Chapter one

Introduction

1- INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems in the market available as oral drug delivery systems.[1]

Gastric emptying of oral dosage form is extremely variable process and ability to prolong and control the emptying time. Gastric transit time is valuable asset for dosage forms, which remain in the stomach for a long period of time than conventional dosage forms.

Conventional oral dosage forms such as tablets provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in the plasma drug levels. Many attempts have been made to develop sustained release preparations with extended clinical effects and reduced dosing frequency.[2]

The problems frequently encountered with conventional sustained release dosage forms are these : [3]

1-inability to increase their residence time in the stomach.
2- no control over drug delivery, leading to fluctuations in the plasma drug level.

1.1.Floating system

The concept of floating drug delivery system was first described in the literature in 1968 (Davis, 1968), when Davis developed a method for overcoming the difficulty experienced by persons of gagging or choking while swallowing medicinal pills. He suggested that such difficulty could be overcome by providing pills with a density of less than 1 g/cm^3, so that the pill will float on water surface. Since then several approaches have been used to develop an ideal floating system.

1.1.1. mechanism of Floating Systems

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. The system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric residence time (GRT) and a better control of fluctuations in the plasma drug concentration**.[4]**

1.1.2. Advantages of Floating Drug Delivery:[5,6,7]

- Enhanced Bioavailability.
- Sustained drug delivery/reduced frequency of dosing.
- Targeted therapy for local ailments in the upper GIT.
- Reduced fluctuations of drug concentration.
- Reduced counter-activity of the body.
- Extended time over critical (effective) concentration.
- Minimized adverse activity at the colon.
- Site specific drug delivery.

1.1.3. Limitations/Disadvantages:[8,9,10]

- Floating system require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritant to gastric mucosa are also not desirable or suitable.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- The dosage form should be administered with a full glass of water (200-250 ml).
- Floating system do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract

1.1.4.classification of floating system

Floating systems can be classified into two distinct categories ; non-effervescent and effervescent systems.

1-Non-effervescent systems of floating dosage form :

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids(e.g. hydroxyl propyl cellulose, hydroxypropyl methyl cellulose(HPMC),hydroxyl ethyl cellulose), polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene.[11]

The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density less than 1.The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass .[11]

2-Effervescent Systems of floating dosage form : These buoyant systems utilize matrices prepared with swellable polymers such as methocel polysaccharides (e.g., chitosan) and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that when it arrives in the stomach carbon dioxide is released, causing the formulation to float in the stomach .[12]

1.2. metformin

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by a hyperglycemia caused by insulin deficiency, often combined with insulin resistance. In diabetes, the homeostasis of carbohydrate and lipid metabolism is improperly regulated by the pancreatic hormone, insulin; this leading to increase glucose level in blood .[13]

Metformin is a biguanide hypoglycemic agent used in the treatment of type2 diabetes mellitus not responding to dietary modification. Metformin lowers the concentration of glucose in blood and improves

insulin sensitivity by reducing hepatic gluconeogenesis and enhancing insulin-simulated peripheral glucose uptake. It also inhibits adipose tissue lipolysis, thereby reducing circulating levels of free fatty acids . [14]

Metformin is usually taken orally as the hydrochloride salt, in a tablet formulation. It exists largely as a hydrophilic cationic species at physiological pH, and has low lipid solubility, making rapid passive diffusion of metformin through cell membranes unlikely. [15, 16]

The drug is stable, does not bind to plasma protein and is excreted unchanged in urine. It has been reported that the absolute bioavailability of Metformin hydrochloride when given orally is 50-60% only because of its narrow absorption window. Plasma elimination half-life of metformin HCl is1.52-4.50 hrs and the main site of its absorption is the proximal small intestines. [17, 18]

Recently, research has been carried out using Metformin hydrochloride in effervescent-type drug delivery system by using different grades of low density polymer .The gastroretentive floating drug delivery system (GFDDS) was planned for Metformin hydrochloride as such a system when administered would remain buoyant on the gastric fluid for a prolonged period of time and release the drug in sustained manner, thus providing the drug continuously to its absorption sites and increasing the magnitude of drug effect. In this way it have an advantage over conventional dosage form, which needs to be administered twice daily or three times in a day. [18]

It is seem that unique pharmaceutical dosage form of metformin with gastro retentive properties would allow an extended absorption phase of the drug with continues supplying to its absorption site in the upper gastrointestinal tract. The bioavailability of the drug will be improved. [19]

1.3. HPMC

HPMC(hydroxypropyl methyl cellulose) until now the most important carrier material for the drug release systems due to its high swellability and thermal gelation properties.[20]

It is an ether hydrocolloid with good film forming properties. The degree of substitution, types of functional groups substitution, and chain length of this polymer affect permeability, mechanical properties and water solubility .[21]

It is physically stable under normal conditions and chemically inert to the active ingredients, compatible with packing components and easily available .[22]

Chapter two

Materials and Methods

2. materials and methods

2.1. materials used

- Metformin HCl powder
- HPMC
- Sodium bicarbonate
- Tartaric acid
- Citric acid
- Mg stearate
- Talc
- PVP
- Hydrochloric acid 37%

2.2 instruments used in this study

- Sensitive balance
- UV-visible spectrophotometer
- PH meter
- Single punch tablet press machine
- dissolution testing apparatus
- Roche friabilator
- Cowe ® hardness tester

2.3 Methods

2.3.1 characterization of metformin HCl

2.3.1.1 Determination of metformin HCl λ_{max}

0.1 N of HCl with pH 1.2 was prepared . 0.25 gram of metformin HCl powder was accurately weighed and then dissolved into 1000 ml of 0.1 N HCl . From this stock solution , a dilute solution was prepared and scanned by UV spectrophotometer at the range of 200-400 nm , in order to determine wave length of maximum absorbance (λ_{max})

2.3.1.2 determination of calibration curve

Calibration curve of Metformin HCl in (0.1 N) HCl (pH 1.2) was obtained by preparing serial dilutions of the drug from 0.25 mg / ml stock solution.

These serial dilution included the following concentrations :

(12.5 , 16.67 , 10 , 8.3 , 7.14) mg / ml

The absorbance of each solution was determined by spectrophotometrical analysis at the wave length 235 nm and plotted against concentration to obtain the calibration curve .

2.3.2 preparation of metformin floating tablets

Floating tablet were prepared by direct compression method (the process by which tablets are pressed directly of API and suitable excipients). For preparation of tablets , all ingredients were weighed accurately , blended and were compressed directly . No pretreated the physical nature of the former being of the powder blend by wet or dry granulation procedure is wanted .

Compounds	Formula 1	Formula 2
Metformin HCl	40% (250 mg)	40% (250mg)
Tartaric acid	1% (6. 25 mg)	1% (6.25mg)
Citric acid	2% (12.5 mg)	2% (12.5mg)
Sodium bicarbonate	2% (12.5 mg)	2% (12.5mg)
HPMC	53% (331.25 mg)	50% (312.5 mg)
Mg . stearate	1% (6.25 mg)	1% (6.25mg)
Talc	1% (6.25 mg)	1% (6.25mg)
PVP	……..	3% (18.75mg)

Metformin and other ingredients were mixed by geometric dilution method . Then the tablets were compressed by using oval shape single punch tablet compression machine .

2.3.2.1 Pre compression parameter

A - Carr' s index

Carr 's index , the bulk and tapped density of the powder was used . It is expressed via the given equation :

$$\text{Carr 's index (\%)} = \frac{(tapped\ density - bulk\ density\ )\ X\ 100}{tapped\ density}$$

Carr 's index is frequently used in pharmaceutics as an indication of the flowability of the powder **.**

B - Bulk density

Bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume . Hence , the bulk density depends on both the density of the powder particles and the spatial arrangement of the particles in the powder bed .

Bulk properties of a powder are dependent upon the preparation, treatment and storage of the sample .

The bulk density is expressed in gram per milliliter (g/ml) although international unit is kilogram per cubic meter (1g/ml = 1000 kg /m^3) . it may also be expressed in grams per cubic centimeter (g/cm^3) .

Bulk density of the powder is dependent on particle packing and change as particle consolidates . it was calculated using the following equation :

$$\textbf{Bulk density} = \frac{mass\ of\ powder}{volume\ of\ untapped\ powder}$$

C - Tapped density

The tapped density is the increased bulk density of the powder obtained by mechanically tapping a cylinder contained the sample until a little further volume change is observed .

$$\text{tapped density} = \frac{mass}{tapped\ volume} .$$

E - Angle of repose (Θ)

Angle of repose is the angle between the free surface of the powder body and the horizontal plane .It has been widely used to describe the powder flowability .

angle of repose the powder mixture was determined using fixed funnel method. The powder were allowed to flow through the funnel fixed on burette stand ,then the angle of repose was obtained by calculating the high and radius of the heap of the powder formed .

Angle of repose **(Θ)** = $\tan^{-1}\left(\frac{h}{r}\right)$, h : high of pile , r : radius of heap

D - Hausner ratio

Hausner ratio is calculated by the formula :

Hausner ratio = $\frac{tapped\ density}{bulk\ density}$

The hausner ratio is used in wide variety of industries as an indication of the flowability of a powder .

2.3.2.2 tablet Evaluation studies

A - In vitro drug release studies

Release rate of metformin HCl floating tablets were determined using dissolution testing apparatus under sink condition .The dissolution media used was 900 ml of 0.1 N HCl solution PH (1.2) at 37± 0.5 C^o. The stirring speed was 50 rpm . Every half hour for each formula 5 ml of dissolution medium was withdrawn ,filtered and again replaced with 5 ml of fresh medium to maintain sink conditions . Suitable dilutions were done with dissolution medium and were analyzed spectro – photometrically at λ_{max} 235 nm using UV- spectrophotometer .

B - floating lag time (FLT) and total floating time (TFT)

(FLT) and (TFT) of floating tablets were measured visually in 200 mlacidic environment (PH 1.2) at 37 C^o . The time taken for metformin tablet to emerge on the surface of 0.1 N HCl is called floating lag time ,whereas duration of floating was measured visually as long as its kept floating in surface .

C- Weight variation

Five tablets are selected at random , weighed and the average weight was calculated .The average weight was compared to the individual weight of the tablets . For a tablet to pass the test , not more than 2 tablets should lie out of the specified percentage . The tablet weight variations must fallwithin certain specification established by USP (7.5) . Percentage of deviation can be calculated by following formula :

$$\text{Deviation } (\%) = [\frac{average\ weight - weight\ of\ the\ tablet}{average\ weight} \times 100\ \%\ ]$$

D - Friability

Pre – weighed tablet sample (20 tablets) was placed in the Roche friabilator which rotated at 25 rpm for 100 revolutions . The tablets are removed from the drum and cleaned with a cloth and weighed once again. The weight variation must not be more than 1.0 % for a conventional tablet .

E - hardness test

Test measures crushing strength properly defined as the compressional force applied diametrically to a tablet which just fracture it .Hardness adjustments are made throughout tablet run to determine the need for pressure adjustment for tableting machine .If the tablet is too hard , it will not disintegrate , will require a period of time or meet the dissolution specification .If too soft , it will not withstand during subsequent processing .

chapter three

results

3. results

3.1 determination of ג max

Wave length of maximum absorbance was obtained at 235 nm (as seen in the figure 1) .The result has corresponded to united states pharmacopoeia .[23]

Figure 1 , $ג_{max}$ of metformin that obtained

3.2 construction of calibration curve

Calibration curve was obtained by plotting the absorbance of serial dilution prepared versus concentration . The calibration curve was found to be linear in the range (7.14 , 16.67) mcg / ml and straight line equation was obtained having the regression coefficient value of (0.997) . the straight line indicates that calibration curve obeys beer 's law within the range of concentration used.

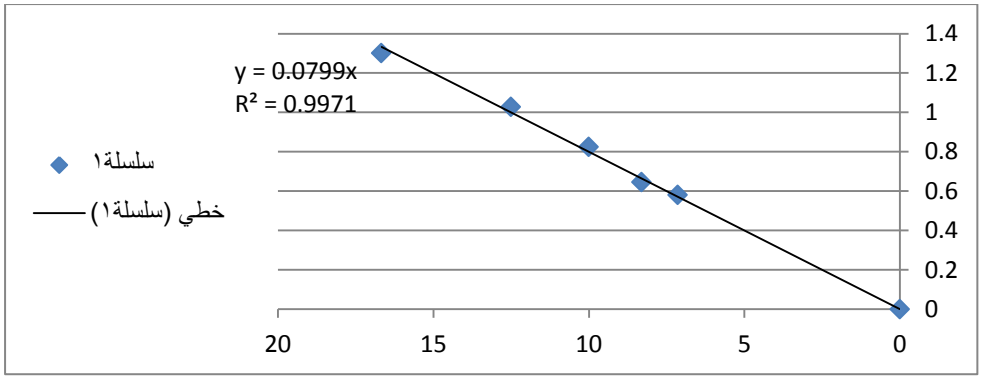

Figure 2 calibration curve (concentation X axis plotted againsted absorption Y axis)

3.3 Precompression parameters

Values of angle of repose , carr ' s index , hausner ratio , bulk density and tapped density are shown in the table below :

Formula no.	Bulk density	Tapped density	Carr's index	Hausner ratio	Angle of repose
Formula 1	0.808	0.909	11.09	1.125	25.66
Formula 2	0.769	1	23.1	1.3	30.87

The results show that Carr's index , hausner ratio and angle of repose were existing with the acceptable limits (indicate an acceptable flow . [25]

3.4 Evaluation studies

3.4.1 Weight variation , hardness and friability

Formula no.	Weight variation	hardness	Friability (%)
Formula 1	2.44± 0.03	58	0.31
Formula 2	3.52 ± 0.02	60	0.44

The results showed that weight variation , hardness and friability were existing with the acceptable limits .

3.4.2 In vivo drug release study

The content of drug was calculated by using a calibration curve a percentage of drug release was plotted against time to determine release profile .

Time	1	2	3	4	6
F. 1	24	32.4	43.7	51.5	63
f. 2	17.8	27.5	36.1	45	56.2

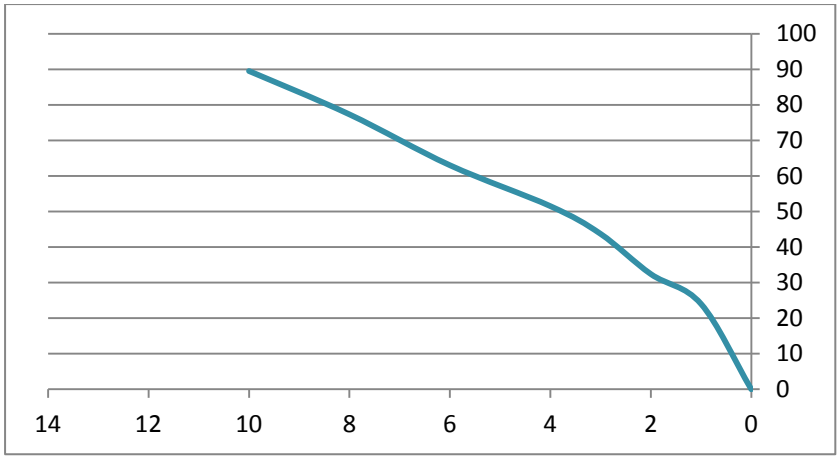

Figure 3 drug release(%) profile for formula1

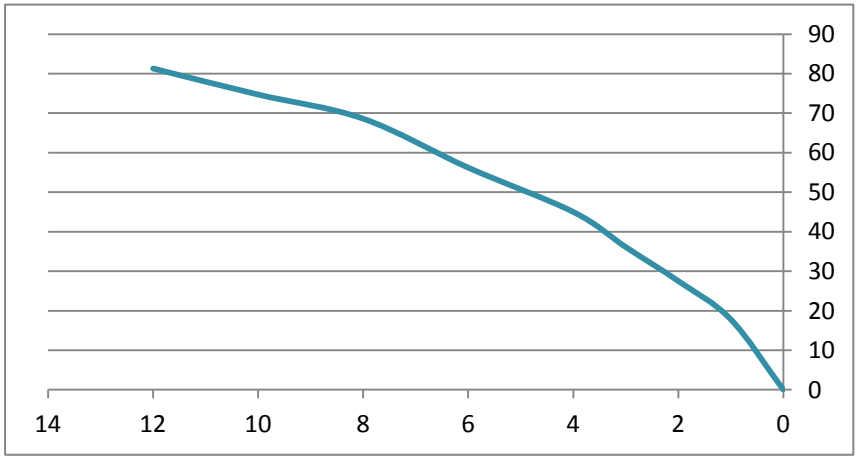

Figure 4 drug release (%)profile for formula2

3.4.3 in vitro buoyancy determination

A) Floating lag time

Formula 1	27± 5 second
Formula 2	19 ± 6 second

B) Total floating time

Formula 1	10.5 ± 0.6
Formula 2	14.4 ± 1.5 hour

Chapter four

DISCUSSION

DISCUSSION

The objective of this study was to develop floating tablets from metformin Hydrochloride to enhance gastro residence time (by using HPMC or HPMC with PVP as sustained polymers) .

HPMC (semi synthetic polymers belongs to the family of hydrophilic polymers)was the most important ingredients of floating tablet based polymers to adjust the release profile of metformin HCL because the ability to swell and make a gel layer around dry core of the polymer matrix and PH independent hydration . In high concentration of HPMC , the viscosity did not significantly affect the drug release .CO2 generated from exposure sodium bicarbonate , tartaric acid and citric acid to acidic fluid of stomach (CO2 will entrapped within gel layer of swollen polymer . It though that PVP effects on the dosage form buoyancy and dug dissolution , because of the water permeation to the matrix and facilitate gelling formation . Tablets were prepared by direct compression methods . Tap density , Carr ،s index , Hausner ratio , angle of repose generally considered as appropriate criteria for evaluation of flow properties of blend . Formula 1 have the following (Carr ، s index 11.09 , Hausner ratio 1.125 , angle of repose 25.66) and formula 2 have the following (Carr ،s index 23.1 , Hausner ratio 1.3 and angle of repose 30.87) that mean the two formula have a good Flow properties and can be used for tablet manufacture . Weight variation and friability of the two formulations were in acceptable limits . Hardness of 58 to 60 was

found optimum to impact the compactness to the system .

FLT of the two formulations was found to be less than 1 minute .

Incorporation of PVP in dosage forms led to decrease in FLT (lower density of PVP compared with HPMC which caused rapid floating of the tablet . Sodium bicarbonate have predominant influence of the floating lag time . The % drug release was in the range of 81.3 % to 89.5 % the optimized formulation was found F2 .

SUMMARY AND DISCUSSION

Metformin HCL immensely utilized in treatment of type 2 diabetes mellitus . It is protonated under strong physiological condition , its pKa is 11.5 and it is a strong base . It was prepared as effervescent floating tablet by using HPMC , PVP ,tartaric acid , citric acid , sod. bicarbonate , Mg stearate and talc . It can be formulated as an approach to increase residence time , thereby improving its bioavailability (metformin have bioavailability 50 -60% under fasting condition , food delays).

Effervescent floating tablets were prepared by direct compression method .Metformin can be liberated constantly at the desired rate from dosage form, while the system is floating on the gastric fluid due to increase in residence time of dosage form in GIT more amount of drug can be released in gastric region .Tablets with ability to float in vitro due to the formation of CO2

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Chapter five

References

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