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Research Article

Formulation, Development and Evaluation of Gastro-retentive Bilayer Tablet of Losartan Potassium.

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ABSTRACT
The aim of present study is to prepare gastro-retentive bilayer tablets of Losartan Potassium with an immediate release and a sustained release layer with an objective to increase gastric residence time, improve absorption, enhance the bioavailability and improve therapeutic efficacy, reduce dosage frequency. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for single drug as immediate dose and maintenance dose. The immediate release layer was prepared using super disintegrant crospovidone and sustained release layer is formulated with different polymers such as xanthum gum, guar gum and hydroxy propyl methyl cellulose K100M, individually in different concentrations and in combinations. The preformulation studies of formulations showed good flow properties and feasibility for direct compression. The compressed bilayered tablets were evaluated for hardness, friability, weight variation, drug content uniformity and in vitro drug release. Formulation contained combination of xanthum gum and guar gum was optimized which showed prolonged release of Losartan Potassium for about 24 hrs. No significant change either in physical appearance, drug content or in dissolution pattern was observed after storing at 40°C/75% relative humidity (RH) for 1 month in respect of the optimized formulation. FTIR studies revealed no chemical interaction between drug and adjuvant as well as adjuvant and adjuvant which indicates the stability of drug in tablets. The mechanism of drug release was found to be non-fickian diffusion.

KEYWORDS
Gastro retentive Drug Delivery System (GRDDS), Bilayer Technology, Bioavailability, Xanthan Gum, Guar Gum, Mucoadhesion.

1. INTRODUCTION

The goal of any delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Oral drug administration has been the predominant route for drug delivery; numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate.[1] From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached. In conventional oral drug, delivery of drugs resides for a shorter period time in absorption window, so bioavailability is less [2].

Losartan potassium possess short biological half-life (1.5- 2 hrs), which demands frequent administration usually thrice a day leading to patient noncompliance exposing him to risk of side effects. In order to overcome this, Losartan potassium sustained release dosage forms are formulated as bilayered tablet which comprises of two layers among which the first layer is immediate release layer and the second layer is sustained release layer. The immediate release portion ensures quicker onset of action by eliciting MEC in less time while the sustained release fractions maintain the same levels offering once a day convenient dosing. The current research is to formulate and evaluate an ideal bilayer matrix tablet of sustained release profile by using suitable methods by using different polymers [3].

Gastro-Retentive drug Delivery System (GRDDS) which provides effectives plasma drugs concentration for longer periods thereby reducing the dosing frequency are being formulated. It also has an advantage of reducing fluctuation in plasma drug concentration by delivering the drug in a controlled manner [5].

1.1 Bio/Mucoadhesive Systems

They bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The epithelial adhesive properties of mucin have been applied in the development of Gastro retentive drug delivery systems [4].

1.2 Drug Profile [5]

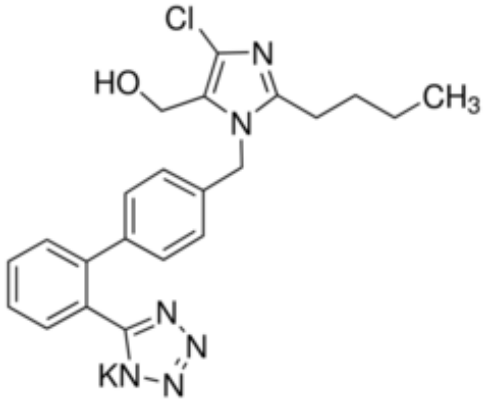

Fig.1 Structure of Losartan Potassium.

Losartan Potassium is the potassium salt of losartan, a non-peptide angiotensin II receptor antagonist with antihypertensive activity. Losartan selectively and competitively binds to the angiotensin II receptor (type AT1) and blocks the binding of angiotensin II to the receptor, thus promoting vasodilatation and counteracting the effects of aldosterone. Converted from angiotensin I by angiotensin-converting enzyme (ACE), angiotensin II stimulates the adrenal cortex to synthesize and secrete aldosterone, decreasing sodium excretion and increasing potassium excretion, and acts as a vasoconstrictor in vascular smooth muscles. [5]

2. MATERIALS AND METHODS

2.1. Materials [6-9]

Pharmaceutical grade of Losartan Potassium was Gift Sample from Lupin Research Park, Pune. Xanthan gum was obtained as Gift sample from CpKelko PVT. LTD, Gaur Gum was procured Sample from Nature Vit., Jodhpur.

2.2. Calibration curve of Losartan Potassium in 6.8 pH phosphate buffer solution

UV scanning and standard calibration of Losartan Potassium was performed by using Shimadzu double beam UV Spectrophotometer (Shimazdu 1280, Japan). The maximum absorption wavelength was recorded in phosphate buffer pH 6.8 at wavelength 205nm.

2.3. Preparation of standard solution

20 mg of Losartan Potassium was dissolved in 100 ml 0.1N Hcl to give a concentration of 8 µg/ml

2.4. Preparation of stock solution

From standard solution take 0.5ml, 1, 2, 3, 4 ml of solution in 10 ml of volumetric flask. The volume was made up to mark with 0.1N Hcl to produce concentration as 1, 2, 4, 6, 8 µg/ml of Losartan Potassium respectively. The absorbance of prepared sample of Losartan Potassium was measured at 205 nm in Shimadzu UV spectrophotometer against 0.1 N Hcl as blank. By using same procedure Calibration curve of Losartan Potassium in distilled water, 0.1N HCl and Phosphate buffer pH 6.8 was plotted.

Beers and Lamberts range: 1-8 µg/ ml.

The absorbance: λ max 205 nm.

2.5. Drug-Excipient compatibility studies [10-12]

The infrared absorption spectra of pure drug, pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 cm^{-1} to 400 cm^{-1} by using FT-IR 8400 (Bruker Advance).DSC study of pure drug, polymer and physical mixture of polymer and drug were performed.

2.6. Dose Calculation

The total dose of Losartan Potassium for the loading dose in immediate layer and maintenance dose in sustained release layer of bilayer tablet was calculated by following equation using available pharmacokinetic data,

Dt. = Dose (1 + 0.693 × t/t1/2) ---Equation 1

Where,

Dt = Total dose of drug

Dose = dose of immediate release part

t = Time (hours) during which the sustained release is desired (24 hr.)

$t_{1/2}$ = Half-life of drug (2.5 hr)

Losartan potassium:

50 = Dose [1+ (0.693 ×24) /2.5)], Dose = 7.60 mg losartan potassium

Hence, in present formulations each bilayer tablet contain total dose of 50 mg which includes 7.0 mg as a loading dose in immediate release layer and 43 mg of Losartan Potassium as maintenance dose in sustained release layer.

2.7. Method of Preparation of Bilayer tablet [13-15]

2.7.1. Formulation of the Gastro-Retentive Bilayer Tablet

2.7.1.1. Development of Sustained Release (SR) layer

Sustained release tablet formulated by non-aqueous wet granulation method. The tablets were of matrix type made in order to achieve desired thickness, hardness and drug release. The sustained release granules were prepared by wet granulation technique. Different polymers such as HPMC K100M, Guar Gum and Xanthum gum are used in different ratios i.e.(1:1, 1:2, 1:3) use to optimized the polymer.

2.7.1.2. Development of Immediate Release (IR) layer

An immediate release layer of the tablet was formulated using direct compression method. Different formulations were made in order to achieve desired disintegration time, drug release, friability, thickness and hardness. Different super disintegrants used to achieve fast disintegration and immediate release of drug for initial loading dose. In Immediate release layer use of Sodium starch glycolate, Croscarmellose sodium & crospovidone in 2, 4 and 6% conc. in formula respectively.

2.8. Formulation of bilayer tablet of Losartan Potassium

The prepared blends of both the layers were compressed on a bilayer compression machine on 11mm flat round shaped punch. The hardness was 8- 9kg/cm^2 and the tablet thickness was 3.8-4.0mm. Both the prepared blend came from two different hoppers to two different feed frames where they occupied the die cavity. The bottom layer was first compressed with lower pressure, which was then followed by filling of the die cavity by the upper layer granules. The final compression was done only after both the granules occupied the die cavity one on top of the other. Both the layers were identified on the basis of color since the immediate release layer had light reddish color and the sustain release layer has white color.

Table 1. Composition of final bilayer tablet of Losartan Potassium.

Ingredients	**Specification**	**Qty. in mg/tab**	**Use in formulation**
Immediate Release Layer (F9)			
Losartan Potassium	USP	7.0	Active Ingredient

MCC PH 101	USP/ Ph. Eur	82.0	Filler
Crospovidone	USP/ Ph. Eur	9.0	Super disintegrants
Magnesium Stearate	EP/ Ph. Eur	1.5	Lubricant
Red Iron oxide E172	USP	0.5	Colour
Total Weight (mg)		100	
Sustained Release Layer (GX3)			
Losartan Potassium	USP	43	Active Ingredient
Gaur gum	_	75	Mucoadhesive polymer
Xanthan gum	USP	75	Mucoadhesive polymer
PVP	USP	15	Binder
Granulac 200	USP/Ph. Eur	86	Diluent
Aerosil 200	USP/ Ph. Eur	3.0	Glidant
Magnesium Stearate	EP/ Ph. Eur.	3.0	Lubricant
Total Weight (mg)	NA	300	
Total wt. for Bilayer tablet	NA	400 mg	

2.9. Evaluation of Tablets [16-20]

2.9.1. Physical evaluation

Twenty tablets from each batch were evaluated for uniformity in tablet weight and thickness. Twenty tablets from each batch were examined for friability using a Roche type friabilator (Electrolab Pvt. Ltd., India) and hardness using a Monsanto type hardness tester (Lab India).

2.9.2. Uniformity of content

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1N HCl. Then suitable dilutions were made and absorbance at 205 nm wavelength was taken by using a UV visible spectrophotometer. Drug content was calculated by using absorbance at wavelength 205 nm. The results obtained were compared with USP standards.

2.9.3. Swelling Index

Tablets were placed in the dissolution medium and their respective weight was checked at 0h, 2h, 4h, 6h, 8h, 12h up to 24 hr. The tablet was taken out from the dissolution medium and the excess water was allowed to drain out and the tablet was weighed. The swelling index was calculated by using following formula,

Swelling index = W1 - W0/ W1 ---Equation 2

2.9.4. In-Vitro Drug Release Study [20]

The *in vitro* dissolution was carried out using USP Dissolution testing apparatus type-II (Paddle method).The tablets were placed in the 0.1N hydrochloric acid for first 1 hours and pH 6.8 phosphate buffers for next 23 hours respectively, then the apparatus was run at 37°C ± 0.5°C and a rotating speed of 50 rpm in a 900 ml dissolution medium. The 10 ml aliquots were withdrawn at intervals of 0.30 min, 1, 2, 3, 4, 5, 6, 7, 8,9, 10,…24 hours and replacement was done each

time with equal amounts of fresh dissolution medium maintained at same temperature. Each 10 ml aliquot was filtered through Whatman filter paper (No.41). 5 ml of sample was diluted to 10 ml 0.1N hydrochloric acid for first 1 hour and then with pH 6.8 phosphate buffers for next 24 hours and absorbance was measured at 205 nm using a Shimadzu-1280 UV spectrophotometer. Drug concentrations in the sample were determined from standard calibration curve.

2.9.5. Mucoadhesion Test [23]

The mucoadhesion was determined by measuring the maximal force required to separate the test material from the mucosal surface. The mucosal surface of goat's small intestine was used in the test. The goat intestine mucosa is relatively free of intestinal content, and provided a macroscopically flat and uniform surface. The middle section, discarding the first 40-50 mm at either ends of fresh intestine was used. This was cut into 2 cm lengths, opened longitudinally to expose the inner mucosal surface, and fixed at the upper part of instrument with a two-sided adhesive tape. The intestine was kept in phosphate buffer solution of pH 6.8 during the preparation time. The texture analyser (CT3 Brookfield Texture analyzer) and associated software was introduced for the measurement of mucoadhesion. Wet mass of test material was filled in a metal cup (height 7mm, diameter 20.2mm), and the mucosa was placed to the upper stamp (diameter 14mm). 30µl of pH 6.8 isotonic phosphate buffer solution was spread with a pipette on the mucosa to standardize hydration prior to testing, and then the mucosa was brought into contact with the test material. After a preload of 1~2N for every 1hr. of contact time, the mucosa was raised at a constant speed of 1 mm/s and the detachment force was recorded.

Since, this value is for contact time area 1.5cm^2 between upper part and test sample, the mucoadhesion force per area was calculated & expressed as 'Mucoadhesion' (N/cm^2).

3. RESULTS AND DISCUSSION

3.1. Calibration curve of Losartan Potassium in phosphate buffer 6.8 Ph.

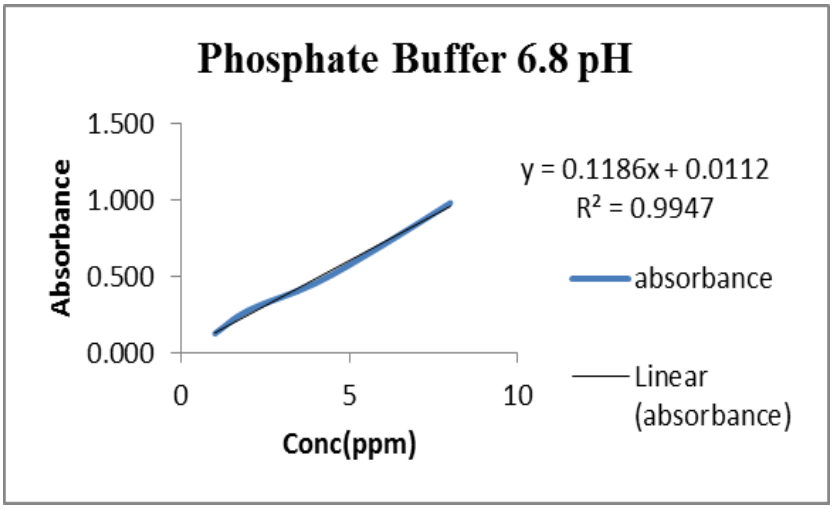

Fig. 2. Calibration curve of Losartan Potassium (Phosphate buffer).

Table 2. Calibration of losartan potassium.

Calibration Losartan in pH 6.8 phosphate buffer solution		
Sr. No.	**Concentration (ppm)**	**Absorbance**
1	1	0.126
2	2	0.278
3	4	0.456
4	6	0.706
5	8	0.980

3.2 Spectral studies:

The observed peak and their functional group are given in Table 2. The IR spectrum (Fig. 4) of losartan potassium showed similar characteristics peaks to that of reported IR spectrum of Losartan potassium. From the FTIR study the sample was authenticated. The IR spectra of pure losartan potassium drug showed the characteristic absorption bands and drug-polymer interaction not observed in the FTIR spectra of the powder mixture of drug and polymers (Xanthan gum and guar gum). Since it is confirmed that the drug and polymers are compatible with each others.

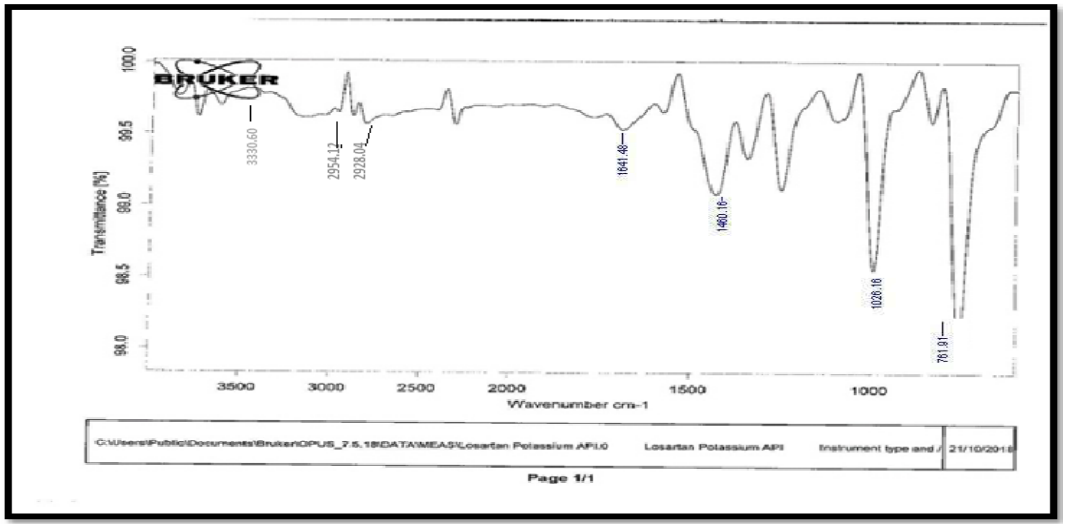

Fig. 3. FTIR spectrum of pure drug losartan potassium.

Table 3. Functional group and observed peak value of losartan Potassium.

Observed Peak (cm^{-1})	**Standard peak (cm^{-1})**	**Bond**	**Functional group**
761.91,1026.16,	**800-830**	**C-H Stretch**	Alkenes
1460.16,1641.48	**800-1200**	**C-H Bend in plane**	Alkynes

2953.12,3150.52	**1300-1500**	**C-H Bend out of**	Alkanes
3250.31,3271.88	**1600-1900**	**C-C Stretch**	Aromatic rings
3330.60	**2100-2400**	**C=O Stretch**	Aldehydes
	1000-1400	**C=N Stretch**	Alcohol
	3000-3700	**O-H Stretch**	Ethers
		N-H Stretch	Monomeric alcohols and phenols
			Hydrogen bonded

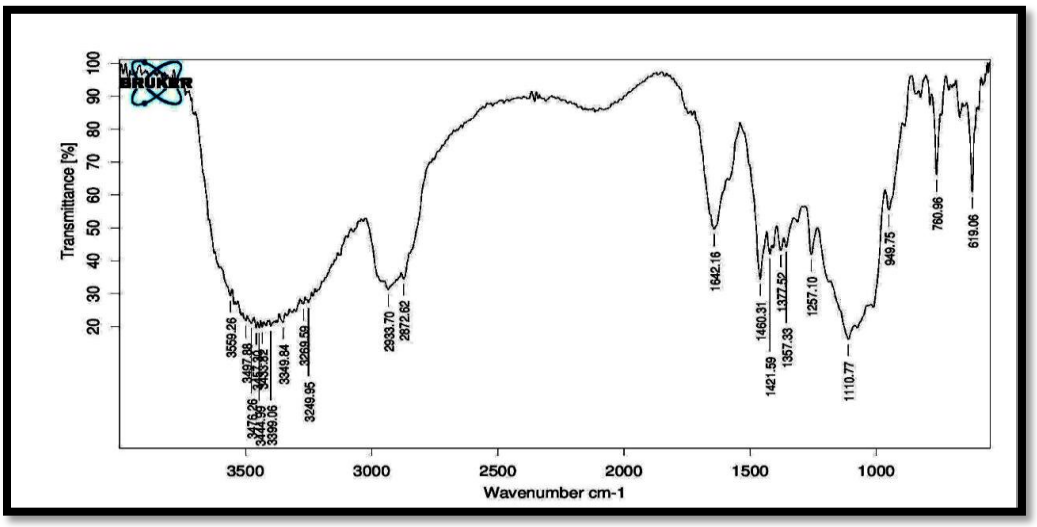

Fig. 4. FTIR of Losartan potassium and polymer.

Table 4. Functional group and major peak observed in Losartan Potassium +Polymer.

Observed Peak (cm^{-1})	**Standard peak (cm^{-1})**	**Bond**	**Functional group**
902.52	**800-830**	**C-H Stretch**	Alkenes
1145.51	**800-1200**	**C-H Bend in plane**	Alkynes
1457.1, 1346.07	**1300-1500**		Alkanes
1658.48,1909.16	**1600-1900**	**C-H Bend out of**	Aromatic rings
3250.31,	**2100-2400**		Aldehydes
3271.88	**1000-1400**	**C-C Stretch**	Alcohol
3330.60	**3000-3700**	**C=O Stretch**	Ethers
		C=N Stretch	Monomeric alcohols
		O-H Stretch	and
		N-H Stretch	phenols
			Hydrogen bonded

3.3. DSC study

The DSC thermogram of Losartan Potassium (Fig. 3) represents sharp endothermic peak at 271.69 ^{o}C which corresponding to melting of losartan potassium ranging from 265-275^{o}C respectively. The DSC thermogram of pure losartan potassium drug showed the characteristic melting point range and drug-polymer interaction not observed in the DSC thermogram of the powder mixture of drug and polymers (Xanthan gum). Since it is confirmed that the drug and polymers (xanthan gum) are compatible with each others.

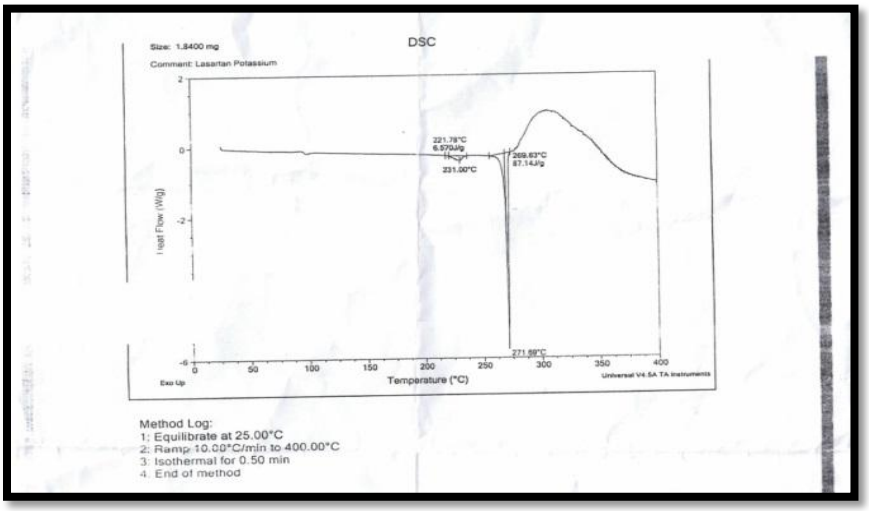

Fig. 5: DSC of Losartan potassium

3.4. Pre-compression Evaluation for Sustained Release layer tablet

Table 5. Preformulation Study of Sustained Release Layer blend.

Formulation Code	Bulk Density g/mL *	Tapped density g/mL *	Compressibility Index (%)*	Hausner's Ratio *	Angle of Repose (Degree)
G1	0.456 ±0.01	0.577±0.012	22.50±0.05	1.26±0.02	24.0±0.03
G2	0.452±0.001	0.576±0.011	21.52±0.06	1.28±0.02	26.5±0.02
G3	0.422±0.005	0.530±0.013	20.37±0.03	1.20±0.04	28.0±0.04
X1	0.460±0.004	0.590±0.008	22.02±0.50	1.28±0.01	24.0±0.06
X2	0.418±0.005	0.529±0.006	20.98±0.04	1.19±0.02	27.5±0.03
X3	0.454 ±0.01	0.578±0.012	21.45±0.02	1.27±0.02	28.5±0.03
K1	0.457±0.001	0.585±0.011	21.88±0.05	1.28±0.02	24.5±0.04
K2	0.421±0.005	0.532±0.013	20.86±0.03	1.21±0.04	25.5±0.01
K3	0.462±0.004	0.595±0.008	22.35±0.04	1.29±0.01	27.5±0.03
GX1	0.490±0.005	0.612±0.006	19.93±0.07	1.24±0.02	25.0±0.06
GX2	0.474 ±0.01	0.590±0.012	19.66±0.03	1.22±0.02	23.5±0.07
GX3	0.492±0.001	0.610±0.011	19.34±0.04	1.21±0.02	28.0±0.09

GK1	0.496±0.005	0.598±0.013	17.05±0.02	1.18±0.04	23.5±0.03
GK2	0.502±0.004	0.620±0.008	19.04±0.02	1.20±0.01	24.5±0.03
GK3	0.510±0.005	0.625±0.006	18.40±0.06	1.21±0.02	27.5±0.05
XK1	0.508±0.004	0.618±0.008	17.79±0.03	1.19±0.01	21.5±0.05

From above all formulation Batch GX-3 was shows good flow property, bulk density 0.492 gm/ml, tapped density -0.610 gm/ml, angle of repose 28^0, and compressibility index is 19.24.

3.5 Post compression parameter of Sustained Release (SR) layer tablet

The post-compression parameter were evaluated after compression of Sustained release layer tablet like weight variation test, friability, thickness, hardness, Drug content for SR layer tablet of Losartan potassium**.**

3.5.1 Swelling index

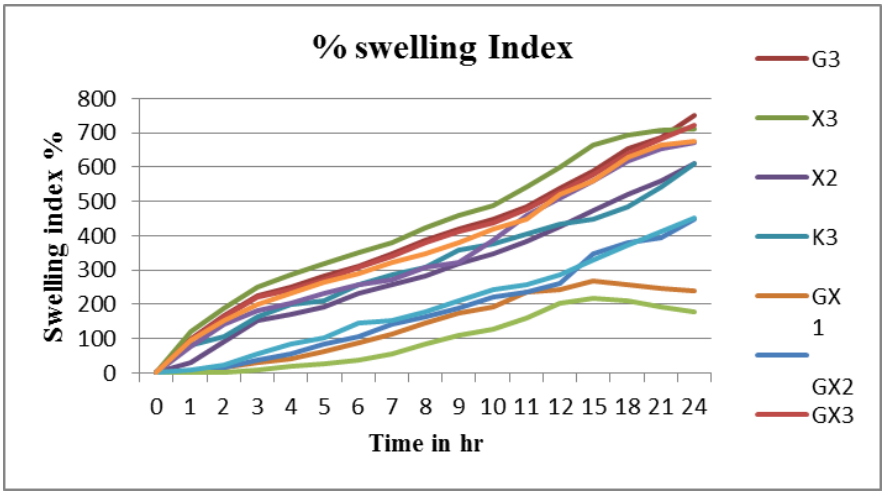

Fig. 6. Swelling index of sustained release layer.

3.5.2 Drug content for Sustained Release layer of Losartan potassium.

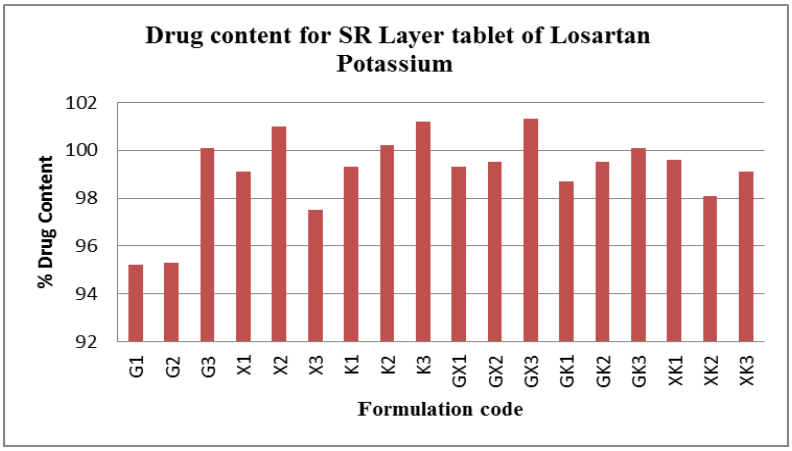

Fig.7. Drug content for SR layer.

3.5.3.Mucoadhesion test

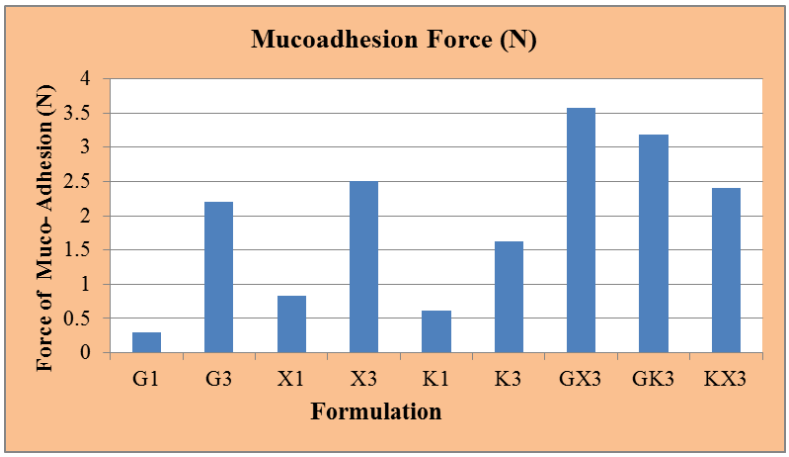

Fig. 8. Mucoadhesion strength of sustained release mucoadhesive layer.

3.6. Pre-Compression Evaluation for Immediate Release Layer Tablet

Table 6. Pre-Compression Study of Immediate Layer Blends.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.491±0.03	0.570±0.05	21.40±0.2	16.1±0.02	1.12±0.03
F2	0.552±0.04	0.561±0.03	22.30±0.4	15.9±0.04	1.11±0.01
F3	0.513±0.05	0.570±0.04	19.76±0.6	17.6±0.01	1.19±0.04
F4	0.554±0.06	0.603±0.06	18.92±0.3	17.6±0.06	1.21±0.05
F5	0.522±0.03	0.562±0.04	17.50±0.4	14.8±0.06	1.18±0.04
F6	0.531±0.05	0.581±0.05	21.40±0.5	15.4±0.09	1.21±0.07
F7	0.512±0.06	0.521±0.02	19.28±0.6	14.4±0.08	1.16±0.04
F8	0.501±0.08	0.544±0.06	17.60±0.4	16.4±0.09	1.19±0.06
F9	0.493±0.07	0.551±0.03	18.20±0.6	13.2±0.07	1.18±0.08

* Mean ± S.D (n = 3)

3.7. Post-compression parameter

3.7.1 Drug Release study for immediate release layer of tablet

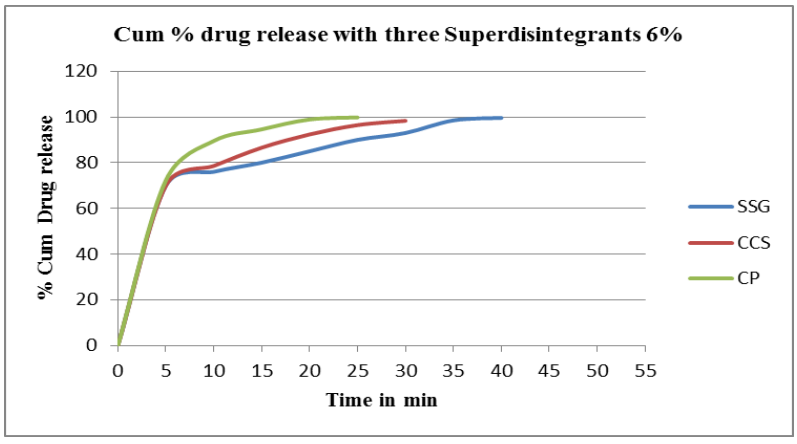

Fig. 9. Drug release study of immediate release layer of bilayer tablet.

3.7. Evaluation of Bilayer Tablet of Losartan Potassium

3.7.1. Pre and post compression parameters

Table 7. Evaluation parameter of Gastro retentive Mucoadhesive bilayer tablet of Losartan Potassium.

Sr. No.	Parameter	Result
1	Colour	Off red(IR),off White(SR)
1	Weight	Complies
2	Thickness (mm)	3.50±0.5
3	Hardness (kg/cm^2)	8.23±1.2
4	Friability	NMT 1%
5	Disintegration	20±5 min
6	Content of uniformity	99.98 ±1.2 %
7	Swelling Index (%)	740 ± 20%
8	Mucoadhesive Strength	3.7± 1.2

All values in Mean ±SD, n=3

3.*7.2 In-Vitro drug release study*

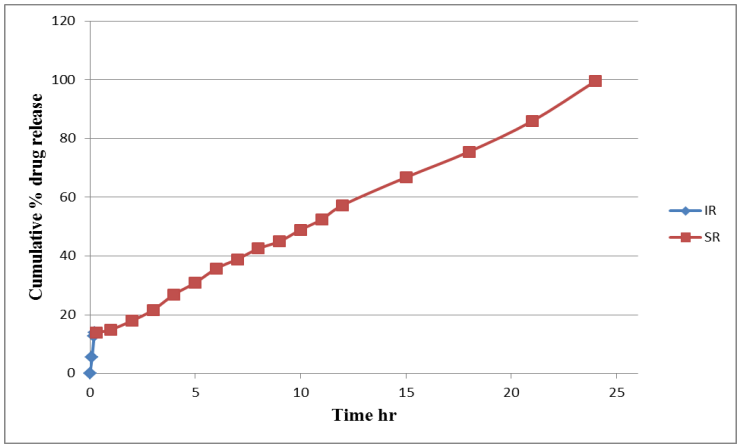

Fig.10. In-vitro Drug Release study for Gastroretentive Bilayer tablet.

3.7.3. Optimized formulation follows Zero order Release kinetics

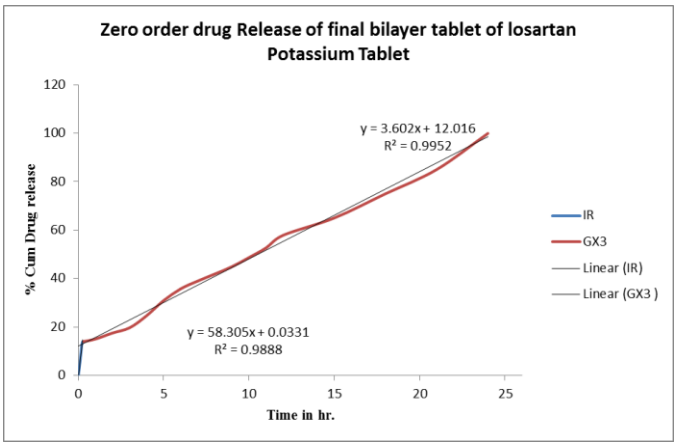

Fig. 11. Zero order drug release from final bilayer tablet of Losartan Potassium.

3.8. Stability Studies [25-28]

The result of stability study of optimized formulation shown in table 6 and figure 13 was done at 40°C/75 % RH for 1 month. There was no significant changes in appearance Hardness, Swelling index, mucoadhesive strength, Drug release of optimized formulation. Thus the formulation of bilayer tablet with F9 (Immediate Release) and GX-3 (Sustained Release) of losartan potassium was found to be stable at end of stability study.

4. CONCLUSION

The Losartan Potassium having narrow absorption window, short half-life so, need to increase residence time of drug at site of absorption. The present research was carried out to develop a Gastro-retentive bilayer tablet of Losartan Potassium to increase gastric residence time of losartan potassium, improve absorption improve bioavailability using superdisintegrant Crospovidone XL(6%) for loading dose and combination of Xanthan Gum and Gaur Gum (1:3)for maintenance dose. The tablets showed an initial burst release to provide the loading dose of drug followed by sustained release up to 24 hours. The gastro retentive tablet was improve gastric residence time of drug, result in improve absorption of Losartan Potassium at site absorption. So, it provides sustained release action of Losartan Potassium for longer period of time. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance. Hence it can be concluded that Xanthum and guar gum combination proved prolonged release of Losartan Potassium upto 24 hrs.

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