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Formulation and Evaluation of Floating Tablets of Diltiazem Employing Hydroxy Propyl Methyl Cellulose and Carbopol

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The objective of the present study is to evaluate HPMC K100, HPMC K4M and carbopol P930 as matrix formers in this design of floating tablets of diltiazem hydrochloride, a highly water soluble drug. Floating tablets of diltiazem (90 mg) were formulated employing (i) hydroxy propyl methyl cellulose (HPMC) K100 (ii) HPMC K4M and (iii) Carbopol P930 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. Diltiazem floating tablets formulated employing hydroxy propyl methyl cellulose K100 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 diltiazem over 24 h and were found suitable for once a day administration (24 h). HPMC K100 and HPMC K4M were better suitable as matrix formers than carbopol P930 for floating tablets of diltiazem, a highly water soluble drug.

Key Words: Floating tablets, Hydroxy propyl methyl cellulose, Carbopol, Diltiazem.

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.

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 K100, HPMC K4M and carbopol P930 as matrix formers in the design of floating tablets of diltiazem hydrochloride, a highly water soluble drug.

Diltiazem is a calcium channel blocker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension.It has short biological half life of about 3.5 h and is rapidly eliminated. It is favourably absorbed from stomach and the oral bioavailability is 40 % in humans[10]. Floating tablets of diltiazem 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 diltiazem were designed employing HPMC K100, HPMCK4M and Carbopol P930 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

Diltiazem hydrochloride was a gift sample from M/s. Micro Labs Ltd., Pondicherry. Hydroxy propyl methyl cellulose (K100 and K4M), carbopol P930 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 90 mg of diltiazem were formulated employing (i) HPMC K100 (ii) HPMC K4M and (iii) carbopol P930, 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. Bees wax was used as floating enhancer at 10 % concentration in all the formulations.

TABLE-1
COMPOSITION AND PHYSICAL PROPERTIES OF DILTIAZEM FLOATING TABLETS FORMULATED EMPLOYING VARIOUS POLYMERS

Formulation	Matrix composition	Diltiazem content (mg/tablet)	Hardness (Kg/cm^2)	Friability (weight loss %)	Floating lag time (min-sec.)	Floating time (h)
F1	HPMC K100 (30%), Sod. Bicarb (7.5 %)	88.6	7.0	0.6	30.00	24
F2	HPMC K100 (50%), Sod. Bicarb (7.5 %)	91.2	8.5	0.4	30.00	35
F3	HPMC K100 (30%), Sod. Bicarb (10 %)	90.5	7.0	0.3	30.00	40
F4	HPMC K100 (50%), Sod. Bicarb (10 %)	89.8	7.5	0.1	1.00	48
F5	HPMC K100 (30%), Sod. Bicarb (12.5 %)	89.6	8.0	0.4	0.56	48
F6	HPMC K100 (50%), Sod. Bicarb (12.5 %)	90.2	8.0	0.2	0.36	48
A1	HPMC K4M (30%), Sod. Bicarb (7.5 %)	89.8	8.5	0.1	30.00	48
A2	HPMC K4M (50%), Sod. Bicarb (7.5 %)	91.2	7.0	0.4	30.00	48
A3	HPMC K4M (30%), Sod. Bicarb (10 %)	89.5	8.0	0.3	30.00	24
A4	HPMC K4M (50%), Sod. Bicarb (10 %)	90.5	8.5	0.3	0.06	35
A5	HPMC K4M (30%), Sod. Bicarb (12.5 %)	89.5	9.0	0.2	0.26	40
A6	HPMC K4M (50%), Sod. Bicarb (12.5 %)	91.2	8.5	0.4	0.12	48
C1	Carbopol P930 (30%), Sod. Bicarb (7.5 %)	90.2	7.0	0.4	100.00	24
C2	Carbopol P930 (50%), Sod. Bicarb (7.5 %)	88.6	8.5	0.5	110.00	24
C3	Carbopol P930 (30%), Sod. Bicarb (10 %)	90.5	7.0	0.2	120.00	24
C4	Carbopol P930 (50%), Sod. Bicarb (10 %)	89.8	8.0	0.4	110.00	6-8
C5	Carbopol P930 (30%), Sod. Bicarb (12.5 %)	88.6	8.5	0.6	100.00	6-8
C6	Carbopol P930 (50%), Sod. Bicarb (12.5 %)	91.2	8.5	0.2	110.00	5-8

The required quantities of diltiazem, HPMC K100 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 ºC 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 8-10 Kg/cm^2. In the case of carbopol P930 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 diltiazem: An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 240 nm in 0.1 N hydrochloric acid was used for the estimation of diltiazem. 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 0.85 and 1.60 %, 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 ºC. 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 240 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 Korsmeyer *et al.*[12] equation models to assess drug release kinetics and mechanism from the tablets.

RESULTS AND DISCUSSION

Matrix tablets of diltiazem hydrochloride were prepared employing (i) HPMC K100 (ii) HPMC K4M and (iii) carbopol P930 as matrix formers, sodium bicarbonate as gas generating agent and bees wax as floating enhancer with an objective of evaluating HPMC K100, HPMC K4M and carbopol P930 as matrix material for floating tablets of diltiazem, a water soluble drug.

Hardness of the tablets was in the range 7-9 Kg/cm^2 (Table-1). Weight loss in the friability test was less than ± 0.6 % in all the cases. All the tablets prepared contained diltiazem hydrochloride 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 (pH 7.4) 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 6 s to 2 h (Table-1).

Formulations F4, F5, F6 and A4, A5, A6 exhibited floating over 35-48 h with a floating lag time of less than 1 min (Table-1). Tablets formulated employing HPMC K100 and HPMC K4M at 50 % strength and sodium bicarbonate at 12.5 % strength exhibited good floating charteristics. Tablets formulated employing carbopol P 930 as matrix former exhibited a floating

TABLE-2
RELEASE CHARACTERISTICS OF FLOATING TABLETS OF DILTIAZEM FORMULATED EMPLOYING VARIOUS POLYMERS

Formulation	T_{50} (h)	T_{90} (h)	$K_{0\,(mg/h)}$	K_1 (h^{-1}) × 10	'n' in Korsmeyer *et al.*[12] equation
F1	4	11	5.409	2.595	0.626
F2	5	>24	4.958	1.870	0.627
F3	5	17	5.471	2.061	0.644
F4	5	>24	5.634	2.148	0.666
F5	4	10	6.174	2.593	0.649
F6	4	24	4.529	1.879	0.575
A1	4	16	5.052	2.277	0.664
A2	5	21	4.437	2.160	0.641
A3	4	12	4.367	3.060	0.608
A4	5	>24	4.239	1.559	0.674
A5	5	12	4.484	3.115	0.635
A6	5	14	4.861	2.715	0.742
C1	1.5	4	15.034	3.141	0.960
C2	3	>24	15.042	3.606	0.753
C3	1.5	4	18.524	5.276	0.606
C4	3	5	11.773	4.976	0.618
C5	1.5	4	15.910	8.009	0.586
C6	2	4	16.545	6.146	0.736

lag time of 2 h and a floating time of 5-8 h. As such HPMC K100 and HPMC K4M are considered as better matrix formers than carbopol P930 for floating tablets employing sodium bicarbonate (12.5 %) as gas generating agent.

Diltiazem 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. Diltiazem 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 analyzed as per Korsmeyer *et al.*[12] equation, the release exponent 'n' was found to be in the range 0.575-0.960 indicating 'non-Fickian diffusion' as the release mechanism from all the floating tablets prepared.

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 P930 gave rapid release when compared to those formulated with HPMC (K100 and K4M). Overall floating tablets formulated with HPMC K100 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

Diltiazem floating tablets formulated employing HPMC K100 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 diltiazem over 24 h and were found suitable for once a day administration (24 h). HPMC K100 and HPMC K4M were better suitable as matrix formers than Carbopol P930 for floating tablets of diltiazem, a highly water soluble drug.

TABLE-3
CORRELATION COEFFICIENT (r^2) VALUES IN THE ANALYSIS OF RELEASE DATA AS PER VARIOUS KINETIC MODELS

Formulation	Zero order	First order	Higuchi	Korsmeyer equation
F1	0.9272	0.9780	0.9711	0.9702
F2	0.8185	0.9619	0.9807	0.9840
F3	0.9608	0.9796	0.9862	0.9808
F4	0.9498	0.9711	0.9735	0.9705
F5	0.9619	0.9737	0.9839	0.9856
F6	0.9237	0.9804	0.9722	0.9690
A1	0.8858	0.9742	0.9488	0.9368
A2	0.8957	0.9835	0.9616	0.9562
A3	0.8475	0.9906	0.9301	0.9301
A4	0.8605	0.9362	0.9284	0.9226
A5	0.8794	0.9859	0.9493	0.9459
A6	0.9043	0.9869	0.9567	0.9504
C1	0.9230	0.9262	0.9951	1.000
C2	0.9749	0.9516	0.9771	0.9802
C3	0.9725	0.9531	0.9858	0.9863
C4	0.9086	0.9234	0.9416	0.9420
C5	0.9559	0.9164	0.9759	0.9758
C6	0.9817	0.8940	0.9927	0.9923

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