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Research Article

Studies on Formulation Development and Evaluations on Losartan Floating and Bioadhesive Drug Delivery System

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Abstract

The present investigation was undertaken to formulate and evaluate the losartan floating and bioadhesive drug delivery system using different polymers in different ratios. The main objective of the present work is to develop a novel osmotically controlled drug delivery system of losartan. It was aimed to prepare for prolonged residence in the stomach over conventional gastro retentive approaches. As the drug has short biological half-life (2 hours) hence it becomes necessary that it should be administered in 2 or 3 doses of 2.5 to 10 mg per day. Thus, the development of controlled-release dosage forms would clearly be advantageous. Formulated tablets gave satisfactory results for various evaluation parameters like tablet hardness, friability, weight variation, thickness, floating lag time, floating duration, content uniformity, ex vivo osmotically controlled strength and in vitro drug release. In all formulations Carbopol 974P is used to add osmotically controlled strength but the concentration of this polymer has significantly influenced the drug release due to its retarding property. Comparing the three different grades of Hydroxy propyl methyl cellulose (HPLC) (K4M, K15M and K100M), it was found that low-viscosity grades of HPMC K4M formulations released drug rapidly compared to K15M HPLC and K100M HPLC. Among all formulations K15M grade provided better controlled release characteristics with excellent drug release and in vitro buoyancy. From the above, it was also evident that at higher viscosity grades of polymer concentrations, the rate of drug release was retarded greatly.

Keywords: Losartan, HPMC, Carbopol, Controlled release dosage forms.

INTRODUCTION

Losartan

(www.wikipedia.org/wiki/Losartan.) is an angiotensin II antagonist drug used mainly to treat high blood pressure (hypertension). It may also delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes, hypertension and microalbuminuria or proteinuria. It is chemically defined as (2- butyl-4-chloro-1-{[2'-(1*H*-tetrazol-5-yl) biphenyl-4-yl] methyl} -1*H*-imidazol-5-yl) methanol. methyl}-1*H*-imidazol-5-yl) methanol. Losartan is a selective, competitive angiotensin II receptor type 1 (AT_1) antagonist, reducing the end organ responses to angiotensin II. Losartan is a uricosuric because losartan can cause hyperkalemia, potassium supplements or salt substitutes containing potassium should not be used without appropriate monitoring by a physician.

Hypertension

(www. wikipedia.org/wiki/Hypertension) is a condition of having high blood pressure. Hypertension results from two major factors, which can be present independently or together. The heart pumps blood with excessive force. The body's smaller blood vessels (known as the arterioles) are narrow; so that blood flow exerts more pressure against the vessels walls. Blood pressure is the force applied against the walls of the arteries as the heart pumps blood through the body. The force, amount of blood pumped

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and the size and flexibility of the arteries determine the pressure. Although the body can tolerate increased blood pressure for months and even years, eventually the heart may enlarge (a condition called hypertrophy), which is a major factor in heart failure.

The concept of Floating Drug Delivery not hold (FDOS) Systems (Singh *et.al*., 2000, Chandel *et.al*., 2012, Khan *et.al*., 2010, Geetha *et.al*., 2012, Bhardwaj *et.al*., 2013, Narang *et.al*., 2011, Suryawanshi *et.al*., 2012, Katta *et.al*., 2013, Arora *et.al*., 2005, Chandel *et.al*., 2012, Khatri *et.al*., 2007, Mayavanshi *et.al*., 2008) was described in the literature as early as 1962. 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. This results in an increased Gastric Residence Time (GRT) and a better control of fluctuations in plasma drug concentration.

Types of floating drug delivery systems

Based on the mechanism of buoyancy and two distinctly different technologies have been utilized in the development of FDDS.

1. Non- effervescent FDDS
2. Effervescent FDDS

1) Non-effervescent FDDS

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in Gastrointestinal tract (GI) tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, hydrophilic gums, polysaccharides and matrix forming materials such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymers such as chitosan and carbopol. Capsule/tablet contains a mixture of drug and hydrocolloids. Upon contact with gastric fluid, the mixture swells and forms a gelatinous barrier thereby remaining buoyant in the gastric juice for an extended period of time.

2) Effervescent FDDS

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 (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

1. Gas generating systems
2. Volatile liquid/vacuum containing systems

HPMC- A polymer of modified release

(www.wikipedia.org/wiki/Hypromellose, www.theherbarie.com/Hydroxypropyl-Methycellulose-HPMC, (Ashutosh *et.al*., 2013): An important hydrophilic carrier material used for the preparation of oral controlled drug delivery systems is (HPMC). One of its most important characteristics is its swellability, which has a pronounced effect on the release kinetics of an incorporated drug. On contact with biologic fluid water diffuses into the device, resulting in polymer chain relaxation with volume expansion. Then, the incorporated drug dissolves and diffuses out of the system. In a typical experimental dissolution vessel and

depending on the type of substitution and chain length of the HPMC type used, the macromolecules disentangle more or less rapidly from the polymer. All these phenomena (water, drug and polymer diffusion, polymer swelling, and drug and polymer dissolution) can contribute to the control of drug release.

For the monolithic matrix approach for slow/controlled drug delivery, cellulose ethers and, more specifically, hypromellose HPMC are the most widely used polymers. When HPMC polymers within the matrix are exposed to an aqueous medium, they undergo rapid hydration and chain relaxation to form a viscous gelatinous layer, which is commonly termed 'gel layer', at the surfaces of the tablet. Failure to generate a uniform and coherent gel may cause a rapid drug release. It is the subsequent physicochemical characteristics of this gel layer that control water uptake and the drug release mechanism from the matrix.

Effect of Polymer grade

With decreasing polymer molecular weight the degree of entanglement of the macromolecules decreases. Thus, the mobility of the polymer chains on water imbibitions increases. According to the free volume theory of diffusion, the probability for a diffusing molecule to jump from one cavity into another consequently increases. This leads to increased water and drug diffusion coefficients and increased drug release rates. In addition, the polymer dissolution rate increased with decreasing molecular weight.

Effect of the type of drug

Various factors contribute to the overall control of drug release, such as the solubility of the drug within the bulk fluid, the size of the drug molecule and its mobility within the swollen polymeric network, the dissolution rate of the polymer and polymer-drug interactions.

Materials Used

The following materials were obtained from commercial sources and used for the formulation. The drug losartan was received as gift sample from Wockard. Other excipients were received from different manufacturer microcrystalline cellulose plain from Ranq Remedies, Mumbai, India; sodium bicarbonate, Colloidal Silicon Dioxide (Aerosil), carbopol 974P from Fisher Ltd., Chennai; talc from Kanpha Labs, Chennai; magnesium stearate from Jain Enterprises, Chennai; HPMC K4M, HPMC K15M and HPMC K100M from Samsung Fine Chemicals, Mumbai India.

Equipments Used

The following equipment were used for the formulation were Single Station Tablet Compression Machine from ACT instruments; Hyderabad, Telagana., digital weigh balance from Shimadzu, Japan; Fluidized bed dryer, double cone blender from Cadmach, Ahmadabad, Gujarat. Rapid mixture granulator from Remi, Mumbai; Monsanto Hardness tester from Pharma lab, Ahmedabad; Roche Friabilator from Tab-Machines, Mumbai, Disintegration tester from Electrolab, Chennai; Dissolution apparatus from Electrolab TDT 08L; UV-VIS Spectrophotometer from Labindia, Mumbai. The hot air oven from Tempo Instruments, Mumbai; and glass wares from Borosil and Anumbra.

Preformulation Studies (Gopinath *et.al*., 2011, Vilegave *et.al*., 2013)

The first step in any formulation activity is careful consideration of a complete physicochemical profile of the active ingredients available, prior to initiating a

formulation development activity. The basic purpose of the preformulation activity are to provide a rational basis for the formulation approaches, to maximize the chances of success in formulating an acceptable product, and to ultimately provide a basis for optimizing drug product quality and performance. Drug-excipient stability study forms heart of such data.

Characterization of the Material

Drug excipients compatibility studies

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added to the formulation. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious and safe.

a. IR Spectrophotometry

The physical properties of the physical mixture were compared with those of drug. Sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 Psig for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 625 cm^{-1} in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

b. Differential scanning calorimetry (DSC)

DSC scan of samples were obtained in a Perkin Elmer thermal analyzer equipped with a monitor and printer. The instrument was calibrated with indium standard. Accurately weighed 5 mg of sample were placed in an open, flat bottom, aluminum sample pans. Thermograms were obtained by heating the sample at a constant rate of 10°C/minute. A dry purge of nitrogen gas (20 mL/min) was used for all samples heated from 35°C – 400°C.

Micromeritical properties

The following micromeritical properties of all the formulations were determined like densities, compressibility index, angle of repose and hausner ratio. They were calculated and all estimated parameters were found within the limits.

Solubility studies

Solubility of samples were determined by saturated solubility experiments. Saturated solutions of samples were prepared by adding an excess amount of sample (1gm) to 10 mL of medium and sealed in closed containers. They were placed on a vibrating shaker and shaken at 25°C $\pm$1°C for 24 hours. Aliquots from clear supernatant layer, after sufficient dilution with distilled water, were analyzed spectrophotometrically at 275 nm. Drug content was calculated by comparison with standard curve which was constructed with corresponding medium. At the same time the drug stability in different solvents was determined by dissolving the known amount of drug in medium and the drug content was calculated after 24 hrs.

Standard graph of Losartan in 0.1 N HCl

The standard graph of Losartan in 0.1 N HCl was developed in the concentration range of 5-50 µg/mL with suitable dilutions and observed under UV- spectrophotometer at an absorption max of 275 nm.

Formulation And Development

(Ali *et.al*., 2007, Arza *et.al*.,2009, Jaimini *et.al*.,2007, Rosa *et.al*., 1995, Pablo *et.al*., 2008, Katyayini *et.al*., 2013, Hingawe *et.al*., 2012, Garg *et.al*., 2009, Manoj *et.al*., 2007, Patel *et.al*.,2009, Sasa *et.al*., 2000, Rosa *et.al*., 1995.)

The following ingredients included were used in the formulations and are represented in table 1.

Table 1: Ingredients used for the formulations

Purpose	Ingredients
Hydrophilic polymers (to modify the release pattern of the drug)	HPMC K4M, HPMCK15M, HPM K100M
Osmotically controlled polymer	Carbopol 974P
Directly compressible diluents	Microcrystalline Cellulose
Anti adherent	Talc
Lubricant	Magnesium stearate
Gas generating agent	Sodium bicarbonate

Preparation of Floating and osmotically controlled tablets of Losartan by direct compression method

The compositions of different formulation trials with different polymers are given in the Tables 2. Accurately weighed quantities of hydrophilic polymers, osmotically controlled polymer, microcrystalline cellulose were taken in a mortar and mixed geometrically. To this mixture required quantity of Losartan was added and mixed slightly with pestle. This mixture was passed through sieve no 40 and later collected in a plastic bag and blended for 5 min. To this required amount of sodium bicarbonate was added and again mixed for 5 min. Later sufficient quantity of magnesium stearate and talc were added and the final blend was again passed through sieve no 40. Thus obtained blend was mixed thoroughly for 10 min and compressed into tablets with 8.5 concave punches and corresponding dies at a hardness of 6 kg/ cm single station tablet punching machine.

Table 2: Composition of Losartan Floating 200mg tablets and having different viscosity HPMC and same values of MCC 35mg, magnesium 2mg, tale 1mg and sodium bicarbonate 35mg.

Ingredient	FM 1	FM 2	FM 3	FM 4	FM 5	F 1
Losartan	10	10	10	10	10	10
HPMC K4M	70	60	50	40	30	100
HPMC K15M	-	-	-	-	-	-
HPMC K100M	-	-	-	-	-	-
Carbopol 974P	30	40	50	60	70	-
HPMC K15M						
Ingredients	**FM 6**	**FM 7**	**FM 8**	**FM 9**	**FM 10**	**F 2**
Losartan	10	10	10	10	10	10
HPMC K4M	-	-	-	-	-	-
HPMC K15M	70	60	50	40	30	100
HPMC K100M	-	-	-	-	-	-
Carbopol 974P	30	40	50	60	70	-
HPMC K100M						
Ingredients	**FM 11**	**FM 12**	**FM 13**	**FM 14**	**FM 15**	**F 3**
Losartan	10	10	10	10	10	10
HPMC K4M	-	-	-	-	-	-
HPMC K15M	-	-	-	-	-	-
HPMC K100M	70	60	50	40	30	100
Carbopol 974P	30	40	50	60	70	-

Evaluation of Tablets

(www.pharmainfo.net/satheeshbabu/blog/evaluation-tablet)

In addition to routine tests for general appearance, hardness, friability, drug content, weight variation, uniformity of

content and *In-vitro* drug release, floating lag time and floating duration time must have to be evaluated.

a. Weight Variation Test

As per IP procedure

b. Hardness: Using the Monsanto Hardness Tester and the average was calculated and presented with standard deviation.

c. Thickness

The thickness of the tablets was determined using a Screw guage.

d. Friability

Using Roche Friabilator.

e. Drug Content: The drug content of the tablet was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount.

Procedure

Ten tablets with pre determined weight from each batch were taken and crushed in a mortar and weight and weight equivalent to one average tablet was taken, transferred to a 250 ml volumetric flask and 0.1 N HCl as added. The flask was kept on mechanical shaker for overnight, later is taken out and volume was made up to 100 ml with 0.1 N HCl. The solution was filtered through a filter paper and the first few ml were discarded. The filtrate was sufficiently diluted and the absorbance was recorded and analyzed in UV spectrophotometer against the blank at 275 nm.

f. Effect of pH

To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) for first 2 hr., acetate buffer (pH 4.5) for next 2 hr, followed by SIF (pH 6.8) for the remaining period of 24 hr. The samples (10 ml) were withdrawn at predetermined intervals and analyzed after filtration through 0.45 µm nylon membrane filters.

g. Effect of agitational intensity

In order to study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP-I (rotating basket) at 50, 100, and 150 rev./min. In another experiment, stirred and stagnant conditions were induced in a single run using USP-I apparatus. The rotational speed was kept at 100 revolution/min (stirred conditions), which, however, was stopped intermittently to induce the stagnant conditions. The protocol used was stirred conditions for first 3 hr. (0 – 3 hr.), stagnant conditions for next 2 hr. (3 – 5 hr.), stirred condition for next 3 hr. (5 – 8 hr.) and stagnant condition for next 2 hr. (8 – 10 hr.). Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45 µm nylon membrane filters.

h. Effect of osmotic pressure

In order to confirm the mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride (osmotically effective solute) was added in SIF [9, 10] and apparatus (100 revolution/min). To avoid any interference in the analysis by sodium chloride residual drug analysis methodology was utilized for construction of release profile [11, 12]. At predetermined time points, specified

numbers of tablets (one or two) were withdrawn from each vessel, cut open, and the contents dissolved in 250 – 500 ml of SIF. The samples were analyzed to determine the residual amount remaining in each tablet. Accuracy of this method was checked in SIF, where results after direct measurement of Losartan into the release media were similar to the results of residual drug analysis method.

***i. In vitro* Drug Release Studies**

The release rate of drug from floating and osmotically controlled tablets was determined using USP type 2 apparatus.

j. Dissolution profile kinetic modeling

Over recent year, the *In vitro* dissolution has been recognized as an important tool in drug development. In vitro dissolution has been recognized as an important parameter in quality control and under certain conditions. It can be used as a surrogate for the assessment of bio-equivalence or prediction of bioequivalence. Guidance recommends USP dissolution apparatus 1, 2, 3 or 4 for modified release dosage forms and generally this equipment is satisfactory. However, modifications of current dissolution equipment or completely new agitation, changing the media, and holding the dosage form in the media without interfering with the release mechanism require careful planning. A good understanding of the release mechanism of the dosage form as well as the physical and chemical properties of the drug will enable development of accurate dissolution tests. There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and Reference dissolution Zero order kinetics, first order kinetics, korsmeyer-Peppas model and higuchi model were applied.

Stability studies

(Wolfgang 1998) The optimized tablets from batch FM 8 were charged for stability studies. There was no change in physical appearance, color. Formulations were analyzed at the end of 3 months for the assay and dissolution studies.

Discussion

The physical attributes of the tablet were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The results of various evaluation studies mentioned above are discussed under the following sections:

1. Drug and Excipients compatibility studies

a. IR Spectrophotometry

The physical properties of total formulation were compared with those of plain drug and physical mixture. Here spectral changes in the mixture are the basis for the determination of compatibility. The obtained spectrums of different formulation combinations are shown below in Figure 1.

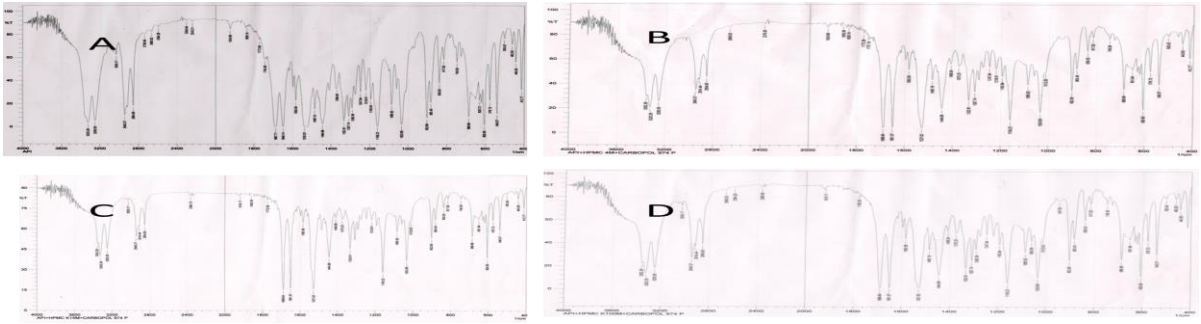

Figure 1: IR spectrum of pure drug with pure drug (A), HPMC K4M (B) HPMCK 15M (C) K100M and Carbopol974P(D)

The above IR spectrums of all the formulations of different excipients were shown no spectral changes when compared with pure drug, hence it was expected that there is no interaction with drug with its formulations.

b. Differential Scanning Calorimetry (DSC)

DSC scan of samples were obtained in a Perkin Elmer thermal analyzer equipped with a monitor and printer. The instrument was calibrated with indium standard. Accurately weighed 5 mg of sample were placed in an open, flat bottom, Aluminum sample pans. Thermograms were obtained by heating the sample at a constant rate of 10˚C/minute. A dry purge of nitrogen gas (20 mL/min) was used for all runs samples heated from 35˚C – 400˚C.

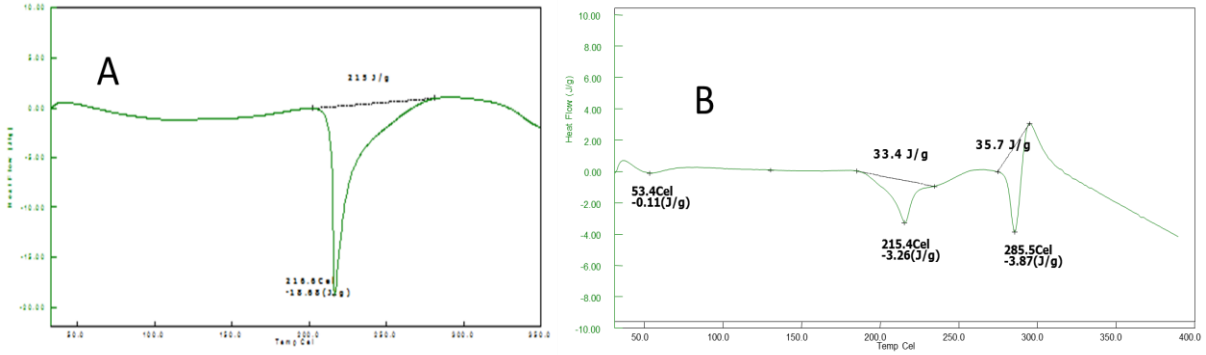

Figure 2: DSC of pure Losartan (A), DSC of Selected formulation (FM 8) (B)

DSC was performed and thermograms were compared. As shown in above, the melting point of Losartan that was recorded using this technique was 215.6^{O} C. The same melting point was obtained in the DSC of the selected formulation (FM 8). This result indicates there was no interaction of drug with excipients.

Micromeritical Properties

The following micromeritical properties of all the formulations were determined like densities, compressibility index, angle of repose and hausner ratio. They were calcula++ted and all estimated parameters were found within the limits. The data are represented in Table 3.

Solubility studies

Solubility of samples was determined by saturated solubility experiments. The data are represented in Table 4.

Table 3: Micromeritics properties of all formulations

Formulation code	Compressibility Index (%)	Angle of repose	Hausner Ratio
FM 1	12.5	28º. 7'	1.15
FM 2	15.9	29º.3'	1.19
FM 3	12.8	27º.5'	1.13
FM 4	15.7	28º.1'	1.17
FM 5	12.4	28º.4'	1.10
FM 6	11.2	27º.9'	1.13
FM 7	12.2	26º.7'	1.16
FM 8	12.3	28º.7'	1.15
FM 9	15.9	29º.3'	1.19
FM 10	12.8	27º.6'	1.13

FM 11	15.7	28º.1'	1.17
FM 12	12.3	28º.4'	1.11
FM 13	11.2	27º.9'	1.13
FM 14	13.4	26º.6'	1.18
FM 15	14.2	27º.6'	1.08
F 1	12.4	28º.4'	1.14
F 2	11.2	27º.9'	1.13
F 3	12.1	26º.7'	1.18

Table 4: Solubility of Losartan in different solvents

Sr. No.	Medium	Conc. in µg/mL	Conc. in gm/L
1.	7.4 pH Phosphate Buffer	3340	3.34
2.	0.1 N HCl	107.44	0.107
3.	Distilled water	465.7	0.465

Standard graph of Losartan in 0.1 N HCl

The standard graph of Losartan in 0.1N HCl showed a good linearity with R^2 of 0.999, and the equation of graph was y = 0.023x. The data is represented in figure 3.

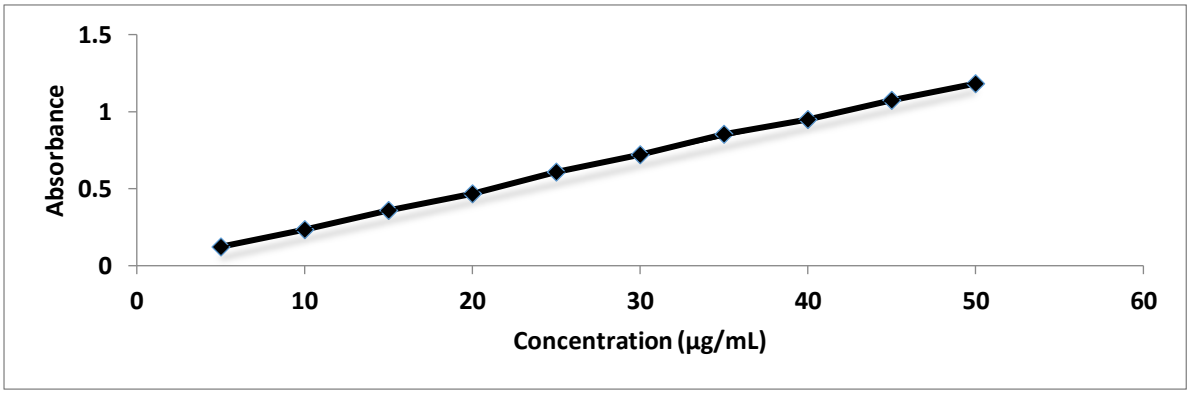

Figure 3: Standard curve of Losartan in 0.1 N HCl

Evaluations of the prepared tablets for physical parameters

All formulations were tested for physical parameters like hardness, thickness, weight variation, friability and found to be within the pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good. The data are represented in table 5.

Table 5: List of Physical parameters

Formulation code	Hardness (m/kg^2)	Weight variation (mg)	Thickness (mm)	Friability (%)	Drug content (%)	Floating Lag Time (sec)	Floating Time (hrs)
FM 1	6.1	200.8	3.21	0.65	99.01	19	18
FM 2	5.8	200.61	3.11	0.71	101.02	18	16
FM 3	5.6	201.01	3.24	0.81	98.2	16	16
FM 4	5.4	200.0	3.22	0.89	97.28	14	15
FM 5	5.1	200.7	3.19	0.91	99.12	13	15
FM 6	6.1	200.1	3.21	0.47	102.06	39	>24
FM 7	5.9	199.8	3.11	054	100.07	30	>24
FM 8	5.8	199.7	3.17	0.63	100.01	24	23
FM 9	5.5	200.9	3.23	0.69	99.01	20	23
FM 10	5.4	200.3	3.10	0.72	101.2	19	22

FM 11	6.2	200.2	3.20	0.31	99.87	107	>24
FM 12	6.0	199.6	3.18	0.39	98.02	104	>24
FM 13	5.7	199.7	3.16	0.47	97.29	83	>24
FM 14	5.5	199.9	3.14	0.51	98.76	80	>24
FM 15	5.4	199.8	3.12	0.58	98.66	79	>24
F1	6.4	200.7	3.15	0.23	99.6	32	>24
F2	6.8	201.1	3.13	0.22	99.98	41	>24
F3	6.9	200.8	3.10	0.20	98.28	74	>24

Floating properties

All formulations were tested for floating properties like floating lag time and total floating time. The results of the tests are tabulated.

***In – vitro* drug release**

The dissolution conditions used for studying the drug release from floating osmotically controlled tablet of Losartan are:

Apparatus, USP Type 2 (paddle) Agitation speed (rpm), 75 Medium , pH 1.2 Volume, 900 ml Temperature, 37.0 ± 0.5 ºC Time, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 & 18 hrs Wavelength, 275 nm The samples were withdrawn at Predetermined time points, and were analyzed spectrophotometrically at 275 nm. The data are represented in Table 6, 7 and 8 and the cumulative percentage release of drug is presented in Figure 4.

Table 6: Drug release profile of losartan floating osmotically controlled tablets prepared with HPMC K4M

Time (hrs)	FM1	FM2	FM3	FM4	FM5	F 1
0.5	22.1 %	20.3 %	19.4 %	16.8 %	10.7 %	20.6 %
1	36.8 %	29.4 %	29.7 %	25.8 %	22.1 %	38.8 %
2	54.8 %	50.4 %	48.7 %	36.5 %	28.2 %	62.8 %
3	75.4 %	59.6 %	55.6 %	49.8 %	56.1 %	71.4 %
4	81.3 %	74.8 %	72.%	67.7 %	64.1 %	89.3 %
6	97.1 %	92.0 %	86.1 %	85.1 %	75.1 %	98%

Formulations FM 1 to FM 5 are composed with HPMC K4M as a hydrophilic polymer and a osmotically controlled polymer carbopol 974P, in increasing ratios of carbopol and decreasing ratios of hydrophilic polymer. Formulation F 1 is composed without osmotically controlled polymer, which is designed to find out the difference in drug release rate compared to floating and osmotically controlled tablets. Here the effect of concentration of hydrophilic polymer to carbopol is observed. The above graph shows that, the decrease in concentration of HPMC retards the drug release from formulation. This may be expected due to the increase in concentration of carbopol 974P which is having high molecular weight as well as more drug release retarding property compared to that of HPMC K4M. There is no much difference in drug release was observed with formulations of FM 1 – FM 5 to that of F 1 which has no osmotically controlled polymer in its formulation.

Table 7: Drug release profile of Losartan floating osmotically controlled tablets prepared with HPMC K15M

Time (hrs)	FM 6	FM 7	FM 8	FM 9	FM 10	F 2
0.5	14.8%	12.9%	15.4%	10.3%	8.1%	18.8%
1	22.7%	20.8%	23.3%	18.8%	16.2%	26.7%
2	29.6%	33.7%	28.7%	26.7%	22.5%	35.8%
3	45.9%	41.6%	38.6%	42.6%	36.8%	59.7%

4	59.5%	63.2%	52.5%	51.0%	48.1%	65.5%
6	74.7%	68.0%	66.3%	63.9%	60.8%	79.7%
8	83.4%	79.7%	75.1%	72.1%	68.4%	94.4%
10	92.1%	85.8%	81.6%	79.2%	75.8%	94..6%
12	95.4%	96.4%	89.9%	86.6%	79.9%	96.9%

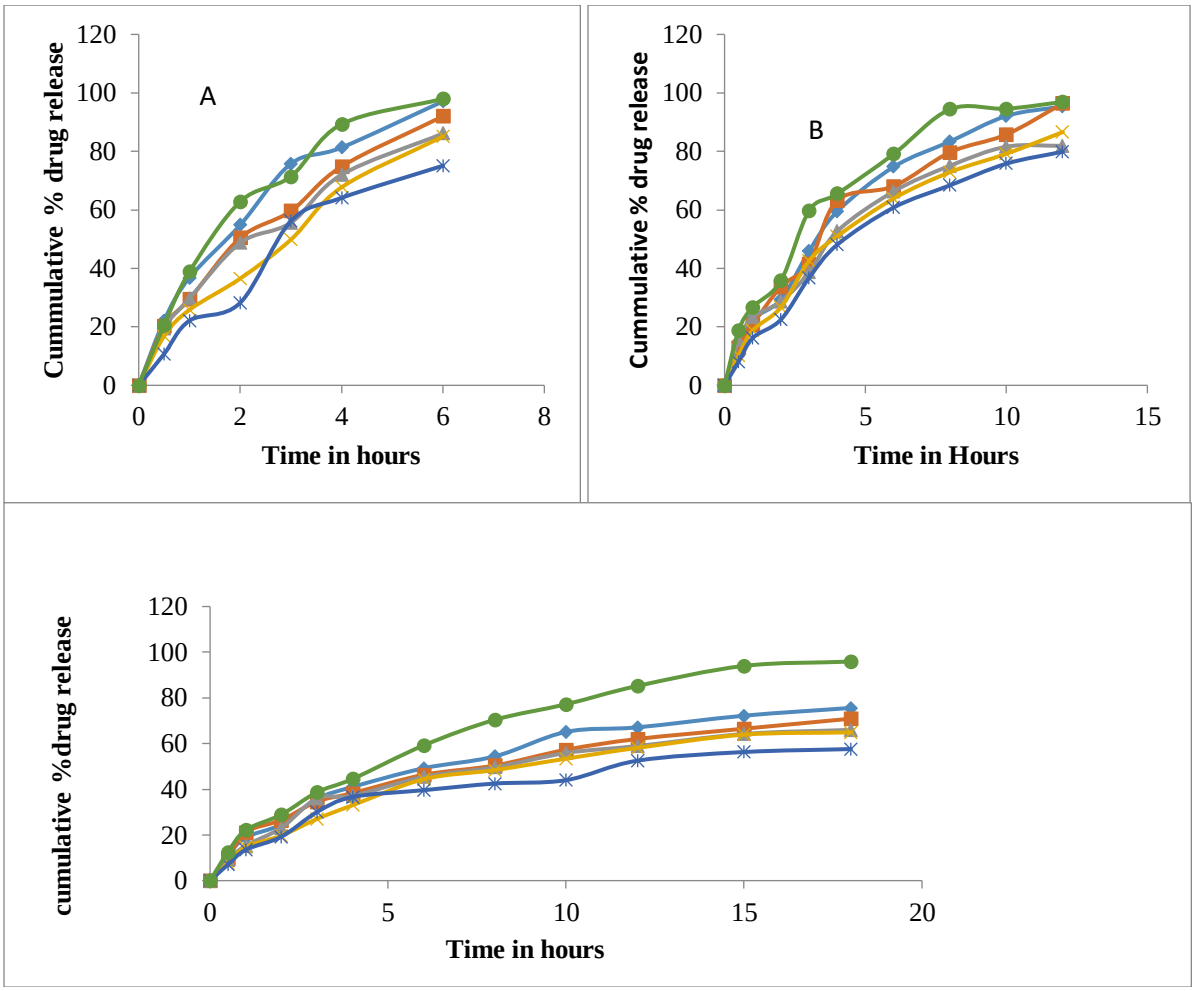

Figure 4: Graphical representation of cumulative percent drug release of Losartan floating and osmotically controlled tablets (n=3) prepared with HPMC (A) K15M (B) / HPMC K15(M C)

Formulations FM 6 to FM 10 are composed with HPMC K15M as a hydrophilic polymer and a osmotically controlled polymer carbopol 974P, in increasing ratios of carbopol and decreasing ratios of hydrophilic polymer. Formulation F 2 is composed without osmotically controlled polymer, which is designed to find out the difference in drug release rate compared to floating and osmotically controlled tablets. Here the effect of concentration of hydrophilic polymer to carbopol is observed.

The above graph shows that, the decrease in concentration of HPMC retards the drug release from formulation. This may be expected due to the increase in concentration of carbopol 974P which is having high molecular weight as well as more drug release retarding property compared to that of HPMC K15M. There is no much difference in drug release was observed with formulations of FM 6 – FM 10 to that of F2 which has no osmotically controlled polymer in its formulation.

The above plot shows the average cumulative percent drug release of Losartan floating osmotically controlled tablets (n=3) formulated with HPMC K100M. Formulations FM 11 to FM 15 are composed with HPMC K100M as a hydrophilic polymer and a osmotically controlled polymer carbopol 974P, in increasing ratios of carbopol and decreasing ratios of hydrophilic polymer. Formulation F3 is composed without osmotically controlled polymer, which is designed to find out the difference in drug release rate compared to floating and osmotically controlled tablets. Here the effect of concentration of hydrophilic polymer to carbopol is observed. The above graph shows that, the decrease in concentration of HPMC retards the drug release from formulation. This may be expected due to the increase in concentration of carbopol 974P which is having high molecular weight as well as more drug release retarding property compared to that of HPMC K100M. There is no much difference in drug release was observed with formulations of FM 11 – FM 15 to that of F 3 which has no Osmotically controlled polymer in its formulation.

All the above plots showed the cumulative percent drug release of Losartan from their formulations of HPMC K4M, HPMC K15M, and HPMC K100M polymer. The effect of hydrophilic polymer on drug release of formulation was explained above. And it has been clearly revealed that the increase in viscosity of HPMC polymers retards the drug release from the formulations.

***Ex-vivo* Osmotically controlled strength:** The study was performed and the data are presented in Table 8.

Table 8: Osmotically controlled strength (n=3) of all formulations

Formulation code	Bioadhesion Strength (gm)	Force of adhesion (N) in dyne
FM1	17.1±0.29	1.67
FM2	18.5±0.47	1.81
FM3	19.3±0.16	1.89
FM4	20.1±0.37	1.97
FM5	22.5±0.15	2.20
FM6	21.4±0.37	2.09
FM7	24.2±0.46	2.37
FM8	26.6±0.31	2.60
FM9	28.2±0.42	2.76
FM10	29.6±0.25	2.90
FM11	43.6±0.21	4.27
FM12	44.2±0.36	4.33
FM13	45.4±0.27	4.45
FM14	48.2±0.16	4.72
FM15	51.6±0.31	5.06
F1	9.4±0.28	0.92
F2	10.1±0.52	0.99
F3	15.6±0.39	1.53

This evaluation test was conducted for all formulations. There is a gradual increase in bioadhesion strength was observed in each batch i.e., from FM1 to FM5, FM6 to FM10 and FM11 to FM15. This is due to the increase in concentration of osmotically controlled polymer carbopol 974P. But compared to the formulations F1, F2, and F3, all the above formulations shown the good osmotically controlled property because F1, F2, and F3 contains no osmotically controlled polymer. Here the study investigates the osmotically controlled properties of formulations from FM1 to FM15. Bioadhesion characteristics were found to be affected by the nature and proportion of osmotically controlled polymers used. As the concentration of carbopol increased the osmotically controlled strength was also increased, the reason for such findings might be the formation of secondary bioadhesion bonds with mucin and interpenetration of the

polymer chains in the interfacial region, while other polymers undergo superficial bioadhesion.

Dissolution Profile Modeling: The dissolution study was performed and the data represented.

The drug release data was fitted in to the zero order equation and graph was plotted between Time in hours Verses Cumulative % drug release. The R^2 value was found to be 0.932.

The drug release data was fitted in to the first order equation and graph was plotted between Time in hours Vs Log Cumulative % drug remaining to be release. The R^2 value was found to be 0.882.

The drug release data was fitted in to the Higuchi's equation and graph was plotted between square root of time in hours Vs cumulative % drug release. The R^2 value was found to be 0.992.

The drug release data was fitted in to the Korsmeyer-Peppas equation and graph was plotted between log times in hours Vs log Cumulative % drug release. The R^2 value was found to be 0.525.

Stability studies: The optimized tablets from batch FM 8 were charged for stability studies. There was no change in physical appearance and color. Formulations were analyzed at the end of 3 months for the assay and dissolution studies. Average drug content of the tablets were found to be 98.5±0.6% of the labeled claim. *In-vitro* dissolution profile showed that there was no significant change in the release rate of the drug from optimized tablets at the end of 3 months.

SUMMARY

Systematic studies were conducted using four different polymers in different concentrations to prepare Losartan floating and osmotically controlled tablets. All the prepared systems were evaluated for the different properties. Formulated tablets gave satisfactory results for various evaluation parameters like tablet, hardness, friability, weight variation, thickness, floating lag time, floating duration, content uniformity, *ex vivo* osmotically controlled strength and *in vitro* drug release. In all formulations carbopol 974P is used to add osmotically controlled strength but the concentration of this polymer has significantly influenced the drug release due to its retarding property. Comparing the three different grades of hydroxypropyl methyl cellulose (K4M, K15M and K100M), it was found that low-viscosity grades of HPMC K4M formulations released drug rapidly compared to K15M and K100M. Among all formulations K15M grade provided better controlled release characteristics with excellent drug release and in-*vitro buoyancy*. From the above results, it was also evident that at higher viscosity grades of polymer concentrations, the rate of drug release was retarded greatly.

All the formulated tablets from FM1 to FM15 shown the excellent osmotically controlled property compared to formulations with no osmotically controlled property i.e., F1, F2, F3. Among these, formulations with HPMC K100M shown the high osmotically controlled strength because of its high viscosity, in this batch formulation FM15 shown the highest osmotically controlled strength. Moreover, there is no much difference is observed in drug release compared to F1, F2, F3. And the rate of drug release is somewhat controlled due to osmotically controlled polymer. Drug release profiles are fitted to kinetic modeling's like zero order, first

order, Higuchi model and Korsmeyer Peppas models. And it was found that the formulations were best fitted to Higuchi model. Stability studies were conducted for optimized formulation at different conditions. And the formulation is found stable in all the conditions.

CONCLUSION

Floating and osmotically controlled tablets of anti-hypertensive drug Losartan can be formulated as an approach to increase gastric residence time thereby improve its bioavailability and to overcome the limitations of conventional approaches of Gastric retention. All the formulations gave better-controlled drug release. Here the polymers used to improve the gastric residence are cellulose polymers HPMC K4M, HPMC K15M, HPMC K100M. Among these formulations with HPMC K100M shown controlled release, but complete drug release is not observed. Hence it was concluded that the formulations with K15M was optimized for better release. And FM 8 formulation was optimized among the 15 Formulations because of its equal combination of osmotically controlled polymer and hydrophilic polymer.

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