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Formulation and Optimization of Stable Floating Tablet of Losartanpotassium for Oral Controlled Drug Delivery System

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Abstract

The present study was to prepare a gastro retentive drug delivery system of Losartan floating tablets, was designed to increase the gastric residence time, thus prolong the drug release. The different type formulations were prepared by using polymers like HPMC K100M, ethyl cellulose, talc and lactose. In the present study Sodium bicarbonate and citric acid were incorporated as a gas generating agent. The Floating tablets were evaluated for pre compression and post compression parameters. And optimisation of formula. The drug release profile and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablet swelled radially and axially during in vitro buoyancy studies. It was observed that the tablet remained buoyant for 8-12 hours. From the study it is concluded that the developed formulation has good appearance with good handling condition, therapeutically efficacious, stable.

Keywords: **Losartan, Floating, Gastro retentive.**

INTRODUCTION

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes [1]. Oral controlled release dosage forms have been developed for the past three decades due to their considerable therapeutic advantages and applications. In today's industrialized society almost every product that eventually reaches the market has a long lineage of testing and modification to its design before it sees the light of the day. So success is the most difficult commodity" to come out, especially with time frame imposed, which is structured by a customer need or by a competitive threat. This leads to experimenters or researchers to find the most efficient schemes of formulating, testing and applying such schemes as broad a gamut of application required, to make a successful product.

The word 'optimize' is defined as, to make as perfect, effective or functional as possible and optimization may be interpreted as the way to find those values of the dependent variable. The application of formulation optimization techniques is relatively new to practice of the pharmacy, when used intelligently, with common sense; these "statistical" methods will broaden the perspective of the formulation process. Before any experiment is conducted at the pre-formulation stage, certain problems arise. It is often known beforehand which variables will significantly influence the response(s). Using screening designs and ANOVA can solve the problem.

The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms [2]. The controlled release drug delivery systems possessing the ability of being retained in the stomach are called Gastro Retentive Drug Delivery Systems and they can help in optimizing the oral controlled delivery of drugs by continuously releasing drug prior to absorption window for prolonged period of time[3]. Since that, various approaches such as floating, bioadhesive, swelling and expanding systems have been developed to increase the gastric retention time of a dosage form[1]. Among all the systems the floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time.

MATERIALS AND METHODS

Materials used

Table 1: List of chemicals used and names of suppliers/ manufacturers

S. No	Materials used	Source
1.	Losartan Potassium	BMR PHARMA, Hyderabad
2.	HPMC K100M	BMR PHARMA, Hyderabad
3.	Ethyl Cellulose	BMR PHARMA, Hyderabad
3.	Sodium bicarbonate	BMR PHARMA, Hyderabad
5.	Citric acid	BMR PHARMA, Hyderabad
6.	Magnesium stearate	S.D. Fine Chem Ltd, Mumbai
7.	Talc	S.D. Fine Chem Ltd, Mumbai
8.	Lactose	S.D. Fine Chem Ltd, Mumbai
9.	Hydrochloric acid	S.D. Fine Chem Ltd, Mumbai

Formulation design of controlled release floating tablets of Losartan Potassium:

The formulation design of controlled floating tablets of Losartan Potassium were prepared by using hydrophilic polymers HPMC K100M, effervescent agent (Sodium

bicarbonate) and Ethyl Cellulose at different concentrations and Floating lag time, Cumulative percent drug release in 6 hours and Cumulative percent drug release in 12 hours were checked and on that basis levels of above ingredients were fixed as follows:

The 3 independent variables were selected were:

- Concentration of HPMC K100M,
- Ethyl cellulose,
- Sodium bicarbonate

The 3 dependent variables were selected [7,8]:

- Floating lag time (FLT)
- Cumulative percent drug release in 6 hours (Q6)
- Cumulative percent drug release in 12 hours (Q12)

Statistical optimization technique was used to know:

- Which of the 3 factors employed had largest effect on dependant variables
- Actual concentrations to be employed to get optimized formulation.
- Obtain empirical equations for dependant variables.

The 3 dependant variables were analyzed by[17,18]:

1. Analysis Of Variance (ANOVA).
2. Multiple Linear Regression Analysis (MLRA).

Optimization of controlled release layer of Losartan potassium using 2^3 full factorial design[21,24]

With 3 factors at 2 levels, a full-factorial experiments consisting of 8 formulations, was designed. (2^3=8).

Preparation of controlled release floating tablets of Losartan Potassium[30, 34]

The floating tablets of Losartan Potassium were prepared by direct compression technique. All the ingredients used in the formulation were initially passed through sieve #40 separately before mixing. The required quantity of Losartan Potassium and other ingredients except talc and magnesium stearate were weighed accurately and transferred to a mortar and triturated for thorough mixing. To the above mixture, talc and magnesium stearate was added and further mixed for 2 minutes. Finally the mixture was compressed into tablets of 300 mg each using approx.10 mm punches in Shiv Pharma Engineers ten station tablet punching machine.

RESULTS & DISCUSSION

Optimisation

Independent Variables:	**Responses:**
X1: HPMC K100M	**Y1**: Floating Lag Time (FLT)
X2: ETHYL CELLULOSE	**Y2**: Cumulative percent drug release in 6 hours (Q6)
X3: SODIUM BICARBONATE	**Y3**: Cumulative percent drug release in 12 hours (Q12)

Table 2: Factorial design batches of Losartan potassium floating tablets

Variables	F1	F2	F3	F4	F5	F6	F7	F8
X_1	-1	+1	-1	+1	-1	+1	-1	+1
X_2	-1	-1	+1	+1	-1	-1	+1	+1
X_3	-1	-1	-1	-1	+1	+1	+1	+1

Table 3: Coded values and Actual values for the Independent variables

Coded Values	X1	X2	X3
-1	1000	20	40
+1	150	40	60

Where,

X_1 = Concentration of HPMC K100M in mg

X_2= Concentration of Ethyl cellulose in mg

X_3 = Concentration of $NaHCO_3$ in mg

Table 4: The actual values of the ingredients for the controlled release floating tablets of Losartan

Sl. No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Losartan Potassium	50	50	50	50	50	50	50	50
2	HPMC K100M	100	150	100	150	100	150	100	150
3	Ethyl Cellulose	20	20	40	40	20	20	40	40
4	Sodium Bicarbonate	40	40	40	40	60	60	60	60
5	Citric acid	5	5	5	5	5	5	5	5
6	Lactose	93	43	73	23	73	23	53	3
7	Magnesium Stearate	6	6	6	6	6	6	6	6
8	Talc	6	6	6	6	6	6	6	6
9	Total Tablet Weight	**320**	**320**	**320**	**320**	**320**	**320**	**320**	**320**

Table 5: Independent Variables and their values

Independent Variables	Units	Lower level	Higher level	Mid point
X1	Mg	100	150	125
X2	Mg	20	40	30
X3	Mg	40	60	50

Table 6: DOE Factorial Design of experimental plan and observed values Y(Q6)&Y (Q12)

S. No	Combinations	X1	X2	X3	Y1 (FLT)	Y2(Q6)	Y3(Q12)
1	I	100	20	40	32	42.91	83.27
2	X1	150	20	40	30	48.58	85.75
3	X2	100	40	40	25	60.85	90.15
4	X1X2	150	40	40	25	45.44	89.33
5	X3	100	20	60	22	49.35	94.77
6	X1X3	150	20	60	24	59.75	92.46
7	X2X3	100	40	60	22	59.92	98.44
8	X1X2X3	150	40	60	20	42.17	95.35
9	Mid point	125	30	50	23	50.56	92.62
10	Mid point	125	30	50	22	51.24	92.91
11	Mid point	125	30	50	23	51.31	93.12
12	Mid point	125	30	50	24	50.96	94.11

Sigma Tech software was used for DOE plan and statistical analysis

Tabe 7: Statistical analysis of factorial Design of Experiments

		For Y(Q6)			For Y (Q12)|		
S. No	**Coefficients**	**Coef values**	**F values**	**SS%**	**Coef values**	**F values**	**SS%**
1	Bo	51.121	-	-	91.17	-	-
2	B1	-2.136	315	8.4	-0.49	4.6	1.1
3	B2	0.974	65	1.7	2.15	88.4	20.2
4	B12	-6.154	2613	69.5	-0.49	4.5	1.0
5	B3	1.676	194	5.2	4.09	319.6	73.0
6	B13	0.299	6	0.2	-0.86	14.1	3.2
7	B23	-2.726	513	13.6	-0.51	4.9	1.1
8	B123	-0.884	54	1.4	0.29	1.6	0.4

Analysis of Y(Q6)

Interaction X1X2 has strong negative influence on Drug release, where as X1 and X2 individuals have not much impact on Drug release in 6 hrs as can be seen from the SS%.

Analysis of Y(Q12)

In case of drug release X3 has largest positive impact on Drug release in 12 hours and next one X2 also has positive impact .

This also infers that we can increase X2 and X3 further.

Table 8: Central Composite Design and observed values

S. No	Combinations	X1	X2	X3	Y1 (FLT)	Y2(Q6)	Y3(Q12)
1	I	100	20	40	32	42.91	83.27
2	X1	150	20	40	30	48.58	85.75
3	X2	100	40	40	25	60.85	90.15
4	X1X2	150	40	40	25	45.44	89.33
5	X3	100	20	60	22	49.35	94.77
6	X1X3	150	20	60	24	59.75	92.46
7	X2X3	100	40	60	22	59.92	98.44
8	X1X2X3	150	40	60	20	42.17	95.35
9	Mid point	125	30	50	23	50.56	92.62
10	Mid point	125	30	50	22	51.24	92.91
11	Mid point	125	30	50	23	51.31	93.12
12	Mid point	125	30	50	24	50.96	94.11
13	X1At -2L	75	30	50	28	40.54	82.25
14	X1At + 2L	175	30	50	24	58.71	96.62
15	X2At - 2L	125	10	50	26	56.29	90.26
16	X2At + 2L	125	50	50	25	58.23	97.52
17	X3At-2L	125	30	30	33	52.93	90.42
18	X3At + 2L	125	30	70	22	58.45	93.21

Y(Q12)= 92.37 + 1.55 X1 + 1.98 X2 + 2.39X3 – 0.49 X1X2 – 0.86 X1X3 -0.51 X2X3 – 0.84 X1^2 + 0.2 X2^2 - 0.24 X3^2

The targeted values used for Contour are, 96%, 97%, 98% , 99% Drug release.

X1= 100 to 125 X2= 50 as constant. X3= 50 to 70 Which gives an output of 97% to 99% of drug release in 12 hours.

Table 9: Results of floating property of the Losartan floating tablets

Formulation code	Floating lag time (sec)	Total floating time (hr)
F1	32	>24
F2	30	>24
F3	25	>24
F4	25	>24
F5	22	>24
F6	24	>24
F7	22	>24
F8	20	>24

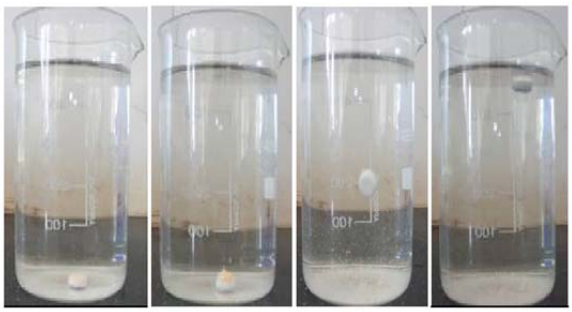

Figure 1: Determination of floating time and floating lag time

Studies to determine the Floating lag time and duration of floating of variousformulations were carried out and the results indicated that floating lag time which wasobserved for all the tablets was within 0-1 minute after immersion into gastric media andtotal floating time was greater than 24 hours for all batches.

Swelling Index

Swelling study was performed on all the batches (F1 to F8) for 8 hours. The swelling index of the tablets increases with an increase in the polymer content. The swelling index was ranging in between 46.57±0.012% to 79.13± 0.0135%.High level of HPMC K100M showed highest water uptake, showed maximum swelling property. The ability of hydrogels to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. As the concentration of NaHCO3 increased from 10% to 15% swelling index was increased due to increase in the rate of pore formation and consequently rapid hydration of the tablets matrices.

Table No. 10: *In-vitro* swelling study of various formulations

Formulation code	% Swelling Index
F1	46.57±0.012
F2	63.12±0.018
F3	59.52± 0.014
F4	63.54± 0.021
F5	79.13± 0.0135
F6	67.21± 0. 04
F7	50.59± 0.036
F8	74.92± 0.0163

***In-vitro* drug release profiles of various formulations**

The results of *in-vitro* dissolution studies are given in table. All the tablet formulations showed more than 12 % release within 1hour, but F8 formulation showed maximum 19.93% drug release within 1hour. After 12 hours study, drug release for formulations F2, F3, and F6 (with HPMC K100M > EC) were found to be 87.84%, 91.01%, and 92.63% respectively. Formulations F4, F7 and F8 with (EC > HPMC K100M) were drug release of 86.72%, 86.98% and 89.45% respectively. Formulations F1, F5 and F8 (with HPMC K100M and EC in equal amount) showed drug release of 88.60%, 91.76% and 89.52% respectively. Formulations containing Lactose showed decrease in the rate of drug release with increase in concentrations. The formulation containing maximum amount of HPMC K100M and minimum amount of EC(F6) showed maximum drug release of 92.63% compared to other formulations.

Table 11: *In vitro* drug release study for F1-F8 formulations

Time (hr)	% Cumulative drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	4.33	9.75	15.05	5.91	12.99	16.71	10.55	8.11
1	10.31	16.35	24.04	13.39	18.85	25.14	21.84	14.15
2	17.26	25.51	32.83	18.33	24.91	33.56	29.83	19.64
3	24.41	33.38	40.52	26.23	32.57	41.25	34.41	24.96
4	31.18	37.59	46.93	32.56	36.97	49.31	40.82	30.27
5	36.13	43.27	54.26	38.96	44.11	53.34	50.31	35.76
6	42.91	48.58	60.85	45.44	49.35	59.75	59.92	42.17
7	46.93	55.17	65.79	51.94	53.21	65.79	64.95	48.58
8	55.61	60.48	70.92	61.44	63.09	71.65	70.37	57.19
9	61.09	67.99	76.23	67.85	71.58	75.23	77.23	76.51
10	69.93	72.94	80.81	75.36	79.34	82.47	84.74	81.01
11	75.51	80.81	85.75	81.93	85.74	87.15	91.61	87.87
12	83.27	85.75	90.15	89.33	94.77	92.46	98.44	95.35

CONCLUSION

Thus the objective of gastro retentive floating drug delivery system of an antihypertensive drug Losartan Potassium with extended release profile was achieved. Characterization, *in vitro* evaluation of these developed drug delivery system of Losartan Potassium showed good correlation with USP standards. Gastro retentive sustained release dosage forms of Losartan Potassium might be beneficial to produce improved patient compliance reducing the dosing frequencies and increased oral bioavailability.

My study achieved

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