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A REVIEW ARTICLE ON MATRIX RELEASE TABLETS

Hina Tousif S.*, Farida Banu S., Karishma S., Shaziya Tanzeem T., Shaguftha T., Jagan V. and Banny S.V.

India.

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***Corresponding Author**
Hina Tousif S.
India.

INTRODUCTION

The progress of the market might induce the development of new formulations and controlled release systems. In the past decades huge efforts were focused on making controlled release systems. These platforms are able to regulate drug dissolution from the formulation in a controlled manner. Regulating and extending drug release is advantageous from many aspects. Reduced fluctuations of the blood concentration of the active ingredient might result decreased occurrence and severity of adverse effects.[1] Prolonging of the plasma concentration of drugs with short half-life also means reduced administration frequency[2],[3] and improved patient compliance.[53] Benefits mentioned above are particularly important not only for patients themselves[4],[5] but for clinicians and pharmaceutical technologists also.[2]

The word matrix originates from the Latin, where the original meaning was dam or womb.[7] Later in different scientific fields it had other meaning with one common, something which embeds various and distinct structures or materials.[8] In pharmacy, the matrix is the carrier or vehicle in which the active pharmaceutical ingredient (API) is homogenously distributed or dispersed. The earliest publication with the title containing tablet matrix is from 1958.[9]

The rate of dissolution is controlled by either of following mechanisms:

* Altering the rate of fluid penetration into tablet by altering the porosity of tablet.
* Decreasing the wettability of tablet.
* Slow dissolution rate of polymer[10,11] (Figure 5).

Matrix Drug Delivery System

These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control

the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.[12] Introduction of matrix tablet as sustained release (SR) has given a new innovation for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.[13]

Matrix systems are broadly used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.[14] Initially, drug particles located at the surface of the release unit will be dissolved and the drug released rapidly. Thereafter, drug particles at sequentially increasing distances from the surface of the release unit will be dissolved and released by diffusion in the pores to the exterior of the release unit. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer. The drug is dispersed in the polymer matrix either by blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross-linking of the polymer chain, mixing drug and polymer at an elevated temperature. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation at an elevated temperature and/or under a vacuum.[15]

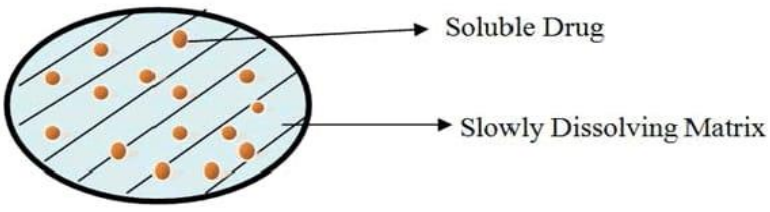

Figure 5. Diagrammatic representation of matrix dissolution sustained system

In this sense, the term “matrix” indicates the three dimensional network containing the drug and other substances such as solvents and excipients required for the specific preparation.[16]

A matrix system consists of active and inactive ingredients that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral extended release technology and the popularity of the matrix systems can be attributed to several factors. The release from matrix type formulations is governed by Fick’s first law of diffusion. In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a hydrophobic polymer (such as wax, polyethylene, polypropylene, and ethyl cellulose) or hydrophilic polymer (such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose, methylcellulose, sodium carboxy methylcellulose, alginates and scleroglucan). In this sense, the term “matrix” indicates the three dimensional network containing the drug and other substances such as solvents and excipients required for the specific preparation. Matrix drug delivery systems release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. Initially, drug particles located at the surface of the release unit will be dissolved and the drug released rapidly. Thereafter, drug particles at successively increasing distances from the surface of the release unit will be dissolved and released by diffusion in the pores to the exterior of the release unit. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer. The drug is dispersed in the polymer matrix either by

1) blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross-linking of the polymer chain.
2) mixing drug and polymer at an elevated temperature. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation at an elevated temperature and/or under a vacuum.

The rate of drug release from this polymer matrix diffusion – controlled drug delivery system is time dependent and is and is defined at steady state by

$Q/t1/2 = (2ACRDp)1/2$

Where,

A is the initial loading drug dose in the polymer matrix;

CR is the drug reservoir concentration in the system;

Dp is the diffusivity of the drug molecules in the polymer matrix.

Drug release is controlled by controlling the loading dose, polymer solubility of drug and its diffusivity in the polymer matrix and the porosity of the release unit.[17]

Matrix Type

Matrix Type A solid drug is dispersed in an insoluble matrix (Figure 6) and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. Higuchi has derived the appropriate equation for drug release for this system:

$Q = D\varepsilon / T [2 A - \varepsilon Cs] Cst^{1/2}$

Where; Q = Weight in gms of drug released per unit area of surface at time t.

D = Diffusion coefficient of drug in the release medium.

ε = Porosity of the matrix.

Cs = Solubility of drug in release medium.

T= Tortuosity of the matrix.

A = Concentration of drug in the tablet, as gm/ml

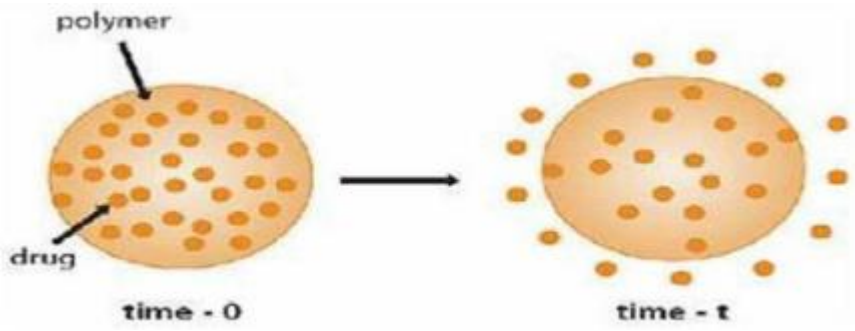

Figure 6 schematic diagram.

The more common type of dissolution sustained dosage form (as shown in figure 6). It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion. Two types of dissolution sustained pulsed delivery systems.

- Single bead type device with alternating drug and rate-controlling layer.
- Beads containing drug with differing thickness of dissolving coats. Amongst sustained release formulations, hydrophilic matrix technology is the most widely used drug delivery system due to following advantages:
- Provide desired release profiles for a wide therapeutic drug category, dose and solubility.

- Simple and cost effective manufacturing using existing tableting unit operation equipment.
- Robust formulation.
- Broad regulatory and patient acceptance.
- Ease of drug release modulation through level and choice of polymeric systems and function coatings[18-22]

Principle of Sustained Release Drug Delivery The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.

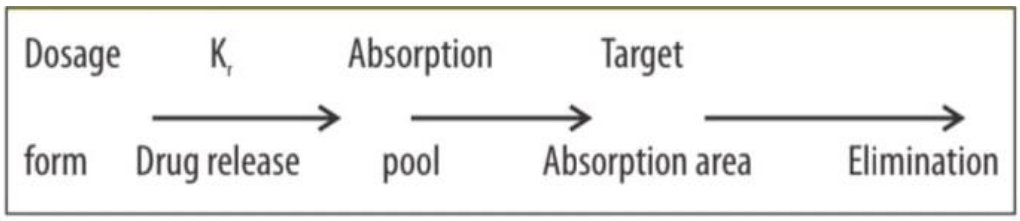

Figure 7. schematic representation of the kinetics of sustained release DDS.

The absorption pool represents a solution of the drug at the site of absorption, K_r, K_a and K_e - first order rate constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that K_r >>>>K_a. For non-immediate release dosage forms, K_r << K_a i.e. the release of drug from the dosage form is the rate limiting step. The drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

Kr°= Rate In = Rate Out = KeCd Vd

Where,

Kr°: Zero-order rate constant for drug release- Amount/time,

K_e : First-order rate constant for overall e drug elimination-time,

C_d : Desired drug level in the body – Amount/volume,

Vd : Volume space in d 4 which the drug is distributed in litre.[23]

Swelling behavior of matrix tablets: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. One tablet from each formulation was kept in a petridish containing pH 7.4 phosphate buffer. At the end of 1h, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 2 h,

weights of the tablet were noted, and the process was continued till the end of 8 h. % weight gain by the tablet was

calculated by formula;

S.I = {(Mt-Mo) / Mo} X 100,

Where, S.I = swelling index,

Mt = weight of tablet at time (insec) Mo

= weight of tablet at time t = 0[24,25]

Rationale of developing sustained release matrix devices

- To extend the duration of action of the drug.
- To reduce the frequency of dosing.
- To reduce inter and intrasubject variability.
- To minimize the fluctuations in plasma level.
- To improve drug utilization.
- To reduce adverse effects.[26,27]

Advantages of Matrix Tablet

- ✓ Easy to manufacture
- ✓ Usage of less total drug.
- ✓ Reduce the local and systemic side effects.
- ✓ Flexible, effective and low cost
- ✓ Reduce the toxicity by slowing drug absorption.
- ✓ Progress in treatment efficacy.
- ✓ Decrease drug accumulation with chronic dosing.
- ✓ The use of sustain release formulations avoids the high blood concentration.
- ✓ Development of the ability to provide special effects.
- ✓ Can be made to release high molecular weight compounds
- ✓ The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- ✓ Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- ✓ Sustain release formulations have the potential toimprove the patient compliance.
- ✓ Enhancement the bioavailability of some drugs.[28]

Disadvantages of Matrix Tablet

- Not all drugs can be blended with a given polymeric matrix.
- The remaining matrix must be removed after the drug has been released.
- Attainment of zero order release is difficult.
- The drug release rates vary with the square root of time

Classification of Matrix Tablet

❖ **Lipid matrix system**

These matrices prepared by the lipid waxes and related materials. In this system the active compound is contained in a hydrophobic matrix that rests intact during drug release. Release depends on an aqueous medium dissolving the channeling agent, which leaks out of the compact, so forming a porous matrix of tortuous capillaries. The active agent dissolve in the aqueous medium and, by way of the water filled capillaries, diffuses out of the matrix.

❖ **Mineral Matrices**

These contain of polymers which are found from various species of seaweeds. Example is Alginic acid which is ahydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

❖ **Hydrophilic Matrices**

These transfer systems are also called swell able – soluble matrices. The systems are capable of swelling, followed by gel formation, erosion and dissolution in aqueous media. The hydrophilic colloid components swell to form a hydrated matrix layer when contact with water. This controls the additional diffusion of water into the matrix. Diffusion of the drug through the hydrated matrix layer controls its rate of release. The outer hydrated matrix Layer will erode as it convert more dilute. The rate of erosion depends on the nature of colloid[29]

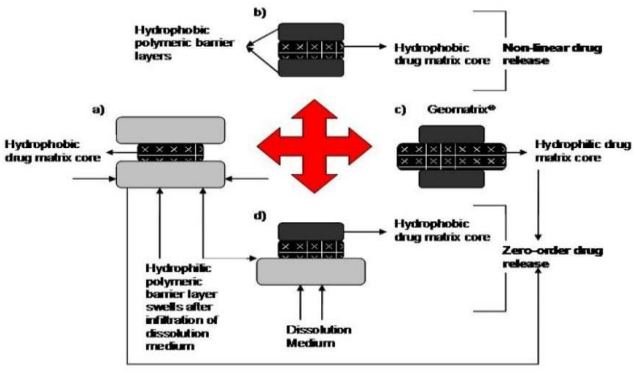

Figure 8: Possible drug release mechanism from various matrix systems.[30]

❖ **Insoluble polymer matrix systems**

In this system drug is surrounded in an inert polymer which is not soluble in the gastrointestinal fluids. The release rate hang on on drug molecules in aqueous solution diffusing through a network of capillaries formed between compacted polymer particles. The release rate of a drug from an inert matrix can be changed by changes in the porosity and tortuosity of the matrix. The pore forming hydrophilic salts or solutes will have a major influence on drug release.[29]

❖ **Biodegradable Matrices**

These systems are involved of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or by non-enzymatic process in to oligomers and monomers that can be metabolized or excreted.[31]

❖ **Sustained Release Matrix Tablet**

The aim of any drug delivery system is to offer a therapeutic amount of drug to the appropriate site in the body to reach punctually and then maintain the wanted drug concentration i.e. the drug-delivery system should deliver drug at a rate spoken by the needs of the body over a specified period of treatment. The two most important aspects of drug-delivery are spatial placement and time-based delivery of a drug. Spatial placement relates to the targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An suitably designed controlled-release drug-delivery system can be a major advance near solving these two problems.[32]

On the Basis of Porosity of Matrix

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

Macro porous Systems

In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 μm. This pore size is larger than diffusant molecule size.

Micro porous System

Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 A°, which is slightly larger than diffusant molecules size.

Non-porous System

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present[33-36]

Polymers Used In Matrix Tablet

Table:1 Polymers Used In Matrix Tablet.

S.NO	TYPE	EXAMPLES
1	**HYDROGELS**	Cross-linked Polyvinyl Pyrrolidone (PVP) Polyethylene oxide (PEO), Polyacrylamide (PA) Cross-linked Polyvinyl Alcohol (PVA) Poly Hydroxy Ethyle Methylacrylate (PHEMA)
2	**Soluble polymer**	Hydroxypropyl methyl cellulose (HPMC) Polyvinyl Pyrrolidone (PVP) Polyvinyl Alcohol (PVA) Polyethylene Glycol (PEG)
3	**Biodegradable polymer**	Polycaprolactone (PCL) Polyglycolic acid (PGA) Polyanhydrides Polylactic acid (PLA) Polyorthoesters.[37]
4	**Non-biodegradable polymer**	Ethyl cellulose (EC) Cellulose acetate (CA) Polyvinyl chloride (PVC) Polyether urethane (PEU) Polyethylene vinyl acetate (PVA) Polydimethylsiloxane (PDS)
5	**Mucoadhesive polymer**	Tragacanth Polyacrylic acid Sodium carboxymethyl cellulose Polycarbophil Methyl cellulose, Pectin.[38]
6	**Natural gum**	Xanthan gum Locust bean gum.[39]

Components of Matrix Tablet

These include Active drug Release controlling agent(s): matrix formers Matrix Modifiers, such as channeling agents and wicking agents Solubilizers and pH modifiers Lubricants and flow aid Supplementary coatings to extend lag time further reduce drug release etc.

Matrix formers

- **Channelling agents**
- **Solubilizers and pH modifiers**
- **Anti adherent or Guidant's**[40]

Methods of Preparation of Matrix Tablet

1. **Dry Granulation Technique**

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

2. **Melt granulation Technique**

- Wax is melted in porcelain dish on a water bath maintained at constant temperature.
- The Drug was gradually added to the molten wax with continuous stirring.
- The molten mixture was allowed to cool and solidified at room temperature.
- The solidified mass was pulverized in mortar and sieved through a screen.
- The granules passed through sieve were mixed with Glidant and compressed into a tablet with 10 mm deep concave punch using single punch tablet machine.

3. **Wet Granulation Technique**

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

4. **Sintering Technique**

- Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat.

- Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure.
- The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering.
- The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.[41]

Matrix are defined as a drug or other active formulations ingredient embedded in insoluble excipients in order to achieve release by a continuous leaching of the drug from the inert matrix core.

Matrix systems can be divided into three types:

1. Monolithic matrix tablets
2. Gel forming hydrophilic matrix tablet[42,43,44]
3. Erodible (hydrophobic) matrix tablets.[45]

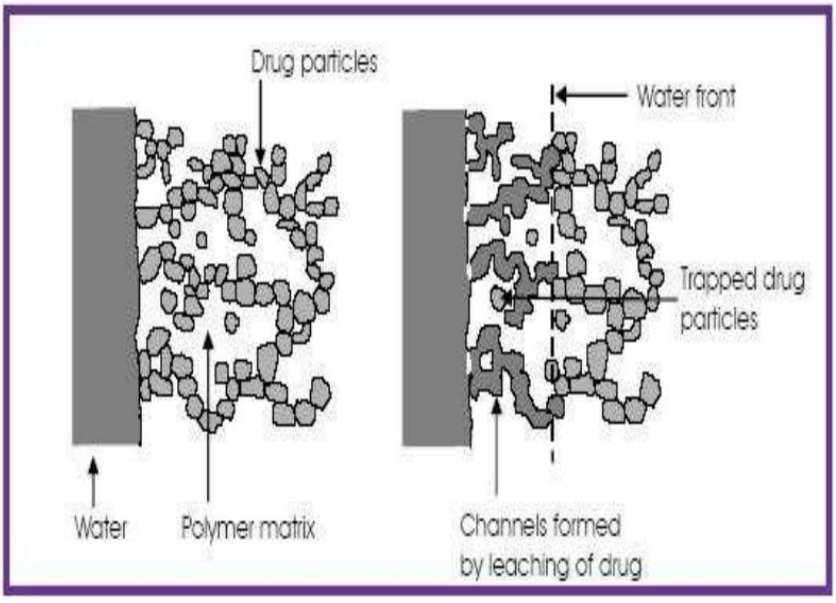

Figure 9: Schematically presentation of a leaching-based release mechanism oxide) (PEO), poly (vinyl alcohol), ethylene vinyl alcoholcopolymers (EVA) and dextrans.

Drugs suitable to be formulated as matrix tablets

Drugs with a low half-life (<5 h.), freely soluble in water and larger therapeutic window can be formulated as sustained release matrix systems. The drugs with suitable polymer and combination of polymers to prepare matrix are enlisted in table 1.

Table 2: Combination of few drugs and polymers formulated into matrix tablets.[46]

Drug	Polymers	Drug	Polymers
Zidovudine	HPMC-K4M, Carbopol-934, EC	Furosemide	Guar gum, Pectin, Xanthan gum
Venlafexine	Beeswax, Caranuaba wax	Acarbose	HPMC, Eudragit
Domperidone	HPMC-K4M, Carbopol-934	Aceclofenac	HPMC-K4M,K15M, K100M,E15,EC, Guar gum
Alfuzosin	HPMC-K15M, Eudragit-RSPO	Ambroxol HCL	HPMC-K100M,
Minocycline	HPMC-K4M, HPMC-K15M, EC	Aspirin	EC, Eudragit-RS100, S100
Ibuprofen	EC, CAP	Diclofenac Na	Chitoson, EC, HPMCP, HPMC
Metformin HCL	HPMC-K100M, EC	Diethylcarbamazine citrate	Guar gum, HPMC-E15LV
Propranolol HCL	Locust bean gum, HPMC	Diltiazem	HPMC-K100M, HPMC-K4M, Karaya gum, Locust bean gum, Sod. CMC
Enalpril meleate	HPMC-K100M,HPMC K4M,	Miconazole	Pectin, HPMC
Flutamide	HPMC-K4M, Sod. CMC, Guar gum, Xanthan gum	Naproxen	HPMC-K100M, HPMC-K15M, PVP
Indomethacin	EC, HPMC	Nicorandil	HPMC, CMC, EC
Chlorpheniramine meleate	Xanthan gum, Chitoson	Ondansertan	HPMC-K100M, HPMC-K4M, HPMC-K15M
Itopride HCL	HPMC-K100M, HPMC-K4M, EC	Phenytoin Na	Tragacanth, Acacia, Guar gum, Xanthan gum
Losartan potassium	HPMC-K100M, HPMC-K4M, Eudragit-RSPO	Ranitidine HCL	Chitoson, Carbopol-940
Metoclopromide	HPMC, CMC, EC, SSG	Theophylline	Carbopol-934P, HPMC-K100M, HPMC-K4M, HPMC-K15M, EC
Tramadol	HPMC-K4M, Karaya gum,	Amlodipine	HPMC, EC

Evaluation of matrix tablets

The tablets were evaluated for their physical properties like weight variation, hardness, and friability.

1. Weight variation

20 tablets of each formulation were weighed using an electronic weighing balance. The average weight was calculated and individual tablet weight was compared with average weight.[47]

2. Hardness and friability

The hardness of three tablets was measured by Monsanto hardness tester. Hardness of tablets was measured in terms of kg/cm 2 Friability of tablets was measured by using Roche friabilator. Ten tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were dedusted and reweighed and friability was calculated using the following equation.[48]

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

3. Uniformity of drug content

10 Tablets were weighed from each formulation and triturated in the mortar to a fine powder. Powder equivalent to 30 mg of metoclopramide was extracted in 100 ml of pH 6.8 phosphate buffer and the liquid was filtered. The drug content was determined by measuring the

absorbance at 272 nm (using UV-Visible spectrophotometer, Lab India) after appropriate dilution with pH 6.8 phosphate buffer. The drug content was determined by calibration curve.

4. In vitro dissolution study

The in vitro dissolution study of matrix tablets of metoclopramide was performed using USP type II (paddle) dissolution apparatus (DBK) at a rotational speed of 50 rpm. In order to simulate gastrointestinal transit conditions, the tablets were subjected to different dissolution media. The dissolution medium consists of 900 ml of pH 1.2 buffer for the first two hours and pH 6.8 phosphate buffer for the next ten hours. The dissolution medium was maintained at a temperature of 37±0.5 ° C. At predetermined time intervals, 5 ml sample of the solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. The collected samples were filtered through a 0.45 µm membrane filter and diluted to a suitable concentration with pH 6.8 phosphate buffer. An absorbance of these solutions was measured at 272 nm. Cumulative percentage of drug release was calculated using equation obtained from a calibration curve.[49]

Applications Sustained Release Matrix Tablets

The Significant role of novel drug delivery system that improve the therapeutic effectiveness of combined drugs by providing sustained, controlled delivery and or targeting the drug to desired site. The design of oral sustained release delivery systems is exposed to several consistent variables of significant importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. Sustain release system contains any drug delivery systems that reaches slow release of drug over prolong period of time. Matrix tablets are careful to be the commercially possible sustained action dosage forms that involve the least processing variables, develop the straight facilities and quarter large doses of drug. There rests an interest in developing novel formulations that allow for sustained the drug release using readily available, cheap excipient by matrix based formulation. During the last two periods there has been notable increase in interest in sustained release drug delivery system. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and the upgrading in therapeutic efficiency and safety achieved by these delivery systems. Now a day the technology of sustained release is also being applied to veterinary products also.[50]

- Sustained release matrix tablets can be used to deliver analgesics, such as opioids.

- Sustained release tablets can provide a controlled and consistent hormone delivery, reducing menopausal symptoms and improving patient compliance.
- Some antibiotics, can be formulated as sustained release tablets to maintain therapeutic concentrations over a more extended period.
- Medications for heart conditions like hypertension, angina, and arrhythmias often benefit from sustained release formulations.
- Sustained release matrix tablets can be used for medications that slow the progression of neurodegenerative diseases like Alzheimer's.

Antihistamines used in the management of allergic conditions like asthma and allergies can be delivered through sustained release matrix tablets to provide symptom relief over an extended period.[51-54]

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