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Multilayer Tablets and Their Drug Release Kinetic Models for Oral Controlled Drug Delivery System

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Abstract: Among all drug delivery systems, oral drug delivery is the most preferred route for administration for various drugs. Recently, pharmaceutical research has focused on controlled drug delivery offer definite advantages over conventional release formulation of the same drug. Controlled delivery systems that can provide zero-order drug delivery have the potential for maximizing efficacy while minimizing dose frequency and toxicity. A new approach to zero- order drug delivery that includes geometric factors is described. Systems such as multilayered tablets and other geometrically altered devices have been created to perform this function. The multi-layered matrix system overcomes inherent disadvantages of non-linearity associated with diffusion controlled matrix devices by providing additional release surface with time to compensate for the decreasing release rate. This technology also demonstrates a wide flexibility for various applications Polymeric materials play an important role in the functioning of these systems. Hydrophilic polymers are mainly used for preparation of matrix type controlled delivery systems. The mathematical models used to determine the kinetics of drug release from drug delivery systems. The quantitative analysis of the values obtained in dissolution/release rates is easier when mathematical formulae are used to describe the process. This review focuses on the controlled drug release of multilayer tablets, drug release mechanism, system design, different process and formulation parameters and drug release kinetics model of modified release dosage forms.

Key words: Controlled Release · Drug Delivery · Multilayered Matrix System · Modelling

INTRODUCTION

Oral drug delivery system is the most convenient and commonly employed drug delivery system. It has some specific advantageous characteristics, such as (a) ease of administration, (b) flexibility in the design and (c) least aseptic constraints, of the dosage form. Conventional drug delivery system is of short duration of action. This is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to+ maintain drug blood levels in the therapeutic range for longer period of time, for example, by increasing the dose, then toxic level may be produced at early times [1].

Some problems associated with the conventional drug delivery system are:

- Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
- The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index whenever over medication occur [1].

However, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Thus, these shortcomings have been circumvented with the introduction of controlled release dosage forms.

Controlled release of drug from the dosage form is another concept of drug delivery system where it ideally exhibit zero-order drug release kinetics which allows for a constant quantity of drug to be released from the dosage

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form in extended period of time without depending upon the initial concentration of drug. This system is extensively used in drug delivery due to low therapeutic index and short half life of drug to reduce the dose dumping and fluctuation [2-5]. Modified release dosage forms are another revolution of the oral drug delivery system which has huge advantages over immediate release formulations of the same drug. Modified dosage form are designed by various methods such as film coated pellets, tablets, capsules or more sophisticated and complicated delivery systems like as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. These products are usually designed to provide continuous and slow delivery of drug over the entire dosing interval to offers maintenance of plasma level within a desired therapeutic range and improve patient compliance and convenience [6-8].

Advantages and Disadvantages of Controlled Release Dosage Forms [9]

Advantages:

- Reduced fluctuations in circulating drug levels.
- Avoidance of night time
- Increased patient compliance dosing
- The frequency of drug administration is reduced
- Drug administration can be made more convenient
- The blood level oscillation characteristics of multiple dosing of conventional dosage form is reduced
- Safety margin of high potency drug can be increased

Disadvantages:

- Unpredictable or poor *in-vitro* and *in- vivo* correlation
- Dose dumping
- Reduced potential for dosage adjustment
- Poor systemic availability in general
- Patient variation
- Increased potential for first pass clearance
- Therapeutic agents for which single dose exceeds 1 gm, the technical process require-ments may make to product very difficult or sometimes impossible to prepare

Inexpensive naturally occurring polysaccharides have been used in the controlled drug delivery to formulate a dosage form unit that-

- Retard the drug release in the upper GIT
- Consist of biodegradable polysaccharides as main constituent
- Degraded by a wide range of microbial species
- Shows a rapid drug release in the tract of colon due to presence of a high concentration of a degradable polysaccharides in the tablet
- Could be formulated using usual tablet techniques [10].

In present time, most of the controlled drug delivery devices are of matrix type in which drug is uniformly dispersed or dissolved all over into the polymer, due to low cost, its effectiveness, ease of manufacturing and prolonged drug release time period [11,12].

Hydrophilic polymers are widely used in formulating oral controlled release dosage form as polymeric retardant materials [13]. Physicochemical properties of drug and polymer such as solubility and molecular weight, relative ratio of polymer and drug content, morphology of the dosage form, degree of coating and incorporation of excipients will be evaluated for their effect on the release kinetics of the drug molecules. Hydrophilic polymer has favourable *in vivo* performance, ease of manufacturing, comparatively low cost and flexibility in controlling the release of drug [14-19]. Hydrophilic matrix shows a typical time dependent profile by which the dissolution medium penetrate into the dosage form and the polymeric material swells and drug molecules start to move out from the system through diffusion [20].

The highly water soluble drug inherently follows near first-order diffusion with an initial high release rate followed by a rapidly declining rate. At the point of beginning, the release rate was observed as rapid, improved and short duration. This is bursting effect of dosage form. Generally, it produces toxicity by increasing the dose of therapeutic concentration above the maximum level. From the bursting of the dosage form consequent several steps followed as hydration, swelling or erosion of retarding agent or polymer. This process released the drug in controlled manner. Some time the diffusion path-length of drug is increased which show progressively slow release of drug. As the resultant saturation concentration is achieved [14-19]. There are various factors that improve the release pattern and helps to overcome from undesirable behaviour of drug in polymeric matrix, these are physiochemical properties of drug like solubility, viscosity, etc.; polymer drug ratio; composition of drugs and polymers in matrices; manufacturing process and route of administration [21-27].

One of the principles involved in altering the geometry factors for constant release of drug to achieve zero order kinetics such as Geometrix, multilayered tablets, donut-shaped tablets, Procise and Smartrix and other geometry factors (solid units having spherical, cylindrical, conical, biconcave, biconvex, hemisphere with cavity, core in cup, circular sectioned cylinder, rings, oval bi-dose divisible tablets etc.), films, erosion/dissolution controlled and swelling controlled mechanisms, non-uniform drug loading and matrix-membrane combination to give from inherent non-linear release to linear release in controlled matrix devices [28-42]. A proper technique relies on the use of controlled release mechanism, among the multilayer matrix tablets as drug delivery devices has more attracted the research scientist in last last two decades.

Controlled Drug Delivery as Multilayer Matrix Tablets: Mutilayered systems (bilayered, triple-layered, quadruple-layered, etc.) are becoming increasingly recognized as controlled-release drug delivery systems. Multilayered tablets possess various benefits, namely the ability to prevent incompatability between drugs and excipients; and by providing multiple release kinetics profiles in single delivery system of either the same or different drugs, by means of different release control mechanisms, immediate drug release using a disintegrating monolithic matrix in order to achieve an initial peak in plasma drug level, delayed drug release achieved using an eroding monolithic matrix which may deliver another active drug to the latter part of gastrointestinal tract, controlled release swelling monolithic matrix carry out together swell as well as erode in which drug constantly released and better management control and regulation of release profiles by retarding initial burst release and achieving zero-order kinetics [43]. It would be useful on further modification of the system focused by the researcher for improved drug release kinetics in controlled drug delivery system.

Multi-layered matrix tablet consist of a matrix core which contains the active solute(s) and one, or more barriers (modulating layers) incorporated during the tabletting process. The function of the modulating layers is to delay the interaction of active solute with dissolution medium by limiting the surface available for the solute release and at the same time controlling solvent penetration rate through the matrix [44].

In this design, the coat layers prevent the water penetration and thus protect the core. This ultimately reduces the hydration rate and controlled area for solute release at the core. Thus burst effect can be minimized and the release can be maintained at a relatively constant level through the barrier layers' by swelling and erosion process. After this phase, during the subsequent portion of the dissolution process, these swollen barriers are erosion dominated and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase of diffusion path-length (saturation effect) is counterbalanced by the simultaneous increase of the area available for drug release [45].

Triple-layer tablets forms are generally formulated as a controlled release formulation. In such tablets, drug forms the inner core layer which is sandwhiched by the polymer layer (also called barrier layer). In general, drug release modulation from the triple layer matrix system can be accomplished via the following geometric modification:

- Formation of drug concentration gradient and differential erosion of the matrix layers
- Restriction of release surface of swellable matrix by barrier layers
- The swelling and differential erosion of external layers to maintain constant surface area and constant release
- Differential layer dissolution for pulsatile or rapid-slow release purposes [29,43]

Triple layer matrix system provide more flexibility in release pattern, their manufacturing is easy as compared to other delivery systems.

The manufacturing of multilayered tablets involves the following steps,

- Dosing of the bottom layer
- Transfer of the prepared core
- Insertion in to die
- Dosing of the top layer
- Final compression and
- Ejection

Multilayered tablets that can provide zero-order sustained release where the tablet consists of either a hydrophilic or hydrophobic core layer with barrier layers that are press coated to the surfaces of the core layer. This leaves the sides of the core layer exposed. It has been shown that generally constant drug release can be achieved when both barrier layers are hydrophilic and the core layer is hydrophobic [44,46]. However, other factors also need to be controlled in order to achieve zero-order drug release.

Table 1: Summary of drug release characteristics of multilayered tablets using different polymer.

Achieved Drug Release	Polymer Used as Drug Carrier	Polymer Used in Barrier Layers
Zero order release kinetics	Hydrophilic (HPMCA&HPMC)	Hydrophobic (EC)
Zero-order or near zero-order release	Hydrophilic (Locust bean gum, Xanthan gum)	Hydrophilic (anionic SCMC)
	Hydrophilic (HPMC K-100M)	Hydrophilic (Xanthan gum)
Zero-order release kinetics	Hydrophilic (Carbopol)	`Hydrophilic (Carbopol)
Zero-order release kinetics	Hydrophilic (Xanthan gum)	Hydrophilic (SCMC)
Zero-order kinetics	Hydrophilic (Guar gum)	Hydrophilic (SCMC)
Zero-order release kinetics	Hydrophilic (Guar gum)	Hydrophilic (Guar gum)
Zero-order release	Hydrophilic (Guar gum)	Hydrophilic (HPMC K4M, HPC, NaCMC)
Zero-order drug release kinetics	Hydrophobic (Carnauba wax)	Hydrophilic (Methocel® K15M) and Hydrophobic (Carnauba wax)
Non-linear drug release	Hydrophobic (Carnauba wax)	Hydrophobic (Carnauba wax)
Zero-order release kinetics	Hydrophobic	Hydrophilic (Methocel® K4M)
Retarded to lesser extent drug release	Hydrophilic	Hydrophobic
Extended drug release	Hydrophilic	Hydrophobic

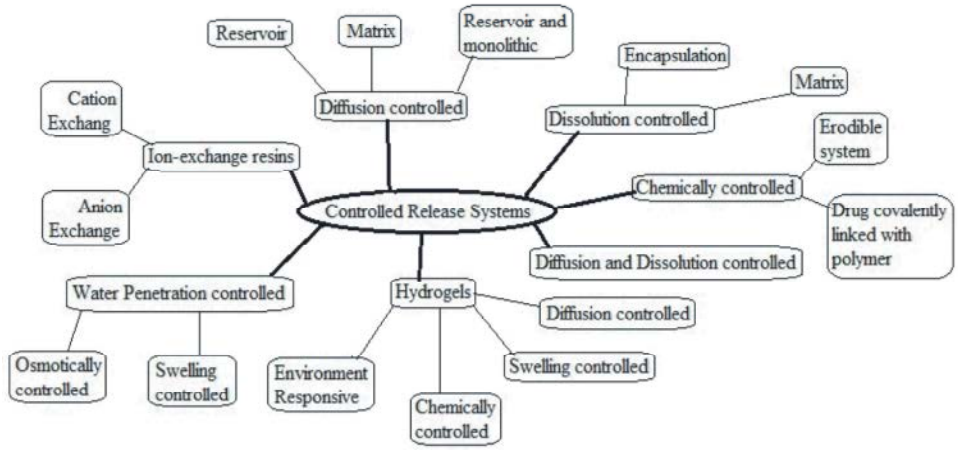

Fig. 1: Schematic representation of various classes of controlled release

Controlled Drug Release Mechanism [9,47-50]: Controlled release polymeric systems can be classified according to the mechanism that controls the release of the therapeutic agent. The schematic representation is given below-

Mechanisms of drug release from oral controlled delivery systems, some has been discussed below:

Dissolution Controlled Release System: Dissolution controlled release can be obtained by slowing down 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. Dissolution-controlled products can be sub-divided into two types:-

- Encapsulation Dissolution controls.
- Matrix Dissolution control.

In these systems the drug particles are coated or encapsulated 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. The common multi-particulate systems are microparticles (microspheres or microcapsules), nanoparticles (nanospheres or nanocapsules) and liposomes.

Matrix Dissolution Control: In these systems, the drug is homogeneously dispersed throughout a rate controlling membrane. The drugs which are highly water soluble can be controlled by using slowly soluble polymers. 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.

Diffusion Controlled Release System: Diffusion of a drug molecule through a polymeric membrane forms the basis of this controlled drug delivery system. 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:

- Matrix Diffusion control
- Reservoir Diffusion control

Matrix devices are very common because of ease of fabrication. Diffusion controlled involves dispersion of drug in either water-insoluble or a hydrophilic polymer. Diffusion occurs when the drug passes from the polymer matrix into the external environment. The surface area of the matrix decreased with the time, with a concomitant decrease in the drug release. since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release. The diffusion depends on the solubility of the drug in the polymer.

Reservoir Diffusion Control: In this system, a core of drug is coated with the water insoluble polymeric material. The drug release mechanism across the membrane involves diffusion of dissolution media through 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.

Ion Exchange Resins: Drug-resin complexes ("resonates") for extended release are known and have been successfully used commercially. Drugs can be bound to ion exchange resins and when ingested, the ionic environment within the GIT determines the release of the drug. The drug is released slowly by diffusion mechanism from the resins particle structure.

Osmotic Controlled Release: Oral osmotic pump, popularly known as ORAS® based on principle of osmotic pressure to release the drug at constant rate. 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. The drug is either mixed with the agent or is located in the reservoir. 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 release is unaltered by the environment of the GIT and it relies simply on the passage of the water into the dosage form. The rate of release can be modified by altering the osmotic agent and the size of the hole.

Design of Multi-Layered Tablets: The design of multi-layer through varying the geometry of the devices or modulating layers which allows different tablet design for the production with specific release properties to achieve different dissolution patterns like pulsatile, bimodal, delayed and multi modal delivery. Different designs have been discussed below:

- Zero order sustained release
- Quick / slow delivery system
- Time programmed delivery system
- Bimodal release profile

Zero order sustained release system comprises hydrophilic or hydrophobic polymer as matrix or barrier layer in their formulation to control the release of drug via coating of polymer to both side of the matrix but leaving other sides for exposure to the dissolution medium to sustain the release of the drug [46,51,52].

Quick / Slow Delivery System: Quick / slow delivery system which is characterised by initial rapid release followed by extended / prolonged release of the drug to achieved immediately a therapeutic effect and to sustain a constant release of drug to maintain plasma level concentration. This concept applied on where doses regimen not satisfies simple release of the drug [53,54].

Time Programmed Delivery System: Time programmed delivery system provide immediate release of the drug followed by time controlled release, when the delivery of drug is required in a time controlled fashion in the gut, rather than release of drug in continuous manner according to circadian rhythm. This system consists of core which is coated with different polymeric barriers. The release of drug from the core tablet after swelling/eroding of hydrophobic or hydrophilic barrier of coating that show pulsatile release of the drug [55,56].

Table 2: Novel technologies for oral controlled release of drug utilize geometric in drug delivery

Technologies	Special characteristics	Company
Geomatrix	Multilayer tablet designed specially to regulate amount location and time of drug release	Skye Pharma Plc. USA
VERSATAB Controlled or Delayed Release Technology	Controlled-release tablets are oral dosage forms from which the active is released over an extended period of time (up to 24 hours) upon ingestion.	IntelGenx Corporation
SODAS or Spheroidal Oral Drug Absorption System	Pulsatile drug release where the drug is released in pulses that are separated by defined time intervals	Elan drug technologies
Smartrix	Geometric design of the drug-containing core with slowly eroding cover layers	Smartrix Technologies Inc. Canada
Procise	System consists of core that contains uniformly dispersed drug and has a hole in the middle	Glaxo Canada Inc.
Multipor	Consists of core of active drug surrounded by water insoluble membrane	Ethical Holdings Plc. UK
$TIMER_X$	Matrix tablet composed of locust bean gum and xanthan gum	Penwest Pharmaceuticals, USA
Ring Cap	Combines matrix tablets and existing capsule banding processes to create controlled release solod oral dosage forms	Alkermes Inc. USA
CONSURF or Constant Surface Area Drug Delivery Shuttle	Concurrent swelling and diffusion of matrix aids in drug release	Biovail Corporation International
Contramid	Uses starch and its modified form as the controlled release excipients, they possess the characteristic gelling of dosage form when in coming in contact with gastric fluid	Labopharm Inc. Canada
MODAS or Multiporous Oral Drug Absorption System	Consists of core surrounded by time release coating, which on interacting with gastric fluid transforms to a semi-permeable membrane which regulates drug release	Elan Corporation Ireland
DUROS	Implants with miniature titanium cylinders designed to provide continuous osmotically driven delivery of drugs within the body	Alza Corporation
Macro Cap	pH regulated polymeric coating of pellets regulates the drug release	Biovail Corporation International
Dimatrix or Diffusion Controlled Matrix System	Consists of beads made either by extrusion-spheronisation or by powder/ solution layering on nonpareil beads or in the form of a tablet matrix	Biovail Corporation International
DUREDAS or Dual Release Drug Absorption System	Bi-layered tablets to ensure two release rates for the dosage form	Elan Corporation
DPHS or Delayed Pulsatile Hydrogel System	Possess characteristic hydrogel matrix which allow initial zero order release followed by fast release	Andrx Pharmaceuticals, USA
Pulsincap	Capsule based system consisting of hydro swellable plug	Scherer DDS, Ltd.
Micro pump Oral Controlled Delivery System	Composed of Micro particulate system having polymeric coating, thickness and polymer composition regulates osmotic pressure driven drug release	Flamel Technologies, France
PRODAS or Programmable Oral Drug Absorption System	Multiparticulate drug delivery technology that is based on the encapsulation of oral controlled-release mini tablets in the size range of 1.5 to 4 mm in diameter	Elan Corporation
Time- Controlled Explosion System	Multiparticulate system in which drug is coated on non-peril sugar seeds followed by a swellable layer and an insoluble top layer	Fujisawa Pharmaceutical Co. Ltd.
Time Clock System	A solid dosage form coated with lipidic barriers containing carnauba wax and bee's wax along with surfactants, polyoxy-ethylene sorbiton mono-oleate	West Pharmaceutical Services Drug Delivery & Research Centre
SCOT or Single Composition Osmotic Tablet System	Uses osmotic principles to achieve zero order drug release	Andrx Pharmaceuticals, USA

Bimodal Release Profile: Bimodal release profile show an initial rapid release followed by slow release and again a second phase of rapid drug release i.e. sigmoidal release profile. This system compensates the slow absorption in the stomach and small intestine and for programmed pulse releases that perform more effectively at the site of action to undertake periodic changes [57,58].

Influence of Process and Formulation Parameters: The initial dose layer affected neither the release of intermediate slow or second fast release phase that influence the process and formulation parameter of final phase of release of modified release dosage forms.

Multi-layered tablet consisting of a core and one or more barrier layers that will be occupied into description while determining the parameters involved in the processing. The following factors should be considered for the process and formulation [59,60].

Granulation with the Layer Consist of Therapeutically Active Substances: During granulation process of therapeutically active substances some fundamental factors are to be considered which includes proportion of the liquid used in granulation, time period required for massing step, temperature that used for air drying step for outlet and milling screen process as well as the interaction between the amount of granulation liquid and the outlet temperature [61]. On these factors the final products have to be considered and the properties can be classified into four categories: (I) granule properties (e.g. bulk density, flowability, ability to settle, particle size distribution), (ii) extensometric responses (e.g. cohesion index, lubrication index, ejection strength, plasticity, elasticity), (iii) physical characteristics of tablet (e.g. hardness, thickness, weight variation, friability) and (iv) analytical results (e.g. content uniformity, *in vitro* profile).

Compression Process: In the compression process turntable speed and compression force are the two main critical parameters for the first second and third layer of the tablet. The crushing strength of the tablet is improved by increasing the compression force. Content uniformity and release pattern of multi-layered, press coated and, bimodal delivery systems are not influenced by these pattern [62,63]. The release rate and lag time is dependent on compression force in the press coated tablet which are intended for the target drug delivery system. Until a critical point is reached, the release rate of drug decreases and the lag time increases with increasing compression. For the prolonged action, tablet must reside in the body for more than 10 hrs. For additives, which have poor wettability are added which prevent the penetration of dissolution medium into the tablet and prevent the drug to come out. To achieve these certain some poorly wettable additives, are added to the outer shell polymer to prevent the penetration of dissolution medium into the pores in the outer shell. For example, magnesium stearate or calcium stearate were added to the hydroxyl propyl methyl cellulose acetate succinate (HPMCAS) polymer to increase the lag time [64]. Eiji Fukui *et al.* [64] reported that the drug release in gastric fluid was completely suppressed till 15 h if tablets contain magnesium stearate, irrespective of compression force tablets containing calcium state, it was necessary to increase the compression force to more than the range applied, to suppress till 12 h. In the intestinal fluid the lag time was not prolonged to more than 2 h by addition of magnesium sterate. In contrast lag time could be prolonged by calcium stearte as long as 9 h by increasing the compression force.

Hardness of Compressed Tablet: Hardness of tablet is essential for the handling, transportation, shipping or breakage during the storage before usage. Monsanto hardness tester was used for the determination of the hardness of the tablet of each formulation. The hardness was measured in kg/cm^2.

Hardness of tablet is expressed in terms of tensile strength. The tensile strength of the tablet is calculated by the formula, according to Fell and Newton [65]:

$$\sigma = \frac{2P}{\pi Dt}$$

where, σ = tensile strength (kg/cm^2), D= tablet diameter (cm), t = tablet thickness (cm), P= force applied to fracture (kg). Tensile strength is inversely proportional to the porosity of the tablet and which is completely depending on the compression force. Release rate of the tablet is slightly affected by the compression force so, hardness of tablet play important role in the formulation.

Polymer Concentration in Core: Polymer plays an important role in controlling the release rate of drug from the tablet. Dissolution rate of the tablet decrease with the increase in the polymer concentration. In certain cases, polymer concentration does not influence the release of layered tablet because the solubility of certain polymers depends on the pH of the surrounding medium. For example [61], in the biomodal system the effect of decreasing HPMCAS-MF is not significant at pH 1.2 but

with increase in pH up to 7.4 drug release also increases. At higher pH dense network of polymer dissolve while at low pH there is no effect on polymer network.

Filler: Fillers are the excipients which are used in the tablet to keep its weight constant but they play an important role in controlling the dissolution rate of the tablet. As fillers come in contact with the dissolution medium, they diffuse out of the tablet and dissolution of the tablet increases. Fillers increase the porosity of the tablet so polymers are adjusted according to different type of tablets. Example of such filler is lactose.

Recently Reported for Multilayer Matrix Tablets: Conte *et al.* [66] presented the modulation of the dissolution profiles from Geomatrix multi-layer matrix tablets containing drugs solubility. It has recently been proposed for constant drug release. It consists in the application of a drug-free barrier layer on one or both bases of an active core (hydrophilic matrix). The partial coating modulates the core hydration process and reduces the surface area available for drug release. The result is an extended release that draws close to a linear profile.

Chavda *et al.* [67] designed an oral controlled drug delivery system for sparingly soluble diclofenac sodium (DCL) using guar gum as triple-layer matrix tablets. Matrix tablets of diclofenac sodium were prepared by compressing three layers one by one. The *in vitro* drug release from proposed system was best explained by the Hopfenberg model indicating that the release of drug from tablets displayed heterogeneous erosion. D3G3, containing 87% of guar gum in guar gum layers and 50% of guar gum in DCL matrix granule layer was found to provide the release rate for prolonged period of time. The results clearly indicate that guar gum could be a potential hydrophilic carrier in the development of oral controlled drug delivery systems.

Izhar Ahmed *et al.* [68] formulated the matrix and triple layer matrix tablets of metoprolol tartrate using xanthan gum as the matrix forming agent and sodium carboxy methyl cellulose (Na CMC) as barrier layers. Results show that layering with Na CMC granules on the matrix core, provided linear drug release with zero order kinetics.

Libo *et al.* [69] studied the novel triple-layer tablet formulation and the effect of punch velocity on the compaction properties was also investigated using compaction simulator. The main formulation components were poly(ethylene oxide) (PEO), lactose and theophylline. Heckel profiles of each layer as well as the combined layers were constructed, the porosity and tensile strength of the compacts were determined and strain rate sensitivity (SRS) values were calculated. Results indicate that the formulation of each layer and the combined triple-layer tablet exhibited similar compression behaviour and the consolidation mechanism was shown to follow predominantly plastic deformation as evidenced by the shape of Heckel plots and high SRS values.

Efentakis *et al.* [70] developed and evaluated different preparations of sustained delivery systems, using carbopols as carriers, in the form of matrices and three-layer tablets with isosorbite mononitrate. Matrix tablets were prepared by direct compression whereas three-layer tablets were prepared by compressing polymer barrier layers on both sides of the core containing the drug. The three-layer formulations exhibit lower drug release compared to the matrices. This was due to the fact that the barrier-layers hindered the penetration of liquid into the core and modified drug dissolution and release. The structure of the tablets and weight/thickness of the barrier-layers considerably affected drug release and the release mechanisms.

Shajahan *et al.* [44] have reported that the modified release dosage forms offer definite advantages over conventional release formulation of the same drug. Hydrophilic polymers are mainly used for preparation of matrix type controlled delivery systems. The system usually provides nonlinear release profile. Different design can be used such as zero order sustained release, quick/slow delivery system, time-programmed delivery system (press coated tablet), bimodal release profile. It was concluded that by considering various formulation parameters, it is possible to get the appropriate release kinetics and the system has the advantages of relatively low cost and potentially feasible to large scale production using layered tablet process.

Al-Saidan *et al.* [71] carried out pharmacokinetic evaluation of guar gum-based three-layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug for oral controlled release formulation (guar gum-based three layer matrix tablets) containing highly soluble metoprolol tartrate as a model drug. Six healthy volunteers participated in the study and a two way crossover design was followed. The plasma concentration of metoprolol tartrate was estimated by reverse-phase HPLC. The pharmacokinetic parameters were calculated from the plasma concentration of metoprolol tartrate versus time data. The delayed T_{max}; lower C_{max}; decreased K_a; unaltered bioavailability and

prolonged $t_{1/2}$ indicated a slow and prolonged release of metoprolol tartrate from guar gum three-layer matrix tablets in comparison with the immediate release tablet dosage form.

Krishnaiah *et al.* [72] have designed oral controlled drug delivery systems for highly water-soluble drugs using guar gum as a carrier in the form of three-layer matrix tablets and evaluated the tablet that indicated guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs such as trimetazidine dihydrochloride.

Streubel *et al.* [65] developed new multi-layer matrix tablets to achieve bimodal drug release profiles (fast release /slow release / fast release). Hydroxypropyl methylcellulose acetate succinate (HPMCAS, type MF) was chosen as a matrix former, because it is water-insoluble at low and water-soluble at high pH values. Studies focused on the elucidation of the drug release mechanisms from HPMCAS-MF:drug tablets. Drug release is affected by water imbibitions, drug diffusion and polymer dissolution and is faster compared to 0.1 N HCl. With knowledge of these underlying release mechanisms, multi-layer matrix tablets were developed to achieve bimodal drug release. The process and formulation parameters affecting the resulting releaseF rates were investigated using theophylline and acetaminophen as model drugs.

Conte Maggi, *et al.* [73] formulated Multi-layered hydrophilic matrices as constant release devices (GeomatrixTM Systems) and also performed the evaluation studies.

Kinetic Modelling on Drug Release: Kinetic models are used to describe on the whole release of drug from the dosage form that is various models. Qualitative and quantitative changes in the formulation may alter drug release and *in vivo* performances, developing equipment that ease product development by reducing the necessity of bio-studies is always desirable. In controlled release formulations, the *in vitro* drug dissolution data to expect the *in vivo* bio- performance is a rational approach [74-76].

This rational approach to examine the kinetics of drug release from controlled release formulation can be classified into three categories:

- Statistical methods (exploratory data analysis method, repeated measures design, multivariate approach [MANOVA: multivariate analysis of variance] [77,78].
- Model dependent methods (zero order, first order, Higuchi, Korsmeyer-Peppas model, Hixson Crowell, Baker-Lonsdale model, Weibull model, etc.) [79,80].
- Model independent methods [difference factor (f1), similarity factor (f2) [81-83].

Mathematical Models [84-87]

Zero-Order Model: The zero order describes the system where the drug release rate is independent of its concentration. The equation is

$$Q = Q_0 + K_0 t$$

Where, Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 is the initial amount of drug in solution (it is usually zero),K_0 is zero order rate constant expressed in units of concentration /time and t is the time. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released *versus* time. The zero order model can be used to depict the drug dissolution of several types of modified release pharmaceutical dosage forms.

First Order Model: The first order describes the release from the system where release rate is concentration dependent. 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:

$$dC / dt = k (C_S - C_t)$$

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:

$$\ln [C_S / (C_S - C_t)] = kt$$
$$\log C = \log C_0 - Kt / 2.303$$

Where, C_0 is the initial concentration of drug and K is the first order constant expressed in units of time^{-1} and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining *vs*. time which would yield a straight line with a slope of -K/2.303.This used to explain the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

Higuchi Model: Drug release from the matrix system was proposed by Higuchi in 1961which is the first example of a mathematical model. This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system thickness; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity is constant; and (vi) perfect sink conditions are always attained in the release environment. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.

$$Q = Kt^{1/2}$$

Where, K is the constant reflecting the design variables of the system. The data obtained were plotted as cumulative percentage drug release versus square root of time. It is used to explain some transdermal system and matrix system of tablets with water soluble drugs.

Korsmeyer-Peppas Model: Korsmeyer-Peppas model describes the release mechanism from polymeric system.

$$M_t / M_8 = Kt^n$$

Where, M_t / M_8 is fraction of drug released at time t, K is the rate constant and n is the release exponent. The n value is used to characterise different release mechanisms. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release *versus* log time.

By incorporating the first 60% of drug release data were fitted in Korsmeyer-Peppas model where value n is the release exponent characterizes the release mechanism of drug. The release exponent 0.45 = n corresponds to a Fickian diffusion mechanism, 0.45 < n < 0.89 to non-Fickian transport, n = 0.89 to Case II (relaxational) transport and n > 0.89 to super case II transport. Fickian diffusion release and a Case-II relaxation release are the limits of this phenomenon. Fickian diffusion release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxation release is the drug transport mechanism associated with stress and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion.

Hixson-Crowell Model: 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.The particles regular area is proportional to the cube root of its volume was acknowledged by Hixson and Crowell (1931). They derived the equation

$$Q_0^{1/3} ? Q_t^{1/3} = Kt$$

Where, Q_0 is the initial amount of drug in the pharmaceutical dosage form, W is the remaining amount of drug in the pharmaceutical dosage form at time t and K is the rate constant for Hixson-Crowell rate. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cube root of drug percentage remaining in matrix *versus* time.

Gompertz Model: Gompertz model is the *in-vitro* dissolution profile which described a simpler exponential model, expressed by the equation:

$$X(t) = X_{max} \exp [-\alpha e^{â \log t}]$$

Where, X(t) = percent dissolved at time t divided by 100; X_{max} = maximum dissolution; α determines the undissolved proportion at time t = 1 and described as site or scale parameter; â = dissolution rate per unit of time described as shape parameter. This model has a sharp increase in the beginning and converges slowly to the asymptotic maximal dissolution. It is used for comparative study of drugs having good solubility and intermediate release profile.

Hopfenberg Model: Hopfenberg developed a mathematical model to compare the drug release from surface eroding polymers thus extended as the surface area leftovers constant during the degradation process. The cumulative fraction of drug released at time t was described as:

$$M_t / M_8 = 1- [1- k_0 t / C_L a]^n$$

Where, k_0 is the zero order rate constant describing the polymer degradation (surface erosion) process, C_L is the initial drug loading throughout the system, a is the system's half thickness (i.e. the radius for a sphere or cylinder) and n is an exponent that varies with geometry n = 1, 2 and 3 for slab (flat), cylindrical and spherical geometry, respectively. This model is used to identify the mechanism of release from the optimized oilispheres using data derived from the composite profile, which essentially displayed site-specific biphasic release kinetics.

CONCLUSION

Oral Controlled release dosage form provides an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamics properties of drugs. Adequate controlled plasma drug levels by reducing dosing frequency to an extent that once daily dose is sufficient for therapeutic management, reduced side effects as well as improved patient compliance are some of the benefits that these systems may offer. Controlled delivery systems that can provide zero-order drug delivery have the potential for maximizing efficacy while minimizing dose frequency and toxicity. One of the techniques is multi-layered tablet system. This system provides zero order or near zero order release. This concept also demonstrates a wide technology for various applications such as quick/slow, bimodal, pulsatile delivery of active ingredients because it allows the precise modulation of drug release process even for drug characteristics by extreme physicochemical properties. Drug transport inside pharmaceutical systems involves multiple steps provoked by different physical or chemical phenomenon and appropriate release kinetics. The release models with major application and best describing drug release phenomena are, in general, the Higuchi model, zero order model, first order model, Korsemeyer-Peppas model, Hixson-Crowell model, Hopfenberg model and Gompertz model. The fact that drug delivery systems with multilayered tablets have shown promising results in drug delivery technology and ease of manufacturing is an added advantage to the pharmaceutical industry.

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