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Sustained release technologies: A review

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Abstract
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. The development of oral controlled release system has been a challenge to formulation scientist due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. Matrix type drug delivery system is an interesting and promising option when developing an oral controlled release system. Availability of wide variety of polymers and frequent dosing intervals helps the formulation scientist to develop sustained/controlled release products. Oral Sustained release (S.R)/Controlled release (C.R) 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. This review describes the various factors influencing the design and performance of sustained/controlled release products along with suitable illustrations.

Keywords: Controlled release system, Drug release mechanisms, *In vitro* drug release characterization models, Absorption Window

Introduction
Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption [1, 2].

These immediate release dosage forms have some limitations such as:

1) Drugs with short half-life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance. A typical peak-valley plasma conc. time profile is obtained which makes attainment of steady state condition difficult.
2) The unavoidable fluctuations in the drug concentration may lead to under medication or over medication as the Css values fall or rise beyond the therapeutic range.

The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever over medication occurs.

Terminology
Controlled drug delivery or modified release delivery systems may be defined as follows:-
Controlled release formulation:
The controlled release system is to deliver a constant supply of the active ingredient, usually at a zero-order rate, by continuously releasing, for a certain period of time, an amount of the drug eliminated by the body. An ideal Controlled drug delivery system is the one, which delivers the drugs at a predetermined rate, locally or systematically, for a specific period of time.

Repeat action preparations
A dose of the drug initially is released immediately after administration, which is usually equivalent to a single dose of the conventional drug formulation. After a certain period of time, a second single dose is released. In some preparation, a third single dose is released after a certain time has elapsed, following the second dose [3, 4].

Advantage: it provides the convenience of supplying additional Dose or doses without the need of re-administration.

Disadvantage: that the blood levels still exhibit the "Peak and valley" characteristic of conventional intermittent drug therapy.

Extended-Release formulation: Extended-Release formulations are usually designed to reduce dose frequency and maintain relatively constant or flat plasma drug concentration. This helps avoid the side effects associated with high concentration.

Delayed release preparations: The drug is released at a later time after administration. The delayed action is achieved by the incorporation of a special coat, such as enteric coating, or other time barriers such as the formaldehyde treatment of soft and hard gelatin capsules. The purposes of such preparations are to prevent side effects related to the drug presence in the stomach, protect the drug from degradation in the highly acidic pH of the gastric fluid [5].

Site specific targeting: These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

Receptor targeting: These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug with in organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems [6].
Advantages of Controlled Release Drug Delivery System [7, 8]

1] Therapeutic advantage
Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

2] Reduction in adverse side effects and improvement in tolerability
Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.

3] Patient comfort and compliance
Oral drug delivery is the most common and convenient for patient and a reduction in dosing frequency enhances compliance.

4] Reduction in Health care cost
The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration.
Avoid night time dosing: It also good for patients to avoid the at night time.

Disadvantages [9]
1] Dose dumping
Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.

2] 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.

3] 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.

4] Increased potential for first pass clearance
Hepatic clearance is a saturable process. After oral dosing, the drug reaches the liver via portal vein. The concentration of drug reaching the liver dictates the amount metabolized. Higher the drug concentration, greater is the amount required for saturating an enzyme surface in the liver. Conversely, smaller the concentration found with the controlled release and a sustained release dosage form, lesser is the possibility of saturating the enzyme surface. The possibility of reduced drug availability due to the first pass metabolism is therefore greater with controlled release and sustained released formulation than with conventional dosage form.

5] 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 patients.

6] Administration of controlled release medication does not permit prompt termination of therapy. Immediate changes in drug levels during therapy, such as might be encountered if significant adverse effects are noted, cannot be accommodated.

7] There is danger of an ineffective action or even absence of it if the therapeutic substance is poorly absorbed from GIT.

8] Therapeutic agents for which single dose exceeds 1 gm, the technical process requirements may make te product very difficult or sometimes impossible to prepare.

9] Therapeutical agents which absorbed by active transport are not good candidates for controlled release dosage form e. g. Riboflavin.

10] Economic factors must also be taken into account, since more costly processes and equipments are involved in manufacturing of many controlled release dosage forms.

While selecting a drug candidate for sustained release system we must be careful. Drugs having fallowing characteristics are not suitable for sustained release systems

1. Those which are not effectively absorbed in the lower intestine
2. Those having short biological half-lives (<1hr) e.g. Furosemide
3. Those having long biological half-lives (>12hrs) e.g. diazepam
4. Those for whom large dose is required e.g. sulphonamides
5. Those with low therapeutic indices e.g. Phenobarbital
6. Those for which no clear advantage of sustained release system e.g. griseofulvin.
7. Those with extensive first pass metabolism.
8. Those candidates with low solubility and/or active absorption

Drug properties influencing the dosage form [10 – 12]

The design of a controlled release system depends on various factors such as the route of delivery, the type of drug delivery system, the disease being treated, the length of therapy, and the properties of the drug. Most important factor is properties of the drug that are as follows.

A] Physicochemical properties

1] Aqueous solubility and pKa

Absorption of poorly soluble drugs is often dissolution rate-limited. Such drugs do not require any further control over their dissolution rate and thus may not seem to be good candidates for oral controlled release formulations. Controlled release formulations of such drugs may be aimed at making their dissolution more uniform rather than reducing it.

2] Partition coefficient

Drugs 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 tissues. Both cases are undesirable for sustained release system.

3] Stability of the drug

Since most oral controlled release systems are designed to release their contents over much of the length of GI tract, drugs that are unstable in the environment of the intestine might be difficult to formulate into prolonged release system.

4] Size of the dose

For drugs with an elimination half-life of less than 2 hours as well as those administered in large dosages, a controlled release dosage form may need to carry a prohibitively large quantity of drug.

5] Molecular size and diffusivity

In addition to diffusion through a variety of biological membranes, drugs in many sustained release systems must diffuse through a rate controlling membrane or matrix. The ability of drug to pass through membranes, it's so called diffusivity, is a function of its molecular size (or molecular weight). An important influence upon the value of diffusivity, D, in polymers is the molecular size of the diffusing species. The value of D thus is related to the size and shape of the cavities as well as size and shape of the drugs.

Generally, the values of diffusion coefficient for intermediate molecular weight drugs i.e., 150-400, through flexible polymers range from 10-6 to 10-9 cm2/sec, with values on the order of 10-8 being most common. For drugs with molecular weight greater than 500, the diffusion coefficients in many polymers frequently are so small that they are difficult to quantify, i.e., less than 10-12 cm2/sec. Thus high molecular weight of drug should be expected to display very slow release kinetics in sustained release devices where diffusion through polymeric membrane or matrix is the release mechanism.

B] Biological properties

1] Absorption

Slowly absorbed drugs or the drugs absorbed with a variable absorption rate are poor candidates for a controlled release system. Water-soluble but poorly absorbed potent drugs and those absorbed by carrier mediated transport processes or absorbed through window are poor candidates for controlled release system.

2] Metabolism

Drug metabolism can result in either inactivation of an active drug or conversion of an inactive drug to an active metabolite. The process of metabolism can take place in variety of tissues but the organ mainly responsible for metabolism is liver as it contains variety of enzyme systems and thus greatest metabolic alteration of a drug takes place after its absorption into the systemic circulation. Thus the metabolic pattern of a drug may influence the choice of the route of administration.

There are two factors associated with metabolism that significantly limit controlled release product design. First, if a drug is capable of either inducing or inhibiting enzyme synthesis it will be difficult to maintain uniform blood levels of drug upon chronic administration. Second, if the drug undergoes intestinal (or other tissue) metabolism or hepatic first pass metabolism, this also will result in fluctuating drug blood levels. Examples of drugs that undergo intestinal metabolism upon oral administration are hydralazine, salicylamide, nitroglycerin, isoproterenol, chlorpromazine, and levodopa. Examples of drugs that undergo hepatic first pass metabolism are; propoxyphene, nortriptyline, phenacetin, propranolol and lidocaine. Successful controlled release products for drugs that are extensively metabolized can be generated as long as the location, rate and extent and metabolism are known and the

rate constant (s) are not too large. It can be assumed that a controlled release product can be developed as long as the metabolism remains predictable.

3] Elimination or Biological half-life

The rate of elimination of drug is described quantitatively by its biological half- life. The biological half-life and hence the duration of action of a drug plays a major role in considering a drug for controlled release systems. Drugs with short half-life and high dose impose a constraint because of the dose size needed and those with long half-lives are inherently controlled.

4] Safety considerations and Side effects

For certain drugs the incidence of side effects is believed to be a function of plasma concentration. A controlled release system can, at times, minimize side effects for a particular drug by controlling its plasma concentration and using less total drug over the time course of therapy. The most widely used measure of the margin of safety of a drug is its therapeutic index (TI), which is defined as

TI = TD50/ED50

Where TD50 is median toxic dose ED50 is median effective dose

In general, larger the value of TI, safer is the drug. Drugs with very small values of TI usually are poor candidates for formulation into CR products primarily because of technological limitations of precise control over release rates. A drug is considered to be relatively safe if its TI value exceeds 10.

5] Protein binding

The characteristics of protein binding by a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug, and such drugs generally do not require a sustained release dosage form.

6] Disease state

Disease state is an important factor in considering a drug for controlled release system. In some instances better management of the disease can be achieved by formulating the drug as controlled release system. For example, in case of rheumatoid arthritis, sustained release form of aspirin would provide desired drug blood levels, particularly throughout the night, thus relieving morning stiffness. Other examples include nitroglycerin in the management of angina pectoris and belladonna alkaloids and synthetic anti-cholinergics in the treatment of peptic ulcers.

7] Circadian rhythm

Many biological parameters like liver enzyme activity, blood pressure, intraocular pressure and some disease states like asthma, acute myocardial insufficiency, and epileptic seizures have been shown to be influenced by circadian rhythm. Hence the response to certain drugs like digitalis glycosides, diuretics, amphetamines, barbiturates, carbamazepine, ethyl alcohol, and chlordiazepoxide display time- dependent nature.

Oral Controlled – Release Products [13]

Based on the release mechanism these are classified as follows:-

1. Diffusion-controlled products.
2. Dissolution-controlled products.
3. Erosion products.
4. Osmotic pump systems.
5. Ion exchange resins.

1. Diffusion – Controlled products [14]

In these systems, there is water – insoluble polymer which controls the flow of water and the subsequent release of dissolved drug from the dosage form. Diffusion occurs when a drug passes through the polymer that forms the controlled release device. The diffusion can occur through pores in the polymer matrix or by passing between polymer chains. These are broadly divided into two categories:-

A. Reservoir Devices.

B. Matrix Devices.

The basic mechanisms of drug release from these two systems are fundamentally different.

A. Reservoir Devices

In this system a water insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particles (or) tablet. The active agent is released to the surrounding environment by diffusion process through the rate limiting membrane. In the reservoir systems the drug delivery rate remains fairly constant.

B. Matrix Devices

In the matrix devices the drug or active is dispersed in polymer matrix to form a homogeneous system known as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release.

2. Dissolution-controlled products

In these products, the rate of dissolution of the drug is controlled by slowly soluble polymers or by micro encapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled. Some preparations contain a fraction of the total dose as an immediate- release component to provide a pulse dose soon after administration. The pellet dosage forms of diffusion- or dissolution- controlled products can be encapsulated or prepared as a tablet. Dissolution-controlled products can be sub-divided into two types:-

a) Encapsulation Dissolution controls.
b) Matrix Dissolution control.

a) Encapsulation Dissolution control

These systems method involves coating of individual particles (or) granules of drug with a slow dissolving material. The coated particles can be compressed directly into tablets (or) placed in capsules. The rate of dissolution of the drug (and thereby availability for absorption) is controlled by micro encapsulation. Once the coating is dissolved, the drug becomes available for dissolution. By varying the thicknesses of the coat and its composition, the rate of drug release can be controlled. These products

should not be chewed as the coating may be damaged. One of the advantages of encapsulated pelleted products is that the onset of absorption is less sensitive to stomach emptying. The entrance of the pellets into the small intestine (where the majority of drug absorption occurs) is usually more uniform than with non-disintegrating sustained-release tablet formulations.

b) Matrix Dissolution control

In this system an alternative approach is to compress the drug with a slow dissolving carrier. Here the rate of drug release is controlled by the rate of penetration of the dissolution fluid into the matrix, porosity, presence of hydrophobic additives and the wet ability of system and surface of particle.

3. Erosion products

In this system drug or active agents are mixed with biodegradable polymers. These materials degrade within the body as a result of natural biological processes and drug release occurs at constant rate. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chains into biologically acceptable and progressively smaller compounds. The release if drug from these products is controlled by the erosion rate of a carrier matrix. The rate of release is determined by the rate of erosion.

4. Osmotic pump systems

The osmotic pump is similar to a reservoir device but contains an osmotic agent (e.g., the active agent in salt form) which acts to imbibe water from the surrounding medium via a semi-permeable membrane. Pressure is generated within the device which forces the active agent out of the device via an orifice (of a size designed to minimize solute diffusion, whilst preventing the build-up of a hydrostatic pressure head which has the effect of decreasing the osmotic pressure and changing the dimensions{volume} of the device). The advantage of this type of product is that the constant release is unaltered by the environment of the gastrointestinal tract and relies simply on the passage of water into the dosage form. The rate of release can be modified by altering the osmotic agent and the size of the hole.

5. Ion exchange resins

Drug-resin complexes ("resonates") for extended release are known and have been successfully used commercially. The drug is bound to the resin and released by exchanging with appropriately charged ions in contact with the ion exchange groups. This technique is applicable to certain drugs which have particular characteristics in terms of their relatively affinity for the polymers being used.

Rationale of controlled drug delivery system

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration. Thus, optimal design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of drug [15].

However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentration (MTC) of drug may be reached with toxic side effects resulting. If doses are missed, periods of sub-therapeutic drug blood levels or those below the minimum effective concentration (MEC) may result, with no patient benefit.

Extended release tablets and capsules are commonly taken only once or twice daily compared with counterpart conventional forms that may need to be taken three to four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drug which then is followed by the gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time (Fig 1) [16].

Figure 2. Characteristic representation of plasma concentrations of a conventional immediate release dosage form (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose).

Drug-candidates suitable for sustained release products [17]

For a successful sustained-release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and be absorbed at a rate that will replace the amount of drug being metabolized and excreted.

Zero order oral drug release can be achieved, in principle, by surrounding a core tablet with a membrane that is permeable to both drug and water, as illustrated in Fig 3a. After swallowing, the core becomes hydrated, and drug dissolves until it reaches its saturation concentration or solubility. The core serves as a saturated reservoir of drug. Drug release proceeds by partitioning from the reservoir into the membrane, followed by diffusion across the membrane into the gastrointestinal fluid. So long as saturation is maintained in the core, there will be a stationary concentration gradient across the membrane, and release will proceed at constant rate. Eventually, the dissolved drug's concentration in the core falls below saturation, reducing the concentration gradient and hence the release rate, which decays to zero. If the membrane consists of a water-soluble polymer of high molecular weight, then it will initially swell into a gel, through which drug diffuses. The thickness of the gel layer initially increases with time due to swelling, but ultimately it decreases due to disentanglement and dissolution of polymer chains. At intermediate times, the gel layer may be of approximately constant thickness, and release occurs at a relatively constant rate.

As an alternative to dissolution/partition/diffusion based devices, osmotic pumps have been developed to provide zero order release. An elementary osmotic pump, illustrated in Fig 3, is a tablet or capsule consisting of a core of drug surrounded by a membrane that is permeable to water but not to the drug. A small hole is drilled into the membrane. Upon ingestion, water is osmotically imbibed into the core through the semi permeable membrane, dissolving the drug. A constant osmotic pressure gradient is established between core and the external medium, setting the stage for water influx, which displaces drug through the hole at a constant rate. Eventually, drug concentration falls below its solubility, and the rate of osmotic pumping decays.

The efficiency of osmotic devices can be improved by enriching the core with excipients such as water soluble

polymers. For example, in push-pull osmotic systems, depicted in Fig 3c, the drug formulation is layered between the water soluble polymer and the exit orifice. As water crosses the semi permeable membrane, drug is dissolved. Meanwhile, swelling of the polymer excipients, which is also caused by osmosis, pushes drug through the orifice
Figure 3. Schematics of devices designed for zero-order drug release. (a) Membrane diffusion controlled release. Drug in core (granulated pattern) dissolves to form saturated solution (dilute dots). Drug then diffuses across membrane (thin tipped arrows). (b) Elementary osmotic pump. Core is surrounded by a semipermeable membrane, with a small, drilled orifice. (c) Push–pull osmotic pump.

Preformulation Studies [18]
Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

a) Determination of Melting Point: Melting point of drug was determined by capillary method. Fine powder of drug was filled in a glass capillary tube (previously sealed at one end). The capillary tube is tied to thermometer and the thermometer was placed in the Thais tube and this tube is placed on fire. The powder at what temperature it will melt was noticed.

b) Solubility: Solubility of drug was determined in pH 1.2 and pH 6.8 buffers. Solubility Studies were performed by taking excess amount of drug in beakers containing the Solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions are analyzed spectrophotometrically at 260.5nm as pH 1.2 as blank and 262.4nm as pH 6.8 as blank.

c) Compatibility Studies: Compatibility study with excipients was carried out by FTIR. The pure drug and its formulations along with excipients were subjected to FTIR studies. In the present study, the potassium bromide disc (pellet) method was employed.

d) Identification of Drug: Weigh accurately about 0.25 gm, dissolve in 50 ml of carbon dioxide-free water and titrate with 0.1 M sodium hydroxide using phenol red solution as indicator. Repeat the operation without the substance under examination. The difference between the titrations represents the amount of sodium hydroxide required.

Methods for Preparation of Controlled Release tablets [19]

1) Wet Granulation Technique
- Milling and gravitational mixing of drug, polymer and excipients.
- Preparation of binder solution
- Wet massing by addition of binder solution or granulating solvent
- Screening of wet mass.
- Drying of the wet granules.
- Screening of dry granules
- Blending with lubricant and disintegrant to produce "running powder"
- Compression of tablet.

2) Dry Granulation Technique
- Milling and gravitational mixing of drug, polymer and excipients
- Compression into slugs or roll compaction
- Milling and screening of slugs and compacted powder
- Mixing with lubricant and disintegrant
- Compression of tablet.

3) Sintering Technique
- Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.
- Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure.
- The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering.
- The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization of drug release.

Factors affecting drug release [20]
Various factors could be accounted for the drug release mechanism from hydrophilic matrices. These factors include ; geometry of matrix , particle size of polymers , matrix swelling ratio (which depend on polymer type and controls water and drug diffusion coefficients),polymer and drug concentration , chain length and degree of substitution on HPMC as well as drug characteristics.
The study of the drug release from the hydrophilic matrices requires knowledge of properties and interaction of the polymers used as the binder.

1. Polymer hydration: Dissolution of a polymer includes absorption/adsorption of water in more accessible place, rapture of polymer-polymer linking with the simultaneous forming of water- polymer linkage, separation of polymeric chain, swelling and finally dispersion of polymeric chain in the dissolution medium. The Methocel K polymer, because of low content of methoxy groups, hydrate quickly, which justifies its application in the controlled release matrices. Larger sized fraction of HPMC can hydrates more rapidly than smaller fraction. The first minutes of hydration are the most important because they correspond to the time when the protective gel coat is formed around matrices containing HPMC.

2. Polymer composition: The complex composition of polymer cellulose ether precedes several reactions, as hydroxyl groups, that can be reacting covalently with many species. Both mono and poly functional, in order to stabilize and insolubilize their structure. The intermolecular interaction include the formation of acetal with non-functional aldehydes, formation of hemeacetal or acetal with dialdehyde, formation of ether or methylene link with reagent containing methyl groups and formation of ether links with epoxies, ethylene imines derivatives, ethylene imine derivatives, sulfones, and labile chlorine compounds.

3. Polymer viscosity: With cellulose ether, polymer viscosity is used as an indication of the matrix weight. Increasing the molecular weight or viscosity of the

polymers in the matrix formulation increasing the gel layer viscosity and thus slows the drug dissolution. Also the greater dilution and erosion thus control the drug dissolution. Viscosity of the gelling agent retards or hastens the initial process of hydration (without altering the release rate). Works applying DSC allows conclusion that temperature affect HPMC hydration. With increase of gel temperature, the HPMC looses hydration water fallowed by decrease in relative viscosity.

4. Drug solubility: Absorption of poorly soluble drugs is often dissolution rate limited. Such drug does not require any further control over their dissolution rate; during the Pre-formulation phase it is necessary to determine drug solubility not only in water but also at various pH values. The aqueous and pH dependent solubility is of important for drug release. The hydro solubility of drug play an important role in drug release mechanism, soluble drugs are generally released by diffusion mechanism while insoluble drugs are release by erosion mechanism.

5. Polymer drug proportion: Studies completed by Salomen, E. Docker demonstrated that the release rate increase for lower amount of HPMC with slightly soluble drug, the proportion is dependent on gel consistency, since it is affected by gel proportion.

6. Polymer drug interaction: The evaluation of water concentration profile was calculated from HPMC matrices with different molecular Weights. The Thermal analysis of cellulose ether polymer demonstrated that the drug polymer interaction occurs at hydrated gel layer around the matrix tablet and is partially responsible for the drug release modulation.
Ford et al developed studies using water soluble drugs (Promethazine hydrochloride) to valuate the temperature effect on the drug release from matrices with several degrees of viscosity and HPMC K15M, drug release decreases with increase of HPMC content, and the increase in temperature leads to increase in drug release rate.

7. Tablet hardness and density: Tablet hardness did not show marked difference in as evaluated by an *in- vitro* method. Ladipus et al utilized to compression forces and observed no significant difference in drug release patterns from tablets of different densities. Valasco MV et al evaluated effect of compression force on drug release from HPMC matrices and reported independence of drug release with compression force.

8. Effect of diluents: The inclusion of water soluble diluents (lactose) and water insoluble diluents (tribasic calcium phosphate) in matrix tablets showed divergence in the release profile of drug, because of the difference in the solubility of the diluents and their subsequent effect on the tortuosity factor. As the water soluble diluents dissolves, they diffuse outward and decrease the tortuosity of the diffusion path of the drug. But tricalcium phosphate does not diffuse outward, but rather get entrapped within the matrix and bring about an increase in the release of the drug by the fact that its presence necessarily decreases the gum concentration.

Scope of polymers in controlled drug delivery systems [21, 22]

Various synthetic and natural polymers have been examined in drug delivery applications. The three key advantages that polymeric drug delivery products can offer are:

1] Localized delivery of drug: The delivery system can be implanted directly at the site where drug action is needed and hence systemic exposure of the drug can be reduced. This becomes especially important for toxic drugs, which produce various systemic side effects (such as the chemotherapeutic drugs).

2] Sustained delivery of drug: The drug encapsulated is released over extended periods and hence eliminates the need for multiple doses. This feature can improve patient compliance especially for drugs meant for chronic indications which requires frequent administrations.

3] Stabilization of the drug: The incorporated polymer can protect the drug from the physiological environment of GIT and hence improve its stability *in- vivo*. This particular feature makes this technology attractive for the delivery of labile drugs such as proteins.

Evaluation Parameters [23, 24]

1) Pre Compression Parameters

A. Bulk density (Db): It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

Db = M / Vo

Where, Db = Bulk density (gm/cc)
M is the mass of powder (g)
Vo is the bulk volume of powder (cc)

B. Tapped density (Dt): Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

Dt = M / Vt

Where, Dt = Tapped density (gm/cc)
M is the mass of powder (g)
Vt is the tapped volume of powder (cc)

C. Compressibility index: The compressibility of the powder was determined by the Carr's compressibility index.

Carr's index (%) = = b=(v/b) X100

Table 1. Grading of powders for their flow properties according to carr's index

S. No	Carr's Index	Flow Properties
1	5-15	Excellent
2	12-15	Good
3	18-21	Fair to Passable
4	23-30	Poor
5	33-38	Very Poor
6	>40	Very Very Poor

D. Hausner ratio: Hausner ratio = tapped density/bulk density

Values of Hausner ratio; < 1.25: good flow

>1.25: poor flow

If Hausner ratio is between 1.25-1.5, flow can be improved by addition of glidants.

E. Angle of repose (θ): It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$\tan\theta = h/r$

$\theta = \tan^{-1}(h/r)$

where, θ = angle of repose,

value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm2.

C. Friability (F)

Tablet strength was tested by Friabilator USP EF-2. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets. The

% friability was then calculated by,

D. Weight variation test [26]

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if not more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the following table,

Table 3. Weight variation limits [27]

h = height of pile,

r = radius of the base of the pile.

Table 2. Comparison between angles of reposes and flow property

S. No. Average weight of tablet(mg)

1

2

3

Maximum % difference allowed

F. Total Porosity: Total porosity was determined by measuring the volume occupied by a selected weight of a powder (Vbulk) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V).

Porosity (%) =Vbulk-V/Vbulkx 100

G. Flow rate: Flow rate of granules influences the filling of die cavity and directly affects the weight of the tablets produced.

2. Post Compression Parameters [25]

A. Thickness and diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness

The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The

Where, PD = Percentage deviation, W avg = Average weight of tablet,

W initial =individual weight of tablet.

E. Uniformity of drug content

Five tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 262.4 nm after suitable dilution using a UV/Visible Spectrophotometer (UV-1800).

***In vitro* drug release characterization models: Mathematical models [28, 29]**

Zero order release kinetics: Ideal delivery of drugs would follow "zero order kinetics", wherein blood levels of drugs would remain constant throughout the delivery period. This ideal delivery is particularly important in certain classes of medicines intended, for example, for antibiotic delivery, heart and blood pressure maintenance, pain control and antidepressants. Consequently, there has been substantial activity by scientists searching for improved methods of achieving both controlled and sustained delivery of drugs.

Zero order release kinetics refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with low-soluble drugs and other delivery systems. In its simplest form, zero order release can be represented as

$Q = Q0 + K0t$

Where,

Q=the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q0=the initial amount of drug in solution (it is usually zero), and

K0=the zero order release constant. The plot made: cumulative % drug release vs. time (zero order kinetic model).

First order release kinetics [30, 31]: The rate laws predicted by the different mechanisms of dissolution both alone and in combination, have been discussed by Higuchi. However, the earliest equation expressing dissolution rate in a quantitative manner was proposed by Noyes and Whitney as:-

$dc / dt = k (Cs – Ct)$

where, dc/ dt is the rate of change in concentration with respect to time, and

k is the rate constant.

The integrated form of the equation is:

In [Cs / (Cs – Ct)] = kt

Log C = Log C0 – kt / 2.303

Where, C0 is the initial concentration of drug and K is first order constant.

The equation in resemblance to the other rate law equations, predicts a first order dependence on the concentration gradient (i.e. Cs – Ct) between the static liquid layer next to the solid surface and the bulk liquid. Noyes and Whitney explained their dissolution data using a concept similar to that used for the diffusion model. These considerations relate to conditions in which there is no change in the shape of the solid during the dissolution process (i. e. the surface area remains constant). However, for pharmaceutical tablets, disintegration occurs during the dissolution process and the surface area generated therefore varies with time.

The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets. For a drug powder consisting of uniformly sized particles, it is possible to derive an equation that expresses the rate of dissolution based on the cube root of the particles.

Q01/3-Qt1/3 =KHCt

Where,

Qt is the amount of drug released in time t,

Q0 is the initial amount of the drug in tablet and

KHC is the rate constant for Hixson-Crowell rate equation.

Higuchi Model [32]: Ideally, controlled drug-delivery systems should deliver the drug at a controlled rate over a desired duration. The primary objectives of the controlled drug-delivery systems are to ensure safety and to improve efficacy of drugs, as well as to improve patient compliance. Of the approaches known for obtaining controlled drug release, hydrophilic matrix is recognized as the simplest and is the most widely used. Hydrophilic matrix tablets swell upon ingestion, and a gel layer forms on the tablet surface. This gel layer retards further ingress of fluid and subsequent drug release. It has been shown that in the case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug-release rate. It is well documented that drug release from hydrophilic matrices shows a typical time-dependent profile (ie, decreased drug release with time because of increased diffusion path length). This inherent limitation leads to first-order release kinetics.

Many controlled-release products are designed on the principle of embedding the drug in a porous matrix. Liquid penetrates the matrix and dissolves the drug, which then diffuses into the exterior liquid. Higuchi tried to relate the drug release rate to the physical constants based on simple laws of diffusion. Release rate from both a planar surface and a sphere was considered. The analysis suggested that in the case of spherical pellets, the time required to release 50% of the drug was normally expected to be 10% of the time required to dissolve the last trace of solid drug in the center of the pellet. Higuchi was the first to derive an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

Qt = [2DS' (A - 0.5S')] 0.5*t0.5

Simplifying, Qt = kH (t) 0.5

Where, Qt is the amount of drug released in time t, D is the diffusion coefficient,

S is the solubility of drug in the dissolution medium, A is the drug content per cubic centimeter of matrix tablet, and KH is the release rate constant for the Higuchi model.

The release of a solid drug from a granular matrix involves the simultaneous penetration of the surrounding liquid, dissolution of the drug, and leaching out of the drug through interstitial channels or pores. The volume and length of the opening in the matrix must be accounted for in the diffusional equation, leading to a second form of the Higuchi equation:

Q = [DK/L (2A- KCs) Cst] 0.5

Porosity, O, is the fraction of matrix that exists as pores or channels into which the surrounding liquid can penetrate.Tortuosity, P, is introduced in equation to account for an increase in the path length of diffusion due to branching and bending of the pores, as compared to the shortest “straight- through” pores. Tortuosity tends to reduce the amount of drug release in a given interval of time. A straight channel has a tortuosity of unity, and a channel through spherical beads of uniform size has a tortuosity of 2 or 3.

Korsmeyer-Peppas Model [33, 34]: Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

Mt/MN = K tn

Where, Mt/ MN is fraction of drug released at time t, and k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table 1 for cylindrical shaped matrices. Table 4: [35, 36]

There are several simultaneous processes considered in this model:

- Diffusion of water into the tablet
- Swelling of the tablet as water enters
- Formation of gel
- Diffusion of drug and filler out of the tablet
- Dissolution of the polymer matrix Key attributes of the model include:
- Tablet geometry is cylindrical
- Water and drug diffusion coefficients vary as functions of water concentration
- Polymer dissolution is incorporated
- Change in tablet volume is considered by incorporating the first 60% of release data, mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and

state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion.

Table 2 describes the limits of this analysis for cylindrical shape, e.g. a tablet. The value of the release exponent in ibuprofen sustained release obtained as 0.2465 which as per table 1 is beyond the limits of Korsmeyer model so-called power law. The power law can only give limited insight into the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate a diffusion controlled drug release mechanism.

Table 5. The following are the general categories which are used in controlled Release Dosage Form [37, 38]

Conclusion

Oral Sustained release (S.R)/Controlled release (C.R) 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. This review describes the various factors influencing the design and performance of sustained/controlled release products along with suitable illustrations. The release models with major application and best describing drug release phenomena are, in general, the Higuchi model, zero order model, first order model and Korsemeyer-Peppas model. Further, it can be added that the physicochemical properties of the drug as well as polymer and the drug to polymer ratio govern the release of drug from the formulation and thus, modify the release kinetics accordingly.

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