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Formulation and evaluation of bilayer tablet of Aceclofenac sodium and Tramadol hydrochloride

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Abstract:

Bilayer tablets concept had long been utilized to develop both immediate release and sustained release formulation. Immediate release bilayer tablets generally contained two layers for two drugs. After administration, such a bilayer tablet was broken down into granules and small fragments that facilitate dissolution by increasing the surface area for both the drugs. Different fast release formulations of aceclofenac sodium and tramadol hydrochloride containing different ratios of croscarmellose sodium and sodium starch glycolate as well as different sustained release formulations containing different ratios of hydroxyl propyl methyl cellulose and xanthan gum were prepared by direct compression method. The fast release formulation F2, containing 12.5% croscarmellose sodium and sustained release formulation S2 containing HPMC (1:1) were selected for the preparation of bilayer tablet of combination of both the drugs by direct compression method. The bilayer formulation, B2 had shown better drug release and followed first order and hixson crowell kinetic model.

Key Words: Bilayer tablet, Aceclofenac sodium, Tramadol hydrochloride, Croscarmellose sodium

Introduction:

Aceclofenac sodium belongs to class II drug in BCS classification i.e. low solubility and high permeability. It is non steroidal anti-inflammatory drug, which is used in the prevention and treatment of rheumatoid arthritis and osteoarthritis. One of the major problems with aceclofenac sodium is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Its solubility in aqueous medium is very low i.e. 0.78 mg/ml in water. Its absolute bioavailability is 99% and biological half-life is only 3.5 hours that results into poor bioavailability after oral

administration [1]. Tramadol Hydrochloride is a synthetic opioid analgesic used for moderate to severe pain like labour pain, traumatic pain, rheumatoid arthritis and cancer pain. Tramadol hydrochloride is rapidly absorbed orally and is subjected to first pass metabolism. The half life of tramadol hydrochloride is 5.5-7 hours and the absolute bioavailability is only 68% [2]. From the above points, it is clear that, aceclofenac sodium and tramadol hydrochloride are suitable drugs to formulate into bilayer tablet and may provide a better therapeutic profile.

Materials and methods:

Aeclofenac sodium and Tramadol hydrochloride were obtained as gift samples from Curetech, Skincare (P) Ltd, Baddi and Ipca pharmaceuticals (P) Ltd, Ratnam respectively. Croscarmellose sodium, Sodium starch glycolate, Hydroxy propyl methyl cellulose, Xanthan gum, Micro-crystalline cellulose, D-mannitol, Magnesium stearate, Talc, Lactose were obtained from Sanjay biological museum, Amritsar and aerosil from HiMedia laboratories (P) Ltd and all other chemicals and reagents used in the study were of analytical grade.

Pre-formulation studies of drug including melting point, solubility, assay of drug, standard plots of drug, and drug excipient compatibility studies by FT-IR were studied by standard methods [3-5].

Preparation of fast dissolving tablets

The fast dissolving tablets were prepared by direct compression method. Aceclofenac sodium, tramadol hydrochloride, sodium starch glycolate, croscarmellose sodium, microcrystalline cellulose was weighed according to the formula given in **Table 1**. The blend was then mixed with D-mannitol, talc and magnesium stearate. The blend was then compressed into tablets using tablet punching machine.

Table 1: Formulation of fast release tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Aceclofenac sodium	100	100	100	100	100	100	_	_	_	_	_	_
Tramadol HCl	_	_	_	_	_	_	15	15	15	15	15	15
Cros -- carmellose sodium	20	25	30	_	_	_	15	18.75	22.5	_	_	_
Sodium starch glycolate	_	_	_	20	25	30	_	_	_	15	18.75	22.5
MCC	40	40	40	40	40	40	30	30	30	30	30	30
D-mannitol	10	10	10	10	10	10	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium stearate	2	2	2	2	2	2	1.5	1.5	1.5	1.5	1.5	1.5
Talc	2	2	2	2	2	2	1.5	1.5	1.5	1.5	1.5	1.5
Lactose	26	21	16	26	21	16	79.5	75.75	72	79.5	75.75	72
Total	200	200	200	200	200	200	150	150	150	150	150	150

Preparation of sustained release tablets

The sustained release tablets were prepared by direct compression method. Aceclofenac sodium, tramadol hydrochloride, hydroxypropyl methyl cellulose, micro crystalline cellulose was weighed according to the formula given in **Table 2**. The powder was then mixed with aerosol and magnesium stearate. The blend was then compressed into tablets using tablet punching machine.

Table 2: Formulation of sustained release tablets

Ingredients (mg)	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
Aceclofenac sodium	100	100	100	100	100	100	_	_	_	_	_	_
Tramadol HCl	_	_	_	_	_	_	100	100	100	100	100	100
HPMC	87.5	100	112.5	_	_	_	87.5	100	112.5	--	--	--
Xanthan gum	_	_	_	87.5	100	112.5	_	_	_	87.5	100	112.5
MCC	37.5	25	12.5	37.5	25	12.5	37.5	25	12.5	37.5	25	12.5
Aerosil	2.5	2.5	2.5	2.5	2.5	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	2.5	2.5	2.5	2.5	2.5
Lactose	20	20	20	20	20	20	20	20	20	20	20	20
Total	250	250	250	250	250	250	250	250	250	250	250	250

Preparation of bilayer tablets

The bilayer tablets of combination of aceclofenac sodium and tramadol hydrochloride were prepared by direct compression technique. The bilayer tablets consisted of an immediate release layer and a sustained release layer of both drugs in combination. The quantity of blend for the sustained release layer was compressed lightly till the tablet did not break using a single punch tabletting machine equipped with round flat and plain punches. Over this compressed layer, the required quantity of the fast release layer was placed and compressed to obtain a bilayer tablet according to the formula given in **Table 3 [**6].

Table 3: Formulation of bilayer tablets

	B1		B2		B3	
Ingredients (mg)	**F1**	**S1**	**F2**	**S2**	**F3**	**S3**
Acceclofenac sodium	100	100	100	100	100	100
Tramadol HCl	15	100	15	100	15	100
Cross carmellose sodium	20	_	25	_	30	_
D-mannitol	10	_	10	_	10	_
HPMC	_	175	_	200	_	225
MCC	40	75	40	50	40	25
Aerosil	_	5	_	5	_	5
Magnesium stearate	2	5	2	5	2	5
Talc	2	_	2	_	2	_
Lactose	11	40	6	40	1	40
Total	700		700		700	

Pre-compression parameters

Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It was expressed in gm/ml and was given by

$$D_b = M/ V_b$$

Where, M and V_b are mass of powder and bulk volume of the powder respectively [6].

Tapped Density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes was less than 2 % (in a bulk density apparatus). It was expressed in gm/ml and was given by

$$D_t = M / V_t$$

Where, M and V_t are mass of powder and tapped volume of the powder respectively[6]..

***Angle of repose of blend*:** For determination of angle of repose (θ), the blends were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. Angle of repose was calculated using following equation.

$$\text{Tan } \theta = (h/r)$$

Where, h = height of pile; r = radius of pile

***Carr's index*:**It indicates powder flow properties. It was expressed in percentage andwas given by:

$$I = D_t – D_b/D_t X\ 100$$

Where, D_t and D_b are tapped density and bulk density respectively.

***Hausner ratio*:** Hausner ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

$$\text{Hausner ratio} = D_t/ D_b$$

Where, D_t and D_b are tapped density and bulk density respectively[7].

Post-compression parameters

Hardness test: Monsanto hardness tester was used for the determination of hardness of tablets [6].

Thickness: The thickness of tablet was determined using verniercaliper (Kayco, India). Six tablets from each batch of formulation were used and mean thickness value and SD was calculated for each formulation [7].

***Weight Variation*:** Twenty tablets were weighed individually. Average weight was calculated and individual tablet weights were compared to the average weight.

Friability: Six tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the roche tablet friabilator. The tablets were then re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets and relative standard deviations were reported[7].

$$\%\ \text{friability} = [(\text{Initial wt. of tablets} – \text{Final wt. of tablets})/ \text{Initial wt. of tablets}] \times 100$$

Drug content: Three tablets were finely powdered and an amount equivalent to 100 mg of drug was weighed & transferred to100 ml volumetric flask containing phosphate buffer pH 6.8. The flask was shaken for 10 min. the solution was filtered, diluted and then it was analyzed by U.V. spectrophotometer [8].

***Wetting time and water absorption ratio*:** A piece of tissue paper folded twice was placed in a petridish. A sample of final tablet was placed in it containing 10ml simulated saliva pH (phosphate buffer PH 6.8) at RT. The tablet was put on the paper and time required for the complete wetting of tablet was measured.

The wetting time is that necessary for the complete wetting of tablet. The wet tablet was weighed. Water absorption ratio "R" was determined using equation:

$$R = \frac{W_a - W_b}{W_b} \times 100$$

W_a=Wt. of tablet after water absorption

W_b=Wt. of tablet before water absorption

***Disintegration test*:** The disintegration time for tablets was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 900 ml of 0.1 N HCl maintained at 37 ± 2˚C, tubes were closed with the baskets and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted [8].

Dissolution Test: In vitro drug release was performed using dissolution apparatus USP type I basket method with a stirring speed of 50 rev/min at 37˚C ± 0.5 in 0.1 HCl for 2 hours and 900 ml of phosphate buffer (pH 6.8) for 24 hours. The samples were taken at pre selected time intervals with replacement of equal volume of dissolution media. The collected samples were filtered, diluted & the absorbance was measured spectrophotometrically[8].

Drug Release Kinetic Models for Dissolution Study: To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order eq. (2) describes the release from system where release rate is concentration dependent. higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on fickian diffusion eq. (3). The hixson-crowell cube root law eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$C = k_o t \quad (1)$$

Where, k_o is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log } C = \text{Log } C_o - kt/2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and k is first order constant.

$$Q = K_t 1/2 \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

$$W_0^{1/3} - W_t^{1/3} = Kt \quad (4)$$

Where, Q_t is the amount of drug released in time t, Q_o is the initial amount of the drug in tablet and KHC is the rate constant for hixson-crowell rate equation.

The following plots were made i.e. cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) log cumulative % drug release vs. log time (korsmeyer model) and cube root of drug % remaining in matrix vs. time (hixson-crowell cube root law) [6].

Results and discussion:

Preformulation studies

Melting Point: The melting point of aceclofenac sodium and tramadol hydrochloride was found to be 150˚C and 182˚C respectively.

Assay: The standard solution of aceclofenac sodium (20µg/ml) was prepared and the HPLC was performed. The detection was carried out at 273 nm and the resulted peak confirmed the drug. The results are shown in **Figure 1 and Table4.**

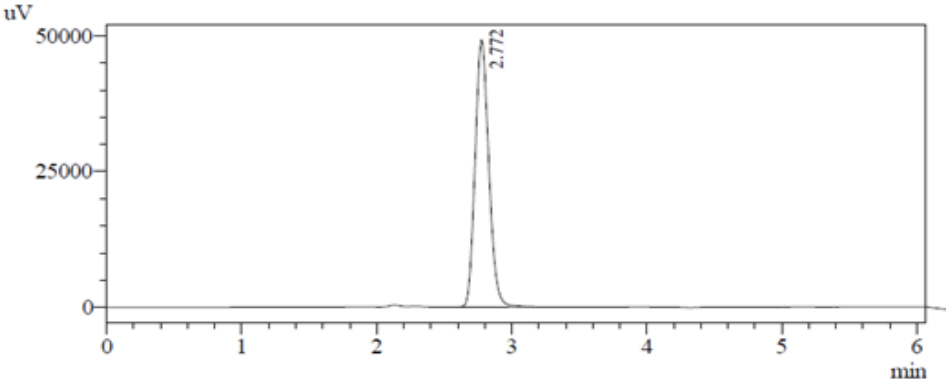

Figure 1:HPLC spectra of aceclofenac sodium

Table 4: HPLC peak table of aceclofenac sodium

Peak	Ret. Time	Area	Height	Area%	Height%
1	2.272	346856	49142	100.000	100.000
Total		346856	49142	100.000	100.000

Standard plots of the drugs: The stock solution of aceclofenac sodium (10 µg/ml) was scanned in the range of 200-400 nm and had shown maximum absorbance at 273 nm. The absorbance data for the drug in phosphate buffer (pH 6.8) and 0.1N HCl was prepared.

The stock solution of tramadol hydrochloride (10 µg/ml) was scanned in the range of 200-400 nm and had shown maximum absorbance at 272 nm. The absorbance data for the drug in 0.1N HCl and phosphate buffer (pH 6.8) was prepared.

The combined stock solution of aceclofenac sodium and tramadol hydrochloride (10 µg/ml) was prepared in both phosphate buffer (pH 6.8) and 0.1 N HCl. The determination of tramadol hydrochloride at the absorbance difference between 266.8 nm and 285 nm and aceclofenac sodium at the absorbance difference between 283 nm and 259.2 nm was done.

Drug- excipient compatibility studies by F.T.I.R:

In the comparison between FT-IR spectra of the pure drug and the combination of the drug with the polymers, it was observed that all the characteristic peaks of aceclofenac sodium and tramadol hydrochloride were present in the combination spectra as well; thus indicating the compatibility of the drugs with the polymers used. The results are shown in **Figure 2-4.**

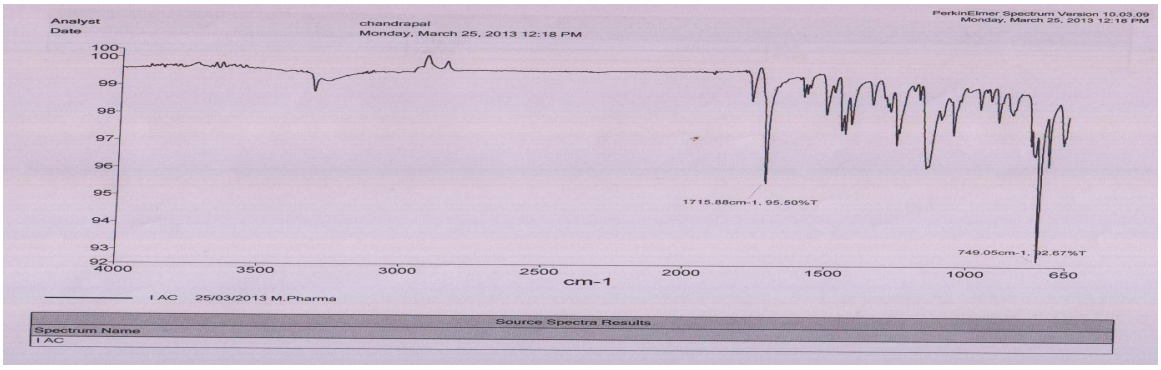

Figure 2: F.T.I.R. spectra of aceclofenac sodium

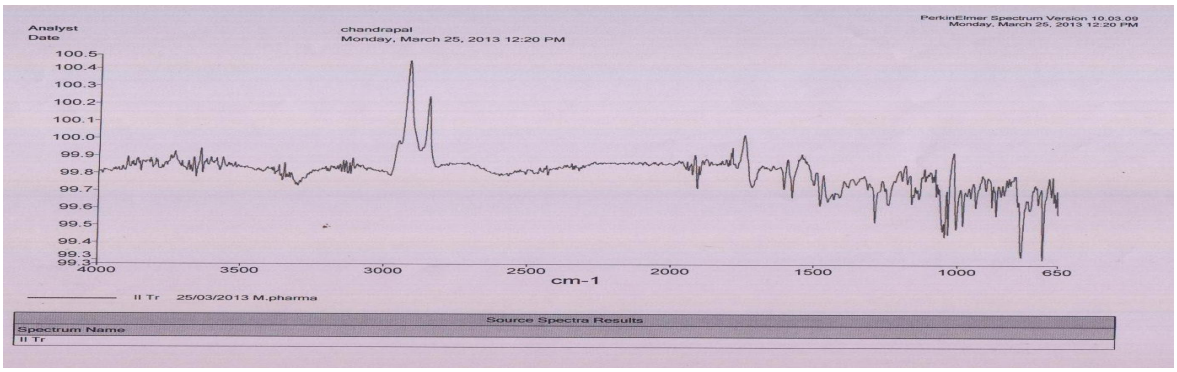

Figure 3: F.T.I.R. spectra of tramadol hydrochloride

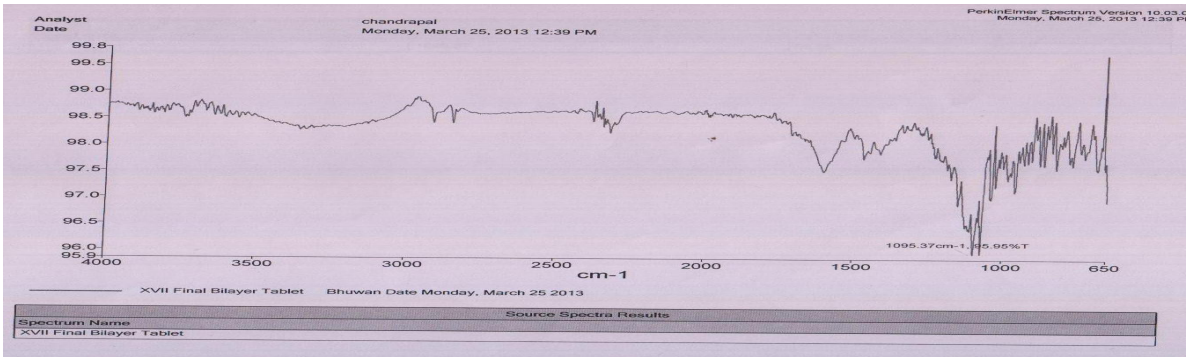

Figure 4:F.T.I.R. spectra of aceclofenac sodium + tramadol hydrochloride + HPMC + CCS + magnesium stearate + talc + mannitol + aerosil + MCC +lactose

PRE-COMPRESSION PARAMETERS

In pre-compression parameters the bulk density, tapped density, angle of response of blend, carr's index, Hausner ratio were determined using standard method and results are tabulated in **Table 5.**

POST-COMPRESSION PARAMETERS

In post-compression parameters the hardness test, thickness, weight variation, friability, drug content, wetting time & water adsorption, disintegration, dissolution were studied and results are shown in **Table 6.**

Dissolution test: The fast release formulations of aceclofenac sodium F1 , F2, F3 having 10% , 12.5% and15% of croscarmellose sodium showed 78%, 97% and 81% drug release respectively in 12 minutes while F4, F5 and F6 containing 10%, 12.5% and 15% sodium starch glycolate showed 69%, 94% and 79% drug release respectively in12 minutes. The fast release formulations of tramadol hydrochloride F7, F8 and F9 having 10%, 12.5% and 15% croscarmellose sodium showed 69%, 96% and 80% drug release respectively in 12 minutes while F10, F11 and F12 with 10%, 12.5% and 15% of sodium starch glycolate showed 70%, 89% and 76% drug release respectively in 12 minutes. Hence, it was observed that both the drugs gave better release with croscarmellose sodium as superdisintegrant in the concentration of 12.5%. The lower concentration of super disintegrant gave less release, the release increased with the increasing concentration of the super disintegrant up to 12.5 % and then decreases with further increase in its concentration (15%).

Table 5:Pre-compression parameters

Formulation code	Bulk density (gm/cc)	Tapped density (gm/ml)	Angle of repose (°)	Carr's index (%)	Hausner's ratio
F1	0.48	0.56	24.60	14.28	01.16
F2	0.50	0.57	24.99	12.28	01.14
F3	0.46	0.58	24.21	20.67	01.26
F4	0.52	0.66	20.03	21.21	01.26
F5	0.63	0.79	29.42	20.25	01.25
F6	0.62	0.76	20.15	18.42	01.23
F7	0.40	0.44	20.36	09.90	01.01
F8	0.41	0.46	20.53	10.87	01.12
F9	0.40	0.41	20.12	02.44	01.02
F10	0.50	0.54	18.36	07.41	01.08
F11	0.48	0.52	18.76	07.69	01.08
F12	0.50	0.55	19.00	09.09	01.01
S1	0.42	0.50	22.34	16.00	01.19
S2	0.42	0.47	22.52	10.64	01.11
S3	0.41	0.45	22.21	08.89	01.09
S4	0.46	0.56	24.26	17.86	01.21
S5	0.44	0.48	22.14	08.33	01.09
S6	0.45	0.50	24.29	10.00	01.11
S7	0.50	0.63	22.54	20.63	01.26
S8	0.52	0.58	24.43	10.34	01.11
S9	0.56	0.69	24.61	18.84	01.23
S10	0.52	0.65	22.69	20.00	01.25
S11	0.48	0.59	24.18	18.64	01.22
S12	0.41	0.48	24.38	14.58	01.17
B1	0.52	0.61	24.22	14.75	01.17
B2	0.52	0.60	24.15	13.33	01.15
B3	0.50	0.59	24.41	15.25	01.18

Table 6:Post-compression parameters

Codes	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg) ± %SD	Friability (%)	Drug content	Wetting time (sec)	Water absorption ratio (%)	Dis - integration time (sec)
F1	3.4	4.0	200±6.50	0.46	97.97±1.23	30	93.44	08
F2	3.7	4.0	200±3.15	0.54	98.00±1.34	35	94.33	05
F3	4.0	4.0	196±6.36	0.52	97.98±1.21	33	88.25	12
F4	4.0	4.0	195±3.68	0.48	97.65±1.32	44	92.10	11
F5	3.4	4.0	199±3.68	0.56	97.99±1.52	50	88.82	17
F6	3.6	4.0	197±4.70	0.48	96.96±1.12	53	91.76	06
F7	3.9	4.0	150±5.71	0.52	96.01±1.75	34	116.66	20
F8	4.75	4.0	150±5.71	0.50	96.05±0.97	40	102.43	27
F9	5.0	4.0	143±4.29	0.48	95.99±0.89	37	105.57	28
F10	3.2	4.0	148±5.65	0.61	96.38±1.04	35	94.29	30
F11	3.25	4.0	150±5.82	0.54	95.92±1.32	41	92.50	34
F12	3.5	4.0	150±5.71	0.54	95.78±0.86	40	98.08	33
S1	5.75	4.5	250±3.66	0.43	97.50±1.25	-	95.00	-
S2	7.0	4.5	250±3.60	0.45	98.00±1.32	-	95.55	-
S3	6.25	4.25	258±3.64	0.52	97.94±0.67	-	91.43	-
S4	5.75	4.25	248±3.80	0.67	97.36±1.21	-	88.18	-
S5	6.25	4.0	250±3.61	0.64	96.34±0.97	-	86.52	-

S6	5.75	4.5	248±4.12	0.61	96.87±0.98	-	86.09	-
S7	7.0	4..5	250±4.10	0.59	97.01±1.98	-	78.26	-
S8	7.25	5.0	248±3.90	0.47	97.36±1.54	-	68.18	-
S9	7.0	5.0	250±3.64	0.44	97.36±1.32	-	69.09	-
S10	6.25	4.5	248±5.72	0.56	96.00±0.17	-	71.66	-
S11	7.25	4.5	250±4.78	0.61	97.95±1.09		66.00	-
S12	7.25	5.0	250±3.86	0.62	96.86±1.98	-	68.09	-
B1	7.0	6.5	698±3.86	0.46	96.07±0.98	-	106.66	-
B2	7.5	6.45	700±4.21	0.45	97.03±0.79	-	116.75	-
B3	7.0	6.5	700±3.94	0.45	96.27±0.87	-	116.87	-

The sustained formulation S1 , S2, S3 having aceclofenac sodium and HPMC in the ratio of 1:0.875, 1:1 and 1:112.5 along with 5%, 10% and 15% of MCC showed 84%, 94% and 89% drug release respectively up to 24 hrs while formulations S4, S5 and S6 containing aceclofenac sodium and xanthan gum in the ratio of 1:0.875, 1:1 and 1:112.5 and 5%, 10% and 15% of MCC showed 80%, 86% and 83% drug release respectively**.**. The sustained release formulations S7, S8 and S9 of tramadol hydrochloride and HPMC in the same ratio as above along with same concentration of MCC gave 86%, 96% and 90% drug release up to 24 hrs. The formulations S10, S11 and S12 with similar ratios of tramadol hydrochloride with xanthan gum and MCC showed 81%, 92% and 87% drug release respectively. Hence, it was observed that both the drugs gave better release with HPMC (1:1) as the release retardant polymer along with MCC (10%) which potentiates the release retarding effect of HPMC. Further increase in the concentration of HPMC and MCC, decreases the sustained effect of the polymers**.**

From the bilayer formulations B1, B2 and B3 having combination of aceclofenac sodium and tramadol hydrochloride, croscarmellose sodium (10%, 12.5% and 15%) as super disintegrant in the immediate release layer and HPMC (1:0.875, 1:1 and 1:112.5) as release retarding polymer in the sustained release layer; aceclofenac sodium showed 93% drug release in 12 hrs, 94% up to 24 hrs and 91% release up to 24 hrs respectively while tramadol hydrochloride gave 90% release in 12 hrs, 95% up to 24 hrs and 92% up to 24 hrs respectively.The results are shown in **Figure 5-9.**

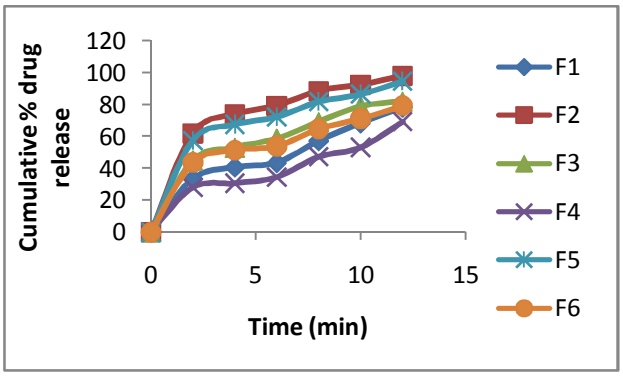

Figure 5: Drug release profile of fast release tablets

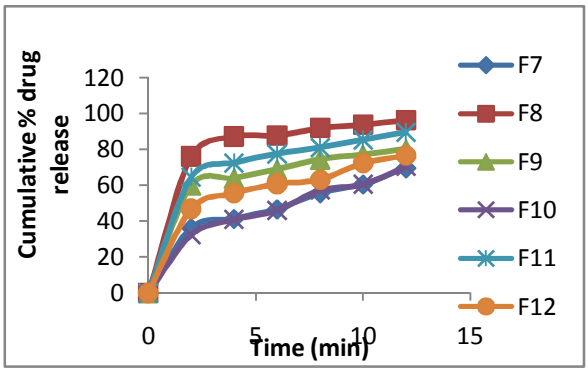

Figure 6: Drug release profile of fast release tablets

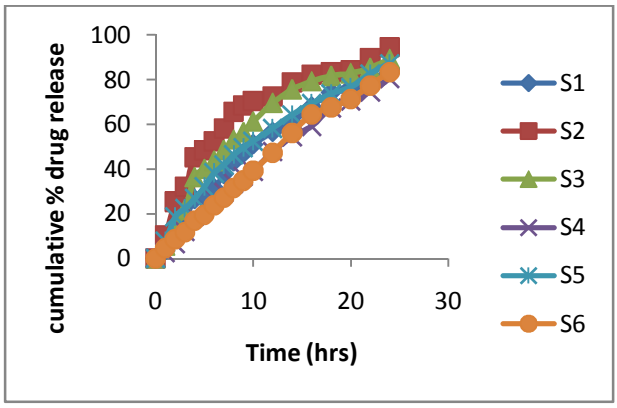

Figure 7:Drug release profile of sustained release tablets

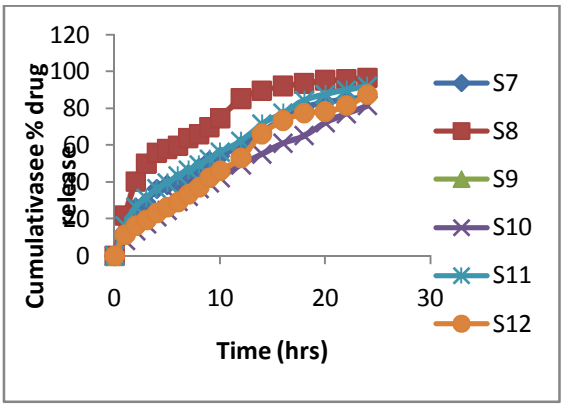

Figure 8: Drug release profile of sustained release tablets

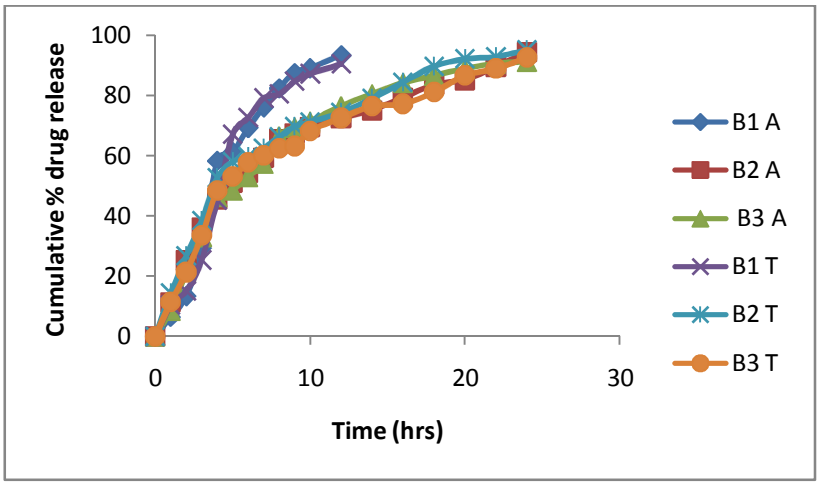

Figure 9:Drug release profile of bilayer tablets

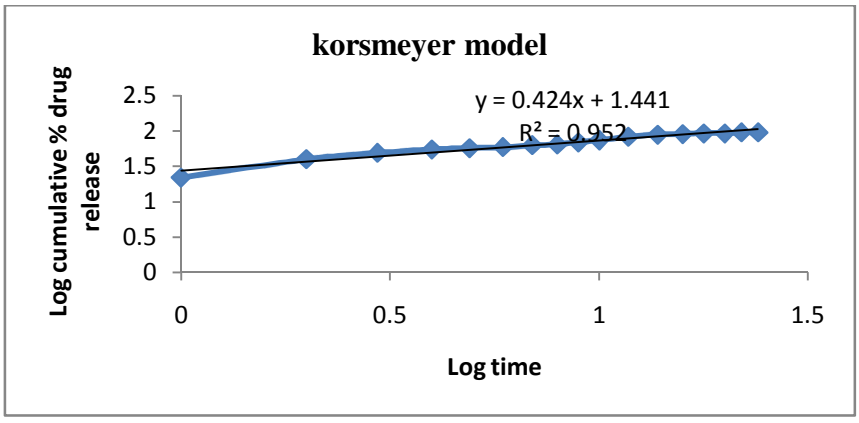

Figure 10: Korsmeyer model of tramadol hydrochloride release from S8

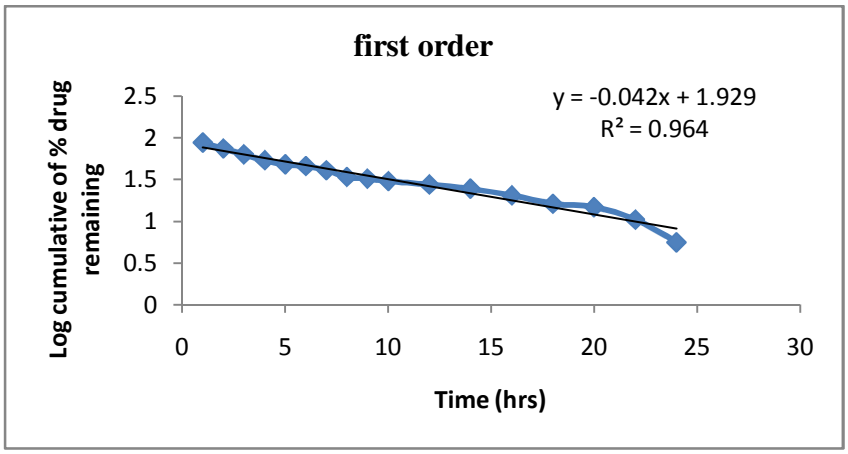

Figure 11: First order release of aceclofenac sodium from B2

Summary and Conclusion:

The melting point of aceclofenac sodium and tramadol hydrochloride was found to be 150˚C and 182˚C respectively. The standard solution of aceclofenac sodium (20µg/ml) was prepared and the HPLC was performed. The detection was carried out at 273 nm and the resulted peak confirmed the drug.

The stock solution of aceclofenac sodium, tramadol hydrochloride (10µg/ml) was scanned in the range of 200-400 nm and had shown maximum absorbance at 273 and 272 nm respectively. The absorbance data for the drug in phosphate buffer (pH 6.8) and 0.1N HCl was taken using U.V. spectrophotometer. The standard plot curve for both was found to be linear and was used for the calculations of % drug content and *in vitro* release.

The combined stock solution of aceclofenac sodium and tramadol hydrochloride (10µg/ml) was prepared in both phosphate buffer (pH 6.8) and 0.1 N HCl. The determination of tramadol hydrochloride at the absorbance difference between 266.8 nm and 285 nm and aceclofenac sodium at the absorbance difference between 283 nm and 259.2 nm was done. The absorbance data for both the drugs was taken**.** The standard plot curve was found to be linear and was used for the calculations of % drug content and *in vitro* release**.**

In the comparison between FTIR spectra of the pure drug and the combination of the drug with the polymers, it was observed that all the characteristic peaks of aceclofenac sodium and tramadol hydrochloride were present in the combination spectra as well; thus indicating the compatibility of the drugs with the polymers used.

The bulk density of the powder blends of fast dissolving tablets; sustained release tablets and bilayer tablets was found to be within 0.41 – 0.63 , 0.41 – 0.56 and 0.50 – 0.52 gm/ml respectively. The tapped density of the powder blends of fast dissolving tablets; sustained release tablets and bilayer tablets was found to be within 0.41 – 0.79 , 0.45 – 0.69 and 0.59 – 0.61gm/ml respectively. The angle of repose for fast release, sustained release and bilayer tablets were in the range of 18.36˚ – 29.42˚, 22.14˚ – 24.61˚ and 24.15˚ – 24.41˚ respectively. These values indicated the excellent flow of the powder blends. The compressibility of indexof all the fast release, sustained release and bilayer tablets was in between 02.44 –

21.21, 08.33 – 20.63 and 13.33 – 15.25 % respectively. These values indicated that the fast release and sustained release tablet powder blends had fair flow properties while bilayer tablet powder blends had good flow properties. The hausner ratio of fast release, sustained release and bilayer tablets was within the range of 01.01 – 01.26, 1.09 – 1.26 and 1.15 – 1.18 respectively. All these values indicated the ease of the powders flow.

The hardness of the fast release, sustained release and bilayer tablets was within the range of 3.4 – 5.0, 5.75 – 7.25 and 7.0 – 7.5 kg/cm^2 respectively. The thickness of fast release, sustained release and bilayer tablets was found in the range of 4.0, 4.0-5.0 and 6.45 – 6.5 mm respectively. The weight variation for all the formulations was in the acceptable limit. It was found to be in the range of 195±3.68 – 200±6.50, 248±3.0 - 258±3.64 and 698±3.86 – 700±4.21 mg for fast release, sustained release and bilayer tablets respectively. The % friability for fast release, sustained release and bilayer tablets was fond to be in the range of 0.46 – 0.61, 0.43- 0.67 and 0.45- 0.46 % respectively and all these were in the acceptable limit.

The drug content of all the formulations was found to be in the range of acceptable limit The wetting time of fast release tablets was found to be in the range of 30 – 53 seconds. The water absorption ratio for fast release, sustained release and bilayer tablets was within the range of 88.25 – 116.66, 66.00 – 95.55 and 106.66 – 116.87 % respectively. The disintegration time for fast release tablets was found to be in the acceptable range of 08 – 34 seconds. The fast release formulations of aceclofenac sodium F1 , F2, F3 having 10% , 12.5% and15% of croscarmellose sodium showed 78%, 97% and 81% drug release respectively in 12 minutes while F4, F5 and F6 containing 10%, 12.5% and 15% sodium starch glycolate showed 69%, 94% and 79% drug release respectively in12 minutes. The fast release formulations of tramadol hydrochloride F7, F8 and F9 having 10%, 12.5% and 15% croscarmellose sodium showed 69%, 96% and 80% drug release respectively in 12 minutes while F10, F11 and F12 with 10%, 12.5% and 15% of sodium starch glycolate showed 70%, 89% and 76% drug release respectively in 12 minutes. Hence, it was observed that both the drugs gave better release with croscarmellose sodium as super disintegrant in the concentration of 12.5%. The lower concentration of super disintegrant gave less release; the release increased with the increasing concentration of the super disintegrant up to 12.5 % and then decreases with further increase in its concentration (15%).

The sustained formulation S1 , S2, S3 having aceclofenac sodium and HPMC in the ratio of 1:0.875, 1:1 and 1:112.5 along with 5%, 10% and 15% of MCC showed 84%, 94% and 89% drug release respectively up to 24 hrs while formulations S4, S5 and S6 containing aceclofenac sodium and xanthan gum in the ratio of 1:0.875, 1:1 and 1:112.5 and 5%, 10% and 15% of MCC showed 80%, 86% and 83% drug release respectively. The sustained release formulations S7, S8 and S9 of tramadol hydrochloride and HPMC in the same ratio as above along with same concentration of MCC gave 86%, 96% and 90% drug release up to 24 hrs. The formulations S10, S11 and S12 with similar ratios of tramadol hydrochloride with xanthan gum and MCC showed 81%, 92% and 87% drug release respectively. Hence, it was observed that both the drugs gave better release with HPMC (1:1) as the release retardant polymer along with MCC (10%) which potentiates the release retarding effect of HPMC. Further increase in the concentration of HPMC and MCC, decreases the sustained effect of the polymers.

From the bilayer formulations B1, B2 and B3 having combination of aceclofenac sodium and tramadol hydrochloride, croscarmellose sodium (10%, 12.5% and 15%) as super disintegrant in the immediate release layer and HPMC (1:0.875, 1:1 and 1:112.5) as release retarding polymer in the sustained release layer; aceclofenac sodium showed 93% drug release in 12 hrs, 94% up to 24 hrs and 91% release up to 24 hrs respectively while tramadol hydrochloride gave 90% release in 12 hrs, 95% up to 24 hrs and 92% up to 24 hrs respectively.

The kinetic models had given linear relationship. In zero order plot the R^2 value obtained for fast release, sustained release and bilayer formulations was in the range of 0.872 – 0.990, 0.850 – 1.0 and 0.830 – 0.879 respectively and first order was within the range of 0.667 – 0.990, 0.923 – 0.994 and 0.974 – 0.992 describing the drug release rate relationship with concentration of drug. The R^2 value found in higuchi's equation plot was in the range of 0.619 – 0.993, 0.950 – 0.998 and 0.928 – 0.951 respectively indicating the release of drug from matrix as a square root of time dependent process based on fickian diffusion. The dissolution data was plotted in accordance with korsmeyer model and had R^2 value in the range of 0.848 - 0.987, 0.921 – 0.998 and 0.899 – 0.937 respectively. The dissolution data was also plotted in accordance with hixson crowell cube root law and had R^2 value ranging from 0.898 – 0.988, 0.857 – 0.997 and 0.943 – 0.973 respectively. Applicability of this data indicated a change in surface area and diameter of tablets with the progressive dissolution of matrix as a function of time. The fast release formulations followed the zero order kinetic model while the sustained release formulations followed higuchi's and korsmeyer's kinetic models. The bilayer tablet formulations followed the first order release kinetic model.

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