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FORMULATION AND EVALUATION OF FLOATING TABLETS OF GLICLAZIDE EMPLOYING HPMC AND CARBOPOL

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ABSTRACT

The objective of the present study is to evaluate HPMC K100M, HPMC K4M and carbopol 934P as matrix formers in this design of floating tablets of gliclazide, a poorly water soluble drug. Floating tablets of gliclazide (60 mg) were formulated employing (i) HPMC K100M (ii) HPMC K4M and (iii) Carbopol 934P as matrix formers at 30% and 50% strength, sodium bicarbonate at 7.5%, 10% & 12.5% strength as gas generating agent and bees wax (10%) as floating enhancer and the tablets were evaluated for floating and drug releases characteristics. Gliclazide floating tablets formulated employing HPMC K100M and HPMC K4M as matrix formers at 50% strength and containing sodium bicarbonate (12.5%) as gas generating agent exhibited floating over 31 to 44 h with a floating lag time of less than 1 min. These floating tablets also gave slow and controlled release of gliclazide over 24 h and were found suitable for once a day administration (24 h). HPMC K100M and HPMC K4M were better suitable as matrix formers than Carbopol 934P for floating tablets of gliclazide, a poorly water soluble drug.

Key words: Floating tablets, HPMC, Carbopol, Gliclazide.

INTRODUCTION

The oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has certain problems such as unpredictable gastric emptying rate, short gastro-intestinal transit time (8-12 h) and existence of an absorption window in the gastric and upper small intestine for several drugs[1,2] leading to low and variable oral absorption over shorter period of time. The real issue in the development of oral drug delivery systems is to prolong the residence time of the dosage form in the stomach or upper g.i. tract until the drug is completely released and absorbed.

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Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems[3], swelling and expanding systems[4,5], floating systems[6,7] and other delayed gastric emptying devices[8,9]. The principle of floating tablets offers a simple and practical approach to achieve increased gastric residence time to enhance the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix forming polymer. The objective of the present study is to evaluate HPMC K100M, HPMC K4M and Carbopol 934P as matrix formers in the design of floating tablets of gliclazide, a poorly water soluble drug.

Gliclazide is an effective oral antidiabetic agent that belongs to the sulfonyl ureas drug class and is widely prescribed in the management of Non insulin dependent (Type II) diabetes mellitus. It is poorly soluble in aquoes fluids and is majorly absorbed from stomach[10]. Gastro retentive controlled release drug delivery system are needed for gliclazide to enhance its oral bioavailability and also for better control of blood glucose levels to prevent hypoglycaemia to enhance clinical efficiency and patient compliance. Floating tablets of gliclazide were designed in the present study to enhance its bioavailability and to achieve controlled release over 24 h for once a day administration. Floating tablets of gliclazide were designed employing HPMC K100M, HPMCK4M and Carbopol 934P as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer and the tablets prepared were evaluated for floating and drug release characteristics.

EXPERIMENTAL

Materials and methods

Gliclazide was a gift sample from M/s. Micro Labs. Ltd., Pondicherry. Hydroxy propyl methyl cellulose (K100M and K4M), Carbopol 934P and Bees wax, I.P were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Preparation of floating tablets

Matrix tablets each containing 60 mg of gliclazide were formulated employing (i) HPMC K100M (ii) HPMC K4M and (iii) Carbopol 934P, each at 30 and 50 % concentration in the formula. Sodium bicarbonate was used as gas generating agent at 7.5%, 10% and 12.5 % strength in each case. Bess wax was used as floating enhancer at 10%concentration in all the formulations.

The required quantities of gliclazide, HPMC K100M or HPMC K4M, sodium bicarbonate, bees wax, lactose were thoroughly mixed in a mortar by following geometric

dilution technique. The granulating fluid (a mixture of water and alcohol in 1 : 1 ratio) was added and mixed thoroughly to form a dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60^0C for 2 h. The dried granules were passed through mesh No. 16 to break the aggregates. The lubricants talc (2%) and magnesium stearate (2%) were passed through mesh No. 60 on to the dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a 16-station tablet punching machine (M/s Cadmach Machinaries Pvt. Ltd., Ahmedabad) to a hardness of 7-9 Kg/cm^2. In the case of Carbopol 934P the tablets were prepared by direct compression method.

Evaluation of tablets

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets was determined using a thermonic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as the test fluids.

Estimation of gliclazide

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 229 nm in 0.1 N hydrochloric acid was used for the estimation of gliclazide. The method obeyed Beer-Lambert's law in the concentration range of 1-10 µm/mL. When a standard drug solution was assayed repeatedly (n = 6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.65% and 1.75%, respectively. No interference from the excipients used was observed.

Floating lag time and floating time

In vitro buoyancy was determined by measuring floating lag time and duration of floating. The tablets were placed in a 250 mL glass 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. The duration in which the tablet remains floating was determined as floating time.

Drug release study

Drug release from the floating tablets was studied using 8-station dissolution rate test apparatus (Labindia, Disso 2000) employing a paddle stirrer at 50 rpm and at a temperature of 37 ± 1^{0}C. Hydrochloric acid, 0.1 N (900 mL) was used as dissolution fluid. A 5 mL aliquot of dissolution medium was withdrawn through a filter (0.45 µm) at different time intervals and assayed spectrophotometrically by measuring absorbance at 229 nm. All drug release experiments were conducted in triplicate (n = 3).

Data analysis

Drug release data were analyzed as per zero order, first order. Higuichi[11] and Peppas[12] equation models to assess drug release kinetics and mechanism from the tablets.

RESULTS AND DISCUSSION

Matrix tablets of gliclazide were prepared employing (i) HPMC K100M (ii) HPMC K4M and (iii) Carbopol 934P as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer with an objective of evaluating HPMC K100M, HPMC K4M and Carbopol 934P as matrix material for floating tablets of gliclazide, a poorly water soluble drug.

Hardness of the tablets was in the range 7-9 Kg/cm^2.Weight loss in the friability test was less than 0.6% in all the cases. All the tablets prepared contained gliclazide within 100 ± 3% of the labeled claim. All the tablets prepared were found to be non-disintegrating in water and aqueous acidic (pH 1.2) and alkaline (pH7.4) fluids. As such, the prepared tablets were of good quality with regard to drug content, hardness and friability. In the *in vitro* buoyancy study,the floating lag time of various tablets was in the range 10 seconds to 60 minutes.

Formulations F4, F5, F6 and A4, A5, A6 exhibited floating over 32-45 h with a floating lag time of less than 80 seconds. Tablets formulated employing HPMC K100M and HPMC K4M at 50% strength and sodium bicarbonate at 12.5% strength exhibited good floating characteristics. Tablets formulated employing Carbopol 934P as matrix former exhibited a floating lag time of 1h and a floating time of 4-7 hours. As such HPMC K100M and HPMC K4M are considered as better matrix formers than Carbopol 934P for floating tablets employing sodium bicarbonate (12.5%) as gas generating agent.

Gliclazide release parameters of the floating tablets formulated are summarized in Table 2. Drug release from the prepared tablets was slow, and spread over more than 24 h and depended on the polymer used and its strength and concentration of sodium bicarbonate in the tablets. Gliclazide release followed first order kinetics. The correlation coefficient (r^2) values were higher in first order model than those in the zero order model (Table 3) in all the cases. First order release rate constants (K_1) are given in Table 2. When the release data were analysed as per Peppas equation, the release exponent ‘n’ was found to be in the range 0.474-0.982 indicating ‘non-Fickian diffusion’ as the release mechanism from all the floating tablets prepared.

Table 1: Composition and physical properties of gliclazide floating tablets formulated employing various polymers

Formula-tion	Matrix composition	Gliclazide content (mg/tablet)	Hardness (Kg/cm^2)	Friability (weight loss %)	Floating lag time (min/sec.)	Floating time (h)
GF1	HPMC K100M (30%), Sod. Bicarb (7.5%)	59.4	7.5	0.4	28.00	20
GF2	HPMC K100M (50%), Sod. Bicarb (7.5%)	60.2	8.0	0.6	27.00	31
GF3	HPMC K100M (30%), Sod. Bicarb (10%)	58.5	7.0	0.5	31.00	36
GF4	HPMC K100M (50%), Sod. Bicarb (10%)	59.8	7.5	0.2	1.20	44
GF5	HPMC K100M (30%), Sod. Bicarb (12.5%)	59.6	7.0	0.4	0.60	44
GF6	HPMC K100M (50%), Sod. Bicarb (12.5%)	61.2	8.0	0.6	0.50	44
GA1	HPMC K4M (30%), Sod. Bicarb (7.5%)	59.8	8.5	0.2	27.00	45
GA2	HPMC K4M (50%), Sod. Bicarb (7.5%)	60.2	7.0	0.3	25.00	45
GA3	HPMC K4M (30%), Sod. Bicarb (10%)	58.5	8.0	0.1	26.00	21
GA4	HPMC K4M (50%), Sod. Bicarb (10%)	59.5	7.5	0.3	0.10	32
GA5	HPMC K4M (30%), Sod. Bicarb (12.5%)	60.5	9.0	0.4	0.40	37
GA6	HPMC K4M (50%), Sod. Bicarb (12.5%)	60.2	8.5	0.6	0.20	45
GC1	Carbopol 934P (30%), Sod. Bicarb (7.5%)	59.2	7.5	0.4	45.00	20
GC2	Carbopol 934P (50%), Sod. Bicarb (7.5%)	60.6	8.5	0.3	40.00	20

Cont…

Formula-tion	Matrix composition	Gliclazide content (mg/tablet)	Hardness (Kg/cm^2)	Friability (weight loss %)	Floating lag time (min/sec.)	Floating time (h)
GC3	Carbopol 934P (30%), Sod. Bicarb (10%)	59.5	7.0	0.5	36.00	20
GC4	Carbopol 934P (50%), Sod. Bicarb (10%)	60.8	8.0	0.2	42.00	5-6
GC5	Carbopol 934P (30%), Sod. Bicarb (12.5%)	61.6	7.5	0.4	55.00	5-6
GC6	Carbopol 934P (50%), Sod. Bicarb (12.5%)	60.2	8.0	0.6	60.00	4-7

Table 2: Release characteristics of floating tablets of Gliclazide formulated employing various polymers

Formulation	T_{50} (h)	T_{90} (h)	K_0 (mg/h)	K_1 (h^{-1}) x 10	'n' in Peppas equation
GF1	7	> 24	2.948	0.0825	0.616
GF2	9	20	2.896	0.0729	0.517
GF3	10	> 24	2.832	0.0712	0.588
GF4	12	> 24	2.769	0.0677	0.982
GF5	7	20	3.612	0.1052	0.611
GF6	9	16	4.147	0.1489	0.830
GA1	24	> 24	1.728	0.0392	0.563
GA2	> 24	> 24	1.581	0.0321	0.619
GA3	10	> 24	2.484	0.0611	0.474
GA4	20	> 24	2.085	0.0482	0.481
GA5	16	> 24	2.331	0.0509	0.751
GA6	12	> 24	2.400	0.0521	0.625
GC1	7	20	3.963	0.1187	0.725
GC2	4	20	4.873	0.1828	0.929
GC3	5	9	5.098	0.2561	0.609
GC4	5	20	4.912	0.1829	0.873
GC5	8	11	4.318	0.2337	0.564
GC6	4	10	5.07	0.2547	0.642

Table 3: Correlation coefficient (r^2) values in the analysis of release data as per various kinetic models

Formulation	Zero order	First order	Higuchi	Peppas equation
GF1	0.9384	0.9796	0.9353	0.9898
GF2	0.9694	0.9447	0.7425	0.8837
GF3	0.9821	0.9640	0.7914	0.9322
GF4	0.9545	0.9807	0.9298	0.9635
GF5	0.9913	0.9700	0.8227	0.9548
GF6	0.9645	0.8435	0.7481	0.9665
GA1	0.9083	0.9286	0.8746	0.9655
GA2	0.9734	0.9742	0.8751	0.9859
GA3	0.9705	0.9666	0.8100	0.9358
GA4	0.9646	0.9711	0.8393	0.9535
GA5	0.9920	0.9736	0.8059	0.9774
GA6	0.9724	0.9494	0.7458	0.9269
GC1	0.9909	0.9556	0.8061	0.9555
GC2	0.9177	0.9825	0.9428	0.9695
GC3	0.9527	0.9652	0.8946	0.9704
GC4	0.9646	0.9775	0.8946	0.9689
GC5	0.9604	0.7424	0.7475	0.9267
GC6	0.9066	0.9877	0.9424	0.9719

Overall, as the polymer concentration was increased, the release rate (K_1) was decreased with all the polymers. When the sodium bicarbonate concentration was increased, the floating time was increased and the release rate was decreased. Tablets formulated employing Carbopol 934P gave rapid release when compared to those formulated with HPMC (K100M and K4M). Overall floating tablets formulated with HPMC K100M and K4M at 50% strength gave slow and complete drug release in 24 h and were found to be the best floating formulations developed based on *in vitro* buoyancy and drug release characteristics and these tablets were found suitable for 24 h i.e., once-a-day administration.

CONCLUSION

Gliclazide floating tablets formulated employing HPMC K100M and HPMC K4M as matrix formers at 50% strength and containing sodium bicarbonate (12.5%) as gas generating agent exhibited floating over 35 to 48 h with a floating lag time of less than 1 min. These floating tablets also gave slow and controlled release of gliclazide over 24 h and were found suitable for once a day administration (24 h). HPMC K100M and HPMC K4M were better suitable as matrix formers than Carbopol 934P for floating tablets of gliclazide, a poorly water soluble drug.

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