



A Detailed Review on Oral Controlled Release Matrix Tablets

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ABSTRACT

Matrix tablets are widely used for controlled release drug delivery system. Controlled release matrix tablets enhance patient compliance by minimizing dose frequency and increase stability by protecting the active ingredient from hydrolysis and degradation. It releases drugs at fixed and expected rate in a controlled manner either by dissolution or diffusion control mechanism. The active content is uniformly dispersed in the rate controlling agent i.e. polymers, which may be hydrophilic, plastic, lipid, or mineral. The polymer acts as release rate retardants. Hence it controls drug blood level with uniform therapeutic level and avoid fluctuation thus prevent local or systemic adverse reactions. The various approaches for matrix tablet preparation, polymers, factors and evaluating methods are discussed in this review.

Keywords: Matrix tablets, Controlled release, Hydrolysis, Dissolution, Diffusion, Hydrophilic, Polymer.

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INTRODUCTION

Tablets are one of the well-known and conventional oral solid dosage forms. First tablet was formulated by hand operated device in 1843. Tablets can be divided into various categories like core (uncoated), coated (sugar and film coating), dispersible, effervescent, chewable, sublingual, buccal, and modifies release tablets (delayed, prolonged sustained and controlled release tablets)¹.

Tablets are of two types, immediate & extended drug release tablets. Immediate release tablets release drugs directly after administration within 30 min and extended release tablets are further categorized as controlled and sustained release tablets. Drug release in a fixed rate for a specific time interval in controlled release tablets where as in sustained release tablets, there is no influence on drug release rate². Controlled release tablets can be further classified delayed-release, prolonged release, site and receptor targeted release³.

The first oral controlled drug release delivery system was developed by Israel lipowski in 1938, who worked on coated pellets. The oral sustained release delivery system developed in 1940, and the development of controlled

release system in 1950⁵. Drug delivery is generally influenced by disintegration and dissolution of matrix in which the active pharmaceutical ingredient is blended⁶.

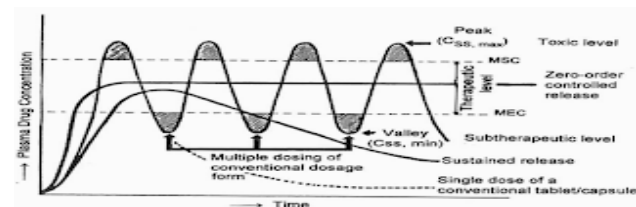


Figure 1: Hypothetical plasma concentration time profile from multiple conventional, sustained and controlled delivery formulation⁴

Controlled release systems release drugs at predetermined and predicted rate in a programmed mode and hence controls therapeutic level and maintains steady state concentration to specific site or receptor⁷. Controlled release tablet formulations offer various advantages such as better patient compliance, drug uniformity in blood, decrease overall dosing frequency, side effects, and enhance safety margin for highly potent medicaments. Among the different CRDDS systems, matrix based formulations are the preferred mostly because of convenient and cost effective formulation process⁸.

MATRIX SYSTEM

Matrix tablets are most common example of controlled release drug delivery system, which release drug either by diffusion or dissolution control mechanism. The active content is uniformly dispersed in the rate controlling material i.e. polymers, which may be hydrophilic, plastic,



lipid, or mineral etc⁹. This polymeric substance acts as release rate retardants. Hence it controls drug blood level with uniform therapeutic level and avoid fluctuation i.e. minimum or toxic concentration, thus prevent local or systemic adverse reactions. Different types of matrices have different release pattern hence the different properties of matrix substance helps to indicate the drug release pattern¹⁰.

Advantages of oral controlled release matrix tablets

1. Improve Patients compliance
 - Oral delivery system is more convenient and robust
 - Reduce in frequent dosing
2. Therapeutic Advantage
 - Maintain therapeutic level for prolonged time
 - Reduce fluctuation in drug level
 - Constant Blood drug concentration and avoid high blood concentration
 - Improvement in the bioavailability¹¹
3. Reduction in Adverse Effects
 - Drug fatality reduces due to low drug absorption
 - Minimize local and systemic drug side effects and moderate efficacy
 - Minimize drug accumulation with chronic dosing¹²
4. Cost Effective
 - Easy to manufacture
 - Decrease health care cost i.e. nursing time¹³
5. Drug stability enhance by shielding the active ingredient from hydrolysis and degradation¹⁴
6. Release high molecular weight compound effectively.

Disadvantages of oral controlled release matrix tablets

1. Decreased systemic availability as compare to conventional tablets due to enhanced first-pass effects, more instability, incomplete release, inadequate gastric residence, particular site absorption, pH-dependent stability¹⁵.
2. The release rate of drugs can be changed by meal and gastric emptying time¹⁶.
3. Break down of tablet lose controlled release property.
4. Development cost increase due to specialized equipment and expensive excipients.

5. In-vitro in-vivo correlation (IVIVC) required thorough analysis¹⁷.
6. Dose adjustment of drugs given in different strength becomes difficult¹⁸.

Manufacturing techniques of matrix tablet

Direct compression

Powders or granules compressed directly into tablets without altering the physicality.

Dry granulation

It is of two types, slugging and roller compaction. In slugging method, granule is recompressed and slugs are crushed to produce granules. Whereas in roller compaction, powder is recompress with pressure rolls.

Wet granulation

It involves massing of drygranule blends in a volatile fluid, wet sizing then drying and followed by dry screening¹⁹.

Steam granulation

Steam is used as a binder for granulation instead of water. It uniformly distributes and diffuses into the granules. The granules become rounded with more surface area and hence enhance drug dissolution rate from granules.

Melt granulation

Moldable binders are used for granulation, which melts at 50-80 °C. Dry granules collected by cooling it to ambient temperature²⁰.

Freeze granulation

It involves spraying droplets of slurry into liquid nitrogen and the drops are then immediately frozen into granules followed by drying process, i.e. lyophilisation.

Foam granulation

Aqueous binders are added as foam which increases surface area of foam and enhance the diffusion of the water in powder bed²¹.

Sintering technique

Powder compact heated at a temperature under the melting point of solid particles in a controlled environment under atmospheric pressure²².

Classifications of The Controlled Release Matrix Tablets

It can be categorized into three types based on following parameters.

1. Void fraction
2. Polymer used
3. Miscellaneous ways²³



Void fraction**Macro porous matrices**

Drug diffusion takes place through pores of relatively larger size of 0.1–1.0 micrometer range. Matrix porous of the system is larger than diffusant dimension. Macro porous matrices are appropriate for drugs with <1 micrometer molecular mass.

Micro porous matrices

Drug diffusion takes place through relatively smaller pores size of 50-200 angstrom range. Micro porous matrices are appropriate for drugs with < 200 angstrom molecular mass²⁴.

Non porous matrices

Drug diffusion take place through the network meshes instead of pores as there are no pores available²⁵.

Polymer used

- i. Hydrophilic matrices
- ii. Hydrophobic matrices
- iii. Fat wax matrices
- iv. Biodegradable matrices
- v. Mineral matrices²⁶

Hydrophilic matrices

It is also known as swellable controlled release matrices. Hydrophilic matrix is widely used modified release delivery system manufacturing due to low cost and flexibility. Matrix tablet is homogenous dispersion of drug and hydrophilic polymer, act as a gelling agent. The release of drug from the matrix tablet is regulated due to the ability of polymers to absorb fluid from G.I. and form 3 D structure²⁷. The drug release from the gel barrier is done by expansion and corrosion of gel which control the release of drug. Drug release kinetic of this system is depends on strength, density, and chemistry of polymers. It has been used for regulation of release rate of drug with different aqueosity²⁸.

Hydrophilic polymers can be classified into following three classes.

- a. *Cellulose derivatives*: hydroxy ethyl cellulose (HEC), ethyl hydroxyl ethyl cellulose (EHEC), Hypromellose (HPMC) methyl cellulose & sodium carboxy methyl cellulose (NaCMC).
- b. *Non cellulose natural and semi synthesized polymers*: agar gum, locust bean gum; algin, treacle, mannose, galactose, chitosan and starches derivatives.
- c. *Carbomers (Poly-acrylic-acid polymers)*: carbopol²⁹.

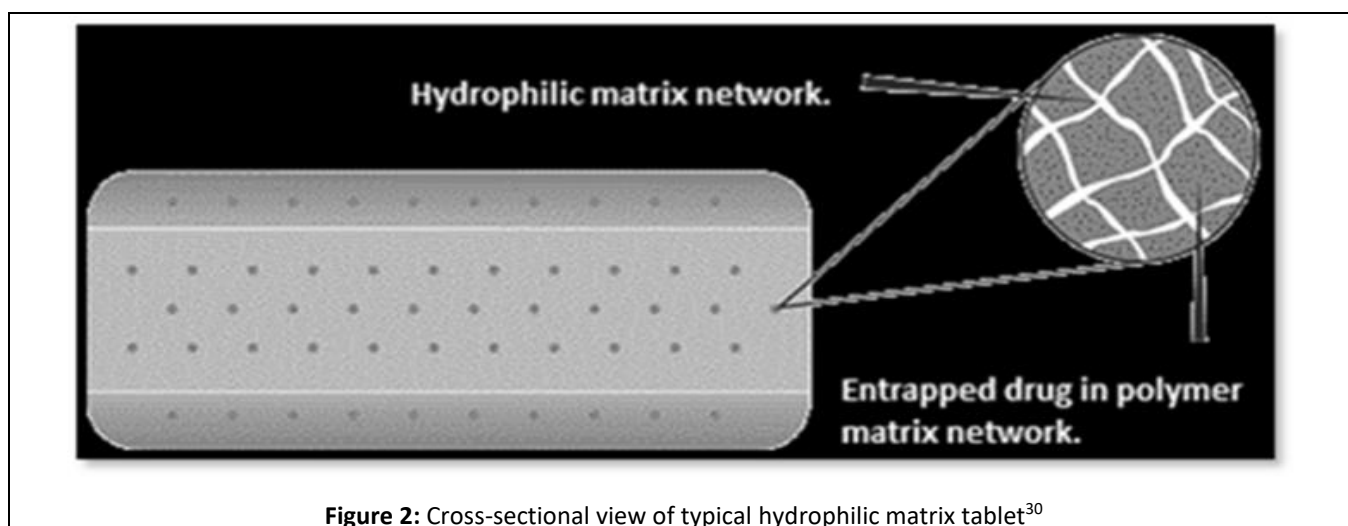


Figure 2: Cross-sectional view of typical hydrophilic matrix tablet³⁰

Hydrophobic matrices

It is also known as plastic matrices. Matrix tablets formulate by granulating drug with hydro phobic polymers using latex / pseudo-latex. Examples of hydrophobic polymers are: poly ethylene, poly vinyl chloride, ethyl and methyl cellulose, cellulose acetate, polystyrene, latex, & carbomers. The rate limiting ingredient in hydrophobic matrices is non-water soluble in nature. Controlled release maintained by drug diffusion through matrix³¹.

The rate limiting step in this system is fluid invasion in the matrices. Insoluble components of matrix system retain

the matrix structure intact during drug release. The release profile of a drug can be modified by addition of soluble excipients e.g. lactose in the matrix. Insoluble drugs are not good candidate for hydrophobic matrix due to steady molecular diffusion and low release profile¹⁵.

Fat wax matrices

It is also known as lipid matrix system. It is composed of fat wax or lipid substance. The drug release from matrix remains uniform through outtime span. The liberation of active ingredients relies on matrix forming agent incorporated fluid media that would leach out from the compact mass resulting in a porous matrix of twisted

tubing³². The drug release in this matrix can be take place by both porous diffusion & erosion mechanism. The matrix encompassed drug diffuse in dissolution media via water filled vessels. Incorporation of the surfactants in the system can also influence the release pattern & the portion of total active ingredients inside the matrices. Drug, other excipients i.e. waxes and diluents can be transformed into granules by compacting, drying, blending, and granulating³³.

Biodegradable matrices

Polymers of this matrix are consists of monomers connected to each other by weak bond in the system, which decompose or degraded & dissolve by enzymatic or non enzymatic mechanism in to oligomers & monomers which may digest and eliminate³⁴. The polymers used in this system are both naturally & synthetically made and composed of ester, ether, & amide functional groups. Examples of polymers are agro polymerand poly-esters (poly lactic acid, polycapro lactone, poly anhydrides, poly glycolic acid, polyortho esters etc)³⁵.

Mineral matrices

Mineral polymers are known as polysialates. Polymers used in this matrix system are collected from the mineral origin as well as different sorts of seaweeds i.e. algins which is polysaccharide & hydrophilic form viscous gum when hydrated³⁶.

Miscellaneous ways

- i. Multi layered matrices devices

- ii. Floating matrix tablets
- iii. pH modulated controlled release system
- iv. Mucoadhesive matrix delivery system³⁷

Classification according to release mechanism of matrix tablets

Matrix dissolution system

It is also known as monoliths. The drug is uniformly dispersed in rate limiting media, i.e. carnauba wax, castor oil etc. Dissolution is regulated by modifying porosity and wettability of matrix and additives. The drug release rate can be determined by dissolution rate of polymers. Solubilization of solid substance in a given solvent is known as dissolution. It is a rate-limiting step; when liquid diffuse from solid particles³⁸.

Matrix diffusion system

The drug particles in system are dispersed in the polymeric matrix. When the drug particles in outer layer goes in the dip medium, it dissolved & release active ingredients by means of diffusion from the matrix¹⁷. Diffusion is a movement of drug particle from higher concentration to lower concentration and take place by inert and water insoluble membrane which is polymeric and work as a barrier. Drug release in diffusional matrix system is adjusted by varying its initial concentration, solubility, polymers used, and aperture size of inert membrane³⁹.

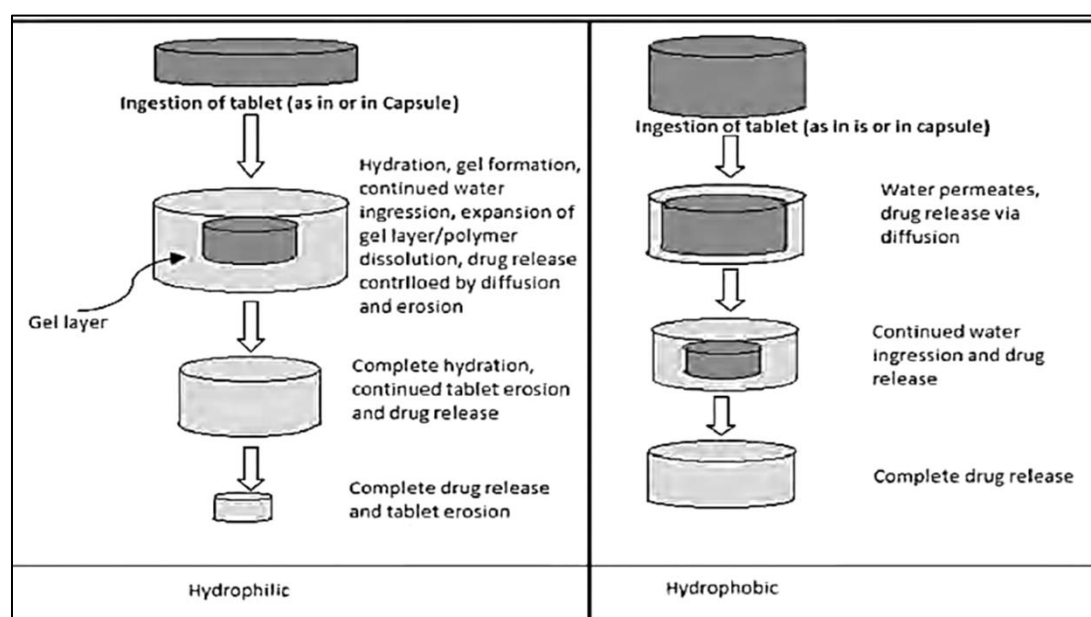


Figure 3: Hydrophilic and hydrophobic matrix system and drug release process⁴⁰

Factors Affecting Drug Release Rate

1. Biological factors
2. Physicochemical factors
3. Release limiting factors

Biological factors

Half life ($t_{1/2}$)

Drugs with half-life less than 2 and greater than 8 is poor candidate for controlled release tablets. Drugs with lesser

half-life require large quantity of active ingredients tablet whereas drug with larger half life are already prolonged²⁸.

Absorption

Drug with slow, irregular and erratic absorption rate is not good candidate for controlled release tablets. Drug which imbibed through particular gastro intestinal site i.e. absorption window & via carrier-mediated transport system are also not relevant candidate⁴¹.

Metabolism

Drugs which undergoes metabolism before being consumption show decreased bioavailability from controlled release drugs. Pro-drug is a good solution for this type of drugs. Drugs with no intestinal reaction are widely used for controlled release system. Drug undergoes metabolism may be convert into another active metabolite or may be inactivation so controlled release system also help to make it metabolized in particular environment⁴².

Distribution

Drugs that have large distributing volume (V_d) can affect the elimination process & not suitable for controlled release as itself is sustained e.g. chloroquine (15000l V_d), digoxin (500l V_d) etc⁴³.

Protein binding

Prolonged and extreme plasma protein binding increased drug half-life and irregular bioavailability and hence poor candidate as the drug remains in system for long time⁴².

Therapeutic index

Drugs with greater therapeutic ratio are preferable due to large safety & efficacy margin. More the ratio, more safe the drug is. In the drugs with narrow therapeutic index, the release kinetics should be more accurate & necessary to retain the plasma drug level under narrow therapeutic & safety margin⁴³.

Side effects

It is due to the oscillation in plasma drug concentration. Matrix tablets decrease fluctuation and release drug in controlled manner and hence prevent side effects⁴⁴.

Disease state

Controlled release delivery system improves disease control. i.e. in rheumatoid arthritis, aspirin controlled release tablets maintain wanted plasma drug level especially over the night and consequently calm morning stiffness³.

Physicochemical factors

Dose of administration

Drugs with large dose of administration are not suitable for controlled release matrix formulation because mass

unit dose will be high enough to administer. Generally, 1 g is considered to be maximum limit⁴⁵.

Ionization

Ionized drug is not good candidate for controlled release tablets. The absorption rate is found be 3-4 times greater in unionized drugs as compare to ionized form of drugs⁴⁶.

Aqueous solubility

Drug with very low solubility i.e. less than 0.01 mg/ml are sustained itself so the solubility of the compound will not be suitable candidate for slightly soluble drugs. The minimum limit for drug solubility of modified release system is 0.1 mg/ml. Very soluble drugs are one of the good candidates for the sustained release system⁴⁷.

Distribution coefficient

High hydrophilic or lipophilic drug moieties have apex distribution coefficients and hence cause either high or low flux into the tissues that consequently affect absorption. So both extremities are undesirable for controlled release system⁴⁸.

Stability

Oral drug delivery systems are prone to both hydrolytic & metabolic degradation. Inconstant drugs can be formulated as extended delivery system and release drug in intestine. Drugs exhibit consistency in small intestine cause reduction in bioavailability if extended form is given, such drug can be modified as gastro retentive dosage form⁴⁹.

Molecular mass & diffusion coefficient

Diffusivity is the rate of drug to spread in polymeric sheet and it is behavior of molecular mass of that drug. The compound with high molecular weight has low release profile in modified release device to spread in the matrix. Diffusion co-efficient is based on size, structure and mass of active pharmaceutical ingredient⁵⁰.

Formulation excipients

The hydrophobic diluents cause resistant gel surface which minimize the drug diffusion and infiltration of aqueous medium. The soluble fillers increase dissolution of soluble drugs by decreasing the tortuosity whereas insoluble fillers affect the diffusion rate by blocking the surface pores of the tablet⁵¹. Surfactant increase drug release rate by solubilization whereas binding agents coat drug particles and alter the rheology of the gel layer thus reduce drug release rate⁵².

Release limiting factors

Polymer hydration (swelling process)

It is a process of dissolution and absorption of polymer in water and the dispersion of polymer in the dissolution medium. More the polymer hydration more will be the release of drug⁵³.



Polymer composition

Functional groups and cross linkages in polymer composition may cause intermolecular interaction with various species making it non soluble and stable. These interactions may influence the pharmacokinetic properties of various drugs⁵¹.

Polymer viscosity

Greater the viscosity of polymer more will be the density of gel surface & hence decrease in the dissolution of drugs. The gel forming moiety retards primary hydration process without affecting rate of release⁴⁸.

Drug solubility

Solubility directly affects the drug release rate from the polymeric membrane. Molecular mass & solubility of drug are important parameters for drug release from dissolution & invasion of matrices. Hydrophilic drug follows diffusion mechanism whereas insoluble drugs release by erosion⁵⁴.

Solution solubility

As all biological dissolution process is controlled by invasion & solubilization so the release pattern is regulated by maintaining dissolution process and must not be affected by factors affecting solubility parameters⁵⁵.

Polymer diffusion

The diffusivity of minute drug particles in matrices is force driving process. Movement of diffusivity is depending on length & extent of polymer series, chemical bonding and complexity of the polymers. There are three factors governs release rate; particle size, viscosity, and concentration.

- Particle size:** Particle size has no influence on release pattern if large quantity of polymer utilized. Particle size is considers when polymer content is low⁵³.
- Viscosity:** With increase in polymer viscosity, more the density of gel surface in matrices and hence slow down dissolution process of active substances⁵⁶.
- Polymer concentration:** More the polymers concentration more will be the gel viscosity; and hence decreases in diffusivity of the drug and hence decrease in drug release and bioavailability⁵³.

Density of polymer diffusional line

The drug release from matrix is typically controlled by Fick's laws of diffusion. i.e.

$$JD = D d_c/d_x$$

JD = Diffusion flux

D = Diffusion coefficient

d_c/d_x = Gradient of concentration along axis⁵⁷

Density of hydrodynamic diffusion bed

The deviation in density of hydrodynamic diffusion layers on matrix influence the release pattern. Drug release rate decreases with increase in the thickness of hydrodynamic diffusion layer⁵⁷.

Surface area

The frequency of drug release is based on area and volume of matrix. The drug release is more in greater surface area dosage form as compare to small⁵⁸.

Fillers effects

The rate of release of fillers/diluents is depends on its property. Water soluble fillers i.e. lactose & mannitol increase the release rate whereas insoluble diluents i.e. calcium phosphate & microcrystalline cellulose decrease diffusivity and enhance matrices eroding⁵⁹.

Additives

The addition of excipients in matrix increases the release rate of water soluble drugs. Drug release will be prominent by using water soluble ingredients⁶⁰.

Loading dose

The loading dose has notable influence on resulting drug release pattern. In poor water soluble drug, with rising drug loading the relative rate of release firstly decline then rises, whereas, absolute release rate monotonically increases. Whereas, in water soluble drug, the porosity of matrix upon release rises with rising drug loading thus enhance absolute release rate⁵⁰.

Polymer drug interaction

The drug release is controlled by diffusion through the polymer matrix and by the erosion of the polymer. The pH of the surrounding medium influences the drug solubility as well as swelling and degradation rate of the polymer and therefore the overall drug release process. Physicochemical interaction between polymer and drug is an additional factor which influences the degree of matrix swelling and therefore its porosity and diffusion release process. The assessment of water concentration profile can be determined using HPMC with various molecular weights⁶¹. Cellulose ether polymer, when analyzed thermally and spectroscopically, it shows interaction between polymer and drug in a gel layer that surrounds the matrix tablet and this partially takes part in drug release modulation⁶².

Temperature

The influence of temperature on release kinetics of drug from the matrix has also been accounted in several researches⁶³.



EVALUATION OF MATRIX TABLETS

Pre compression evaluation

Drug excipient compatibility studies

Any incompatibility or interactions between drug and the polymer were studied through DSC and FTIR spectra³⁵.

Fourier transform infrared spectroscopy

It is conducted for configuration characterization and drug excipient compatibility. All samples dry in hot air oven at 50°C for 2 hrs then prepare as KBr disk compress under 10 ton/nm² pressure. Additional peak or lack of characteristic peak due to chemical interaction related to drug and polymer⁶⁴.

Differential scanning calorimetry

It is conducted to study the chemical interaction between active and non-active ingredients. The sample to be assayed takes in the perforated DSC aluminum pans and scan in the specified temperature range. The heating rate is maintained and nitrogen served as purged gas. The system was cooled down by liquid nitrogen. The differential thermal analyzer use for this purpose⁶⁵.

X ray diffraction pattern

XRD analysis of the drug, polymer and their physical mixture were carried out by X ray diffractometry. It is run to conduct full scan with the counts being accumulated for 1s⁻¹ after each step⁶⁶.

Determination of solubility

Solubility determine by adding an amount of compound well in excess of its saturation solubility to the solvent. Excess drug substances agitate in each buffer for few hours and then centrifuged. The solubility is checked by testing aliquot of supernatant after 24hrs⁴⁷.

Moisture content determination

Moisture content determine by Infra-red drying (gravimetric method) and Karl-fischer titrations (chemical method). Thermo-gravimetric moisture balances determine moisture content in terms of the extent of weight loss that occurs as the sample is heated. Whereas in Karl Fischer titration, a reagent is added to the sample that reacts with the water and produce a non-conductive chemical⁴⁷.

Particle Size Analysis

Various sieves and agitation devices are used to study sieve analysis. Each method may give different results for sieve analysis and endpoint results. Mechanical or electro-magnetic agitation method can induce vertical oscillation or a horizontal circular motion, or tapping or both. Entrainment of the particles in an air stream may also be used⁵⁵.

1. Angle of repose

The slope of heap is checked by fixed funnel method. The height and diameters of conical pile is measured and angle of repose (Θ) is obtained by:

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

h = height of cone

r = radius of conical base⁶⁷

2. Porosity

Porosity is the amount / volume of void as compared to the total amount.

$$\text{Porosity} = \text{Void volume} / \text{Apparent volume}^{67}$$

3. Density

Both apparent & tap denseness are measured by introducing powders into a measuring cylinder. Apparent & tap denseness can be measured by:

$$\text{Apparent density} = \text{Mass} / \text{Apparent volume of occupied powder}$$

$$\text{Tapped density} = \text{Mass} / \text{Tapped volume of powder}^{67}$$

4. Compressibility (Carr's) index & Hausner's ratio

These percentage and ratio are determined by using following formula:

$$\text{Carr's index (\%)} = [(\text{Tapped density} - \text{Apparent density}) \times 100] / \text{Tapped density}$$

$$\text{Hausner ratio} = \text{Tapped density} / \text{Apparent density}^{67}$$

Post compression evaluation

It includes uniformity of weight, rigidity, consistency, diameters, fragility, disintegration, swelling, active drug-uniformity, and in-vitro dissolution testing⁶⁸.

Weight uniformity

Weighing 20 tablets separately weigh using analytical-balance. The weight variation should be within the specified limits. Test will be failed if >2 tablets are not within specified values⁴⁹.

Dimension (Hardness and thickness)

Hardness & thickness are an important parameter to check uniformity of tablet size. Hardness, thickness and diameter are determined simultaneously by hardness tester⁴⁹.

Friability

Ten tablets are weighted and placed in a friabilator then rotate for four minutes at 25 rpm. The tablets then dedusted & reweighed. It should be preferably between 0.5 to 1.0%. Formula for measuring percent friability is:

$$[(W_1 - W_2) \times 100] / W_1^{49}$$



Swelling studies

Swelling index is measured by putting tablets in water filled beaker. Each tablet is weighted after different time intervals. Formula for calculating swelling index is:

$$\%S = W_t - W_o / W_o$$

(W_t = weight after putting, and W_o = weight before putting)⁶⁹

Disintegration test

The test is done by putting 6 tablets in given fluid filled beaker in disintegration tester at normal body temperature (37°C) & time measured till no residue remains.

Dissolution

Dissolution test of carried out by specified dissolution USP method at a maintained body temperature i.e. 37°C with specified USP pharmacopeial conditions. Samples taken out at different intervals of time by using syringe filter & assay by developed HPLC or ultraviolet-visible spectrophotometer method³³.

Analysis of dissolution data

Active content in dissolution sample is determined by drug release profile equation. Release pattern of drug assess by using the model dependent and independent methods⁷⁰.

Model independent method

In this model, similarity factor (f_2) & differential factor (f_1) use to evaluate the dissolution profile. f_1 predicts the release rate of arches of two profile at each point to identify relative error whereas f_2 signifies two arches similarity in their % dissolution⁷¹. It can be determined by using following equations:

$$f_1 = \frac{\sum_{j=1}^n |R_j - T_j|}{\sum_{j=1}^n R_j}$$

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{N} \right) \sum (R_i - T_i)^2 \right]^{-0.5} \right\} \times 100$$

n = sample number

R_j and T_j = reference and test drug release percentages at different time intervals

(If f_2 of two dissolution profiles is 50-100, then both profiles are similar)⁷²

Model dependent method

Model dependent method included following equations to interpret the kinetics of drug release⁷³.

$$C_1 = C_o + K_o t \quad (\text{Zero order kinetics})$$

C = drug release concentration at time 't'

C_o = drug concentration before dissolved in solution

K_o = zeroorder rate constant (conc. / time)

$$\log C = \log C_o - (K_t / 2.303) \quad (\text{First order kinetics})$$

C = drug release concentration at time 't'

C_o = drug concentration before dissolved in solution

K_t = first order rate constant

$$Q_t = K_h \cdot T_{1/2} \quad (\text{Higuchi model})$$

Q_t = drug release quantity at time 't'

K_h = dissolution constant

$$W_o^{1/3} - W_t^{1/3} = K_s t \quad (\text{Hixson crowell model})$$

W_o = initial active content

W_t = drug release concentration at time 't'

K_s = release rate constant

$$Q_t / q_\infty = k t^N \quad (\text{Korsmeyer peppas model})$$

Q_t / q_∞ = fraction of active content release at time 't'

K = release rate constant

N = drug release exponent

$$f_1 = \frac{3}{2} \left[1 - \left(1 - \frac{M_t}{M_\infty} \right)^{2/3} \right] - M_t / M_\infty = k t \quad (\text{Baker Lonsdale model})$$

M_t = drug release concentration at time t

M_∞ = drug release concentration at an infinite time

K = release rate constant

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{K_o}{C_o a_0} \right]^N \quad (\text{Hopfenberg model})$$

$\frac{M_t}{M_\infty}$ = drug dissolved ratio

K_o = rate constant

C_o = initial drug in concentration before erosion

a_o = initial matrix radius

N = Number for slab, cylinder & sphere

$$\log [-\ln(1 - m)] = b \cdot \log (t - T_i) - \log a \quad (\text{Weibull model})$$

m = drug portion in solution

a = time scale constant

b = shape constant

T_i = location constant

$$X_t = X_{max} \exp [-\alpha e^{\beta \log t}] \quad (\text{Gompertz model})$$

X_t = drug dissolved percentage at time 't'

X_{max} = maximum dissolution

α = scale constant

β = shape constant⁴⁰



Surface morphology

Scanning electron micrographs of matrix tablets prior and later to dissolution obtain by surface morphology. The samples were covered under vacuum with gold in argon atmosphere before analyzing. The scanning electron microscope (SEM) runs at 30 kV and examine sample with 200X and 1000X magnification⁷⁴.

Stability studies

The prepared matrix tablets will be subjected to accelerated stability condition at 0, 1, 2, 3 and 6 day (40±2 °C & 75±5 % relative humidity)⁴⁹. Differential scanning calorimetry (DSC) thermograms reported after 6 months accelerated stability condition in order to confirm product stability.

In Vivo Studies

Developed tablet batches subject to in vivo pharmacokinetic testing in human subjects or animal testing. The subjects can be divided into 3 groups. One batch taken reference drug and other three selected for matrix tablets. Obtain each blood samples, heparinized and store in freezer. Plasma samples and deproteinized solution combine and add to a polypropylene micro centrifuge tube then vortex mixed and the suspension was centrifuged at 4000 rpm for 10 minutes. Separate plasma by micropipette. The supernatant fluid collect and dilute with mobile phase and analyze by chromatography⁷⁵. The pharmacokinetic measurements i.e. peak serum concentration (C_{max}), time to reach C_{max} (T_{max}), half-life ($T_{1/2}$), area under curve (AUC)_(0-t) and elimination rate constant (K_{el}) calculate using specific formulas⁷⁶.

Analytical method

RP HPLC is widely used for the drug quantitative determination. HPLC equipment with specified column is use in this method. The mobile phase is used for the estimation of drug in plasma and the flow rate adjusts to 1 ml.min⁻¹. The detection execute by ultraviolet spectroscopy.

In-vitro in-vivo correlation (IVIVC)

It is perform by plotting drug absorbed against drug released percentage. The drug released percentage collected from the in-vitro data and drug absorbed percentage calculated by using Wagner nelson formula:

$$F_a = [(C_t + k_E AUC_{(0-t)}) / k_E AUC_{(0-\infty)}] \times 100$$

F_a = drug absorbed fraction

C_t = plasma concentration at time 't'

k_E = elimination rate constant

AUC = area under curve⁷⁷

Statistical analysis

The collected data are also processed for each subject statistically to calculate mean, standard deviation and

level of significance by computer based programs i.e. ANOVA at a level of significance of $p < 0.05$ ⁷⁸.

CONCLUSION

Oral control release matrix tablet is one of the safe, effective and convenient route dosage forms. Different types of controlled release system can be design by using different polymers. The successful preparation of matrix tablet system is dependent on various biological and physicochemical parameters of drug and excipients.

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