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Research Article

Development and Evaluation of Losartan Potassium Floating Matrix Tablet

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Abstract

The present study was aimed towards the development of controlled release formulations of Losartan Potassium based on designed to enhance the bioavailability by prolonging its duration in the stomach via the floating dosage forms with controlled release. This study was intended to evaluate the influence of formulation variables like levels of polymer, amount of mannitol concentrations, and coating solution ratios of semi permeable membrane on the drug release from the developed formulations. Thus, there is a strong clinical need and market potential for a dosage form that will deliver Losartan Potassium in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance. This study was designed to enhance the bioavailability of drug by prolonging its duration in the stomach via the floating dosage forms with controlled release. Floating matrix tablets of Losartan Potassium were prepared by the direct compression method, using locust bean gum and HPMC K 15M as polymers and Sodium bicarbonate as floating agent. The effect of the nature of polymers was studied by preparing various formulations of tablets. In all these formulations, a constant amount of drug (100 mg) was maintained. The blend was initially characterized for pre-compression and post- compression parameters. Pre-compression characterization was done for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The results of pre-compression characterization were indicated good to excellent flow characteristics. Post-compression characterization includes thickness, hardness, friability, weight variation, drug content, buoyancy lag time, floating time and in-vitro drug release. All the results were satisfactory as per the guideline of pharmacopoeia. The in vitro drug release studies found that formulations LPFT4 showed best sustained release profile in 24 hrs. Among the nine formulations (LPFT1 to LPFT9) prepared formulations LPFT4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation and followed supercase II transport diffusion kinetic models.

Keywords: Oral drug delivery system, Gastroretentive technology, losartan potassium, floating tablet, matrix tablet

INTRODUCTION

Most of the conventional drug delivery systems for treating the colon disorders such as inflammatory bowel diseases (e.g. irritable bowel syndrome, ulcerative colitis, Crohnís disease etc.), infectious diseases (e.g. amoebiasis) and colon cancer are failing as the drugs do not reach the site of action in appropriate concentrations. Thus, an effective and safe therapy of these colonic disorders, using site-specific drug delivery systems is a challenging task to the pharmaceutical technologists. The therapeutic advantages of targeting drug to the diseased organ include (a) delivery of drug in its intact form as close as possible to target site, (b) the ability to cut down the conventional dose, and (c) reduced incidence of adverse side effects. The drug-delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of time. The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body, so that the desired drug concentration can be achieved promptly and then maintained [1-2]. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics[3-4].

GRDDS are one of the novel drug delivery systems, which are increasingly gaining importance these days with regulatory approval for several formulations. GR formulations are usually developed for drugs having absorption window in upper parts of the gastrointestinal tract (GIT) [5]. The concept of floating drug delivery systems (FDDS) for gastroretention is very simple in which the underlying principle is to make the density of delivery system less than that of the gastric fluids due to which it can float on the surface of gastric fluids. Numerous techniques have been employed to develop an ideal floating delivery system [6]. The various buoyant preparations include hollow microspheres (microballoons), granules, powders, capsules and tablets. Single-unit systems are most commonly reported floating systems in literature, such as the hydrodynamically balanced systems (HBS) and floating tablets. While the system is floating on the gastric contents present in the stomach, the drug is released slowly at the predetermined rate from the formulation. After release of drug, the residual system is emptied from the stomach to the next part of GIT. Gastric emptying is much more rapid in the fasting state and floating systems rely heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy [7].

An FDDS either floats over gastric fluids due to its lower density than the stomach contents or due to its inherently lower density or the gaseous phase formed inside the system after it comes in contact with the gastric environment. Non-effervescent and effervescent systems are the two different technologies which have been utilized in the development of FDDS and are based on the mechanism of buoyancy. This sustained release, floating single unit dosage form consists of a capsule, which contains a mixture of drug and hydrocolloids. Hydrodynamically balanced systems (HBS) are suitable for drugs having a better solubility in an acidic environment and also for the drugs having a specific site of absorption in the upper part of the small intestine [8]. Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. Losartan Potassium is an angiotensin II receptor antagonist with anti-hypertensive activity. It is readily absorbed from the GI tract following oral administration but the bioavailability is about 33% due to substantial first-pass metabolism. Peak plasma concentration occurs at about 2 hrs after an oral dose and has short terminal elimination half-life is about 1.5 to 2 hrs respectively, thereby requiring two to three times daily dosing in large number of patients, which often leads to non-compliance. The proposed work containing development and evaluation of an extended release matrix tablet of Losartan Potassium for antihypertensive therapy. The formulations of Losartan Potassium based on designed to enhance the bioavailability by prolonging its duration in the stomach via the floating dosage forms with controlled release. This study was intended to evaluate the influence of formulation variables like levels of polymer, amount of mannitol concentrations, and coating solution ratios of semi permeable membrane on the drug release from the developed formulations. Accordingly, this study was designed to enhance the bioavailability of drug by prolonging its duration in the stomach via the floating dosage forms with controlled release.

MATERIAL AND METHODS

Analytical methods: The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer (Shimadzu, UV-1800, A11454500755/UV-1800, Shimadzu Corporation, Kyoto, Japan). A spectrophotometric method based on the measurement of absorbance at 251 nm in distilled water was used in the present study for estimation of Losartan Potassium.

Preformulation studies of drug sample: Physicochemical properties of Losartan Potassium were evaluated. The various parameters i.e. organoleptic properties, microscopic examination, particle size, flow properties, solubility determination, partition coefficient, Fourier-Transform Infrared (FTIR) Spectroscopy of drug sample were estimated.

Formulation of matrix tablet: The formulation was developed using different polymers. The prepared formulation was studied for its in-vitro release profile, content uniformity and drug assay. The optimized floating tablets will be studied for in-vitro dissolution study, floating time, floating lag time, water up-take study and erosion index determination.

- Selection of polymer based on physicochemical property of drug.
- Selection of method for Matrix Tablets

The tablets were prepared by direct compression method. Losartan Potassium, locust bean gum and HPMC K15M were sieved through #30 sieves. $NaHCO_3$, Magnesium stearte and MCC were sieved through #60 sieves before the use. The amount of drug was kept constant in each formulation (i.e. 100 mg). All the materials were accurately weighed and blended using hand blender and directly compressed on a manual single punch tablet compression machine into 100mg tablets using flat-faced, round punches 8 mm in diameter. The various formulation of 9 batches of the formulation were prepared using Carbopol 971P and HPMC K15M as polymers, with the ratio of drug to polymer kept as 1:3 **(Table 1).**

Table 1: Various formulations of floating matrix tablets batches

Formulation code	Drug (mg)	Locust bean gum	HPMC K15M (mg)	$NaHCO_3$ (mg)	Magnesium stearate (mg)	MCC (mg)
LPFT1	100	35	20	15	5	15
LPFT2	100	30	25	15	5	15
LPFT3	100	25	30	15	5	15
LPFT4	100	25	20	25	5	15
LPFT5	100	20	25	25	5	15
LPFT6	100	15	30	25	5	15
LPFT7	100	15	20	35	5	15
LPFT8	100	10	25	35	5	15
LPFT9	100	5	30	35	5	15

Evaluation of granules (Flow properties): Irregular flow of powder from the hopper produces tablets with nonuniform weights. As a result, content uniformity and dose precision cannot be achieved in the production of tablets. Flow properties depend on particle size, shape, porosity and density of the bulk powder. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\Theta = h/r$

Where h=height of pile, r = radius of the base of the pile, Θ=angle of repose.

Bulk density: Bulk density depends on the density of the powder particles and on the arrangement of the powder particles. The bulk density is obtained by adding a known mass of powder to a graduated cylinder. The density is

calculated by formula:

$$Bulk\ Density = \frac{Mass\ of\ Powder}{Bulk\ Volume}$$

Tapped density: The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until little further volume change is observed.

$$Tapped\ density = \frac{Mass\ of\ powder}{tapped\ volume}$$

Carr's index: The bulk and tapped density were used to calculate the carr's index and Hausner's ratio to provide a measure of the flow properties and compressibility of powder.

$$Carr's\ Index = \frac{Tapped\ density - Fluff\ density}{Tapped\ density} X\ 100$$

Hausner ratio: Hausner ratio can be used to estimate the flow characteristic of the powder.

$$\text{Hausner ratio} = \frac{\text{Tapped volume}}{\text{Bulk volume}}$$

Evaluation parameters for floating matrix tablet

Weight variation: Not more than two of the individual weights deviate from the average weight by more than the percent shown below and none deviates by more than twice that percent.

$$Deviation\ (\%) = \frac{Average\ weight - weight\ of\ tabl}{Average\ weight}$$

Hardness: Hardness of tablet is defined as the force required to break a tablet a in a diametric direction. A tablet was placed between two anvils. Force was applied to anvils and crushing strength that causes the tablet to break was recorded. Hardness is thus the tablet crushing strength. Monsanto tester is used for hardness testing.

Friability: Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches. The chamber is allowed to rotate for 100 revolutions. Then the tablets are removed, dusted and again the weight is taken. The difference in the weigh is calculated and the weight loss should not be more than 1%.

Thickness and diameter: The thickness and diameter of tablets was performed on 20 tablets from each formulation by using Vernier caliper.

Buoyancy lag time and total floating time: The Buoyancy lag time and total floating time were determined by immersion of tablets of different formulation in 0.1 N HCL at 37±.5°C.

Swelling Property: Swelling property was determined by dissolution apparatus. Tablets were introduced in dissolution apparatus containing 900ml of 0.1 N HCL at 50 rpm. The tablets at definite intervals and swollen weight of each tablets was determined by formula.

$$\text{Swelling Index} = \frac{\text{Wt} - \text{Wo}}{\text{Wo}} \text{X100}$$

Where-

Wt= weight of tablet at time t

Wo= weight of tablet before immersion

Percent Drug content: 20 tablets from all batches were taken randomly and crushed in pestle-mortar. The weight equivalent to one tablet was taken in volumetric flask (100 ml) and dissolved in 0.1 N HCL and filtered. This solution was analyzed in UV spectrophotometer at λmax 251 nm.

***Ex-vivo*mucoadhesive strength:** The mucoadhesive strength of the tablet formulations was determined by modified physical balance. The assembly consist of a modified double beam physical balance in which left sided pan is removed and attached with glass slide with an additional weight is added with slide to balance the weight of both the pan. Fresh intestine mucosa of goat was used as membrane obtained from local slaughter house and kept in kerb solution during transportation and 0.1 N HCL was use for moistening the mucosa. The underlying mucous membrane was separated by the help of surgical blade and tied with the glass slide with the help of thread. Now the tablet was made to stick with the wooden block and made contact with the mucous membrane and the tablet. The additional weight was increased on the right pan until the tablet detaches from the membrane and the weight used was noted as mucoadhesive strength in grams and force of adhesion was calculated.

***In vitro* Dissolution study:** In vitro dissolution study was carried out using USP type II (basket type) apparatus with 0.1N HCl as a dissolution medium. The temperature was maintained at 37±0.5^{0}C with 50 rotations per minute. 1ml of aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were analyzed for drug content at λ max 251 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported.

Drug release kinetic study: Mechanism of drug from floating bioadhesive tablet (LPFT1 – LPFT9) were investigated by various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. Drug dissolution behaviors depend on the value of correlation coefficient (r^2). According to this model, the drug release was described as a square root of time dependent diffusion process based on Fick's law.

RESULTS AND DISCUSSION

The current research work aimed at developing a novel drug delivery system, in the form of floating bioadhesive tablet to improve the release of drug for longer period of time to treat the hypertension symptomatically using optimization approach. The absorbance maxima of the Losartan Potassium pure drug was 251 nm measured by double beam UV spectrophotometer **(Figure 1).** The calibration curve of drug Losartan Potassium with the concentration of 2, 4, 6, 8, 10 µg/ml was measured at 251 nm was rectilinear and have r2 value 0.999 **(Table 2 and Figure 2)**. The FTIR spectra of pure drug Losartan Potassium and drug with excipients were recorded by FTIR spectrophotometer (IR Affinity, Shimadzu, Japan) and result was concluded that there was no interaction between both materailas due to presence of same wavelength in both FTIR spectra **(Figure 3-4)**. The peaks were determined and observed peaks were compared with standard Floating matrix tablets of Losartan Potassium were prepared by the direct compression method, using locust bean gum and HPMC K 15M as polymers and Sodium bicarbonate as floating agent. The effect of the nature of polymers was studied by preparing various formulations of floating matrix mucoadhesion tablets. In all these formulations, a constant amount of drug (100 mg) was maintained. The blend was initially characterized for pre-compression and post-compression parameters. Pre-compression characterization was done for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The results of pre-compression characterization includes angle of repose (21.65-26.77°), bulk density (0299-0.385 g/cm^3), tapped density (0.417 - 0.473 g/cm^3), Carr's index (14-25 - 36.78 %) and Hausners ratio was found to be (1.16 – 1.58) **(Table 3)**. Post-compression characterization includes thickness, hardness,

friability, weight variation, drug content, buoyancy lag time, floating time and in-vitro drug release. %. The average weights of the entire prepared tablet were 97.15±.05mg to 103.27±.01mg which was within the specified limit. The thickness of all the tablets was in the range of 2.59 to 2.51 um. The hardness of all the formulated tablets was found to be in the range of 4-7kg/cm^2. Friability was found to be 0.31 to 0.91 **(Table 4).** Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium resulted in immediate tablet floatation with a lag time in between 50 to 180 seconds. Total floating and mucoadhesion time of all the prepared formulation was found between 3.29±0.6 hrs to 5.52±0.8 hrs. The swelling Index for all tablets was found in the range of 66.25±0.21 to 70.08±0.37. The bioadhesive strength was found to be in the range of 11.03 to 23.12. The results of the present research work indicated the successful formulation of floating bioadhesive tablet with excellent ex-vivo bioadhesive properties and drug release profile. The drug content of the entire prepared tablet was found to be 95.29±0.98 to 102.32±2.16 **(Table 5)**. The drug content of tablets complied with the limit as 85-110% as per IP specifications (IP 2007). From the in vitro drug release studies, it was found that in formulations LPFT4 showed best sustained release profile. The retarded drug release was found to be in the following order: LPFT4> LPFT5> LPFT7> LPFT6> LPFT3> LPFT8> LPFT2> LPFT1> LPFT9. Cumulative drug release of all the prepared formulation was found to be in between 95.5% to 99% in 24 hrs. The comparison of drug release profile of the entire batch is shown in **(Table 6 and Figure 5–8)**. Among the nine formulations (LPFT1 to LPFT9) prepared formulations LPFT4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation. The regression coefficient (r^2) value of various models was found to be 0.962, 0.826, 0.981 and 0.978 respectively **(Table 7)**.

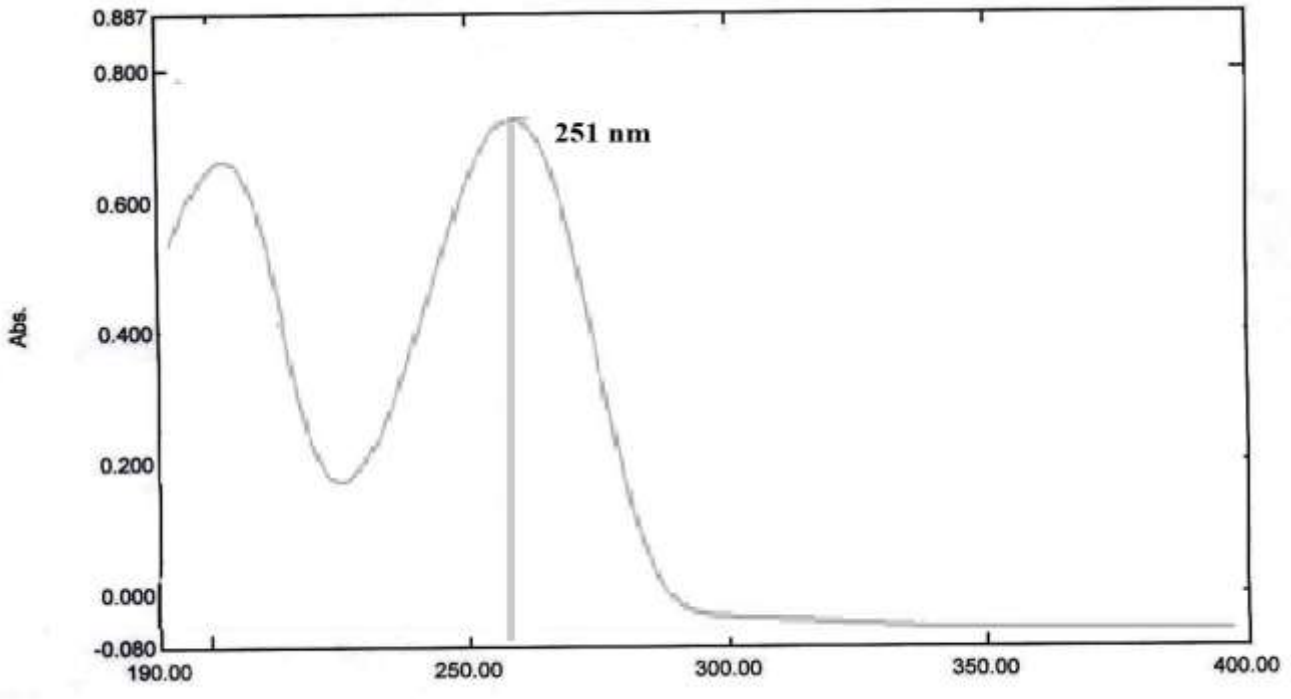

Figure 1: Absorption maxima of losartan potassium drug

Table 2: Calibration curve of drug losartan potassium in 0.1 NHcl

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.166
3	4	0.315
4	6	0.456
5	8	0.607
6	10	0.738

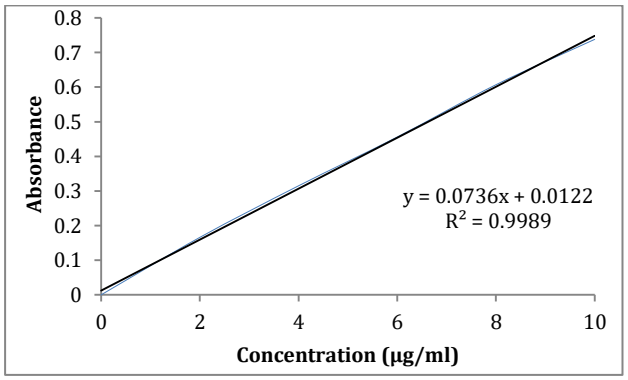

Figure 2: Calibration curve of drug losartan potassium in 0.1 NHcl

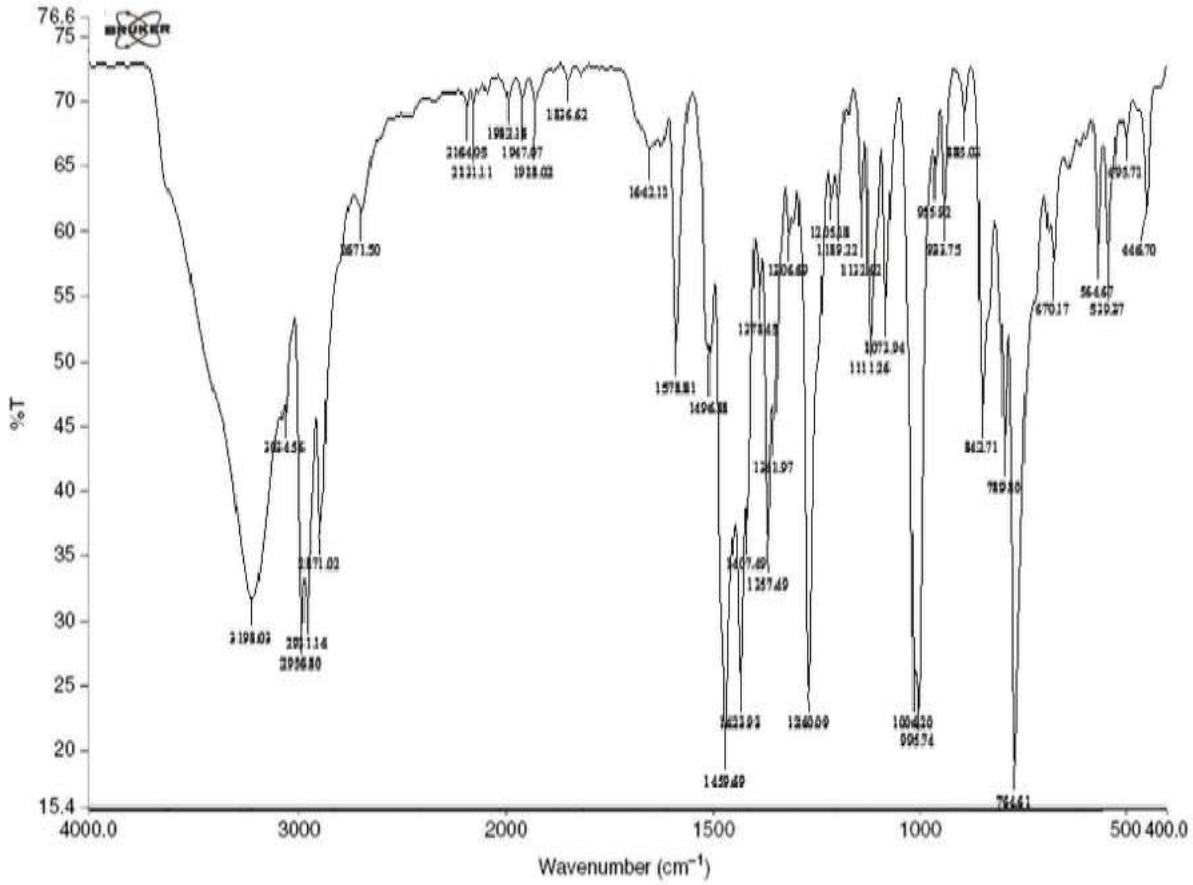

Figure 3: The I. R. Spectrum of sample of pure losartan potassium (S1)

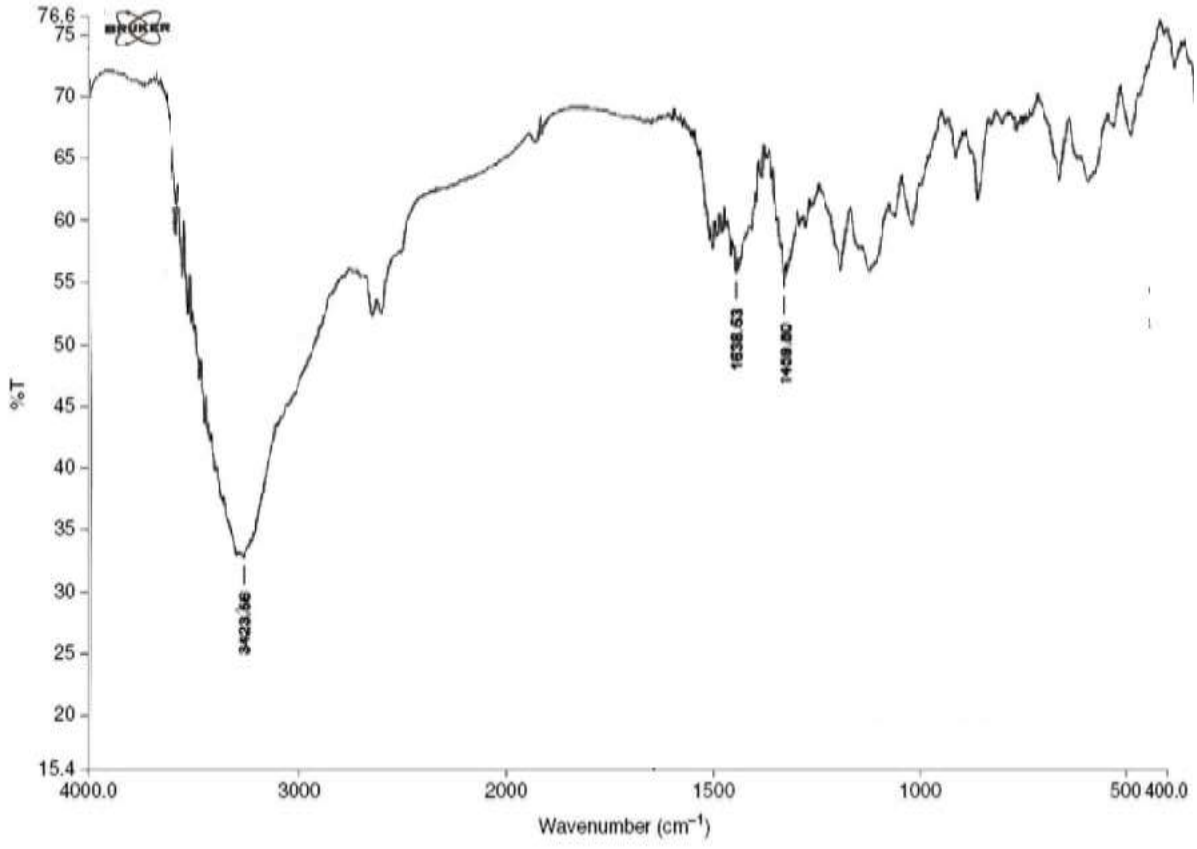

Figure 4: The I. R. Spectrum of sample of losartan potassium and all excipients (S2)

Table 3: Pre-compression characterization

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's Ratio	Angle of Repose (θ)
LPFT1	0.358	0.433	17.32	1.21	26.77
LPFT2	0.365	0.464	21.33	1.27	22.33
LPFT3	0.385	0.449	14.25	1.16	26.18
LPFT4	0.343	0.437	21.51	1.27	24.88
LPFT5	0.369	0.465	20.64	1.26	21.65
LPFT6	0.278	0.421	33.81	1.51	27.64
LPFT7	0.299	0.473	36.78	1.58	22.62
LPFT8	0.315	0.417	21.25	1.26	25.75
LPFT9	0.335	0.423	20.81	1.26	26.13

Table 4: Post compression characterization

Formulation code	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)
LPFT1	190.59±0.04	2.54±0.09	8.1±0.02	5.74±0.78	0.91±0.89
LPFT2	190.07±0.01	2.51±0.04	8.2±0.01	5.54±0.42	0.41±0.46
LPFT3	191.28±0.04	2.59±0.01	8.1±0.02	5.51±0.91	0.46±0.43
LPFT4	193.27±0.01	2.53±0.01	8.1±0.02	7.04±0.41	0.31±0.67
LPFT5	191.73±0.03	2.59±0.01	8.1±0.01	6.31±0.27	0.52±0.43
LPFT6	194.24±0.06	2.56±0.02	8.1±0.01	6.30±0.28	0.65±0.23
LPFT7	193.14±0.01	2.56±0.03	8.1±0.02	4.85±0.44	0.85±0.57
LPFT8	193.15±0.05	2.51±0.02	8.1±0.01	4.36±0.10	0.48±0.56
LPFT9	191.82±0.02	2.56±0.06	8.1±0.01	4.31±0.23	0.58±0.41

Table 5: Post compression characterization

Formulation code	Buoyancy lag time (sec)	Total floating & bioadhesion time (h)	Swelling Index	Bioadhesive strength (gm) ±SD	Drug content (%)
LPFT1	65±4	4.55±0.3	70.08±0.37	23.12±0.1	97.52±0.26
LPFT2	60±2	4.52±0.1	69.05±0.08	21.02±0.5	97.08±0.08
LPFT3	80±4	4.38±0.9	66.87±0.19	20.17±0.2	95.29±0.98
LPFT4	57±1	5.52±0.8	68.88±0.25	19.36±0.4	97.15±0.45
LPFT5	58±1	5.21±0.3	67.62±0.03	18.56±0.2	95.65±1.14
LPFT6	61±1	5.35±0.2	66.71±0.31	14.52±0.1	96.91±0.82
LPFT7	130±3	4.19±0.5	67.18±0.11	12.24±0.4	96.16±1.44
LPFT8	150±2	3.55±0.9	66.59±0.15	11.25±0.2	97.14±1.08
LPFT9	180±1	4.05±0.7	66.25±0.09	11.03±0.5	102.32±2.16

Table 6: In vitro drug release study of different formulations

Time (h)	LPFT1	LPFT2	LPFT3	LPFT4	LPFT5	LPFT6	LPFT7	LPFT8	LPFT9
0	0	0	0	0	0	0	0	0	0
2	3.2	3.8	4.1	2.1	2.5	2.9	5.2	8.3	12.5
4	14.2	14.6	15.2	10.1	11.1	11.7	17.2	21.3	25.4
6	22.2	23.8	24.3	18.2	19.3	20.8	28.4	32.1	328.3
8	38.8	37.2	39.1	33.3	35.2	38.2	45.2	50.2	58.2
10	49.3	49.9	52.3	41.2	45.5	47.1	55.3	58.2	66.8
12	58.2	59.2	61.2	49.5	52.3	54.3	59.1	69.1	76.1
14	60.2	62.1	63.3	57.2	61.4	64.2	68.2	78.2	88.4
16	71.2	72.8	73.2	60.3	68.4	67.9	76.2	86.2	96.3
18	79.3	79.2	79.8	69.2	75.1	76.9	82.2	92.2	98.5
20	87.2	87.3	88.2	76.2	80.2	82.3	91.3	97.3	99.2
22	91.3	91.3	92.1	84.6	87.4	89.3	94.1	99.1	99.7
24	98.2	98.6	98.9	95.5	96.1	96.9	99.2	99.9	99.9

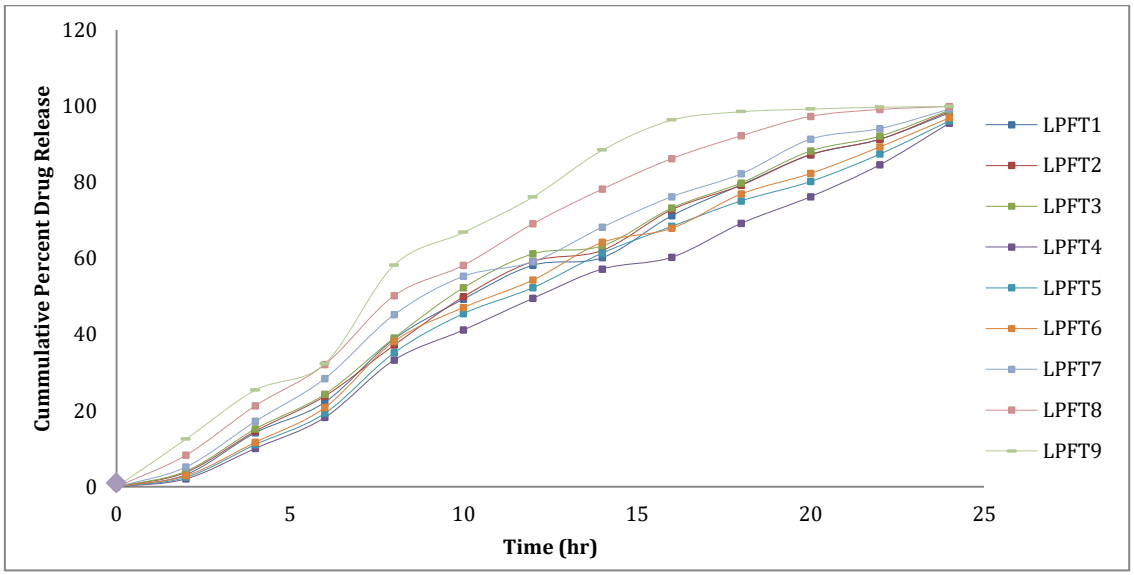

Figure 5: Zero-order release of various batches (LPFT1-LPFT9)

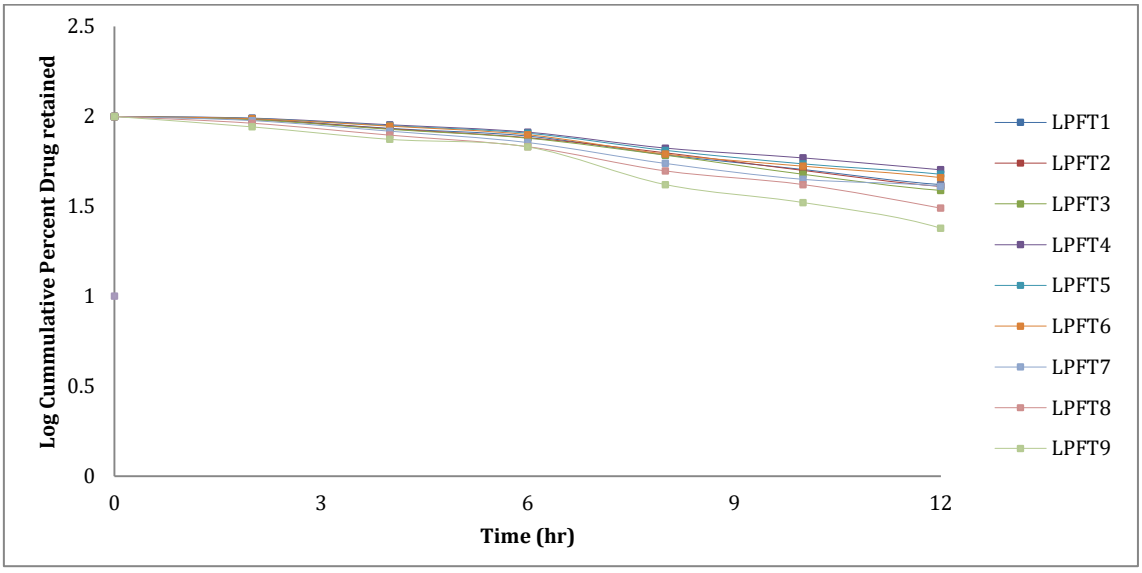

Figure 6: First-order release of various batches (LPFT1-LPFT9)

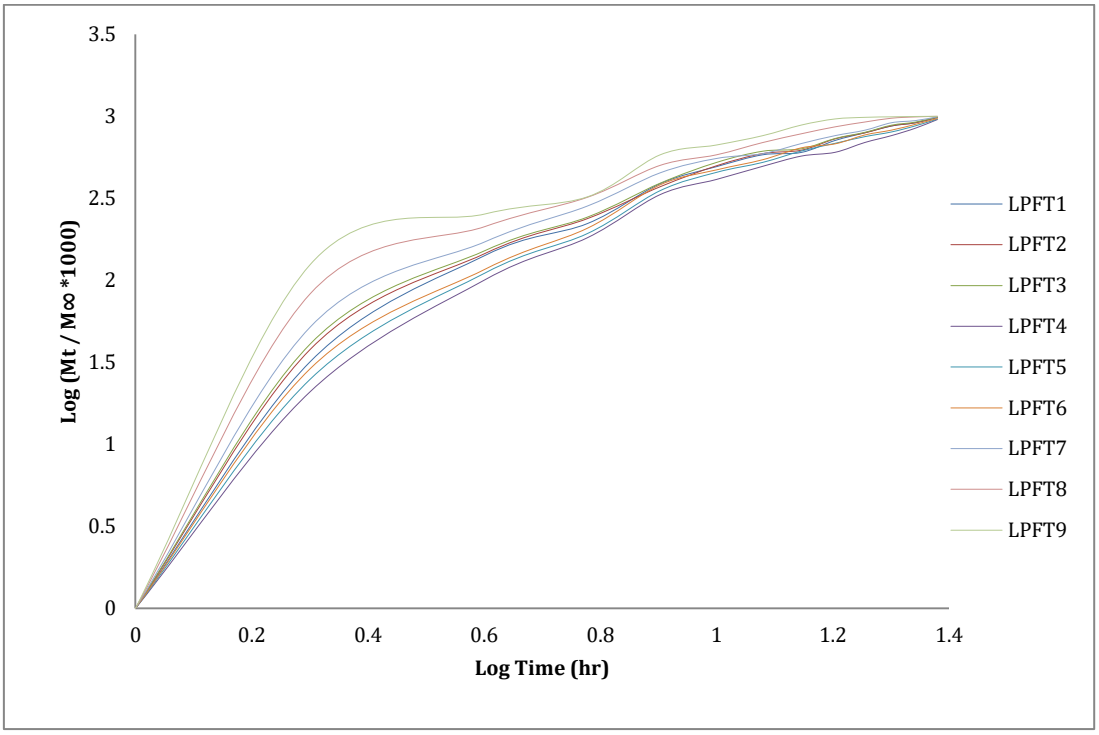

Figure 7: Korsmeyer-peppas release of various batches (LPFT1-LPFT9)

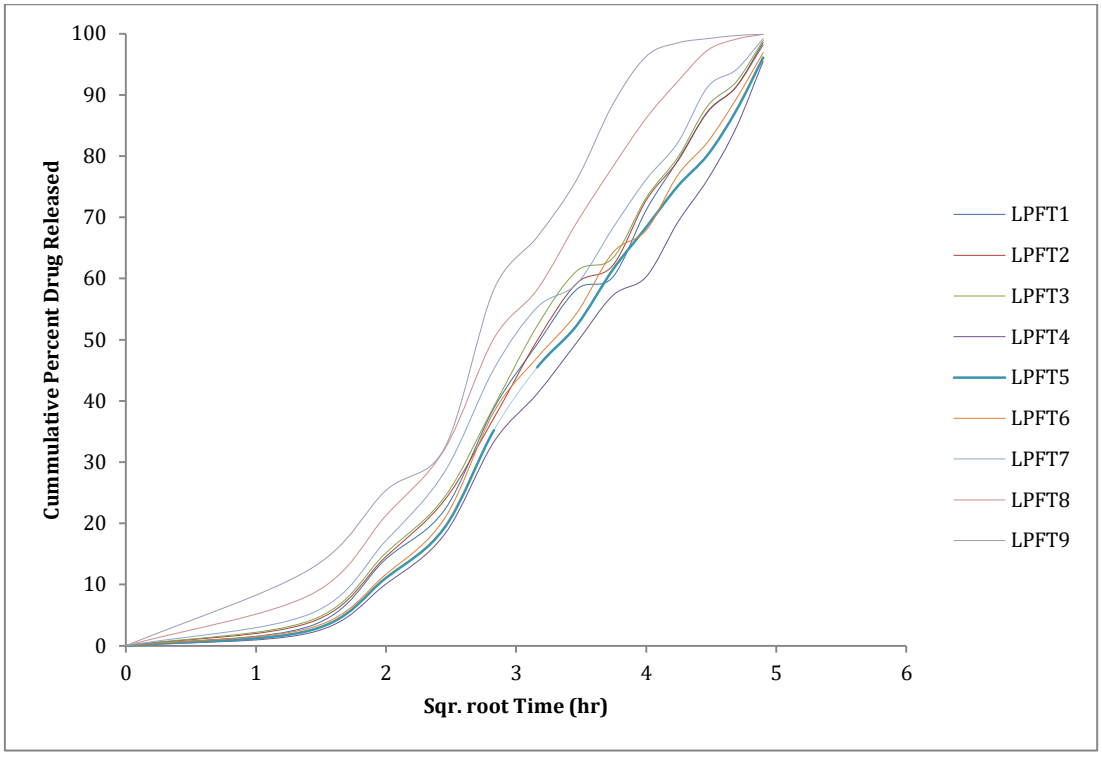

Figure 8: Higuchi release of various batches (LPFT1-LPFT9)

Table 7: Various release models (LPFT4)

Models	Graphical Value	Regression coefficient
Zero order	CPDR v/s Time	0.962
First order	Log% CDRet v/s time	0.826
Korsmeyer-Peppas	Log mt/m ∞ v/s log time	0.981
Higuchi model	%CDR v/s square root of time	0.978

SUMMARY AND CONCLUSION

The proposed work was under the investigation of an extended release matrix tablet of Losartan Potassium for antihypertensive therapy. The formulation was able to drug released from controlled-release oral preparations in the stomach region for absorbed, specifically in the gastrointestinal tract, leads to bioavailability problems. The formulations of Losartan Potassium based on designed to enhance the bioavailability by prolonging its duration in the stomach via the controlled release. Losartan Potassium released in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance. Accordingly, this study was designed to enhance the bioavailability of drug by prolonging its duration in the stomach via the floating dosage forms with controlled release. Floating matrix tablets of Losartan Potassium were prepared by the direct compression method, using locust bean gum and HPMC K 15M as polymers and Sodium bicarbonate as floating agent. The effect of the nature of polymers was studied by preparing various formulations of floating matrix mucoadhesion tablets. In all these formulations, a constant amount of drug (100 mg) was maintained. The blend was initially characterized for pre-compression and post-compression parameters. Pre-compression characterization was done for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The results of pre-compression characterization were indicated good to excellent flow characteristics. Post-compression characterization includes thickness, hardness, friability, weight variation, drug content, buoyancy lag time, floating time and in-vitro drug release. All the results were satisfactory as per the guideline of pharmacopoeia. The in vitro drug release studies found that formulations LPFT4 showed best sustained release profile in 24 hrs. Among the nine formulations (LPFT1 to LPFT9) prepared formulations LPFT4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation and followed supercase II transport diffusion kinetic models.

REFERENCES:

1. Fellermann K, Stange EF, "Defensins - innante immunity at the epithelial frontier", European Journal Gastroenterology Hepatology, 2001; 13:771- 5. https://doi.org/10.1097/00042737-200107000-00003

2. Gewirtz AT, "Intestinal epithelial pathobiology: past, present and future", Best Pract Research Clinical Gastroenterology, 2002, 16, 851-859. https://doi.org/10.1053/bega.2002.0339

3. Singh BN, Kim KH. In Drug Dlivery: Oral Route. In: Swarbrick J, editor. Encyclopedia of Pharmaceutical Technology. 3rd Edn; New York: Informa Healthcare USA, Inc., USA, 2007, pp 1242- 1244.

4. Friend DR, "New oral delivery systems for treatment of inflammatory bowel disease", Advanced Drug Delivery Reviews, 2005; 57:247-65. https://doi.org/10.1016/j.addr.2004.08.011

5. Someshwar K, Chithaluru K, Ramarao T, Kumar KK. Formulation and evaluation of effervescent floating tablets of tizanidine hydrochloride. Acta Pharm. 2011; 61(2):217-226. https://doi.org/10.2478/v10007-011-0015-5

6. Kotreka UK, Adeyeye MC. Gastroretentive floating drug-delivery systems: a critical review. Crit. Rev. Ther. Drug Carrier Syst. 2011; 28(1):47-99. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v28.i1.20

7. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Release 2000; 63(3):235- 259. https://doi.org/10.1016/S0168-3659(99)00204-7

8. Ali J, Arora S, Ahuja A, Babbar AK, Sharma RK, Khar RK, Baboota S. Formulation and development of hydrodynamically balanced system for metformin: in vitro and in vivo evaluation. Eur. J. Pharm. Biopharm. 2007; 67(1):196-201. https://doi.org/10.1016/j.ejpb.2006.12.015