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Formulation and evaluation of Lisinopril floating tablets

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Abstract

The floating drug delivery system is site-specific and allows the drug to remain in the stomach for a prolonged period of time so that it can be released in a controlled manner in gastrointestinal tract. The model drug is Lisinopril which has narrow absorption window, only 25% of the drug is absorbed and the remaining drug is excreted unchanged in urine. By increasing the gastric residence time of the lisinopril, the frequency of administration and drug wastage can be reduced The present study was carried out to develop a floating drug delivery system using gum karaya, chitosan and carrageenan as release controlling polymers to prolong the residence time of the model drug lisinopril in the stomach. The floating ability of gum karaya, chitosan and carrageenan was increased by addition of NaHCO3 as a gas-generating agent. The floating tablets were prepared by direct compression method and evaluated for pre compression and post compression studies. The lisinopril release through 20% gum karaya and 20% carrageenan was delayed by 12 hours when compared to a preparation available on the market which released the complete drug in 0.5 hours. The drug release study of lisinopril from the formulation follows zero order kinetics using a diffusion controlled mechanism. The results from the present study revealed that gum karaya and carrageenans provides the required delay in the release of drug and hence are ideal for the formulation of floating drug delivery systems.

Keywords: Lisinopril, Floating drug delivery, Gastro retentive drug delivery, Swelling index.

INTRODUCTION

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach [6]. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas [1].

Types of floating drug delivery systems

Based on the mechanism of buoyancy [7], two distinctly different technologies have been utilized in development of FDDS which are:

- Effervescent System
- Non-Effervescent System

Effervescent system

Effervescent systems include use of gas generating agents, carbonates (e.g. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of system and making it float on the gastric fluid [8]. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature.

These effervescent systems further classified into two types [2].

- Gas generating systems
- Volatile liquid/vacuum systems

Non effervescent systems

The FDDS belonging to this class are usually prepared from gel forming or highly swellable cellulose type hydrocolloids, polysaccharide or matrix forming polymers like poly-acrylate [9], polycarbonate, polystyrene and poly-methacrylate. Sheth and Tossounian suggested that "when non-effervescent floating dosage forms come in contact with an aqueous medium, the hydrocolloids absorb water and start to hydrate, forming a gel at the surface." The resultant gel layer subsequently control the trafficking of drug out and passage of solvent into the dosage form [10]. The drug in the dosage form dissolves in and diffuses out with the diffusing solvent forming a 'receding boundary' within the gel structure [3].

AIM AND OBJECTIVES

Aim

The aim is to formulate and evaluate the floating tablets of Lisinopril.

Objectives

- To carry out pre-compression studies.
- To carry out drug and excipients interaction studies of the optimized product and their stability as per ICH guidelines.
- To carry out post compression studies.

METHODOLOGY

Formulation of floating tablets of lisinopril by direct compression method

Floating tablets of Lisinopril were prepared by direct compression method employing sodium bicarbonate as gas-generating agent. Gum karaya, chitosan and carrageenan were used as rate controlling polymers [11]. The concentrations of the above ingredients were optimized .All the ingredients were weighed accurately. The drug was mixed with the release rate controlling polymers and other excipients [12], except lubricants and glidants, in ascending order of their weight [13]. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, glidants were added and mixed for not more than 1 min (to ensure good lubrication). The powder blend was weighed and punched [4].

RESULTS AND DISCUSSION

Table 1: Formulation Table

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Lisinopril(mg)	5	5	5	5	5	5	5
Gum Karaya	15%	-	-	20%	-	-	
Carrageenan	-	15%	-	-	20%	-	20%
Chitosan	-	-	15%	-	-	20%	-
Ethylcellulose							15%
Sodium bi carbonate	10%	10%	10%	10%	10%	10%	10%
Citric acid	2%	2%	2%	2%	2%	2%	2%
Mannitol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Mg stearate	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Total wt.	150	150	150	150	150	150	150

Pre formulation studies

Table 2: Organoleptic properties

S.NO	Parameter	Drug
1	Color	White to off White color
2	Odor	Odorless
3	Taste	Tasteless
4	Appearance	Crystalline powder

Melting point determination

Table 3: Melting Point Determination

Reported Melting Point	Observed Melting Point
107ºC	**107-109ºC**

Determination of solubility

Table 4: Determination of Solubility

Soluble	Water , DMSO, N,N -dimethyl formamide,0.1N HCl
Sparingly soluble	Ethanol, Propylene glycol
Slightly soluble	Hexane, Dichloromethane, and Methylbenzene.

Compatibility studies of drug with excipient

Compatibility between lisinopril and the excipient proposed to be taken in the formulation was carried out by FTIR. Results shown that there was no chemical interaction of the drug and excipients, hence computable [14].

Pre compression studies

Table 5: Pre Compression Studies

Formulation code	Bulk density (gm /ml)	Tapped density (gm/ml)	Hausner ratio	Carr's index (%)	Angle of repose (θ)	Type of Flow
F1	0.541	0.691	1.276	21.02	37^0	**Fair**
F2	0.484	0.615	1.27	21.30	37^0	**Fair**
F3	0.710	0.873	1.251	19.714	39^0	**Fair**
F4	0.712	0.870	1.206	17.126	36^0	**Fair**
F5	0.718	0.871	1.223	18.513	37^0	**Fair**
F6	0.410	0.483	1.178	15.113	34^0	**Good**
F7	0.250	0.384	1.156	15.11	35^0	**Good**

Post compression studies

Pre compression studies shows that the granules have fair to good flow.

Post compression parameters

Table 6: Post Compression Studies

Formulation code	Weight variation	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity(%
F1	200	6.4	0.72	2.6	99.28
F2	201	6.3	0.68	2.6	97.16
F3	200	5.8	0.69	2.7	99.10
F4	202	5.6	0.66	2.75	97.68
F5	204	5.7	0.68	2.6	98.19
F6	198	5.9	0.65	2.62	98.41
F7	200	6.3	0.61	2.54	99.76

***In-vitro* buoyancy studies**

Table 7: In-Vitro Buoyancy Studies

Formulation Code	Floating lag time(sec)	Swelling index (%)	Floating duration (hrs)
F1	25	100.85	7
F2	24	139.5	8
F3	30	101.5	9
F4	44	121.2	12
F5	54	140.5	10
F6	2min	142.5	10
F7	1min 24sec	144.85	12

In-vitro dissolution studies

Medium : 0.1N HCL
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Temperature : 37ºC± 0.5
Time : 12hrs

In vitro dissolution for floating tablets was performed in 0.1N HCL for 12hrs.

In -vitro drug release study

Table 8: In -Vitro Drug Release Study

Time(Hours)	F1	F2	F3	F4	F5	F6	F7
1	12	11.5	10.2	7.5	11.3	12.5	9.3
2	20	16	13	12.3	15.2	20	15
3	34	28	27	25	36.4	35	34
4	45	37	35	34	45.2	46	42
5	61	55	52	42	42.4	59	57
6	70	71	67	53	50.2	68	70
8	94.28	97.16	74	65	65.3	77	79.6
10	--	--	99.10	78	98.19	98.41	83.4
12	--	--	--	95.68	--	--	99.76

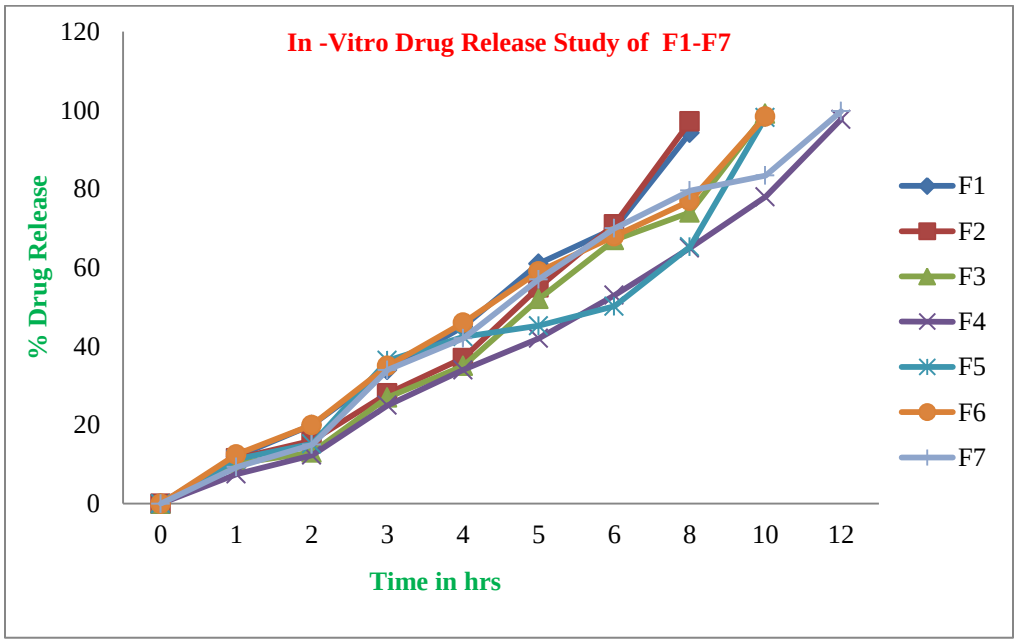

Fig 1: In -Vitro Drug Release Study

Discussion

From the dissolution studies it was evident that only F4 and F7 are showing the drug release till 12th hour. F7 was optimized since it was showing highest i.e 99.76% of drug release at 12th hour [5].

Release kinetics of optimized formulation (F7)

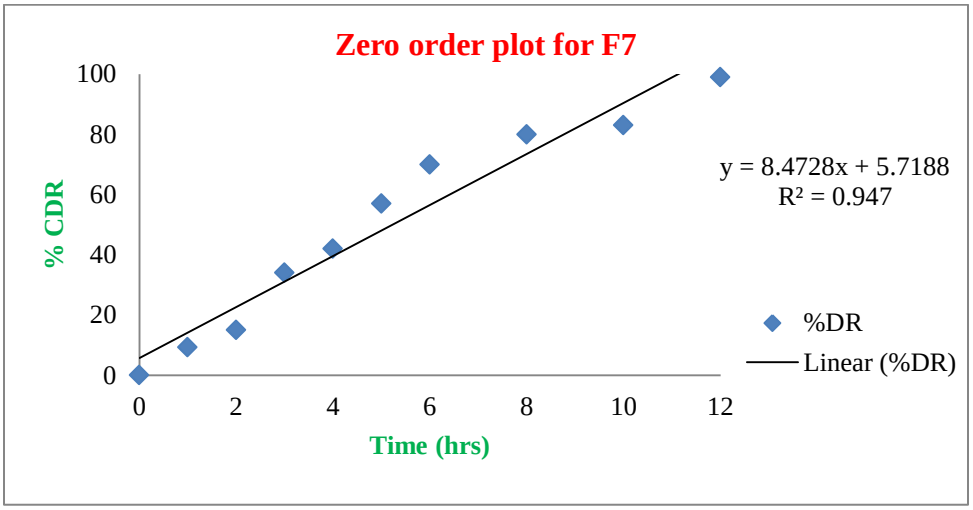

Fig 2: Zero order plots for the optimized formulation

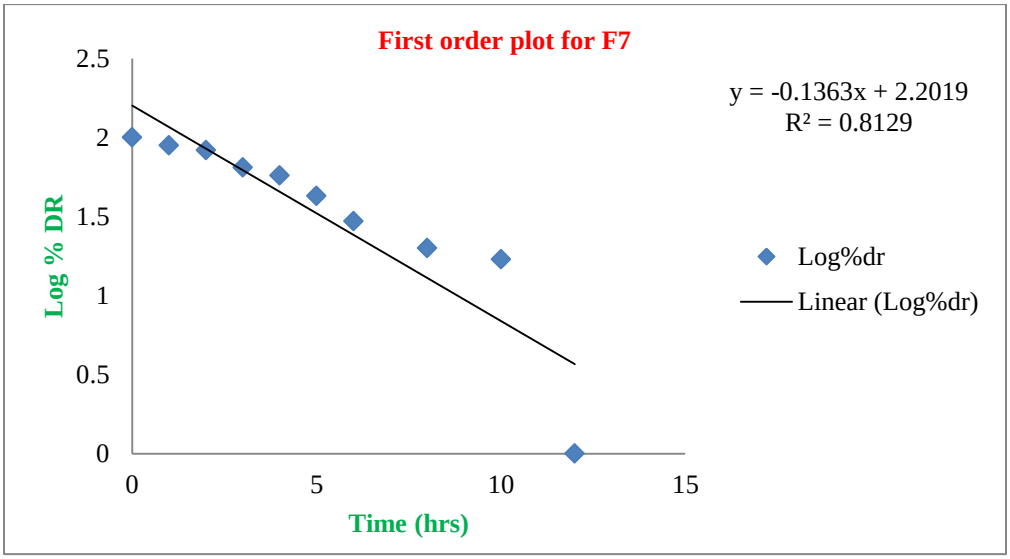

Fig 3: First order plot for the optimized formulation

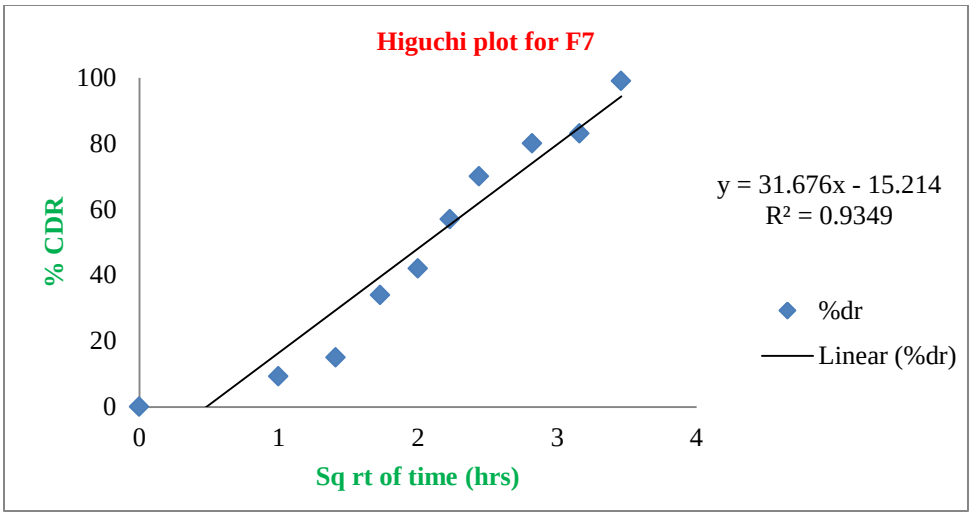

Fig 4: Higuchi plot for the optimized formulation

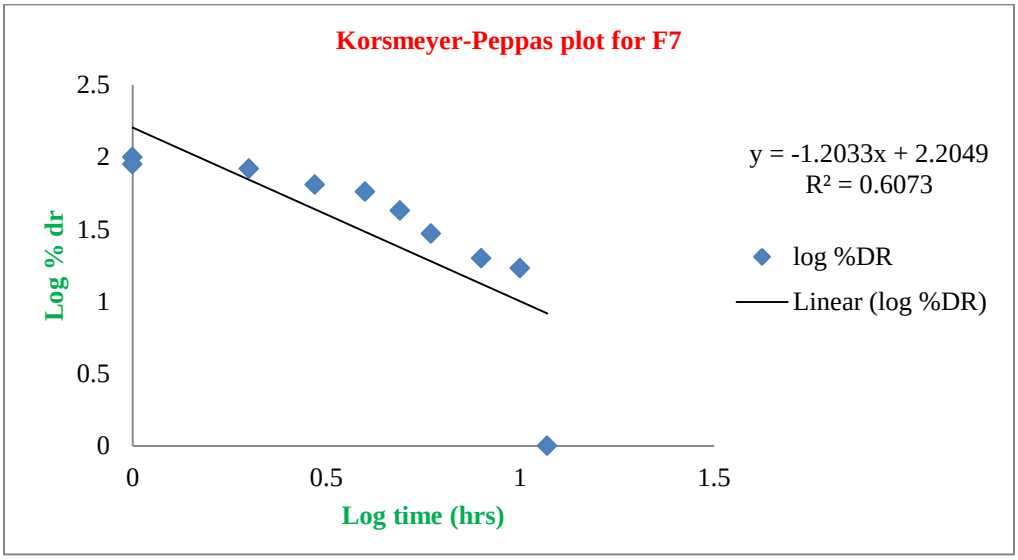

Fig 5: Korsmeyer-Peppas plot for the optimized formulation

Release Kinetics models

Table 9: Release kinetics for F7 formulation

	Zero	First	Higuchi	Peppas
	% CDR Vs T	**Log % Remain Vs T**	**%CDR Vs √T**	**Log C Vs Log T**
Slope	8.472	0.136	31.67	1.203
R 2	0.947	0.812	0.934	0.607

Discussion

The release order kinetics of optimized formulation was performed, and it was evident from the table that the optimized formulation is showing zero order release and the higuchi model proved that the drug release was by diffusion.

Stability studies for optimized formulation

Table 10: Stability Studies for F7 formulation

Percentage drug release			
Sampling interval	**25^0C/60%RH**	**30^0C/65%RH**	**40^0C/75%RH**
0 Days	99.76	99.76	99.76
15 Days	98.41	98.35	98.31
30 Days	97.70	97.57	97.40
90 Days	96.52	97.60	97.66

DISCUSSION

Stability studies of the formulation F7 of Lisinopril floating tablets were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 25^O C/60%RH, 30 ºC/65% RH and 40 ºC/75% RH for 90 days. There was no significant change in the physical property and percept of drug release was within the limits ±4 during 12 hour during the stability period.

CONCLUSION

Floating drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. They prolong the gastric retention time (GRT) of drugs. The Floating tablets of lisinopril were successfully prepared by direct compression method using gum karaya, chitosan and carrageenan as rate controlling polymers. The physiochemical evaluation results for the powdered blend of all trials pass the official limits in angle of repose, compressibility index and hausner's ratio. The optimized formulation F7 showed the average thickness of 2.54 mm, average hardness of 6.3 Kg/Cm2, average weight variation of 0 %, friability of 0.61 %, floating lag time of 1min 24 sec, swelling index 144.85 % and floating duration 12hours. The optimized formulation F7 showed the highest drug release of 99.76% at 12th hour. Drug release from the floating tablet was prolonged and hence reduces the frequency of administration and drug wastage.

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