MATRIX CONTROLLED DRUG RELEASE DRUGDELIVERY

Abstract

Formulations that are able to control the release of drug have become an integral part of the pharmaceutical industry. In particular oral drug delivery has been the focus of pharmaceutical research for many years. This type of drug delivery has been at the centre of research due to its many benefits over conventional dosage. The focus of this review is on matrix tablets due to their widely use and simplicity of the formulation. This includes the discussion of various types of matrix tablets and factors affecting the drug release from these formulations. The development of oral controlled release systems has been a challenge to expression scientists due to their incapability to restrain and localize the system at targeted areas of the gastrointestinal tract. There are several advantages of matrix bias including bettered patient compliance due to lower frequent medicine administration, reduction of change in steady- state medicine situations, maximum application of the medicine, increased safety periphery of a potent medicine.

Keywords: Matrix tablet, Controlled Delivery,Polymers

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I. INTRODUCTION

1. Oral drug delivery is most convenient and commonly used drug delivery system comparing to another drug delivery system. There are so many dosages form is available in oral drug delivery system. Tablet is well known and conventional oral solid dosage form. Tablet are divided in different categories on the basis of manufacturing process (coated & uncoated) on the basis of route of administration (chewable, sublingual, buccal)are tablet categories on mode of release of tablet (delayed, Controlled, prolonged &sustained release).[1]

2. There are two main categories of tablet on basis of mode of release. The Immediate release &Extended-release tablet. The immediate release tablet release after 30minute of administration. The extended-release tablets are categories into two types depend on mode of release (control release & sustained release). In control release tablet the drug release in a fix rate for a specific time interval and sustained release there is no influence on drug release rate.[2]

The control release tablet is can be divided in different category as follows:

- **Delayed- release matrix.**
- **Prolonger-release matrix**.
- **Site & receptor targeted release.**

Matrix tablet can be defined as the oral solid dosage form in which the drug is homogeneously dispersed or dissolve within the hydrophilic or hydrophobic polymer matrices. The preparation of matrix tablet involves the direct compression of blend powder mixture of drug, retardant material and other additive to formulate matrix tablet inwhich drug dispersed in a matrix of retardant. Alternatively other additive, retardant blend and drug may be granulated prior to compression.

3. The oral route is the most frequency used for the administration of drug. There are many types of pharmaceutical dosage form are formulated as sustain release rrelat4ed to release of therapeutic agent.[3] (Interfacial elastic relaxation during the ejection of bi-layeredtablets. Int. J. Pharm. 387, 42-47.)

- **Component of matrix tablet**
  - Active drug
  - Releasing controlling agent (S):- Matrix form.
  - Matrix modifier: Channeling agent & wicking agent.
  - Solubilizers and PH modifiers.
  - Lubricant and flow aid.
  - Supplementary coating to extend lag time further reduces release etc.
  - Density modifiers.

- **Matrix formers:** Hydrophobic material that solid at room temperature and does not melt at body temperature are used in matrix tablet as matrix formers. This material contains hydrogenated vegetable oils, cotton, seed oil microcrystalline wax and form carnauba wax.[4]

- **Solubilizes and pH modifiers:** It is necessary to enhance the dissolution of the drug. This is achieving by using solubilizing agent polymers and surfactant. If the drug is ion sable then the buffer or counter ion may be appropriate of dissolution enhancer may also be the channeling agent.[5]

- **Anti- adherent or glidant:** Heat is generated during compaction of matrix can cause meeting of wax matrix formation compound. This melted compound can stick to punch something is needed to remove stitching material the suitable ant-adherent include Talc and and colloidal silicon dioxide. This also act as a glidant increase flowof tablet during formation.[6]

Classification of a matrix tablet

The matrix tablet are classified as followed

- **Void fraction**
  - Macro-porous matrices.
  - Micro-porous matrices.
  - Non-porous matrices.

- **Polymer used**
  - Hydrophilic matrices.
  - Hydrophobic matrices.
  - Fat wax matrices.
  - Biodegradable matrices.
  - Mineral matrices.[7]

II. CLASSIFICATOIN OF CONTROL RELEASE TABLET

1. **Delayed-release matrix:** This is the medications that are design to release API after taking it which can help to control release of drug in body. This medication release in medication site or body (e.g. small intestine). This medication prevents the breakdown or lessens potential side effects of the drug in body.

2. **Prolonged-release matrix:** This medication are design to release drug slowly after administration and thi9s drug provide a continuous supply of drug over an extend period of time.

3. **Site and receptor targeted release matrix:** This medication refer to targeting of a drug directly to a certain biological action, site or receptor. In case of site specific release ,the

Drug release at the site of action. In case of receptor release the drug release at specificsite receptor.[8]

III. CLASSIFICATION BASED ON MECHANISM

ACTIONVoid fraction

Matrix system can be classified according to their porosity and consequently asfollows.

1. **Macro-porous matrices:** The diffusion of drug take place through the larger pore size of 0.1-1.0micrometer range. The porous of this matrix is larger than diffusant dimension. The drug with <1micrometer molecular mass is appropriate for macro porous matrices.

2. **Micro-porous matrices:** The diffusion of the drug take place through the smaller pores size of 50-200 angstrom molecular mass is appropriate for micro-porous matrices.

3. **Non-porous matrices:** The diffusion of drug take place through the network meshes instead of pores as there are no pores present.[9]

IV. CLASSIFICATION BASED ON POLYMER USED

1. **Hydrophilic matrices**: it is also called as swellable controlled release matrices. This matrix is used for the modified release delivery system manufacturing due to low cost andflexibility. Matrix tablet is homogenous dispersion of hydrophilic polymer and drug act asgelling agent. The release of tablet is maintained by the polymer ability to absorb fluid of form G.I. the polymer expansion and the corrosion of polymer control the release of drug.The release kinetic of drug system is depending on strength, density and chemistry of the polymer. The hydrophilic polymers are divided into different class.

    - **Cellulose derivatives:** it includes hydroxyl ethyl cellulose (HEC), ethyl hydroxylethyl (EHEC), hypromellose (HPMC), methyl cellulose.
    - **Non-cellulose:** Non-cellos natural and semi synthesized polymer, locust bean gum,aligns, treaclmannose, GA lactose.
    - **Carbomers:** carbopol.[10]

2. **Hydrophobic matrices:** Plastic matrices are the second name for hydrophobic matrices. Hydrophobic matrices are formulated by granulating drug with hydrophobic polymer using latex or pseudo latex. Some example of hydrophobic matrices poly-vinal chloride, ethyl and methyl cellulose, latex, carbomers, polystyrene. In nature is non-water soluble itis rate limiting ingredient. Fluid invasion in the matrices is rate limiting step of system during release of drug insoluble component of matrix system retain matrix structure. The release of drug can modified by using suitable excipients e.g. lactose in matrix, insoluble drug are not good candidate for plastic matrices due to low release profile.[11]

3. **Fat wax matrices:** liquid matrix system is second name for fat wax matrices. It is composed of fat wax matrices drug release is uniform throughout-time span. The liberationof API depends on the matrix in forming agent incorporated fluid media that

water would reach out from the whole mass. There are two mechanism in drug release in matrix tablet are as followers porous diffusion and erosion mechanism. The surfactant can influencethe release pattern of matrix tablet.[12]

4. **Biodegradable matrices:** polymer of matrix are consist of single monomer this are bonded to each other by weak bond in the system , this are dissolve and decomposed by enzymatic or non- enzymatic system breaking to monomer and oligomer which may digested and eliminated through body . The polymer of matrix are naturally occurring, synthetic or semi-synthetic made up of ester, amide , ether group. This linked to each other by weak bond this bond can easily break .Example:- poly-lactic acid, poly-caprolacton.[13]

5. **Mineral matrices:** polysialate is another name for mineral polymers. This are used in matrix collected from the mineral origin as well as different seaweed i.e. aligns which is polysaccharide gum. Give viscous solution of hydration.[14]

6. **Miscellaneous ways**
   - Multi layered matrices.
   - PH modulated controlled release system.
   - Floating matrix tablet.
   - Mucoadhesive matrix.

V. CLASSIFICATION ACCORDING TO RELEASE MECHANISM OF MATRIX TABLET

1. **Matrix diffusion system:** The particle of drug in system is dispersed in the polymeric matrix. When the drug particle in outer layer goes in dip medium, the drug release and dissolves by diffusion form of matrix. Diffusion means movement of drug from higher concentration to low concentration this diffusion through inert insoluble membrane which is polymeric and work as barrier. Drug release in diffusion matrix is adjusted by adjusting concentration of API , solubility of API polymer used in matrices.[15]

2. **Matrix dissolution system:** This system is also known as monoliths. in this System drug is uniformly dispersed in rate limiting area, ex i.e. Castor oil etc. dissolution is modified by adjusting porosity and Wettability of matrix. And other ingredient. The rate of drug release identify by determining dissolution of rate of polymers. dissolution is the process by which Solubilisation of Solid Substance take place in given solvent.[16]

VI. FACTOR AFFECTING DRUG RELEASE

RATE.Physicochemical factor.
Biological factor
Release limiting
factor.

1. **Physicochemical Factor**

- **Dose of administration:** Daring for controlled release matrix day with large dose is not suitable. Because mass unit close will be high. Enough to administer. 1gm is considered to be maximum limit.

- **Ionization:** Ionized drug are not good for controlled release tablet: The 'absorption rate is bound to be 3-4 time higher in unionized drug.

- **Aqueous solubility:** Drug having very low solubility. i.e. less than 0.01 mg/ml are 'Sustained. So the solubility of which compound will not be suitable candidate for slightly soluble drug.

- **Stability** oral drug delivery system are suitable both hydrolytic and metabolic degradation. Inconstant drug can be formulated as released in drug in intestine. If extended form is given Then drug exhibit system and release consistency in small intestine such drug can be a modified as gastro retentive dosage.

- **Formulation excipients:** The resistant gel surface minimizes the drug diffusion and infiltration of aqueous medium. This resistance created by hydrophobic diluents. Surfactant increase drug release rate by decreasing surface tension.[17]

2. **Biological of factor**

- **Half-life:** Drug having half-life is less than 2 and greater than 8 is poor candidate for controlled release tablet. The drug with lesser half life required large amount of active ingredient whereas drug with large half- life are already prolonged.

- **Side effects: It** is produce due to oscillation in plasma drug concentration: Matrix tablet decrease fluctuation and release of drug in Controlled manner hence prevent side effect.

- **Metabolism:** Drug which undergoes metabolism before administration slow decrease bioavailability from control release drug. Pro drug is good option for this type of drug. Drug having no intestinal reaction are widely used in control release system. Drug undergoes metabolism give active and inactive metabolite. Control release system also helps to make metabolite in special environment.

- **Distribution:** Drug which having large distribution volume (V_d) can affect the elimination process and not suitable for the control release because itself it sustained.

- **Protein binding:** prolong and extreme plasma protein binding increase the half-life of the drug in the systemic circulation and irregular bioavailability hence drug remain in system for long time.

- **Disease state:** controlled release delivery System help to Cure disease • i.e. in rheumatoid arthritis, aspirin. Controlled release tablet maintains wanted plasma drug level over long time.

- **Therapeutic index:** drug having large therapeutic ratio are used preferable due to large Safety and efficacy margin. The higher value value of Therapeutic ratio will safer drug. The drug having w less therapeutic index by modifying.[18]

3. Release limiting factor

- **Polymer hydration (Swelling process):** The process of dissolution of polymers orthe process of absorption of polymer in water and the dispersion of polymer in dissolution medium. Higher the polymer hydration more will be the release of drug.

- **Polymer composition:** The functional group present in the polymer from a cross-linked in the polymer may cause intermolecular interaction with various species making it non-soluble and stable. This interaction of polymer may affect the pharmacokinetic properties of various drugs.
- **Polymer viscosity:** Higher the viscosity of polymer in matrix will more the density ofgel surface and hence decrease the release of drug from matrix.

- **Drug solubility:** Solubility may directly affect the solubility of drug from the polymeric membrane. Molecular mass and the solubility of drug is main factor that affect the release of drug.

- **Temperature:** The temperature also effect the release of drug from matrix has also been accounted in several researches.

- **Additives:** The addition of excipients to matrix will increase the release rate of watersoluble drug.

- **Density of hydrodynamic diffusion bed:** The deviation in density of diffusion layers on matrix effect the release pattern. Release of drug decrease with increase in thickness of hydrodynamic diffusion layers.

- **Surface area:** The frequency of drug release is base on area and volume of matrix. Greater the surface area greater the contact with liquid medium greater the release of drug .[19]

VII. ADVANTAGE OF ORAL CONTROLLED RELEASE MATRIX TABLET

1. Improve patient compliance

- Oral drug delivery system is more convenient.
- Reduce in frequent dosing.

2. Therapeutically advantages

- Therapeutically level maintained by prolonged time
- Fluctuation in drug level is reduce
- Improve bioavailability
- Constant blood drug concentration and avoid high concentration of drug in blood.

- **Reduction in adverse effect**

- Minimize local and systemic drug side effect and moderate efficiency.
- Reduce drug accumulation with chronic dosing

3. **Cost effective**
   - Manufacturing is easy.
   - Reduce health care cost.

4. **Drug stability enhance by shielding the active ingredient from degradation.[20]**

- Disadvantage of oral controlled release matrix tablet

  - The release of drug can be affect by meal and gastric emptying time.
  - Berating of tablet lose controlled release property.
  - Cost of manufacturing increase due to specialized equipment and expensive excipient.[21]

VIII. MANUFACTURE TECHNIQUE OF MATRIX TABLET

1. **Direct compression** without altering the physicality powder or granules compressed directly to tablet.
2. **Dry granulation** The dry granulation is of two types slugging and roller compaction. In slugging, granule is recompressed and slug is crushed to produce granule and in roller compaction powder is compress with pressure rolls.
3. **Wet granulation** It is the processes in which the dry granule blend in a volatile fluid wet sizing then drying then followed by dry screening.
4. **Steam granulation inserted** of water stem is used as a binder for granulation .steamis uniformly distributed and diffuses into the granule. The granule become rounded shape with more surface area and hence enhances drug dissolution.
5. **Melt granulation Moldable** binder is used for granulation which melts at 50-80^{o}c. Dry granule collected by coaling it to normal temperature.
6. **Freeze granulation It** involve spraying droplet of slurry into liquid nitrogen. Then drops get frozen into granules. Then this frozen granule on drying gives granule.
7. **Foam granulation** Binder are added in aqueous state which binder from a foam which increase surface area of foam and increase the diffusion of the water in powder bed.[22]

IX. EVALUATION OF MATRIX TABLET Pre compression evaluation.

1. **Drug excipient compatibility studies** This is conduct for configuration characterization and drug excipients compatibility. All sample dry in hot air oven at 50^{0}c for time period of 2 hours. Then prepare as kbr disk compressed less than 10to n/nm^{2} pressure. The peak or lack of characteristic peak due to chemical interaction related to drug and polymer.

Fourier transforms infrared spectroscopy. This is Conduct fox Configuration characterization and drug excipient. Compatibility Sample in hot air oven dry at 50°C for time period of 2 hrs then prepare as KBY disk compress under 10 ton/mm² pressure. The peak or lack of characteristic peak due to chemical interaction related to drug polymer.

2. **Differential scanning calorimeter:** It is conduct to study the chemical interaction between active ingredients and excipients. The sample to be studied is taken in perforated DCS aluminum pan and scan in particular temperature range. The temperature rate maintained and nitrogen served as purged gas the temperature is maintain by the liquid nitrogen.

3. **Determination of solubility:** Solubility is determined by adding an amount of compound in excess of its saturation solubility to the solvent. The extra drug agitated in each buffer then centrifuged. The solubility is checked by aliquot of supernatant after 24hrs.

4. **Moisture contains determination:** Moisture contain determine by infra-red drying and karl-fischer titration. Thermo-gravimetric moisture balance determines moisture by extent of weight loss. Which is occurring by heating sample but karl-fischer titration a, reagent is sample and that reacts with water and gives non-conductive chemical.

5. **Angle of repose:** The heap slope chemical by fixed funnel method .The height and diameter of conical pipe is measure and angle of repose is observed.
   $\Theta=\tan^{-1}(h/r)$.
   H= Height of cone. ; r:- radius of conical base.

6. **Porosity:** Amount or volume of void as compared to total amount of porosity. Porosity=void volume/apparent volume.

7. **Density:** The powder is introduced in measuring cylinder and both apparent and tapped density is measured.
   Apparent density=mass/apparent volume of occupied powder.Tapped density=mass/tapped density of powder.

8. **Compressibility (carr's) index and hausher's ratio:** Ratio determined by using following formula.
   Carr's index (%) = (tapped density-apparent density/tapped density) ×100.
   Hauser ratio= tapped density/ apparent density.

9. **Post compression evaluation:** post compression evaluation uniformity include of weight, rigidness, consistency, diameter, fragility disintegrate, Swelling active drug uniformity, and in-vitro dissolution testing.

10. **weight uniformity:** 20 tablet are weighing Separately using analytical balance. "The weight variation should be within the limit.

11. **Dimension [Hardness and thickness]:** Hardness and thickness are main find uniformity of tablet size. Hardness, thickness and diameter are determined by hardness tester.

12. **Friability:** 10 tablets are weighted in kept in the friabilator than rotate for four minutes at 250rmp. The tablet then deducted and reweighted it should be between 0.5% to 0.1% formula to measure per cent friability is:- H= Height of cone. ; r:- radius of conical base.

$((W_1-W_2)\times100)/W_1$.

13. **Swelling studies:** Swelling index is measure by pleasing tablet in water filled beaker. Each tablet in weighted after different time interval. $\%S=W_t-W_o/W_o$.. W_t= weight after putting; W_o= weight before putting

14. **Disintegration test:** In this the 6 tablet placed in disintegration taste which contain fluid filled beaker. The temperature adjusted to body temperature.

15. **Dissolution:** At the maintained body temperature dissolution test is carried out by specified dissolution USP method. Specified USP pharmacopeia condition. The Sample is taken at different interval of time by using syringes filter and assay by HPLC.

16. Analysis of dissolution data: Active content in dissolution sample is obtained by drug release profile equation. Release pattern of drug asses in model dependent and independent method.

17. Stability studies: The matrix tablet will be subjected to accelerate stability condition differential scanning calorimeter (DSC) thermo gram after 6 month accelerated stability condition in order to confirm product stability.

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