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RESEARCH ARTICLE

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DESIGN AND IN VITRO EVALUATION OF FLOATING DILTIAZEM HYDROCHLORIDE TABLETS BASED ON GAS FORMATION

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ABSTRACT

The gastroretentive dosage forms have potential for use as controlled-release drug delivery systems. The use of floating dosage forms is one method to achieve prolonged gastric residence times, providing opportunity for both local and systemic drug action. The present investigation involve the development and in vitro evaluation of the floating matrix tablets, which after oral administration can prolong the gastric residence time, increase the drug bioavailability. A polymer (sodium carboxymethyl cellulose or hydroxypropylmethylcellulose K4M, K15M) was added to control the drug release. The time to flotation could be controlled by the composition (type of filler, concentration of effervescent agents) and hardness of the tablet. Six different formulations were prepared i.e. D1, D2, D3, D4, D5, and D6 by varying the polymers ratio. All the formulations were evaluated for hardness, friability, weight variation, drug content uniformity, buoyancy studies, and *in vitro* drug release study. The formulation D4 shows 99% drug release at the end of 12 h *in vitro* and floating lag time was 30 sec and tablet remained buoyant throughout studies.

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KEYWORDS

Floating dosage form, Diltiazem HCL*, In vitro* drug release, controlled release.

1. INTRODUCTION

Gastroretentive dosage forms,, i.e. those designed to exhibit a prolonged gastric residence time (GRT), have been a topic of interest in terms of their potential for controlled drug delivery. It is widely accepted that gastric emptying of a conventional dosage form in humans is affected by numerous factors and the time taken shows wide inter- and intra-subject variation. This variability, in turn, can lead to unpredictable times to achieve peak plasma drug levels and bioavailability, since many drugs are absorbed to the greatest extent in the upperpart of the small intestine. A drug that is released from a dosage form in a controlled manner in the stomach will empty together with fluids and have the whole surface area of the small intestine available for absorption[1]. When the drug is formulated with a gel forming polymer such as semisynthetic derivatives of cellulose, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats in the gastric fluid, without affecting a gastric emptying rate for prolonged period of time. While the system is floating in the gastric content, the drug is released slowly from the system at a desired rate. This floating dosage form is well known as a hydrodynamically balanced system (HBS) [2].

For drugs with a narrow absorption window in the gastrointestinal tract or acting locally in the stomach, the challenging task is not only to prolong drug release but the retention of the dosage form in the upper gastrointestinal tract. This results in a higher bioavailability, reduced time intervals for drug administration and thus a better patient compliance. Various approaches for gastroretentive dosage forms have been proposed including mucoadhesive systems, swellable and floating systems[3].

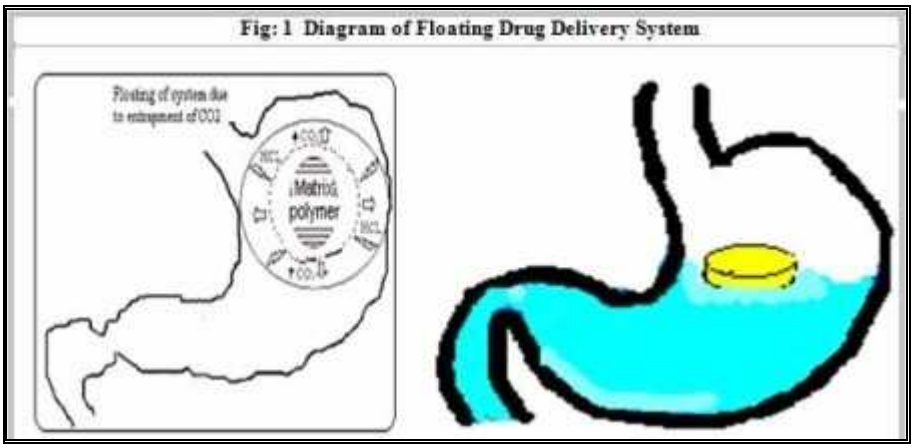

Fig:- Floating drug delivery system

Diltiazem hydrochloride, a calcium channel blocker is widely used for the treatment of hypertension, angina pectoris, supraventricular tachycardia and myocardial infraction. It is completely absorbed (90%) from the gastrointestinal tract after oral administration but has very low bioavailability of 22±8%. The low bioavailability is owing to the rapid biotransformation in the liver with a biological half-life of 4.0±1.5 hours. The short biological

half-life and poor bioavailability of drug favours development of controlled release formulation[4]. The objective of the present work was to develop and evaluate floating tablet of Diltiazem hydrochloride, which after oral administration could prolong the gastric residence time and increase the drug bioavailability.

2. MATERIAL AND METHODS

2.1. Material

Diltiazem hydrochloride was received as a gift sample from Nicholas Piramal Ltd., Mumbai. Hydroxypropylmethylcellulos (HPMC K4M, HPMCK100M), Sodium carboxymethyl cellulose, Lactose, Sodium bicarbonate, Microcrystalline cellulose, Talc, Hydrochloric acid were taken from Sd fine Chem Ltd. All the other chemicals used were of analytical grade.

2.2. Method

Formulation of floating tablet

A variety of floating tablet formulations were formulated with HPMC--K4M, HPMC-K100M polymers alone or/and in combination. Adding an gas generating agent i.e sodium bicarbonate provided floating. Polymers and the effervescent mixture were blended in a mortar by using direct compression technology; all ingredients were compressed at compression forces of 6 kg/cm^2 in a multiple tableting punching machine with a 12-mm concave punch diameter (Cadmach Machinery, India). Before compression, 0.2% talc was added as lubricant. Each formulation were blended and compressed (100 tablets) and tested for hardness (n = 10), weight variation (n = 20) and floating behavior (n = 6). The hardness of floating tablet was in the range 6.12 to 6.43 kg/cm^2 on a Monsanto Hardness tester. The weight of floating tablet was 360 ± 05 mg[5].

3. EVALUATION OF TABLETS [6,7,8]

3.1. Hardness test. Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shock of handling in manufacture, packing and shipping. Monsanto hardness tester measured the hardness of tablet. Five tablets from each batch were used for hardness studies and results were expressed in Kg/cm^2.

3.2. Thickness and diameter, The thickness and diameter of tablets was carried out using vernier caliper. Five tablets were used for the above test from each batch results were expressed in millimeter.

3.3. Weight variation test, Twenty tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was calculated. The uniformity of weight was determined according to I.P. specification. As per I.P. not more than two of individual weight should deviate from average weight by more than 5% and none deviate more than twice that percentage.

3.4. Friability test, It was done in Roche friabilator apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at a distance of six inches with each revolution. Preweighed samples of 20 tablets were placed in the friabilator, which is then operated for 100 revolutions. The tablets were then dusted and reweighed. Conventional compressed tablets that loss than less than 0.5 to 1.0% of their weight are generally considered acceptable.

Friability = Weight loss ⁄ Weight of tablets before operations X 100

3.5. Drug content uniformity, The tablets were weighed and taken in a mortar and crushed to powder. A quantity of powder

weighed equivalent to 100 mg of Diltizem hydrochloride was taken in a 100 ml volumetric flask and 0.1 N HCL was added. It was then heated at 60°C for 30 minutes. The solution was filtered using membrane filter (0.45nm) and then its absorbance was measured at 278 nm. The amount of drug was calculated using standard graph.

3.6. Floating behavior, Floating behavior studies were performed on the floating tablet,. The buoyancy of the tablets was studied at 37±0.5 °C, in 100 ml of simulated gastric fluid at pH 1.2 (without pepsine). The time of duration of tablet floatation was observed visually. The following parameters were determined: the time needed to go upward and float on the surface (floating lag time), floating duration and relative matrix integrity. The latter parameter was determined on the basis of visual inspection after the floating studies[9].

3.7. Differential thermal analysis and thermogravimetric analysis (TG/DTA), Thermogravimetry/differential thermal analysis was performed to characterize drug-excipient compatibility. The TG/DTA thermograms of pure drug and mixtures were recorded in a TG/DTA analyzer at a heating rate of 10°C/min from 25-300°C in a nitrogen atmosphere[10].

3.7. Infrared Spectroscopy

The Identification and drug excipients interaction were studied using FTIR. IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer (using Perkin Elmer) by KBr pellet method was carried out on drug and polymer. They are compressed under 10 tone pressure in a hydraulic press to form a transparent pellet. The pallet was scanned from 4000 to 400 cm^{1} in a spectrophotometer and peaks obtained were identified.

3.8. In vitro dissolution, the Diltizem hydrochloride release from different Floating Tablet formulations was determined using a USP XXII paddle apparatus under sink condition. The dissolution medium was 900 mL SGF (pH 1.2, no enzyme) at 37±0.5°C; paddle speed 100 rpm, to simulate *in vivo* conditions. All experiments were done in triplicate and average values were taken. The formulation prepared was subjected to dissolution tests for 12 h. Sample was withdrawn at predetermined time intervals, filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined at 236 nm by UV Spectrophotometer. (Lab India Disso 2000)[11,12].

3.9. Stability Studies, Stability studies were carried out for optimized formulation. The tablets were packed in aluminium foil placed in air tight container and kept at 4°C in refrigerator, 45°C/75% RH in stability chamber and 60°C in incubator for 3 months. At the interval of 15 days, the tablet were withdrawn and evaluated for physical properties, in-vitro drug release.

Table 1
Formulation of fabricated floating tablet

	BATCH CODE					
INGREDIENTS	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**
Diltiazem Hydrochloride	90	90	90	90	90	90
HPMC K100M	100	120	140	--	--	--
HPMCK4M	--	--	--	100	120	140

Sodium Bicarbonate	25	25	25	25	25	25
SCMC	30	30	30	30	30	30
MCC	52.5	42.5	32.5	52.5	42.5	32.5
Lactose	52.5	42.5	32.5	52.5	42.5	32.5
Talc	10	10	10	10	10	10

4. RESULT AND DISCUSSIONS

Different grades of HPMC (K4M and K100M) and SCMC were used as swellable polymers. HPMC was chosen because it is widely used as a low density hydrocolloids system upon contact with water a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in the stomach pH. SCMC was used in combination with HPMC to slow the drug release; SCMC's ability to do this may be caused by the solubility at pH 1.2-3.0. Sodium bi carbonate is used as a buoyancy imparting agent.

The formulations were prepared by using combination of different grades of HPMC and SCMC with buoyancy imparting agent. The prepared gastric floating formulations were prepared by direct compression method and evaluated for different physicochemical characteristic such as thickness, drug content, weight variation, hardness and friability. The release characteristics of the formulation were studied in in-vitro conditions. The evaluation parameters such as thickness were found in between 3.95 to 4.17 mm and the hardness for all batches were in between 5.98 to 6.22 kg/cm^2, friability were in between 0.8 to 0.9%.The weight variation also found within a specified limit given by Indian pharmacopoeia. The average drug content was found in between 98.12 to 99.23%. The floating lag time was in between 30 to 70 sec and total floating time was 12 h. *In vitro* % drug release was found in between 92.63 to 98.72 at the end of 12 h.

Table 2
Evaluation of Fabricated Tablets

	BATCH NUMBER					
Evaluation parameters	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**
Hardness(kg/cm2)	6.11	6.14	5.98	6.13	6.39	6.22
Friability (%)	0.9	0.8	0.9	0.8	0.8	0.9
Average weight(mg)	360.5	360.7	360.3	360.2	360.1	360.6
Drug content (%)	98.12	98.89	98.92	99.21	98.72	99.23
Thickness(mm)	4.11	4.17	3.98	3.98	3.97	3.95
Floating lag time(sec)	50	60	30	30	50	70
Total floating time(h)	>12	>12	>12	>12	>12	>12

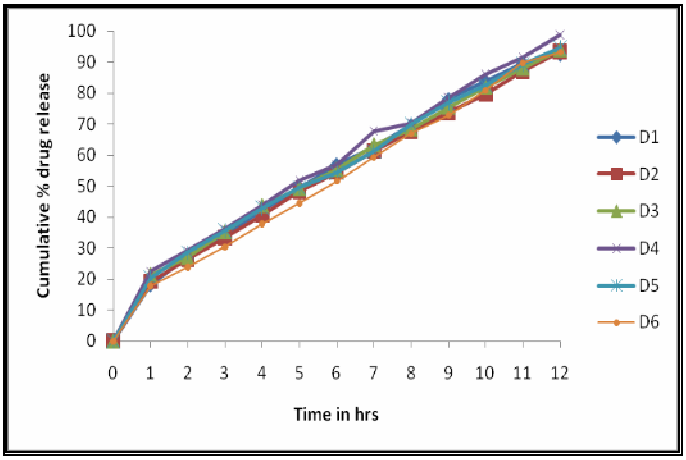

Fig 2
In vitro drug dissolution study of all six formulations

5. CONCLUSION

The Diltiazem hydrochloride table were successfully prepared as a floating dosage form with controlled mechanism using HPMC, K-grade and SCMC polymer as a carrier. *In vitro* dissolution studies showed controlled release up to 12 h, The uniformity of weight, hardness friability, drugcontent were all lying within the limits,the drug release from formulation D4 was found to follow zero order kinetics. It was also found linear in Higuchi's plot, which confirms that diffusion is one of the mechanisms of drug release. Thus, results of the current study clearly indicate, a promising potential of the Diltiazem hydrochloride floating system as an alternative to the conventional dosage form. The results showed the floating tablets are a feasible approach for the controlled-release preparation of drugs, which have limited absorption sites in the stomach.

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