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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLET OF METFORMIN HYDROCHLORIDE USING SODIUM ALGINATE AND PECTIN: A REVIEW

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ABSTRACT

This study was aimed to formulate and evaluate matrix tablets of Metformin HCl using Sodium Alginate/Pectin polymer. Matrix tablets were prepared by direct compression method in different drug polymer ratios. Drug & polymers interaction was assessed by FTIR spectroscopy & results indicated absence of chemical interactions between them. The physico- chemical compatibility of the drug with polymer was evident from the thermal analysis using DSC. The thermogram obtained showed distinctive and characteristic exothermic peaks of the API indicating its crystalline nature. Blends prepared using different drug polymer ratio were evaluated for pre-compression studies and formulated matrix tablets were evaluated for weight variation, thickness, hardness, friability and Drug content. In-vitro release studies of the matrix tablets were carried out in acidic buffer (pH1.2) as well as in phosphate buffer (pH 6.8) along with the evaluation of Swelling & Erosion studies behavior if the tablets. It is evident from in-vitro drug release studies that, the drug release decreases with increase in the amount of polymer added. Studies also indicated that the extent of swelling and erosion of matrix tablets influences the drug release. A bi-phasic release with an initial burst effect in the matrix tablets is evident from the data obtained. Swelling and erosion studies of Metformin tablets indicated that matrix tablets swell almost from the beginning and its erosion increase with swelling and the time. Cumulative drug release in percentage was found to be sustained for all formulations. The best formulation was MA3 with 93.06% drug release in 12th hr. From further extrapolation of the drug release data it is evident that out of the total 9 formulation studied, seven formulations were good fitted into Korsmeyer-Peppas model and rest of the

two formulations were good fitted in Higuchi matrix model.

KEYWORDS: Matrix Tablet, Drug release, Swelling, Erosion, Pectin, Sodium Alginate, Metformin HCl.

INTRODUCTION OF SUSTAIN RELEASE DRUG DELIVERY SYSTEM

Conventional drug therapy requires periodic doses of therapeutic agents depending upon the necessity of maintaining a desired drug plasma concentration. These conventional drugs are formulated to produce maximum stability, bioavailability and therapeutic activity.[1] For most drugs, conventional methods of drug administration are effective but some drugs are toxic or unstable and have narrow therapeutic ranges. In other cases some of the drugs may also have solubility or absorption problems.[2] In such drugs/cases, it is desirable to have a method of continuous administration of therapeutic agent to maintain fixed plasma levels as shown in Figure 1.1

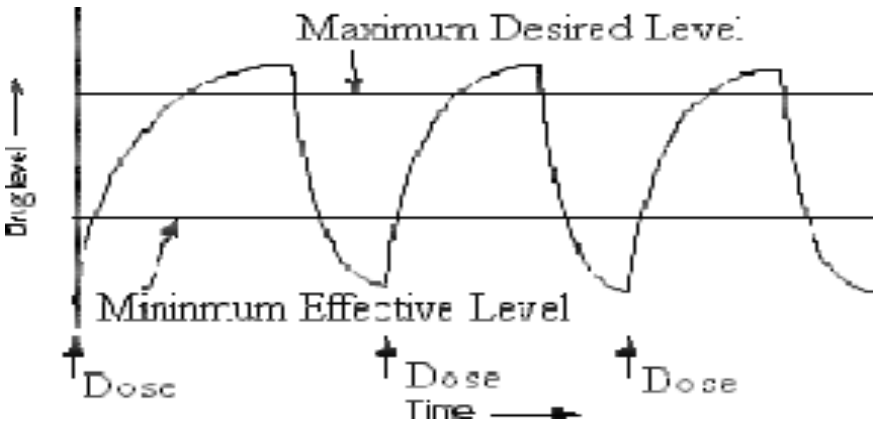
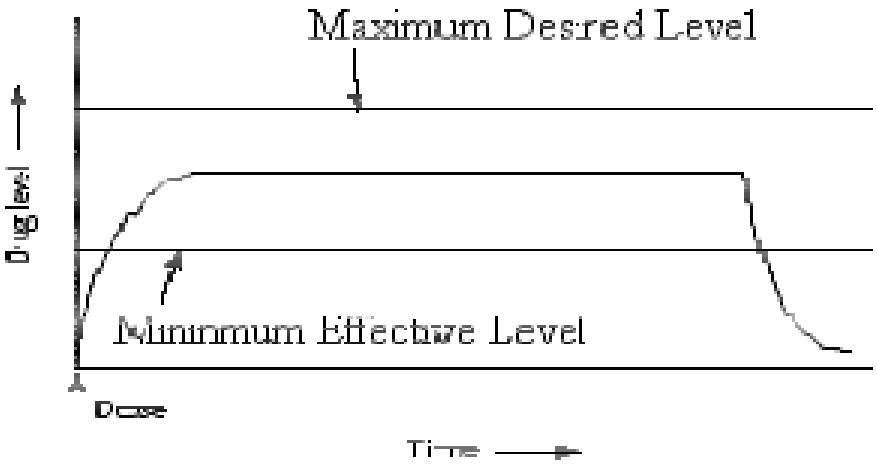


Figure 1.1: Drug levels in the blood with Conventional drug delivery system.



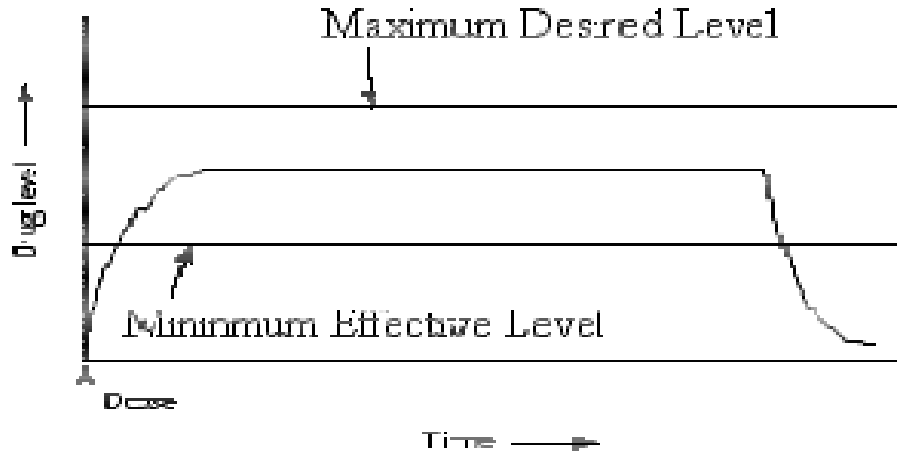


Figure 1.2: Drug levels in the blood with Controlled drug delivery systems.

Three Decades ago, controlled drug delivery systems were introduced to overcome these problems. Controlled drug delivery systems have number of advantages over traditional or conventional systems such as reduced toxicity, improved efficiency and improved patient convenience.[3] The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.[4] Simple definition of sustained release drug system is "any drug or dosage form modification that prolongs the therapeutic activity of the drug"[5] Ideally a sustained release oral dosage form is designed to release rapidly some pre determined fraction of the total dose in to GI tract. This fraction of drug is defined as loading dose and is an amount of drug, which will produce the desired pharmacological response as promptly as possible. The remaining fraction of the total dose is defined as maintenance dose and it release at a constant rate after loading dose. The rate of the drug absorption from the entire maintenance dose into the body should be equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required.[6] The controlled-release system of oral dosage form displays a typical pattern of drug release in which the drug concentration is maintained for a prolonged period of time (sustained release) in the therapeutic window, thereby ensuring sustained therapeutic action.[7] Hence, the release commences as soon as the dosage form is administered as in the case of conventional dosage forms. Controlled drug Delivery – It's the delivery of drug at a rate or at a location determined by needs of body or disease state over a specified period of time. For these systems, ideally two main objectives exist: Spatial drug delivery, which is related to the control over the location of drug release. Temporal drug delivery, in which the drug is delivered over an extended period of time during treatment.[8]

Disadvantagesofconventionaldrugdelivery system

Inconvenient to the patients due to the requirement of frequent dosing, Careful dosing calculation is necessary to avoid overdosing, Large amounts of drug can be "lost" when they don't get to the target organ, Difficult to monitor, Drug goes to non-target cells and can cause damage or increase toxicity, Expensive (using more drug than necessary).[9]

Advantages of controlled drug delivery system

Avoid patient compliance problems, Minimize or eliminate local rate effects., Employ less total drug, Minimize or eliminate systemic side effects.[10] Improve efficiency in treatment, Obtain less potentiating or reduction in drug activity with chronic use, Minimize drug accumulation with chronic dosing, Cure or control condition more promptly.[11] Improve bioavailability of some drugs, Improve control of condition, i.e. reduce fluctuation in drug level, Make use of special effects, e.g. sustained-release aspirin for morning relief of arthritis by dosing before bedtime.[12]

Disadvantages of controlled release drug delivery systems

Decreased systemic availability in comparison to immediate release conventional dosage forms, Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient, Poor in vitro and in vivo correlation.[13] Increased risk of toxicity, Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions, Higher cost of formulation.[14]

Types of non-immediate release drug delivery system

The conventional dosage forms are immediate release type. Non-immediate release delivery systems may be divided conveniently into three categories.[15,16]

Delayed release

Delayed release systems are those system that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release system include repeat action tablets and capsules. A delayed release dosage form does not produce or maintain uniform drug and blood levels within the therapeutic range.[17]

Sustained release system

It includes any drug delivery system that achieves slow release of drug over an extended

period of time.[18]

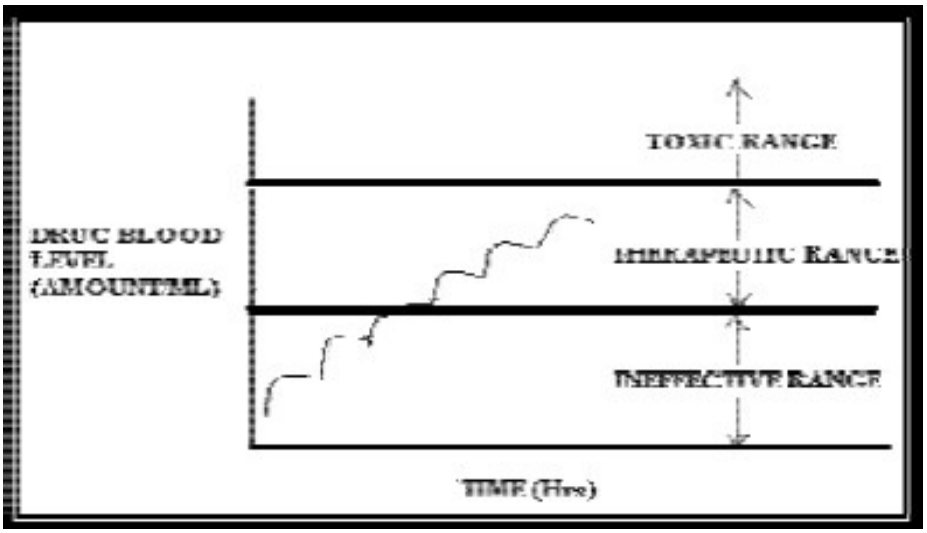


Figure 1.3: Typical drug blood level time profiles for delayed release drug delivery by repeat action dosage form.

Controlled release system

If the system is successful at maintaining constant drug level in the blood or target tissues, it is considered as a controlled release system. Drug delivery systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time are called as controlled drug delivery systems.[19]

Prolonged release system

If without maintaining constant level, the duration of action is extended over that achieved by conventional delivery; it is considered as a prolong release.[20] This is illustrated in Fig 1.4

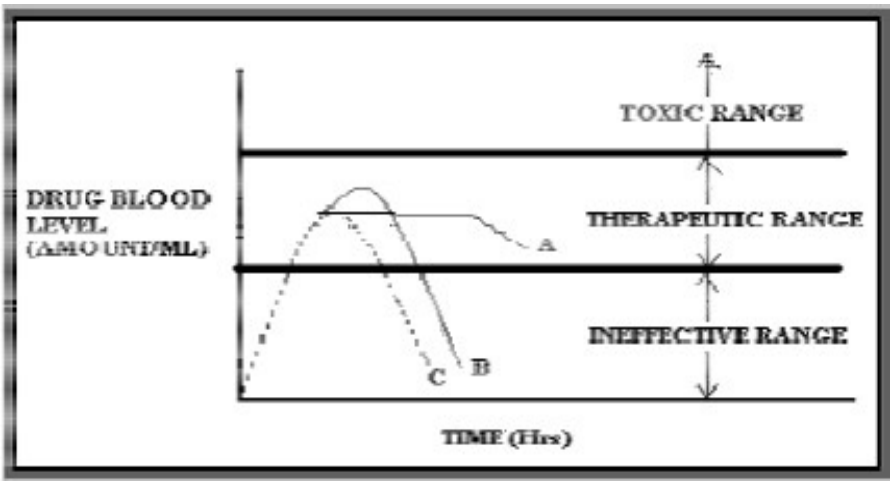


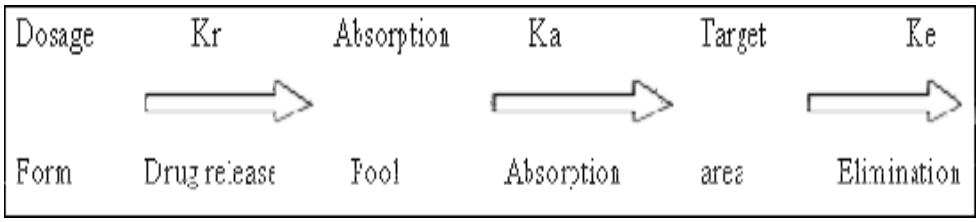
Figure 1.4: Drug levels in the blood with prolonged release drug delivery system.

Site-Specific and Receptor release

It refers to targeting of a drug directly to a certain biological case of site-specific release, the target is a certain organ or tissue, while for receptor release; the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspects of drug delivery.[21]

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.



The absorption pool represents a solution of the drug at the site of absorption, and the term Kr, Ka and Ke are first order rate and overall elimination respectively.[27] Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. Alternatively speaking the absorption of drug across a biological membrane is the rate dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. This cause the above kinetics scheme to reduce to the following:

Essentially, the absorptive phase of the kinetic scheme become insignificant compared to the drug release phase. Thus, the effort to develop a non immediate release delivery system must be directed primarily at altering the release rate.[22] The main objective in designing a sustained release delivery system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion given to the patient at a constant rate. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. It means that the drug release from the dosage form should follow zero-

order order kinetics, as shown by the following equation:[23]

$$Kr° = Rate\ In = Rate\ Out = Ke\ Cd\ Vd$$

Where, Kr°: Zero-order rate constant for drug release, Ke: First-order rate constant for overall drug elimination-time Cd: Desired drug level in the body – Amount/volume, and, Vd: Volume space in which the drug is distributed-Litters The value of Ke, Cd and Vd are obtained from appropriately designed single dose pharmacokinetic study.[24] The equation can be used to calculate the zero order release rate constant. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level. It is important to recognize that while zero- order release may be desirable theoretically, non zero-order release may be equivalent clinically to constant release in many cases.[25] Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this being of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.[26]

Monolithic systems (Matrix system)

Monolithic (matrix) devices are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrix, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug, (0 to 5% W/V) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10% W/V), the release mechanism will be complicated by the presence of cavities formed near the surface of the device as the drug is lost: such cavities fill with fluid from the environment increasing the rate of release of the drug.[27] It was deduced that the enhancement of their

permeability was as a result of the effective decrease in thickness caused by the PEG leaching.

This was evinced from plots of the cumulative permeant flux per unit area as a function of time and film reciprocal thickness at a PEG loading of 50% W/W: plots showing a linear relationship between the rate of permeation and reciprocal film thickness, as expected for a (Fickian) solution-diffusion type transport mechanism in a homogeneous membrane. Extrapolation of the linear regions of the graphs to the time axis gave positive intercepts on the time axis: the magnitude of which decreased toward with decreasing film thickness. These changing lag times were attributed to the occurrence of two diffusional flows during the early stages of the experiment (the flow of the 'drug' and also the flow of the PEG), and also to the more usual lag time during which the concentration of permeant in the film is building-up. Caffeine when used as a permeant, showed negative lag times. No explanation of this was forthcoming, but Donbrow noted that caffeine exhibited a low partition coefficient in the system, and that this was also a feature of aniline permeation through poly ethylene films which showed a similar negative time lag.

Diffusion controlled by Fick's law

$$J = -D\frac{dC_m}{dx}$$

Where,

J = flux of the drug across a membrane in the direction of decreasing concentration, D = Diffusion coefficient of the drug, and, dCm /dx = Change in the concentration of the drug in the membrane.

Mechanisms of drug release from matrix systems

The release of drug from controlled devices is via dissolution or diffusion or a combination of the two mechanisms.

Dissolution controlled systems

A drug with slow dissolution rate will demonstrate sustaining properties since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water soluble. This can be done by: Preparing an appropriate salt or derivative, Coating the drug with a slowly dissolving material encapsulation dissolution control,Incorporating the

drug into a tablet with a slowly dissolving carrier matrix dissolution control (a major disadvantage is that the drug release rate decreases continuously with time).[28] The dissolution process can be considered diffusion. The rate of diffusion from the solid surface to the bulk solution liquid film is the rate described by the Noyes -Whitney equation:

$$\frac{dC}{dt} = \frac{DA(C_s - C)}{h}$$

Where, dC/dt = dissolution rate, D = the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h), Co = saturation solubility of the solid, C = concentration of solute in the bulk solution A = Surface area, h = Diffusion layer thickness.

Diffusion controlled systems

Diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer. In general, two types or subclasses of diffusional systems are recognized: reservoir devices and matrix devices. It is very common for the diffusion-controlled devices to exhibit a non-zero order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.[29

Diffusion in matrix devices

In this model, 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 obviously 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.

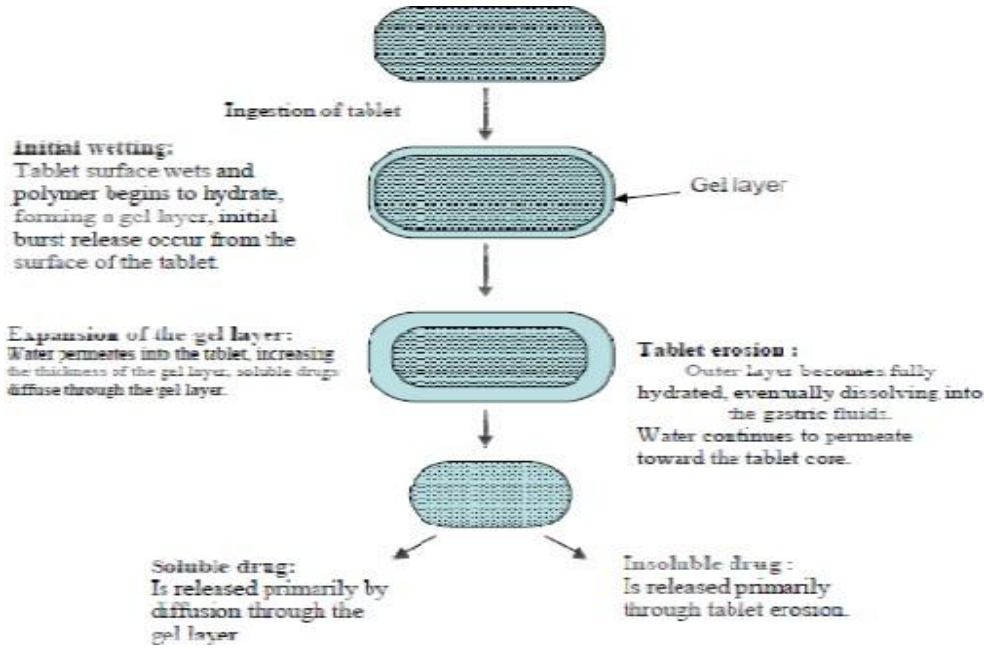


Figure 1.5: Drug release from hydrophilic matrix tablet.

Bio erodible and combination of diffusion and dissolution systems

Strictly speaking, therapeutic systems will never be dependent on dissolution or diffusion only. In practice, the dominant mechanism for release will overshadow other processes enough to allow classification as either dissolution rate-limited or diffusion- controlled release. As a further complication these systems can combine diffusion and dissolution of both the drug and the matrix material. Drugs not only can diffuse out of the dosage form, as with some previously described matrix systems, but also the matrix itself undergoes a dissolution process. The complexity of the system arises from the fact that as the polymer dissolves the diffusional path length for the drug may change. This usually results in a moving boundary diffusion system. Zero-order release is possible only if surface erosion occurs and surface area does not change with time. Swelling-controlled matrices exhibit a combination of both diffusion and dissolution mechanisms. Here the drug is dispersed in the polymer, but instead of an insoluble or non- erodible polymer, swelling of the polymer occurs. This allows forth entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer-swelling rate and drug solubility. This system usually minimizes burst effects, as rapid polymer swelling occurs before drug release.[30] With regards to swellable matrix systems, different models have been proposed to describe the diffusion, swelling and dissolution processes involved in the drug release mechanism. However the key element of the drug release mechanism is the forming of a gel layer around the matrix, capable of

preventing matrix disintegration and further rapid water penetration. When a matrix that contains a swellable glassy polymer comes in contact with a solvent or swelling agent, there is an abrupt change from the glassy to the rubbery state, which is associated with the swelling process.

The individual polymer chains, originally in the unperturbed state absorb water so that their end-to-end distance and radius of gyration expand to a new solvated state. This is due to the lowering of the transition temperature of the polymer (Tg), which is controlled by the characteristic concentration of the swelling agent and depends on both temperature and thermodynamic interactions of the polymer– water system. A sharp distinction between the glassy and rubbery regions is observed and the matrix increases in volume because of swelling. On a molecular basis, this phenomenon can activate a convective drug transport, thus increasing the reproducibility of the drug release. The result is an anomalous non-Fickian transport of the drug, owing to the polymer-chain relaxation behind the swelling position. This, in turn, creates osmotic stresses and convective transport effects. The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethyl cellulose, hydroxypropyl cellulose or tragacanth gum, do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices. The swelling behavior of heterogeneous swellable matrices is described by front positions, where ‘front’ indicates the position in the matrix where the physical conditions sharply change. Three fronts are present, as shown in Figure 1.6. The ‘swelling front’ clearly separates the rubbery region (with enough water to lower the Tg below the experimental temperature) from the glassy region (Where the polymer exhibits a Tg that is above the experimental temperature). The ‘erosion front’, separates the matrix from the solvent. The gel-layer thickness as a function of time is determined by the relative position of the swelling and erosion moving fronts. The ‘diffusion front’ located between the swelling and erosion fronts, and constituting the boundary that separates solid from dissolved drug, has been identified. During drug release, the diffusion front position in the gel phase is dependent on drug solubility and loading. The diffusion front movement is also related to drug dissolution rate in the gel.

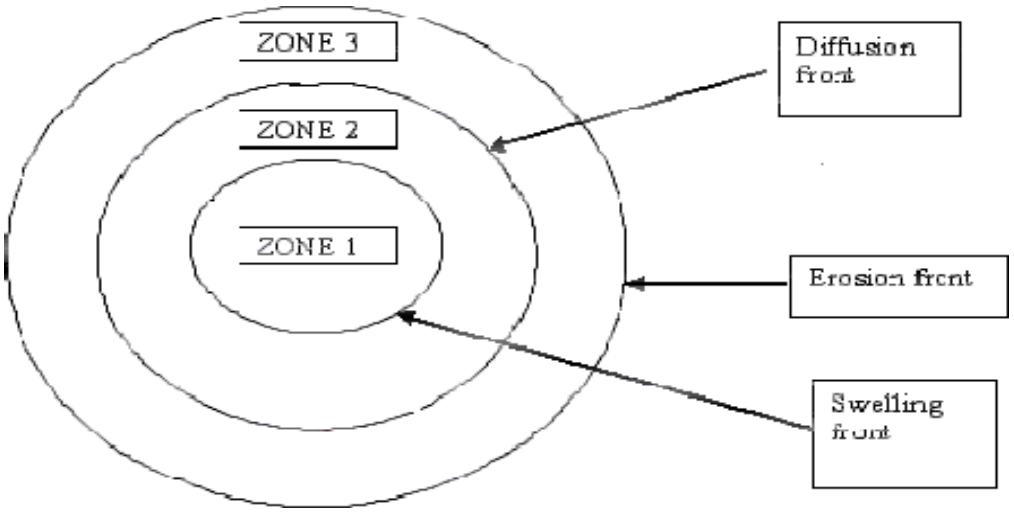


Figure 1.6 The fronts in a swellable matrix

Zone 1: Undissolveddrug, glassypolymerlayer.

Zone 2: Undissole.

Gel layer thickness = Difference between erosion and swelling front position

Drug release is controlled by the interaction between water, polymer and drug. The delivery kinetics depends on the drug gradient in the gel layer. Therefore, drug concentration and thickness of the gel layer governs the drug flux. Drug concentration in the gel depends on drug loading and solubility. Gel relative contributions of solvent penetration, chain disentanglement and mass (polymer and drug) transfer in the solvent. Initially solvent penetration is more rapid than chain disentanglement, and a rapid build However, when the solvent penetrates slowly, owing to an increase in the diffusional distance, little change in gel thickness is observed since penetration and disentanglement rates are similar. Thus gel matrix tablet s exhibit three distinct patterns. The thickness increases when solvent penetration is the fastest mechanism, and it remains constant when the disentanglement and water penetration occur at a similar rate. Finally, the gel-layer thickness decreases when the entire polymer has undergone the glassy–rubbery transition. In conclusion, the central element of the release mechanism is a gel-layer forming around the matrix in response to water penetration. Phenomena that govern gel-layer formation, and consequently drug-release rate, are water penetration, polymer swelling, drug dissolution and diffusion, and matrix erosion. Drug release is controlled by drug diffusion through the gel layer, which can dissolve and/or erode.

Drug selection for oral sustained release drug delivery systems

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the GI tract, the general absorbability, the drug's molecular weight, solubility at different pH and apparent partition coefficient.[31]

Etiology of diabetes mellitus

Diabetes mellitus is a group of syndromes characterized by hyperglycemia, glycosuria, hyperlipidemia, negative nitrogen balance and sometimes ketonemia. A wide spread pathological changes are - increase in vessel wall matrix, thickening of capillary basement membrane and cellular proliferation resulting in vascular complications like lumen narrowing, early atherosclerosis, sclerosis of glomerular capillaries, retinopathy, neuropathy, and peripheral vascular insufficiency. Diabetes is not a disease, but a disorder which requires continuous use of drugs for its maintenance.[32] Two major types of diabetes mellitus are:

Type I: Insulin dependent diabetes mellitus (IDDM): Juvenile onset diabetes There is 'β' cell destruction in pancreatic islets; majority of cases are autoimmune (type I A) antibodies that destroy 'β' cells are detectable in blood, but some are idiopathic (type II B)- no 'β' cell antibody is found. In all type I cases, circulating insulin levels are low or very low and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition.[33]

Type 2: Non insulin dependent diabetes mellitus (NIDDM), maturity onset diabetes: This typically involves abnormal 'β' cell function that result in relative insulin deficiency, insulin resistance is accompanied by decreased glucose transport into muscles and fat cells, and increased hepatic glucose output, all of which contribute to hyperglycemia. Type II diabetes characteristically comprises of pathophysiologic abnormalities like relative insulin deficiency, insulin resistance involving myocytes & adipocytes and hepatic insulin resistance (resulting in increased gluconeogenesis and impaired glycogen synthesis). These drugs must be administered repeatedly to the diabetic patients. Sustained Release provides the most desirable dosing regimens with effective pharmacokinetic profile and pharmacodynamic response in diabetes treatment. This approach help the patient to lower blood sugar and help body to use insulin more efficiently through maintenance of consistent drug input and it may ease the variability involved in the administration of multiple doses per day. Thus Sustained Release Dosage Form of anti-diabetic drug like Metformin HCl tablet improves patient

compliance. Diabetes mellitus (DM) is fast expanding throughout the world and particularly in developing countries like India. Metformin HCl is a biguanide-type drug used along with a diet and exercise program to control high blood sugar in patients with type 2 diabetes. To reduce frequency of administration and to improve patient compliance, a sustain release formulation is required.

Natural polymers

Natural polysaccharides (polymer) like sodium alginate, pectin, agar, guar gum play a significant role in the formulation development of a new controlled release dosage forms as well as in human health care system. Now a days, natural hydrophilic polymer has been widely used to control drug release from solid dosages, such as sustained release or controlled release system. Natural polymers are much safer than synthetic. They provide many applications in the formulation development of a new controlled release dosage form, such as binder, disintegrator, diluents and release modifier. Therefore, they needs a novel approach to enhance the use of natural polymer in the formulation development of controlled released dosage form, because of the ease availability at an affordable price, high safety margin and higher productivity. In recent years, natural polymers are growing rapidly and it continues to remain and important in the new formulation development of the controlled released dosage form.

Formulation & evaluation aspects of sustained- release dosage form

OSD formulations i.e. tablets and capsules represent the preferred class of products. Out of the two oral solid dosage forms, the tablets have number of advantages like low cost, tamper proof, speed of manufacturing (like direct compression), ease of administration, patient compliance and flexibility in formulation etc.

Excipients

Excipient in a formulation may be Diluents, Disintegrants, Lubricants, glidants, colouring & flavouring agents etc.

Diluents are fillers designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce this bulk.

Disintegrants facilitate a breakup or disintegration of the tablet when it contacts water. Lubricants and Glidants have overlapping functions. Lubricants reduce the friction during

tablet ejection between the walls of the tablet and the die cavity while glidants are intended to promote flow of the tablet granulation.

Colouring and flavouring agents are used for disguising of off-colour drugs, product identification and production of a more elegant product.[34]

Granulation

For free and even flow of the powder mixture from the hopper into the dies of a tablet press, it is usually necessary to convert the powder mixture to free flowing granules. A granule is an aggregation of component particles that is held together by the presence of bonds of finite strength. The strength of a wet granule is mainly due to the surface tension of the granulation liquid and capillary forces. These forces are responsible for initial agglomeration of the wet powder. Granulation refers to the processes whereby powder particles agglomerates with sizes ranging from 0.1 to 2 mm are produced. The most important points for a granulation step prior to tableting are to improve the flow properties of the powder mix, to have uniformity of the dose to prevent segregation of the ingredients in the hopper of tablet press, to improve the compression characteristics of the tablet mixture and to reduce dust during handling. There are various techniques like dry and wet granulation, extrusion or spray drying for producing granules.[35]

Dry granulation

Dry granulation is an important & valuable technique in situations where the drug is sensitive to heat, moisture or both, which precludes wet granulation and the effective dose of a drug is too high for direct compaction. The mixture/blend of powders is forced into dies of a large heavy-duty tableting press/Slugger and compacted to slugs. The slugs or roller compacts are then milled and screened in order to produce a granular form of tableting material which flows more uniformly than the original powder mix.

Wet granulation

Wet granulation process is the most widely used method for Tableting of pharmaceutical materials. This is accomplished by adding a liquid binder or an adhesive to the powder mixture, passing the wetted mass through a screen of the desired mesh size, drying the granulation and then passing through a second screen of smaller mesh to reduce further the size of the granules. Granulation was mainly performed in planetary mixers with low speed and low shear forces. Now there is a trend toward using machines that can carry out the entire

granulation sequence in a single piece of equipment – the mixer- granulator – dryer. Example is the FBP (Fludized Bed Processor). Such equipment's has many advantage over conventional equipment's like of these machines include reduced handling of excipients, reduced exposure of excipients to heat, and a better opportunity to precisely control the moisture level in the granulation and reduced granulation time. High shear mixers are also recently introduced with short process time and production of very dense granules with low porosity. In wet granulation, liquid bridges are developed between particles and the resulting tensile strength of these bonds increases as the amount of liquid increases. During drying, inter particulate bonds result from fusion or recrystallisation and curing of the binding agent.

Evaluation of Pre-formulation studies[36,37]

Preformulation study

I) Pre-compression evaluation parameters

a) Angle of repose. b) Bulk density. c) Tapped density. d) Hausner's ratio. e) Compressibility index (%).

II) Drug polymer interaction study

a) FTIR studies. b) DSC studies.

Pre compression evaluation parameters

Micromeritic properties

Angle of repose (θ)

The frictional strength in a movable powder or granules can be determined through the angle of repose and that is the most angles possible among the outside of a quantity of powder or granule and the flat plane.

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

Where, θ = angle of repose, h = height, r = radius.

Method: A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, there by evaluating the flow ability of the granules. Height of the pile was also measured.

Bulk density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of

the particles to adhere to one another.

Method: Together Loose Bulk Density (LBD) and Tapped Bulk Density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, previously surprised to break some agglomerates shaped was introduced into a 25ml measuring cylinder. After the early quantity was experiential, the cylinder was allowable to drop below it's possess weight on to a solid outside from the height of 2.5cm at 2 sec interval. The taping was sustained pending no additional alter in amount was noted.

LBD (Loose Bulk Density) = Weight of the Powder/Volume of Packing

TBD (Tapped Bulk Density) =Weight of the Powder/ Tapped Volume of Packing

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (λt) was calculated using the following formula t = m/v

Hausner's ratio

Hausner's ratio is a not direct catalog of ease of powder flow. It is measured through the following method

Hausner's ratio = t/d

Where t = tapped density, d = bulk density

Lower H (<1.25) indicate improved flow property than superior ones (>1.25)

Percentage compressibility

Percentage compressibility of mixed powder was determined by Carr's compressibility index calculated by following formula.

Carr's Index % = TBD – LBD/TBD x 100

Where, LBD = Loose Bulk Density, TBD = Tapped Bulk Density.

Evaluation of the tablet properties

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, and in-vitro drug release with different media.

Weight variation

The tablet weight being complete was regularly determined to make sure that tablets contain

the appropriate quantity of drug. The USP weight difference test is done by weighing 20 tablets separately, the average weight calculated and the individual weight compared to the average weight. The tablets meet the USP requirement that not supplementary than 2 tablets are exterior the proportion limits and no tablet differ through more than 2 times the proportion limit. USP official limits of percentage deviation of tablet are presented in the Table.

Table 1: Weight variation limits.

Sr. No.	Average weight of tablet (mg)	Maximum %difference allowed
1	130 or less	10
2	130-324	7.5
3	324<or more	5

Tablet hardness

The confrontation of tablets to delivery or under breakage condition of the storage, carrying and handling earlier than custom depends on its rigidity. The rigidity of each lot of tablet was checked by using the apparatus (Monsanto hardness tester). The rigidity was calculated in conditions of kg/cm^2 3 tablets were chosen at random and tested for rigidity. The standard rigidity of 3 determinations was recorded.

Friability

Friability usually refers to weight loss of the tablets in the containers outstanding to elimination of fine from the tablet exterior. Friability usually reflects deprived consistency of tablet ingredients.

Method

20 tablets were weighing and the weight of these tablets was recorded and placed in apparatus (Roche friabilator) and rotate at the velocity of 25 rpm for 100 revolutions and then tablets were detached from the apparatus, dusted rancid the fines and weighed again. The recorded the weight.

$$\% \text{ Friability} = \frac{\text{Initial Wt. of tablet - Final Wt. of Tablet}}{\text{Initial Wt. of tablet}} \times 100$$

Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each

formulation.

Content uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 500 mg was weighed accurately and dissolved in 100ml of phosphate buffer of pH 6.8. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whattman's filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 263 nm. The concentration of the drug was computed from the standard curve of the RC in phosphate buffer of pH 6.8.

Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electro Lab USP disintegration test equipment. It contains 6 glass tubes which are 3 inches extended, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing pH 1.2 Buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm under the outside of the liquid. The disintegration time of the tablet was noted.

In-vitro dissolution time

In-vitro dissolution studied of center and encrusted drug of HMG-COA reductase inhibitor was carried out using Electro lab TDT-08L USP dissolution test equipment. The particulars be known as below:

Electro lab TDT-08L USP dissolution test apparatus

Medium: pH 1.2 buffer solution and pH 6.8 buffer solution, RPM: 50

Time: 2hrs in pH 1.2 followed by dissolution in pH 6.8 buffer solutions.

Procedure

Tablet was introduced into the basket of the Electro Lab TDT-08L USP dissolution test equipment and the equipment was put in activity, 5 ml of test was reserved for 1st half hour at 10 min intervals and after that at 15min intervals and replace by the personal buffer solution. Reserved sample are analyze through UV spectrophotometer for presence of drug using buffer solution as blank.

CONCLUSION

This study was aimed to formulate and evaluate matrix tablets of Metformin HCl using Sodium Alginate/Pectin polymer. Matrix tablets were prepared by direct compression method in different drug polymer ratios. Drug & polymers interaction was assessed by FTIR spectroscopy & results indicated absence of chemical interactions between them. The physico- chemical compatibility of the drug with polymer was evident from the thermal analysis using DSC. The thermogram obtained showed distinctive and characteristic exothermic peaks of the API indicating its crystalline nature. Blends prepared using different drug polymer ratio were evaluated for pre-compression studies and formulated matrix tablets were evaluated for weight variation, thickness, hardness, friability and Drug content. In-vitro release studies of the matrix tablets were carried out in acidic buffer (pH1.2) as well as in phosphate buffer (pH 6.8) along with the evaluation of Swelling & Erosion studies behavior if the tablets. It is evident from in-vitro drug release studies that, the drug release decreases with increase in the amount of polymer added. Studies also indicated that the extent of swelling and erosion of matrix tablets influences the drug release. A bi-phasic release with an initial burst effect in the matrix tablets is evident from the data obtained. Swelling and erosion studies of Metformin tablets indicated that matrix tablets swell almost from the beginning and its erosion increase with swelling and the time. Cumulative drug release in percentage was found to be sustained for all formulations. The best formulation was MA3 with 93.06% drug release in 12^{th} hr. From further extrapolation of the drug release data it is evident that out of the total 9 formulation studied, seven formulations were good fitted into Korsmeyer-Peppas model and rest of the two formulations were good fitted in Higuchi matrix model.

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