CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.14542805

https://www.iajps.com/volumes/volume11-december-2024/69-issue-12-december-24/

Available online at: http://www.iajps.com Research Article

PREPARATION AND CHARACTERIZATION OF GASTRORETENTIVE TABLETS OF LOSARTAN POTASSIUM

Ch Mounika[1], Zeenath Ruhy[2]

[1]Mother Teresa College of Pharmacy, N.F.C Nagar, Ghatkesar, Medchal, Telangana.

Article Received: October 2024 Accepted: November 2024 Published: December 2024

Abstract:

The goal of a gastro-retentive drug delivery system is to target the upper GIT and maintain the medicine at a specific region of the GIT for a longer period. In this study, one of the least reported approaches, expandable drug delivery, was utilized. Losartan potassium expandable tablet was prepared by direct compression method. Various polymer concentrations were employed. To improve the drug's bioavailability and prolong its duration in the stomach, expandable losartan potassium tablets were prepared. Based on the results of the evaluation it was found that the evaluatory parameters of tablets were within the acceptable limit of Pharmacopoeia. Formulations F8 and F12 could only keep the drug's release continuing for 12 hours. All formulations were following zero order release. In contrast to formulations F2, F3, F5, and F8, which followed nonfickian (anomalous) drug release, F1, F4, F6, and F7 followed Fickian drug release. Formulation F8 was chosen as the optimal formulation.

Keywords: *Losartan potassium, Gastroretentive expandable tablets, residence time, in-vitro release.*

Corresponding author:

Zeenath Ruhy,

Mother Teresa College of Pharmacy,

N.F.C Nagar, Ghatkesar, Medchal, Telangana.

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Please cite this article in press ***Zeenath Ruhy*** *et al* ***., Preparation And Characterization Of Gastroretentive Tablets Of Losartan Potassium .,****Indo Am. J. P. Sci, 2024; 11 (12).*

INTRODUCTION:

Drugs that have a narrow absorption window in the gastrointestinal tract will have a poor absorption window [1]. For these drugs, gastrointestinal drug delivery offers the advantage of prolonging the gastric emptying time. Gastroretentive controlled release systems are widely used for controlled drug administration. These systems are attractive approaches from an economic as well as process development point of view. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract [2]. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [3].

Various approaches have been reported in the literature for the formulation of gastroretentive systems: mucoadhesion, flotation, sedimentation, expansion, and modified shape systems. Both single-unit systems and multiple-unit systems have been reported in the literature. Floating drug delivery systems also called hydro dynamic balanced systems are an effective technology to prolong the gastric residence time to improve the bioavailability of the drug [4]. This technology is suitable for drugs with an absorption window in the stomach or in the upper part of the small intestine, drugs acting locally in the stomach, and drugs that are poorly soluble or unstable in the intestinal fluid [5].

Losartan potassium is a potent, highly specific angiotensin II type 1(AT 1) receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with an oral bioavailability of about 33% and a plasma half-life ranging from 1.5 to 2.5 hours [6]. Floating matrix tablets of losartan potassium were developed to prolong gastric residence time, leading to an increase in drug bioavailability.

MATERIALS AND METHODS:

Materials:

Losartan potassium drug was received from Sun Pharmaceutical Industries Ltd as a gift sample. Hydroxypropyl methylcellulose (HPMC K4M) was procured from Otto Chemie Pvt. Ltd, sodium carboxyl methyl cellulose (SCMC) was procured from High Media Ltd. and carbopol 934 NF grade, lactose, talc, or magnesium stearate was procured from Loba Chemie Pvt. Ltd. and all the other chemicals used are analytical grade.

Methods:

Preparation of Expandable Gastroretentive tablet of Losartan Potassium:

The direct compression technique is utilized to create the expandable gastro-retentive tablets. Table 4.3 and Table 4.4 provide a breakdown proportionate composition of various ingredients. Based on the results of trial batches, hydrophilic matrix-forming polymers like HPMC K4M, SCMC, carbopol 934NF, and methyl cellulose were used in each formulation. Lactose served as a diluent; glidant and lubricating properties were provided by magnesium stearate and talc, respectively in the formulation [7]. After meticulously combining all of the ingredients, the tablets were created using a rotating tablet machine with a 4 mm punch.

Table 1: Composition of expandable tablet of losartan

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Losartan potassium	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	20	10	10	20	20	50	50	100	20	10	10	20
SCMC	15	25	15	25	55	25	50	25	15	25	15	25
Carbopol 934NF	15	15	25	55	25	25	50	25	-	-	-	-
Methyl cellulose	-	-	-	-	-	-	-	-	15	25	50	55
Lactose	280	280	280	230	230	230	180	180	280	280	280	230
Talc	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10	10	10	10	10
Total Wt. of tablets	400 mg											

SCMC-Sodium Carboxy Methyl Cellulose

Evaluation of Expandable Tablet:

Pre-compression parameters

Angle of Repose (θ):

Funnel technique was utilized to find out the angle of repose (θ). The mixture was poured through a funnel with a maximum cone height (h) that can be attained by vertically raising it [8]. After calculating the radius of the heap (r), the formula is used to find out the angle of repose (θ).

$$\tan\theta = \frac{h}{r}$$

Bulk Density(ρ_b):

The prepared mixture was placed into a calibrated cylinder to determine the apparent bulk density (ρb). Utilizing the following formula, the bulk density was determined.

$$Bulk\ density, \rho b = \frac{M}{V_b}$$

In contrast, M is the powder's weight and Vb is its bulk volume.

Tapped Density(ρt):

A density instrument was used to tap the cylinder 100 times containing a measured blend quantity. The blend's mass (M) and minimal volume (Vt) occupied in that cylinder were calculated. The following formula was used to determine the tapped density.

$$\boldsymbol{Tapped\ density, \rho t = \frac{M}{V_t}}$$

Hausner's ratio:

Another indirect method for calculating flow characteristics is Hausner's proportion.

$$\boldsymbol{Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}}$$

Compressibility Index:

The following formula is utilized to determine the Compressibility index (I)

$$\boldsymbol{Compressibility\ Index(I) = \frac{Tapped\ density\ - Bulk\ density}{Tapped\ density}}$$

Compatibility studies:

Drug identification and the detection of drug interactions with polymers are done using FTIR spectra. On an FTIR (Shimadzu) instrument, FTIR spectrums of the pure medication and polymers were produced [9]. To identify any potential ingredient interactions, the drug's pure spectrum was compared to the drug's formulation spectrum.

Weight variation:

The average weights of twenty randomly chosen tablets were determined after precise weight measurements [10]. After calculating the mean and individual weights' deviations, the standard deviation was determined.

Drug Content uniformity:

Twenty tablets were individually examined to determine the quantity of medication contained in each tablet [11].

Hardness:

A Monsanto hardness test apparatus was utilized to calculate the hardness of five randomly selected tablets from an individual batch of formulations [12].

Uniformity of Thickness and Diameter:

The tablet's average diameter and thickness were recorded after the assessment of the diameter and thickness of the dosage form by utilizing the Vernier Calliper apparatus. If none of the individual dimension and thickness values fall beyond the permitted ranges, the tablets pass the test [13].

Friability:

The first ten tablets are dusted, then weighed, and put in a double drum friability tester machine. The machine is spun for four minutes at a speed of 25 rpm to assess the friability [14]. Following dusting, the total mass of the tablets that remained after dusting was noted, and the % friability was determined using the formula below.

$$\%\ Friability = \frac{Initial\ weight\ of\ tablets - Final\ weight\ of\ tablets}{Initial\ weight\ of\ tablets} \times 100$$

Swelling index property:
The swelling index (SI) of tablets is computed by submerging the tablet in a 900 ml buffer of 0.1N HCl at a temperature of 37°C ± 0.5°C. At predetermined intervals of 1 h to 12 h, the tablets are removed from the dissolving media. The tablet is used to assess weight increase after being dried off using blotting paper [15]. According to the equation, swelling properties were described in terms of SI or water uptake percentage.

$$Swelling\ Index\ (SI) = \frac{weight\ of\ swollen\ tablet - Initial\ weight\ of\ tablet}{Initial\ weight\ of\ tablet} \times 100$$

Dissolution study:
With 900ml of 0.1N HCl buffer spinning at 50 rpm, a paddle-type dissolution apparatus (USP-II type) was cast off to examine the tablet's drug release characteristics [16]. The volume of the dissolving medium was maintained constant by adding an equal volume of fresh dissolution media each time 5 ml of sample were removed. The sample's absorbance was measured spectrophotometrically after the proper dilution, and the relevant concentrations were estimated using the related calibration curve [17]. Every study was carried out in triplicate by keeping a constant temperature of 37 ± 0.5°C throughout the process.

Kinetic modeling of drug release:

- ***Zero order model***

The equation below can be used to model how the drug releases gradually from the dosage form without disintegration [18].

$$\mathbf{Q_t = Q_o + K_o t}$$

Here,

Q_t : Quantity of medicine dissolves in time
Q_o : Primary quantity of drug solution
K_o : is the zero-order release constant

First order model:
The following equation explains how the model is utilized to calculate the absorption and elimination of a drug that followed first-order kinetics [19].

$$\mathbf{dC/dt = -Kc}$$

Higuchi model:
Higuchi created models to analyse how drugs (water soluble/less soluble) release when they are put into semisolid and solid matrices.

$$\mathbf{A = [D\ (2C - Cs)\ Cs\ x\ t]^{1/2}}$$

Here,

A- Quantity of medication free per unit area in time t
D- Drug permeability in matrix compounds
C- The drug's initial concentration
Cs- Solubility of drug in matrix medium

Korsmeyer - Peppas model:
The following equation provides the empirical form of the Korsmeyer and Peppas model, which compares to the expression of time for diffusion-controlled processes:

$$\mathbf{Mt / Ma = Kt^n}$$

Here,

Mt / Ma is the proportion of drug released
t is time
K is the constant value
n is drug release component/mechanism

Stability study:
Stability studies were directed by ICH and WHO guidelines to examine the medication and formulation stability. The prepared expandable optimized formulation was opted for stability study based on their physical properties, swelling studies and *invitro* controlled drug release. The selected tablets were individually wrapped in aluminum foil, in screw-top amber-colored bottles, and stored at the recommended 40°C/75%RH conditions for 6 months. At different interval (1^{st},3^{rd} and 6^{th} months), samples were observed for the physical properties, drug content, *invitro* dissolution, and swelling behavior [20].

RESULTS AND DISCUSSION:

Table 2: Calibration curve of losartan potassium in 0.1 N HCl (248 nm)

Concentration (µg/ml)	Absorbance
2.0	0.158
4.0	0.221
6.0	0.294
8.0	0.405
10.0	0.472

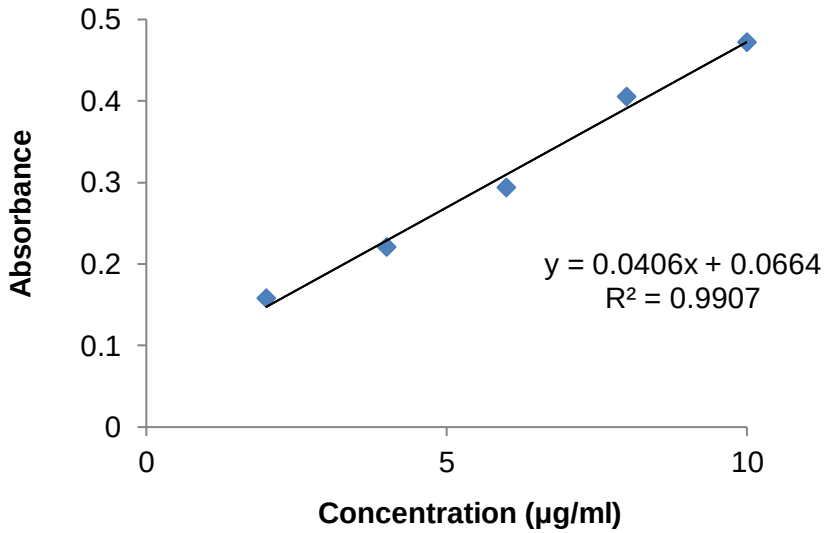

Figure 1: Calibration curve of losartan potassium in 0.1N HCl

Pre-compression evaluation parameters:

The bulk density of the first set of formulations (F1-F8) was found to be from 0.37±0.41 to 0.51±0.56 whereas tapped density was found to be from 0.52 ±0.45 to 0.78±0.51. However, the bulk density of the second set of formulations (F9-F16) was found to be from 0.42±0.84 to 0.49±0.38 and the tapped density was found to be 0.52±0.27 to 0.62±0.54. The compressibility index and Hausner's ratio of granules of formulation F1-F8 were found to be in the range of 16.56 to 19.11 and 1.16 to 1.27 respectively. The compressibility index and Hausner's ratio of granules of formulation F9-F16 were found to be in the range of 17.30 to 22.58 and 1.20 to 1.29 respectively. From the results of the Compressibility index and Hausner's ratio, it was confirmed that both the set of formulations has better to excellent flow properties.

Table 2: Result of evaluation of precompression parameters of formulation with batch code (F1-F16)

Batch	Angle of Repose	Bulk density g/cm³	Tap density g/cm³	Compressibility Index (%)	Hausner's Ratio
F1	21.67±0.19	0.42± 0.84	0.53 ±0.15	20.75	1.26
F2	23.14±0.76	0.44±0.93	0.56±0.49	21.42	1.27
F3	22.45±0.47	0.45±0.24	0.57±0.61	21.05	1.26
F4	21.56±0.35	0.48±0.19	0.62±0.54	22.58	1.29
F5	24.89±0.29	0.43±0.53	0.52±0.27	17.30	1.20
F6	23.35±0.31	0.46±0.49	0.57±0.41	19.29	1.23
F7	25.71±0.63	0.47±0.21	0.59±0.69	20.33	1.25
F8	26.13±0.72	0.49±0.38	0.60±0.55	18.33	1.22
F9	23.21±0.34	0.39±0.23	0.52 ±0.45	16.56	1.16
F10	22.11±0.46	0.37±0.41	0.58±0.34	17.67	1.19
F11	24.23±0.52	0.42±0.37	0.63±0.46	16.73	1.23
F12	25.42±0.38	0.47±0.46	0.58±0.54	18.44	1.27

Values are mean ± S.D

Post-compression evaluation parameters:

Table 3: Properties of compressed tablets of formulation F1-F16

Batch	Thickness* (mm)	Weight variation† (%)	Drug Content* (%)	Hardness* (kg/cm²)	Friability* (%)
F1	4.67±0.08	3.25±1.12	96.38±0.04	5.7±0.21	0.34±0.02
F2	4.36±0.05	3.10±0.22	97.27±0.12	5.7±0.11	0.52±0.03
F3	4.69±0.04	2.65±1.12	96.48±0.05	5.8±0.18	0.41±0.06
F4	4.66±0.02	1.76±0.81	97.37±0.13	5.9±0.37	0.29±0.03
F5	4.83±0.04	3.76±2.10	98.89±0.72	5.6±0.26	0.53±0.02
F6	4.76±0.05	1.65±0.84	98.26±0.87	6.2±0.57	0.42±0.04
F7	5.58±0.04	3.14±1.93	96.46±0.34	6.4±0.22	0.26±0.08
F8	5.26±0.03	2.39±0.33	99.36±0.63	5.9±0.34	0.29±0.12
F9	4.67±0.08	3.25±1.12	96.38±0.04	5.7±0.21	0.34±0.02
F10	4.36±0.04	2.89±0.04	94.39±0.03	6.5±0.26	0.54±0.02
F11	4.64±0.05	2.14±0.03	96.44±0.02	6.6±0.19	0.67±0.04
F12	4.33±0.03	1.98±0.02	97.29±0.02	6.6±0.22	0.48±0.07

* All values are expressed as mean ± SE, n = 3
† All values are expressed as mean ± SE, n = 20

Expandable losartan potassium tablets of formulations F1–F8 were prepared to range in thickness from 4.28±0.02 to 4.87±0.03. Weight variation was in the range of 1.98±0.02 to 2.89±0.04

which was well within the permitted range, according to the US Pharmacopoeia. It was also found that the drug content is within the accepted range of 94.39±0.03 to 98.62±0.11. The tablet was found to range in hardness from 6.5±0.23 to 6.8±0.25. Friability was determined to range between 0.28±0.07 to 0.67±0.04. All formulations have friability substantially below the permitted limit of 1%.

Expandable losartan potassium tablets of formulations F9–F16 were prepared to range in thickness from 4.28±0.02 to 4.87±0.03. Weight variation was in the range of 1.65±0.84 to 3.76±2.10 which was well within the permitted range, according to the US Pharmacopoeia. It was also found that the drug content is within the accepted range of 96.38±0.04 to 99.36±0.63. The tablet was found to range in hardness from 5.6±0.26 to 6.4±0.22. Friability was determined to range between 0.26±0.08 to 0.53±0.02. All formulations have friability substantially below the permitted limit of 1%.

Swelling properties:

Table 4 shows the % SI of all the formulations. Water molecules enter the matrix and hydrate the polymer, causing it to form a gel. The size of the tablet was increased as a result of the water becoming trapped within the gel. The tablet's density rises, and it stays in the stomach rather than passing through the pylorus. According to the findings, the produced tablets had good gel strength and showed prolonged swelling. For 12 hours, the tablets maintained good integrity.

Table 4: Swelling index for F1-F16

Batch	Swelling index (%)
F1	33.96±0.32
F2	34.49±0.85
F3	35.44±0.46
F4	35.31±0.23
F5	36.29±0.54
F6	33.03±0.62
F7	34.25±0.37
F8	33.74±0.74
F9	36.14±0.27
F10	37.21±0.54
F11	38.43±0.71
F12	34.82±0.64
F13	36.91±0.23
F14	37.29±0.41
F15	35.5±0.51
F16	36.28±0.68

Values are mean ± S.D

SI of formulations F1-F8 was found to be in the range of 33.03±0.63 to 36.29±0.56 whereas formulations F9 – F16 was found to be in the range of 34.82±0.64 to 38.43±0.71. The results demonstrate that formulations comprising a combination of HPMC K4M, SCMC, and MC had a higher capacity for swelling than formulations including a combination of HPMC K15M, SCMC, and carbopol 934NF.

Compatibility study:

All of the drug's significant peaks are seen in the FTIR spectrum. It was discovered that the IR spectra of the pure drug resembled the typical spectrum of losartan potassium (Figure 18). It showed characteristics peaks belonging to measure functional groups such as CH Stretching (2956.87), C=O (1747.51), C=C (1602.85), A1-CH (1456.26), Ar-CH (1093.64), C-O-C (1188.15) cm^{-1}. The spectrum of the optimized batch's FTIR analysis displays all notable peaks.

The important IR peaks seen in the optimized formulation were CH Stretching (2956.87-2951.09), C=O (1747.51- 1745.93), C=C (1602.85- 1600.06), A1-CH (1456.26-1456.26), Ar-CH (1093.64-1087.85), C-O-C (1188.15-1186.22) cm^{-1}.

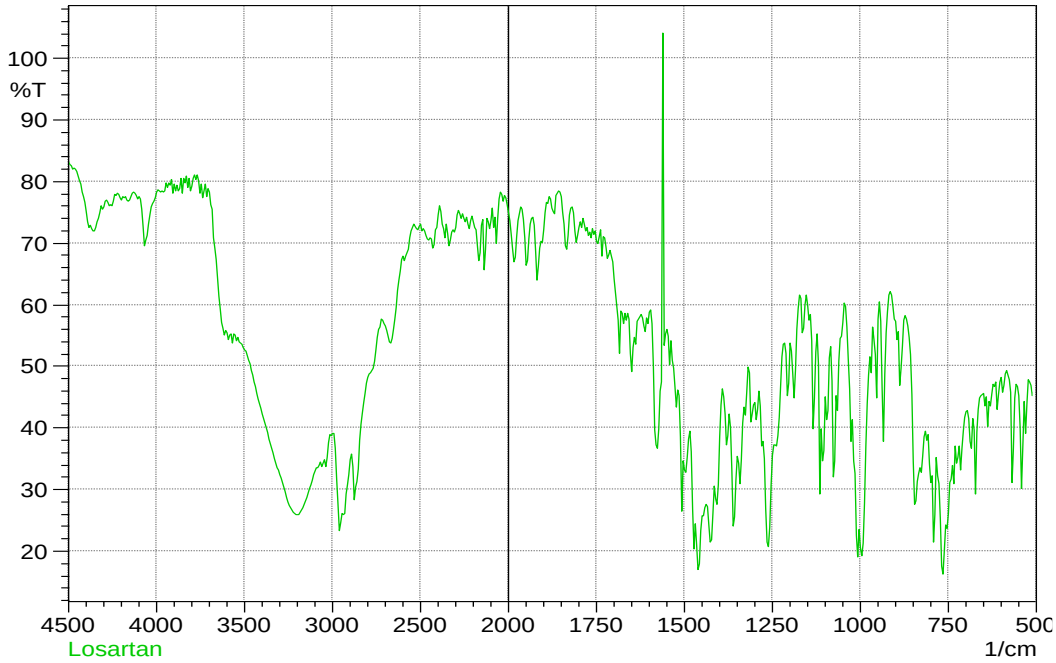

Figure 2: Infrared spectrum of Losartan Potassium

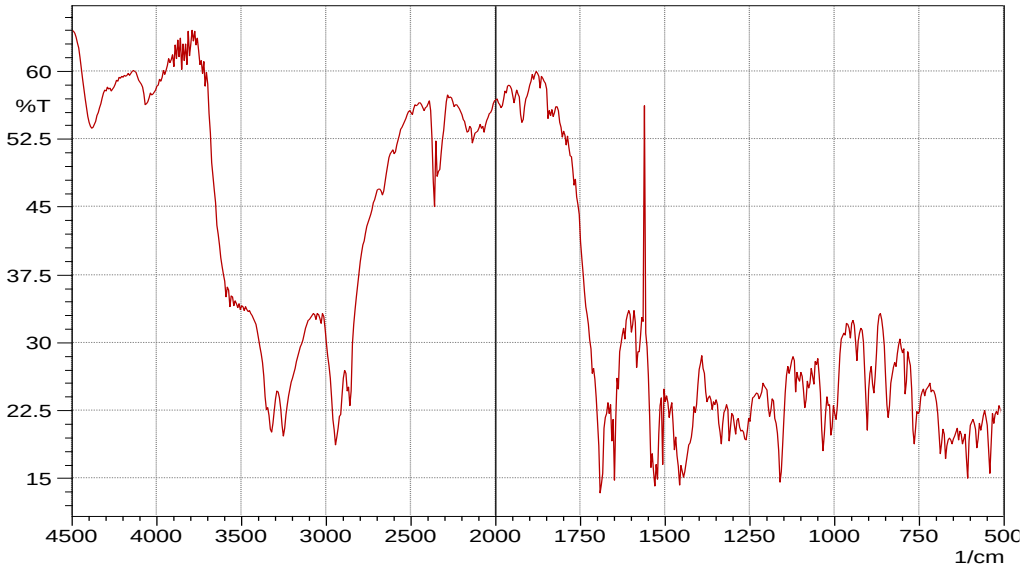

Figure 3: Infrared Spectrum of Pure Drug losartan potassium with polymers

Table 5: IR Spectrum comparison of pure Losartan Potassium and formulation

Functional Group	Principal peaks of pure Losartan potassium (cm^{-1})	Principal peaks of Losartan potassium in formulation (cm^{-1})
CH Stretching (Aliphatic)	2955.87	2951.09
C=O	1746.51	1745.93
C=C	1601.85	1600.06
Al-CH	1457.26	1456.26
Ar-CH	1092.64	1087.85
C-O-C	1186.15	1186.22

In vitro drug release study:
It was noted that all of the tablets expanded considerably within the first hour and continued to grow until the release studies were finished. The tablet's swelling behavior had an impact on the release. The sustained release studies of drug was conducted for 12-hour.

Release of losartan potassium from formulated tables was studied in 0.1N hydrochloric acid medium. The release data is shown in Table 15 and 16 respectively. In contrast to formulation F2, which continues the release of the drug for nine hours, formulation F1 only releases the drug for seven hours. Formulation F3 could only continue the medication release for 11 hours. F4 can only keep the drug release going for 8 hours. Drug release from formulations F5 and F6 might last for 11 hours. The medication might last for 10 hours in Formulation F7. Only formulation F8 was capable of sustaining drug release for a full 12 hour.

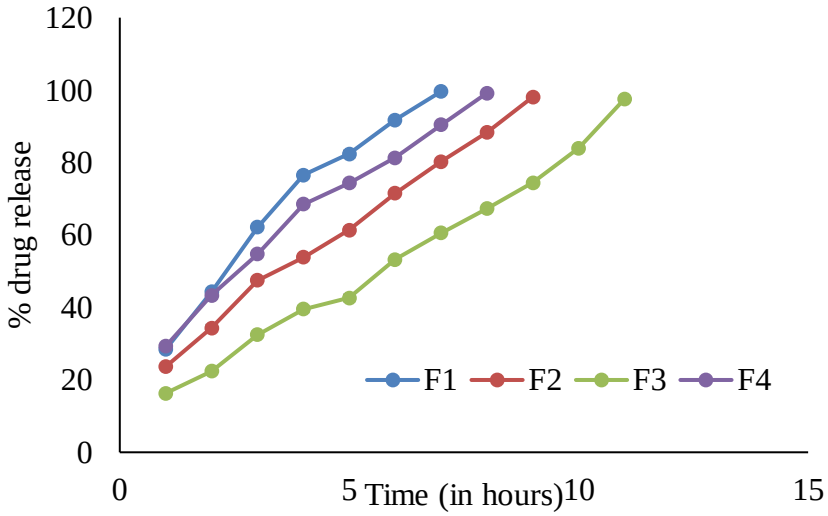

Figure 4: % Drug release of formulations F1 – F4

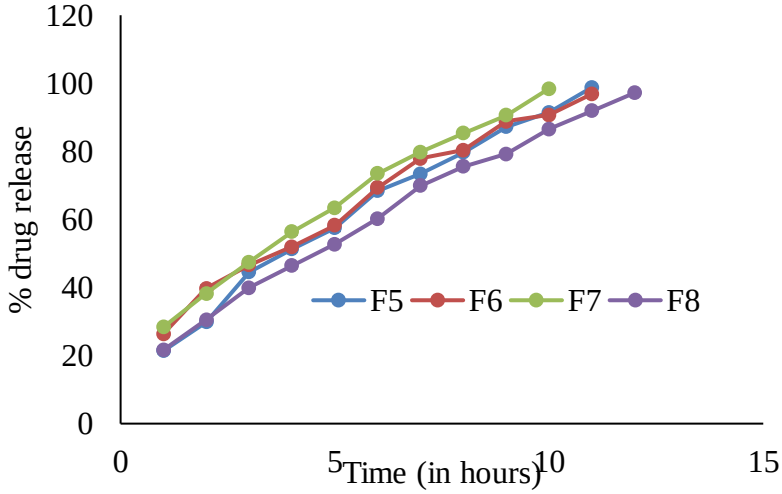

Figure 5: % Drug release of formulations F5 – F8

Formulation F9 could only maintain the release of the drug for 8 hours until it stopped, however, Formulation F10 could sustain the release of the drug for 10 hours. Formulation F11, however, could only continue to deliver the medicine till 11 hours. Only Formulation F12 was capable of sustaining medication release for a full 12 hours. Formulation F13 might continue the medication delivery for 11 hours. Only formulations F14, F15, and F16 were capable of sustaining the medication for 10 hours.

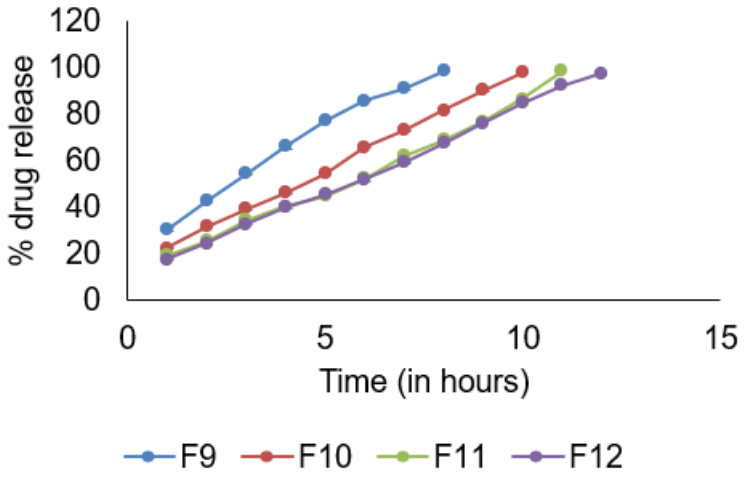

Figure 6: % Drug release of formulation F9 – F12

Kinetics of drug release:

The various models were tested to explain the drug release kinetics. The analysis of drug release rate kinetics of dosage form, the model with the higher correlation coefficient was considered to be the best model. The collected dosage form data were fitted into the Higuchi (Matrix), zero order kinetics, first order kinetics, and Korsmeyer-Peppas release models.

Table 6: Release kinetics of formulations F1 – F8

Batch	Zero-order		First-order		Higuchi model		Korsemeyer-Peppas	
	R^2	k(mg/h^{-1})	R^2	k(h^{-1})	R^2	K_H($h^{-1/2}$)	R^2	n
F1	0.993	11.732	0.930	0.420	0.993	43.956	0.992	0.447
F2	0.996	9.050	0.790	0.374	0.987	36.843	0.984	0.493
F3	0.991	7.746	0.719	0.259	0.956	33.838	0.975	0.617
F4	0.983	9.648	0.964	0.314	0.996	37.857	0.992	0.421
F5	0.985	7.584	0.804	0.327	0.995	33.910	0.995	0.508
F6	0.983	6.901	0.906	0.276	0.990	30.811	0.963	0.412
F7	0.991	7.681	0.821	0.343	0.994	32.877	0.989	0.438
F8	0.992	6.826	0.876	0.257	0.992	31.506	0.987	0.497
F9	0.996	9.778	0.771	0.476	0.996	38.338	0.997	0.580
F10	0.999	8.427	0.819	0.325	0.975	35.584	0.985	0.654
F11	0.991	7.644	0.689	0.286	0.949	33.280	0.973	0.683
F12	0.998	7.347	0.822	0.263	0.968	33.406	0.985	0.710

The "R^2" values (Table 17) for zero order kinetics were in the range of 0.983 - 0.996 when the release data were examined using zero and first order models, whereas the R^2 values for first order kinetics were found to be in the range of 0.719 - 0.964. Since all floating tablets were constructed with R^2 values that were substantially greater in the zero order model, the drug release from all of these tablets (F1 to F8) was consistent with zero order kinetics.

Release data from formulations F1–F8 followed the equations proposed by Higuchi and Peppas, with R^2 values greater than 0.956 showing that the drug release from all of these tablets was diffusion regulated.

The release exponent 'n' was found to be between 0.421 and 0.497 when the release data were examined using Korsmeyer Peppa's equation. Formulations F1, F4, F6, and F7 followed fickian drug release, whereas Formulations F2, F3, F5, and F8 used non-fickian (anomalous) diffusion as the release mechanism.

The "R^2" values (Table 18) for zero order kinetics were in the range of 0.986 – 0.998 when the release data were examined using zero and first order models, whereas the R^2 values for first-order kinetics

were found to be in the range of 0.689 – 0.938. Since all floating tablets were constructed with R^2 values that were substantially greater in the zero-order model, the drug release from all of these tablets (F9 to F16) was consistent with zero-order kinetics. For formulations F1 to F8, the zero order rate constant values vary from 7.347 – 9.778, whereas the first release rate constant values range from 0.246 – 0.476.

Release data from formulations F9–F12 followed the equations proposed by Higuchi and Peppas, with R^2 values greater than 0.949. All of the manufactured floating tablets showed linear regressions with 'R^{2}' values greater than 0.949 when cumulative percent drug release was plotted against square root of time, showing that the drug release from all of these tablets was diffusion regulated.

Stability study:

The result of stability study showed that there was no change in physical appearance in the prepared tablets. There was no changes in the percentage cumulative drug release of optimized after 6 month. The release rate of expandable losartan potassium tablet did not significantly change when they were stored. Stability studies were conducted using formulation F8. Cumulative drug release from batch F8 at 1 hour and 12 hours after 6 months was 19.67% and 99.64%, respectively, with swelling indexes of 32.5 and 41.3. After six months, there was no noticeable change in the drug's swelling or release characteristics, indicating the formulation was stable.

Table 7: Cumulative % drug release & swelling index for F8 batch

Time (hr)	When prepared		After 6 months	
	% CDR	Swelling index	% CDR	Swelling index
1.	21.66	32.8	19.67	32.5
2.	30.49	28.9	28.24	28.3
3.	39.93	41.3	40.95	41.3
4.	46.38	34.7	48.37	34.7
5.	52.73	28.5	55.74	28.4
6.	60.27	36.4	61.44	36.4
7.	69.92	32.3	70.83	32.2
8.	75.59	38.6	77.31	38.5
9.	79.21	40.2	84.33	40.3
10.	86.56	34.2	88.45	34.2
11.	91.88	36.2	94.26	36.1
12.	97.21	41.2	99.64	41.2

The result of stability study was showed no remarkable changes in the formulation. It indicates the optimized formulation of losartan potassium tablet was stable.

SUMMARY AND CONCLUSION:

In this study, one of the least reported approaches, expandable drug delivery, was utilized. Losartan potassium expandable tablet was prepared by direct compression method. Various polymer concentrations were employed. Based on the results of the evaluation it was found that the evaluatory parameters of tablets were within the acceptable limit of Pharmacopoeia. All of formulations were following zero order release. Formulation F8 was chosen for animal testing based on tablet performance, drug release, and kinetics. When the concentration of drugs were estimated during animal studies, there was very less difference between observed concentration and predicted concentration, which indicates that the observed concentration is in sync with the predicted concentration. There was a significant increase in $t_{1/2}$ of pure drugs and prepared formulation. This indicates that the residence time of drug administered as floating tablets was increased significantly.

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