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SUSTAINED RELEASE MATRIX - A MODERN REVIEW

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ABSTRACT

Presently pharmaceutical industries are focusing on development of sustained release formulations due to its inherent boons. Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. The basic rationale of sustained release drug delivery system optimizes the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, reduction of fluctuation in steady-state drug levels, maximum utilisation of the drug, increased safety margin of potent drug, reduction in healthcare costs through improved therapy and shorter treatment period. The basic goal of sustained release is provide promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body and increase patient compliance by reducing frequency of dose.

KEYWORDS

Sustained release, Matrix tablet, Patient compliance, Advantages and Disadvantages.

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INTRODUCTION[1-2]

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by

conventional delivery, it is considered as a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system includes any drug delivery systems that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system. Matrix tablets are considered to be the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained the drug release using readily available, inexpensive excipients by matrix based formulations.

The Following are the Rationale of Developing SR Matrix DDS:

- To extend the duration of action of the drug.
- To reduce the frequency of dosing.
- To minimize the fluctuations in plasma level.
- Improved drug utilization.
- Less adverse effects.

Advantages of SR Matrix DDS

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus:
  - Maximizing availability with minimum dose.
  - Minimize or eliminate local side effects.
  - Minimize or eliminate systemic side effects.
  - Minimize drug accumulation with chronic dosing.
- Safety margins of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.
  - Cure or control condition more promptly
  - Improve control of condition
  - Improve bioavailability of some drug
  - Make use of special effects; e.g. sustain release aspirin for morning relief of arthritis by dosing before bed-time.
- Economy.

Disadvantages of SR matrix DDS

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor *in vitro* and *in vivo* correlations.

Characteristics that make drugs suitable for sustained release matrix drug delivery system[3-4]

Biological characteristics

Biological Half-Life

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The elimination rate is quantitatively described by the half-life. Each drug has its own characteristic elimination rate, which is the sum of all elimination process, including metabolism, urinary excretion, and all other

processes that permanently remove drug from the bloodstream.

Therapeutic compound with short half-lives are excellent candidates for sustained release preparations, since this can reduce dosing frequency. However, this is limited, in that drug with very short half-lives may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become limiting large. In general, drugs with half-lives shorter than 2 hours are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hours, are also generally not used in sustaining forms, since there effect is already sustained.

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained-release product. Since the purpose of forming a sustained-release product is to place control on the delivery system, it is necessary that the rate of release much slower than the rate of absorption. If we assume that the transits time of most drugs and devices in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. This corresponds to a minimum apparent absorption rate constant of 0.17-0.23 $hours^{-1}$ to give 80-95% over this time period. The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. Compounds that demonstrate true lower absorption rate constants will probably be poor candidates for sustaining system.

Distribution

The distribution of drugs into tissue can be an important factor in the overall drug elimination kinetics since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibration with blood and extracellular fluid. One aspect of this distribution is binding of drug to tissue and proteins in blood. The apparent volume of distribution of a drug is frequently used to describe the magnitude of distribution, including binding, within the body. For design of sustained/controlled release products one would like to have as much information on drug disposition as possible but, in reality, decisions are usually based on only a few pharmacokinetic parameter, one of which is the apparent volume of distribution.

Metabolism

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability from slower-releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during specific period, allowing more complete conversion of the drug to its metabolites. Formulation of these enzymatically susceptible compounds as prodrugs is another viable solution.

Physicochemical characteristics[5-6]

Aqueous Solubility

Compounds with very low solubility (less than 0.01mg/ml) are inherently sustained, since there release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained-release system has been reported to be 0.1mg/ml, so it is obvious that the solubility of the compound will limit the choice of mechanism to be employed in sustained delivery system. Diffusional systems will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

Dose Size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0gm is considered maximal for a conventional dosage form. This also holds for sustained-release dosage forms. Those compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid system. Another consideration is the margin of safety involved in

administration of large amounts of a drug with narrow therapeutic range.

Partition Coefficient

When a drug is administered to the GI tract it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore, the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Partition coefficient is generally defined as the ratio of the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly, compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility.

Protein Binding

It is well known that many drugs bind to plasma proteins with concomitant influence on the duration of drug action. Since blood proteins are four the most part recirculated and not eliminated, drug protein binding can serve as the depot for drug producing a prolonged release profile, especially if high degree of drug binding occurs. There are, however, other drugs – protein interaction that have bearing on drug performance.

Stability

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in the solid state; therefore, this is the preferred composition of delivery for problem cases. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transits in the GI tract are beneficial; likewise, for systems that delay release until the dosage form reaches the small intestine. Compound that is unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation.

APPROACHES TO SUSTAIN RELEASE DRUG DELIVERY SYSTEM[7-9]

- Diffusion controlled release systems.
- Dissolution controlled release systems.
- Dissolution and diffusion controlled release systems
- Ion exchange resin- drug complexes.
- Osmotic pressure controlled systems.
- pH dependent formulation.

Diffusion controlled release systems

In diffusion release models, the diffusion of dissolved drug through a polymeric membrane is a rate limiting step. In this system, the drug release rate never follows zero-order kinetics, because the diffusional path length increases with time as the insoluble matrix is drug depleted. The mechanism of diffusion process shows the movement of drug molecules from a region of a higher concentration to region of lower concentration. The flux of the drug J (in amount / area -time), across a membrane in the direction of decreasing concentration is given by

Fick's law. $J = -D\, dc/dx$

Where,

J = flux of the drug across a membrane in the direction of decreasing conc.,

D = Diffusion coefficient of the drug, and

dc /dx = Change in the concentration of the drug in the membrane

Whereas when drug present in a water insoluble membrane, it must diffuse through the membrane. The drug release rate dm/ dt is given by

$$dm = ADK\Delta C/dt\ L$$

Where,

A = Area.

K = Partition coefficient of drug between the membrane and drug core.

L = Diffusion path length (i.e. thickness of coat)

ΔC = Concentration difference across the membrane.

Dissolution controlled release systems[10-11]

These systems are easy to formulate. Drug which are formulated using system have slow dissolution rate, produce slow dissolving forms with gastric intestinal fluids and the drugs which are having high aqueous solubility and dissolution rate.

Dissolution controlled release system can be classified into two techniques:

Matrix dissolution controlled release system

Matrix dissolution system is known as monolithic because the drug present in the matrix is completely dissolved in the medium which controls the drug release. They are mostly made of waxes like beeswax, carnauba wax, hydrogenated castor oil, etc. and play important role to control the drug release rate by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The drug release generally follows first order kinetics from such matrices system.

Reservoir dissolution controlled release system

In reservoir system, the drug particles are coated or encapsulated with one of the several microencapsulation techniques using slowly dissolving materials like cellulose, polyethylene glycol and waxes. This unit can be encapsulated in capsules or may be compressed into tablets Solubility and thickness of the coating play important role in dissolution rate of drug.

Dissolution and diffusion controlled release systems

In this kind of system, the drug is enclosed in a membrane which is partially water soluble. The dissolution of the membrane take place due to which pores are formed and these pores allows aqueous medium to enter in the membrane. This results in the dissolution of the drug in membrane followed by the diffusion of the dissolved drug from the system. Example of such coating is combination of ethyl cellulose with PVP or methyl cellulose.

Ion exchange resin- drug complexes

Resins are the materials which are insoluble in water. Resin contains anionic groups such as amino or quaternary ammonium groups and cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the chain. A drug–resin complex is formed by prolonged exposure of drug to the resin. The drug from these complexes gets exchanged in gastrointestinal tract and later they are released with excess of Na^+ and Cl^- present in gastrointestinal tract.

$Resin^+ – Drug^– + Cl^–$ ----------->>> $resin^+ Cl^– + Drug^–$

Where, x^- is Cl^- conversely

$Resin^– – Drug^+ + Na^+$ ----------->>> $resin^– Na^+ + Drug$

Water insoluble cross linked polymer compounds are used for this system.

Osmotic pressure controlled systems

These types of system are also known as oros, which follows the mechanism of osmatic pressure where the drug is released at constant zero order rate. The reservoir is made up of the drug and osmotic agent like mannitol or KCl, which is surrounded by semipermeable membrane. A small orifice is present in the dosage form, which allows the entry of water in the reservoir and helps the dissolved drug to pumped out at the determined rate due to osmotic pressure. The release of the drug from the reservoir is unaffected by the conditions of the GIT. The release of drug is depended on factors like size of orifice, thickness of semipermeable membrane, permeability of membrane, osmotic properties of core and stability of the drug.

pH dependent formulation

Some drugs on dissolution and absorption in GIT, changes the pH present in the gastrointestinal tract, so dosage forms are formulated using sufficient amount of buffering agent like salt of phosphoric, citric or tartaric acids. These salts adjust the pH to the desired value when dosage form move across the gastrointestinal tract. Permeable coating agents are used to coat the drug and buffer present in the dosage form, which allows the aqueous medium to enter in it and prevents the dispersion of the tablets.

MARKETED PRODUCTS[12]

Table No.1: Brand Name Products

S.No	Trade Name	Generic Name	Sponsor
1	Avinza	Morphine sulfate extended-release capsules	Pfizer
2	Butrans	Buprenorphine transdermal system	Purdue Pharma
3	Dolophine	Methadone hydrochloride tablets	Roxane
4	Duragesic	Fentanyl transdermal system	Janssen Pharmaceuticals
5	**Embeda	Morphine sulfate and naltrexone extended-release capsules	Pfizer
6	Exalgo	Hydromorphone hydrochloride extended-release tablets	Mallinckrodt
7	Kadian	Morphine sulfate extended-release capsules	Actavis
8	MS Contin	Morphine sulfate controlled-release tablets	Purdue Pharma
9	Nucynta ER	Tapentadol extended-release oral tablets	Janssen Pharmaceuticals
10	Opana ER	Oxymorphone hydrochloride extended-release tablets	Endo Pharmaceuticals
11	OxyContin	Oxycodone hydrochloride controlled-release tablets	Purdue Pharma
12	*Palladone	Hydromorphone hydrochloride extended-release capsules	Purdue Pharma

*No longer being marketed, but is still approved.
**Not currently available or marketed due to a voluntary recall, but is still approved.

Table No.2: Generic Products

S.No	Drug Name	Generic Name	Sponsor
1	Fentanyl	Fentanyl extended-release transdermal system	Actavis
2	Fentanyl	Fentanyl extended-release transdermal system	Lavipharm Labs
3	Fentanyl	Fentanyl extended-release transdermal system	Mallinckrodt
4	Fentanyl	Fentanyl extended-release transdermal system	Mylan Technologies
5	Fentanyl	Fentanyl extended-release transdermal system	Noven
6	Fentanyl	Fentanyl extended-release transdermal system	Aveva

7	Fentanyl	Fentanyl extended-release transdermal system	Watson
8	Methadone Hydrochloride	Methadone hydrochloride concentrate	Roxane
9	Methadone Hydrochloride	Methadone hydrochloride tablets	The Pharm network
10	Methadone Hydrochloride	Methadone hydrochloride tablets	Mallinckrodt
11	Methadone Hydrochloride	Methadone hydrochloride tablets	Sandoz
12	Methadone Hydrochloride	Methadone hydrochloride oral solution	Roxane
13	Methadone Hydrochloride	Methadone hydrochloride oral solution	Vista pharm
14	Morphine Sulfate	Morphine sulphate extended-release capsules	Watson
15	Morphine Sulfate	Morphine sulfate extended-release tablets	Endo
16	Morphine Sulfate	Morphine sulfate extended-release tablets	Mallinckrodt
17	Morphine Sulfate	Morphine sulfate extended-release tablets	Mylan
18	Morphine Sulfate	Morphine sulfate extended-release tablets	Nesher
19	Morphine Sulfate	Morphine sulfate extended-release tablets	Ranbaxy
20	Morphine Sulfate	Morphine sulfate extended-release tablets	Rhodes
21	Morphine Sulfate	Morphine sulfate extended-release tablets	Watson Labs
22	Oxymorphone Hydrochloride	Oxymorphone hydrochloride extended-release tablets	Impax
23	Oxymorphone Hydrochloride	Oxymorphone hydrochloride extended-release tablets	Actavis

CONCLUSION

The Sustained release drug delivery system is very helpful in increasing the efficiency of the dose, safety of dose as well as the patient compliance. Nowadays, the oral route of administration for Sustained release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance. The design of oral Sustained release drug delivery system depends on various factors like, physic-chemical properties of drug, type of delivery system, disease being treated, patient condition, treatment duration, presence of food, gastrointestinal motility and co- administration of other drugs. From the above discussion, we can concluded that moreover; the reasonable cost of oral Sustained release drug delivery system has lead ease of market penetration as replacement of oral conventional drug delivery system.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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