A REVIEW OF ORAL MATRIX TYPE CONTROLLED DRUG DELIVERY SYSTEM

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Abstract:

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Polymers which are used as release retarding materials in the design of controlled release drug delivery systems (CRDDS) play a vital role in controlling the delivery of drug from these systems. The success of controlled release drug delivery systems depends on how well the polymer regulates the release of drug from the system. In conventional drug therapy, a tablet provides only a single and transient burst of drug .It doesn't maintain drug blood level with in therapeutic range for extended period of time. The short duration of action is due to the inability of conventional dosage form to control the temporal delivery. As long as the amount of drug is above the minimum effective concentration, a pharmacological response is observed. Problems occur when the therapeutic range is very narrow or when the peak is beyond the upper limit of range. The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration. The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Sustained release can be achieved by formulating drugs as matrix devices using HPMC, Sodium CMC and other swellable polymer. Also the matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior.

Key Words: Controlled drug delivery systems (CRDDS), Matrix tablet, HPMC, Sodium CMC, Swellable polymer

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INTRODUCTION:

In the last several decades, several types of dosage forms have been developed by scientists with certain patient favorable modifications, one of which is the oral drug delivery system which is the oldest one and has got popularity in for more than a century. Oral drug delivery system have the advantages that these are easy to administer, ease of manufacturing and higher patient compliance [1,2]. In oral drug delivery systems certain modifications were done to achieve certain specific objectives, the most profound need of which was to maintain constant drug plasma concentrations for a certain period of time to reduce the dosage frequency which was achieved by controlled release drug delivery systems. Despite of the advancements in other drug delivery systems, oral sustain/controlled release drug delivery systems is dominating the market and have an increased safety and patient compliance[3,4]. These dosage forms can deliver the drug in a predetermined manner to the site of action. To control the release of drug from a controlled release dosage forms, polymers are used, which release the drug in a slow and nearly constant manner to obtain nearly constant peak plasma level. The drug is release from such type of controlled release matrices occurs by diffusion or degradation 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 [5]. 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.

Reason for the selection of -API as a model drug,

1)   Being BCS class II drug it is low soluble in water and highly permeable.
2)   And it is necessary to sustain the drug release.
3)   Bioavailability after oral administration is 20% Silent features to design formulation in sustain release tablets.
4)   Less risk of dose dumping.
5)   Less inter and intra subject variability.
6)   High degree of dispersion in the digestive tract thus minimizing the risk of high local drug concentrations.
7)   Drug may reach the site of optimum absorption in a reproducible fashion so reproducible bioavailability.
8)   Transport of drug is independent of gastric emptying.

Drawback of Conventional Dosage Form:

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 [6-9].

Advantages of Matrix Tablet:

1)   Easy to manufacture
2)   Versatile, effective and low cost
3)   Can be made to release high molecular weight compounds
4)   The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
5)   The use of sustain release formulations avoids the high blood concentration.
6)   Sustain release formulations have the potential to improve the patient compliance.
7)   Reduce the toxicity by slowing drug absorption.
8)   Increase the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.
9)   Minimize the local and systemic side effects.
10) Improvement in treatment efficacy.
11) Minimize drug accumulation with chronic dosing.
12) Usage of less total drug.

13) Improvement the bioavailability of some drugs.

14) Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing.

Disadvantages of Matrix Tablet:

1)   The remaining matrix must be removed after the drug has been released.
2)   High cost of preparation.

3) The release rates are affected by various factors such as, food and the rate transit through the gut.

4) The drug release rates vary with the square root of time.

5) Release rate continuously diminishes due to an increase in diffusion resistance and/or a decrease in effective area at the diffusion front. However, a substantial sustained effect can be produced through

the use of very slow release rates, which in many applications are indistinguishable from zero-order

Classification of Matrix Tablets:

On the Basis of Retardant Material Used:
Matrix tablets can be divided in to 5 types.

1) Hydrophobic Matrices (Plastic matrices)
The concept of using hydrophobic or inert materials as matrix materials was first introduced in 1959. In this method of obtaining sustained release from an oral dosage form, drug is mixed with an inert or hydrophobic polymer and then compressed in to a tablet. Sustained release is produced due to the fact that the dissolving drug has diffused through a network of channels that exist between compacted polymer particles. Examples of materials that have been used as inert or hydrophobic matrices include polyethylene, polyvinyl chloride, ethyl cellulose and acrylate polymers and their copolymers. The rate-controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such type of tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid [10-13].

2. Lipid Matrices:
These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearyl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

3. Hydrophilic Matrices:
Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The formulation of the drugs in gelatinous capsules or more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients is of particular interest in the field of controlled release. Infect a matrix is defined as well mixed composite of one or more drugs with a gelling agent (hydrophilic polymer). These systems are called swellable controlled release systems.

The polymers used in the preparation of hydrophilic matrices are divided in to three broad groups,

A. Cellulose derivatives:
B. Methylcellulose 400 and 4000cPs, Hydroxyethylcellulose; Hydroxypropylmethylcellulose (HPMC) 25, 100, 4000 and 15000cPs; and Sodium carboxymethylcellulose.
C. Non cellulose natural or semi synthetic polymers:
D. Agar-Agar; Carob gum; Alginates; Molasses; Polysaccharides of mannose and galactose, Chitosan and Modified starches.

Polymers of acrylic acid: Carbopol-934, the most used variety.

4. Biodegradable Matrices: These consist of the polymers which 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 nonenzymetic process in to oligomers and monomers that can be metabolized or excreted.

Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices: 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.

On the Basis of Porosity of Matrix:
Matrix system can also be classified according to their porosity and consequently, Macro porous; Micro porous and Non- porous systems can be identified:

1. 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.

2. 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.

3. 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.

Polymers Used In Matrix Tablet:

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

2) Soluble polymers
Polyethyleneglycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Hydroxypropyl methyl cellulose (HPMC)

3) Biodegradable polymers
Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters

4) Non-biodegradable polymers
Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC)

5) Mucoadhesive polymers
Polycarbophil, Sodium carboxymethyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Pectin

6) Natural gums
Xanthan gum, Guar gum, Karaya gum, Locust bean gum

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 [14-18].
Derivation of the mathematical model to describe this system involves the following assumptions:

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,

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

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

$$dM/dh = Co. \, dh - Cs/2 \qquad \text{.................. (1)}$$

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:

$$dM = (Dm. \, Cs / h) \, dt \qquad \text{.......................... (2)}$$

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:

$$M = [Cs. \, Dm \, (2Co - Cs) \, t] \, ½ \qquad \text{.................. (3)}$$

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

$$M = [2Cs.Dm.Co.t] \, 1/2 \qquad \text{.......................... (4)}$$

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:

$$M = [Ds. \, Ca. \, p/T. \, (2Co - p.Ca) \, t] \, 1/2 \qquad \text{......(5)}$$

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:

$$M = [2D.Ca .Co (p/T) t]^{1/2} \dots\dots\dots\dots (6)$$

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

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

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:

$$M = k. t^{1/2} \dots\dots\dots\dots (8)$$

Where, k is a constant, so that 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:

• Initial concentration of drug in the matrix   • Porosity • Tortuosity • Polymer system forming the matrix • Solubility of the drug.

Effect Of Release Limiting Factor On Drug Release [19-22]: -
The mechanistic analysis of controlled release of drug reveals that partition coefficient; diffusivity; diffusional path thickness and other system parameters play various rate determining roles in the controlled release of drugs from either capsules, matrix or sandwich type drug delivery systems.

A. Polymer hydration:
It is important to study polymer hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important step in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling and finally dispersion of polymeric chain in dissolution medium.

B. Drug solubility:
Molecular size and water solubility of drug are important determinants in the release of drug from swelling and erosion controlled polymeric matrices. For drugs with reasonable aqueous solubility, release of drugs occurs by dissolution in infiltrating medium and for drugs with poor solubility release occurs by both dissolution of drug and dissolution of drug particles through erosion of the matrix tablet.

C. Solution solubility:
In view of in vivo (biological) sink condition maintained actively by hem perfusion, it is logical that all the in vitro drug release studies should also be conducted under perfect sink condition. In this way a better simulation and correlation of in vitro drug release profile with in vivo drug administration can be achieved. It is necessary to maintain a sink condition so that the release of drug is controlled solely by the delivery system and is not affected or complicated by solubility factor.

D. Polymer diffusivity:
The diffusion of small molecules in polymer structure is energy activated process in which the diffusant molecules moves to a successive series of equilibrium position when a sufficient amount of energy of activation for diffusion Ed has been acquired by the diffusant is dependent on length of polymer chain segment, cross linking and crystallanity of polymer. The release of drug may be attributed to the three factors viz,

i. Polymer particle size

ii. Polymer viscosity

iii. Polymer concentration.

i. Polymer particle size:
Malamataris stated that when the content of hydroxyl propyl methylcellulose is higher, the effect of particle size is less important on the release rate of propranolol hydrochloride, the effect of this variable more important when the content of polymer is low. He also justified these results by considering that in certain areas of matrix containing low levels of hydroxyl propyl methylcellulose led to the burst release.
ii. Polymer viscosity:
With cellulose ether polymers, viscosity is used as an indication of matrix weight. Increasing the molecular

weight or viscosity of the polymer in the matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution.

iii. Polymer concentration:

An increase in polymer concentration causes an increase in the viscosity of gel as well as formulation of gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore reduction in drug release. The mechanism of drug release from matrix also changes from erosion to diffusion as the polymer concentration increases.

E. Thickness of polymer diffusional path:

The controlled release of a drug from both capsule and matrix type polymeric drug delivery system is essentially governed by Fick's law of diffusion:

$JD = D \, dc/dx$

Where,

JD is flux of diffusion across a plane surface of unit area D is diffusibility of drug molecule, dc/dx is concentration gradient of drug molecule across a diffusion path with thickness dx.

F. Thickness of hydrodynamic diffusion layer:

It was observed that the drug release profile is a function of the variation in thickness of hydrodynamic diffusion layer on the surface of matrix type delivery devices. The magnitude of drug release value decreases on increasing the thickness of hydrodynamic diffusion layer δd.

G. Drug loading dose:

The loading dose of drug has a significant effect on resulting release kinetics along with drug solubility. The effect of initial drug loading of the tablets on the resulting release kinetics is more complex in case of poorly water soluble drugs, with increasing initial drug loading the relative release rate first decreases and then increases, whereas, absolute release rate monotonically increases.

In case of freely water soluble drugs, the porosity of matrix upon drug depletion increases with increasing initial drug loading. This effect leads to increased absolute drug transfer rate. But in case of poorly water soluble drugs another phenomenon also has to be taken in to account. When the amount of drug present at certain position within the matrix, exceeds the amount of drug soluble under given conditions, the excess of drug has to be considered as non-dissolved and thus not available for diffusion. The solid drug remains within tablet, on increasing the

initial drug loading of poorly water soluble drugs, the excess of drug remaining with in matrix increases.

H. Surface area and volume:

The dependence of the rate of drug release on the surface area of drug delivery device is well known theoretically and

and experimentally. Both the in vitro and in vivo rate of the drug release, are observed to be dependent upon surface area of dosage form. Siepman et al. found that release from small tablet is faster than large cylindrical tablets.

I. Diluents' effect:

The effect of diluent or filler depends upon the nature of diluent. Water soluble diluents like lactose cause marked increase in drug release rate and release mechanism is also shifted towards Fickian diffusion; while insoluble diluents like dicalcium phosphate reduce the Fickian diffusion and increase the relaxation (erosion) rate of matrix. The reason behind this is that water soluble filler in matrices stimulate the water penetration in to inner part of matrix, due to increase in hydrophilicity of the system, causing rapid diffusion of drug, leads to increased drug release rate.

J. Additives:

The effect of adding non-polymeric excipients to a polymeric matrix has been claimed to produce increase in release rate of hydro soluble active principles. These increases in release rate would be marked if the excipients are soluble like lactose and less important if the excipients are insoluble like tricalcium phosphate.

Biological Factors Influencing Release From Matrix Tablet [23-26]:

Biological half-life.
  Absorption.
  Metabolism
  Distribution
  Protein binding
Margin of safety

1) Biological half-life:

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life (t1/2). Each drug has its own characteristic elimination rate, which is the sum of all elimination processes, including metabolism, urinary excretion and all over processes that

permanently remove drug from the blood stream. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-life shorter than 2 hours such as furosemide or levodopa are poor candidates for SR preparation. Compounds with long half- lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples.

2)   Absorption:
Since the purpose of forming a SR product is to place control   on the delivery system, it is necessary that the rate of release is much slower than the rate of absorption. If we assume that the transit time of most drugs in the absorptive areas of the GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours; otherwise, the device will pass out of the potential absorptive regions before drug release is complete. Thus corresponds to a minimum apparent absorption rate constant of 0.17-0.23h-1 to give 80-95% over this time period. Hence, it assumes that the absorption of the drug should occur at a relatively uniform rate over the entire length of small intestine. For many compounds this is not true. If a drug is absorbed by active transport or transport is limited to a specific region of intestine, SR preparation may be disadvantageous to absorption. One method to provide sustaining mechanisms of delivery for compounds tries to maintain them within the stomach. This allows slow release of the drug, which then travels to the absorptive site. These methods have been developed as a consequence of the observation that co-administration results in sustaining effect. One such attempt is to formulate low density pellet or capsule. Another approach is that of bio adhesive materials.

3)   Metabolism:
Drugs those are significantly metabolized before absorption, either in the lumen or the tissue of the intestine, can show decreased bioavailability from slower-releasing dosage form. Hence criteria for the drug to be used for formulating Sustained-Release dosage form is,
□ Drug should have law half-life (<5 hrs.) □ Drug should be freely soluble in water. □ Drug should have larger therapeutic window. □ Drug should be absorbed throughout the GIT

Even a drug that is poorly water soluble can be formulated in SR dosage form. For the same, the solubility of the drug should be increased by the suitable system and later on that is formulated in the SR dosage form. But during this the crystallization of the drug, that is taking place as the drug is entering in the systemic circulation, should be prevented and one should be cautious for the prevention of the same.

4)   Distribution:
Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral SR drug delivery system e.g. Chloroquine.

5)   Protein Binding:
The Pharmacological response of drug depends on unbound drug concentration drug rather than total concentration and all drug bound to some extent to plasma and or tissue proteins. Proteins binding of drug play a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half-life and thus sometimes SR drug delivery system is not required for this type of drug.

Margin of safety:
As we know larger the value of therapeutic index safer is the drug. Drugs with less therapeutic index usually poor candidate for formulation of oral SR drug delivery system due to technological limitation of control over release rates.

Physicochemical Factors Influencing Release from Matrix Tablet [27-30]:

1)   Dose size:
For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5-1.0g is considered maximal for a conventional dosage form. This also holds for sustained release dosage form. Compounds that require large dosing size can sometimes be given in multiple amounts or formulated into liquid systems. Another consideration is the margin of safety involved in administration of large amount of a drug with a narrow therapeutic range.

2)   Ionization, pka and aqueous solubility:
Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pka of the compound and the absorptive environment. Presenting the drug in an unchanged form is advantageous for drug permeation. Unfortunately, the situation is made more complex by the fact that the drug's aqueous solubility will generally be decreased by conversion to unchanged form. Delivery systems that are

dependent on diffusion or dissolution will likewise be dependent on the solubility of the drug in aqueous media. These dosage forms must function in an environment of changing pH, the stomach being acidic and the small intestine more neutral, the effect of Phone the release process must be defined. Compounds with very low solubility (<0.01mg/ml) are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. So it is obvious that the solubility of the compound will be poor choices for slightly soluble drugs, since the driving force for diffusion, which is the drug's concentration in solution, will be low.

3) Partition Coefficient:

When a drug is administered to the GI tract, it must cross a variety of biological membranes to produce a therapeutic effect in another area of the body. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil-soluble drugs becomes important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer

time. In case of compounds with very low partition coefficient, it is very difficult for them to penetrate the membrane, resulting in poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes. The choice of diffusion-limiting membranes must largely depend on the partitioning characteristics of the drug.

4) Stability:

Orally administered drugs can be subject to both acid-base hydrolysis and enzymatic degradation. Degradation will proceed at a reduced rate for drugs in solid state; therefore, this is the preferred composition of delivery for problem cases. For the dosage form that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial; this is also true for systems that delay release until the dosage form reaches the small intestine. Compounds that are unstable in small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form. This is because more drugs is delivered in the small intestine and, hence, is subject to degradation. Propentheline and probanthine are representative example of such drug

Below table show the drug to be formulated as a matrix tablet with polymer and method used for its preparation:

DRUGS USED	CATEGORY	METHOD USED	POLYMER USED
Zidovudine	Anti-viral	Direct Compression	HPMC-K4M, Carbopol-934,
Venlafexine	Anti-depressant	Wet Granulation	Beeswax, Caranuaba wax
Domperidone	Anti-emetic	Wet Granulation	HPMC-K4M, Carbopol-934
Ibuprofen	Anti-inflammatory	Wet Granulation,	CAP
Metformin HCL	Anti-diabetic	Direct Compression	HPMC-K100M, EC,
Aceclofenac	Anti-inflammatory	Wet Granulation	HPMC-K4M,K15M,
Ambroxol HCL	Expectorent, Mucolytic	Direct Compression	HPMC-K100M,
Naproxen	Morphine antagonist	Direct Compression	HPMC-K100M, K15M,
Nicorandil	Ca+2 channel blocker	Wet Granulation	HPMC, CMC, EC
Ondansertan	Anti-Emitic	Wet Granulation	HPMC-K100M, K4M,
henytoin Na	Anti-epileptic	Wet Granulation	Tragacanth, Acacia,
Ranitidine HCL	H2 antagonist	Direct Compression	Chitoson, Carbopol-940
Theophylline	Respiratory depressant	Direct Compression	Carbopol-934P, HPMC K4M,
Tramadol	B2 blocker	Wet Granulation	HPMC-K4M, Karaya gum,
Verapemil	Ca+2 channel blocker	Direct Compression	HPMC-K100M -
Amlodipine	Anti-arrythmatic	Direct Compression	HPMC, EC

CONCLUSION:

By the above discussion, it can be easily concluded that controlled-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.

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