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FORMULATION AND EVALUATION OF GASTRORETENTIVE BILAYER MUCOADHESIVE TABLETS OF VERAPAMIL HYDROCHLORIDE

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Abstract

The objective of the current investigation is to reduce dosing frequency and improve patient compliance by designing and systematically evaluating Bilayer mucoadhesive tablets of Verapamil HCl. Frequent administration and variable low bioavailability (40-60%) after oral administration are problems of conventional dosage forms of Verapamil HCl and this can be overcome by designing a suitable form of Bilayer mucoadhesive Tablets containing an immediate release layer and a sustained release layer.

Different formulations of Verapamil HCl immediate release and sustained release having polymers at different concentrations were prepared by direct compression method. Results of dissolution profiles of various IR formulation showed that formulation F4 containing polymer Sodium alginate showed 96.40% drug release at the end of 30 minutes .Thus due to fast release of drug within stipulated time IR F4 was chosen as best formulation. Similarly from all the six batches of SR formulation it was found that batch F3 showed 98.36 % drug release gives desirable sustained effect for 12 hours. Therefore SR F3 containing polymers like HPMC and Carbopol 934P was chosen as best formulation. All the formulations showed uniformity in hardness, weight variation, thickness, friability and content uniformity within limits. The optimized bilayer mucoadhesive tablets were evaluated for hardness, thickness, friability was found to be 5.97 kg/cm^2, 3.75 mm, 0.39% respectively. The Bioadhesive strength (gm) was found to be 13.94gm. The In vitro Residence time (hr) was found to be upto 12hr. %Swelling index was found to be 71.5%.The amount of drug release for optimized Bilayer formulation was found to be 97.50% in 30 mins followed by the SR release i.e, 95.60% in 12 hrs following zero

order release kinetics and non fickian mechanism. Stability studies were carried out in accordance with ICH Guidelines Q1 showed that there was no significant change in % release of drug after 3 months indicating that the formulation is stable.

Keywords: Verapamil Hydrochloride,Sodium alginate, HPMC, Carbopol 934P, Gastroretentive, Bioadhesive strength, Invitro residence time.

1. Introduction

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time.

After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT)

Bioadhesive system

Bioadhesive systems are used to localize a delivery device within the lumen cavity of the body to enhance the drug absorption process in a site-specific manner. In this approach, Bioadhesive polymers are used that can adhere to the epithelial surface of the gastrointestinal tract. Mechanistically, bioadhesion involves the formation of hydrogen and electrostatic bonding at the mucus polymer interface. Bilayer tablet is an improved technology to overcome the shortcoming of the single layered tablet. Bilayer tablets contain immediate and sustained release layers. The immediate release layer delivers the initial dose, and second layer is maintenance dose. In which the 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 controlled release, 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 fast 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 sustaining layer.

Verapamil hydrochloride is a calcium channel blocker which is used in the control of supraventricular arrhythmia, hypertension and myocardial infraction. The usual dose of verapamil is 200-280 mg/day.The conventional tablet and capsule is administered 3 or 4 times a day due to its short biological half-life of about 2-5 hr. The problems of frequent administration and variable low bioavailability (40-60%) after oral administration of conventional tablet or capsules. The sustained release forms are administered two to four times a day due to its limited residence time in the gastrointestinal tract. An attempt for localising the drug into the stomach by mucoadhesion can be done for Verapamil HCl to enhance its bioavailability and to reduce the frequency of dosing.

2. Materials and Methods

2.1) Materials: Verapamil HCL was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad, India. Polyvinyl Pyrolidine K-30, Guar gum, Xanthan gum was purchased from MYL CHEM Mumbai. Carbopol 934P, Sodium Alginate, HPMC K4M, Ethyl cellulose was purchased from S.D Fine chem. LTD Mumbai.

2.2) Methods

Preparation of bilayer gastroretentive mucoadhesive tablets

The tablets were prepared by Direct Compression Method. Accurately weighed amounts of drug, polymer, and diluent were mixed geometrically in a mortar. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate and for 2 minutes and compressed into tablets on a 16-station rotary tableting machine using 9 mm round, flat-faced punches.

Table-1: Formulation table for immediate release layer.

Ingredients (mg)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
Verapamil Hcl	40mg	40mg	40mg	40mg	40mg	40mg
Acacia (%)	5	5	5	5	5	5
MCC	q.s	q.s	q.s	q.s	q.s	q.s
Talc (%)	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate(%)	2.5	2.5	2.5	2.5	2.5	2.5
Sodium Alginate(%)	7.5	-	-	10	-	-
HPMC (%)	-	7.5	-	-	10	-

Carbopol 934P (%)	-		7.5	-	-	10
Total weight	200mg	200mg	200mg	200mg	200mg	200mg

Table-2: Formulation table for sustained release layer.

Ingredients (mg)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**
Verapamil Hcl	120mg	120mg	120mg	120mg	120mg	120mg
MCC	q.s	q.s	q.s	q.s	q.s	q.s
HPMC (%)	-	-	15	-	15	-
EC(%)	10	10	-	-	-	-
Guargum(%)	-	-	-	15	-	15
Talc (%)	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate(%)	2.5	2.5	2.5	2.5	2.5	2.5
Sodium Alginate(%)	-	10	-	-	10	10
Carbopol 934P (%)	10	-	10	10	-	-
Total weight	300mg	300mg	300mg	300mg	300mg	300mg

Table-3: Composition of Bilayer tablet (mg/tablet).

Ingredients	IR Formulation (F4)	SR Formulation (F3)	Bilayer Tablet (BF)
Verapamil HCl	40	120	160
Acacia	10	-	10
MCC	119.75	90	210
Sodium alginate	20	-	20
HPMC	-	45	45
Carbopol 934P	-	30	30
Talc	5	7.5	12.5
Magnesium stearate	5	7.5	12.25
Iron oxide red	0.25	-	0.25
Total weight	200	300	500

MCC- Micro crystalline cellulose, EC – Ethyl cellulose, PVP- Poly vinyl pyrrolidine, HPMC – Hydroxy Propyl methyl cellulose.

2.2.1) Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rationale development of dosage form.

2.2.1.1) Drug-Excipients compatibility studies by FT-IR

. In the preparation of mucoadhesive tablet, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Verapamil HCl and the selected polymers. The individual drug and drug with excipients were scanned separately.

2.2.1.2) Evaluation of Precompression parameters

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flowability of powder/granules.

$$\theta = \tan^{-1} (h/r) = \tan^{-1} (\text{height of pile}/0.5\text{base})$$

Bulk density

Apparent Bulk density (gm/ml) of the drug was determined by pouring (preseived 40-mesh) gently 4 gm of sample through a glass funnel into a 10 ml graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density was calculated by following formula.

$$\text{Bulk density} = \text{Weight of powder} / \text{Bulk volume}$$

Tapped density

Tapped densities the drug was determined by pouring gently 4 gm of sample through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated.

Tapped density = Weight of powder / Tapped volume

Compressibility index (carr's index)

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density.

Carr's index = (Tapped density – Bulk density / Tapped density) X 100

Hausner's ratio

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa.

Hausner's Ratio = Tapped density /Bulk density

2.2.2) Evaluation of tablets

Hardness

Hardness of tablet was measured by Monsanto hardness tester. For each batch three tablets were tested and results are expressed in **Kg/cm^2**.

Thickness

Tablets were randomly selected from each batch and their thickness was measured by using vernier calipers. It is expressed in millimeter (mm).

Friability

Friability of buccal tablet was determined using Roche friabilator. Preweighed sample of tablets (10 tablets) was placed in a friabulator and operated at 25 rpm for 4 minutes or run up to 100 revolutions After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The percentage friability was determined by the formula:

$$\% \text{ Friability} = (W_1 - W_2) / W_1 \times 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

Weight variation test

Ten tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Drug content uniformity

10 tablets were taken and powdered. Powder equivalent to one tablet was weighed accurately and allowed to dissolve in 10ml phosphate buffer and make up volume upto 100ml. The solution was filtered, 1 ml of filtrate was taken in 50 ml of volumetric flask and diluted up to mark with 6.8 phosphate buffer and analyzed spectrophotometrically at 278nm.

Invitro bioadhesive strength

The working of a double beam physical balance formed the basis of the mucoadhesion test. The two pan of a physical balance was removed and replaced with a same volume of beakers hanged with a lightweight thread. The height of this total set-up was adjusted to accommodate a glass petriplate below it, leaving a head space of about 0.5 cm in between petriplate and left beaker. The two sides were then balanced. The sheep mucus membrane was excised and washed (equilibrated at 37ºC ± 1ºC for 30 min in 0.1N HCl medium before the mucoadhesion evaluation study) and tied tightly with the thread to mucus on glass side, which was then filled with 0.1N HCl kept at 37ºC ± 1ºC, such that 0.1N HCl just reaching the surface of mucosal membrane and keeping it moist. This was then kept below the left beaker and the left beaker was then lowered into the petriplate of the balance. The tablet was then stuck to the bottom of left beaker, using two way adhesive and the balance beam. A constant weight was then placed over the left beaker for the total contact of tablet to mucus for a period of 5 min. Bioadhesive strength was then assessed by adding weights on the right beaker till the tablet separated from the mucosal surface, in terms of the weight (in gm) required to detach tablet from the membrane. The modified physical double beam balance was shown in figure no.

Fig-1: Modified physical double beam balance for Invitro Bioadhesive strength.

Invitro residence time

The invitro residence time was carried out by using disintegration test apparatus. The disintegration medium was composed of 800 ml of 0.1N HCl maintained at 37°C. The sheep stomach mucosa or epithelial cell was tied to the surface of a glass slab using thread, vertically attached to the apparatus. The mucosal tablet was hydrated from one surface using 0.5 ml of 0.1N HCl and then the hydrated surface was brought in contact with the mucosal membrane. The glass slide was vertically fixed to the apparatus and allowed to run in such way that the tablet completely immersed in the 0.1N HCl at the lowest point. and was out at the highest point. The time taken for complete erosion or dislodgment of the tablet from the mucosal surface was noted.

Fig-2: Assembly of invitro residence time.

Invitro drug release study

In-vitro release studies were carried out USP II paddle type dissolution test apparatus. 900 ml of 0.1 N HCl (pH 1.2) was filled in dissolution vessel and the temperature of the medium were set at 37° C ± 0.1°C.The speed was set at 50 rpm. 5

ml of sample was withdrawn at predetermined time intervals. The samples were analyzed for drug content against 0.1N HCl as a blank at λmax 278nm using spectrophotometer.

Stability studies

Stability studies were performed at a temperature of 40^0 C at 75 % RH, over a period of three months (90 days) for the optimized tablets. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in stability chamber maintained at $40^0 \pm 1^0$C & 75 % RH. Samples were taken at monthly intervals for drug content estimation. At the end of three months period, dissolution test and drug content studies were performed to determine the drug release profiles and drug content.

3. Results and Discussion

3.1) Preformulation studies

3.1.1)Drug excipient compatibility studies by FTIR.

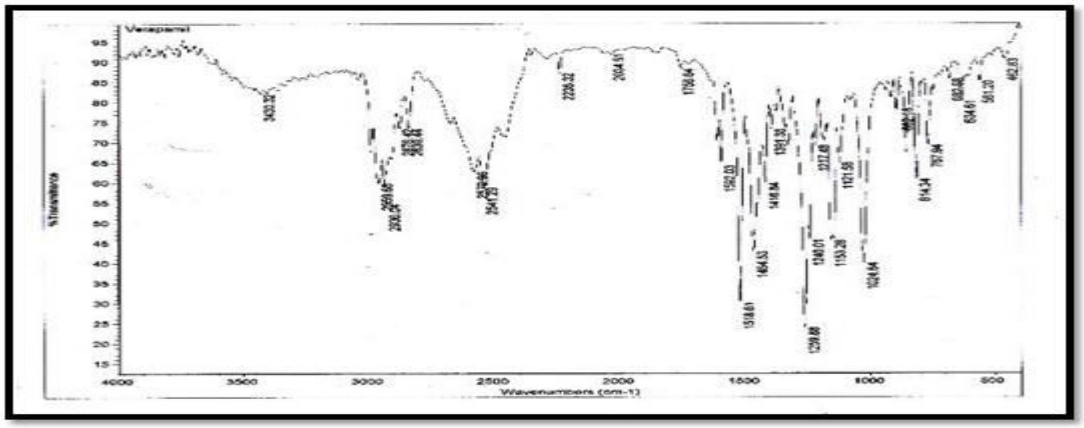


Fig no3: FTIR Spectra of Verapamil Pure drug.

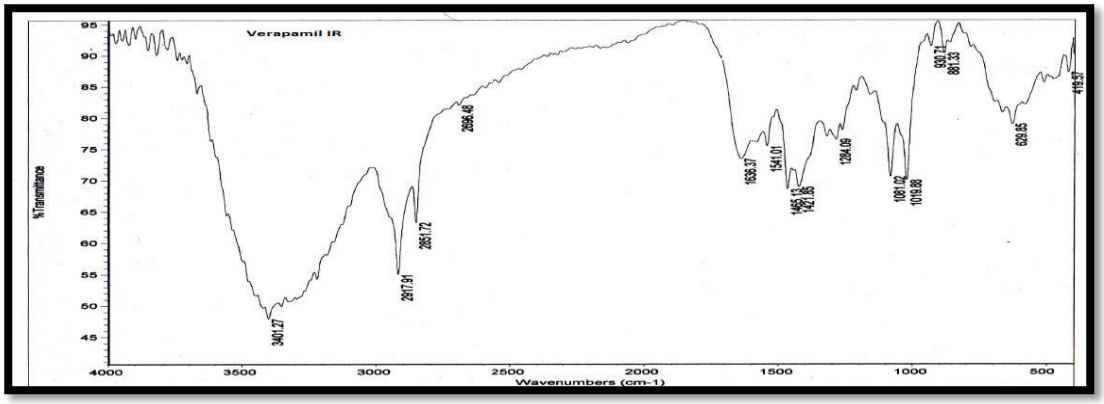


Fig-4: FTIR Spectra of Immediate Release Verapamil HCl formulation.

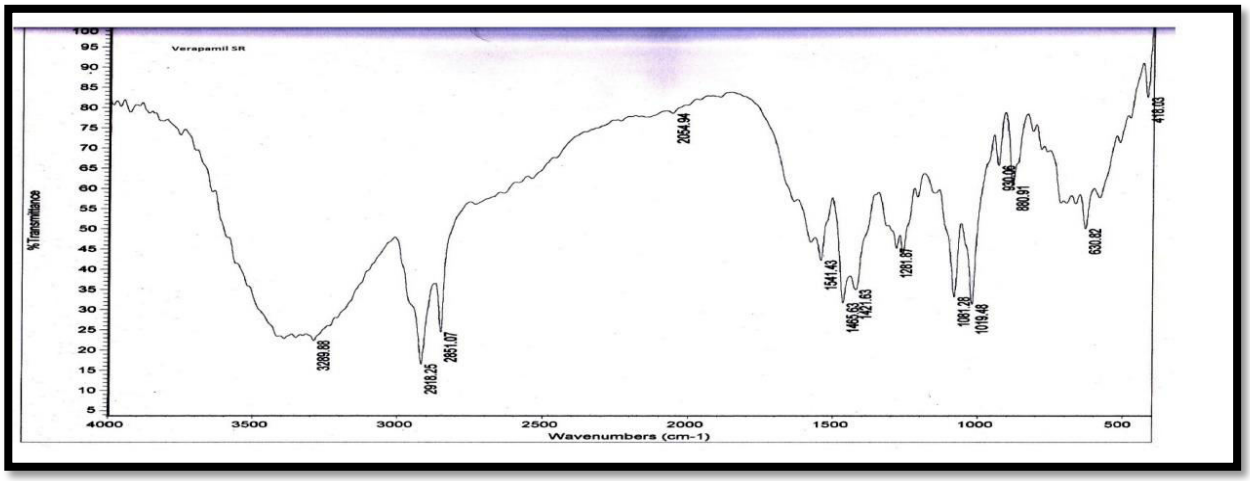


Fig. no. 5: FTIR Spectra of Verapamil HCl SR formulation.

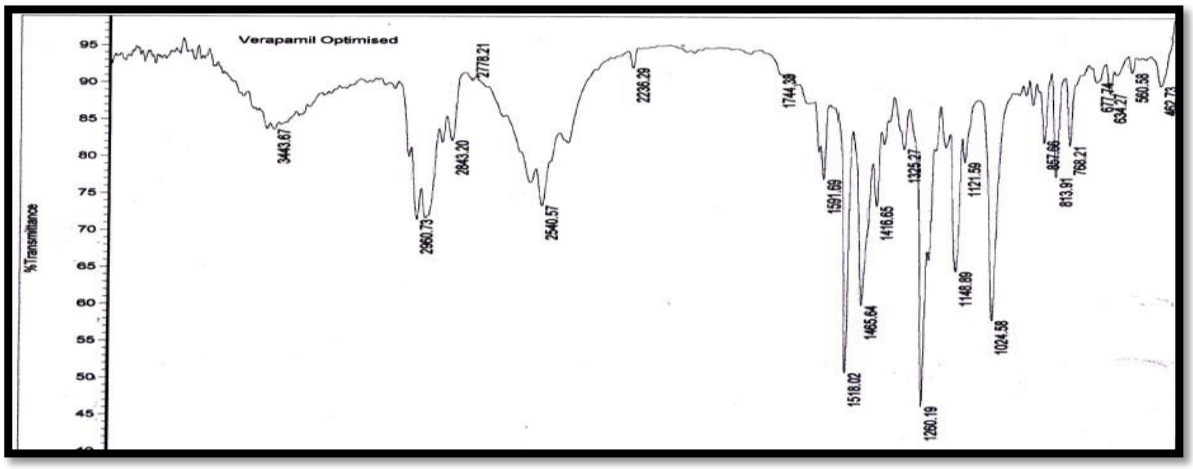


Fig-6: FT-IR Spectrum of Optimized bilayer formulation.

Discussion

There is no significant change in the shift of major peaks of drug (C=O str, C-H str , OH-str) in the above graph ,hence there is no drug and excipient interactions was found.

3.1.2) Evaluation of pre compression parameters.

Table-4: Precompression Parameters of Immediate Release Layer of Verapamil HCl.

Formulation Code	Angle of repose(ø)	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Hausener's ratio	Flow
F1	27	0.445	0.490	9.183673	1.101124	Good
F2	25.6	0.380	0.445	14.60674	1.171053	Good
F3	23	0.278	0.312	10.89744	1.122302	Good
F4	20	0.452	0.520	13.07692	1.150442	Good

F5	22	0.332	0.389	14.65296	1.171687	Good
F6	21.5	0.551	0.610	9.672131	1.107078	Good

Table -5: Precompression parameters for the sustained release layer of Verapamil HCl.

Formulation Code	Angle of repose(ø)	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Hausener's ratio	Flow
F1	25	0.320	0.395	18.98	1.234375	Fair
F2	26	0.420	0.500	16.0	1.190476	Fair
F3	19	0.321	0.399	19.54	1.242991	Fair
F4	28	0.325	0.400	18.75	1.230769	Fair
F5	22	0.555	0.692	19.79	1.246847	Fair
F6	23	0.332	0.408	18.62	1.228916	Fair

Discussion:

From the above pre-compression parameters it was clear evidence that powdered blend has Good (in IR) and fair (in SR) flow properties and is suitable for direct compression.

3.2) Evaluation of post compression parameters.

Table -6:.Evaluation tests for various formulations of immediate release layer of Verapamil HCl .

Formulation Code	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content * (%)
F1	200± 2.54	3.93 ± 0.023	3.23 ± 0.022	0.31	99.53±1.80
F2	198 ± 2.63	3.94 ± 0.019	3.23 ± 0.041	0.16	98.28±1.99
F3	196.4 ± 2.41	3.25 ± 0.031	3.34 ± 0.027	0.24	98.35±1.14
F4	199± 2.64	3.13 ± 0.013	3.43 ± 0.012	0.26	99.32±0.58
F5	197 ± 2.43	3.84 ± 0.029	3.33 ± 0.031	0.22	100.24±0.05
F6	198.4 ± 2.71	3.85 ± 0.021	3.44 ± 0.017	0.34	98.38±2.32

Table -7: Evaluation tests for various formulations of sustained release layer of verapamil HCl.

Formulation Code	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content * (%)
F1	300± 1.34	6.93 ± 0.020	3.53 ± 0.035	0.21	97.35±0.37
F2	298 ± 1.33	5.50 ± 0.015	3.63 ± 0.032	0.26	99.88±1.80
F3	296.4 ± 1.31	6.25 ± 0.026	3.44 ± 0.025	0.24	97.12±1.37
F4	299± 1.64	5.83 ± 0.012	3.53 ± 0.017	0.36	100.12±0.98
F5	297 ± 2.13	6.10 ± 0.024	3.43 ± 0.028	0.32	101.22±0.25
F6	298.4 ± 2.11	5.98 ± 0.029	3.54 ± 0.018	0.34	98.33±0.87

Discussion

All the formulations showed uniformity in hardness, weight variation, thickness, friability and content uniformity within limits.

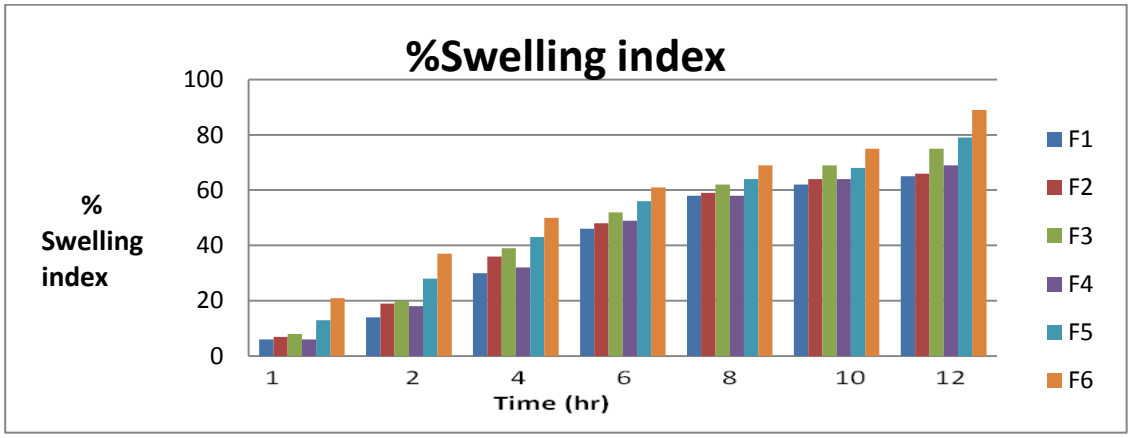


Fig-7: %Swelling index of SR tablet.

Discussion: Optimized formulation F3 % swelling index was found to be 75% after 12hrs.

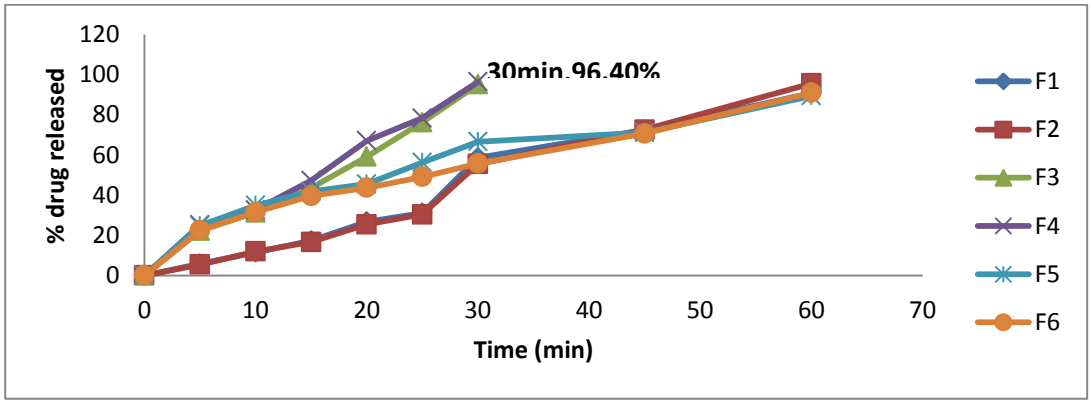


Fig-8 Comparative Dissolution graph for Immediate release formulations (F1-F6)

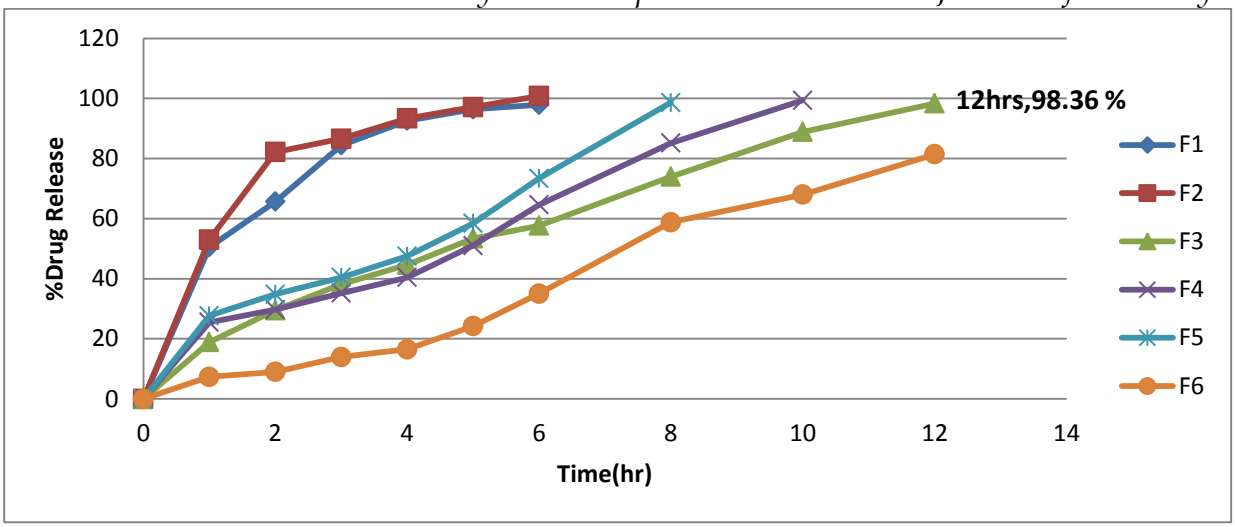


Fig-9: Comparative Dissolution graph for sustained release formulations (F1-F6).

Bioadhesive Strength

Table-8: Bioadhesive strength and Invitro Residence Time of F_1, F_2, F_3, F_4, F_5 and F_6 of sustained release Tablets of Verapamil Hcl.

Formulation code	Bioadhesive strength Weight (Gms)	Invitro residence time
F1	10.33	10hr 15min
F2	13.67	7hr5min
F3	12.95	12h 2min
F4	11.67	9hr 20min
F5	9.50	8hr10min
F6	11.00	11hr7min

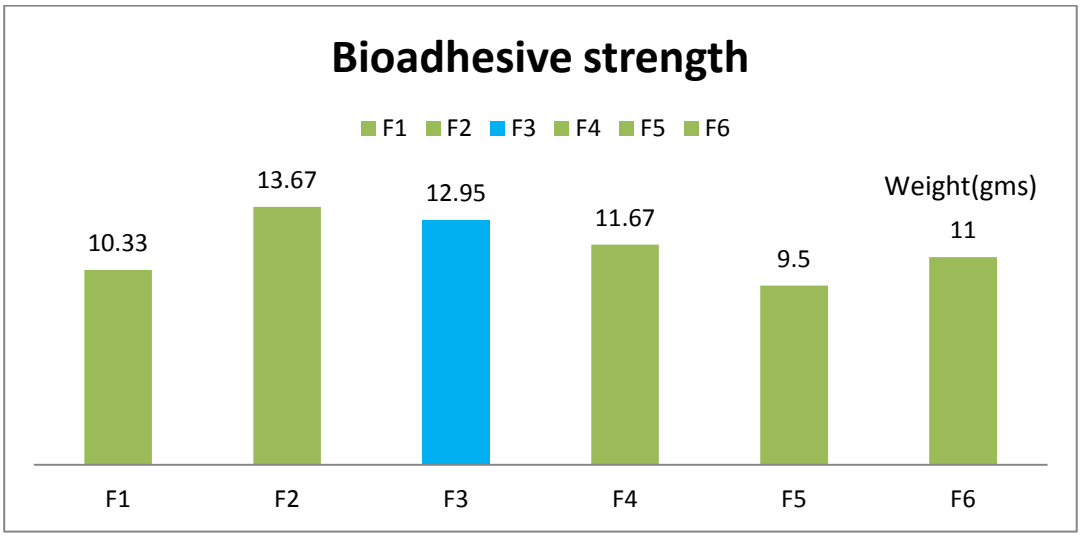


Fig-10: Comparision of Bioadhesive strength of F_1, F_2, F_3, F_4, F_5 and F_6 of sustained release tablets of Verapamil HCl

Discussion: Bioadhesive strength of optimized SR formulation (F3) was found to be 12.95 gms and Invitro residence time was upto 12hours 2min.

S.No.	Evaluation Parameter	Bilayer tablet values
1.	Hardness(kg/cm^2)	5.97±0.45
2.	Thickness(mm)	3.75±0.15
3.	Friability(%)	0.39±0.12
4.	Bioadhesive strength(gm)	13.94±0.52
5.	In vitro Residence time(hr)	12

Table- 9: Evaluation parameters for optimized Bilayer tablet

Discussion: The optimized Gastroretentive bilayer mucoadhesive tablets of verapamil HCl were evaluated for hardness, thickness, friability and it was found to be 5.97±0.45 kg/cm^2, 3.75 ±0.15 mm, 0.39 ±0.12% respectively. The Bioadhesive strength (gm) was found to be 13.94gm ±0.52 and In vitro Residence time (hr) was upto 12hr.

Table-10: %Swelling index of optimized bilayer tablet.

S.No.	Time (in hrs)	%Swelling index
1.	1	13
2.	2	19
3.	4	32
4.	6	43
5.	8	54
6.	10	65
7.	12	71.5

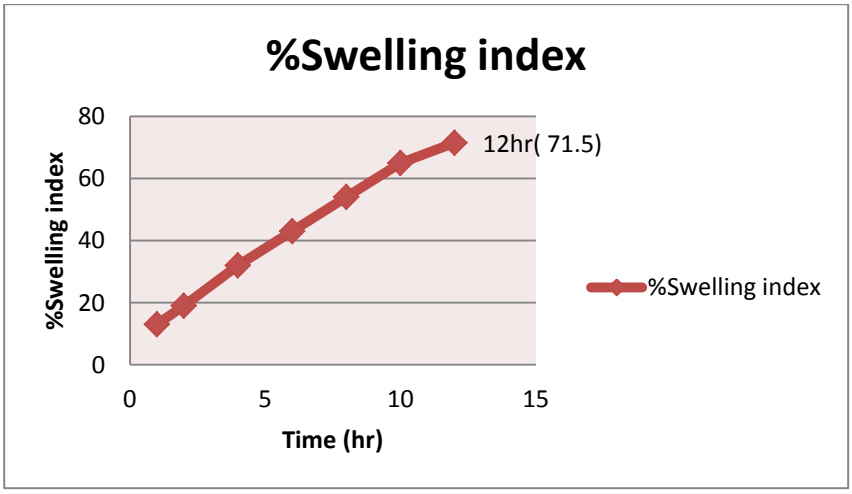


Fig-11: %Swelling index of optimized bilayer tablet

Discussion: The % Swelling index of Optimized bilayer mucoadhesive tablets of Verapamil was found to be 71.5%.

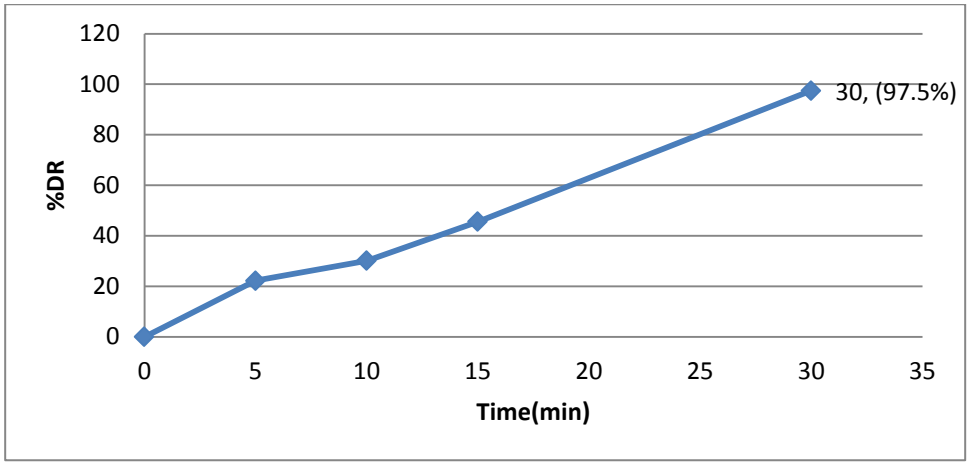


Fig 12: Dissolution graph of bilayer tablet – verapamil HCL IR layer.

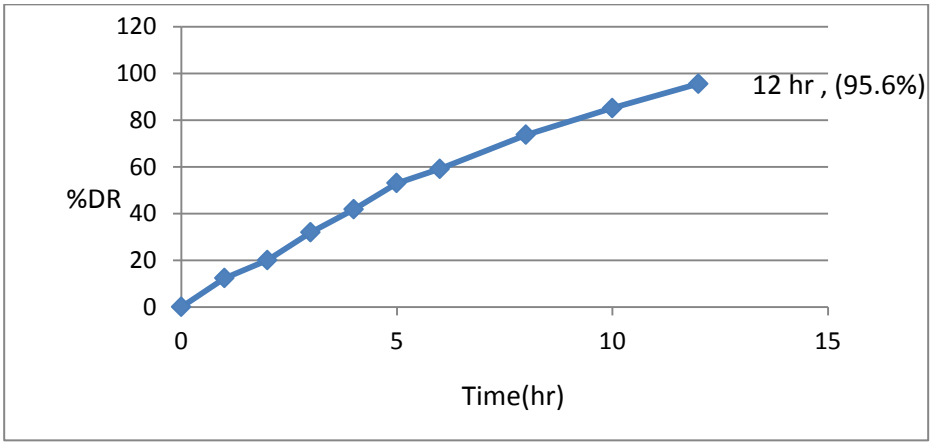
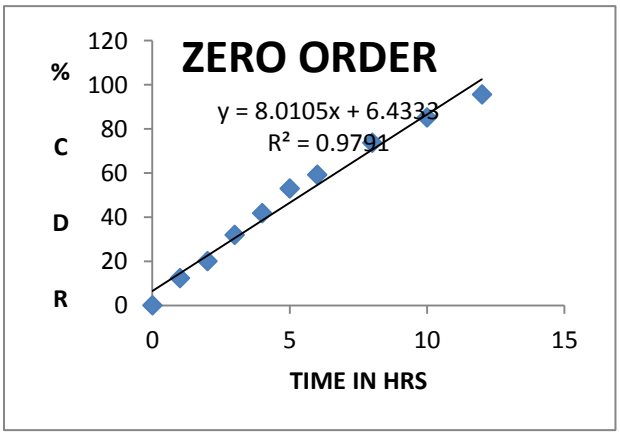
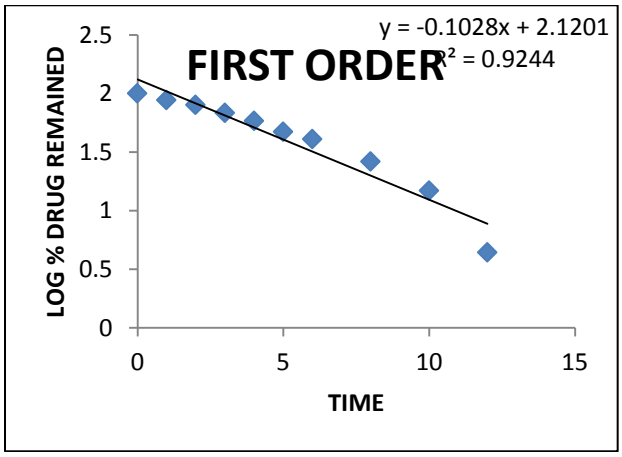


Fig 13: Dissolution graph of bilayer tablets – verapamil HCL SR layer.

Discussion: The amount of drug release from optimized Bilayer formulation was found to be 97.50% in 30 mins followed by the SR release i.e, 95.6% in 12 hrs.

3.3) Analysis of dissolution data





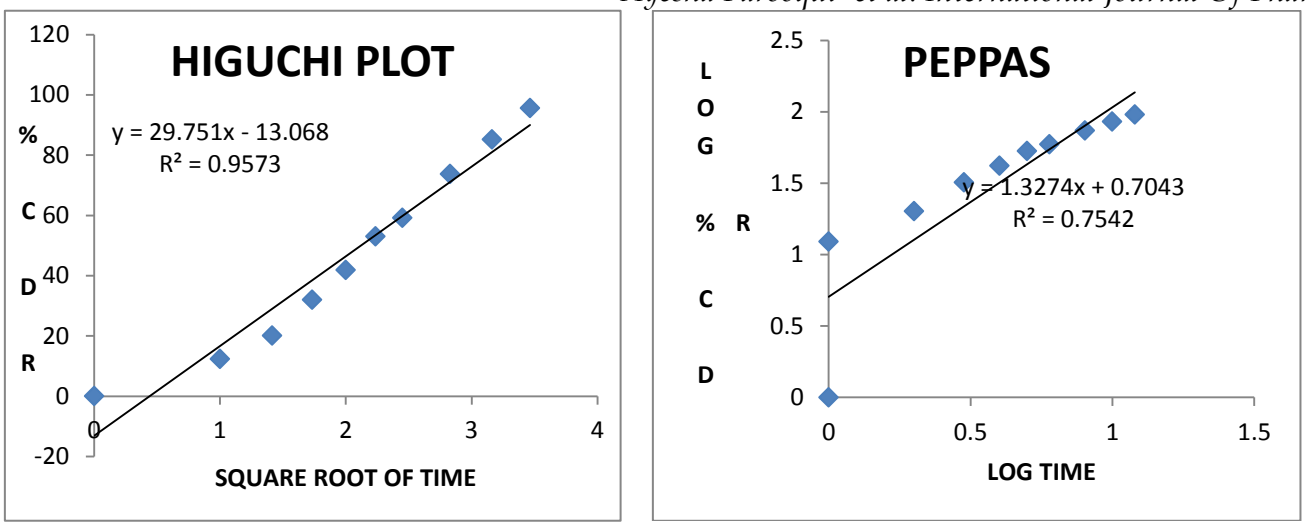


Fig 14: Drug release kinetics of optimized bilayered tablet.

Discussion:

The Dissolution data were fitted into different kinetic models like Zero-order, First order, Higuchi's model and Peppa's models. The correlation coefficient values (R^2) of optimized Bilayered tablet of verapamil HCl indicate that the drug release was following Zero order release kinetics and non -fickian mechanism.

3.4) Stability Studies

Table-11: Stability studies as per ICH guidelines.

Time	Colour	Assay		Cumulative % drug release at 30minutes		Cumulative % drug release at 12 hrs	
		25±2^{0}c and 65±5%RH	**40±2^{0}c and 75±5%RH**	**25±2^{0}c and 65±5%RH**	**40±2^{0}c and 75±5%RH**	**25±2^{0}c and 65±5%RH**	**40±2^{0}c and 75±5%RH**
First day	White	97	98	100	99.7	99	97.5
30 days	White	99.98	98.35	99.18	98.71	98.8	97.1
60 days	White	99.89	98.75	97.85	99.36	96.18	96.63
90 days	White	98.36	98.59	99.55	98.52	99.45	99.22

Discussion: Short term stability studies were carried out at accelerated conditions of 25±2^{0}c and 65±5%RH and 40±2^{0}c and 75±5%RH in accordance with ICH Guidelines Q1. There was no change in physical appearance in the optimized batch over a period of three months .There was no significant change in % release of drug after 3 months indicating that the formulation is stable.

4. Conclusion

From the present study it was concluded that Gastroretentive Bilayer mucoadhesive tablets of Verapamil HCl formulated with 10% sodium alginate for immediate release layer and 15% HPMC and 10% carbopol 934p as bioadhesive polymers for sustained release layer showed promising results of drug release characteristics and also an effective bioadhesive strength, invitro residence time upto 12hrs.Short term stability studies (3 months) showed that the formulation is stable .Therefore, necessitating to continue further research on Invivo small animal experimentation and also intermediate and long term stability studies.

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