FORMULATION AND EVALUATION OF GASTRO RETENTIVE EXPANDABLE DRUG DELIVERY SYSTEM OF ANTIHYPERTENSIVE DRUG

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ABSTRACT:

The present study concerns the preparation and evaluation of gastroretentive expandable tablets of Losartan potassium, which enhance the gastric residence time and bioavailability after oral administration. Losartan potassium drug is a class of drug called as angiotensin receptor blockers (ARBs). It works by relaxing blood vessels, so that can flow more easily, systemic hypertension. Formulations were prepared using various polymers HPMC K4M, Sodium Carboxy Methyl Cellulose, Carbopol 934NF, Methyl cellulose by direct compression method. Various formulation batches were evaluated for various parameters like weight variation, thickness, hardness, friability, swelling index, drug content and *in-vitro* drug release. The study has revealed that the swelling and release rate from tablets depends on type and concentration of polymer. Formulations with the codes F8 and F12 could only keep the drug's release continuing for 12 hours. Formulation F8 was chosen for animal testing based on tablet performance, drug release, and kinetics. 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 expandable tablets was increased significantly.

KEYWORDS: Losartan potassium, Gastro retentive, HPMC K4M, Sodium Carboxy Methyl Cellulose, Carbopol 934NF, Methyl cellulose

INTRODUCTION:

The gastroretentive drug delivery system is a way to prolong the residence time of the dosage form. It is also applied for targeting drug in upper GIT for generating local and systemic effect. The Expandable drug delivery systems are the many gastro retentive drug delivery systems. Controlled drug delivery creates a window of absorption that release drug for a longer duration of time before reaching absorption site. Gastro retentive drug delivery systems have gained wide variation of oral drug distribution in the area of late. It includes all the approaches that keep the dosage form in the stomach for a longer duration of time. The increase bioavailability, reduced dose, and frequency for drug administration. The approaches for gastro-gastro retentive dosage forms have been proposed including mucoadhesive systems, swellable, and floating systems. Losartan potassium drug is a class of drug called as angiotensin receptor blockers (ARBs). It works by relaxing blood vessels, so that can flow more easily, systemic hypertension. Its half-life is about 1.5-2.5, active metabolism 6-9 hr. It absorbed approximately 33% orally bioavailability. Expandable gastroretentive tablets of losartan potassium were developed to prolong gastric residence time, thereby increasing drug bioavailability.

MATERIALS AND METHODS:

Materials

Losartan potassium drug was received from Sun Pharmaceutical Industries Ltd Sikkim as 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 LobaChemie Pvt. Ltd. and all the other chemicals used are analytical grade.

Method & Preparation of Expandable Gastroretentive Drug Delivery Systems

The direct compression method is used to create the expandable gastro-retentive tablets. Table 1 provides a breakdownproportionate composition of various ingredients. Based on the results of trial batches, hydrophilic matrix forming polymers such as hydroxy propyl methyl cellulose (HPMC K4M), sodium carboxy methyl cellulose (SCMC), carbopol were used in each formulation.Lactose, talc and magnesium stearate were served as diluent, lubricant and glidant respectively in the above formulation. 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	F1	F2	F3	F4	F5	F6	F7	F8
Losartan potassium (mg)	50	50	50	50	50	50	50	50
HPMC K4M(mg)	20	10	10	20	20	50	50	100
SCMC (mg)	15	25	15	25	55	25	50	25
Carbopol 934NF (mg)	15	15	25	55	25	25	50	25
Lactose (mg)	280	280	280	230	230	230	180	180
Talc (mg)	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10
Total Wt. of tablets	400	400	400	400	400	400	400	400

Ingredients	F9	F10	F11	F12	F13	F14	F15	F16
Losartan potassium (mg)	50	50	50	50	50	50	50	50
HPMC K4M(mg)	20	10	10	20	20	50	50	100
SCMC (mg)	15	25	15	25	55	25	50	25
Methyl cellulose (mg)	15	15	25	55	25	25	50	25
Lactose (mg)	280	280	280	230	230	230	180	180
Talc (mg)	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10
Total Wt. of tablets	400	400	400	400	400	400	400	400

Evaluation of Expandable Tablet

Pre-compression parameters (Bahadur, Roy, Chanda, *et al.*, 2016)**,** (Strübing, Metz and Mäder, 2008)**,** (Nerurkar *et al.*, 2005)

Angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were among the different characterizations performed on the powder mixture.

Angle of Repose

The funnel technique was used to determine the angle of repose. A funnel that can be elevated vertically to achieve a maximum cone height (h) was used to pour the mixture through. The following formula was used to determine the angle of repose (θ)after measuring the radius of the heap (r).

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

Bulk Density

The mixture was poured into a graduated cylinder to calculate 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

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

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

Hausner's ratio

The following formula is used to calculate the Hausner's ratio

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

Compressibility Index

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

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

Compatibility studies

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

Appearance and Shape

The tablet's overall look was observed and noted. The physical properties like size, shape, colour, odour, etc. were included. Additionally, lines, break-marks, and possible symbol or other symbols were seen on tablets.

Weight variation

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

Drug Content uniformity

To ascertain the amount of drug contained in each tablet, 20 tablets were individually analysed.

Hardness

A Monsanto-style hardness tester was used to measure the hardness of five randomly selected tablets from each batch of formulations.

Uniformity of thickness and Diameter

The tablet's average diameter and thickness were recorded after the assessment of the thickness and diameter of the tablet by using Vernier Calliper. If none of the individual dimension and thickness values fall beyond the permitted ranges, the tablets pass the test.

Friability

Ten tablets are dusted, weighed, and placed in a double drum friability tester machine. The machine is spun for four minutes at a speed of 25 rpm to assess the friability. 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 calculated by submerging the tablet in 900 cc of 0.1N HCl at 37°C ± 0.5°C. At predetermined intervals of 1 h to 12 h, the tablets are removed from the dissolving media. Tablet is used to assess weight increase after being dried off using blotting paper. 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

The drug release properties of the floating tablets were investigated using paddle type dissolution apparatus (USP-II type) using 900ml of 0.1N HCl buffer at 50 rpm. At regular intervals, 5 ml of sample were taken out, and the volume of the dissolving medium was kept constant by adding the same amount of new dissolution media. With the appropriate dilution, the absorbance of the sample was measured spectrophotometrically, and the corresponding concentrations were calculated using the associated calibration curve. Every study was carried out in triplicate by keeping a constant temperature 37 $\pm$ 0.5°C throughout the process.

Kinetic modeling of drug release

The dissolution of each batch of expandable tablets of losartan potassium was carried out. The kinetics of drug release was determined for zero order, first order, Higuchi's model and

Korsmeyer-Peppas model to check the phenomena controlling the drug release from tablets. The invitro drug release data of all the formulations (F1-F16) were fitted into zero order, first order, Higuchi's model and Korsmeyer-Peppas model and the values of slope, R^2 value were derived in each case.

- ***Zero order model***

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

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

Where,

Q_t : Amount of drug dissolve in time

Q_o: Initial amount of drug solution

K_o: is the zero order release constant

First order model

The following equation describes how this model is used to describe the absorption and elimination of a drug that followed first order kinetics.

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

- ***Higuchi model***

Higuchi created models to analyse the drug release from semisolid and solid matrices that contain water soluble and low soluble drugs.

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

Where,

A is the quantity of drug release in time t per unit area

D is diffusivity of drug molecules in the matrix substances

C is initial drug concentration

Cs is drug solubility in matrix media

- ***Korsmeyer - Peppas model***

The empirical expression of the Korsmeyer and Peppas model, which relates the function of time for diffusion-controlled mechanisms, is provided by the following equation:

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

Where,

Mt / Ma is fraction of drug released

t= time

K is constant

n is drug release component/mechanism

Stability study

All tablets of the optimized formulation were individually wrapped in aluminum foil, placed in amber-colored screw-top bottles, and stored at the recommended 40°C/75% relative humidity (RH) conditions for six months. The remaining parameters were left unchanged from the dissolution study, and the dissolution profile was examined after 6 months.

Invivo study of prepared formulations

The New Zealand male albino rabbit are divided into three groups. Healthy 1.5-2.5 kg male or female rabbits were fasted overnight. Each group consists of 6 rabbits with wash out period of one month. First group is blank (control group), second group was administered with standard drug, losartan potassium. Third group was administered with prepared optimized formulation. The prepared tablet was administered orally to the rabbits. After administering the medications, blood samples (1 ml) were taken from the rabbit's marginal ear vein at various time intervals. The sample was put into heparinized tubes, which were then centrifuged for 10 minutes at 10,000 rpm. The drug analysis was carried out using the HPLC technique after the separated plasma was collected in dry tubes.

With a few minor modifications, the HPLC technique was used to determine the plasma concentration of losartan potassium. HPLC analysis of the samples was performed at room temperature.

Mobile Phase:

The pH of the mobile phase was adjusted to 6.0 with the addition of 0.1% v/v glacial acetic acid and the phase is a combination of 60:40 acetonitrile and water. Before usage, a 0.45 µm membrane filter was used to filter the mobile phase, which was then run at a flow rate of 1 ml/min, with the eluent being examined.

In each instance, the pharmacokinetic parameters like peak concentration (Cmax), time at which the peak occurred (Tmax), area under the curve (AUC), and absorption rate constant—were determined using established standard procedures.

RESULT AND DISCUSSION:

Now a days, Controlled drug delivery is consider to be topic of great interest in pharmaceutical technology. In contrast to their corresponding conventional dosage forms, formulations with controlled release drug delivery systems are made to release an active component at predefined rates. (Gupta and Aggarwal, 2007; Kale and Tayade, 2007).

Pre-compression evaluation parameters

Table 2: Result of evaluation of precompression parameters of formulation with batch code (F1-F8)

Batch	Angle of Repose	Bulk density g/cm^3	Tap density g/cm^3	Compressibility Index (%)	Hausner's Ratio
F1	23.21±0.34	0.39± 0.23	0.52 ±0.45	16.56	1.16
F2	22.11±0.46	0.37±0.41	0.58±0.34	17.67	1.19
F3	24.23±0.52	0.42±0.37	0.63±0.46	16.73	1.23
F4	25.42±0.38	0.47±0.46	0.58±0.54	18.44	1.27
F5	26.54±0.67	0.45±0.51	0.66±0.72	18.98	1.14
F6	25.63±0.44	0.43±0.48	0.72±0.32	19.11	1.25
F7	28.44±0.58	0.50±0.39	0.77±0.55	18.76	1.21
F8	27.37±0.62	0.51±0.56	0.78±0.51	17.57	1.17

Values are mean ± S.D.

Table 3: Result of evaluation of precompression parameters of formulation with batch code (F9-F16)

Batch	Angle of Repose	Bulk density g/cm3	Tap density g/cm3	Compressibility Index (%)	Hausner's Ratio
F9	21.67±0.19	0.42± 0.84	0.53 ±0.15	20.75	1.26
F10	23.14±0.76	0.44±0.93	0.56±0.49	21.42	1.27
F11	22.45±0.47	0.45±0.24	0.57±0.61	21.05	1.26
F12	21.56±0.35	0.48±0.19	0.62±0.54	22.58	1.29
F13	24.89±0.29	0.43±0.53	0.52±0.27	17.30	1.20
F14	23.35±0.31	0.46±0.49	0.57±0.41	19.29	1.23
F15	25.71±0.63	0.47±0.21	0.59±0.69	20.33	1.25
F16	26.13±0.72	0.49±0.38	0.60±0.55	18.33	1.22

Values are mean ± S.D.

The quality of the physicochemical characteristics of blends, once established by regulation, often determines the quality of the tablet. The features of the blend that is created can be impacted by the several formulations and process factors that are used in the mixing stage. Powder flow properties such as bulk density, tapped density, Hausner's ratio, compressibility index, and angle of repose are used to characterize mixed blends.

Bulk density of 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, bulk density of 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. Compressibility index and Hausner's ratio of granules of formulation F1-F8, was found to be in the range of 16.56 to 19.11 and 1.16 to 1.27 respectively. Compressibility index and Hausner's ratio of

granules of formulation F9-F16 was found to be in the range of 17.30 to 22.58 and 1.20 to 1.29 respectively. From the results of Compressibility index and Hausner's ratio it was confirmed that both the set of formulation has better to excellent flow properties.

Post-compression evaluation parameters

Table 4: Properties of compressed tablets of formulation F1-F8

Batch code	Thickness* (mm)	Deviation in Weight Variation† (%)	Drug Content* (%)	Hardness* (kg/cm^2)	Friability† (%)
F1	4.36±0.04	2.89±0.04	94.39±0.03	6.5±0.26	0.54±0.02
F2	4.64±0.05	2.14±0.03	96.44±0.02	6.6±0.19	0.67±0.04
F3	4.33±0.03	1.98±0.02	97.29±0.02	6.6±0.22	0.48±0.07
F4	4.28±0.02	2.16±0.01	97.67±0.03	6.5±0.23	0.39±0.04
F5	4.76±0.04	2.23±0.02	97.58±0.05	6.8±0.25	0.67±0.03
F6	4.37±0.01	2.26±0.04	98.26±0.09	6.7±0.46	0.51±0.03
F7	4.87±0.03	2.87±0.03	97.67±0.04	6.5±0.27	0.28±0.07
F8	4.48±0.02	2.68±0.03	98.62±0.11	6.6±0.42	0.36±0.10

* All values are expressed as mean ± SE, n = 5

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

Table 5: Properties of compressed tablets of formulation F9-F16

Batch code	Thickness* (mm)	Deviation in Weight Variation† (%)	Drug Content* (%)	Hardness* (kg/cm^2)	Friability† (%)
F9	4.67±0.08	3.25±1.12	96.38±0.04	5.7±0.21	0.34±0.02
F10	4.36±0.05	3.10±0.22	97.27±0.12	5.7±0.11	0.52±0.03
F11	4.69±0.04	2.65±1.12	96.48±0.05	5.8±0.18	0.41±0.06
F12	4.66±0.02	1.76±0.81	97.37±0.13	5.9±0.37	0.29±0.03
F13	4.83±0.04	3.76±2.10	98.89±0.72	5.6±0.26	0.53±0.02
F14	4.76±0.05	1.65±0.84	98.26±0.87	6.2±0.57	0.42±0.04
F15	5.58±0.04	3.14±1.93	96.46±0.34	6.4±0.22	0.26±0.08
F16	5.26±0.03	2.39±0.33	99.36±0.63	5.9±0.34	0.29±0.12

* All values are expressed as mean ± SE, n = 5

† 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

According to an invitro swelling investigation, all batches displayed favorable swelling characteristics. The Swelling index of each batch was calculated, and each batch had a high enough SI to keep the tablet in the stomach.

The swelling index of tablets was examined by placing the tablet in 900 ml of 0.1 N HCl dissolution medium at 37°C ± 0.5°C. The tablets are taken out of the medium at predetermined intervals ranging from 1 hour to 12 hours. Tablet is weighed after being dried off from the water using blotting paper.

Table 13 shows the % SI of all the formulations. Water molecules enter the matrix and hydrate the polymer, causing it to form 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 showing prolonged swelling. For 12 hours, the tablets maintained good integrity.

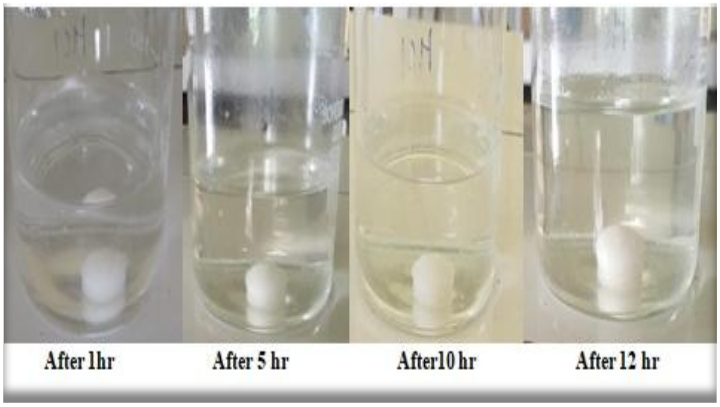

Figure 1: In vitro swelling study of F4 batch

Table 6: Swelling index for F1-F16

Batch	Swelling index (%)	Batch	Swelling index (%)
F1	33.96±0.37	**F9**	36.14±0.27
F2	34.49±0.82	**F10**	37.21±0.54
F3	35.44±0.48	**F11**	38.43±0.71
F4	35.31±0.27	**F12**	34.82±0.64
F5	36.29±0.56	**F13**	36.91±0.23
F6	33.03±0.63	**F14**	37.29±0.41
F7	34.25±0.37	**F15**	35.5±0.51
F8	33.74±0.74	**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

The main application of FTIR spectrophotometry is identification of a compound by means of spectral comparison with that of an authentic sample and verification of the presence of functional groups in an unknown molecule(Mohamed *et al.*, 2017; Seçilmiş Canbay, Polat and Doğantürk, 2019).

The samples were powdered and intimately mixed with dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning. In order to rule out any potential interactions between drugs and excipients, the IR spectra of the drug was compared to that of the physical mixture.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 2). 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.

Figure 3 displays the optimized batch's FTIR spectrum analysis. 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}. The confirmation of the drug's stability in the formulation came from the observation of all of the principal drug peaks.

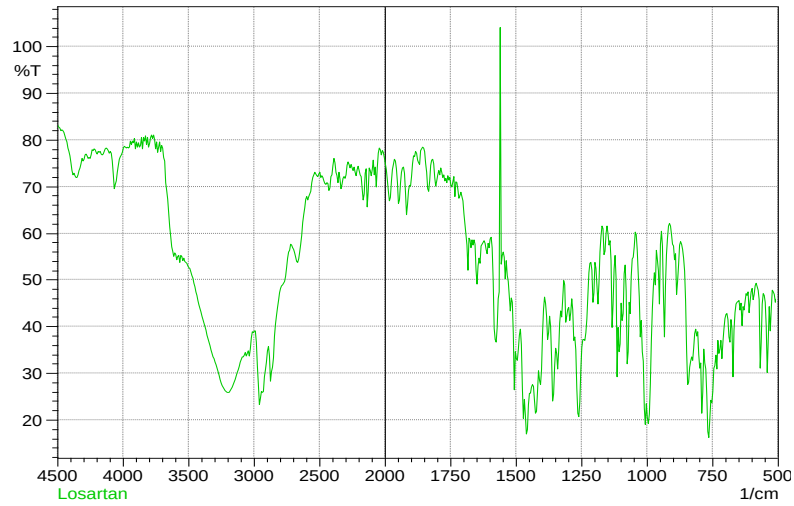

Figure 2: Infrared spectrum of Losartan Potassium

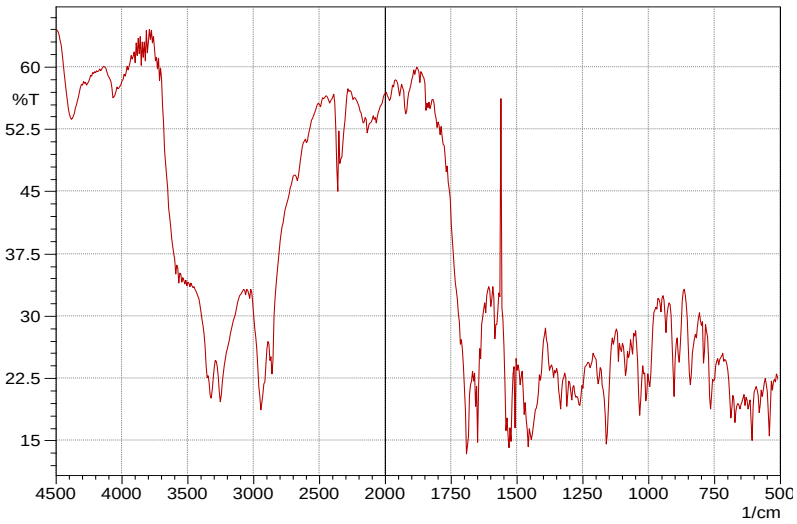

Figure 3: Infrared Spectrum of Pure Drug losartan potassium with polymers

Table 7: IR Spectrum comparison of pure Losartan Potassium and formulation

S No	Functional Group	Principal peaks of pure Losartan potassium (cm^{-1})	Principal peaks of Losartan potassium in formulation (cm^{-1})
1.	CH Stretching (Aliphatic)	2956.87	2951.09
2.	C=O	1747.51	1745.93
3.	C=C	1602.85	1600.06
4.	Al-CH	1456.26	1456.26
5.	Ar-CH	1093.64	1087.85
6.	C-O-C	1188.15	1186.22

5.5 Invitro drug release study

USP dissolution apparatus type II (paddle type) was utilized to carry out the invitro drug release studies of losartan potassium tablet. The dissolution test was performed using 900 ml of acidic buffer and the temperature of medium was set at 37±0.5℃. In each interval of 5 ml sample was withdrawn with fresh buffer at hr. The samples were filtered using whatman filter paper. By using UV spectrophotometer the absorbance of the each sample was measured at 248 nm.

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 8 and 9 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. Formulation 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 hours.

Table 8: Cumulative % Drug release of losartan potassium expandable tablets (F1 – F8)

Time in hr	Cumulative percentage drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
1	28.42 ±0.67	23.63± 0.39	16.31± 0.47	29.27± 0.51	21.37± 0.16	26.39± 0.86	28.38± 0.27	21.66± 0.53
2	44.31 ±0.25	34.35± 0.85	22.38± 0.11	43.36± 0.48	29.84± 0.49	39.76± 0.14	38.22± 0.49	30.49± 0.36
3	62.15 ±0.21	47.51± 0.49	32.44± 0.52	54.72± 0.38	44.53± 0.27	46.58± 0.61	47.41± 0.87	39.93± 0.73
4	76.52 ±0.76	53.82± 0.32	39.55± 0.86	68.55± 0.74	51.33± 0.18	51.92± 0.48	56.39± 0.56	46.38± 0.13
5	82.34 ±0.94	61.32± 0.71	42.61± 0.92	74.33± 0.21	57.49± 0.36	58.28± 0.18	63.47± 0.28	52.73± 0.76
6	91.71 ±0.31	71.48± 0.58	53.18± 0.37	81.34± 0.83	68.38± 0.82	69.39± 0.58	73.51± 0.11	60.27± 0.45
7	99.59 ±0.53	80.23± 0.33	60.56± 0.26	90.45± 0.47	73.43± 0.31	77.88± 0.71	79.78± 0.73	69.92± 0.29
8		88.34± 0.28	67.23± 0.71	99.18± 0.42	79.67± 0.64	80.38± 0.32	85.38± 0.25	75.59± 0.12
9		98.11± 0.61	74.46± 0.45		87.24± 0.52	88.78± 0.63	90.62± 0.58	79.21± 0.79
10			83.98± 0.49		91.45± 0.74	90.67± 0.78	98.43± 0.19	86.56± 0.57
11			97.56± 0.23		98.79± 0.13	96.86± 0.45		91.88± 0.42
12								97.21± 0.82

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.

Table 9: Cumulative % Drug release of losartan potassium expandable tablets (F9 – F16)

Time in hr	Cumulative percentage drug release							
	F9	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**
1	30.42 ±0.86	22.33 ±0.43	19.26± 0.12	17.66± 0.48	24.46± 0.63	27.54± 0.29	26.24± 0.47	20.37± 0.55
2	42.78 ±0.31	31.67 ±0.66	25.31± 0.61	24.48± 0.71	30.14± 0.54	37.22± 0.74	34.56± 0.28	28.43± 0.17
3	54.37 ±0.73	39.28 ±0.27	34.51± 0.84	32.71± 0.55	42.88± 0.38	44.54± 0.35	44.12± 0.92	36.61± 0.38
4	65.89 ±0.59	46.19 ±0.51	40.17± 0.23	39.84± 0.98	50.62± 0.51	51.36± 0.20	52.93± 0.49	44.55± 0.61
5	77.13 ±0.64	54.44 ±0.41	44.67± 0.57	45.36± 0.26	58.21± 0.76	63.77± 0.33	61.49± 0.54	53.16± 0.44
6	85.54 ±0.42	65.79 ±0.38	52.43± 0.34	51.92± 0.39	64.48± 0.28	74.19± 0.58	72.73± 0.76	62.94± 0.88
7	90.82 ±0.68	72.85 ±0.85	61.86± 0.39	59.14± 0.54	72.31± 0.91	81.57± 0.63	80.47± 0.81	71.68± 0.63
8	98.48 ±0.43	81.59 ±0.16	68.91± 0.42	67.26± 0.31	80.74± 0.32	89.43± 0.35	88.18± 0.23	83.86± 0.12
9		90.22 ±0.62	76.55± 0.59	75.92± 0.19	89.35± 0.45	91.71± 0.82	93.29± 0.43	91.24± 0.82
10		97.63 ±0.51	86.35± 0.73	84.47± 0.21	91.78± 0.69	98.56± 0.65	97.89± 0.16	99.31± 0.67
11			98.44± 0.15	92.11± 0.36	99.51± 0.24			
12				97.38± 0.45				

5.6 Kinetics of drug release

The various models were tested for explaining the drug release kinetics. The analyzed 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. Tables 10 and 11 provide summaries of the observations.

Table 10: Release kinetics of formulations, F1 – F8

Batch	Zero Order model		First order model		Higuchi model		Korsmeyer Peppas	
F1	R^2	0.993	R^2	0.930	R^2	0.993	R^2	0.992
	K (mg/h^{-1})	11.732	K (hr^{-1})	0.420	K_H ($h^{-1/2}$)	43.956	n	0.447
F2	R^2	0.996	R^2	0.790	R^2	0.987	R^2	0.984
	K (mg/h^{-1})	9.050	K (hr^{-1})	0.374	K_H ($h^{-1/2}$)	36.843	n	0.493
F3	R^2	0.991	R^2	0.719	R^2	0.956	R^2	0.975
	K (mg/h^{-1})	7.746	K (hr^{-1})	0.259	K_H ($h^{-1/2}$)	33.838	n	0.617
F4	R^2	0.983	R^2	0.964	R^2	0.996	R^2	0.992
	K (mg/h^{-1})	9.648	K (hr^{-1})	0.314	K_H ($h^{-1/2}$)	37.857	n	0.421
F5	R^2	0.985	R^2	0.804	R^2	0.995	R^2	0.995
	K (mg/h^{-1})	7.584	K (hr^{-1})	0.327	K_H ($h^{-1/2}$)	33.910	n	0.508
F6	R^2	0.983	R^2	0.906	R^2	0.990	R^2	0.963
	K (mg/h^{-1})	6.901	K (hr^{-1})	0.276	K_H ($h^{-1/2}$)	30.811	n	0.412
F7	R^2	0.991	R^2	0.821	R^2	0.994	R^2	0.989
	K (mg/h^{-1})	7.681	K (hr^{-1})	0.343	K_H ($h^{-1/2}$)	32.877	n	0.438
F8	R^2	0.992	R^2	0.876	R^2	0.992	R^2	0.987
	K (mg/h^{-1})	6.826	K (hr^{-1})	0.257	K_H ($h^{-1/2}$)	31.506	n	0.497

The "R^2" values(Table 10) 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. For formulations F1 to F8, the zero order rate constant values vary from 6.826 to 11.732, whereas the first release rate constant values range from 0.257 to 0.420.(El-Kamel *et al.*, 2001; Rajinikanth and Mishra, 2007).

Release data from formulations F1–F8 followed the equations proposed by Higuchi and Peppas, with R^2 values greater than 0.956. All of the manufactured floating tablets showed linear regressions with 'R^{2}' values greater than 0.956 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. (El-Kamel *et al.*, 2001; Rajinikanth and Mishra, 2007).

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 nonfickian (anomalous) diffusion as the release mechanism.

Table 18: Release kinetics of formulation, F9 – F16

Batch	Zero Order model		First order model		Higuchi model		Korsmeyer Peppas	
F9	R^2	0.996	R^2	0.771	R^2	0.996	R^2	0.997
	K (mg/h^{-1})	9.778	K (hr^{-1})	0.476	K_H ($h^{-1/2}$)	38.338	n	0.580
F10	R^2	0.999	R^2	0.819	R^2	0.975	R^2	0.985
	K (mg/h^{-1})	8.427	K (hr^{-1})	0.325	K_H ($h^{-1/2}$)	35.584	n	0.654
F11	R^2	0.991	R^2	0.689	R^2	0.949	R^2	0.973
	K (mg/h^{-1})	7.644	K (hr^{-1})	0.286	K_H ($h^{-1/2}$)	33.280	n	0.683
F12	R^2	0.998	R^2	0.822	R^2	0.968	R^2	0.985
	K (mg/h^{-1})	7.347	K (hr^{-1})	0.263	K_H ($h^{-1/2}$)	33.406	n	0.710
F13	R^2	0.993	R^2	0.938	R^2	0.988	R^2	0.986
	K (mg/h^{-1})	7.596	K (hr^{-1})	0.246	K_H ($h^{-1/2}$)	33.706	n	0.617
F14	R^2	0.986	R^2	0.851	R^2	0.983	R^2	0.983
	K (mg/h^{-1})	8.158	K (hr^{-1})	0.371	K_H ($h^{-1/2}$)	34.812	n	0.583
F15	R^2	0.991	R^2	0.889	R^2	0.988	R^2	0.988
	K (mg/h^{-1})	8.304	K (hr^{-1})	0.357	K_H ($h^{-1/2}$)	35.433	n	0.607
F16	R^2	0.998	R^2	0.895	R^2	0.968	R^2	0.982
	K (mg/h^{-1})	8.955	K (hr^{-1})	0.256	K_H ($h^{-1/2}$)	37.691	n	0.711

The "R^2" values (Table 11) 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–F16 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.

The release exponent 'n' was found to be between 0.58 to 0.711 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 nonfickian (anomalous) diffusion as the release mechanism. (Sato *et al.*, 2003; Dave, Amin and Patel, 2004).

Stability study

The accelerated stability study of optimized formulation is shown in table 12. 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 12: Cumulative % drug release & swelling index for F8 batch

Time (hr)	When prepared		After 6 months	
	C % DR	Swelling index	C%DR	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.

Invivo study

Based on the result of tablets, drug release and kinetics, formulation F8 of was selected for animal studies. Plasma concentrations of losartan potassium were determined by the HPLC method.

Mobile Phase: The pH of the mobile phase was adjusted to 6.0 with the addition of 0.1% v/v glacial acetic acid and the phase is a combination of 60:40 acetonitrile and water. Before usage, a 0.45 µm membrane filter was used to filter the mobile phase, which was then run at a flow rate of 1 ml/min, with the eluent being examined. The column effluent was monitored at

248 nm. Following an initial analysis of plasma samples containing various levels of drug, a calibration curve was created for the quantification of drug in plasma samples.

Calibration Curve

A 0.1 ml drug solution containing 0.1, 0.2, 0.4, 0.6, 0.8, and 1.0 g of drug was introduced to a series of tubes each holding 0.2 ml of plasma. One ml of acetonitrile was added to each tube, properly mixed, and centrifuged for 20 minutes at 5000 rpm. Acetonitrile was evaporated after the organic layer (0.5 ml) was being added into a dry tube. In order to reconstitute the dried residue, 0.5 ml of mobile phase (a 60:40 combination of acetonitrile and water with a pH adjustment of 0.1% v/v glacial acetic acid) was added. For HPLC analysis, 20 pi were then injected onto the column.The drug's plasma concentrations are listed in Table 13 and depicted in Figure 4 along with the associated peak regions. The estimate of losartan potassium in the plasma samples obtained during the pharmacokinetic analysis was done using this calibration curve. The calibration curve was used to assess 0.2 ml of plasma for drug content as previously mentioned.

Table 13: Calibration Curve for the Estimation of drug in Plasma Samples by HPLC Method

Concentration (µg/ 0.2 ml of plasma)	Mean Peak Area (mV.s)	RSD (%)
0.1	42.48	0.63
0.2	87.64	1.18
0.4	179.35	0.54
0.6	267.14	0.79
0.8	349.57	0.87
1.0	446.50	0.76

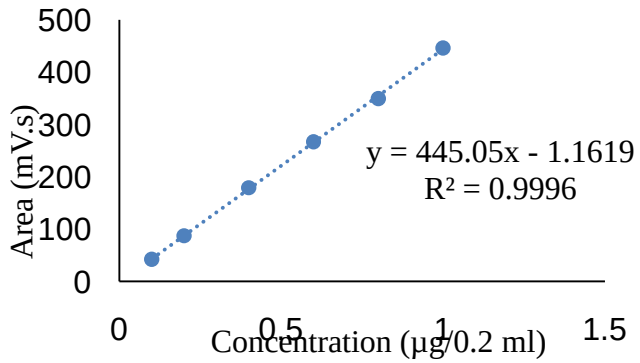

Figure 4: Calibration Curve for the Estimation of drug in Plasma Samples by HPLC Method

Animals were divided into 3 groups. Each group consists of 6 rabbits with wash out period of one month. First group is blank (control group), second group was administered with standard drug. Third group was administered with prepared formulation F8

The expandable tablet was administered orally to the rabbits. The blood samples (1 ml) were collected from marginal ear vein of rabbit at different time intervals (1, 2, 3, 4, 5, 6, 8, 10, 12, 24 hours) after administration of drugs. The material was put into heparinized tubes, which were then centrifuged for 10 minutes at 10,000 rpm. The drug analysis was carried out using the HPLC technique after the separated plasma was collected in dry tubes. PK solver add-in in Excel was used for calculation of various pharmacokinetic parameters.

Table 14: Plasma concentration of drug and formulation

Time (hours)	Plasma concentration of losartan potassium* (µg/ml)	
	Group 2**	Group 3***
1	1623.24±4.8	2654.9±3.39
2	1821.26±4.41	2715.94±3.04
3	2436.21±4.36	2899.03±4.1
4	2945.36±5.7	3124.85±4.14
5	2436.25±4.19	3167.58±3.92
6	2015.67±5.29	3527.67±3.74
8	1824.02±4.36	3625.32±4.78
10	1568.24±4.49	3674.15±3.36
12	1263.57±4.33	3827.16±4.03
18	986.35±4.27	3546.74±2.98
24	534.83±5.03	2948.34±4.32

* Average ± Standard deviation;

** Group administered with pure losartan potassium,

*** Group administered with formulation, F8

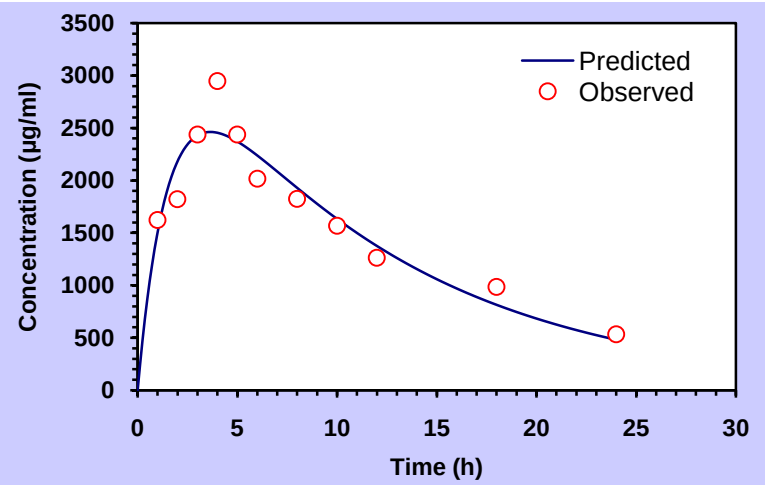

Figure 51: Predicted Vs. observed plasma concentration of pure losartan potassium

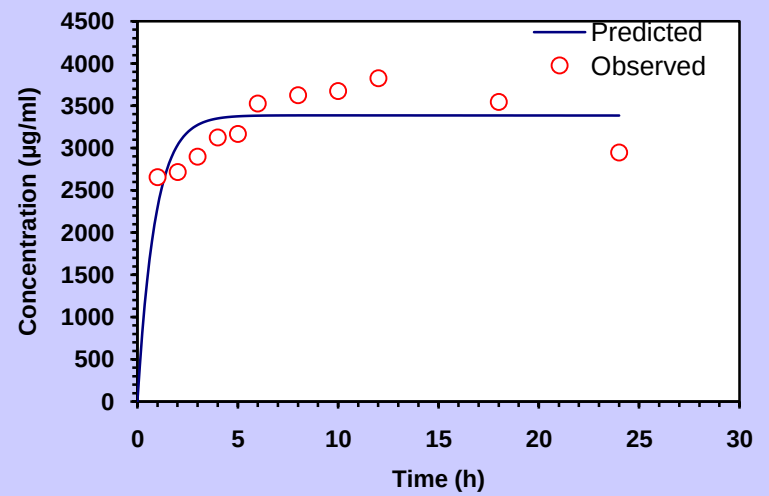

Figure 6: Predicted Vs. observed plasma concentration of formulation, F8

Table 15: An overview of the pharmacokinetic characteristics determined after oral administration of drug and formulation in Rabbits (n=6)

Pharmacokinetic Parameters	Group 2	Group 3
$t_{1/2}$ (h)	7.91	18.56
T_{max} (h)	3.64	9.12
C_{max}(µg/ml)	2460.31	3386.94
AUC(0-t) (µg/ml*h)	33183.61	78283.15
AUC(0-inf) (µg/ml*h)	38683.4	90724387
AUMC (µg/ml*h^2)	503566.2	769440.06
MRT (h)	13.01	26.78
K_a (h^{-1})	0.62	1.13

The observed concentration of different groups was in accordance with the predicted concentration, as depicted in figure 5 and 6. There was very less difference between observed concentration and predicted concentration, which indicates that the observed concentration is in sync with the predicted concentration. The pharmacokinetic parameters are shown in table no. 15. Elimination half-life ($t_{1/2}$) of pure drug was found to be 7.91 hour whereas it increased to 18.56 hour when administered by preparing floating tablets. MRT of drug formulation increased significantly as compared to pure drug. MRT of pure drug was found to be 13.01 hour whereas its expandable tablet MRT was found to be 26.78 hour. This may be due to expanding of formulation which helps the formulation to stay at stomach and significantly improve the mean residence time of drug in GIT.

CONCLUSION:

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 of time. In this study, one of the least reported approach, expandable drug delivery, was utilized. Losartan potassium expandable tablet was prepared by direct compression method. Various polymer concentrations were employed. In order to improve the drug's bioavailability and prolong its duration in the stomach, expandable losartan potassium tablets were prepared. Based on the results of evaluation it was found that evaluatory parameters of tablets were within the acceptable limit of Pharmacopoeia. Formulations with the codes F8 and F12 could only keep the drug's release continuing for 12 hours. 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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