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Studies on formulation and *in vitro* evaluation of Glimepiride floating tablets

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ABSTRACT

Floating matrix tablets of glimepiride were developed to prolong the gastric residence time and thereby increased drug bioavailability. Diabetes condition influences the gastric emptying time which affect the absorption of the drug. Glimepiride was chosen as model drug because it has incomplete absorption due to less gastric residence time. The tablets were prepared by direct compression technique, using various grades of rate controlling polymers, Carbopol 934P either alone or in combination and other standard excipients. Tablets were evaluated for physical characteristics viz. hardness, % friability, floating capacity and content of dosage form. Tablets were evaluated for in vitro release characteristics for 8 h. In vitro drug release mechanism was evaluated by linear regression analysis. Floating matrix tablets based on the combination of polymers exhibited desired floating and prolonged drug release for 8h.

Keywords: Glimepiride, release kinetics, floating matrix tablets, fickian diffusion.

INTRODUCTION

Diabetes mellitus is a group of metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, action or both. In, 1990, 23.4 million of oral antidiabetic agents were dispensed. By 2001, this number had increased to 91.8 million prescriptions. Consistent with the reported increase in the prevalence of type 2 diabetes, the number of dispensed outpatient prescription of oral antidiadetic drug increased rapidly between 1990 and 2001[1].

Glimepiride is a FDA approved sulfonayl urea oral antidiadetic drug, which has rapid and complete absorption after oral administration [2]. Diseased state (diabetes) influences the gastric emptying rate. Modulated gastric emptying rate affects the absorption of the drug. Incomplete absorption of the drug is often accompanied by lesser bioavailability [3]. Enhanced gastric retention would enable extended the absorption phase of the drug. After oral administration of

gastro retentive dosage form of Glimepiride would be retained in the stomach and release the drug in a sustained manner, so that the drug could be released continuously to its absorption site in the upper GIT. This mode of administration would be best achieving the hypoglycemic effect of the drug. Based on this, an attempt was made to formulate floating matrix tablet of Glimepiride using different grades of polymers and combinations. The prepared tablets were evaluated for physical characteristics such as hardness, thickness, %friability, floating capacity. All the tablets were evaluated for *in vitro* drug release profile and release kinetics.

EXPERIMENTAL SECTION

Glimepiride was obtained as gift sample from Dr.Reddy's Laboratories (Hydrabad, India). Hypromellose K4M CR and K100M CR (Hydroxypropyl methyl cellulose 4000 and 100000 cps respectively) were obtained as gift sample from Colorcon Asia Pvt. Ltd and were used as received. Carbopol 934P was obtained from B.F Goodrich. Other ingredients were commercially obtained from S.D Fine chemicals, (Mumbai, India) and used and as received.

Preparation of glimepiride floating tablets:
Direct compressible blend was prepared in the weight proportion as mentioned in the table 1 using Glimepiride, Lactose monohydrate, Sodium bicarbonate, Hypromellose K4M CR or Hypromellose K100M CR, Carbopol 934P and Magnesium stearate. The homogenous blend was compressed into tablets on a single punch tablet press (Rimek mini press, India) equipped with 7mm diameter standard concave punch and die.

Physical characterization:
The fabricated tablets were characterized for weight variation (n=20), hardness (n=6, Monsanto hardness tester), thickness using Vernier caliper and % of friability (n=20, Roche friabiliator, Electrolab, Mumbai, India)

Assay of tablets:
Twenty tablets from each batch were weighed and powdered. Powder equivalent to 4 mg of Glimepiride was accurately weighed and transferred into a 100 ml volumetric flask and shake with 100 ml of methanol for 10 min. The 10 ml of methanolic solution was diluted up to 100 ml with 0.1N HCl with 0.5% w/v of sodium lauryl sulphate and sonicated for 5 min. to get a concentration in the range of 4 µg/ml. A portion of the sample was filtered through 0.45µ membrane filter and analyzed by Shimadzu UV/VIS double beam spectrometer (Kyoto, Japan) at 236nm.

Buoyancy test:
The fabricated tablets were subjected to the buoyancy test (n=6). As per method described by *Rosa et.al* [4]. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

***In vitro* dissolution studies:**
The drug release profile of fabricated Glimepiride floating tablets (n=6) were determined using USP 31 apparatus I (Electrolab dissolution tester, Mumbai, India). The dissolution medium was 900 ml, 0.1 N HCl with 0.5% w/v of sodium lauryl sulphate (pH 1.2) at 37±0.5^{0}C with agitation speed of 50 rpm. Samples were withdrawn at regular intervals over an 8 h period, filtered through 0.45µ membrane filter. Filtered samples analyzed by Shimadzu UV/VIS double beam spectrometer (Kyoto, Japan) at 236nm.

Drug release kinetics:

To study the release mechanism of the drug release profile, *in vitro* drug release studies were plotted in various kinetic models. Zero order as cumulative amount of drug released *Vs* time. First order as log cumulative amount of drug remaining *Vs* time and Higuchi's model as cumulative percentage of drug released *Vs* square root of time.

$$C = K_0 t$$

Where K_0 is the zero order rate constant expressed in units of concentration and t is the time in hours. A graph concentration *Vs* time would yield a straight line with a slope equal to K_0 and intercept origin of the axes [5].

$$\text{Log } C = \text{Log } C_0 - Kt/2.303$$

Where C_0 is the initial concentration of drug. K is the first order rate constant and t is the time in hours [6].

$$Q = Kt^{1/2}$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence the drug release rate is proportional to the reciprocal of the square root of the time [7].

To evaluate the mechanism of drug release from Glimepiride floating tablets, drug release were plotted in Korsmeyer equation as log cumulative percentage of drug released Vs log time, and the exponent n was calculated through the slope of the straight line [8].

$$M_t/M_\infty = Kt^n$$

Where M_t/M_∞ is the fractional solute release, it is the release line. K is the kinetic constant characteristic of the drug polymer system and n is an exponent that characterizes the mechanism of the drug release. For cylindrical matrix tablets, if the exponent n=0.45, then the drug release mechanism is Fickian diffusion. If $0.45 < n < 0.89$, then it is non Fickian or anomalous diffusion.

RESULTS AND DISCUSSION

Compressed tablets of all the batches were circular in shape with no visible cracks. All the formulations showed reasonably good hardness value. Friability of the fabricated tablets was less than 0.5%w/w. Assay value of the all batches are within the range of 98% - 101%. Results are shown in the Table2.

Floating capacity of the fabricated tablets was determined in 0.1N HCl, and the results are presented in Table 2. The tablets of all the batches exhibited floating lag time less than 100 s. The tablets of Carbopol 934P batches more floating lag time compared to other batches. Tablets formulated with Carbopol 934P exhibited total floating time less than 7 h. This might be due to high affinity of Carbopol 934P toward water that promotes water penetration in tablet matrices leading to increased density.

In vitro drug release profile of all the fabricated batches are shown in the Figure 1. Addition of surfactant in dissolution medium was used to provide sink condition, which simulated the physiological environment [9]. All the batches showed sustained release pattern. As expected,

the drug release profile was dependent on the viscosity grade and concentration of the release rate controlling polymers used. Tablets of the batches F1, F2 and F3 contained Hydroxypropyl methyl cellulose (Hypromellose K4M CR) in the concentration of 7%, 14% and 21% respectively. The drug release profile of these batches was not good and drug release was completed within 5 h. Where as the batch F7 contained Hydroxypropyl methyl cellulose (Hypromellose K100M CR) along with Carbopol 934P exhibited slow drug release profile up to 7 h. As mentioned in the literature, Hydroxypropyl methyl cellulose and Carbopol combination control the swelling rate of the matrix tablets; this might be reason for the retarded the drug release profile and good buoyancy [10].

The zero order release rate describes the system where the drug release rate is independent of its concentration. The first order release rate describes the release from the system is concentration dependent, which shows log cumulative percent drug remaining *Vs* time. Higuchi's model describes the release of the drug from an insoluble matrix as a square root of time dependent process based on Fickian diffusion. Higuchi's root kinetics, showing the cumulative percentage drug release *Vs* the square root of time. The release rate constant was calculated from the slope of the appropriate plots and regression coefficient (r^2) was determined. (Table 3) It was found that *in vitro* drug release profile of fabricated tablets was best explained by Higuchi's equation, as the plots showed the highest linearity ($r^2 = 0.985$), followed by first order ($r^2 = 0.975$) and zero order ($r^2 = 0.971$). This explains the drug diffused at a comparatively slow rate as the distance for diffusion increased, which is referred to as square root kinetics or Higuchi's kinetics. However, drug release was also found to be very close to zero order release kinetics, indicating that the concentration was nearly independent of drug release profile.

The corresponding plot log cumulative percentage of drug release *Vs* time for Korsmeyer-Peppas indicated good linearity ($r^2 = 0.986$). The release exponent n was within the range of 0.490 – 0.816, which appears to indicate a coupling of the diffusion and erosion mechanism so called anomalous diffusion may indicate that drug release profile was controlled by more than one process [11]. In near future, Glimepiride floating tablet may be the drug of choice for the treatment of Type2 diabetes mellitus to improve the clinical efficiency.

TABLE 1: FORMULATION DETAILS OF GLIMEPIRIDE FLOATING TABLETS

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7
Glimepiride	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Lactose monohydrate	75.0	65.5	55.0	65.5	55.0	35.0	75.0
Sodium bicarbonate	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Hypromellose K4M CR	10.0	19.5	30.0	10.0	10.0	30.0	-
Hypromellose K100M CR	-	-	-	-	-	-	10.0
Carbopol 934P	10.0	10.0	10.0	19.5	30.0	30.0	10.0
Magnesium Stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Tablet weight	150.0	150.0	150.0	150.0	150.0	150.0	150.0

TABLE 2: QUALITY CONTROL PARAMETERS OF GLIMEPIRIDE FLOATING TABLETS

Parameters	F1	F2	F3	F4	F5	F6	F7
Hardness (kg/cm^2)	4.7	4.7	4.8	4.7	4.7	4.2	4.5
Friability (%w/w)	0.052	0.041	0.040	0.032	0.021	0.011	0.012
Assay (%w/w)	98.70	99.89	100.30	98.00	99.06	98.32	99.64
Floating time (h)	5	5	5	8	8	5	8

TABLE 3: KINETIC AND STATISTICAL PARAMETER OBTAINED FROM DRUG RELEASE DATA OF GLIMEPIRIDE FLOATING TABLETS

Formulation	Zero order		First order		Higuchi's		Korsmeyer's	
	k	r^2	k	r^2	k	r^2	n	r^2
F1	19.6	0.950	0.709	0.952	45.9	0.978	0.71	0.985
F2	16.8	0.971	0.432	0.819	37.6	0.917	0.679	0.915
F3	19.4	0.971	0.571	0.929	44.10	0.946	0.816	0.985
F4	5.5	0.935	0.078	0.952	17.2	0.967	0.510	0.960
F5	4.9	0.851	0.069	0.791	14.7	0.814	0.490	0.776
F6	19.6	0.954	0.700	0.952	45.4	0.976	0.729	0.986
F7	11.2	0.956	0.280	0.975	34.2	0.963	0.753	0.983

k is release rate constant with units mg/h, h^{-1}, $\%/(h)^{1/2}$ for zero order, first order and Higuchi's model respectively.r^2 is correlation coefficient. n is release component.

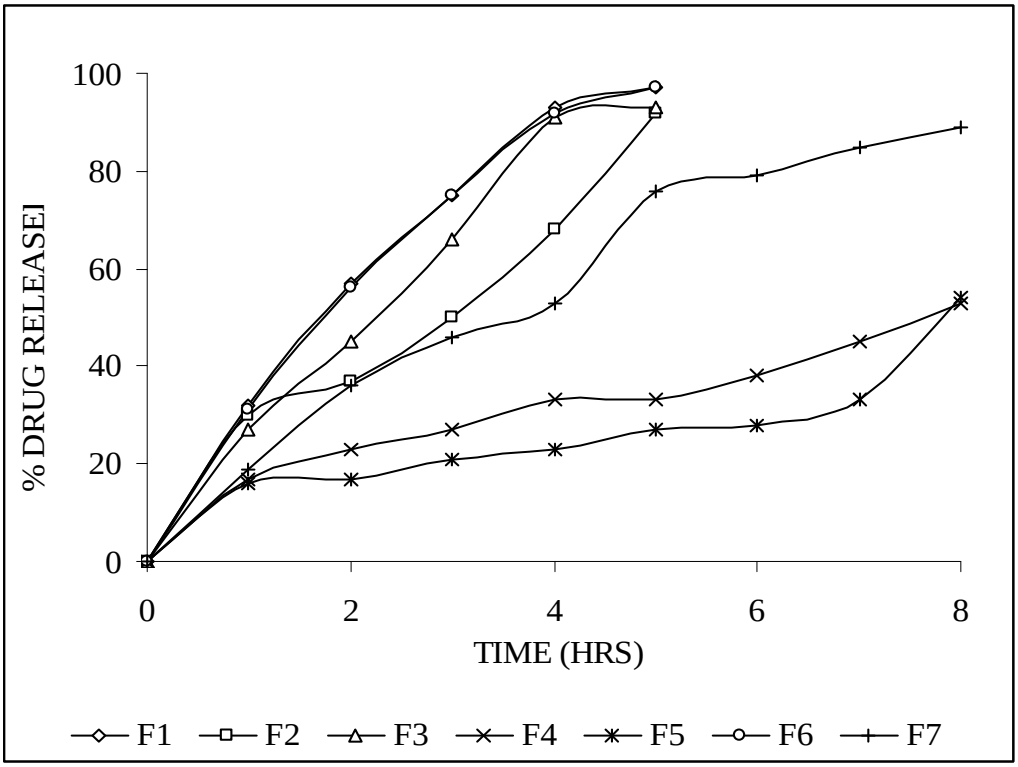

Figure1: Mean dissolution profiles of glimepiride floating tablets

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