International Journal for Advanced Review and Research in Pharmacy (IJARRP)

FORMULATION AND EVALUATION OF GASTRORETENTIVE MUCOADHESIVE BILAYER TABLETS OF LOSARTAN POTASSIUM

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Abstract
The objective of the present study was to develop and evaluate gastro retentive mucoadhesive bilayered tablets of losartan potassium. Bilayered tablets were prepared by direct compression method by using crosscarmellose sodium (CCS) and sodium starch glycolate (SSG) in different strengths (4%, 5% and 6% w/w) for immediate release (loading dose). The IR formulation containing CCS (6% w/w) showed better drug release. Mucoadhesive materials such as sodium alginate, guar gum and xanthan gum (natural gums) in different strengths (15%, 25%, and 35% w/w) were used for controlled release (maintenance dose) layer. FTIR studies revealed that there was no interaction between the drug and excipients used in the study. Precompression parameters like angle of repose, bulk density, tapped density Carr's index and Hausner's ratio were within the limits. Postcompression parameters thickness, friability, weight variation test and drug content compiled with pharmacopeia limit for tablets. Further, bilayered tablets were evaluated for exvivo mucoadhesion time, mucoadhesive strength and swelling index. In-vitro release studies were carried out using USP type II (paddle) dissolution apparatus at 50 rpm by taking 900ml of 0.1N HCl (pH 1.2) as dissolution medium at 37±0.5°C for 24 hrs. The result of in-vitro dissolution studies indicated bilayered tablets containing 15%w/w of guar gum and 20 %w/w of xanthan gum in combination (F12) has better control release over 24 hrs. The release of Losartan potassium was found to follow Korse-Meyer Peppas diffusion model, zero order kinetics and the drug shows anomalous (Non-Fickian) diffusion.

Key words: Losartan potassium, Bilayered tablets, Controlled release, Mucoadhesive materials.

1. Introduction

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration as well as to recover the side effects. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. It enhances bioavailability, reduces drug wastage and improves solubility for drugs that are poorly soluble in a high pH environment [1, 2, 3].

Generally, conventional extended release dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. Immediate release drug delivery system is intended to disintegrate rapidly and exhibit instant drug release. It is associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the drug delivery system several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion [4, 5]. A relatively constant plasma level of a drug is often required to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve especially for drug diffusion and absorption varies along the gastrointestinal tract. On the basis of these considerations, we have proposed a bilayer tablet, in which one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a modified release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from immediate releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the control release layer [6, 7, 8].

2. Objective

The objective of the present study was to formulate and evaluate the bilayered tablet having immediate and controlled release layer containing Losartan potassium by using different mucoadhesive gums. To estimate the preformulation, pre compression and post compression properties of the various formulations.

3. Materials and methods

3.1. Materials

Losartan potassium was received as a gift sample from Dr. Reddy's lab, Ltd, Hyderabad. Sodium alginate, guar gum and xanthan gum (X175M) were obtained from krystal colloid Ltd., Mumbai. Mico crystalline cellulose (PH102), PVP K-30, Sodium starch glycol

ate and Cross carmellose sodium were obtained from Loba chemicals, Pvt, Ltd. Magnesium stearate and Talc were obtained from S.D Fine Chem., Mumbai. All the reagents and chemicals used were of analytical grade.

3.2 Methods

3.2.1 Drug Excipient Compatibility Studies [9, 10]

Compatibility study was carried for pure Losartan potassium and combination of Losartan potassium with excipients. Fourier transfer infra red (FTIR) spectroscopic (shimadzu, Japan) studies were carried out by approximately diluting the drug sample with dried potassium bromide (1:100) and acquiring infrared (IR) spectrum in the range of 400 to 4000cm-1 .

3.2.2 Calculation of Loading and Maintenance Dose [11]

The total dose of Losartan potassium for a once daily controlled release formulation was calculated by using available pharmacokinetic data.

Volume of distribution (Vd) = 34L, Cmax = 0.25 mg/L, Loading dose (di) = Cmax * Vd, therefore (di) = 8.5 mg ≡ 10 mg.

Total dose (Td) = di (1+ 0.693*t/t1/2)

Where t = time during which controlled release is required (24hrs), t1/2 = biological half life of the drug (2hrs).

Therefore Td = 79.186 ≡ 80mg.

Maintenance dose (control release dose), Dm is calculated from the following formula.

Td = Di + Dm, Dm = Td- Di, therefore Dm= 70mg

3.2.3 Formulation of Bilayer tablet

Various formulation batches of Losartan potassium were prepared using 4%, 5% and 6% superdisintegrants (Ac-Di-sol and Sodium starch glycolate). Those formulations showing good results were used for the preparation of immediate release layer. Losartan potassium, MCC and super disintegrants were mixed properly in a mortar according to compositions. The resulting blend was passed through sieve # 60. Accurately weighed 100mg of powder blend fed manually into each die of 10 station Cadmach tablet compression machine and compressed by using 8mm flat faced punch by direct compression method. Compression force was kept constant for all formulations.

The controlled release layer was prepared by direct compression method. Drug and various concentrations of polymer were mixed properly in a mortar. Later, MCC and PVPK-30 were added. The resulting blend was passed through sieve #60. Initially IR powder blend was fed manually into the die of 10 station Cad mach tablet compression machine and compressed at low compression force to form uniform layer. Subsequently controlled release layer powder was added over that layer and completely compressed on rotary tablet punching machine by using flat faced punch 8mm.

3.2.4 Evaluation of powder blend

Angle of repose

Static angle of repose was determined according to the fixed funnel method; where by accurately weighed powder (3g) were carefully poured through the funnel with its tip at 2cm height (H), until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter 2R of the base for the powder cone was measured and the angle of repose (Ø) was calculated using the following equation.

$$\tan(\text{Ø}) = H/R$$

Bulk density and tapped density

Both poured bulk and tapped bulk densities were determined, where by a quantity (3g) of powder blend from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2-second intervals. The tapping was continued until no further change in the volume was noted.

Carr's Compressibility Index and Hausner's ratio

The compressibility of the powder was determined by carr's compressibility index (CI). The Hausner's ratio (HR) is number that is correlated to the flow ability of powder.

$$CI = ((TD-BD)/TD)*100$$

where TD= tapped density and

BD= bulk density.

$$HR = (100/100-CI)$$

3.2.5 Evaluation of tablets [12, 13, 14]

The prepared bilayer tablets were evaluated for hardness, thickness, friability, weight variation test and drug content. Hardness of tablets was tested using Monsanto hardness tester (Serve well, Bangalore). Friability of the tablets was determined in a Roche Friabilator (Electro lab, Mumbai). The thickness of tablets was measured by vernier calipers. Weight variation test was performed according to official method. Drug content for Losartan potassium was carried out by measuring the absorbance of samples at 238nm using Shimadzu UV-1800 spectrophotometer Japan and

comparing the content from a calibration curve of Losartan potassium.

3.2.6 Invitro drug release study [15, 16]

Release of the prepared tablets was determined up to 24hr using USP XX1V (typeII) dissolution rate test apparatus (Model TDT 6P Electro lab Mumbai). 900 ml of 0.1N HCl was used as dissolution medium. The rotation of paddle was fixed at 50rpm and the temperature of 37±0.5oC was maintained throughout the experiment. Samples of 5ml were withdrawn at known time intervals and were placed with same volume of fresh dissolution media after each with drawn. The samples were analyzed spectrophotometrically for drug contents on double beam UV/Visible spectrophotometer (Shimadzu 1800 Japan) at 238nm.

3.2.7 Swelling studies [17, 18]

The swelling studies were carried out by determining the swelling index using USP type I apparatus (basket) and revolved at 50 rpm for 6hr. At intervals of 1hr, tablets were removed from basket and weighed (Wt). The swelling index was calculated by using the formula given below.

Swelling index = ((Wt-Wo)/Wo)*100

Wt= weight of swollen tablet at each time interval, Wo= initial weight of tablet.

3.2.8 Invitro Mucoadhesion studies [19]

The mucoadhesive strength of tablets was measured on modified physical balance. The apparatus consist of a modified double beam physical balance in which the right and left pan were with lighter pans. The left side of the balance was made heavier than the right side by placing a 5g weight on left side pan. Teflon block fabricated with an upward protrusion on one side was kept in the beaker, which was then placed below the left-hand set of the balance. The goat gastric mucus membrane was used as the model membrane and 0.1 N HCl buffer solution was used as the moistening fluid. The mucus membrane was tied to a Teflon- coated glass slide and this slide was fixed over the protrusion in the Teflon block using a thread. The block was then placed in a beaker containing 0.1 N HCl buffer solutions at level that just touches the membrane inorder to moisten the membrane. By keeping a 5g weight on the right pan that two sides were balanced. The beaker with the Teflon block was kept below the left hand set up of the balance. The tablet was stuck on to the lower side of the left hand side pan. 5 g weight from the right pan was then removed; this lowers the left pan along with the tablet over the membrane with the weight of 5g. This was kept undisturbed for 3 min. then the weight on the right hand side was added in an increment of 0.5 g until the tablet just separates from the membrane surface. The excess weight on the right pan i.e. total weight minus 5g was taken as the measure of the mucoadhesive strength. From the mucoadhesive strength, the force of adhesion was calculated by using following formula.

Force of adhesion (N) = (Mucoadhesive strength *9.81)/1000.

3.2.9 Ex vivo mucoadhesion time

The exvivo mucoadhesion time studies were performed (in triplicate) after application of tablets on freshly cut goat stomach mucosa. The mucosa was fixed on a glass slide using cyanoacrylate adhesive and kept in a slanting position in the beaker. A side of each tablet was wetted with 50µl fluid and was attached to the mucosa by applying a light force with a finger tip for 20 s. the beaker was filled with 900 ml of simulated gastric fluid and kept at 37±0.5oC, after 2 minutes a stirring rate of 75 rpm was applied to simulate the stomach. Tablet behaviour and mucoadhesive time were monitored until complete detachment or dissolution occurred.

3.2.10 Stability studies [20]

The stability study of the formulation F12 was carried out according to ICH guidelines at 40 ± 2o C / 75 ± 5% RH for one month by storing the samples in stability chamber (Lab-care. Mumbai).

Table 1: Formulation development of immediate release layer

Ingredients (g)	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**
Losartan potassium	10	10	10	10	10	10
Ac-Di-Sol	4	-	5	-	6	-
Sodium starch glycol ate	-	4	-	5	-	6
MCC PH 102	83.75	83.75	82.75	82.75	81.75	81.75
Color	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Total weight	100	100	100	100	100	100

Figure 1: Comparitive dissolution profiles of immediate release layer.

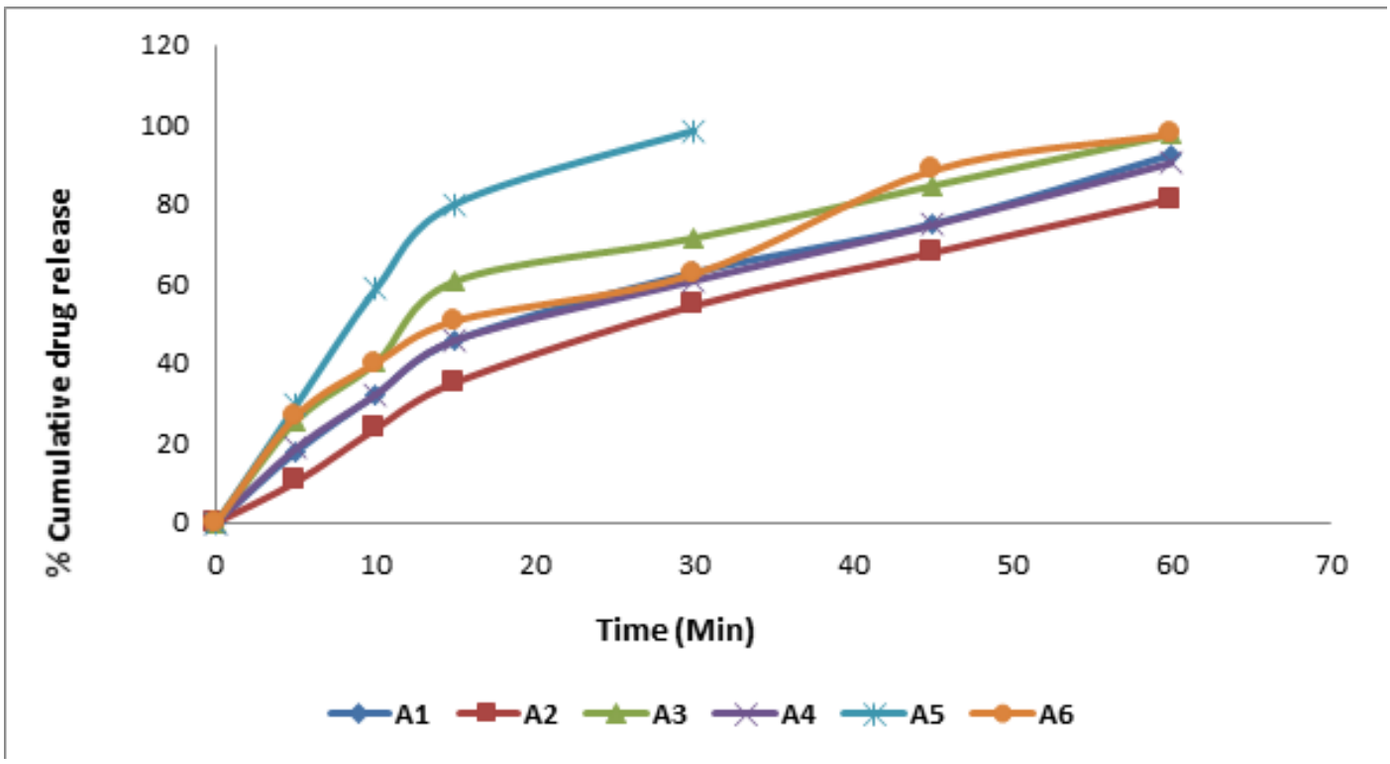


Table 2: Formulations for Losartan potassium bilayered tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
IMMEDIATE RELEASE COMPONENT												
Losartan potassium	10	10	10	10	10	10	10	10	10	10	10	10
Ac-Di-Sol	6	6	6	6	6	6	6	6	6	6	6	6
MCC PH 102	81.75	81.75	81.75	81.75	81.75	81.75	81.75	81.75	81.75	81.75	81.75	81.75
Color	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100	100	100	100	100
CONTROL RELEASE COMPONENT												
Losartan potassium	70	70	70	70	70	70	70	70	70	70	70	70
Sodium alginate	45	-	-	75	-	-	105	-	-	45	45	-
Guar gum	-	45	-	-	75	-	-	105	-	60	-	45
Xanthan gum	-	-	45	-	-	75	-	-	105	-	60	60
MCCPH 102	164	164	164	134	134	134	104	104	104	104	104	104
PVPK-30	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3											
Total weight	300	300	300	300	300	300	300	300	300	300	300	300

Table 3: Pre compression parameters

Formulation	Bulk density (gm/ml)*	Tapped density (gm/ml)*	Hausner ratio *	Compressibility index *	Angle of repose (θ)*
IR	0.36 ± 0.05	0.44 ± 0.01	1.21 ± 0.05	17.74 ± 1.15	35.12±0.67
F1	0.37 ± 0.04	0.43 ± 0.03	1.17 ± 0.05	15.22 ± 0.21	28.64±0.46
F2	0.37 ± 0.04	0.44 ± 0.03	1.16 ± 0.02	14.34 ± 1.03	33.26±1.02
F3	0.38 ± 0.04	0.44 ± 0.03	1.15 ± 0.03	13.24 ± 2.35	33.25±1.21
F4	0.36 ± 0.05	0.41 ± 0.06	1.13 ± 0.04	11.96 ± 0.44	28.82±0.84
F5	0.37 ± 0.05	0.45 ± 0.04	1.23 ± 0.04	19.0 ± 2.62	34.38±0.36
F6	0.37 ± 0.04	0.46 ± 0.04	1.22 ± 0.01	18.13 ± 1.32	32.16±0.23
F7	0.36 ± 0.04	0.41 ± 0.01	1.14 ± 0.02	12.90 ± 2.01	29.30±0.32
F8	0.36 ± 0.05	0.44 ± 0.01	1.21 ± 0.01	17.74 ± 1.22	33.61±1.15
F9	0.36 ± 0.02	0.44 ± 0.01	1.20 ± 0.02	16.85 ± 0.34	33.67±1.22
F10	0.37 ± 0.08	0.44 ±0 .01	1.19 ± 0.04	16.06 ± 1.27	33.01±0.62
F11	0.37 ± 0.02	0.47 ± 0.08	1.26 ± 0.05	21.02 ± 1.64	30.23±0.93
F12	0.37 ± 0.04	0.48 ± 0.09	1.28 ± 0.01	21.94 ± 1.91	32.40±1.42
*** All values are expressed as mean ± SD, n=3**					

Table 4: Post compression parameters

Formulation	Hardness (Kg/cm2) (Mean ± SD, n=5)	%Friability	Thickness (mm) (Mean ± SD, n=5)	Weight variation (Mean ± SD, n=20)	% Drug content (Mean ± SD)
F1	5.5 ± 0.2	0.28	4.45 ± 0.02	399.2 ± 2.33	98.93
F2	6.5 ± 0.3	0.28	4.50 ± 0.02	399.8 ± 2.99	101.15
F3	6.3 ± 0.2	0.40	4.54 ± 0.04	401.8 ± 1.89	99.46
F4	5.7 ± 0.1	0.32	4.52 ± 0.04	401.3 ± 2.72	99.31
F5	5.9 ± 0.1	0.37	4.48 ± 0.02	400.3 ± 2.45	98.87
F6	6.5 ± 0.1	0.36	4.51 ± 0.02	401.5 ± 2.30	101.35
F7	5.9 ± 0.1	0.48	4.48 ± 0.02	400.7 ± 1.75	98.24
F8	6.2 ± 0.3	0.36	4.54 ± 0.03	401.4 ± 2.13	98.18
F9	7.2 ± 0.2	0.23	4.46 ± 0.02	401.3 ± 2.47	99.00
F10	6.5 ± 0.1	0.36	4.53 ± 0.03	401.3 ± 2.13	101.42
F11	6.1 ± 0.3	0.48	4.48 ± 0.02	400.6 ± 1.81	98.81
F12	6.3 ± 0.1	0.42	4.51 ± 0.02	401.3 ± 2.96	99.53

Table 5: Swelling index of Muco adhesive tablets

T(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	5.69	9.32	12.74	6.62	11.5	11.8	13.29	15.25	17.86	22.41	24.5	29.45
2	12.11	18.27	29.95	15.29	24.86	30.6	29.43	28.8	30.21	37.73	41.61	46.41
3	23.88	33.39	42.93	28.77	34.04	36.28	40.52	47.54	51.12	53.47	60.72	67.6
4	43.52	54.83	68.92	62.47	68.38	76.07	79.32	77.18	76.53	78.54	82.42	93.89
5	57.68	69.09	79.83	71.7	82.66	89.38	87.87	92.48	93.26	99.74	103.94	119.9
6	72.22	81.66	92.86	83.06	92.9	99.48	106.29	112.4	122.7	128.98	135.86	149.7

Table 6: Muco adhesive studies of all formulations.

Formulation code	Muco adhesive strength (g) (Mean ± SD, n=3)	Muco adhesive force(N)	Muco adhesion time (Hrs)
F1	10.5 ±1.5	0.10	>10
F2	14.5 ±1.4	0.14	>13
F3	18.7 ±1.0	0.18	>15
F4	15.9 ±1.8	0.15	>12
F5	19.3 ±1.5	0.18	>15
F6	24 ±1.5	0.23	>17
F7	19 ±1.6	0.18	>15
F8	25.1 ±1.7	0.246	>17
F9	30 ±1.0	0.29	>18
F10	25.2 ±1.6	0.24	>16
F11	29.6 ±2.0	0.29	>19
F12	35.6 ±1.5	0.34	>22

Table 7: Kinetic values obtained from different plots of formulations F1 to F12

Formulation code	Zero order (R2)	First order (R2)	Higuchi (R2)	Korse-Meyer Peppas	
				(R2)	n
F1	0.983	0.683	0.923	0.966	0.616
F2	0.990	0.716	0.964	0.988	0.605
F3	0.993	0.913	0.964	0.979	0.592
F4	0.982	0.827	0.981	0.993	0.619
F5	0.989	0.680	0.940	0.973	0.578
F6	0.981	0.727	0.929	0.965	0.568
F7	0.992	0.875	0.952	0.97	0.623
F8	0.991	0.775	0.934	0.947	0.556
F9	0.993	0.736	0.937	0.95	0.569
F10	0.979	0.704	0.902	0.936	0.531
F11	0.982	0.703	0.911	0.934	0.530
F12	0.992	0.779	0.931	0.937	0.543

Table 8: Stability study of optimized formulation F12.

Formulation code	*Hardness(kg/cm2)*	*%Friability*	*%Drug content*	*Mucoadhesive strength(g)*	*Mucoadhesion time (Hrs)*	*%Invitro release (24hrs).*
F12	***6.50±0.53***	***0.6***	***99±0.54***	***37.4±1.5***	***>22***	***97.4±1.65***

Figure 2: %CDR of formulations F1 to F12.

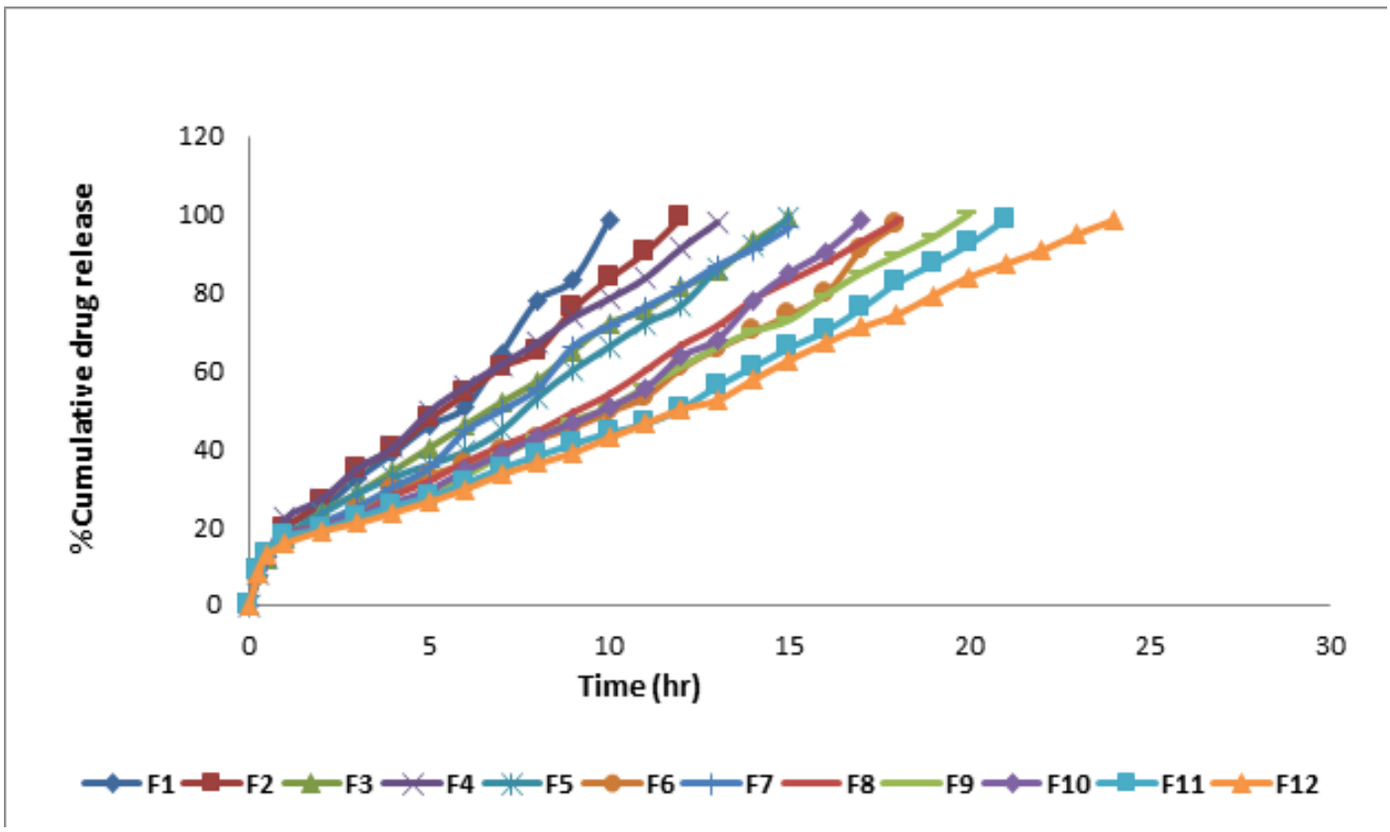


Figure 3: Swelling studies of formulations F1 to F12.

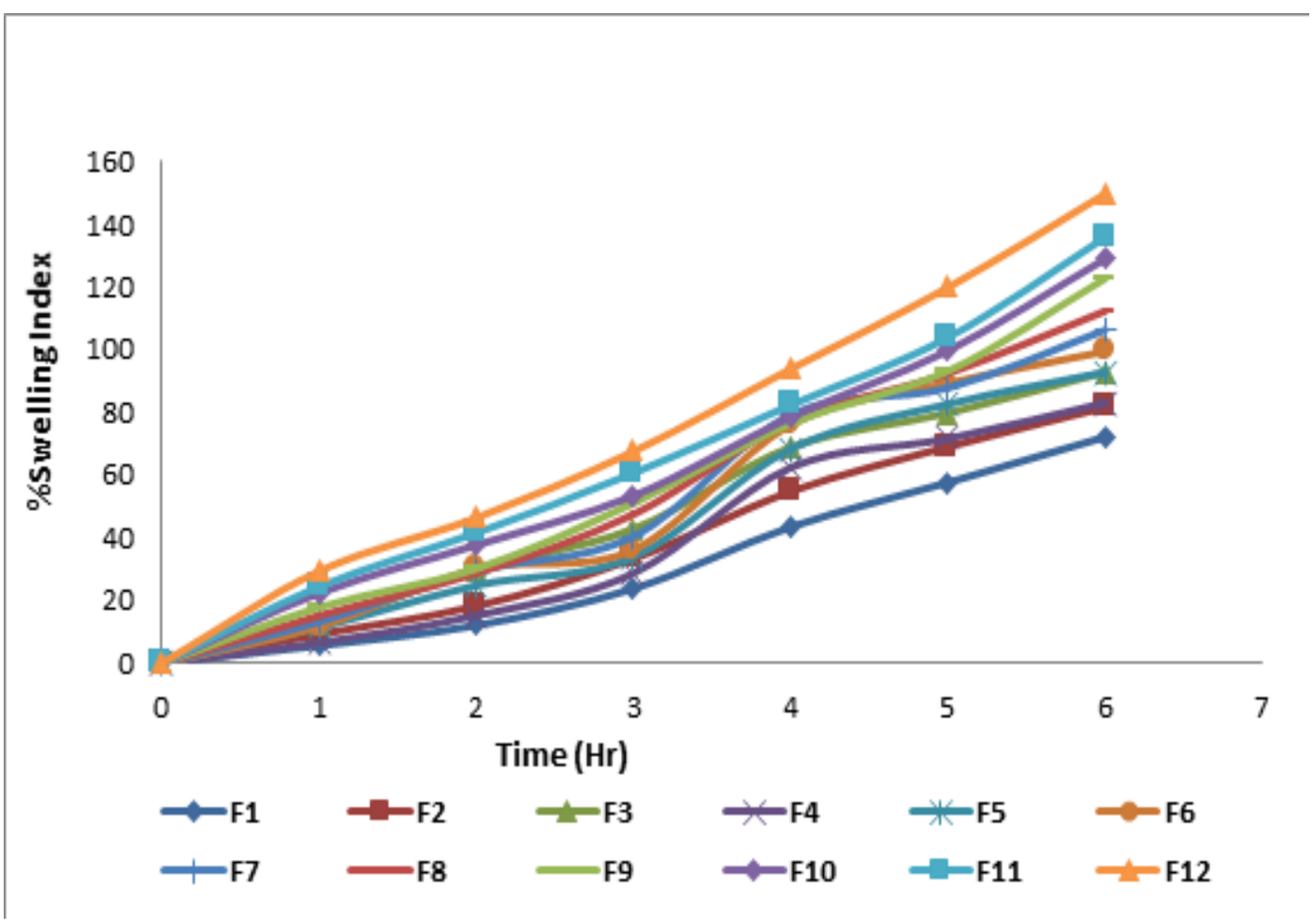


Figure 4: Comparision of Muco adhesive strength of F1 to F12.

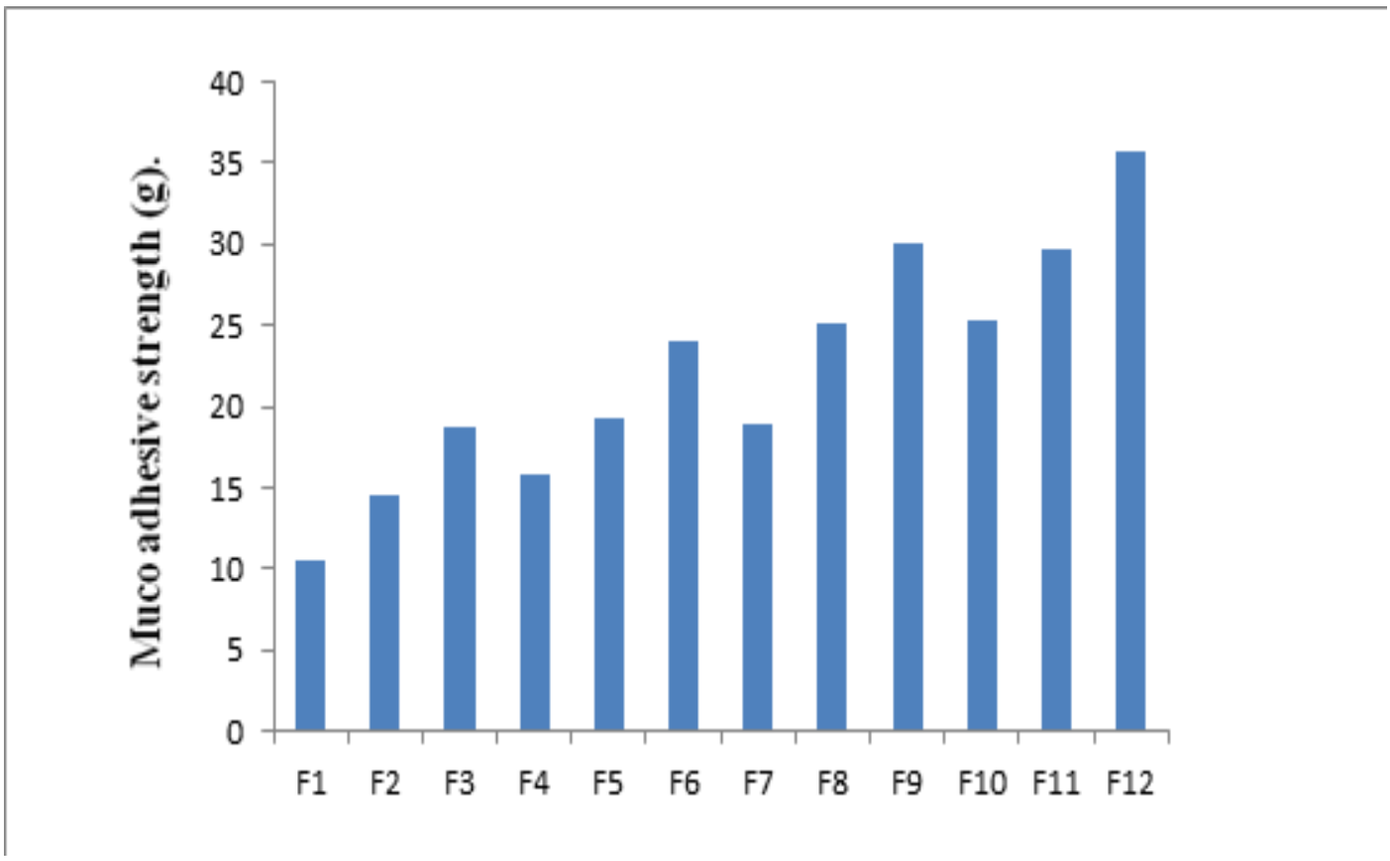


Figure 5: FTIR of pure losartan potassium

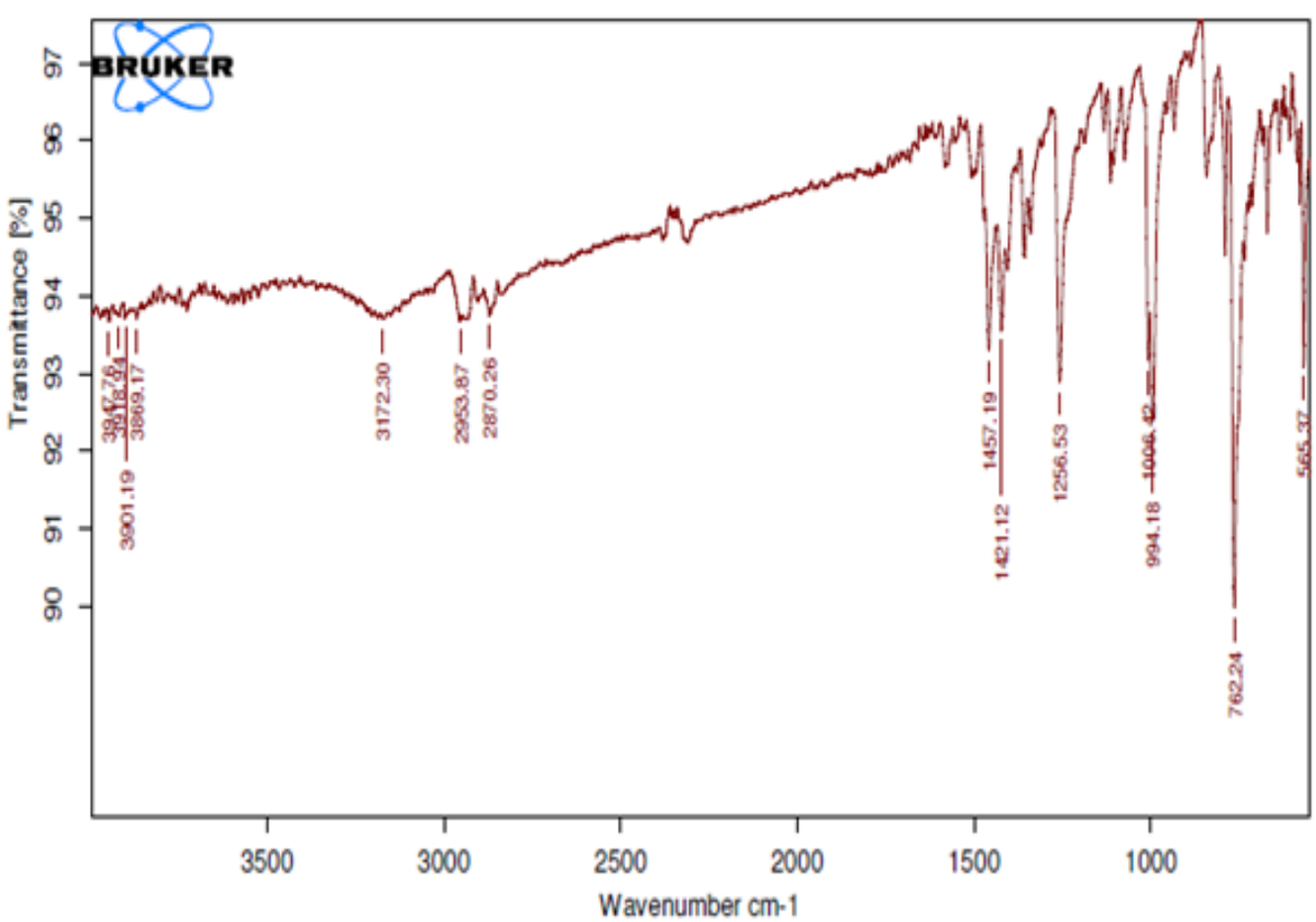
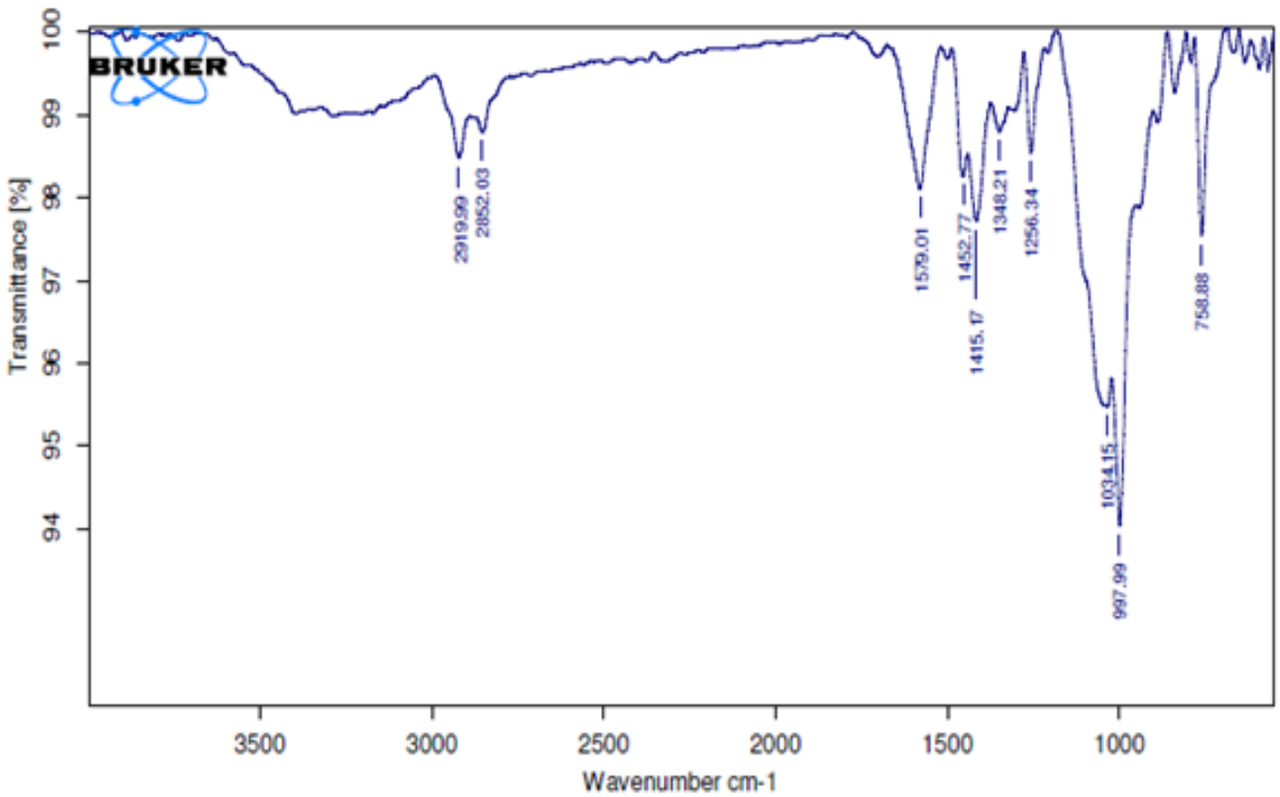


Figure 6: FTIR of F12 formulation



4. Results and Discussion

4.1 Drug Excipient Compatibility Studies

The pure drug Losartan potassium and the solid admixture of drug and various polymers used in the preparation of bilayered tablets were characterized by FTIR spectroscopy to know the compatibility. As shown in the figure 5-6, there was no significant difference or the characteristic peak of pure drug was unchanged in spectrum of optimized formulation (F12).

4.2 Micromeritic properties

In the present study, direct compression was adopted for tableting. Plain Losartan potassium exhibited angle of repose 38.42o indicating fair flow property. It showed Carr's index of 23.45 (passable) and Hausner's ratio 1.3. Hence lubricants were added to improve the flow property of drug. Table 3 shows the micromeritic properties of all formulations. It exhibited the angle of repose value of 28.64-38.42o, Carr's index value of 11.96-23.45 and Hausner's ratio 1.14-1.3 indicating flow property excellent to fair. Hence powder mixture was found suitable for direct compression method.

4.3 Post compression parameters of tablets

Post compression parameters are given in the table 4. The tablets of different batches of sodium alginate, guar gum and xanthan gum, alone and in combination were found uniform with respect of thickness 4.45-4.54 mm, hardness 5.5-7.2 kg/cm2 and friability 0.23-0.48% were also found uniform indicating good handling property of the prepared bilayer tablet. Weight variation 1.75-2.99% and drug content 98.18-101.42% were within prescribed limits. Hence tablets containing drug, polymer, diluents, binder and lubricants could be prepared satisfactorily by direct compression method.

4.4 In vitro release study

IR layer of all the formulation showed the burst release (10mg) of losartan potassium within 30 min. Presence of super disintegrant (Ac-Di-Sol) 6% w/w in immediate release layer showed faster disintegration of the layer. This can attributed to the extent of water uptake and consequently the strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration. Formulation containing 15%, 25%, 35% w/w of sodium alginate (F1, F4, F7) exhibited release over 10, 13, 15 hr respectively. Formulation containing 15%, 25%, 35% w/w of guar gum (F2, F5, F8) exhibited release over 12, 15, 18 hr respectively. Formulation containing 15%, 25%, 35% w/w of xanthan gum (F3, F6, F9) exhibited release over 15, 18, 20 hr respectively. This clearly indicates that release rate was influenced by polymer concentration. Formulations containing

polymer combination F10 (15%w/w sodium alginate and 20% w/w guar gum) showed release over 17 hr, F11 (15%w/w sodium alginate and 20% w/w xanthan gum) showed release over 20 hr, F12 (15% w/w guar gum and 20% w/w xanthan gum) showed release upto 24 hr. among all the formulations F12 has released better controlled release over 24 hr.

4.5 Swelling study

The swelling index of bilayer tablets as shown in the table 5, were directly proportional to the concentration of the polymer, as the polymer concentration increase there was increase in the swelling index. On comparing the swelling index, it was observed that F12 (15% w/w guar gum and 20% w/w xanthan gum) showed maximum swelling index. The order of swelling of polymeric tablets were XG-GG > SA-XG > SA-GG > XG > GG > SA.

4.6 In – vitro mucoadhesive study

The in-vitro mucoadhesive study was performed on modified physical balance and measures the mucoadhesive strength (g) requires to detach the tablet. The mucoadhesive characteristics were affected by the concentration of the gum. Increase in concentration of gum increases mucoadhesive strength and mucoadhesive time of the formulation. Optimized formulation F12, with 15% w/w guar gum and 20% w/w xanthan gum shows greater mucoadhesive strength with mucoadhesive time over 24 hr. The results were shown in the table 6.

4.7 Mechanism of drug release [21, 22]

As observed from the table 7, all the formulations followed zero order kinetics as correlation (R2) values 0.979-0.993 are higher than that of first order release kinetics. The prepared bilayered tablets showed Non-Fickian (anomalous) release, as the values of release exponent (n) lies between 0.53-0.623 with their correlation coefficient (R2) values between 0.934-0.993 which are greater than the values of Higuchi model.

4.8 Stability study

The stability studies were carried out for the formulations F12 at 40 ± 2oC/75 ± 5% RH for one month. Table 8, shows the values of pre and post compression parameters after stability studies at different temperature and humidity conditions. The result indicated that the tablets did not show any prominent changes during the study period. This indicates that tablets are fairly stable at storage conditions.

5. Conclusion

The present research was carried out to develop a bilayer tablet of Losartan potassium using super disintegrant Ac-Di-Sol (6%) for the immediate release layer and sodium alginate, guar gum, xanthan gum alone and in combination at different strengths for the controlled release layer. Bilayer tablets showed an initial burst to provide the loading dose of the drug followed by the controlled release for 24 hr, indicating a promising potential of the losartan potassium bilayer tablet as an alternative to the conventional dosage form.

Acknowledgements

The authors are thankful to the Spectrum labs, Hyderabad and CMR College of Pharmacy, Hyderabad for providing necessary facilities to carry out this work.

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