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Matrix tablet: A Promising Technique for Controlled Drug Delivery

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ABSTRACT

From the last decade great interest generated on replacing conventional administration of drug by delivery system which would release effective quantities from a protected supply at a controlled rate over a long period of time. An appropriately designated controlled release drug delivery system is the major advance toward solving problems concerning targeting of a drug to a specific organ or a tissue and controlling the rate of a drug delivery to the target site. Matrix system are favoured because of their simplicity, patient compliance etc, than traditional drug delivery(TDS) which have many drawbacks like repeated administration, fluctuation in blood concentration level etc. Developing oral sustained release matrix tablet with constant release rate has always been a challenge to the pharmaceutical technologist. Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. So that selecting appropriate polymers have become product of choice as an important ingredient for formulating sustained release formulations.

Keywords: Sustained release, Conventional tablet, Controlled release system, Matrix tablet.

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INTRODUCTION

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.[1]

Oral drug delivery is the most widely utilized route of administration among all the routes [nasal, ophthalmic, rectal, transdermal and Parentral routes] that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe [in respect to Parentral route] due to its ease of administration, patient acceptance, and cost-effective manufacturing process.[2]

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration.[3,4]

Objective of the work is to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate sustain release system in order to achieve even plasma concentration profile up to 24 hrs.[5]

Drawback of Conventional Dosage Form:[6]

- 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 (TI) whenever over medication occur.

CONTROLLED DRUG DELIVERY SYSTEMS

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to tissue. Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.[1]

1) Delayed release

2) Sustained release

3) Site-specific targeting

4) Receptor targeting

More precisely, controlled delivery can be defined as :[1,5]

Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

MATRIX TABLETS

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 ethylcellulose) or hydrophilic polymer (such as hydroxyl propyl cellulose, hydroxyl propyl methyl cellulose, methylcellulose, sodium carboxymethylcellulose, 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.[7]

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.[8]

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,[9] (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.[10]

Advantages of Matrix Tablet:

- Improvement of the ability to provide special effects. [3]
- Easy to manufacture
- Versatile, effective and low cost
- Can be made to release high molecular weight compounds [11]

- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption. [12]
- Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy. [13]
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improvement the bioavailability of some drugs.

Disadvantages of Matrix Tablet:[11-13]

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

CLASSIFICATION OF MATRIX TABLET:

Lipid matrix system:[14,15]

These matrices prepared by the lipid waxes and related materials. In this system the active compound is contained in a hydrophobic matrix that remains intact during drug release. Release depends on an aqueous medium dissolving the channeling agent, which leaches 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.

Insoluble polymer matrix systems:[16]

In this system drug is embedded in an inert polymer which is not soluble in the gastrointestinal fluids. The release rate depends 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 modified 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.

Hydrophilic Matrices:[14,15]

These delivery systems are also called swellable – soluble matrices. The system 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 the controls the further 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 become more dilute. The rate of erosion depends on the nature of colloid.

Biodegradable Matrices:[16]

These system are comprised 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 enzymetic process in to olegomers and monomers that can be metabolized or excreted.

Mineral Matrices:[17]

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaephyceae) by the use of dilute alkali.

Polymers Used In Matrix Tablet:

Schematic representation of various polymers used in matrix tablet are given in figure 1,2 and 3.

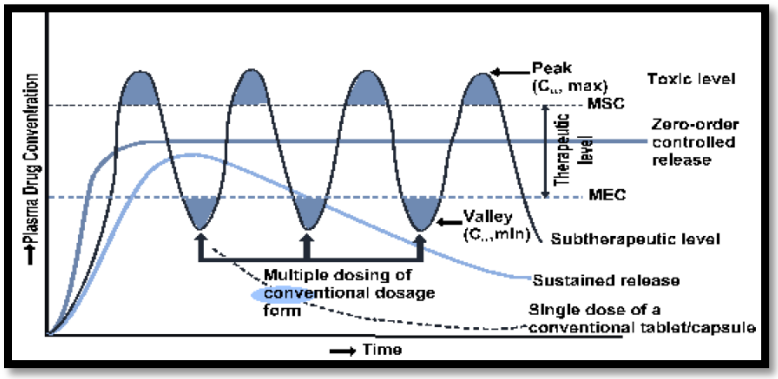

Figure 1: A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

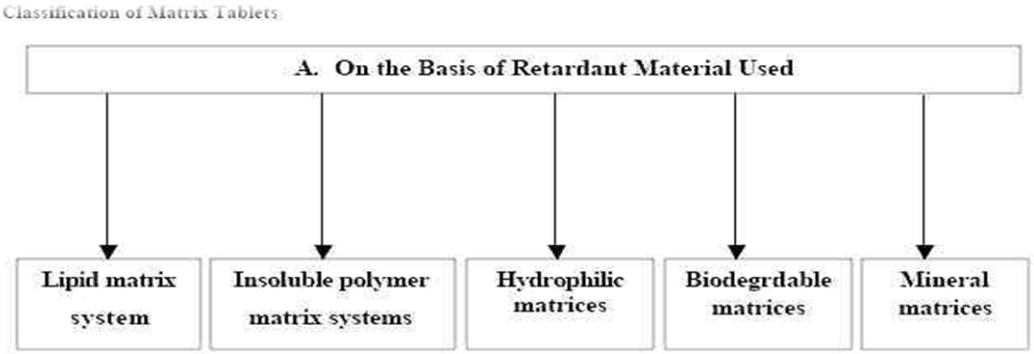

Figure 2: Classification of Matrix Tablet on the basis of Retardant Material Used

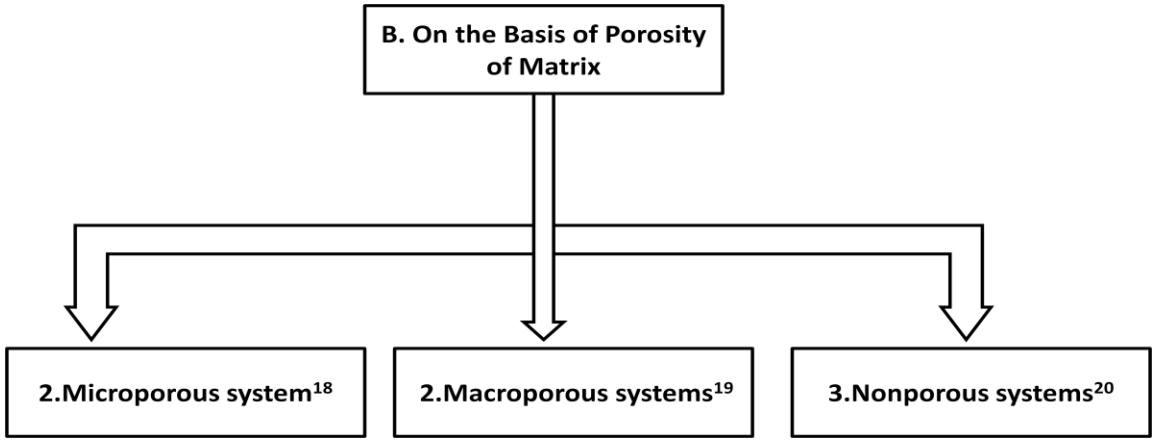

Figure 3: Classification of Matrix Tablet on the basis of Porosity of Matrix

Hydrogels :[20]

Polyhydroxyethylemethylacrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO), Polyacrylamide (PA).

Soluble polymer :[20]

Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC).

Biodegradable polymer :[21]

Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.

Non-biodegradable polymer :[20]

Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

Mucoadhesive polymer :[22]

Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin.

Natural gum :[22]

Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

Components of Matrix Tablet:[23]

These include:

- Active drug
- Release controlling agent(s): matrix formers
- Matrix Modifiers, such as channelling 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:

Hydrophobic materials that are solid at room temperature and do not melt at body temperature are used as matrix formers. These include hydrogenated vegetable oils, cotton seed oil, soya oil, microcrystalline wax and carnauba wax. In general such waxes form 20-40% of the formulation.

Channelling agents:

These are chosen to be soluble in gastrointestinal tract and to leach from the formulation, so leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released. The drug itself can be a channelling agent but a water soluble pharmaceutical acceptable solid material is more likely to be used. Typical examples include sodium chloride, sugars and polyols. This choice will depend on the drug and desired released characteristics. These agents can be 20-30% of the formulation.

Solubilizers and pH modifiers:

It is often necessary to enhance the dissolution of drug. This may be achieved by the inclusion of solubilizing agents such as PEGs, polyols and surfactants. If the drug is ionisable then the inclusion of buffers or counter ions may be appropriate. On occasions the dissolution enhancer may also be the channelling agent.

Anti adherent or glidants:

Heat is generated during compaction of the matrix can cause melting of the wax matrix forming compounds and sticking to the punches. Something is needed to cope with the sticking; suitable anti adherents include talc and colloidal silicon dioxide. These materials also can act as glidants and improve the flow of formulations on the tablet machine. The typical amounts used will depend on the anti adherent used, for example 0.5-1% for colloidal silicon dioxide and 4-6% for talc. Magnesium stearate, if added, can also act as an anti adherent.

Method of Preparation of Matrix Tablet:

Wet Granulation Technique:[13]

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.

Dry Granulation Technique: [13]

· 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.

Melt granulation Technique: [9]

- 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.

SinteringTechnique:[21]

- 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.

Mechanism of Drug Release From Matrix Tablet:

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. [23]

Derivation of the mathematical model to describe this system involves the following assumptions:[24]

a) A pseudo-steady state is maintained during drug release,

b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix,

c) The bathing solution provides sink conditions at all times.

The release behaviour for the system can be mathematically described by the following equation:

dM/dh = Co. dh - Cs/2 …… (1)

Where,

dM = Change in the amount of drug released per unit area

dh = Change in the thickness of the zone of matrix that has been depleted of drug

Co = Total amount of drug in a unit volume of matrix

Cs = Saturated concentration of the drug within the matrix. Additionally, according to diffusion theory:

dM = (Dm. Cs / h) dt..... (2)

Where,

Dm = Diffusion coefficient in the matrix.

h = Thickness of the drug-depleted matrix

dt = Change in time

By combining equation 1 and equation 2 and integrating:

M = [Cs. Dm (2Co −Cs) t] ½ …… (3)

When the amount of drug is in excess of the saturation concentration then:

M = [2Cs.Dm.Co.t] 1/2 …… (4)

Equation 3 and equation 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores.

The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

M = [Ds. Ca. p/T. (2Co – p.Ca) t] 1/2 ……. (5)

Where,

p = Porosity of the matrix

t = Tortuosity

Ca = solubility of the drug in the release medium

Ds = Diffusion coefficient in the release medium.

T = Diffusional path length

For pseudo steady state, the equation can be written as:

$M = [2D.Ca .Co (p/T) t] ½$ …….. (6)

The total porosity of the matrix can be calculated with the following equation:

$p = pa + Ca/ \rho + Cex / \rho ex$ …… (7)

Where,

p = Porosity

ρ = Drug density

pa = Porosity due to air pockets in the matrix

ρex = Density of the water soluble excipients

Cex = Concentration of water soluble excipients

For the purpose of data treatment, equation 7 can be reduced to:

$$M = k. t 1/2 \text{ …….. (8)}$$

Where,

k is a constant,

The amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters: [25,26]

• Initial concentration of drug in the matrix

• Porosity

• Tortuosity

• Polymer system forming the matrix

• Solubility of the drug.

Factors Influencing Release From Matrix Tablet:

Effect of Release Limiting Factors on Drug Release:[27,28]

A. Polymer hydration

B. Drug solubility

C. Solution solubility

D. Polymer diffusivity

E. Thickness of polymer diffusional path

F. Thickness of hydrodynamic diffusion layer

G. Drug loading dose

H. Surface area and volume

I. Diluents effect

J. Additives

Biological Factors Influencing Drug Release From Matrix Tablet:[29,30]

A. Biological half-life

B. Absorption

C .Metabolism

D. Distribution

E. Protein binding

F. Margin of safety

Physicochemical Factors Influencing Drug Release From Matrix Tablet:[31,32]

A. Dose size

B. Ionization, *pka* and aqueous solubility

C. Partition Coefficient

D. Stability

PRECOMPRESSION CHARACTERIZATION:

A. Bulk Density[33]

Bulk density of a powder is defined as the ratio of the mass of the powder and its bulk volume. For bulk density determination a weigh quantity of the powder material is introduce into a graduated measuring cylinder and volume of powder is determine.

Bulk Density = Mass of the powder/ Bulk volume

B. Granule Density[33]

Granule density is the ratio of the mass of the granular powder and the volume occupied by the granular material together with its intraparticle spaces.

Granule density = Mass of the granular powder/ Granule volume

C. Tapped Density[34]

For determination of the bulk density, a weigh quantity of the granular powder is introduced into a graduated measuring cylinder and is tapped mechanically either manually or using a tapping device till a constant volume is obtain.

Tapped density = Mass of the granular powder/ Tapped volume of granules

D. Compressibility Index[35]

C= 100(1 - ?B / ?T)

Where B is the freely settled bulk density of the granules,

and T is the tapped bulk density of the granules.

A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

E. Angle of Repose[35]

The angle of repose is determine by allowing a mss of powdered to flow freely through an orifice from a certain height and form a conical heap on the horizontal surface. The angle of repose is determined by the formula:

tanq = h/r

q = tan-^{1}h/r

where,

q is the angle of repose,

h si the height of the heap of powder and

r is the radius of the base of the heap of powder.

POST COMPRESSION CHARACTERIZATION:

A. Weight Variation Test:[13]

With a tablet designed to contain a specific amount of drug in specific amount of tablet formulation. The weight of tablet is measured to ensure that a tablet contain the proper amount of drug.

1. The weight variation test is run by weighing 20 tablets individually.
2. Calculate the average weigt.
3. Comparing the individual tablet weights to the average weight
4. The tablets pass the test if not more than 2 tablets go outside the percentage limit.

Average weight of tablet (mg)	Maximum % difference allowed
130 or less	10%
130 – 324	7.5%
More than 324	5%

B. Friability Test:[13]

This test evaluates ability of tablet to with abrasion and edge damage during packing, handling and shipping. Friability is measured by the help of Roche friabilitor . A number of pre weigh tablet is placed in plastic chamber that revolves at 25rpm for 100 revolutions.

The tablet are then de-dusted and reweighed. The friability is calculated by the formula

F =(1- w/w*)100

Where – W* is the original wt. of tablet

W is the final wt. of tablet after test.

Acceptance limit of friability is - 0.5 – 1%.

C. Hardness Test:[13]

Tablet require a certain amount of hardness to with stand mechanical shock of handling in manufacture , packaging , and shipping. Hardness is thus some time termed as tablet crushing strength.

Hardness is measured with the help of hardness tester like:

a) Monsanto tester

b) Pfizer tester

c) Strong cob tester

Hardness is measured with the help of Monsanto tester. The tester consist of a barrel containing a compressed spring held between two plungers. The lower plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is record and the zero force reading is deducted from it.

Hardness is measured in kg/ semi sq.

D. In- Vitro Drug Release profile:[13,36]

In vitro drug release profile of matrix tablet is determine with the help of USP dissolution apparatus type 2. In general , a single matrix tablet is placed in dissolution flask which contain 900 ml dissolution medium. The flask is maintained at 37º ± 0.5º C by a constant temperature bath. The motor is adjusted to turn at the specified speed (50 rpm), and sample of the fluid are withdrawn at intervals to determine the amount of drug in the solution. Matrix tablet slowly release the drug for a prolong period of time as compare to conventional tablet.

Table 1:Some Reported Examples Of Matrix Tablets:[37-45]

Drugs used	Category	Method used	Polymer used
Zidovudine[37]	Anti-viral	Direct Compression	HPMC-K4M, Carbopol-934, EC
Tramadol[38]	B2 bloker	Wet Granulation	HPMC,K4M,K15M,K100M,E15
Domperidone	Anti-emetic	Wet Granulation	HPMC-K4M, Carbopol-934
Ondansertan[40]	Anti-hypertensive	Direct Compression	HPMC-K100M, HPMC-K15M, EC, HPMC-K4M
Minocycline	Antibiotic	Wet Granulation	HPMC-K15M, EC, HPMC-K4M,EC
Ibuprofen[44]	Anti-inflammatory	Wet Granulation	EC, CAP
Metformin HCL[41]	Anti-diabetic	Direct Compression	HPMC-K100M, EC
Propranolol HCL[45]	Beta-adrenergic blocker	Wet Granulation	Locust bean gum, HPMC

Furosemide	Anti-diuretic	Direct Compression	Guar gum, Pectin, Xanthan gum
Aceclofenac	Anti-inflammatory	Wet Granulation	HPMC-K4M,K15M, K100M,E15,EC, Guar gum
Aspirin	Anti-inflammatory	Direct Compression	EC, Eudragit-RS100, S100
Diclofenac Na[39]	Anti-inflammatory	Wet Granulation	Chitoson, EC, HPMCP, HPMC
Diltiazem HCL[42]	Ca^{+2} channel blocker	Direct Compression	HPMC-K100M, HPMC-K4M, Karaya gum,Locust bean gum,Sod.CMC
Naproxen[43]	Morphine antagonist	Direct Compression	HPMC-K100M, HPMC-K15M
Flutamide	Anti-androgen	Direct Compression	HPMC-K4M, Sod.CMC, Guar gum, Xanthan gum
Chlorphenarimine meleate	H1 antagonist	Melt-extrusion	Xanthan gum,Chitoson
Itopride HCL	Prokinetic agent	Direct Compression	HPMC-K100M, HPMC-K4M, EC
Losartan potassium	Anti-hypertensive	Direct Compression	HPMC-K100M, HPMC-K4M, Eudragit RSPO
Metoclopromide	Anti-emetic	Direct Compression	HPMC, CMC, EC, SSG
Miconazole	Anti-fungal	Wet Granulation	Pectin, HPMC

CONCLUSION

By the above discussion, it can be easily concluded that sustained-release formulation are helpful in increasing the efficiency of the dose as well as they are also improving the patient's compatibility. More over all these comes with reasonable cost. The dosage form is easy to optimize and very helpful in case of the antibiotics in which irrational use of the same may result in resistance.[46] The suitability of matrix forming polymers, to various drug delivery systems preparation confirms the importance of these specialized excipients in pharmaceutical application. They represent the choice solution for many oral delivery problems like fluctuating drug plasma levels, low bioavailability, more frequent dose administration etc. So matrix tablets can overcome the above problems of conventional oral drug delivery.[47]

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