated.
ii. The drug can be dissolved in the plastic by using an organic solvent and then a granulated upon evaporation of the solvent.
iii. Using latex or pseudo latex as granulation fluid to granulate the drug and plastic masses.

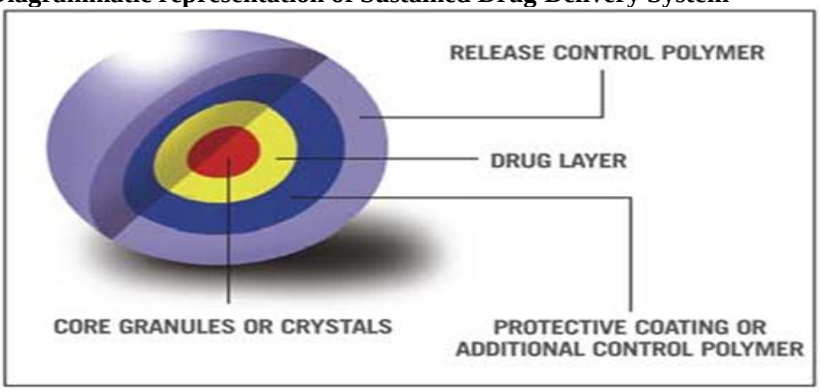
Since the mechanism of controlling drug release in the plastic matrix is the pore structure of the matrix , any formulation factors affecting the release of a drug from the matrix may be consequence of their primary effect on apparent porosities and tortuosities of the matrices.

Drug release from the inert plastic matrices was affected by varying formulation factors such as the matrix materials, amount of drug incorporated in the matrix, drug solubility in the dissolution media and in the matrix, matrix additives and the release media (Indian Pharmacopoeia, 1996; Matthews BR, 1999).

Evaluation Parameters for Sustained Release Tablets

To design a tablet and later monitor its quality, quantitative evaluation and assessment are done on the basis of its physical, chemical, and pharmacokinetic properties. The tablets made are evaluated for the routine checks for the tablets such as Average weight, Thickness, Hardness, weight variation etc. The main parameter required to be monitored while formulating an extended release tablets is in vitro release of the drug and that is in turn demonstrated by dissolution Profile (Cooper J and Gunn C, 1986; Raja Chakraverty, 2012).

Fig 1. Diagrammatic representation of Sustained Drug Delivery System



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. Presence of food, gastrointestinal motility and concomitant administered or present material will influence the therapeutic response. The market for extended release drug delivery has come a long way and will continue to grow. There are varied technologies for manufacturing extended release tablets with significant advantages and some limitations.

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