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CONTROLLED DRUG DELIVERY SYSTEM: A REVIEW

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Abstract:

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. An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target site. Oral Sustained release (SR) / Controlled release (CR) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance. The present article contains brief review on various formulation approaches for controlled release drug delivery system.

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

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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].

Advantages of Controlled Drug Delivery [3-6]

- 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 cost
- Improved efficiency in treatment:
- Reduction in adverse side effects and improvement in tolerability

Mechanism of Controlled Drug Release Systems [7, 8]

1. Diffusion Controlled System[9,10]

Basically diffusion process shows the movement of drug molecules from a region of a higher concentration to one 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, D = diffusion coefficient in area/ time
dc/dx = change of concentration 'c' with distance 'x'

Diffusion systems are characterized by release rate of drug is dependent on its diffusion through inert water insoluble membrane barrier. There are basically two types of diffusion devices.

(a) Reservoir Type [11, 12]:

In the system, a water insoluble polymeric material encloses a core of drug, which controls release rate. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet .Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The polymers commonly used in such devices are Ethyl cellulose and Poly-vinyl acetate.

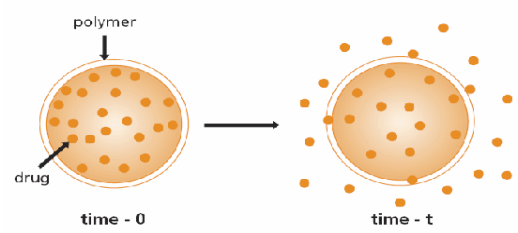

Fig 1: Schematic Representation of Reservoir Diffusion Controlled Drug Delivery Device

The rate of drug released (dm/dt) can be calculated using the following equation

$$\frac{dm}{dt} = ADK \frac{\Delta C}{\ell}$$

Where, A = Area,
D = Diffusion coefficient,
K = Partition coefficient of the drug between the drug core and the membrane,
ℓ = Diffusion pathlength and
ΔC= Concentration difference across the membrane.

Advantage: By this system Zero order delivery is possible, release rates variable with polymer type.

Disadvantages: System must be physically removed from implant sites. Difficult to deliver high molecular weight compound, generally increased cost per dosage unit, potential toxicity if system fails.

(b) Matrix Type [13, 14]:

A solid drug is homogenously dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution.

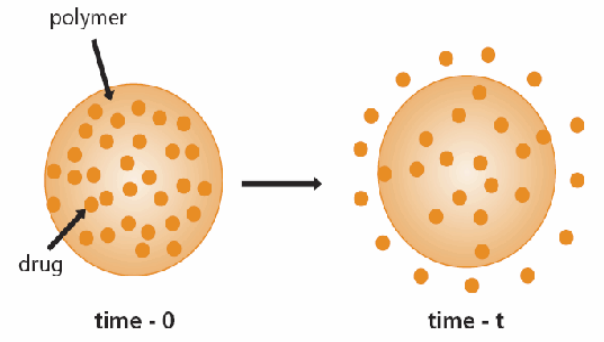

Fig 2: Schematic Representation of Monolithic (matrix) Diffusion Controlled Drug Delivery Device

Advantages: Easier to produce than reservoir or encapsulated devices, can deliver high molecular weight compounds.
Disadvantages: Cannot provide zero order release, removal of remaining matrix is necessary for implanted system.

2. Dissolution Controlled Systems [15, 16]
Drugs having high aqueous solubility and dissolution rate, shows challenge in controlling their dissolution rate. Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by

$$\frac{dm}{dt} = \frac{ADS}{h}$$

Where, S = Aqueous solubility of the drug.
A = Surface area of the dissolving particle or tablet.
D = Diffusivity of the drug and
h = Thickness of the boundary layer.

(a) Encapsulation Dissolution Controlled Systems[17] :

The drug particles are coated or encapsulated by microencapsulation techniques with slowly dissolving materials like cellulose, poly ethylene glycols, polymethacrylates, waxes etc. the dissolution rate of coat depends upon the solubility and thickness of the coating. Those with the thinnest layers will provide the initial dose. The maintenance of drug levels at late times will be achieved from those with thicker coating.

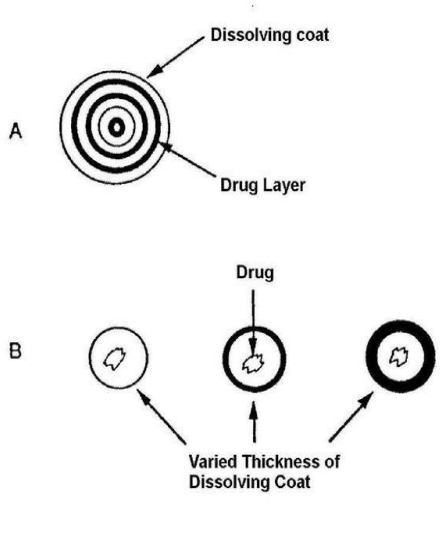

Fig 3: Encapsulation Dissolution Controlled Systems

(b) Matrix Dissolution Controlled Systems[18] :
In matrix systems the drug is homogeneously dispersed throughout a rate controlling medium. They employ waxes such as beeswax, carnauba wax, hydrogenated castor oil etc which control drug dissolution 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 is often first order from such matrices. The wax embedded drug is generally prepared by dispersing the drug in molten wax and solidifying and granulating the same.

3. Dissolution and Diffusion Controlled Release Systems[19-21]:
The drug core is enclosed in a partially soluble membrane. Pores are thus created due to dissolution of parts of the membrane which permit entry of aqueous medium into the core and hence drug dissolution and diffusion of dissolved drug out of the system. An example of obtaining such a coating is using a mixture of ethyl cellulose with poly vinyl pyrrolidiene or methylcellulose

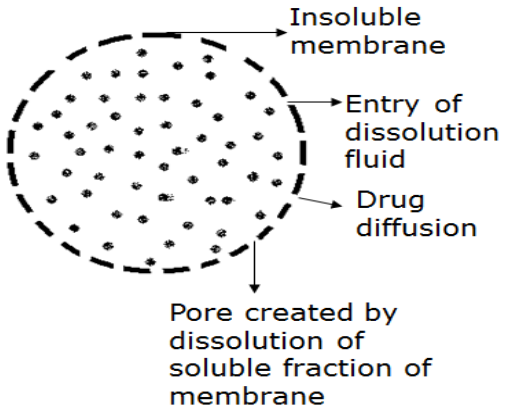

Fig 4: Dissolution and Diffusion Controlled Release System

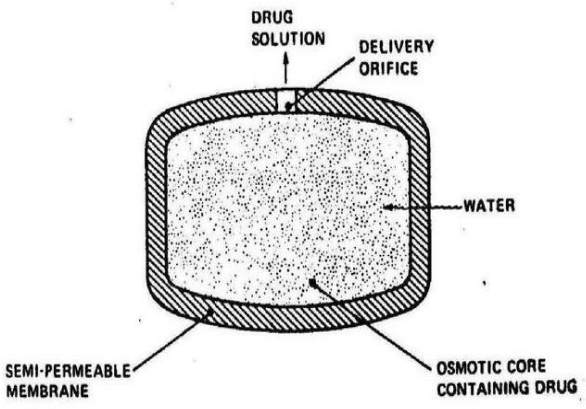

Fig 5: Osmotically Controlled Release System

4. Water Penetration Controlled Systems [22]

In water penetration controlled delivery systems, rate control is obtained by the penetration of water into the system. They are

(a) Swelling Controlled Systems [23]

Swelling controlled release systems are initially dry and when placed in the body absorbs water or other body fluids and swells. Swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment.

(b) Osmotically Controlled Release Systems [24,25]

These systems are fabricated by encapsulating an osmotic drug core containing an osmotically active drug (or a combination of an osmotically inactive drug with an osmotically active salt eg NaCl) within a semi permeable membrane made from biocompatible polymer, e.g. cellulose acetate. A gradient of osmotic pressure is they created, under which the drug solutes are continuously pumped out of tablet through small delivery orifice in tablet coating over a prolonged period of time through the delivery orifice. This type of drug system dispenses drug solutes continuously at a zero order rate. Release of drug is independent on the environment of the system.

5. Methods using Ion Exchange [26-28]:

This system is designed to provide the controlled release of an ionic or ionizable drug. It is prepared by first absorbing an ionized drug onto the ion-exchange resin granules such as codeine base with Amberlite, and then after filtration from the alcoholic medium, coating the drug resin complex granules with a water permeable polymer, e.g. a modified copolymer of polyacrylic and methacrylic ester, and then spray drying the coated granules to produce the polymer coated drug resin preparation. The drug is released by exchanging with appropriately charged ions in the GIT. The drug is then diffuse out of the resin.

$$\mathbf{Resin^{+} - drug^{-} + X^{-} \longrightarrow resin^{+} - X^{-} + drug^{-}}$$

Where X- are ions in the GI tract

- ✓ The rate of diffusion control by: the area of diffusion, diffusion path length and rigidity of resin.
- ✓ Thus, drug release depends on the ionic environment (pH, electrolyte conc.) and the properties of resin.
- ✓ **Advantage** - for those drugs which are highly susceptible to degradation by enzymatic processes since it offers a protective mechanism by temporarily altering the substrate.
- ✓ **Limitation** - The release rate is proportional to the conc. of the ions present in the vicinity of administration site. So variable diet, water intake & intestinal contents affects the release rate of drug.

✓ They are mainly of **2 types -** cation exchange and anion exchange resin.

❖ **Cationic Drugs**

A cationic drug forms a complex with an anionic ion-exchange resin e.g. a resin with a SO_3^- group. In the GI tract Hydronium ion (H^+) in the gastrointestinal fluid penetrates the system and activity the release of cationic drug from the drug resin complex.

H^+ + Resin – SO_3 - Drug + ⟶ Resin – SO_3 - H^+ + $Drug^+$

❖ **Anionic Drugs**

An anionic drug forms a complex with a cationic ion exchange resin, e.g. a resin with a [N $(CH_3)_3^+$] group. In the GI tract, the Chloride ion (Cl^-) in the gastrointestinal fluid penetrates the system and activates the release of anionic drug from the drug resin complex.

Cl^- + Resin – [N $(CH_3)_3^+$] - $Drug^-$ ⟶ Resin – [N $(CH_3)_3^+$] - Cl^- + $Drug^-$

6. Chemically Controlled Release Systems[29]

Chemically controlled release systems are the systems that change their chemical structure, when exposed to biological fluid. Mostly, biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically safe and progressively smaller moieties. It is of two types and they are **Erodible systems** and **Pendent chain system**

(i) Erodible Systems: In erodible systems, the mechanism of drug release occurs by erosion. Erosion may be two types and they are

- **Bulk Erosion** process polymer degradation may occur through bulk hydrolysis
  - ✓ When the polymer is exposed to water hydrolysis occurs
  - ✓ Hydrolysis degrades the large polymers into smaller biocompatible compounds
  - ✓ These small compound diffuse out of the matrix through the voids caused by swelling
  - ✓ Loss of the small compounds accelerates the formation of voids thus the exit of drug molecules
  - ✓ e.g. poly lactide, polyglycolic acid
- **Surface Erosion** process Polymers like polyorthoesters and polyanhydrides etc occurs degradation only at the surface of the polymer, resulting in a release rate that is proportional to the surface area of the delivery system.
  - ✓ When the polymer is exposed to water hydrolysis occurs
  - ✓ Hydrolysis degrades the large polymers into smaller biocompatible compounds
  - ✓ These small compound diffuse from the interface of the polymer
  - ✓ Loss of the small compounds leads to drug loss
  - ✓ Note these polymers do not swell.
  - ✓ e.g polyanhydrides

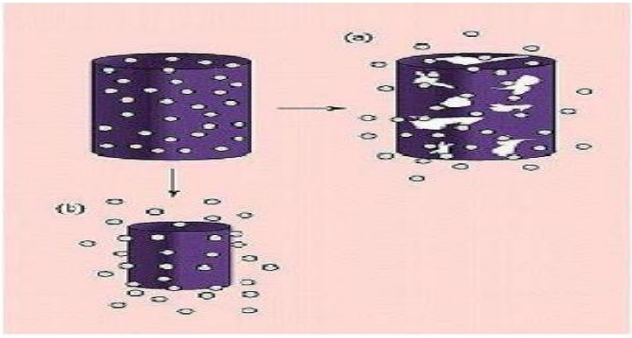

Fig 6: Bulk Erosion and Surface Erosion

(ii) Pendent Chain System

Pendent chain systems consist of linear homo or copolymers with the drug attached to the backbone chains. The drug is released from the polymer by hydrolysis or enzymatic degradation of the linkages. Zero order can be obtained and the cleavage of the drug is the rate controlling mechanism. Example for polymers used in pendent chain systems like n-(2-hydroxy propyl)methacrylamide etc.

7. pH– Independent Formulations [30,31]

The gastrointestinal tract present some unusual features for the oral route of drug administration with relatively brief transit time through the gastrointestinal tract, which constraint the length of prolongation, further the chemical environment throughout the length of gastrointestinal tract is constraint on dosage form design. Since most drugs are either weak acids or weak bases, the release from sustained release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to the formulation, to help to maintain a constant pH thereby rendering pH independent drug release. A buffered controlled release formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust

the fluid inside to suitable constant pH thereby rendering a constant rate of drug.

8. Hydrogels [32,33]

Hydrogels are water swollen three dimensional structures composed of primarily hydrophilic polymers. They are insoluble because of chemical or physical cross-links. The physical cross-links include crystallites, entanglements or weak associations like hydrogen bonds or vander waals forces. These cross-links provide the physical integrity and network structure. Hydrogels provide desirable protection of labile drugs, peptides and proteins.

9. Altered Density Formulations [34,35]

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract like High density approach and Low density approach.

CONCLUSION:

Now a day's modern technologies including target concept have emerged for successful oral controlled delivery. Oral controlled release products provide advantages over conventional dosage form by optimizing bio-pharmaceutics, pharmacokinetics and pharmacodynamics properties of drug in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration provide maximum utility of drug. From the above discussion it is concluded that the oral controlled release drug delivery system has been commonly adopted and most convenient route for drug delivery.

REFERENCES:

1. John, C., & Morten, C. (2002). The Science of Dosage Form Design Aulton: Modified release peroral dosage forms. Churchill Livingstone.
2. Nalla C, Gopinath H, Debjit B, Williamkeri I and Reddy TA. Modified release dosage forms. J Chem Pharm Sci,2013; 6(1): 13-21.
3. Vyas, S.P., & Khar, R.K. (2002). Controlled Drug delivery: Concepts and Advances. Concepts and Advances. Vallabh prakashan.
4. Shargel, L., & Yu, A.B.C. (1999). Modified release drug products. In:Applied Biopharmaceutics and Pharmacokinetics. McGraw Hill.
5. Ummadi S, Shravani B, Rao NGR, Reddy MS and Nayak BS. Overview on controlled release dosage form. Int J Pharm Sci, 2013;3(4): 258-269.
6. Patnaik AN, Nagarjuna T and Thulasiramaraju TV. Sustained release drug delivery system: a modern formulation approach. Int J Res Pharm Nano Sci,2013; 2(5): 586- 601
7. George, M., Grass, I.V., & Robinson, J. Modern Pharmaceutics. Marcel Dekker.
8. Pundir S, Badola A and Sharma D. Sustained release matrix technology and recent advance in matrix drug delivery system: A review. Int J Drug Res Tech,2013; 3 (1): 12-20.
9. Crank, J. (1975). The Mathematics of Diffusion. New York: Oxford Press.
10. Leon, L., & Herbert, L.A. (2002). Pharmaceutical Dosage Forms. New York: Marcel Dekker.
11. Kar RK, Mohapatra S and Barik BB. Design and characterization of controlled release matrix tablets of Zidovudine. Asian J Pharm Cli Res, 2009;2: 54.
12. Salsa T, Veiga F and Pina ME. Oral controlled release dosage form. I. Cellulose ether polymers in hydrophilic matrices. Drug Develop Ind Pharm,1997; 23: 929-938.
13. Kumar S, Shashikant and Bharat P. Sustained release drug delivery system: a review. Int J Inst Pharm Life Sci, 20122(3): 356-376.
14. Cristina M, Aranzaz;u Z and Jose ML. Critical factors in the release of drugs from sustained release hydrophilic matrices. J Control Rel,2011; 154: 2011, 2-19.
15. Theeuwes, F. Elementary Osmotic Pump. J Pharm Sci, 1975;64, 1987–1991.
16. Mamidala R, Ramana V, Lingam M, Gannu R and Rao MY. Review article factors influencing the design and performance of oral sustained/controlled release dosage form. Int J Pharm Sci Nanotechnology,2009; 2, 583.
17. Chugh I, Seth N, Rana AC and Gupta S. Oral sustained release drug delivery system: an overview. Int Res J Pharm, 2012;3(5): 57-62.
18. Bhargava A, Rathore RPS, Tanwar YS, Gupta S and Bhaduka G. Oral sustained release dosage form: an opportunity to prolong the release of drug. Int J Adv Res Pharm Bio Sci, 3(1), 2013, 7-14.
19. Thakor RS, Majmudar FD, Patel JK and Rajpit JC. Review: osmotic drug delivery systems current scenario. J Pharm Res, 2010;3(4):771-775.
20. Parashar T, Soniya, Singh V, Singh G, Tyagi S, Patel C and Gupta A. Novel oral sustained release technology: a concise review. Int Res J Dev Pharm Life Sci, 2013; 2(2): 262-269.
21. Modi K, Modi M, Mishra D, Panchal M, Sorathiya U and Shelat P. Oral controlled release drug delivery system: an overview. Int Res J Pharm, 2013;4(3): 70-76.
22. Ratnaparkhi MP and Gupta JP, Sustained release oral drug delivery system - an overview. Int J Pharm Res Rev, 2013; 2(3): 11-21.
23. Shah N, Patel N, Patel KR and Patel D. A review on osmotically controlled oral drug delivery

systems. J Pharm Sci Bio Res, 2012;2(5): 230-237.
24. Thombre NA, Aher AS, Wadkar AV and Kshirsagar SJ. A review on sustained release oral drug delivery system. Int J Pharm Res Sch, 2015;4(2): 361-371.
25. Dusane AR, Gaikwad PD, Bankar VH and Pawar SP. A review on: sustained released technology. Int J Res Ayu Pharm, 2011;2(6): 1701-1708.
26. Swabrick, J., & Boylan, J.C. (1996). Encyclopedia of pharmaceutical technology. Newyork: Marcel Dekker.
27. Patel PN, Patel MM, Rathod DM, Patel JN, Modasiya MMK. Sustain Release Drug Delivery: A Theoretical Prospective. J Pharm Res, 2012; (8): 4165-4168.
28. Shamma SP, Haranath C, Reddy CPS and Sowmya C. An overview on SR tablet and its technology. Int J Pharm Drug Ana,2014; 2(9): 740-747.
29. Chauhan MJ and Patel SA. A concise review on sustained drug delivery system and its opportunities. Am J Pharm Tech Res, 2012;2(2): 227-238.
30. Allen, L.V., Popvich, G.N., & Ansel, H.C. (2004). Ansel's Pharmaceutical dosage forms and drug delivery system.
31. Robinson, J.R., & Lee, V.H. (1987). Controlled drug delivery. Marcel Dekker.
32. Kube RS, Kadam VS, Shendarkar GR, Jadhav SB and Bharkad VB. Sustained release drug delivery system: review. Int J Res Pharm Biotech,2015; 3(3) 246:-251.
33. Mali AD and Bathe AS. A review on sustained release drug delivery system. GCC J Sci Tech,2015; 1(4): 107-123.
34. Lapidus H and Lordi NG. Studies on controlled release formulations. J Pharm Sci, 1968;57, 1292.
35. Kamboj S and Gupta GD. Matrix Tablets: An important tool for oral controlled release dosage forms. Pharmainfonet, 2009;7, 1-9.