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FORMULATION AND EVALUATION OF BILAYER TABLET OF ALMOTRIPTAN MALATE AND DICLOFENAC POTASSIUM

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ABSTRACT

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. The word derives from the Greek ἡμικρανία (hemikrania), "pain on one side of the head", from ἡμι- (hemi-), "half", and κρανίον (kranion), "skull".Typically the headache affects one half of the head, is pulsating in nature, and lasts from 2 to 72 hours. That affects approximately 17% of adult women and 6% of adult men. It is most common among people age 25 to 55, though it can affect children and teens as well. Migraine is about three times more prevalent in women than men; roughly one in five women and one in 16 men suffer from migraine Associated symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell.

The objective of present study was to formulate and evaluate bilayer tablet of Almotriptan malate (AM) and Diclofenac potassium (DP) for the effective treatment of migraine. The combination of almotriptan malate and diclofenac potassium is used as almotriptan malate establishes the immediate release layer (initialdose) and diclofenac potassium as the sustained release layer (maintenance dose) respectively. The bilayer tablets of AM and DP was particularly designed to minimize the risk of rebound migraine and improve the therapeutic efficacy and to prolong the release of drug and patient compliance. Formulation variables for immediate release layer include sodium starch glycolate and crospovidone as super disintegrants and micro crystalline cellulose as filer. HPMC K100, HPMC K15, was used as sustained release polymers. The result of in-vitro release data showed that HPMC K15 and HPMC K100 combination can sustain the drug release up to 12hrs. From these studies HPMC K15 and HPMCK100 combination has been selected for further studies of bilayer tablet. Almotriptan malate and diclofenac potassium bilayer tablet were prepared by direct compression method. The hardness of the bilayer tablets was 6.30 ± 0.17kg/cm^2. The thickness of the bilayer tablets was 5.19 ± 0.10mm. The drug content of Almotriptan malate and Diclofenac potassium was 98.10 ± 0.90 (SR) and 98.84 ± 0.09 (IR). The *in-vitro* drug release of bilayer tablets have Almotriptan malate immediate release was within 45minutes and Diclofenac release from the tablets was found sustained over 12 hours with Zero order equation to analyze the release pattern of the drug from the polymeric system. The value of "n" were in the range of 8.0454, indicating the drug release followed Super case-II transport diffusion, possibly owing to chain distanglement and swelling of hydrophilic polymer. The Fourier transform infrared spectroscopy (FT-IR) analyses indicated that there was absence of any chemical interaction between the drugs and excipients.

The results of Accelerated stability studies showed that all parameters were within the expected specifications and there was no significant changes observed from initial to 2month, indicating good stability.

Thus, the objective of bilayer drug delivery system of anti-migraine drug almotriptan malate and diclofenac potassium with sustained release profile was achieved.

INTRODUCTION:

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. The term migraine is originally derived from the Greek word "hemicrania" which means "half of the head" from hemi means (half) and cranion means (skull). And for 70% of migraine suffers, the headache is unilateral or occurring on one half of the head. is pulsating in nature and lasts from 2 to 72 hours. Migraine is considered a vascular headache because it is associated with changes in the size of the arteries in and outside of the brain and irritation of nerves that surround the brain. The brain tissue itself is not sensitive to pain because it lacks pain receptors. Mostly pain sensitive structures are present a round the brain and several areas of the head and neck portions. They are present with in cranium and outside the cranium disturbance in these pain sensitive structures causes headache. The brain chemical serotonin may play an important role in this process as it does in other conditions, including depression and eating disorders. The changes in serotonin in the blood vessels and the brain lead to shifts of blood flow bypassing the capillaries and going through shunts to the veins. The distention of vessels contributes to the pain of migraine. Migraines are believed to be due to a mixture of environmental and genetic factors. About two-thirds of cases run in families. Changing hormone levels may also play a role, as migraines affect slightly more boys than girls before puberty, but about two to three times more women than men. The risk of migraines usually decreases during pregnancy. While migraines occur in childhood they generally strike in the twenties or thirties [1,2].
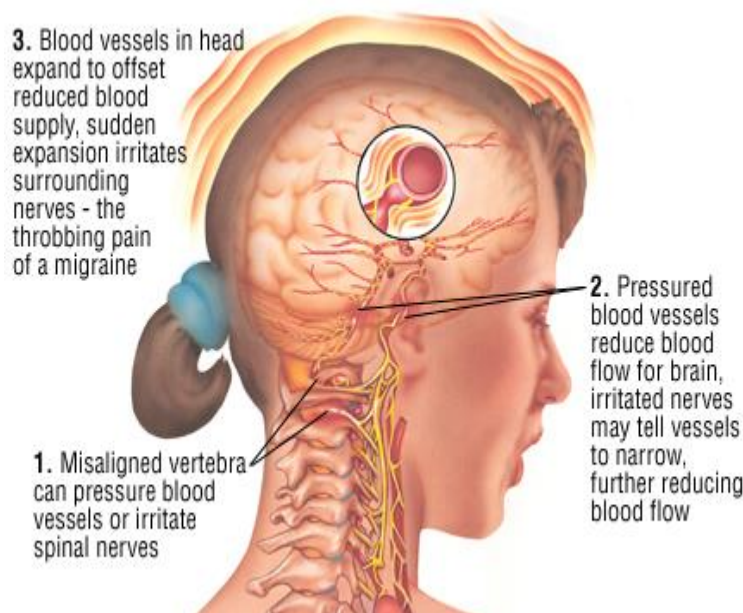

FIG-1. Diagram showing the pathways of Migraine.

Bilayer tablet is new concept for successful development of sustained release formulation along with various features to provide a way of successful drug delivery system that include an immediate release (IR) layer and a Sustained release (SR) layer. Immediate release layer provides therapeutically effective plasma drug concentration for a short period of time and Sustained release (SR) layer maintain uniform drug levels over a sustained period to reduce dosing intervals and side effects, increase the safety margin for highly-potent drugs and thus offer better patient compliance. It also includes bimodal drug delivery profile (fast release / slow release / fast release). This type of system is used primarily when maximum relief needs to be Achieved quickly and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive, antihistaminic, and antiallergic agents, anti-psychotics, hypnotics [3,4].
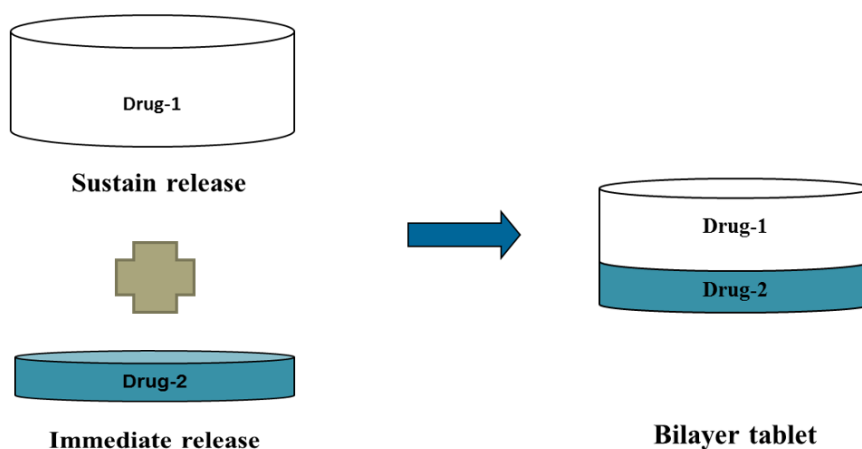

FIG-2. Diagram of Bilayer Tablet.

MATERIALS:

Almotriptan Malate, Sodium Starch glycolate, Crospovidone was obtained from MSN laboratoires, Diclofenac Potassium, PVP K 30 were obtained from BMR PHARMA, Hydroxy propyl methyl cellulose K15, K100, Microcrystalline cellulose were obtained from Dr. Reddy's laboratories, Sun set yellow, Magnesium stearate, Talc, Sodium hydroxide (NAOH), Potassium phosphate (KH_2PO_4), 0.1N Hydrochloric acid (HCL) were obtained from S.D fine chem. Ltd.

METHODS:

Drug-excipient compatibility studies [5]: Sample were reduced to powder and analyzed by using a Fourier transform infrared (FT-IR) spectroscope (Bruker) and results were represented in FIG-3,4,5. Table.5,6,7.

Flow properties were studied by determining various parameters like the Angle of repose, Bulk density, tapped density, Compressibility Index and Hausner ratio and results were represented in Table 11 for (IR) and Table 12 for (SR).

Dose Calculation: Dose of individual drugs were calculated as per below formula

$$Dt = Dose (1 + 0.693 \times t/t_{1/2})$$

Where, Dt = Total dose, Dose = Immediate release dose, t = Total time period for which sustained release is required, $t_{1/2}$ = Half-life of drug. Half-life of Diclofenac potassium ranges from 1.5-2 hr.

According to dose calculation, IR dose of drug can be taken in between range of 9.316 mg to 12.08 mg for the preparation of bilayer tablets; thus 10 mg of Almotriptan malate was taken in IR layer and 50 mg of Diclofenac potassium was taken in SR layers.

Preparation and evaluation of individual layer (IR) & (SR):

Ingredients	IR1	1R2	1R3	1R4	1R5	1R6	1R7	IR8
Almotriptan malate	10	10	10	10	10	10	10	10
Sodium starch glycolate	2	4	6	8	–	–	–	–
Crospovidone	–	–	–	–	2	4	6	8
Microcrystalline cellulose	83	81	79	77	83	81	79	77
Magnesium stearate	2	2	2	2	2	2	2	2
Sun set yellow	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2
Total weight of tablets	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

All quantities in mg per tablet, IR=formulation codes

Table 1. Composition of Almotriptan malate immediate release layer.

Ingredients	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
Diclofenac potassium	50	50	50	50	50	50	50	50	50
HPMC K100	120	110	100	–	–	–	60	55	50
HPMC K15	–	–	–	120	110	100	60	55	50
Microcrystalline cellulose	10	20	30	10	20	30	10	20	30
PVP K30	16	16	16	16	16	16	16	16	16
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total Weight of tablets	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

All quantities in mg per tablet, SR=formulation codes

Table 2. Composition of Diclofenac potassium sustained release layer.

Evaluation of Almotriptan malate immediate release layer, Diclofenac potassium sustained release layer: Post compression Parameters like Hardness, Thickness, Weight variation, Friability, Drug content uniformity, *In vitro* dissolution studies were performed results were mentioned in tables 13,14.

Preparation of bilayer tablet of Almortiptan malate and Diclofenac potassium: Optimized batch of almotriptan malate (IR4) and diclofenac potassium (SR7) layers were selected for preparation of bilayer tablet. The quantity of powder blend for the sustained release layer was compressed lightly at 10 station shiv phama tablet press using 8mm round concave punches. Over this compressed layer, required quantity of powder blend for immediate release layer was placed and compressed with the hardness in the range of 5-7 kg/Cm^2 to form a bilayer matrix tablet Prepared bilayer tablet are shown below FIG-2.

Ingredients	BF1
Diclofena potassium	50
HPMC K100	60
HPMC K15	60
Micro crystalline cellulose	10
PVP K30	17
Magnesium stearate	2
Talc	1
Almotriptan malate	10
Sodium starch glycolate	8
Micro crystalline cellulose	78
Sun set yellow	1
Magnesium stearate	2
Talc	1
Total weight of the tablet	**300**

Table 3. Composition of bilayer tablet of Diclofenac potassium and Almotriptan malate.

FIG-2. Bilayer tablet of Almotriptan malate and Diclofenac potassium.

Evaluation of Bilayer layer tablet: Prepared bilayer tablets were evaluated for following parameters Hardness, Thickness, Weight variation, Friability, Drug content uniformity, *In vitro* dissolution studies were performed results were mentioned in tables 17, 18.

Accelerated Stability study of the optimized batch [6]: The purpose of stability testing is to provide evidence on how the quality of drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. In order to determine the change in evaluation parameters and in vitro release profile on storage, stability study of optimized batch was carried out at accelerated storage condition at temperature 25°C±2°C/60%RH, 40° ± 2°C/75% ± 5% RH in a humidity chamber for 2 months. Sample were withdrawn after 30 days interval and evaluated for changes in the drug release.

Kinetic modeling of drug release [7]:

Zero-order model:

$$F = K_0 t$$

Where, F represents the fraction of drug released in time t, and K_0 is the apparent release rate constant or zero-order release constant. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released *versus* time [8, 9].

First-order model:

$$\log C = \log C_0 \, n \, Kt / 2.303$$

Where, C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time [53]. The data obtained are plotted as log cumulative percentage of drug remaining *versus* time which would yield a straight line with a slope of K/2.303.

Higuchi Model:

$$F = K_H \, t^{1/2}$$

Where, F represents the fraction of drug released in time t, and K_H is the Higuchi dissolution constant. The data obtained were plotted as cumulative percentage drug release versus square root of time [10].

Hixsonn-Crowell model:

$$W_0^{1/3} - W_t^{1/3} = \kappa \, t$$

Where, W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and κ (kappa) is a constant incorporating the surface-volume relation. To study the release kinetics, data

Korsmeyer-Peppas Model:

$$Mt / M\infty = Kt^n$$

Where, Mt / M∞ is a fraction of drug released at time t, K is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted as log cumulative percentage drug release *versus* log time. Again, The Korsmeyer-Peppas model was employed in the *in-vitro* drug release behavior analysis of these formulations to distinguish between competing release mechanisms: Fickian release (diffusion-controlled release), non-Fickian release (anomalous transport), and case-II transport (relaxation-controlled release). For spheres, a value of n ≤ 0.43 indicates the Fickian release.

The n value between 0.43 and 0.85 is an indication of non-Fickian release (both diffusion controlled and swelling controlled drug release). When, n ≥ 0.85, it is case-II transport and this involves polymer dissolution and polymeric chain enlargement or relaxation [11, 12].

Release exponent (n)	Drug-transport mechanism	Rate as a function of time
< 0.45	Fickian diffusion	$t^{-0.5}$
0.45< n =0.89	Non – Fickian transport	t^{n-1}
0.89	Case II transport	Zero order release
Higher than 0.89	Super case II transport	t^{n-1}

Table 4. Interpretation of release mechanism from polymeric films.

Results and Discussion:

Drug-excipient compatibility studies: FT-IR spectra of pure almotriptan malate and diclofenac potassium, pure almotriptan malate and diclofenac potassium mixture and its blend with other excipients were presented in (FIG- 3, 4, 5) and in (Table 5, 6,7) respectively. The characteristic peaks of pure almotriptan malate and diclofenac potassium (899.17cm⁻¹, 761.88cm⁻¹,1480.67cm⁻¹,1615.45cm⁻¹,1668.38cm⁻¹,2909.08cm⁻¹, 3327.06cm⁻¹) appeared in both the spectra of almotriptan malate, diclofenac potassium pure drugs , the physical mixture of almotriptan malate and diclofenac potassium HPMC K 100M, HPMC K15, MCC, SSG, PVP K30, and the pure drugs without or with very minute shifting. The characteristic peaks 899.17 cm⁻¹ due to N-H of 5 membered ring ,1480.67 cm⁻¹ due to O-H, 1615.45cm⁻¹ and 1668.38cm⁻¹ C=N peaks, 761.88cm⁻¹ C-Cl, 2909.08 cm⁻¹ is due to Methyl group,3327.06cm⁻¹ C=O. In optimized formulation C=O is observed at 3326.95 cm⁻¹, OH at 1457.49 cm⁻¹, C=N at 1608.34 cm⁻¹, C=Cl at 745.57 cm⁻¹, N-H at 844.76 cm⁻¹, 2948.00cm⁻¹ methyl group. This phenomenon indicates that there was absence of any chemical interaction between the drug and the excipients.
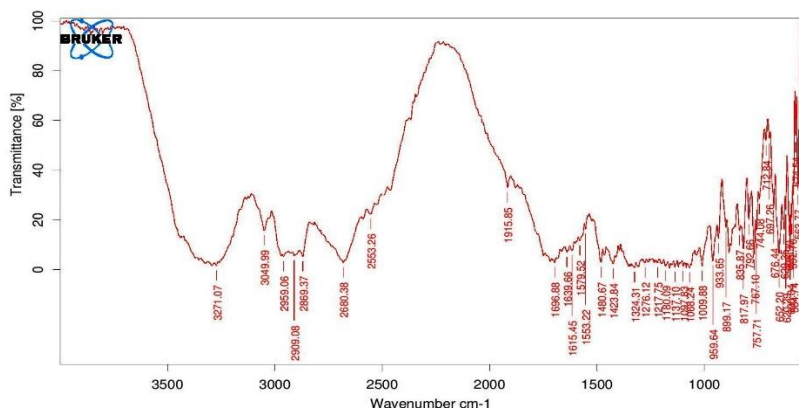

Functional group	Wavelengthcm⁻¹	Range(cm⁻¹)
N-H Rocking	899.17cm⁻¹	700-900cm⁻¹
O-H bending	1480.67cm⁻¹	1200-1500cm⁻¹
C=N stretching	1615.45cm⁻¹	1600-1700cm⁻¹
Methyl group	2909.08cm⁻¹	2850-2960cm-1

FIG-3. FT-IR spectra of Almotriptan malate pure drug.   **Table 5. Characteristic peak of Almotriptan malate pure drug.**

FIG-4. FT-IR spectra of Diclofenac potassium pure drug.

Table 6. Characteristic Peak of Diclofenac potassium pure drug.
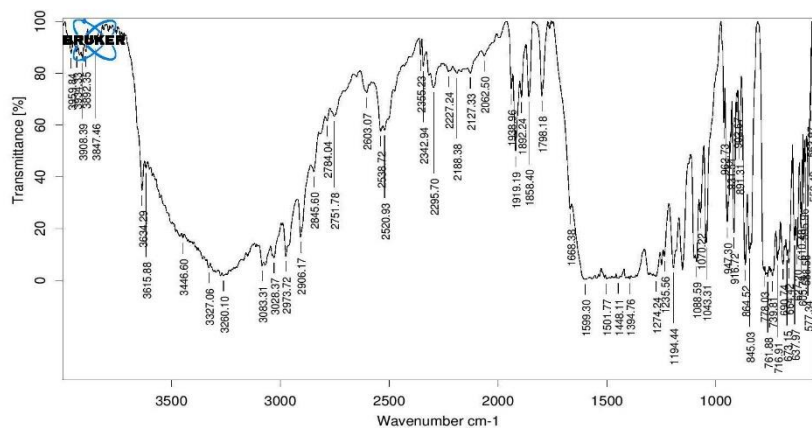
Functional group	Wavelengthcm^{-1}	Range(cm^{-1})
C-Cl stretching	761.88cm^{-1}	600-800cm^{-1}
C=Nstretching	1668.38cm^{-1}	1600-1700cm^{-1}
C=O stretching	3327.06cm^{-1}	3300-3600cm^{-1}

FIG-5. FT-IR spectra of pure almotriptan malate and diclofenac potassium mixture and its blend with other excipients.

Table 7. Characteristic Peak of pure almotriptan malate and diclofenac potassium mixture and its blend with other excipients.
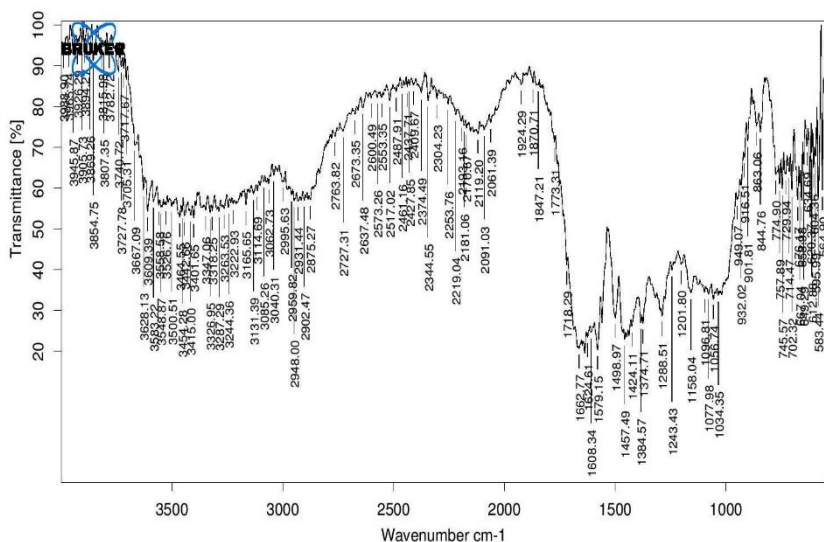
Functional group	Wavelengthcm^{-1}	Range(cm^{-1})
N-H Rocking	844.76cm^{-1}	700-900cm^{-1}
O-H bending	1457.49cm^{-1}	1200-1500cm^{-1}
C=N stretching	1608.34cm^{-1}	1600-1700cm^{-1}
Methyl group	2948.00cm^{-1}	2850-2960cm-1
C-Cl stretching	745.57cm^{-1}	600-800cm^{-1}
C=O stretching	3326.95cm^{-1}	3300-3600cm-1

Analytical Method Development:

The Almotriptan malate was estimated using 0.1N HCl solution and the calibration curve was constructed at 231 nm (Table-7 and FIG-6.). It obeys Beer-Lambert's law in the studied range of 2-12 µg/ml with high R^2 value of 0.9994.

The Diclofenac potassium was estimated using 0.1N HCl solution and the calibration curve was constructed at 280 nm (Table-8 and FIG-7). It obeys Beer-Lambert's law in the studied range of 10-50 µg/ml with high R^2 value of 0.9997.

The calibration curve for diclofenac potassium was constructed in phosphate buffer pH 6.8 at   280nm as shown in (Table-9 and FIG-8). The method obeyed Beer-Lambert's law in the studied range of 10-50µg/ml with a High R^2 in 0.9995.

Concentration (μg/ml)	Absorbance
0	0
2	0.17
4	0.34
6	0.49
8	0.68
10	0.84
12	0.99

Table 8. Calibration curve absorbances of Almotriptan malate in 0.1 N HCl solution.

ALMOTRIPTAN MALATE STANDARD CURVE

$y = 0.083x + 0.0032$
$R^2 = 0.9994$
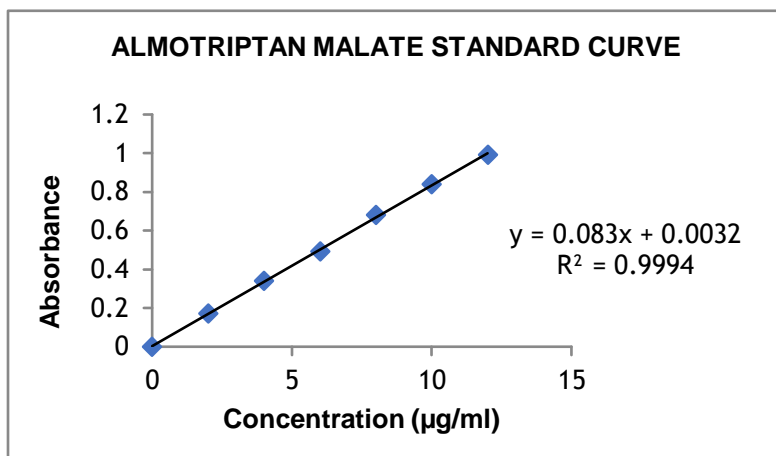
FIG-6. Calibration curve absorbances of Almotriptan malate in 0.1 N HCl solution.

Concentration (μg/ml)	Absorbance
0.00	0.00
10.00	0.211
20.00	0.411
30.00	0.601
40.00	0.802
50.00	0.998

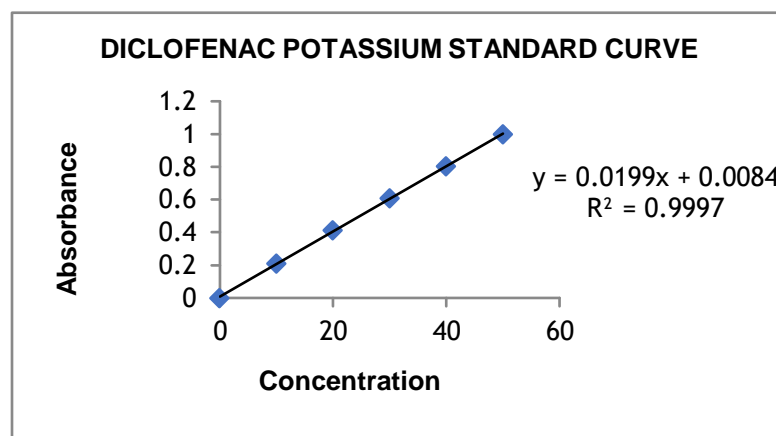**Table 9. Calibration curve absorbances of Diclofenac potassium in 0.1 N HCl solution.**

DICLOFENAC POTASSIUM STANDARD CURVE

$y = 0.0199x + 0.0084$
$R^2 = 0.9997$

FIG-7. Calibration curve absorbances of Diclofenac potassium in 0.1 N HCl solution.

Concentration (μg/ml)	Absorbance
0.00	0.00
10.00	0.112
20.00	0.219
30.00	0.322
40.00	0.431
50.00	0.551

Table 10. Calibration curve absorbances of Diclofenac potassium in pH6.8 phosphate buffer   solution.

DICLOFENAC POTASSIUM STANDARD CURVE

$y = 0.0109x + 1E\text{-}15$
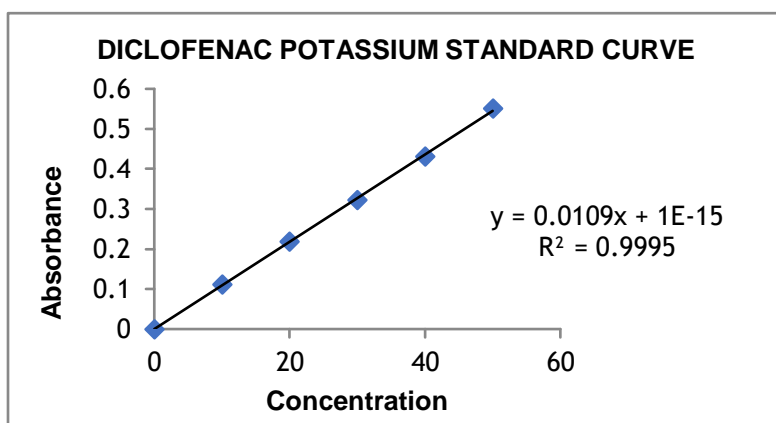$R^2 = 0.9995$

FIG-8. Calibration curve absorbances of Diclofenac potassium in pH6.8 phosphate buffer   solution.

Pre-Compression Properties:

Batch code	Bulk density(gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner ration (HR)	Angle of repose(θ)
IR1	0.27±0.07	0.30±0.05	10.00±0.10	1.11±0.07	23.12±0.05
IR2	0.25±0.01	0.29±0.01	13.79±0.01	1.16±0.01	21.66±0.01
IR3	0.26±0.05	0.28±0.05	7.14±0.10	1.08±0.04	22.05±0.05
IR4	0.27±0.01	0.31±0.01	12.90±0.05	1.14±0.02	21.96±0.05
IR5	0.27±0.07	0.29±0.01	6.89±0.05	1.07±0.07	23.11±0.01
IR6	0.28±0.05	0.31±0.01	9.67±0.05	1.10±0.07	26.00±0.05
IR7	0.25±0.01	0.28±0.07	10.71±0.10	1.12±0.01	26.20±0.01
IR8	0.26±0.07	0.30±0.07	13.33±0.05	1.15±0.05	25.49±0.05

Table 11. Precompression parameters for Almotriptan malate Immediate release layer.

Batch code	Bulk density(gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner ration (HR)	Angle of repose(θ)
SR1	0.375±0.04	0.454±0.05	17.40±0.09	1.21±0.07	29.08±0.00
SR2	0.362±0.02	0.446±0.04	18.99±0.06	1.23±0.03	27.67±0.01
SR3	0.430±0.01	0.508±0.01	15.35±0.07	1.18±0.02	21.96±0.01
SR4	0.381±0.04	0.443±0.05	14.03±0.11	1.16±0.04	26.76±0.05
SR5	0.409±0.01	0.486±0.02	15.90±0.09	1.18±0.08	28.36±0.00
SR6	0.332±0.07	0.374±0.03	11.22±0.11	1.12±0.03	24.85±0.10
SR7	0.420±0.05	0.476±0.03	11.76±0.10	1.13±0.04	27.26±0.05
SR8	0.450±0.05	0.500±0.06	9.80±0.09	1.10±0.07	26.11±0.05
SR9	0.436±0.07	0.496±0.07	12.10±0.05	1.14±0.05	25.09±0.05

Table 12. Precompression parameters for Diclofenac potassium sustained release layer.

All the drugs and excipients were mixed in separately for the preparation of individual layer. The precompression parameters for Almotriptan malate immediate release layer are show in Table-11. The bulk density may influence the tablet compressibility, porosity and dissolution. The bulk density was found in range of 0.25 to 0.28 gm/cm^3. This value of bulk density indicated good packing characteristic. The tapped density was found between 0.28 to 0.31 gm/cm^3. The bulk and tapped density was used to calculate compressibility index and hausner ratio. The carr's compressibility index was in the range of 6.89 to 13.79% suggested good compressibility of blend. The values of hausner ratio where found in the range of 1.07 to 1.16 suggested good flowability of powder blend. The angle of repose of all the blend was within range of 21.66 to 26.20 indicated excellent flow property of powder blend.

The precompression parameters of powder blend for Diclofenac potassium sustained release layer are shown in Table.12. The bulk density was within range of 0.332 to 0.450 gm/cm^3 with tapped density in range if 0.374 to 0.500 gm/cm^3 indicated good packaging capacity of blend. The carr's compressibility index was within 9.80 to 18.99 value suggested good compressibility of powder blend. The angle of repose was 21.96 to 29.08 with hausner ratio of 1.10 to 1.23 suggested good flowability of powder blend.

Hence all the precompression parameter obtained for the powder blends to be compressed as Almotriptan malate immediate release layer and Diclofenac potassium sustained release layer were within the acceptable limits of pharmacopeial specification.

Post-Compression Properties:

Batch code	Hardness (Kg/cm^2)	Thickness (mm)	% Friability	Weight variation (mg)	Drug content %	Disintegration time(sec)
IR1	3.50±0.00	2.17±0.04	0.53±0.05	100±0.02	97.26±1.26	38.64±1.15
IR2	3.53±0.11	2.19±0.03	0.50±0.05	101±0.01	98.63±0.90	33.66±1.00
IR3	3.76±0.05	2.27±0.04	0.16±0.05	99±0.57	96.89±0.90	31.00±2.88
IR4	3.83±0.05	2.23±0.04	0.20±0.00	100±0.02	98.84±0.09	22.66±2.51
IR5	3.46±0.05	2.24±0.05	0.43±0.05	99±0.01	95.09±1.20	53.33±2.51
IR6	3.43±0.05	2.23±0.04	0.40±0.01	101±0.01	98.89±0.90	40.61±1.15
IR7	3.56±0.05	2.24±0.05	0.56±0.05	101±0.01	93.89±1.09	35.33±1.15
IR8	3.70±0.02	2.24±0.05	0.20±0.01	99±0.57	95.78±1.27	27.62±2.51

Table 13. Evaluation parameters of Almotriptan malate Immediate release layer.

Batch code	Hardness (Kg/cm^2)	Thickness (mm)	%Friability	Weight variation	Drug content%
SR1	5.26±0.05	4.81±0.01	0.83±0.03	202±0.01	98.83±0.17
SR2	5.00±0.05	3.86±0.02	0.43±0.05	199±0.02	99.33±0.90
SR3	5.36±0.04	4.71±0.02	0.63±0.05	200±0.57	83.16±0.66
SR4	5.96±0.01	4.21±0.01	0.50±0.00	200±0.05	89.66±0.90
SR5	5.63±0.05	4.33±0.02	0.23±0.04	201±0.02	96.32±0.54
SR6	5.73±0.03	4.16±0.02	0.43±0.03	199±0.57	97.16±1.26
SR7	5.06±0.02	4.73±0.01	0.26±0.05	202±0.02	98.01±0.90
SR8	5.93±0.05	4.03±0.01	0.73±0.05	199±0.02	99.32±0.90
SR9	5.53±0.05	4.26±0.01	0.76±0.05	200±0.02	85.02±1.28

Table 14. Evaluation parameters of Diclofenac potassium sustained release layer.

Almotriptan malate was formulated as immediate release layer using sodium starch glycolate and crospovidone in different concentration (2, 4, 6 and 8%) by direct compression as represented in Table-1. The Almotriptan malate immediate release layer was evaluated for hardness, thickness, friability, weight variation, drug content uniformity and *in vitro* disintegration time in Table 13. The hardness was in the range of 3.43 to 3.83 kg/cm^2 which was in accordance with The Immediate release tablet. The thickness was from 2.17 to 2.27mm suggested uniformity in thickness for immediate release layer. The friability was less than 1% indicated good handling of the layer. The weight variation results suggested uniformity in weight of layers. The content uniformity was in range of 93.89% to 98.89% indicated uniform dispersion of Almotriptan malate in the layer. The *in vitro* disintegration time for the layer containing sodium starch glycolate was 22.66 to 38.64 sec, for the layer containing crospovidone 27.62 to 53.33 sec. The disintegration time follow the order according to super disintegrants as sodium starch glycolate<crospovidone. As the concentration of super disintegrants was increased there was decreased in the disintegration time, which was due to the fact that higher level of disintegrants probably made the large pores with continuous network of skeleton providing enough pressure within matrix for faster disintegration. Hence the disintegration time for all the prepared layer was less than 1 minutes indicated that the prepared layer was immediate release layer tablet.

Diclofenac potassium was formulated as sustained release layer using matrix forming polymer like HPMC K100, HPMC K15, alone and in combination by direct compression method as shown in Table-2 The prepared sustained release layer of Diclofenac potassium was evaluated for post compression parameters and drug content and results in Table 14. The hardness of prepared Diclofenac potassium layer was in the range of 5.00 to 5.96 kg/cm2 which was in acceptable range of sustained release formulation. The thickness of all the formulated sustained release layer was in range of 3.86 to 4.81mm due to the constant tablet press setting across all the batches irrespective of weight variation. The average weight of formulated layer was found to be uniform in the range of 199 to 202 and the percent deviation in weight variation for all the formulated layer was within the acceptable range of pharmacopeial specification. The percent friability value for all formulated layer was in range 0.23 to 0.83% indicated good handling properties of formulated layers. The drug content was in range of 83.16 to 99.33% for all the formulated

layer suggested uniform dispersion of Diclofenac potassium in formulated sustained release layer.

Time in minutes	*In vitro* drug release of Almotriptan malate Immediate release layer							
	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8
0	0	0	0	0	0	0	0	0
5	14.782	20.165	22.421	25.691	15.512	19.132	26.483	31.004
10	25.534	28.109	34.722	43.553	24.589	27.655	37.646	44.058
15	33.926	37.421	45.439	58.432	33.326	36.675	48.130	56.150
20	43.113	48.132	56.449	70.987	41.418	44.142	56.878	64.426
30	55.393	62.255	69.321	84.342	53.133	56.746	67.241	75.003
45	67.577	74.044	81.234	99.586	64.655	69.401	79.326	87.754
60	78.254	83.816	90.115	-	73.253	78.809	88.567	98.322
75	86.421	91.848	97.199	-	80.207	87.915	96.493	-
90	91.041	98.082	-	-	86.674	96.196	-	-
120	96.993	-	-	-	95.705	-	-	-

Table 15. *In vitro drug* release data of Almotriptan malate immediate release layer (% drug release).
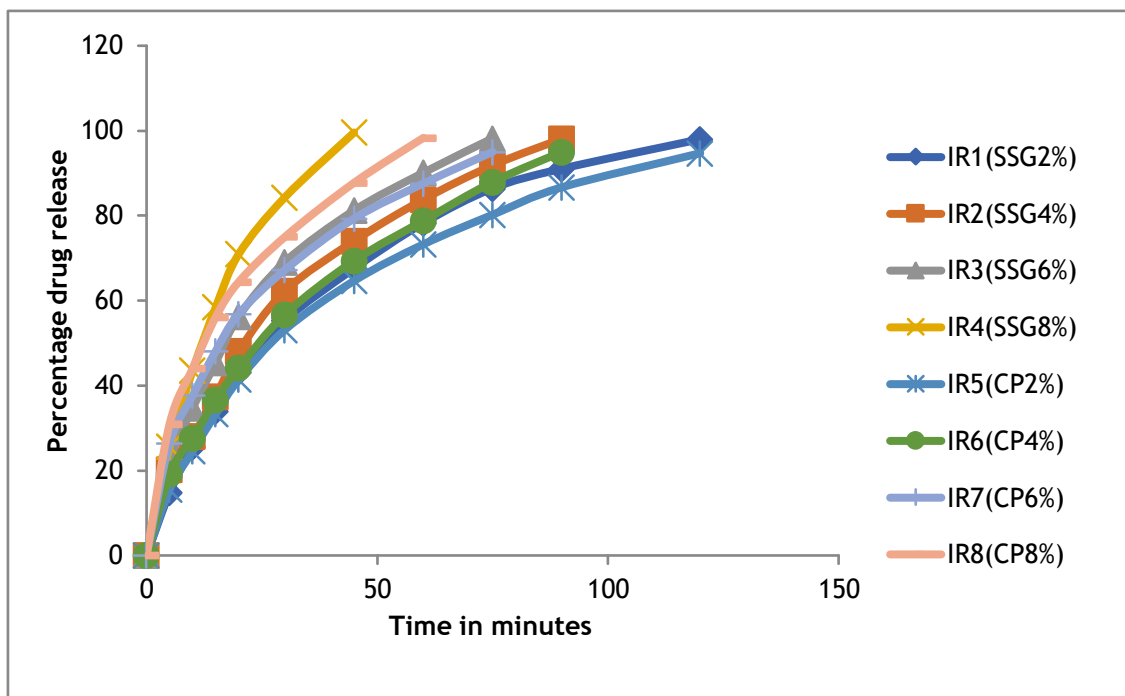

FIG-9. *In vitro* release of Almotriptan malate from immediate release layer containing sodium starch glycolate and Crospovidone.

Time in minutes	SR1	SR2	SR3	SR4	SR5	SR6	SR7	SR8	SR9
0	0	0	0	0	0	0	0	0	0
15	4.12	6.35	7.34	5.01	6.89	7.19	3.98	5.18	7.55
30	11.02	13.88	16.51	14.55	18.32	18.24	9.96	12.26	17.59
45	18.12	20.11	24.56	22.78	26.14	27.31	16.52	19.69	26.75
60	25.24	27.23	32.07	30.19	34.32	36.96	23.81	26.57	35.94
2hr	32.98	34.18	40.77	37.28	42.11	45.43	30.38	34.19	44.31
3hr	39.51	41.05	48.02	45.06	50.27	54.45	37.45	41.28	53.87
4hr	46.11	49.88	56.68	53.32	59.54	63.12	44.78	48.06	62.73
5hr	53.21	57.65	64.13	61.65	67.09	72.09	51.21	56.65	70.59
6hr	60.52	65.90	72.67	69.71	75.12	81.37	58.45	63.20	78.22
7hr	67.27	73.43	80.65	77.34	83.65	89.10	65.13	70.71	86.57
8hr	74.55	81.15	88.19	84.94	91.25	97.26	71.97	78.22	98.26
9hr	81.10	89.04	96.27	92.89	98.57	-	78.33	85.41	-
10hr	88.15	98.88	-	99.19	-	-	85.62	96.36	-
11hr	97.39	-	-	-	-	-	91.96	-	-
12hr	-	-	-	-	-	-	98.03	-	-

Table 16. *In vitro* release data of Diclofenac potassium from sustained release layer (percentage drug release).
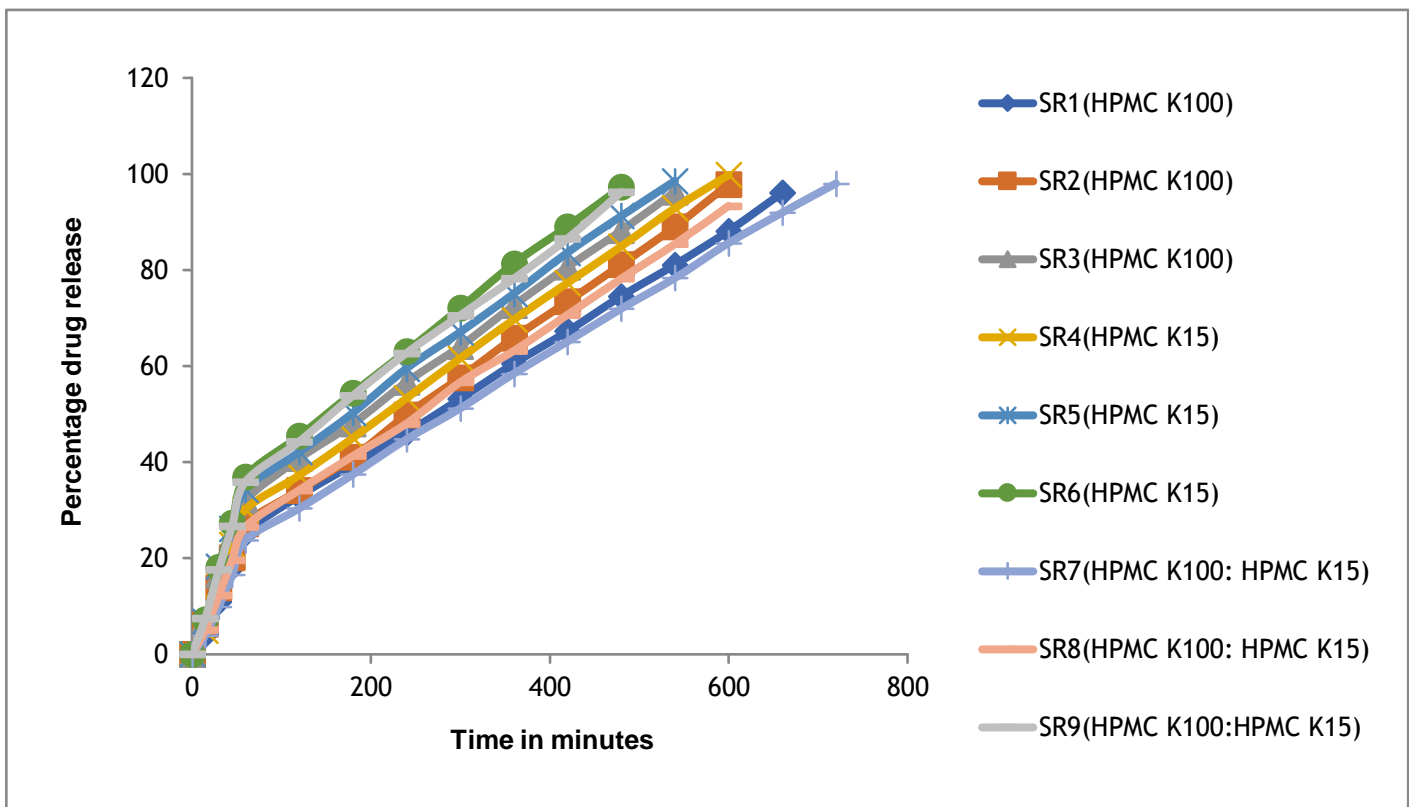

FIG-10. *In vitro* release of Diclofenac potassium from sustained release layer containing HPMC K100, HPMC K15

The dissolution study of Almotriptan malate immediate release layer was conducted using 0.1N HCl as dissolution media. The *in vitro* release data of Almotriptan malate is show in Table-15. The *in vitro* release of Almotriptan malate was plotted as percent drug release versus time as depicted in FIG-9. The *in vitro* release of Almotriptan malate was rapid from all the layers. The layer prepared by using sodium starch glycolate showed 67.577 to 99.586% within 45 mins which was due to enormous swelling followed by rapid disintegration. The *In vitro* release of Almotriptan malate was 73.253 to 98.322% within 60 min from immediate release layer containing crospovidone as super disintegrating agent which was attributed to high capillary activity with pronounced hydration capacity of the superdisintegrants. The *in vitro* release of Almotriptan malate followed the rank order of sodium starch glycolate>crospovidone as the concentration of super disintegrants increased in all the formulated layers, the release was more and rapid which was due to rapid disintegration in shortest time.

Hence based on the disintegration time and in vitro release study IR4 (SSG 8%) layer was selected as Almotriptan malate immediate release layer of Almotriptan malate for further preparation of bilayer tablet.

The *in vitro* release study of Diclofenac potassium from sustained release layer was conducted for first 2 hours in 0.1N HCl and then the dissolution study was continued replacing with pH 6.8 phosphate buffer for next 10 hour. The *in vitro* release data of Diclofenac potassium from sustained layer is in Table-16 and illustrated in FIG-10. The *in vitro* release of Diclofenac potassium was slow in 0.1N HCl due to the slow swelling of polymer matrix used in the preparation of sustained release layer. After two hours the formulation SR1,SR2, SR3 have 32.98, 34.18, 40.77% from HPMC K100 and formulation SR4, SR5, SR6 have 37.28, 42.11, 45.43% from HPMC K15 and The formulation SR7,SR8,SR9 show 30.48, 34.19 and 44.31% from combination of HPMC K100 and HPMC K15 polymer matrix of sustained release layer was released.

The *in vitro* release was rapid in pH 6.8 phosphate buffer due to the more swelling of polymer matrix in alkaline medium. A maximum of 97.39%, 97.88%,96.27% from HPMC K100, 99.19%, 98.57%,97.26% from HPMC K15, polymer matrix of sustained release layer was released within 12hr. The *in vitro* release is depending upon nature of drug, nature of polymer, drug to polymer ratio and the medium used. In the present work HPMC K100, HPMC K15 were used as hydrophobic polymer as a matrix in the preparation of sustained release layer. The *in vitro* release followed the rank order according to polymer matrix as HPMC K15>HPMC K100. The highest release was observed with HPMC K100 which is commonly used hydrophobic matrix, gets swelled and dissolved in aqueous media forming viscous gel thereby rapidly releasing the drug. The formulation SR7, SR8 and SR9 show 98.03%, 96.36% and 98.26% containing combination of HPMC K100, HPMC K15. Hence based on the in vitro release study formulation SR7 (HPMC K100: HPMC K15) layer was selected as Diclofenac potassium sustained release layer of Diclofenac potassium for further preparation of bilayer tablet.

PREPARATION OF BILAYER TABLET:

Batch code	Hardness (Kg/cm2)	Thickness (mm)	%Friability	Weight variation	Drug content%	Disintegration time(sec)
BF1	6.30±0.17	5.19±0.10	0.50±0.09	300±0.05	98.10±0.90(SR)	22.66±2.15
					98.84±0.09(IR)	

Table 17. Evaluation parameters of Bilayer tablet formulation (BF1):

The bilayer tablets were prepared by double compression of optimized Diclofenac potassium sustained release layer (SR7) and Almotriptan malate immediate release layer (IR4) as shown in Table 3 using 8 mm round punches on a shiv pharma tablet press. The bilayer tablets were evaluated for different physical parameter like hardness, thickness, friability, weight variation and *in vitro* disintegration time. The results of parameters are represented in Table 17. The hardness of bilayer tablet was found to be 6.30±0.17 kg/cm^2 which was more as compare to individual layer because of double compression. The thickness of the bilayer tablet was found to be 5.19±0.10 mm which was increased as compare to individual layer because of increase in amount of excipients. The friability was 0.50 ±0.09% for all the bilayer tablet which was less than 1% indicating good handling of tablet. The weight variation of the bilayer tablet 300±0.05mg was found to be within the limits (100±5%). content uniformity of Diclofenac potassium and Almotriptan malate in the bilayer tablet was found to be 98.10±0.90 and 98.84±0.09% respectively. The *in vitro* disintegration time was 22.66±2.15sec for all the tablets suggested rapid disintegration of only Almotriptan malate layer whereas the Diclofenac potassium layer was not disintegrated but swells. Hence the physical parameter evaluated for all the bilayer tablet were within acceptable range of pharmacopeial norm with good physical properties.

Time	% drug release	
	Immediate release layer	sustained release layer
0.1N HCL buffer solution		
10	22.45	1.08
15	41.08	1.72
20	60.13	2.68
30	78.26	3.43
45	99.62	5.11
pH6.8 phosphate buffer solution		
1hr	-	9.19
2hr	-	17.69
3hr	-	25.34
4hr	-	33.09
5hr	-	41.21
6hr	-	49.64
7hr	-	57.38
8hr	-	65.05
9hr	-	73.47
10hr	-	81.30
11hr	-	89.26
12hr	-	97.12

Table 18. *In vitro* release data of Almotriptan malate (IR4) and diclofenac potassium (SR7) Bilayer formulation (BF1).
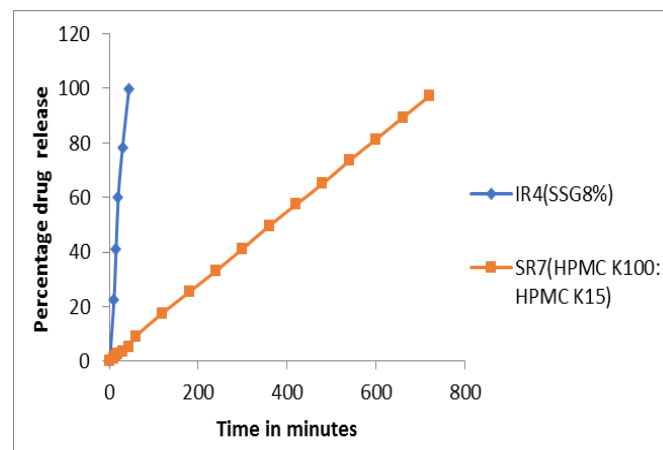

FIG-11. *In vitro* release data of Almotriptan malate (IR4) and diclofenac potassium (SR7) Bilayer formulation (BF1)

The *in vitro* release study of Bi-layer tablets of Almotriptan malate immediate release layer and Diclofenac sustained release layer was conducted for first 2 hours in 0.1N HCl and then the dissolution study was continued replacing with pH 6.8 phosphate buffer for next 10 hour. The dissolution study suggested that Almotriptan malate was released within 45min in simulated gastric fluid, while Diclofenac potassium was released in much smaller amount (1.08 to 5.11%) within 45minutes. Subsequent to replacing media with phosphate buffer (pH6.8), Diclofenac potassium dissolution was found to be increased. The graphical representations of cumulative percent drug release vs time plot for Almotriptan malate and Diclofenac potassium in bilayer tablet are represented in FIG-11.

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsemeyer-peppas		Hixson crowell R^2	Best fitting model
				R^2	N		
BF1	0.9998	08055	0.9195	0.9996	0.9533	0.8764	Zero order

Table 19. Kinetic modeling of drug release.

The *In vitro* drug release from various Bi-layer tablets was evaluated by using various release kinetic models. The drug release kinetics was evaluated by using the linear regression method (Table 19.). For Zero order, R^2 value were in 0.9998, for first order, R^2 value were in 0.8055, for Higuchi, R^2 values were in 0.9195 and for Hixson crowell, R^2 value were in 0.8764 and for Korse Meyer, R^2 values were in 0.9996, The best fit with the highest determination R^2 coefficients was shown by both the Zero order equations FIG-12.

The results of the *in-vitro* release data were fitted to the Zero order equation to analyze the release pattern of the drug from the polymeric system. The values of "n" were in the range of 8.0454, indicating the drug release followed super case-II transport diffusion, possibly owing to chain distanglement and swelling of hydrophobic polymer.
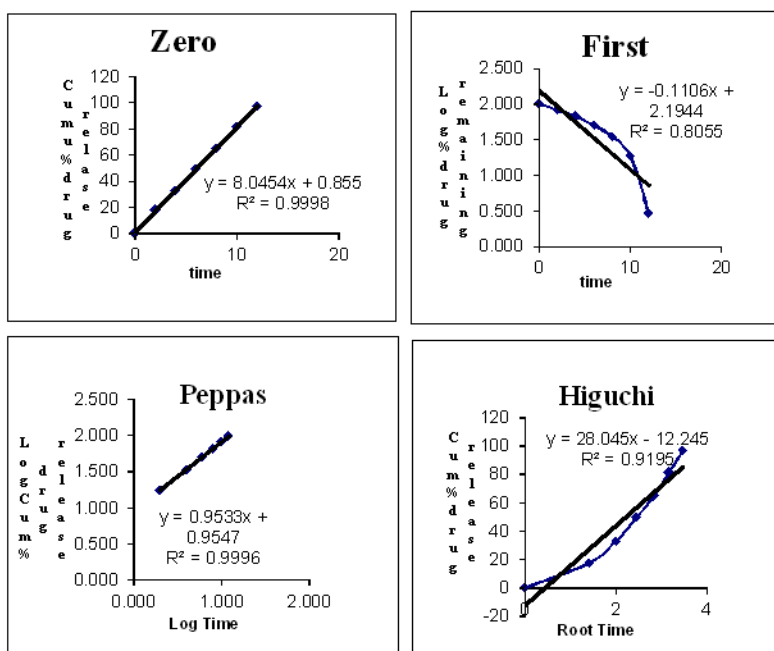

FIG-12. Drug release kinetics of Bilayer tablet formulation (BF1).

Accelerated Stability studies of Bi-layer tablet of Almotriptan malate and Diclofenac potassium

A drug product may undergo changes in its physicochemical characteristics during storage and these changes can affect the bioavailability of drug from the dosage forms. Bilayer tablet have to meet the pharmacopeial specifications, such as weight variation, friability, hard ness, thickness, and the drug release during its shelf life (Nalluri *et al.*, 2007). Accordingly, the effect of storage at room temperature, 25°C /60%RH and 40°C/75% RH for 2 months on the *in vitro* characterization and *in vitro* release of formulation BF1 was investigated [ICH Q1A (R2), 2003]. All the stored Bilayer tablets didn't show any change in their colour or appearance throughout the storage period. The physical characteristics of the stored Bilayer tablets in comparison to the fresh ones are compiled as the stability data and presented in Table 18,19 and 20 It is evident that the drug content of formulation BF1 remained within the acceptable limits. A slight decrease in hardness (kg/cm^2) was observed compared to the fresh ones. Evidently, a slight increase in drug release was observed on comparing the fresh Bilayer tablets to the stored Bilayer tablets. *In vitro* release profiles of formulation BF1 at room temperature, 25°C /60%RH and 40°C/75% for 2 months are represented in Table. 21, 22, 23 and Figure 13,14, 15 respectively. However, even with this increment, the stored Bilayer tablets compiled with the reported specifications of sustained-release products. This indicates that the formulation BF1 is fairly stable at accelerated storage condition.

Time (months)	Hardness (kg/cm^2)	Thickness (mm)	% friability	Weight variation (mg)	Drug content %	Disintegration
0 month	6.30±0.17	5.19±0.10	0.50±0.09	300±0.05	98.10±0.90 (SR)	22.66±2.15
					98.84±0.09 (IR)	
1 month	6.10±0.15	5.19±0.12	0.51±0.09	299±0.04	98.01±0.70 (SR)	23.19±2.17
					98.60±0.08 (IR)	
2 month	5.93±0.15	5.19±0.14	0.53±0.10	298±0.03	97.87±0.60 (SR)	23.06±2.19
					98.00±0.06 (IR)	

Table 18. *In vitro* characterization of formulation BF1 at room temperature.

Time (months)	Hardness (kg/cm^2)	Thickness (mm)	% friability	Weight variation (mg)	Drug content %	Disintegration
0 month	6.30±0.17	5.19±0.10	0.50±0.09	300±0.05	98.10±0.90 (SR)	22.66±2.15
					98.84±0.09 (IR)	
1 month	6.20±0.17	5.19±0.14	0.52±0.08	301±0.02	98.04±0.60 (SR)	22.98±2.16
					98.40±0.02 (IR)	
2 month	5.96±0.15	5.19±0.16	0.53±0.10	299±0.04	97.99±0.90 (SR)	23.10±2.19
					98.20±0.06 (IR)	

Table 19. *In vitro* characterization of formulation BF1 at 25°C±2°C/60%RH.

Time (months)	Hardness (kg/cm^2)	Thickness (mm)	%friability	Weight variation (mg)	Drug content%	Disintegration
0 month	6.30±0.17	5.19±0.10	0.50±0.09	300±0.05	98.10±0.90 (SR) 98.84±0.09 (IR)	22.66±2.15
1 month	6.15±0.13	5.17±0.11	0.53±0.11	300±0.00	98.00±0.70 (SR) 98.40±0.05 (IR)	22.24±2.05
2 month	5.99±0.16	5.20±0.13	0.51±0.09	299±0.03	97.98±0.60 (SR) 97.89±0.03 (IR)	23.16±2.01

Table 20. *In vitro* characterization of formulation BF1 at 40°c ±2°C/75%RH.

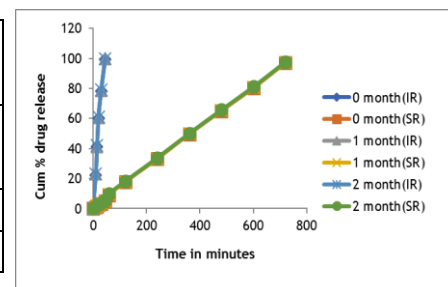| Time (hrs)	0	10 (IR)	15 (IR)	20 (IR)	30 (IR)	45 (IR)	60 (SR)	2 (SR)	4 (SR)	6 (SR)	8 (SR)	10 (SR)	12 (SR)
Time 0(mns)	0	**22.45**	**41.08**	**60.13**	**78.26**	**99.62**	**9.19**	**17.69**	**33.09**	**49.64**	**65.05**	**80.30**	**97.12**
1	0	22.90	41.30	60.75	78.82	99.92	9.34	17.93	33.31	49.90	65.35	80.73	97.36
2	0	23.03	41.89	61.01	79.00	100	9.83	18.06	33.72	50.00	65.70	81.12	97.80

Table 21. *In vitro* dissolution profiles of formulation BF1 at room temperature.

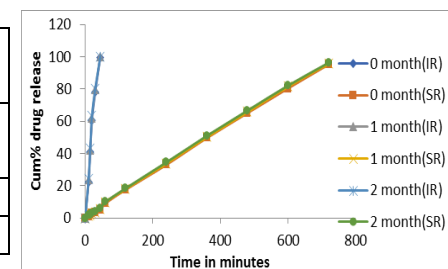| Time (hrs)	0	10 (IR)	15 (IR)	20 (IR)	30 (IR)	45 (IR)	60 (SR)	2 (SR)	4 (SR)	6 (SR)	8 (SR)	10 (SR)	12 (SR)
Time 0(mns)	0	**22.45**	**41.08**	**60.13**	**78.26**	**99.62**	**9.19**	**17.69**	**33.09**	**49.64**	**65.05**	**80.30**	**97.12**
1	0	23.98	42.12	61.82	79.39	99.95	9.91	18.23	33.89	50.31	65.80	81.53	97.75
2	0	24.21	42.99	63.27	80.00	100	10.12	18.62	34.41	51.11	66.71	82.22	98.32

Table 22. *In vitro* dissolution profiles of formulation BF1 at 25°C±2°C/60%RH.

Time (hrs)	0	10 (IR)	15 (IR)	20 (IR)	30 (IR)	45 (IR)	60 (SR)	2 (SR)	4 (SR)	6 (SR)	8 (SR)	10 (SR)	12 (SR)
Time 0(mns)	0	**22.45**	**41.08**	**60.13**	**78.26**	**99.62**	**9.19**	**17.69**	**33.09**	**49.64**	**65.05**	**80.30**	**97.12**
1	0	24.89	43.63	63.52	80.11	99.87	10.45	18.93	34.62	50.71	66.86	81.21	97.87
2	0	25.12	44.21	65.93	82.77	100	11.18	19.00	35.67	51.82	67.32	82.48	98.50
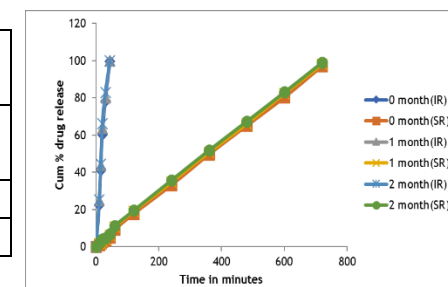
Table 23. *In vitro* dissolution profiles of formulation BF1 at 40°c ±2°C/75%RH.

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