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THE STUDY OF CAPTOPRIL FLOATING MATRIX TABLETS USING DIFFERENT POLYMERS AS RELEASE RETARDING AGENT

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ABSTRACT

The various approaches to increase the gastric residence of dosage forms are: effervescent single/multiple unit dosage forms, non-effervescent single/multiple unit dosage forms, high density dosage forms, expandable systems, swelling systems, unfolding systems, and adhesion- mucoadhesive systems. The floating drug delivery systems of this class contains one or more gel forming swellable cellulose, polysaccharide. Captopril was used with various grades of HPMC in varying ratios to formulate the floating tablets. Lactose was used as a diluent in the preparation of the tablets. Sodium bicarbonate was incorporated into the tablets to aid buoyancy of the tablets. it was concluded that the formulation F1 is the best formulations as the extent of drug release was found to be around 85 %. This batch also showed immediate floatation and floatation duration of more than 8hr. The drug release model of this formulation complies with zero order kinetics. Based on the results we can certainly say that floating type gastro retentive drug delivery system holds a lot of potential for drug captopril.

KEYWORDS: Sustained Release, HPMC, floating tablet, gastro retentive, Captopril, Retarding Agents

1. INTRODUCTION

Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy and minimize the adverse effects and increase the bioavailability of drugs. Delivery of drugs at a specific region in gastrointestinal tract, the so called absorption window needs the development of gastro retentive dosage forms.

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The attempts to develop gastro retentive drug delivery systems may be largely divided into two classes: such as size or floatation, which rely on delayed emptying from the stomach, depend on the normal physiological duration of the fed state of 4-8 hr, following a meal and rather reproducible transit time through the small intestine.

The optimization of the gastro retentive devices is based on the principles such as gastric emptying, small intestine transit, colonic transit etc [Read *et al.*, 1988], the study of the pharmacokinetics of the drugs such as absorption of drugs at different sites of gastrointestinal tract and the factors affecting absorption of the dosage forms. Drugs which are

predominantly absorbed from the upper part of gastrointestinal tract such as Captopril, sulpiride, theophylline, and salbutamol are the potential candidates of designing a gastro retentive dosage form for improvement and prolonging their limited oral bioavailability [Kohri *et al.*, 1996, Devereux *et al.*, 1990, Agyilirah *et al.*, 1991]. Table 3 enlists the examples of various drugs formulated as different forms of floating drug delivery systems.

Following conditions must be met during the formulation of a hydrodynamic balanced systems (HBS) dosage form-:

- It must have sufficient structure to form a cohesive gel barrier.
- It must maintain an overall specific gravity lower than that of gastric contents. (1.004-1.01 g/ml)
- It should dissolve slowly enough to serve as a reservoir for the delivery system.

Approaches to increase gastric retention

The various approaches to increase the gastric residence of dosage forms are: effervescent single/multiple unit dosage forms, noneffervescent single/multiple unit dosage forms, high density dosage forms, expandable systems, swelling systems, unfolding systems, and adhesion-mucodhesive systems.

Non Effervescent Floating Drug Delivery System

The floating drug delivery systems of this class contains one or more gel forming swellable cellulose, polysaccharide or matrix forming polymers like polyacrylates, polycarbonates, polystyrene and polymethacrylates. [Hilton *et al.*, 1992]. The air thus entrapped by the swollen polymers thus imparts buoyancy to the dosage form. [Sheth and Tossounian, 1984],

A HBS system has been developed by [Sheth and Tossounian, 1978], [Desai and Bolton (1989, 1993)] developed theophylline floating tablets by using agar as the gel matrix and binding agent.

Effervescent systems

Gas generating systems [Rubinstein *et al.*, 1994]. Swellable polymers such as Methocel® or polysaccharides e.g. chitosan [Rubinstein *et al.*, 1994] and effervescent components e.g. sodium bicarbonate and citric acid or tartaric acid [Ritchel, 1991, Michaels, 1974, 1975]. These tablets may be either single layered wherein the CO_2 generating components are intimately mixed with in the tablet matrix [Hashim *et al.*, 1987].

Expandable systems

The expanding or swelling types of dosage forms [Klausner *et al.*, 2003].

Swelling Gastroretentive Dosage Forms

[Mamajek and Moyer *et al.* (1980)] developed a swelling dosage form consisting of three parts; the inner drug reservoir surrounded by a layer of swellable expanding agent. [Urqhart and Theeuwes (1984)] developed a highly swellable dosage form exhibiting a 2-50 folds increase in volume. [Shalaby *et al.* (1990, 1992)] developed albumin crosslinked polyvinyl pyrolidone hydrogel with swelling and degradation property.

2. MATERIALS & METHODS

2.1 Materials

Captopril and was obtained as a generous gift by Modi-Mundipharma Private Ltd. (U.P., India) respectively.

2.2 Method

Captopril was used with various grades of HPMC in varying ratios to formulate the floating tablets. Lactose was used as a diluent in the preparation of the tablets. Sodium bicarbonate was incorporated into the tablets to aid buoyancy of the tablets due to liberation of CO2 when tablets come in contact with acidified dissolution medium. Magnesium stearate (0.5% w/w) was added in the formulation as a lubricant. The level of the drug in all of the formulations was kept constant at 12.5% and tablet weight was adjusted so as to contain 25 mg of Captopril in each tablet.

The floating matrix tablets were prepared by mixing drug, lactose, Mag. stearate and HPMC geometrically in a pestle and mortar until homogenized. All the ingredients were passed through sieve #80 before processing. Sodium bicarbonate was added only in effervescent tablets and was omitted in non-effervescent tablets. The mixture was directly compressed in a R&D tablet compressing machine fitted with flat punches and dies (8 mm diameter). The tablet weight was adjusted to 200mg and 25 tablets for each batch were prepared. The formula for the different batches is given in the Table-1.

2.3 Preparation of Floating Tablets

Table-1. Formula for formulation F1 –F9 (per tablet in mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	25	25	25	25	25	25	25	25	25
HPMC K4M	60		-	100	-	-	50	-	50
HPMC K15M	-	60			100	-	50	50	-
HPMC K100M	-	-	60			100	-	50	50
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20
Lactose	94	94	94	64	64	64	64	64	64
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total	200	200	200	200	200	200	200	200	200

3. RESULTS AND DISCUSSION

3.1 Scanning for λmax of Captopril

For UV scanning for λmax of Captopril, about 10 mg of pure drug weighed and transferred to a 100ml volumetric flask containing 100 ml of 0.1 N HCl solution and shaked to dissolve. Then 10 ml of this solution was diluted to 100ml with 0.1 N HCl in a volumetric flask to obtain a solution of 10 µg/ml and scanned for λmax. From the curve, peaks for the Captopril were found at 202nm. Table-2

Table-2. Data of standard curve

S.No	Conc. (µg/ml)	Absorbance ± SD
1	5	0.31 ± 0.01
2	10	0.50 ± 0.07
3	15	0.71 ± 0.06
4	20	0.89 ± 0.05
5	25	1.11 ± 0.09
6	30	1.34 ± 0.07

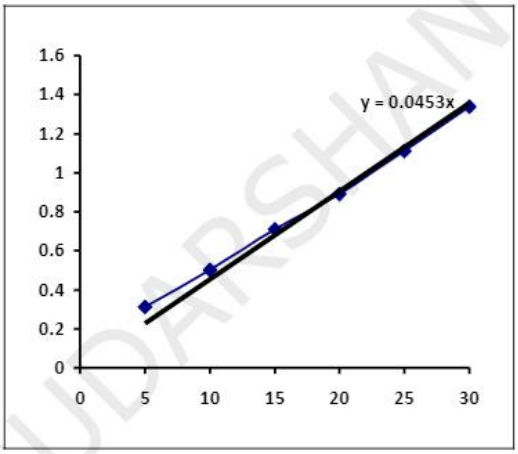

Fig-1 Calibration curve

Table-3 Precompression parameters of Formulation F1-F9

Batch	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.521	0.585	10.34	1.12	22°
F2	0.533	0.597	10.16	1.13	24
F3	0.562	0.611	8.19	1.08	21
F4	0.543	0.583	6.89	1.06	21
F5	0.582	0.661	9.37	1.13	24
F6	0.566	0.613	8.19	1.08	21
F7	0.544	0.593	8.19	1.09	20
F8	0.580	0.633	7.93	1.07	22

Table-4 DSC data of different samples

Serial	Sample	Peak Max. ^{0}C
a	HPMC K4M	106.04
b	HPMC K15M	112.29
c	HPMC K100M	100.85
d	Spray Dried Lactose	145.09, 213.86
e	Captopril	109.95, 235.46
f	Tablet Sample	138.22, 198.15, 287.29

Table-5 Physico-chemical parameters of Formulations

Parameters / Batch No.	Weight variation	Hardness (kg/cm2)	Friability (%)	Drug Content (%)
F1	Pass	5.6	0.65	97.08

F2	Pass	5.8	0.70	98.15
F3	Pass	6.0	0.72	99.28
F4	Pass	5.7	0.77	97.59
F5	Pass	5.3	0.69	98.87
F6	Pass	6.1	0.72	99.91
F7	Pass	5.9	0.79	97.56
F8	Pass	6.1	0.80	98.38
F9	Pass	6.5	0.77	99.52

(n=3, the data represents the mean of three observations)

In Vitro Dissolution Studies

In vitro dissolution studies of the prepared floating/ non-floating matrix tablets of Captopril was carried out on USP-II dissolution apparatus using paddle. The dissolution study of all the prepared tablets was carried under following conditions:-

Medium	:	900 ml
0.1 N HCl (pH 1.2)		
RPM	:	50 rpm
Sample taken	:	10 ml
λmax	:	202 nm

Table-6 Comparison of dissolution study of different formulations

		Log Cumulative Release								
S.no.	Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0		0	0	0	0	0
2	30	1.29	1.21	1.12	1.06	0.97	0.89	1.26	1.15	1.21
3	60	1.44	1.39	1.37	1.33	1.27	1.03	1.36	1.31	1.34
4	120	1.59	1.60	1.55	1.45	1.41	1.23	1.44	1.41	1.46
5	180	1.69	1.66	1.64	1.56	1.52	1.34	1.59	1.56	1.57
6	240	1.76	1.74	1.72	1.62	1.61	1.44	1.67	1.64	1.65
7	300	1.82	1.80	1.79	1.70	1.68	1.59	1.74	1.72	1.72
8	360	1.88	1.85	1.84	1.75	1.74	1.70	1.79	1.77	1.78
9	420	1.91	1.89	1.88	1.80	1.79	1.75	1.82	1.81	1.83
10	480	1.93	1.92	1.91	1.83	1.81	1.78	1.87	1.85	1.86

Figure: Release profile of Formulation

In vitro Buoyancy

Their was an increase in the floatation lag time which could be attributed to the fact that tablets containing low viscosity HPMC swell rapidly than tablets with high viscosity HPMC. Also higher floatation time of these tablets could be explained by a slower CO_2 formation because of the presence of the effervescent agents within the HPMC matrix (Krogel and Bodmeier, 1999 b). Medium can penetrate these tablets easily and react with Sod. bicarbonate to liberate CO_2.

It is because the buoyancy force build up due to the entrapment of CO_2 is strong enough for the whole tablet to go up to the surface and maintain the tablet on the surface for as long as 8hr. Tablets of all batches remained floatable throughout the study.

Table-7 In vitro Buoyancy study of formulations F1-F9

Batch	Buoyancy Lag Time (sec.)	Total Floatation time(hr.)
F1	60	8
F2	65	8
F3	80	8
F4	72	8
F5	84	8
F6	100	8
F7	96	>12
F8	100	>12
F9	98	>12

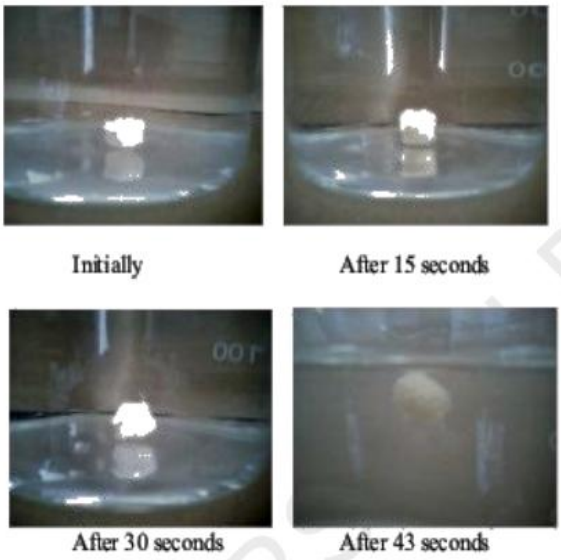

Fig-2 Floating of tablets

Table-8 **Comparison of the Release Kinetics of Different Formulations**

Modal Batch	Zero order	First order	Higuchi modal	Korsmeyer peppas modal
F1	0.9527	0.5371	0.9958	0.9846
F2	0.955	0.5576	0.9943	0.9912
F3	0.9619	0.5851	0.9918	0.9965
F4	0.9666	0.5945	0.9877	0.9955
F5	0.9748	0.6308	0.9830	0.9983
F6	0.9871	0.7640	0.9159	0.9824
F7	0.9658	0.5596	0.9826	0.9820
F8	0.9735	0.5933	0.9822	0.9922
F9	0.9719	0.5734	0.9845	0.9884

Discussion

Standard curve of captopril was prepared at λmax 202 nm and the correlation was found to be 0.9984. The tablet hardness was found to be in range of 4.0 to 7.0kg/cm3.

From the in vitro buoyancy studies, it was found that almost all the batches containing effervescent agent 30% w/w) showed immediate floatation followed by floatation period of more than 8hr.

The values of diffusion exponent 'n = 0.5-1'determined from the Korsmeyer-Peppas equations obtained from modeling of dissolution profiles showing percent drug release of a 60.0% indicates an anomalus transport mechanism and that the mass transfer follows a nonfickian model.

Differential Scanning Calorimetry (DSC) studies showed that no polymorphic changes occurred during manufacturing of tablets as all the peaks were present in the DSC graph of tablet sample.

Conclusion

From the results obtained, it was concluded that the formulation F1 is the best formulations as the extent of drug release was found to be around 85 %.

This batch also showed immediate floatation and floatation duration of more than 8hr. The drug release model of this formulation complies with zero order kinetics.

Based on the results we can certainly say that floating type gastroretentive drug delivery system holds a lot of potential for drug having stability problem in alkaline pH or which mainly absorb in acidic pH. We can certainly explore this drug delivery which may lead to improved bioavailability and ensured therapy with many existing drugs. It is the responsibility of future scientists working in this area to effectively use the potential of this drug delivery system for the benefit of mankind.

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