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STUDY ON CONTROLLED DRUG DELIVERY SYSTEMS: REVIEW ARTICLE

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ABSTRACT

Controlled drug release devices have been developed to maintain constant concentrations of drug within the therapeutic range in the patient's body. There, it helps to reduce the variability of performance of the active drug. Such systems offer many advantages over traditional systems drug management methods. Targeted delivery systems are also considered controlled drugs Distribution system. These devices are designed to improve continuous drug therapy released after application of a single dose to stabilize blood levels, thereby reducing side effect. Polymer membranes are commonly used for controlled drug delivery. These systems acts on various mechanisms such as osmotic pressure, matrix systems, controlled dissolution, etc. This paper presents a brief review of the preparation of controlled drug release devices, and underlying mechanisms that influence drug release, including types of devices to control with basic mathematical equations.

Oral drug delivery is the most convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness to drugs when administered by oral conventional method in the form of tablets and capsules.

Keywords*: Drug, Polymer, Stability, Controlled drug delivery system, Drug release mechanism, Modified Release, Sustained Release.*

1. INTRODUCTION

Drugs can be administered through various routes; however, of all the routes of administration, oral route of administration is the most convenient for administering and for dosage adjustments. Important reason for their popularity is their convenience of application and the ease of preparation on an industrial scale [1].

Controlled drug delivery occurs when a polymer is combined with a drug or active agent such that the release from the bulk material is pre-designed. Controlled and Sustained Release, both has been used in consistent and confusing manner. Both represent separate delivery process. Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally don't attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters [2].

The modified release oral drug delivery systems classified as are:

1) Extended release dosage forms:

It is defined as the one that allows at least a twofold reduction in the dosing frequency as compared to that of conventional dosage form.

2) Delayed release dosage forms:

It is defined as one that releases the drug at a time other than "immediately" after administration.

3) Rationale of controlled drug delivery:

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration.

Different terminologies have been used for the new drug delivery system by different authors.

1) A] Controlled Action:

In this type of dosage forms it provides a prolonged duration of drug release with predictability and reproducibility of drug release kinetics. In this case, the rate of drug absorption is equal to the rate of drug removal from body.

2) Sustained Action:

In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response. The remaining fraction is released periodically and is required to maintain the maximum initial pharmacological activity for some desirable period of time in excess of time expected from usual single dose.

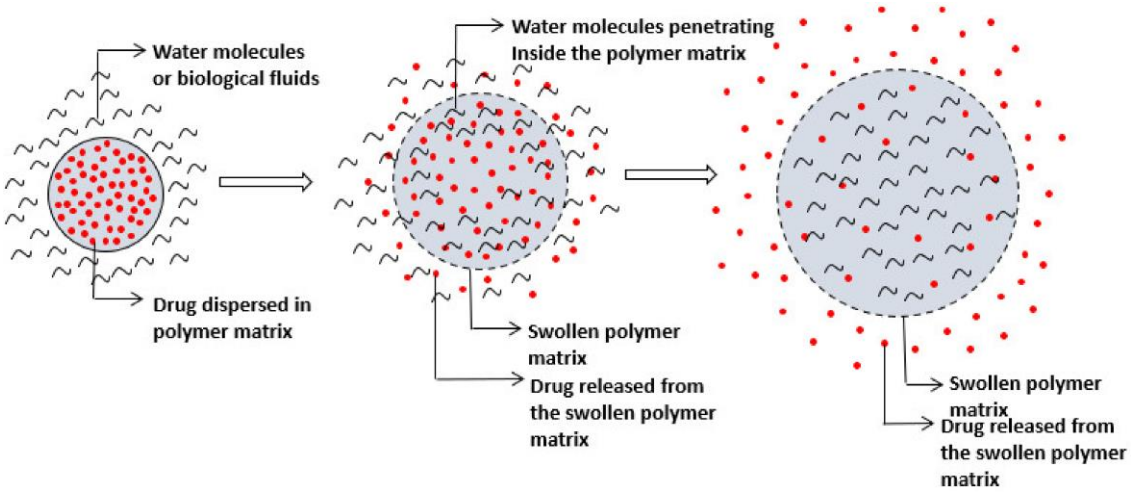
3) Prolonged Action:

These types of dosage form are designed in such a way that it release the drug over an extended period during which pharmacological response is obtained but does not necessarily maintain the constant blood level.

4) Site specific and receptor release:

It refers to targeting of drug directly to a certain biological location.

Potential advantages and disadvantages of controlled release dosage forms



Advantages of Controlled Drug Delivery:

- Maintenance of drug levels within a desired range.
- Delivery of "difficult" drugs: slow release of water-soluble drugs, fast release of low solubility drugs
- Less dosing and increased patient compliance.
- Eliminate over or under dosing
- Prevention of side effects
- Reduction in Health care c

i) Patient Compliance:

Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process,

patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule. Also the complexity of therapeutic regimens, the cost of therapy and magnitude of local and or systemic side effect of the dosage form.

The problem of lack of patient compliance can be resolved to some extent by administering controlled release drug delivery system.

ii) Reduced 'see- saw' fluctuation:

Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see – saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well designed controlled release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a more steady drug concentration in blood circulation and target tissue cells.

iii) Reduced total dose:

Controlled release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

iv) Improved efficiency in treatment:

Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A controlled release dosage forms leads to better management of the acute or chronic disease condition.

Disadvantages of Controlled drug delivery systems:

i) Dose dumping:

Dose dumping is a phenomenon where by relatively large quantities of drug in a controlled release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.

ii) Less flexibility in accurate dose adjustment:

In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

iii) Poor In Vitro – In Vivo correlation:

In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called 'Absorption window' becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.

iv) Patient variation:

The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

Criteria to be met by drug proposed to be formulated in controlled release dosage forms.5,6

a) Desirable half-life.
b) High therapeutic index
c) Small dose
d) Desirable absorption and solubility characteristics.
e) Desirable absorption window.
f) First past clearance.

(a) Desirable half-life:

The half life of a drug is an index of its residence time in the body. If the drug has a short half life (less than 2 hours), the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half life of eight hours or more are sufficiently sustained in the body, when administered in conventional dosage from, and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of three to four hours.

(b) High therapeutic index:

Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to fatalities eg. Digitoxin.

(c) Small dose:

If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.

(d) Desirable absorption and solubility characteristics:

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.

(e) Desirable absorption window:

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the 'absorption window'. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable

(f) First pass clearance:

As discussed earlier in disadvantages of controlled delivery system, delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.

DESIGN AND FORMULATION OF ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM AND THE FACTORS AFFECTIG:

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral controlled release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu.

Theoretically and desirably a controlled release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion.

Controlled (zero-order) drug release can be schematically illustrated as follows:

Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order controlled release formulation.

Controlled (zero-order) drug release has been attempted to be achieved, by following classes of controlled drug delivery system:

A) Diffusion controlled system.

i) Reservoir type ii) Matrix type

B) Dissolution controlled system.

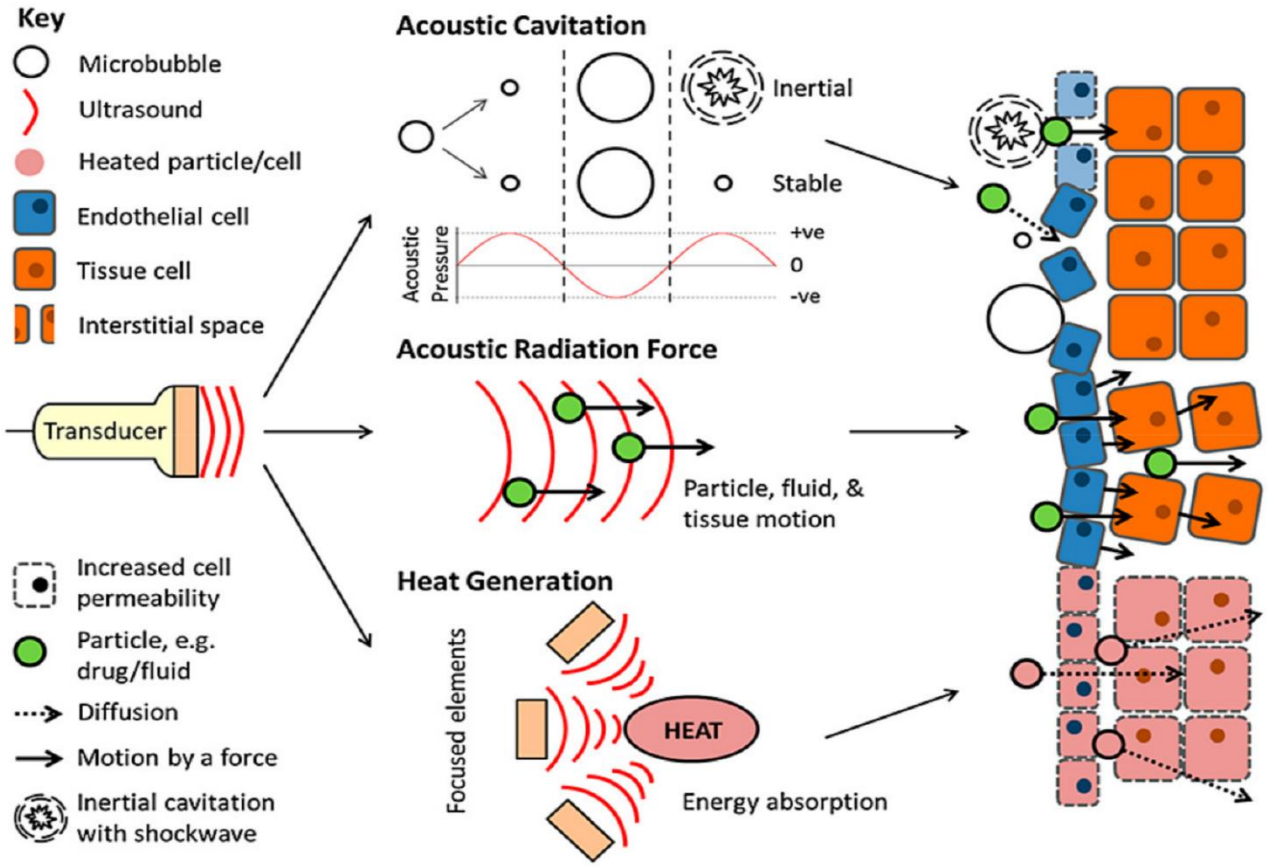
i) Reservoir type ii) Matrix type

C) Methods using Ion-exchange

D) Methods using osmotic pressure

E) pH independent formulations.

F) Altered density formulations.



MODELLING AND COMPARISON OF DISSOLUTION PROFILE:

Several theories and kinetic 10, 11, 12, 13models were described the drug release characteristics of immediate release and modified release dosage forms, by using dissolution data and quantitative interpretation of values obtained in dissolution assay if facilitated by the usage of the generic equation dosage form that mathematically translates the dissolution curve in function of some parameters related with pharmaceutical dosage form. In the present work, some analytical models were used to study the mechanism of drug release of extended release by following models

Zero order Drug dissolution from pharmaceutical dosage form that doesn't disaggregates and release the drug slowly can be represented by the following equation

$$Qt = Q0 + K0.t$$

Where Qt =amount of drug released in time t

Q0= initial amount of drug in solution

K0 =zero order release constant

Application:

This relation can be used to describe the drug dissolution of several types of modified release dosage forms as in the case of transdermal systems and matrix tablets with low solubility of drugs, coated forms, osmotic systems etc Pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is ideal method of drug release in order to achieve a pharmacological prolonged action

First order model:

Application of this model to drug dissolution study was first proposed by Gibaldi and Feldman (1967) later by Wagner (1969) In this model the decimal logarithm of amount remained VS time will be linear. It indicates first order release and expressed by following equation

$$\log Qt = \log Qe + (Ki.t/2.303)$$

Qt = amount of drug released in time t

Qe = initial amount f drug in solution

Ki = first order release constant

Higuchi model:

Higuchi in (1961, 1963) developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in solid matrices; mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as diffusion media and this model describes the drug release characteristics as diffusion process based on fick's law relatedwith square root of time dependent and it expressed by using the formula

Qt=KH√t Where

Qt = amount of drug released in time t

KH=Higuchi Constant

√t =dependent square root of time

Application:

Higuchi model can be used to describe the drug dissolution of several types of modified release dosage forms as in the case of transdermal systems and matrix tablets with low solubility of drugs

Korsmayer's and Peppa's model Korsmayer's and Peppa's in 1983 developed a simple empirical model relating exponentially the drug release to the elapsed time by using 'n' values, in order to characterize several release mechanisms . Under some experimental conditions the release mechanism deviate from the fick's equations following an anomalous behaviour in this case it should be expressed by the following equation m m K n t t f log( ) = log + .log Where mt=amount of drug released at time t mf=amount of drug released at infinite time t K=release rate constant n= diffusion expression (drug release mechanism) Application This model generally used to analyze the release of pharmaceutical polymeric dosage form, when the release mechanism is not well known or when more than one type release mechanism could be involved. Hixson-Crowell model Hixson-Crowell (1931) recognising that particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner:

2. CONCLUSION

The best new therapeutic entity in the world is of little value without an appropriate delivery system. Tablet delivery system can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount & at the appropriate rate.

However it should meet other important criteria such as physical & chemical stability, ability to be mass-produced in a manner that assures content uniformity

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