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Review Article

A NEW TREND IN ORAL SUSTAINED RELEASE TECHNOLOGY

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ABSTRACT

In all drug delivery system, Oral drug delivery remains the most preferred system for administration of various drugs. The sustained released dosage forms means that a single dose of a drug that is released over an extended period of time instead of numerous doses is now a day's area of interest for formulation scientists in Pharmaceutical industry. Ranitidine has been formulated as sustained release matrix tablets. Sustained release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of therapeutic concentration of the drug in the body. Sustained release system are considered a wiser approach for the drugs with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of absorption process from gastrointestinal tract after oral administration. Hydrophilic polymers have become product of choice as an important ingredient for formulating sustained release formulations. This article contains the basic information regarding design sustained release formulation.

Keywords: *Matrix tablets, Half life, Polymer.*

Sustained release, Sustained action, Prolonged action, Controlled release, Extended action, Timed release depot and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage forms, this period may vary from days to months. In the case of orally administered dosage forms, however this period is measured in hours and critically depends on residence time of dosage form in the gastrointestinal (GIT) tract.[1] these are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms.

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To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellabl ehydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.[2] Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed. A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers.[3]Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example Enteric coated tablet[4]. A sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio.[5, 6]

SUSTAINED RELEASE DRUG DELIVERY SYSTEM[7]

It includes any drug delivery system achieves release of drug over an extended period of time, which not depend on time. Hydrophilic polymer matrix is widely used for formulating an Sustained release dosage form.

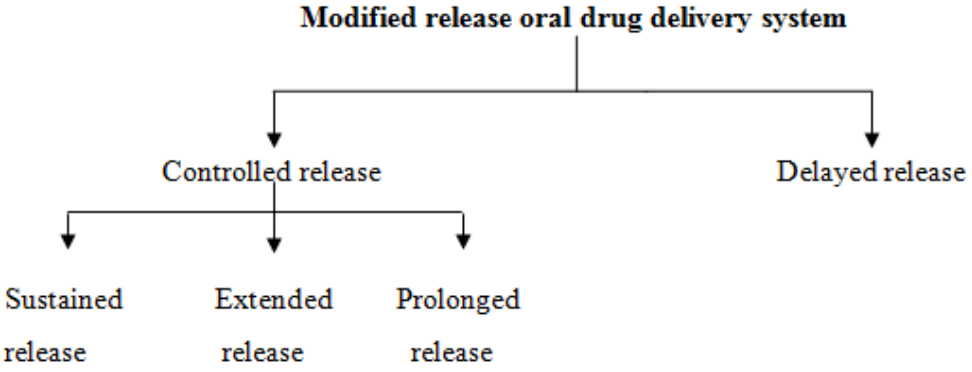

Figure 1: Classification of Modified Release Drug Delivery System.

Terminology

Sustained release

These are drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug.[14]

Controlled-release dosage forms

They are class of pharmaceuticals or other biologically active products from which a drug is released from the delivery system in a planned, predictable, and slower-than-normal manner for longer period of time.[15]

Extended release

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate & necessarily reduce the dosage frequency by two folds.[16]

Delayed release

Delayed release systems are those systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form.[17]

Prolonged release system

They are designed to release the drug slowly and to provide a continuous supply of drug over an extended period. They prevent very rapid absorption of the drug, which could result in extremely high peak plasma drug concentration.[18]

Advantages of Sustained Release Drug Delivery System[8]

- Reduced dosing frequency.
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided.
- better patients compliance

Disadvantages of Sustained Release Drug Delivery[9-11]

- Increased cost.
- Toxicity due to dose dumping.
- Unpredictable and often poor *in vitro-in vivo* correlation.
- Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
- Increased potential for first- pass clearance.
- Need for additional patient education and counseling

Parameters for Drug to Be Formulated In Sustained Release Dosage Form

There are some physicochemical parameters for the drug selection to be formulated in sustained release dosage form which mainly includes the knowledge on the absorption mechanism of the drug form the Gastro Intestinal (G.I.) tract, its general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient as shown in Table 1 [12-13]

Table 1: Physicochemical parameters for drug selection

Parameters	Preferred value
Molecular weight/size	< 1000 Daltons
Solubility	> 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability	From all GI segments
Release	Should not be influenced by pH and enzymes

Similarly there are some pharmacokinetic parameters for drug selection which includes drug's elimination half- life, total clearance, absolute bioavailability, possible first-pass effect, and the desired steady concentrations for peak and trough as shown in Table 2[12-13]

Table 2: Pharmacokinetic parameters for drug selection

Parameters	Comments
Elimination half-life	Preferably between 2 to 8 hrs
Total clearance	Should not be dose dependent
Elimination rate constant	Required for design
Apparent volume of distribution (Vd)	The larger Vd and MEC, the larger will be the required dose size
Absolute bioavailability	Should be 75% or more
Intrinsic absorption rate	Must be greater than release rate
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required
Toxic concentration	Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.

Factors Influencing Oral Sustained Release Dosage Form Design

Two factors involved in oral sustained-release dosage form design.

A. Biological Factors

Biological Half Life

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of
time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours such as Furosemide or Levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in

sustaining form, since their effect is already sustained. Digoxin and Phenytoin are the examples [18-19]

Absorption

Rate of absorption of a sustained formulating depends upon release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport the absorption is limited to intestine.[20]

Since the purpose of forming a SR product is to place control on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of mostdrugs 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.[18-21]

Therapeutic index

Drugs with low therapeutic index are unsuitable for incorporation in Sustained release formulations. If the system fails in the body, dose dumping may occur, which leads to toxicity [22].

Metabolism

Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.[18-23]

B. Physicochemical Factors

Partition Coefficient

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce atherapeutic 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. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug [18-23].

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 solid state; therefore, this is the preferred Composition of delivery for problematic cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in 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. Propentheline and Probanthine are representative example of such drug [24]

Drug pKa and ionization at physiological pH

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of the unionized drug. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0% [25]

Molecular size and diffusivity

Diffusivity depends on size & shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10-6-10-9 cm2/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.[26]

CONCLUSION

From the above discussion, it concludes that thesustained release dosage form are drug delivery system which by virtue of formulation and product design, provide drug release in a modified form. These formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. The design of oral Sustained release drug delivery system depends on various factors like, physico-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.

REFERENCES

1. *The theory and practice of industrial pharmacy , leonlachman , Herbert A. Lieberman sustained release dosage forms page no. 430*
2. *Jaimini Manish*, Kothari Abhay Journal of Drug Delivery & Therapeutics; 2012, 2(6), 142.*
3. *http//www.ijrdpl.com ISSN: 2278-0238 February - March, 2013, Vol. 2, No.2, pp 262.*
4. *Lee BJ, Ryu SG, Cui JH, "Formulation and release characteristics of hydroxypropyl methylcellulose matrix tablet containing melatonin", Drug Dev Ind Pharm, 1999, 25, 493-501.*
5. *Prajapati ST, Patel LD, Patel DM, "Gastric floating matrix tablets: Design and optimization using combination of polymers", Acta Pharm, 2008, 58, 221-229.*
6. *Jantzen GM and Robinson JR, Sustained and controlled-release drug delivery systems, In Banker GS, Rhodes CT (Eds.) Modern Pharmaceutics, Third Ed., Revised and Expanded, Drugs and The Pharmaceutical Sciences, Marcell Dekker, Inc., New York, 1995, vol 72. 575-609.*
7. *Ratnaparkhi M P et.al, IJPRR 2013; 2(3) 11*
8. *Wani MS et al. Controlled Release System-A Review. 2008; 6. Available on www.pharmainfo.net/review. URL: http://www.pharmainfo.net/reviews/controlled-released-system-review*
9. *Hoffman A, "Pharmacodynamics aspects of sustained release preparations", Advance Drug Deliv Rev., 1998, 33, 185-199.*
10. *Gren T, Bjerre C, Camber O, "In vitro drug release from porous cellulose matrices", IntJ Pharm, 1996,141, 53-62.*
11. *Munday DC, Cox PJ, "Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms", Int J Pharm, 2000, 203, 179-192.*
12. *Chien YW, Rate controlled drug delivery systems, 2nd edition, Marcel Dekker, New York, revised and expanded, 2005.*
13. *Chauhan MJ, Patel SA. A Concise Review on Sustained Drug Delivery System and Its Opportunities. Am. J. PharmTech Res. 2012; 2(2): 227-238.*
14. *Aulton ME, Modified release peroral dosage forms, Pharmaceutics- The science of Dosage form Design, 2nd edition, Churchill Livingstone, New York, 290.*
15. *Marroum PJ. Bioavailability/Bioequivalence for Oral controlled release products, Controlled release drug delivery systems.*
16. *Kumar KPS, Bhowmik D, Srivastava S. Sustained Release Drug Delivery System Potential. The PharmaInovation. 2012; vol 1, No 2: 48-60.*
17. *Lee TW, and Robinson JR, In Remington: The science and practice of pharmacy, Gennaro, 20th edition, Baltimore, Lippincott Williams and Wilkins, 2000, 903-929.*
18. *Chugh I, Seth N, Rana AC and Gupta S, "Oral sustained release drug delivery system: an overview", IRJP, 2012, 3 (5), 57-62.*
19. *Robinson JR, Vincent H, Lee L. Controlled drug delivery fundamentals and applications, Marcel Dekker Inc., New York, 2002, 3-61.*
20. *Bhargava A et al ISSN: 2277-6222 IJARPB: 2013, 3(1), 7-14.*
21. *Shirwaikar AA, Jacob S, Grover V, "Formulation and evaluation of sustained release tablets using an insoluble resin matrix system", Indian J. Pharm. Sci., 2005, 67 (1), 80-83.*
22. *Ho WH, Lee HLV. Sustained Drug Delivery Fundamentals and Applications:Design and fabrication of oral controlled release drug delivery system. 2nd ed. Marcel Dekker Inc, New York: 1987; 373-420.*
23. *Popli H, Sharma SN, "Trends in oral sustained release formulation-I", The Eastern Pharmacist,1989, 32, 99-103.*
24. *Shabaraya AR, Narayanacharyulu R, "Design and evaluation of chitason matrix of metoprolol tartrate for sustained release", J. Pharm. Pharmaceutical Sci., 2000, 8 (1), 231-236.*
25. *Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: Pharmacokinetics. 2nd ed. VallabhPrakashan, Delhi: 2009; 399-401.*
26. *Kar RK, Mohapatra S, Barik BB. Design and characterization of controlled release matrix tablets of Zidovudine. Asian J Pharm Cli Res. 2009; 2:54-6.*