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Formulation and Evaluation of Floating Tablets of Diltiazem Employing HPMC K100M, Starch acetate and Carbopol 934P

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ABSTRACT

The objective of the present study is to evaluate HPMC K100M, Starch acetate and Carbopol 934P 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) HPMC K100M (ii) Starch acetate 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. Diltiazem floating tablets formulated employing HPMC K100M and Starch acetate as matrix formers at 50% strength and containing sodium bicarbonate (12.5%) as gas generating agent exhibited floating over 44 to 48 h with a floating lag time of less than 36 sec. These floating tablets also gave slow and controlled release of diltiazem over 24 h and were found suitable for once a day administration (24h). HPMC K100M and Starch acetate were better suitable as matrix formers than Carbopol 934P for floating tablets of diltiazem, a highly water soluble drug.

Key words: Floating tablets, HPMC, Starch acetate, Carbopol, Diltiazem

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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 three Polymers namely (i) HPMC K100M, (ii) Starch acetate and (iii) Carbopol 934P 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 K100M, Starch acetate 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.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was a gift sample from M/s. Micro Labs. Ltd., Pondicherry. Hydroxy propyl methyl cellulose, K100M, Starch acetate (DS 2.72), Carbopol 934P and Bees wax, I.P were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods

Preparation of Floating Tablets

Matrix tablets each containing 90 mg of diltiazem were formulated employing (i) HPMC K100M (ii) Starch acetate 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 diltiazem, HPMC K100M or Starch acetate, sodium bicarbonate, bees wax, and lactose were thoroughly mixed in a mortar by following geometric dilution technique. The granulating fluid (a mixture of water and alcohol in 1:1ratio) 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 6-8Kg/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, 0.1N HCl and phosphate buffer of pH7.4 as the test fluids.

Estimation of Diltiazem

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 240 nm in 0.1N hydrochloric acid was used for the estimation of diltiazem. The method obeyed Beer-Lambert's law in the concentration range of 1-10µm/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 0.1N 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^{o}C. Hydrochloric acid, 0.1N (900 mL) was used as dissolution fluid. A 5mL aliquot of

dissolution medium was withdrawn through a filter (0.45µm) 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 Peppas [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 K100M (ii) Starch acetate 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, Starch acetate and Carbopol 934P as matrix material for floating tablets of diltiazem, a water soluble drug.

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 K100M (30%), Sod. Bicarb (7.5%)	88.6	7.0	0.6	30.00	24
F2	HPMC K100M (50%), Sod. Bicarb (7.5%)	91.2	8.5	0.4	30.00	35
F3	HPMC K100M (30%), Sod. Bicarb (10%)	90.5	7.0	0.3	30.00	40
F4	HPMC K100M (50%), Sod. Bicarb (10%)	89.8	7.5	0.1	1.00	48
F5	HPMC K100M (30%), Sod. Bicarb (12.5%)	89.6	8.0	0.4	0.56	48
F6	HPMC K100M (50%), Sod. Bicarb (12.5%)	90.2	8.0	0.2	0.36	48
DSA1	Starch acetate (30%), Sod. Bicarb (7.5%)	89.6	7.5	0.4	28.00	24
DSA2	Starch acetate (50%), Sod. Bicarb (7.5%)	90.2	8.0	0.3	26.00	32
DSA3	Starch acetate (30%), Sod. Bicarb (10%)	91.5	7.5	0.6	26.00	38
DSA4	Starch acetate (50%), Sod. Bicarb (10%)	88.8	7.5	0.1	0.55	46
DSA5	Starch acetate (30%), Sod. Bicarb (12.5%)	89.6	8.5	0.4	0.40	44
DSA6	Starch acetate (50%), Sod. Bicarb (12.5%)	89.2	8.0	0.4	0.25	46
C1	Carbopol 934P (30%), Sod. Bicarb (7.5%)	90.2	7.0	0.4	100.00	24

C2	Carbopol 934P (50%), Sod. Bicarb (7.5%)	88.6	8.5	0.5	110.00	24
C3	Carbopol 934P (30%), Sod. Bicarb (10%)	90.5	7.0	0.2	120.00	24
C4	Carbopol 934P (50%), Sod. Bicarb (10%)	89.8	8.0	0.4	110.00	6-8
C5	Carbopol 934P (30%), Sod. Bicarb (12.5%)	88.6	8.5	0.6	100.00	6-8
C6	Carbopol 934P (50%), Sod. Bicarb (12.5%)	91.2	8.5	0.2	110.00	5-8

Hardness of the tablets was in the range 7-8.5 Kg/cm^2.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 (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 25 seconds to 120 minutes.

Formulations F4, F5, F6 and DSA4, DSA5, DSA6 exhibited floating over 44-48 h with a floating lag time of less than 36 seconds. Tablets formulated employing HPMC K100M and Starch acetate at 50% strength and sodium bicarbonate at 12.5% strength (F6 and DSA6) exhibited good floating characteristics, a floating time of 48 and 46 h respectively after a lag time of 25-36 sec. Tablets formulated employing Carbopol 934P as matrix former exhibited a floating lag time of 2h and a floating time of 5-8 hours. As such HPMC K100M and Starch acetate are considered as better matrix formers than Carbopol 934P 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 24h 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 analysed as per Peppas equation, the release exponent 'n' was found to be in the range 0.572 – 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 934P gave rapid release when compared to those formulated with HPMC K100M and Starch acetate. Overall floating tablets formulated with HPMC K100M and Starch acetate at 50% strength gave slow and complete drug release in 24h and were found to be the

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best floating formulations developed based on *in vitro* buoyancy and drug release characteristics and these tablets were found suitable for 24h i.e., once-a-day administration.

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}) X 10	'n' in Peppas 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
DSA1	6	16	5.478	1.7811	0.621
DSA2	5	16	5.334	1.7508	0.584
DSA3	5	16	5.400	1.8766	0.572
DSA4	7	20	4.561	1.1809	0.617
DSA5	5	12	6.247	2.7470	0.609
DSA6	6	16	5.673	2.0232	0.656
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

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
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
DSA1	0.9769	0.9895	0.9907	0.9914
DSA2	0.9780	0.9864	0.9955	0.9951
DSA3	0.9817	0.9739	0.9968	0.9972
DSA4	0.9834	0.9912	0.9958	0.9979
DSA5	0.9691	0.9674	0.9904	0.9842
DSA6	0.9804	0.9828	0.9922	0.9924
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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CONCLUSION

Diltiazem floating tablets formulated employing HPMC K100M and Starch acetate as matrix formers at 50% strength and containing sodium bicarbonate (12.5%) as gas generating agent exhibited floating over 44 to 48 h with a floating lag time of less than 36 sec. These floating tablets also gave slow and controlled release of diltiazem over 24 h and were found suitable for once a day administration (24h). HPMC K100M and Starch acetate were better suitable as matrix formers than Carbopol 934P for floating tablets of diltiazem, a highly water soluble drug.

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