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DEVELOPMENT & EVALUATION OF FLOATING BILAYERED TABLETS OF METFORMIN HCL & GLIMEPIRIDE

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ABSTRACT

Formulation development is an important part of drug design and development. Bioavailability and bioequivalence are totally dependent on formulation development. Now-a-days formulation development is done by following QbD (Quality by Design).The aim of present study is to formulate Metformin HCl sustained release (SR) and Glimepiride immediate release (IR) bilayer tablet by different concentration of Hydroxypropyl methyl cellulose (HPMC) HPMC E-15and HPMC K4M to control the release pattern. The sustained release layer of Metformin HCL was prepared by using different grades of HPMC like, HPMC K-15, HPMC K-4 along with other excipients by direct compression technique. The immediate release layer of Glimepiride was prepared by Povidone, Crospovidone and by direct compression technique. The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. Bi-layered tablet were characterized by FT-IR and in vitro dissolution studies. The drug release study of Bi-layered tablet was evaluated using USP-II paddle type dissolution apparatus. From the 5 batches F5 batch showed good release behaviors 95.61% of drug is released over 20 hours. Total 5 trial batches of each drug have been manufactured to optimize and develop a robust and stable formulation.

KEYWORDS: Bilayer tablet, Metformin HCl, Glimepiride, Hydroxy propyl methyl Cellulose, Povidone, Crospovidone.

INTRODUCTION

The basic goal of therapy is to achieve a steady-state blood or tissue level that therapeutically effective for an extended period of time. In the recent past, controlled release concept and technology have received increasing attention in the face of growing awareness to toxicity and effectiveness of drugs when administered or applied by conventional methods. Thus, drugs applied in the form of tablets, capsules, injectables and ointments etc., usually produce wide range of fluctuations in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor as well such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems or therapeutic systems.[1-3] The aim of the present work is to formulate and evaluate Bilayer Floating tablets of Metformin HCl and Glimepiride for the treatment of type-2Diabetes Mellitusby using Hydrophilic polymers like HPMC K4M, HPMC E-5 and HPMC E-15. Individual tablet was formulated and optimized separately by *in-vitro*studies.To study the effect produced by employing various viscosity grades of Hydrophilic polymer, reduced-dose frequency, economically cheaper, Reduced pill burden, providing easy medication and Improve patient compliance.[4,5]

Table 1: Formulation of Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR.

S.No.	Ingredients	Formulation code (amount per tablet in mg)				
1.	Metformin HCl	250	250	250	250	250
2.	HPMC K4M	50	50	-	-	100
3.	HPMC E-15	-	100	50	100	150
4.	Carbopol 934	100	100	100	100	100
5.	Sodium Bicarbonate	100	100	100	100	100
6.	Citric Acid	50	50	50	50	50
7.	Povidone	60	60	60	60	60

8.	Glimepiride	1	1	1	1	1
9.	Povidone	10	10	10	10	10
10.	Dicalcium Phosphate	38.98	38.98	38.98	38.98	38.98
11.	Magnesium Stearate	1%	1%	1%	1%	1%
12.	Talc	1%	1%	1%	1%	1%

Weight of active ingredient = 250mg
Total weight of tablet = 650mg

Evaluation of Granules

Bulk Density and Tapped Density

Bulk density is the ratio between a mass of granules and its bulk volume (Vo). It is expressed by g/cc.[6,7]

Bulk Density = Mass of Powder Bulk/ Volume of Powder (Vo).

Tapped density is the ratio between mass of granules and volume of the granules after tapping (VF). It is expressed by gm/cc.

$$\text{Tapped Density} = \frac{\text{Mass of powder}}{\text{Tapped volume of powder(VF)}}$$

Compressibility Index and Hausner's Ratio

The compressibility index and Hausner's ratio are measures the flow property of a powder to be compressed.[8,9]

The compressibility index and Hausner's ratio are calculated by measuring the values for bulk density (ρ bulk) and Tapped Density (ρ tapped) as follows, and official limits are shown in the table.

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio is the measurement of frictional resistance of the drug and the ideal range should be 1.2-1.5 and the official limits are shown in table.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Angle of repose

The angle of repose is defined as the maximum angle possible between the surface of a pile powder and the horizontal plane. The tangent of the angle is equal to the coefficient of friction between the particles.[10,12]

$\tan\theta = h/r$

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

Where, h = height of the pile

r = radius of the pile.

Physical Evaluation of Tablet

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual weight deviates from the average weight by more than the percentage shown in the table no. (20) and none should deviate by more than twice the percentage shown.[13-16]

Hardness

The tablet-crushing load is the force required to break a tablet by compression. Hardness was measured by using hardness tester (Pfizer hardness tester). For each batch, six tablets were selected randomly and evaluated. Hardness of about 4-6 kg/cm2 is considered to be minimum for uncoated tablets and for mechanical stability.[17-20]

Friability[21]

$$\text{Percentage Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} \times 100$$

Floating Lag[22]

Time The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Total Buoyancy Time[23]

The time for which the tablets constantly float on the surface was determined as total buoyancy time.[24]

Drug content analysis

For Metformin hydrochloride

Weigh accurately a Metformin hydrochloride, shake with 70ml of water for 15 minutes, make up to 100ml with water, and filter. Dilute 10ml of the filtrate to 100ml with water. Further 10ml of the filtrate were make up to 100ml with water and measure the absorbance of the resulting solution at the maximum about 232nm. Calculate the content of C4H11N5, HCl taking 798 as the specific absorbance at 232nm.[25]

For Glimepiride

Twenty tablets from each batch were weighed and powdered. Powder equivalent to 4mg of Glimepiride was accurately weighed and transferred into 100ml volumetric flask and dissolve in acetonitrile until clear solution is obtained. The resulting solutions was made to 100ml with 0.1N HCl and shake for 10 mins. The 10ml of the above solution was diluted up to 100ml with 0.1N HCl and filtered through 0.45µ membrane filter analyzed by Shimadzu UV/VIS double beam spectrometer at 226.7nm.

$$\text{Percentage purity of Drug content} = \frac{\text{Amount of drug}}{\text{Label claim}} \times 100$$

$$\text{Amount of Drug} = \frac{\text{Sample}}{\text{A (1\% 1cm)}} \times \frac{\text{OD Sample Dilution}}{\text{Sample Weight}} \times \text{Average Weight}$$

$$\text{Sample Weight} = \frac{\text{Average weight}}{\text{Label claim}} \times \text{Equivalent Weight}$$

In-Vitro Drug Dissolution Test

The in-vitro dissolution study of Floating Metformin HCl SR tablet, Glimepiride IR tablet and optimized Bilayer Floating tablet of Metformin HCl SR and Glimepiride IR were performed according to USP apparatus II (Basket type). The following parameters are considered for the dissolution study. The dissolution study was carried out for all the formulations and the best release profiles were compared using kinetic model.[26]

Drug release kinetics

Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time‘t’ or Q(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models. These models are used to characterize drug dissolution/release profiles.

RESULT AND DISCUSSION

Table 2: Precompression parameters of Floating bilayer tablet of Metformin HCl and Glimepiride.

Formulation batch code	Angle of repose (°)	Bulk density (gm)	Tapped density (gm)	Carr’s Index (%)	Hausner’s Ratio
F1	23.98 ± 0.6	48.6 ± 0.05	62.3 ± 0.1	13.20 ± 0.56	1.26 ± 0.65
F2	23.21 ± 0.3	50.2 ± 0.02	59.5 ± 0.5	15.21 ± 0.25	1.19 ± 0.27
F3	25.01 ± 0.5	51.06 ± 0.03	61.0 ± 0.3	14.01 ± 0.29	1.12 ± 0.51
F4	24.8 ± 0.4	51.20 ± 0.07	62.7 ± 0.7	14.21 ± 0.19	1.31 ± 0.27
F5	25.1 ± 0.7	47.9 ± 0.04	60.8 ± 0.1	19.01 ± 0.51	1.25 ± 0.41

Table 3: Physicochemical Characteristics of Floating Bilayer tablet of Metformin HCl SR & Glimepiride IR.

Formulation batch code	Average weight of tablets(g)	Hardness (Kg/cm2)	Friability (%)	Drug content (%)	Floating lag time (Secs)	Total buoyancy time (Hrs)
F1	652 ± 0.32	6.0 ± 0.5	0.23 ± 0.03	98.99 ± 0.21	25 ± 0.23	22 ± 0.19
F2	648 ± 0.25	6.5 ± 0.25	0.27 ± 0.04	99.12 ± 0.19	22 ± 0.17	19 ± 0.25
F3	653 ± 0.55	5.0 ± 0.5	0.19 ± 0.05	99.16 ± 0.18	29 ± 0.09	22 ± 0.51
F4	650 ± 0.55	6.0 ± 0.5	0.16 ± 0.02	98.95 ± 0.51	24 ± 0.16	21 ± 0.49
F5	647 ± 0.41	5.5 ± 0.35	0.25 ± 0.02	98.96 ± 0.42	30 ± 0.05	20 ± 038

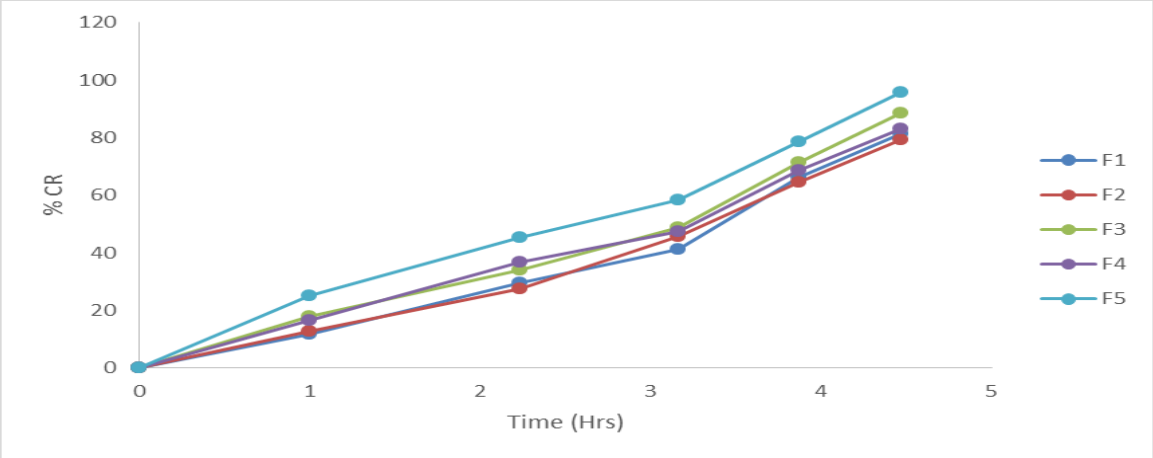

Figure 1: Release profile of the prepared formulations.

The physico-chemical and *in-vitro* release of floating Bilayer tablet kept at 40ºC 75% RH were studied for 3 months as per ICH guidelines. The parameters are shown in the table.

CONCLUSION

This study discusses the preparation and evaluation of gastro-retentive bilayer tablets of Metformin-HCl and Glimepiride. Floating Bilayer tablet were formulated using HPMC K4M, HPMC E-15 in alone (80%) and in combination of different percentage of polymer. Different formulations(F1,F2,F3,F4,F5)are prepared by employing the hydrophilic polymer HPMC in different viscosity grades in the percentage of 80%. From that F5 formulation were found to be suitable for formulating SR tablet by its *in-vitro* release. From the F5 formulation, it was clear that when the polymer concentration increases it decreases the release rate. Floating Bilayer tablet of Metformin HCl SR and Glimepiride IR were formulated using HPMC K4M, HPMC E-15 in alone (80%) and in combination of different percentage of polymer.From the dissolution profile of formulation F5 it was well understood that the release of drug from its formulation can be improved by combining the low and high viscosity polymers compared to formulating high viscosity polymer alone. From this study it was concluded that Floating time increases, it decreases the release rate. So, it suitable for sustained release formulation.

The effervescent based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel forming polymer HPMC K4M and gas generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. Stable and persistent buoyancy was achieved by trapping the gas in the gel formed by the hydration of HPMC K4M.Tablets containing HPMC K4M showed satisfactory buoyancy characteristics and longer floatation time. The drug release from the tablets depends upon the nature of gel matrix. It was observed that polymer swelling play an important role in drug release from the floating tablets. Hence it can be concluded that the effervescent based floating drug delivery is a promising approach to achieve buoyancy.

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