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FORMULATION AND EVALUATION OF EFFERVESCENT MATRIX FORMING FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of the study was to prolong the gastric residence time of Metformin Hydrochloride by designing its floating tablets and to study the influence of different polymers on its release rate. Different formulations of Metformin Hydrochloride containing varying concentrations of polymers were prepared. The floating matrix tablets of Metformin Hydrochloride were prepared by direct compression method. The prepared tablets were evaluated for physicochemical parameters such as hardness, floating properties (floating lag time, floating time), and drug content. The physicochemical parameters of formulated tablets were found to be within normal range. All the formulations showed good matrix integrity and retarded the release of drug for 10 hours. Thedrug release from final optimized formulation was found to follow Higuchi's model, which confirms that diffusion is one of the mechanisms of drug release.

Keywords: Metformin HCl, Floating lag time, Drug release, Polymers.

INTRODUCTION

Floating drug delivery systems were first described by Davis in 1968. It is possible to prolong the gastric residence time of drugs using these systems. Several techniques are used to design gastro retentive dosage forms. These include floating, swelling, inflation, adhesion, high density systems and low density systems that increase the gastric residence time. Gastric retention is useful for drugs which (i) act locally; (ii) have a narrow absorption window in the small intestinal region; (iii) unstable in the intestinal environment; (iv) low solubility at high pH environment. Various dosage forms developed for gastric retention include, floating tablets, floating beads, pellets, floating granules, floating microspheres. In this investigation, an attempt was made to design floating tablets of Metformin HCl using different release retarding polymers along with an effervescent agent [1, 2].

Metformin HCL is a biguanide glucose-lowering agent that has been widely used in management of Non Insulin dependent Diabetes Mellitus (NIDDM). It improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose [3-9]. Metformin HCL is incompletely absorbed from the gastrointestinal tract (GIT) with oral bioavailability of 50% due to narrow absorption window in the upper part of GIT.

A single immediate release dose of Metformin HCL exhibits a flip-flop model and a bio-availability of about 61%. Metformin HCL is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68 [10-11]. The t_{max} of Metformin HCL is 2 hours and $t_{1/2}$ is 2.6 hours. Metformin HCL is stable but the narrow absorption window of metformin hydrochloride in the upper part of GIT provides a rationale for developing a Floating Drug Delivery System (FDDS) for this drug [12-18]. Such a dosage form (FDDS) would be retained for prolonged periods of time in stomach and release drug in a sustained manner, thus providing drug continuously to its absorption sites in a controlled manner and increases the magnitude of drug effect. Dose of 500 mg was found to be optimum in formulating the tablets to counteract the most common gastrointestinal side effects, as well as to increase compliance by reducing dosage burden. Polymers like HPMC K 100M, Polyox resins 301 and 303 were selected

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as polymer to decrease the density of the dosage form. Poloxamer F-68 and Sodium Lauryl Sulphate were selected as solubility enhancers. Avicel PH-200 was selected as diluent in the formulation. Talc and Magnesium stearate were selected as lubricants and anti-adherents.

MATERIALS

Metformin HCl is an Active Ingredient (Aarti Drugs, Sion) and Excipients used in this formulation are hydroxyl propyl methylcellulose K100M, Poly Ethylene oxide used as a Polymer (Colorcon Ltd), Sodium bi carbonate used as a Effervescent agent (LobaChemie, Mumbai), Avicel PH 200 as a Diluent (Meyer Organics Ltd), Magnesium stearate and talc as a Lubricant (Alkem Labs, Mumbai), Hydrochloric acid and Double Distilled water. Digital balance and Tablet punching machine. Digital dissolution apparatus USP XXIII paddle, Monsanto tablet hardness tester, Screw gauge (Thickness tester), Rochefriabilator.

METHODS

Direct Compression technique

Tablets were prepared by direct compression technique**.**All the ingredients were mixed in increasing order of weights and then blended. Blend was compressed on single punch compression machine using caplet shaped bevelled punch for 950 mg. The tablets were evaluated for appearance, hardness, friability, and floating behaviour and in-vitro drug release.

Determination of bulk density and tap density

Apparent bulk density (ρ_o) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) was determined. The bulk density was calculated using the formula.

$$\rho_o = M/V_b$$

The measuring cylinder containing a known mass of powder or granules was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ) was calculated using the following formula.

$$\rho = M/V_t$$

Compressibility index

The measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as

$$I = (\rho - \rho_o/\rho) \times 100$$

ρ = tapped density, ρ_o = initial bulk density

The value below 15% indicates a powder which usually give rise to good flow characteristics whereas above 25% indelicate poor flow ability [17, 18]. Haunsner ratio is an indirect index of ease of powder flow. It is calculated by the formula which follows:

Haunsner ratio= $\rho t / \rho d$ Where, ρt = tapped density, ρ = bulk density.

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose (□). It was determined using funnel method. The powder or granules were poured through a funnel that can be raised vertically unit a maximum cone height (h) was obtained. Radius of the heap(r) was measured and the angle of repose (q) was calculated (□□).

□□= $Tan^{-1}(h/r)$

Hardness test

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packing and shipping. Monsanto hardness tester was used to measure and results were expressed in kg/cm^2.

Flow rate

The flowability characteristic of a powderis directly related to both thephysical properties of the materialitself, as well as thespecific processing conditions in the handling system**.**

Thickness and diameter

The thickness and diameter of the tablet was measured using vernier caliper. Five tablets were used for the above test from each batch and results were expressed in millimeter.

Weight variation test

Twenty tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to I.P. specification.

Drug content uniformity

5 tablets were randomly selected and weighed. Tablets were powdered in a glass mortar. Powder equivalent to 100 mg was weighed and dissolved in 70 ml of 0.1 N HCL in 100 ml volumetric flask and solution was sonicated to obtain the clear solution. Volume was made upto 100 ml then filtered. 10 ml was pipetted out and diluted with the HCL solution to 100 ml. Then, 10 ml of solution was pipetted out and diluted to obtain the concentration of 100 ug/ml. The absorbance of this solution was noted at 232.2 nm in each case.

In-Vitro Buoyancy Studies

The time tablet took to emerge on the water surface (floating lag time) and the time for which tablet constantly float on the water surface (duration of floating) were evaluated in a dissolution vessel containing 900 ml of 0.1N HCL (pH1.2) previously set at $37^0 \pm 0.5^oC$.

Dissolution Studies

In vitro drug release studies of Metformin HCl were done using dissolution apparatus USP type II paddle method with a stirring speed of 100 rpm at $37^{O}C \pm 0.5^{O}C$ in 900 ml of (pH 1.2) simulated gastric fluids for 10 hours. The samples were taken at pre-selected for 10 hours with replacement of equal volume of dissolution media. The collected samples were diluted and the absorbance was measured spectrophotometrically at 232 nm. The percentage of Metformin HCl released at various time intervals were calculated from the standard graph.

Release kinetic studies

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. To describe the kinetics of the drug release from matrix tablet, mathematical models such as zero-order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

- The zero-order kinetics describes the systems in which the drug release rate is independent of its concentration.
- The first order kinetics describes the systems in which the drug release rate is concentration dependent.
- Higuchi describes the release of drug from an insoluble matrix as square root of time dependent process. The Higuchi square root model also gives the drug release from a planar surface of an insoluble heterogeneous matrix by diffusion through the intragranular openings created by porosity of the matrix tablet.
- The Hixson-Crowell cube root law describes the drug release from systems in which there is a change in the surface area and the diameter of particle present in tablet.

In case of Korsmeyer-Peppas model, the drug release from such devices having constant geometry will be observed till the polymer chains rearrange to equilibrium state. Korsmeyer-Peppas model describes theraction released $Qt/Q\infty$ as powerfunction of time t for short time period.

Formulation of floating tablets

Initially the batches were taken with HPMC K100M and were checked for in vitro release and lag time. The batches showed good lag time, but failed *in vitro* release profile as per specification. Batches F_5, F_6 and F_7 were taken by varying the concentration level of Polyox resins, but these batches showed less than 25% release in 1 hour and less than 80% release at 10 hour, which was not as per the specification. Batches F_8-F_{13}were taken by using Polyox 303 with varying concentration of sodium bicarbonate to evaluate its effect on drug release. These batches showed less than 64% release in 10 hours. Batches $F_{14} - F_{16}$ were taken by using Polyox 303 with varying the concentration levels of Polyox 301, these batches also showed less than 64% release in 10 hours. Batches F_{17}-F_{25}were prepared using Poloxamer F-68 as solubility enhancer. Batches F_{17}-F_{19} contained Polyox 301 and 303 in equal proportion with variation in concentration of sodium bicarbonate. Batches F_{20} and F_{21} were prepared using only one grade of Polyox. Batches F_{22}-F_{25} were prepared using lower concentration of Polyox 303. All these batches showed less than desired release. Thus it was concluded that Poloxamer F-68 did not have substantial effect on release of drug from formulation. Further batches F_{26}-F_{31} were taken using SLS as solubility enhancer. SLS used as a solubiliser was found to improve the release of drug from the matrix formulation. F_{26} showed release upto 82% and batches F_{27} and F_{28} showed good lag time and release upto 83.11% at 10 hrs. Hence, it was decided to further increase the concentration of SLS. SLS was used in the concentration range of 1-2% and it was found that 1% SLS in batch F_{29} gave more than 85% release. Formula as shown in below table. 2, the optimum batch

F_{30} and F_{31} showed release 83% and 82% respectively compared to F_{29} with 89% release in 10 hours and lag time of more than 40 secs compared to F_{29} with lag time of 4 secs. Thus, F_{29} was found to be the optimum batch.

Stability Studies of Optimized batch

The stability study of dosage form is essential in determining the stability of active pharmaceutical ingredient along with the other excipients. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under exacerbated conditions of temperature. Tablets of batch F29.were subjected to stability studies.

Experimental

Tablets of the optimized formulation (F_{29}) were tested for stability under two conditions for a period of three months. All the tablets were packed in Aluminium type strip package. The tablets stored in stability chambers maintained at $40^{0}C$/ 75% RH, were evaluated for their physical characteristics, *in vitro* release and content of active ingredient at the end of 0 day, 15 days, 30 days, 60 days and 90 days of storage period. Following parameters were evaluated for the optimized formulation:

Physical characteristics

Various parameters evaluated were appearance, thickness, diameter, hardness and friability using the method described earlier.

Uniformity of weight

Twenty tablets were randomly selected from stability batches and weighed individually to check for weight variation and results were compared with the

specification.

Drug content

The drug content of Metformin Hydrochloride was determined using following procedure; five tablets were accurately weighed and finely powdered. An accurately weighed amount of the powdered tablets equivalent to 100 mg was transferred into a 10 ml volumetric flask to which 5.0 ml diluent (Water pH 3: Acetonitrile) was added.

The solution was sonicated for 2 hours, and then 5.0 ml diluent was added. The solution was further diluted, filtered and then centrifuged to obtain concentration of 100µg/ml and then solution was injected into the column.

RESULTS OF STABILITY BATCHES

Physical parameters

The physical parameters after 0 day, 15^{th}, 30^{th}, 60^{th} and 90^{th} day were as mentioned in **Table. 3**. All the physical parameters were in the acceptable limits which showed that formulation was stable.

In vitro dissolution studies

From the physical parameters and vitro release profile it was found that stability batches ofoptimized batch was stable.

The stability studies of the optimized formulation (F_{29}) revealed that there were no significance changes in the physical parameters when stored in accelerated temperature and humidity conditions hence no special storage conditions are required and the optimized formulation did not show any significant change in the drug release profile.

Comparative study of release profiles of Marketed Preparation and the Optimum Batch (F_{29})

Release profile of plain drug, marketed product and the optimum batch were compared using same dissolution protocol as mentioned earlier. It was observed that Marketed product showed 90.22% release and optimised batch showed 89.66% release in 10 hrs.

Similarity (f_2) and dissimilarity (f_1) factors were observed as 100.95 and 12.14 respectively. Different kinetic models were studied from dissolution profile of the final optimized formulation (F_{29}). Table. 4indicates the r^2 value for each model. It was observed that Higuchi model was the dissolution model followed by the optimum batch.

Table 1. Formulation of Metformin HCl floating tablets

Ingredients	Quantity per Tablet (mg)					
	F_{26}	F_{27}	F_{28}	F_{29}	F_{30}	F_{31}
Metformin HCL	500	500	500	500	500	500
Polyox 303	300	300	300	300	300	300
Sodium bicarbonate	60	60	60	60	60	60
SLS	2.85	3.8	4.75	9.5	14.25	19
Avicel PH-200	81.15	80.2	79.25	74.5	69.75	65
Magnesium stearate	1	1	1	1	1	1
Talc	5	5	5	5	5	5
Total	950	950	950	950	950	950

Table 2. Formulation of finalized batch.

Ingredients (Quantity in mg)	Formulation code (F_{29})
Metformin HCl	500
Polyox 303	300
Sodium Bicarbonate	60
SLS	1%
Avicel PH-200	74.5
Magnesium Stearate	1
Talc	5
Total	950

Table 3. Evaluation of Optimized batch

Physical parameters	Stability Conditions	0 Day	15^{th} Day	30^{th} Day	60^{th} Day	90^{th} Day
Appearance	40^0C/75%RH	Good	Good	Good	Good	Good
Thickness(mm)	40^0C/75%RH	0.89±0.011	0.91±0.012	0.88±0.02	0.943±0.01	0.91±0.01
Hardness Kg/cm^2)	40^0C/75%RH	4.5	4	3.5	4.5	4.5

Friability (%)	40^0C/75%RH	1.09	0.12	0.724	0.88	0.787
Uniformity of weight (mg)	40^0C/75%RH	Passes	Passes	Passes	Passes	Passes
Lag time(sec)	40^0C/75%RH	5	2	4	6	3
Total time (hrs)	40^0C/75%RH	12.5	12	12	12.5	12
Swelling Index (%)	40^0C/75%RH	89.01	87.13	81.91	90.04	89.98
Drug Content (%)	40^0C/75%RH	99.473	102.67	101.98	97.76	98.60

Table 4. Drug release kinetics of optimised batch (F_{29})

Formulation	Zero Order	First Order	Higuchi Model	Korsmeyer Model	Hixon Crowell Model
F_{29}	0.865	0.901	0.994	0.855(n=0.786)	0.871
Reference Product	0.909	0.922	0.996	0.921(n=0.922)	0.912

Fig 1. In vitro release profile of Stability Batch

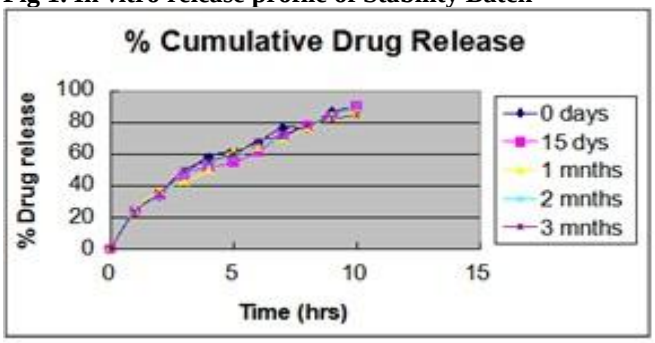
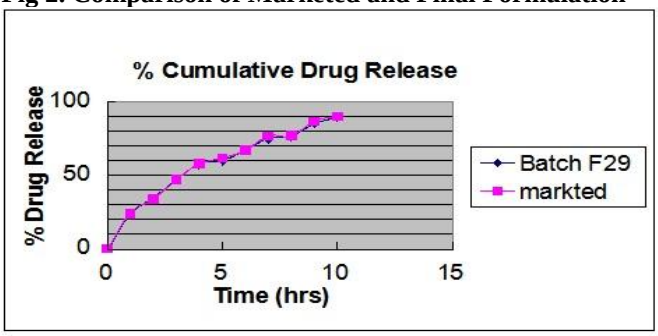


Fig 2. Comparison of Marketed and Final Formulation



RESULTS AND DISCUSSION

Batch F_1 was formulated using HPMC K100M and sodium bicarbonate as effervescent agent showed good texture, lag time of 1 min and 75.90% drug release. F_2 batch was formulated using lower concentration of HPMC that showed lag time of 2.5 min, drug release 77.99% with bad tablet appearance. Both the batches showed greater lag time hence sodium bicarbonate was used in ascending concentration in the further formulations. To attain desired dissolution rate, lag time and appearance, batches F_3 and F_4 were taken using increasing concentration of sodium bicarbonate. It was found to have improved lag time and texture, but decrease in release rate. Batches F_5 onwards were formulated using various grades of Polyox. Batches F_5 - F_7 were formulated without sodium bicarbonate, but were found to show more lag time, thus, these batches were not selected irrespective of their texture and release rate of drug. Batches F_8 – F_{11} were taken using different concentration levels of sodium bicarbonate in order to evaluate the effect of bicarbonates on drug release. These batches showed comparatively similar lag time and drug release without good tablet texture compared to earlier batches. Batches F_{12} and F_{13} showed good texture, lag time upto 40 sec, but the release rate was not found to be changed. Batches F_{14}-F_{16} showed release upto 66%, hence, it was concluded that increase in Polyox concentration results into greater sustained release of drug. It was decided to keep the concentration of Polyox in the range of 30-40%, since good release was obtained in this concentration range. Batches F_{17}-F_{21} implies the use of Poloxamer F-68 (5%) as solubilising agent, these batches showed relatively less lag time and tablet texture was found to be improved. The release rate was found still confined to less than 75%. Thus, the solubilising agent was changed to SLS to increase the drug release rate. Batches F_{26}-F_{31}were taken with SLS in range from 0.3%-2%. These batches showed lag time upto 58 sec, F_{29} and F_{31} showed very good texture. F_{29} showed lag time of 4 sec and release obtained in 10 hrs was greater than 89%. Thus, this batch was selected as optimum batch and was kept for 3 months stability studies.

CONCLUSION

Metformin HCL is a biguanide glucose-lowering agent that has been widely used in management of Non Insulin dependent Diabetes Mellitus (NIDDM). It improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. Metformin HCL is incompletely absorbed from the gastrointestinal tract (GIT) with oral bioavailability of 50% due to narrow absorption window in the upper part of GIT. A single immediate release dose of Metformin HCL exhibits a flip-flop model and a bio-availability of about 61%. Metformin HCL is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin

hydrochloride is 6.68. The Tmax of Metformin HCL is 2 hours and t1/2 is 2.6 hours. Therefore the selected drug was suitable candidate for the Floating Drug Delivery system (FDDS). The present research was directed towards the development of floating drug delivery system which will float on the gastric fluid and thus, sustained release of drug is obtained.

Authentication of drug was done by UV spectrophotometry, FTIR and melting point methods. Powder characteristics of drug were examined. Calibration curve of Metformin HCL was constructed in dil.HCL by using U.V. spectrophotometer. Mobile phase [pH 3.0 water: Acetonitrile (80:20)] was used to develop calibration curve by HPLC method. pH solubility profile of Metformin HCL was established. The compatibility of drugs with excipients was checked by DSC and FTIR studies. Force degradation studies of drug were done under acidic, basic, aqueous, oxidation, photo and dry heat conditions.

FDDS were formulated using such as HPMC K100M, Polyox resins 301 and 303. Sodium bicarbonate was used as effervescent agent. Poloxamer F-68 and SLS were used as solubility enhancers. Avicel PH-200, a directly compressible diluent was used in the formulations. For all formulations talc and magnesium stearate were used as glidant and lubricant respectively. Tablets were formulated by direct compression of the above excipients using caplet shaped bevelled punch.

Tablets were evaluated for various physical parameters such as appearance, hardness and friability. Formulations were evaluated for in vitro lag time, assay, swelling index, uniformity of content and *in vitro* drug release. Drug release of optimised batch (F29) was compared with marketed product. The optimized batch was subjected to stability study at 40°C/ 75% RH for three months.

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CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

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