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FORMULATION AND EVALUATION OF BILAYER BUCCOADHESIVE TABLETS OF ALMOTRIPTAN MALATE

Sana Ahmed*, Dr. Syed Abdul Azeez Basha, Ayesha Farooqui
Department of Pharmaceutics, Deccan School of Pharmacy, Nampally, Dar-us-salaam-643 001 Telangana, India.
Email:sana_ahmed3777@yahoo.com

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Abstract:

The drug delivery via buccal route is considered to be one of promising alternative to oral route and quick entry of drug into the systemic circulation through the internal jugular vein. The conventional dosage forms available are associated with severe side effects like gastrointestinal upset and bloody diarrhoea & where in antimigrane agents are also characterized by short biological half life, due to which frequency of dosing is increased, which results in patient incompliance. In order to overcome these drawbacks, an attempt was made to design and evaluate bilayer buccoadhesive tablets of Almotriptan malate.

Different formulations of Almotriptan malate immediate and sustained release having polymers at different concentrations were prepared by direct compression method. In immediate release layer (IR), among seven formulations, the formulation (F4) containing sodium alginate (9%) was nominated as best formulation as it exhibited an in-vitro drug release of 99.33% within 30 min. whereas in sustained release layer (SR), among six formulations, the formulation (F6) containing ethyl cellulose (7.5%) and carbopol 934P (10%) showed desired drug release of 98.67% in 12 hr along with good bioadhesive strength (14.24 gm). All the formulations showed uniformity in hardness, weight variation, thickness, friability and content uniformity within the specified limits. The optimized bilayer Buccoadhesive tablets were evaluated for hardness, thickness, friability was found to be 5.98 kg/cm^2, 3.71mm, 0.26% respectively. The Bioadhesive strength (gm) was found to be 14.98gm. In-vitro residence time was long enough for delivery of the drug upto 12hrs with %Swelling index of 68%. The amount of drug release for optimized Bilayered formulation was found to be 98.04% in 30 mins followed by the SR release i.e, 96.81% in 12 hrs following zero-order kinetics and non-

fickian release mechanism. Stability studies as per ICH guidelines on the promising bilayer buccoadhesive tablets indicated that there are no significant changes in the drug content.

Key words: Buccoadhesive tablet, Almotriptan malate, Migraine, HPMC, Carbopol 934P, Swelling index, Bioadhesion, In vitro residence.

1. Introduction

Oral route is the most preferred route for administration of drugs. Orally administered dosage forms e.g., tablets, capsules are convenient dosage form for many drugs but they are challenging to formulate if the active substance has poor dissolution or lower bioavailability. The main aim of any drug delivery system is to provide correct therapeutic amount of drug in the appropriate site in the body to achieve and maintain the desired drug concentration. The drug delivery system should thus produce desired therapeutic output and clinical efficacy. The new drug development technology is thus engrossed in exploiting the oral drug delivery route and coming out with innovative forms like fast dissolving forms, oral mucosal drug delivery forms. 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. Oral mucosal drug delivery the term describe the delivery of drugs across the oral mucosa. This is an alternative method of systemic drug delivery that offers several advantages over both injectables and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation. The preferred site for retentive oral transmucosal delivery systems and for sustained and controlled-release delivery devices is the buccal mucosa. Therapeutic agents administered through buccal mucosa enters directly to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability.

Almotriptan is a second- generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. Examination of adverse events found, Almotriptan to be superior over other triptans. It has a selective action on serotonin receptors. The conventional dosage forms available are associated with severe

side effects like gastrointestinal upset and bloody diarrhoea & where in antimigrane agents are also characterized by short biological half life i.e; 3-4 hrs, due to which frequency of dosing is increased, which results in patient incompliance. In order to overcome these drawbacks, an attempt was made to design and evaluate bilayer buccoadhesive tablets of Almotriptan malate. Literature survey was carried out on the proposed topic and the survey reveals that, no work has been undertaken on the proposed topic.

2. Materials and Methods

2.1) Materials: Almotriptan malate 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) Method

Preparation of bilayer buccoadhesive 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: Composition of bucco-adhesive tablets of Almotriptan malate (Immediate release layer).

Ingredients	F1	F2	F3	F4	F5	F6	F7
Almotriptan malate (mg)	12.5	12.5	12.5	12.5	12.5	12.5	12.5
PVP K30 (%)	5	5	5	5	5	5	5
Carbopol 934P (%)	7.5	-	-	-	10	-	-
Sodium Alginate (%)	-	7.5	-	9	-	10	-
Guar gum (%)	-	-	7.5	--	-	-	10
Talc (%)	2.5	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	2.5
Microcrystalline cellulose (MCC)	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Sodium saccharin (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Vanillin (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Total weight (mg)	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**	**200mg**

Table-2: Composition of bucco-adhesive tablets of Almotriptan malate (Sustained release layer).

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Almotriptan malate (mg)	12.5	12.5	12.5	12.5	12.5	12.5
HPMC(%)	15	-	-	15	-	-
Xantham gum (%)	-	15	-	-	15	-
Ethyl cellulose (%)	-	-	7.5	-	-	7.5
Sodium Alginate (%)	10	10	10	-	-	-
Carbopol 934P	-	-	-	10	10	10
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
Microcrystalline cellulose(MCC)	q.s	q.s	q.s	q.s	q.s	q.s
Sodium saccharin (%)	2.5	2.5	2.5	2.5	2.5	2.5
Vanillin (%)	2.5	2.5	2.5	2.5	2.5	2.5
Total weight (mg)	**250mg**	**250mg**	**250mg**	**250mg**	**250mg**	**250mg**

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

Ingredients	**IR Optimized Formulation Batch (F4)**	**SR Optimized Formulation Batch (F6)**	**Bilayer Tablet**
Almotriptan malate	12.5	12.5	25
Polyvinyl pyrrolidine K30	10	-	10
Ethyl cellulose	-	18.75	18.75
Sodium alginate	18	-	18
Carbopol	-	25	25

Microcrystalline cellulose	148.45	180.25	328.7
Talc	5	6.25	11.25
Magnesium Stearate	5	6.25	11.25
Sodium saccharin	0.4	0.5	0.9
Vanillin	0.4	0.5	0.9
Iron oxide	0.25	-	0.25
Total weight	**200 mg**	**250 mg**	**450 mg**

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 buccal 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 Almotriptan malate 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.

Bulk density = Weight of powder / 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: **% Friability = (W_1-W_2) / W_1 X 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 234nm.

In-vitro bioadhesion studies

Mucoadhesive strength was measured using a modified physical balance. It is a double beam balance in which a glass beaker replaced the right pan and a glass slide attached to the base of a glass beaker replaced the left pan .The mucosal

membrane was fixed to the base of an inverted glass beaker. The total set-up was adjusted in a way that any increase in the weight of the right side will exert a force pulling the tablet attached to the mucosal membrane upward till detachment .The tablet was wetted from one surface with 0.5 ml pH 6.8 phosphate buffer then brought in contact with the mucosal surface for 5 min. Distilled water was added inside the right side glass beaker from a burette till the detachment of the tablet. The volume of the distilled water needed was recorded and it represented the mucoadhesive strength in grams.

Figure-1: Schematic representation of modified physical balance for bioadhesion strength measurement

In vitro *R*esidence time

Invitro residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 500 mL pH 6.8 phosphate buffer maintained at 37^0 C. The sheep buccal tissue was glued to the surface of a glass slab, vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5 mL of phosphate buffer pH 6.8 and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to run in such a way that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded.

Figure-2: Modified disintegration apparatus for Invitro residence measurement

Surface p^H Evaluation

The surface p^H of the tablets was determined in order to investigate the possibility of any side effect, in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was our attempt to keep surface p^H as close to neutral as possible.The tablets were placed in glass tubes and allowed to swell in contact with 1ml of distilled water for 2 hours. The surface pH was noted by bringing glass micro electrode near the surface of tablet and allowing it to equilibrate for 1 min. Thereafter surface pH measurements were recorded.

Swelling index

The swelling index of the prepared Almotriptan malate buccal tablets was determined by weighing 3 tablets and recording their weights before placing them separately in weighed beakers. The total weights were recorded. 10 ml of distilled water was added to each beaker and were placed in an incubator at 37^{O} C. at time intervals of 1, 2, 4, 6, 8, 10 and up to 12 hrs. Excess water is carefully removed and the swollen tablets were weighed (W2). The experiment was repeated and the average W1 and W2 were reported. The swelling index was determined from the formula

$$\textbf{Swelling Index} = [(W2-W1) \div W1] \times 100$$

Where, W_1- initial weight of the tablet, W_2- weight of the tablet after swelling.

In-vitro release study

USP type II rotating paddle method was used to study the drug release from the tablet . The dissolution medium consisted of 500 ml of phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5^{o}C, with a rotation speed of 50 rpm. 5ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Whattsman filter and analyzed for drug content against pH 6.8 Phosphate buffer as a blank by UV/Visible spectrophotometer at 234 nm and the percentage drug release was calculated.

Stability studies as per ICH guidelines

Stability studies were performed at a temperature of 40^0C at 75 % RH, over a period of three months (90 days) on the promising buccal tablets of Almotriptan malate formulation. 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 as per ICH guidelines.

3. Results & Discussion

3.1) Preformulation Studies

3.1.1) Drug-Excipients compatibility studies by FT-IR:

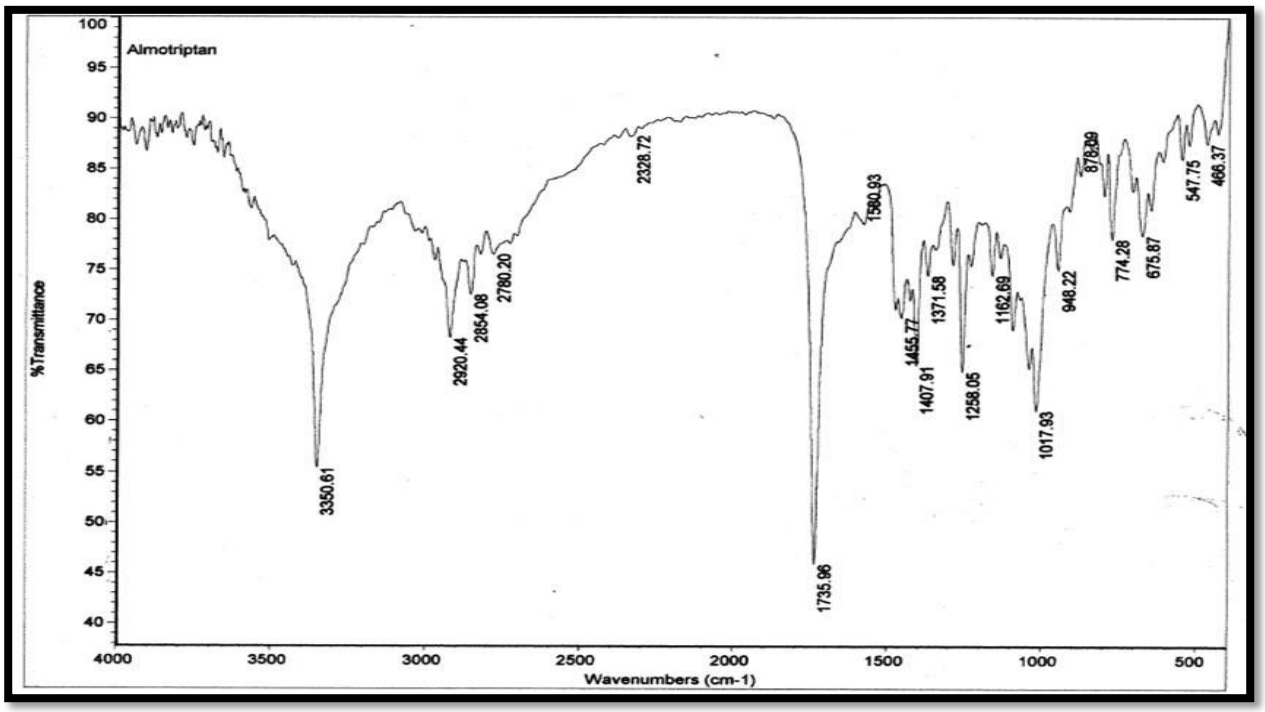

Figure-3: FT-IR Spectrum of pure drug Almotriptan malate.

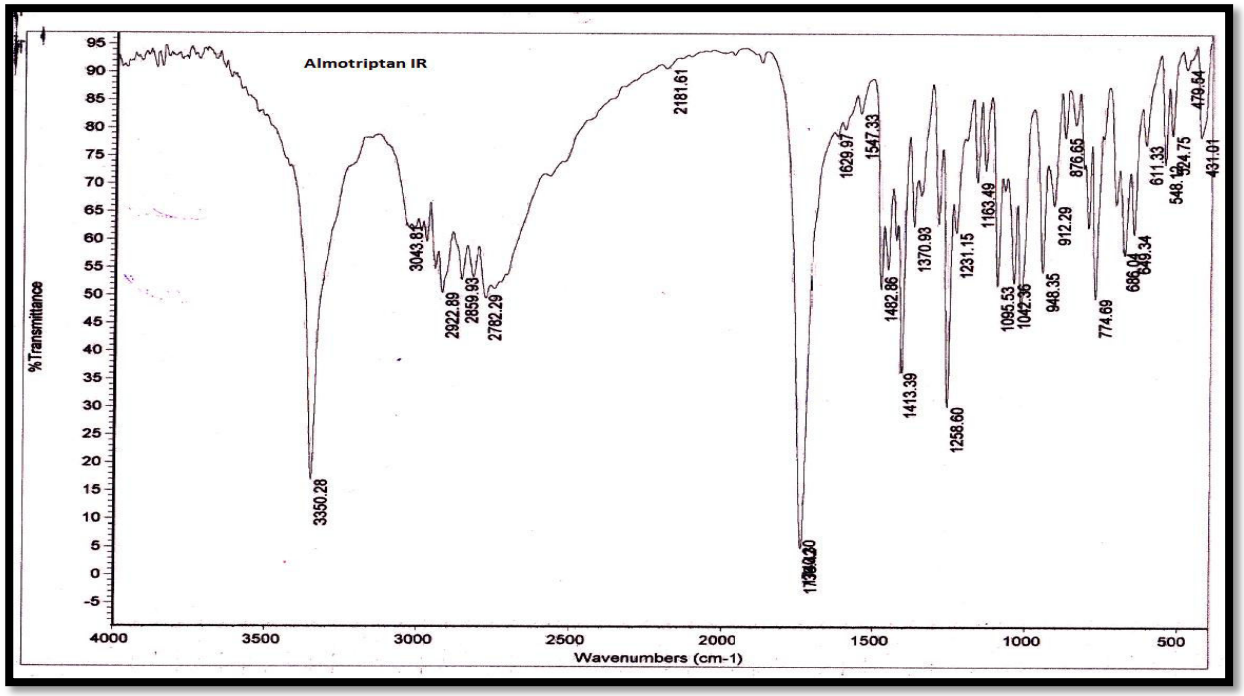

Figure-4: FT-IR Spectrum of optimized Immediate release formulation of Almotriptan malate.

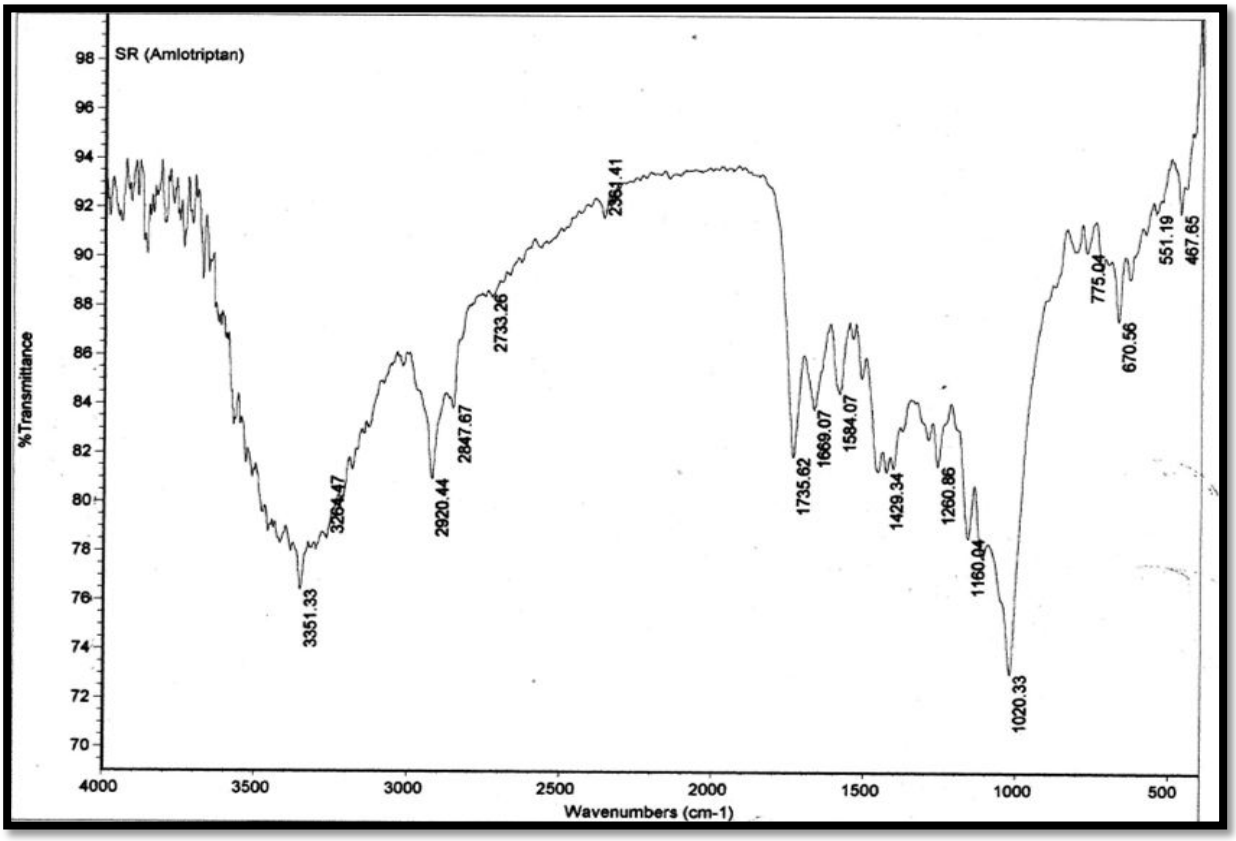

Figure-5: FT-IR Spectrum of optimized Sustained release formulation of Almotriptan malate.

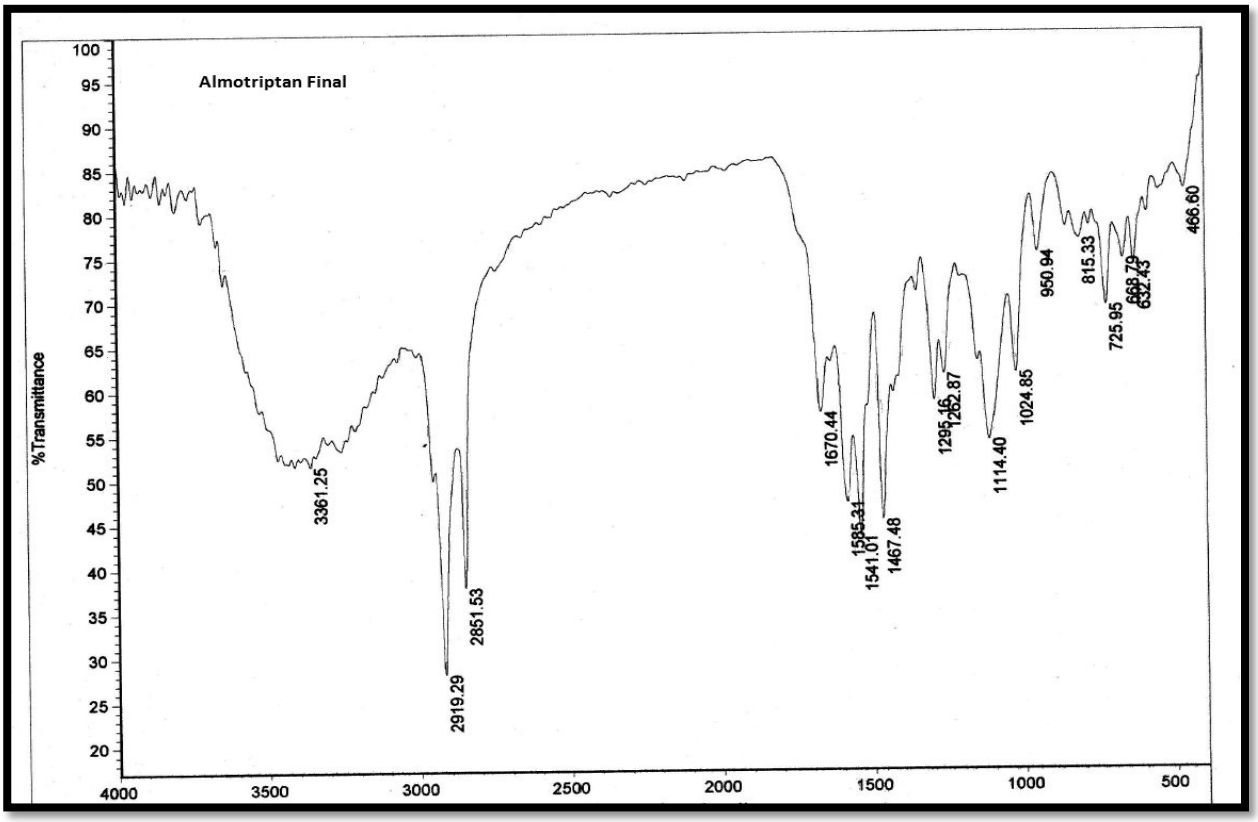

Figure-6: FT-IR Spectrum of optimized bilayer tablet of Almotriptan malate

Discussion: There is no significant change in the shift of major peaks of drug in the above graphs, hence there were no drug and excipient interactions found in either IR, SR, or Bilayer tablets.

3.1.2) Evaluation of pre compression parameters.

Table-4: Precompression parameters of various formulations of Immediate release layer of Almotriptan malate.

Formulation Code	Angle of repose(ø)	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Hausner's ratio	Flow
F1	21.5	0.489	0.552	11.41304	1.128834	Good
F2	22.5	0.782	0.881	11.23723	1.126598	Good
F3	25.6	0.689	0.777	11.32561	1.127721	Good
F4	19	0.741	0.855	13.33333	1.153846	Good
F5	28	0.792	0.888	10.81081	1.121212	Good
F6	25	0.38	0.45	15.55556	1.184211	Good
F7	27	0.278	0.312	10.89744	1.122302	Good

Table -5: Precompression parameters of various formulations of Sustained release layer of Almotriptan malate

Formulation Code	Angle of repose(ø)	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's index (%)	Hausener's ratio	Flow
F1	26	0.323	0.403	19.85112	1.247678	Fair
F2	27	0.321	0.398	19.34673	1.239875	Fair
F3	25.6	0.225	0.301	25.24917	1.337778	Fair
F4	23	0.228	0.295	22.71186	1.29386	Fair
F5	22	0.229	0.285	19.64912	1.244541	Fair
F6	21	0.255	0.302	15.56291	1.184314	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: Postcompression Parameters of various formulations of Immediate release tablets of Almotriptan malate.

Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Drug content * (%)
F1	3.85 ± 0.021	3.44 ± 0.017	0.34	198.4 ± 2.71	99.53±1.80
F2	3.73 ± 0.033	3.33± 0.022	0.21	200± 2.74	98.28±1.99
F3	3.74 ± 0.039	3.23± 0.031	0.17	208± 2.63	98.35±1.14
F4	3.81 ± 0.021	3.35± 0.028	0.29	198.4 ± 2.71	99.32±0.58
F5	3.84 ± 0.033	3.27± 0.026	0.21	195± 2.40	100.24±1.05
F6	3.76 ± 0.029	3.28± 0.031	0.26	199± 2.63	99.53±1.32
F7	3.95 ± 0.011	3.34 ± 0.017	0.27	196.4 ± 2.41	98.28±1.99

Discussion: The values of hardness, thickness, friability, weight variation and drug content of all the Immediate release formulation were found to be within the limits as stated in the Indian Pharmacoepia. The optimized Immediate release formulation (F4) was found with hardness 3.81 kg/cm^2, thickness-3.35mm, %friability-0.29, weight variation-198.4 ± 2.71 and drug content- 99.32±0.58 indicated by the low values of standard deviation and were found to be in the range.

Table-7: Postcompression Parameters of various formulations of Sustained release tablets of Almotriptan malate

Formulation Code	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Drug content * (%)
F1	6.71± 0.809	3.53± 0.015	0.27	250± 1.64	98.25±1.37

F2	6.51± 0.370	3.63± 0.023	0.28	248±1.53	98.48±0.80
F3	6.13± 0.118	3.44 ± 0.015	0.21	256.4 ± 1.51	99.12±2.47
F4	5.32± 0.200	3.53± 0.027	0.26	249± 1.61	101.22±0.88
F5	6.74± 0.390	3.43± 0.018	0.30	247± 2.11	100.24±1.25
F6	6.11± 0.104	3.54 ± 0.028	0.30	248.4 ± 3.11	99.53±1.87

Discussion: The values of hardness, thickness, friability, weight variation and drug content of all the Sustained release formulation were found to be within the limits as stated in the Indian Pharmacoepia. The optimized Sustained release formulation (F6) was found with hardness- 6.11kg/cm^2, thickness-3.54 mm, %friability-0.30, weight variation-248.4 ± 3.11and drug content- 99.53±1.87 indicated by the low values of standard deviation and were found to be in the range.

Table-8: Ex-vivo Mucoadhesive strength, In- vitro residence time and Surface pH values of Sustained release formulations.

Formulation code	Mucoadhesive strength (gms)	In vitro residence time (hrs)	Surface pH (±SD)
F1	8.54	8hrs 10min	6.46±0.057
F2	9.0	6hrs	6.36±0.057
F3	9.5	7hr 25min	6.43±0.071
F4	15.72	13hrs	6.43±0.208
F5	9.83	11hrs 5min	6.56±0.057
F6	14.24	12hrs	6.48±0.10

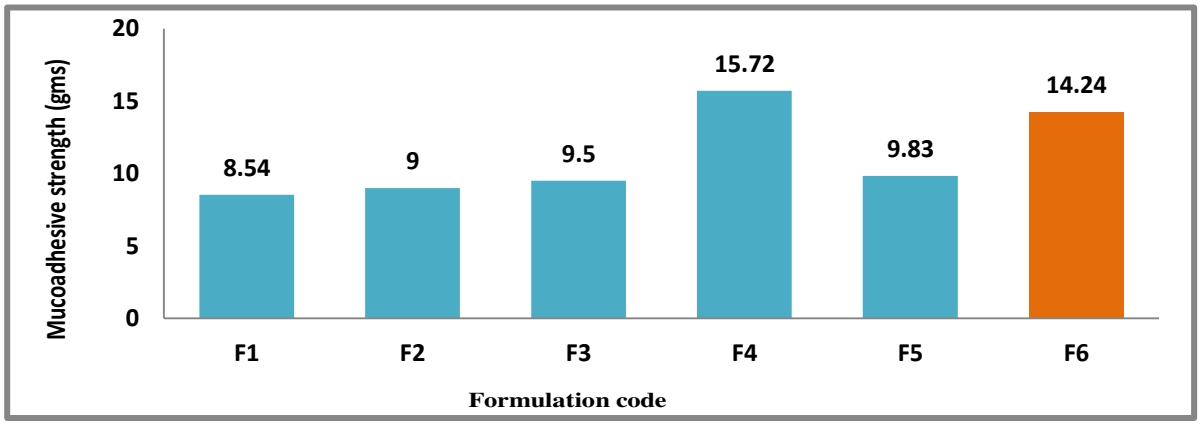

Figure-7: Mucoadhesive Strength of different formulation.

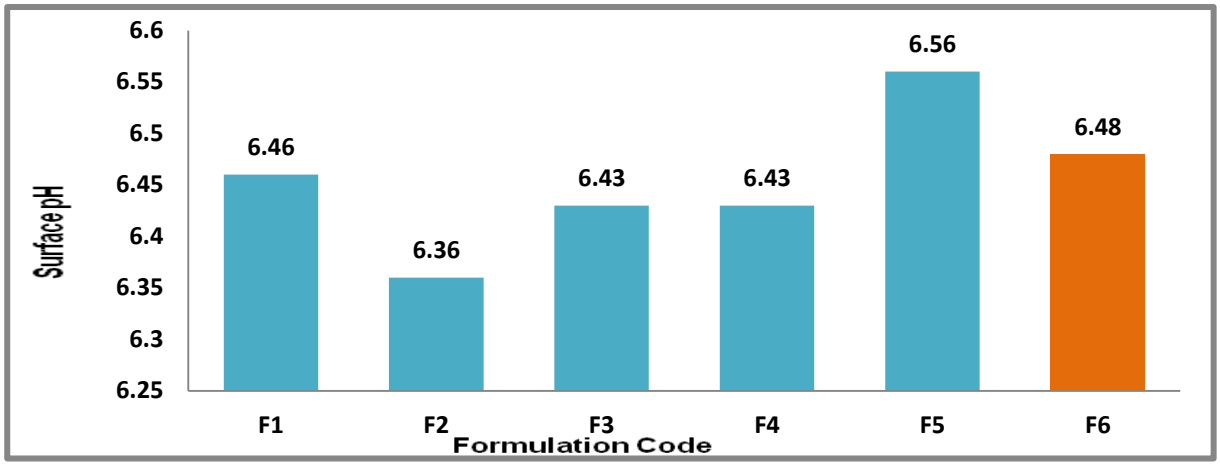

Figure-8: Surface pH of SR formulation.

Discussion: The optimized sustained release formulation (F6) was found with mucoadhesive strength-14.24 gm, In vitro residence time - 12hrs, and surface pH – 6.48 which was close to neutral pH.

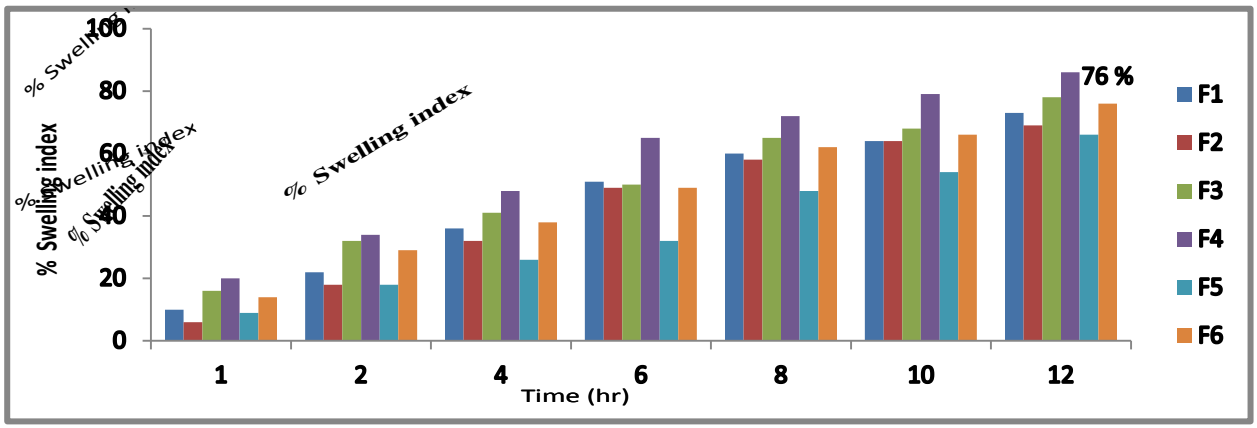

Figure-9: % Swelling index of different formulation.

Discussion: The % swelling index of optimized sustained release formulation (F6) after 12hrs was found to be 76%.

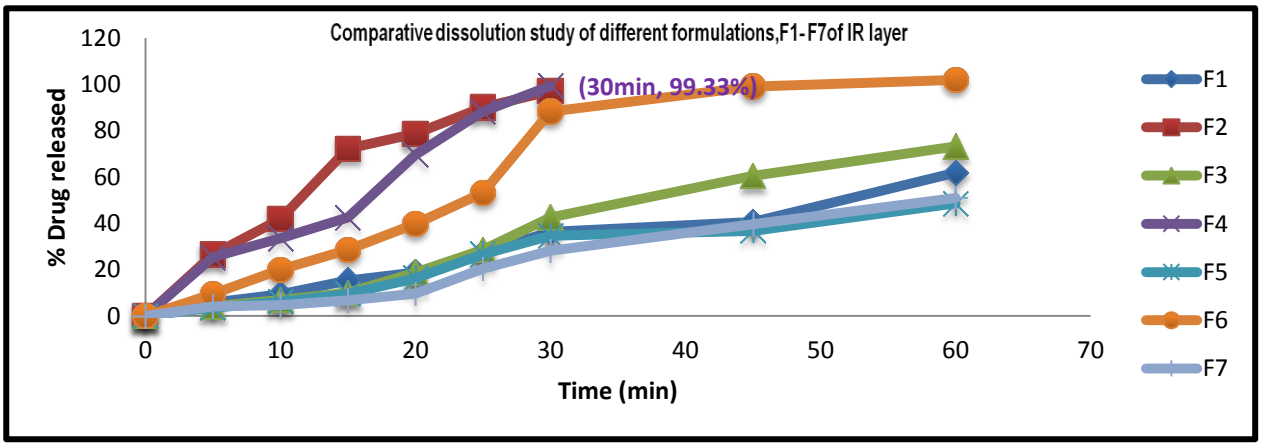

Figure-10: Comparative In vitro drug release profiles of IR Formulations (F1- F7).

Discussion: The optimized immediate release layer of Almotriptan malate show drug release of 99.33 % within 30 min which is much more than the other formulation. Thus due to fast release of drug within stipulated time, F4 was chosen as best formulation.

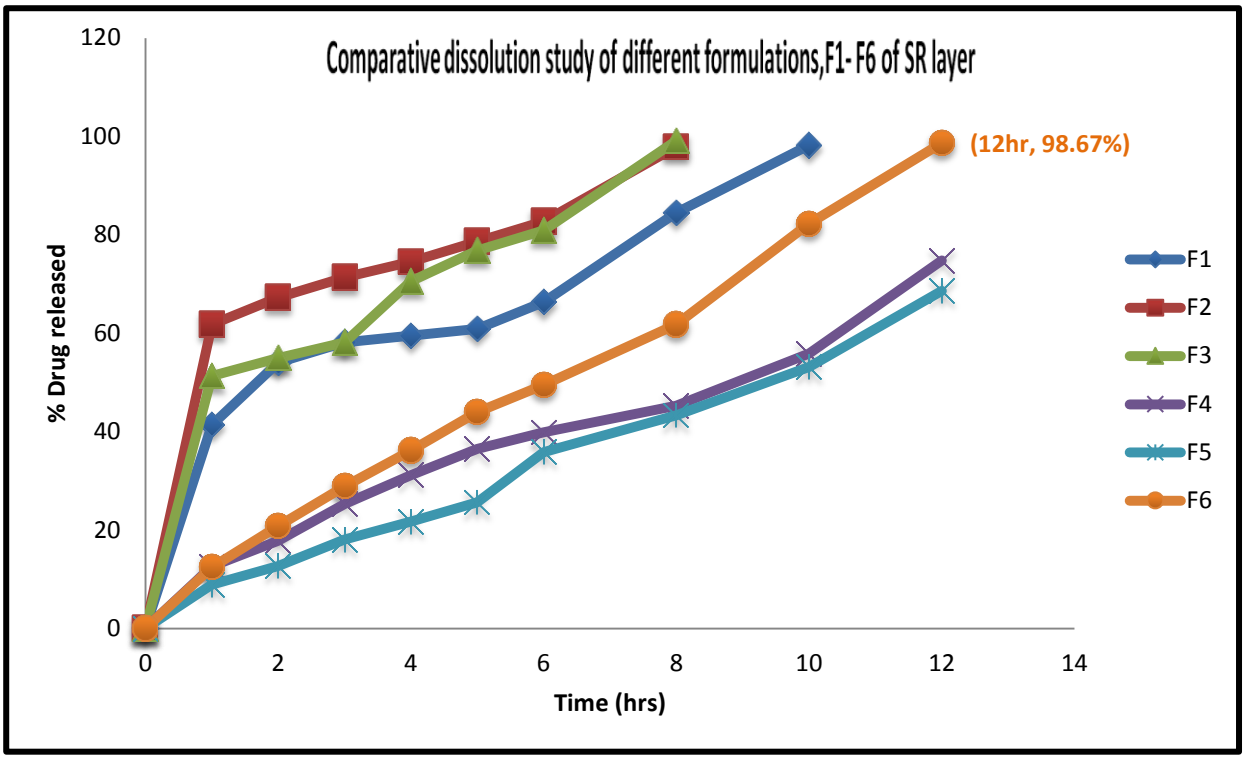

Figure-11: Comparative In vitro drug release profiles of SR Formulations (F1- F6).

Discussion: From all the six batches of SR formulation it was found that batch F6 showed 98.67 % drug release in 12 hours. Therefore F6 containing polymers like ethyl cellulose and Carbopol 934P was chosen as best formulation.

Table-9: Evaluation parameters of optimized Bilayer Buccoadhesive tablet.

S.no	Evaluation parameters	Bilayer tablet values
1.	Hardness (kg/cm^2)	5.98 ± 0.343
2.	Thickness (mm)	3.71 ± 0.391
3.	Friability (%)	0.26 ± 0.038
4	Mucoadhesive strength (gm)	14.98 ± 0.598
5	Invitro residence time (hrs)	12 hrs
6	Surface pH	6.37 ± 0.176

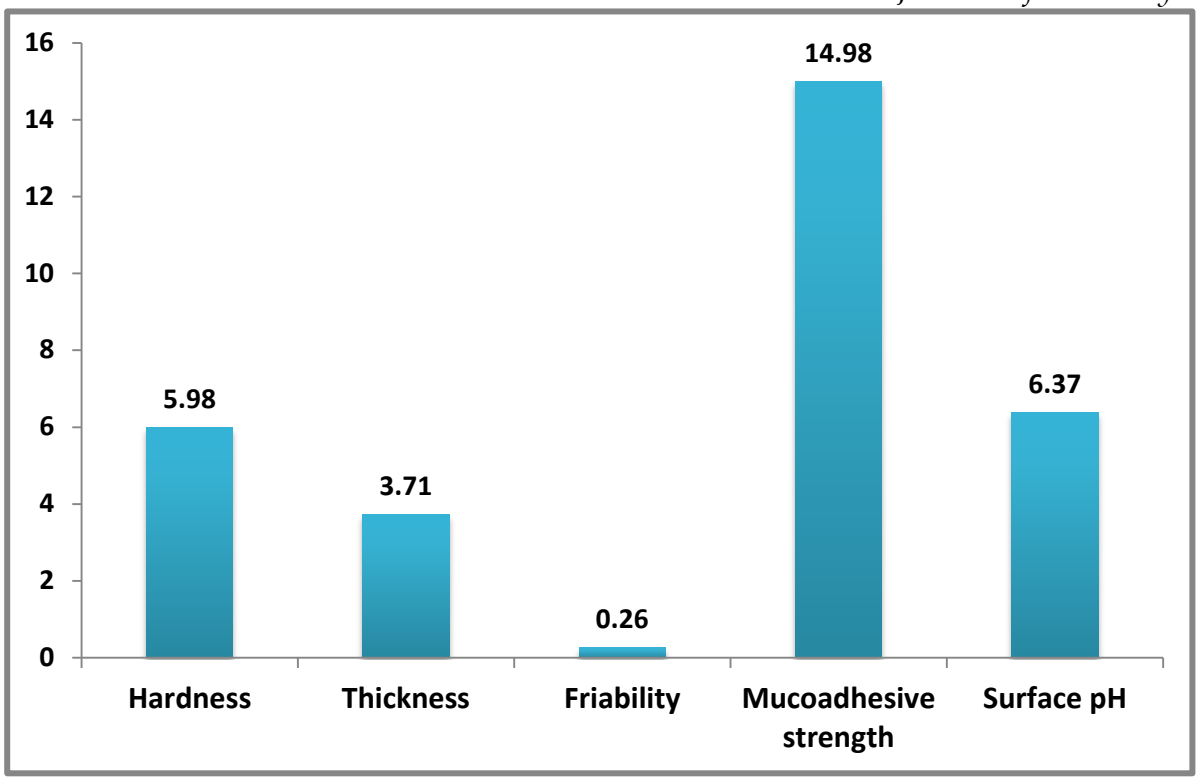

Figure-12: Hardness, Friability, Thickness, mucoadhesive strength and Surface pH of Bilayer Buccoadhesive tablet.

Discussion: The optimized bilayer mucoadhesive tablets were evaluated for hardness, thickness, friability i.e. 5.98 kg/cm^2, 3.71 mm, 0.26%. The Mucodhesive strength (gm) was found to be 14.98 gm. The In vitro Residence time (hr) was found upto 12hrs and surface pH was almost neutral.

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

S.no	Time (hr)	% Swelling Index
1	1	11
2	2	14
3	4	29
4	6	38
5	8	49
6	10	62
7	12	68

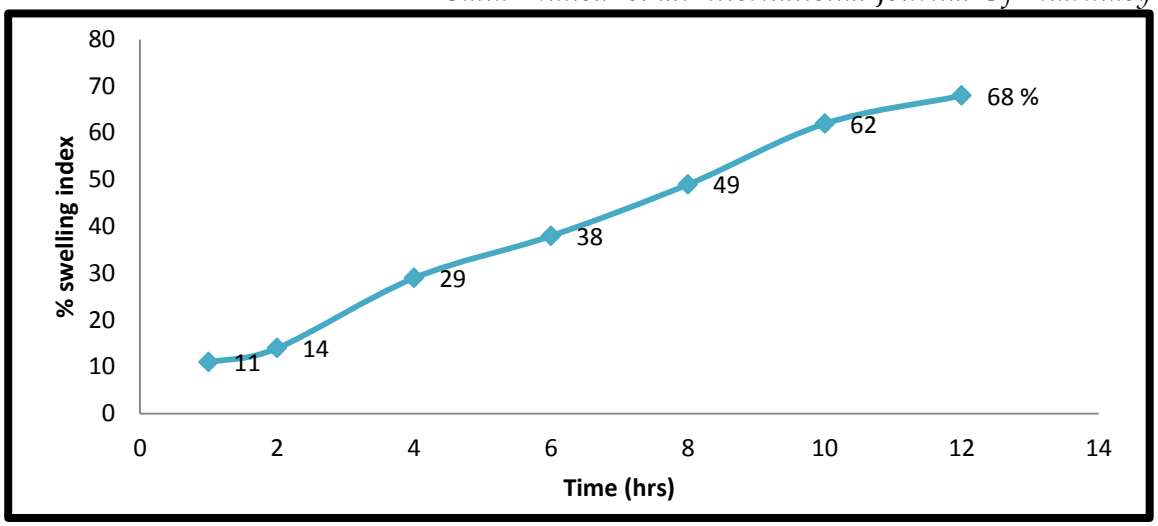

Figure-13: % Swelling index of optimized bilayer buccoadhesive tablets.

Discussion: % Swelling index of optimized bilayer tablet after 12 hr was found to be 68%.

In vitro dissolution study of optimized bilayer tablet of Almotriptan malate.

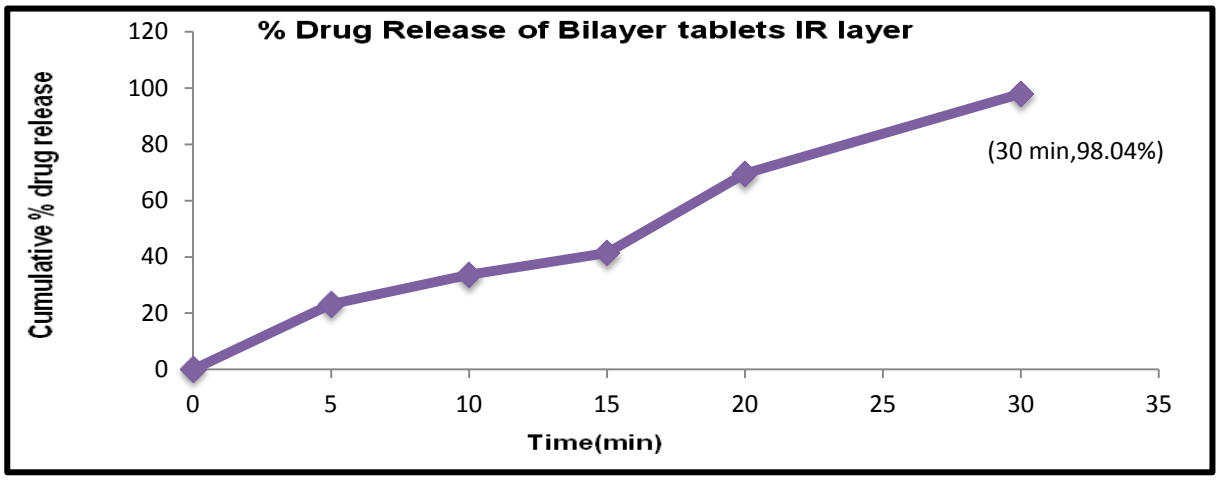

Figure-14: % Drug release from optimized bilayer buccoadhesive tablet after 30 min(IR Layer).

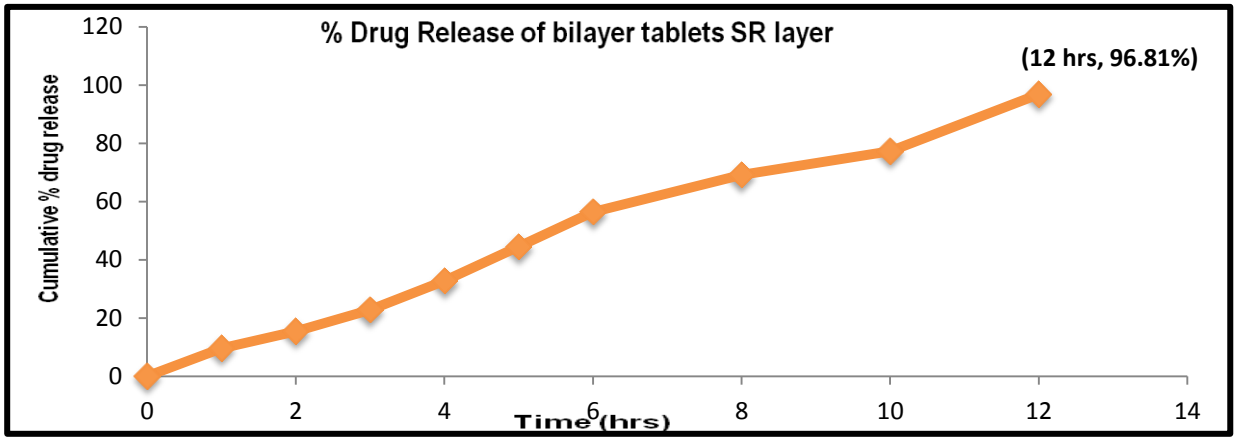

Figure-15: Drug release from optimized bilayer buccoadhesive tablet after 12 hr(SR layer).

Discussion: The cumulative amount of drug release from optimized Bilayer formulation was found to be 98.04% in 30 mins followed by the SR release i.e, 96.81% in 12 hrs.

3.3) Release kinetics of Bilayer Buccoadhesive tablet:

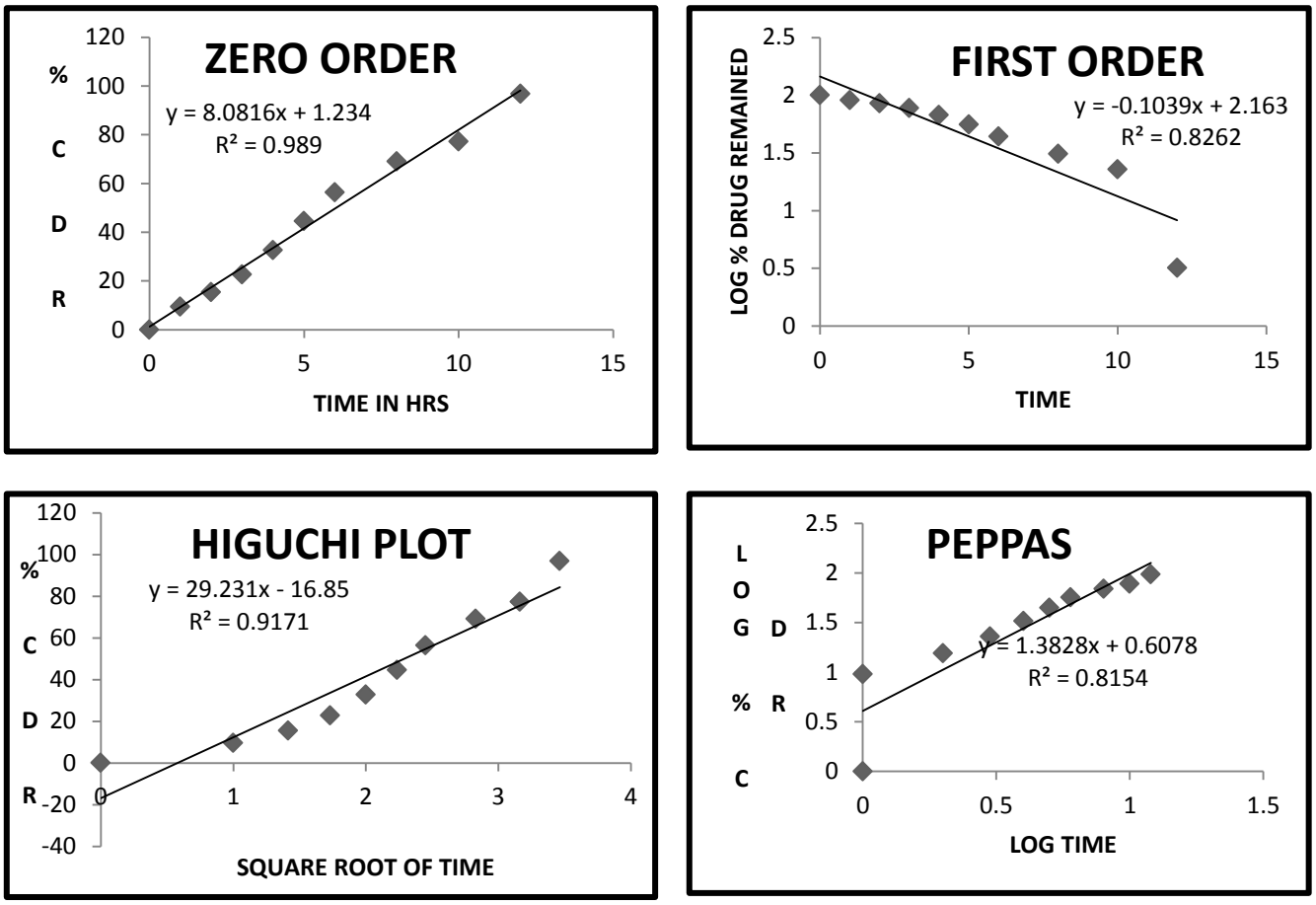

Figure-16: Drug release kinetics of Optimized Buccoadhesive tablet.

Discussion: When the data was subjected to zero order and first order kinetic model, a linear relationship was observed with high " r^2" value for zero order model as compare to first order suggested that the formulation were zero order controlled release. Higuchi model applied to the in-vitro release data, high " r^2" value suggested that the drug release from tablets followed diffusion mechanism. In order to define a perfect model which will represent a better fit model for the in-vitro release data, Korsemeyer-peppas model was applied which defined exact release mechanism when more than one type of release phenomenon was observed. The value of release exponent "n" was calculated as slope defined the release mechanism. The value of "n" obtained for all tablet formulation suggested that the drug release followed non-fickian release mechanism.

3.4) Stability studies as per ICH guidelines.

Time	Colour	Assay.		Cumulative % drug release at 30minutes		Cumulative % drug release at 12 hrs	
		25 ± 2^0c and 65±5%RH	40 ± 2^0c and 75±5%RH	25 ± 2^0c and 65±5%RH	40 ± 2^0c and 75±5%RH	25 ± 2^0c and 65±5%RH	40 ± 2^0c and 75±5%RH
First day	White	98	98	98	98	99	98.5
30 days	White	97.93	97.85	98.38	98.31	99.28	98.91
60 days	White	97.83	97.65	98.25	98.16	97.28	99.36
90 days	White	97.76	97.49	98.05	97.82	99.45	98.12

Table-11: Stability studies of optimized bilayered buccoadhesive as per ICH guidelines.

Discussion: Results from stability studies indicate that the formulated bucoadhesive tablets are stable for a period of 3 months under 2 different conditions at 25 ± 2^0c, 65±5%RH and 40 ± 2^0c and 75±5%RH. There were no remarkable changes were observed during the period of storage.

4. Conclusion

Buccoadhesive Bilayered Tablets of Almotriptan malate was developed by using 9% sodium alginate for immediate release layer and carbopol 934P (10%) and ethyl cellulose (7.5%) as bioadhesive polymer for sustained release layer. Results of the study reveal that the mucoadhesive buccal tablets of Almotriptan malate exhibit a unique combination of bioadhesion and drug release pattern. Further studies such as intermediate and long term stability studies, pharmacokinetic study, in-vivo studies and controlled clinical studies are needed to investigate the formulations. From this study, the optimized Bilayered buccoadhesive tablets of Almotriptan malate appear to be a novel alternative for effective management of Migraine.

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Corresponding Author:

Sana Ahmed*,

Email: *sana_ahmed3777@yahoo.com*