RESEARCH ARTICLE

FORMULATION AND EVALUATION OF BILAYER TABLETS OF BACLOFEN USING SYNTHETIC POLYMERS

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ABSTRACT

Aim of study was to develop bilayer drug delivery for treatment of spasticity by delivering loading and maintenance dose for fast achievement of peak plasma concentration and maintaining the same respectively. The prepared drug loaded bilayer tablets were evaluated for pre and post compression parameters. Stability study of the promising formulation was also performed. The tablets were prepared by direct compression and wet granulation method. The loading dose was delivered in the form of immediate release layer prepared by different super-disintegrations and maintenance dose was delivered through sustained release layer prepared by using polymers like HPMC K4, HPMC K15M, HPMC K100, PEO WSR 303 and Precirol. Both the immediate release layer and sustained release layers were separately optimized and then combined to optimize the bilayertablets. No interactions were found between drug and excipients. Formulation containing Kyron T314 shows immediate drug release. Formulation Containing PEO WSR 303 shows sustained release action and bilayer formulations F6 shows releases up to 24 hours. Bilayer tablets with release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy.

Key words: Baclofen, Bilayer tablet, sustain release tablet

INTRODUCTION:

Oral route is the most commonly employed route of drug administration. Although different Route of administration are used for the delivery of drugs, oral route remain the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product. Even for sustained release systems the oral route of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers. With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non-toxicfor an extended period of time.[1-4]

Bi-layer tablet concept has long been utilized to develop sustained released formulation. Such

Tablet has a fast releasing layer and may contain one (bi-layer), to sustain the drug release. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state as the release from sustaining layer.[5-8]

Baclofen is structural analogue of gamma-amino butyric acid is a centrally acting skeletal muscle relaxant, which is widely used in the treatment of spasticity resulting from multiple sclerosis, muscle spasms, muscular rigidity and spinal cord injuries.[9,10]

Baclofen is rapidly absorbed from gastrointestinal tract and the peak plasma concentration is achieved within about 2 hr. It is largely excreted in the urine, 80% as unchanged drug and, the rest as metabolites. The elimination half-life has been reported to be 4 hr and thus make it a potent candidate for sustained release dosage form.[11,12]
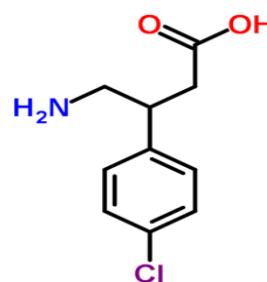
Figure 1: Structure of baclofen

Chemical name: 4-Amino-3(p-chlorophenyl) butyric acid

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Mechanism of action:

Baclofenis is a structural analogue of g-amino butyric acid (GABA). Baclofen decreases spasticity by binding to GABAB receptors on presynaptic terminals of spinal interneurons. Binding to presynaptic GABAB receptors results in hyperpolarization of the membrane, which reduces Ca++ influx and decreases the release of the excitatory neurotransmitters, glutamate, and aspartate.[13]

MATERIALS:

Baclofen was obtained as gift sample from Unicure Pvt.remedies, Vadodara. SSG, Crospovidon, CrossCarmellose and Kyron T 314 were obtained as gift sample from colorcon, Goa. HPMC grades, ethyl cellulose, Carbopol 934, PVP K-30, Mannitol, and Magnesiumstearate, Talc were procured commercially from chem dyes corporation Vadodara.Precirol ATO 5 was gift sample from GATTEFOSSÊ S.A.S., Mumbai, India, and PEO WSR 303 was gift sample from colorcon, Goa.

METHOD OF PREPARATION:

Direct compression was used for preparation of the immediate release layer and wet granulation technology was used for Sustained release layer containing baclofen. For both the layer, granulation was carried out separately, as follows:

Preparation of immediate release layer (IR)

All the ingredients were accurately weighed and passed through mesh 60#.In order to mix the ingredients thoroughly drug, superdisintegrant, microcrystalline cellulose, magnesium stearate and talc were mixed in a mortar and pestle. The powder was passed through 60# sieve and compressed on rotary tablet punching machine. (Made- Krishna Engineering)

Preparation of sustained release layer (SR)

It was performed by wet granulation method. The required amount of sustained release polymer were blended with baclofen and passed through 80 mesh sieve. Binding solution was prepared by dissolving required amount of PVP k 30 in iso propyl alcohol (IPA).Blended powders were granulated with IPA solution and sieved using 40 mesh sieves. The granules were dried at 45˚c for 30 min in tray dryer to evaporate the IPA and then lubricated with required amount of talc, magnesium stearate, store the lubricated granules with suitable label till it's further used.

Final compression of bilayer tablets

Bilayer tablets were prepared by feeding 200 mg of SR granules manually into punch and compressed them with pre compression force. Then 100 mg of IR granules were manually fed into same die cavity SR granules and applied final compression force into rotary tablet punching machine.

Evaluation parameter

1.   Physical appearance

All the immediate and sustained release tablets were visually inspected for any tablet defects like capping, lamination, presence of any coloured particle.

2.   Hardness

This can be determined by using Monsanto hardness tester.

3.   Friability

Friability can be measured by Roche friability tester. 10 tablets are kept in the friability tester and it is rotated at 25 rpm for 4 minutes. Initial and final weights are then recorded and friability is calculated by following formula.

$$\%F = [1 - (Wt/W)] * 100$$

W – Initial weight of tablet
Wt- Weight of tablet after revolution.

If % Friability of tablets is less than 1% is considered acceptable.

4.   Weight variation test

Weight variation test can be done as per the Indian Pharmacopoeia. 20 tablets were generally taken and were weighed individually and the weight variation was calculated with the use of standard deviation.

5.   In Vitro drug release studies:

In Vitro drug release studies were performed using USP dissolution test apparatus (Type 1). The dissolution studies were performed in 900ml of dissolution medium which was stirred at 50 rpm at 37±0.5°C following a pH progression method. i.e. pH 1.2 for first 2h, pH 6.8 for 24hr. Aliquots was withdrawn periodically and replaced with fresh medium.

FORMULATION

Table 1: Composition of immediate release layer tablet

Immediate release layer				
	F1(mg)	F2(mg)	F3(mg)	F4(mg)
Baclofen	5	5	5	5
Cros Povidone	2	-	-	-
Cross Carmellose	-	2	-	-
SSG	-	-	2	-
Kyron T 314	-	-	-	2
MCC	90	90	90	90
Mg Stearate	2	2	2	2
Talc	1	1	1	1
Total	100	100	100	100

Table 2: Composition of immediate release layer tablet

Immediate release layer				
	F5(mg)	F6(mg)	F7(mg)	F8(mg)
Baclofen	5	5	5	5
Cros Povidone	5	-	-	-
Cross Carmellose	-	5	-	-
SSG	-	-	5	-
Kyron T 314				5
MCC	87	87	87	87
Mg Stearate	2	2	2	2
Talc	1	1	1	1
Total	100	100	100	100

Table 3: Composition of sustained release layertablet

Sustained release layer						
	F1(mg)	**F2(mg)**	**F3(mg)**	**F4(mg)**	**F5(mg)**	**F6(mg)**
Baclofen	21	21	21	21	21	21
HPMC K4 M	60	-	-	-	-	-
HPMC K15 M	-	60	-	-	-	-
HPMC K 100 M	-	-	60	-	-	-
PEO WSR 303	-	-	-	20	40	60
PVP K 30	10	10	10	10	10	10
DCP	103	103	103	143	123	103
Magnesium Stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
IPA	q.s	q.s	q.s	q.s	q.s	q.s
Total	200	200	200	200	200	200

Table 4: Composition of sustained release layertablet

Sustained release layer									
	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)
Baclofen	21	21	21	21	21	21	21	21	21
Ethyl cellulose	20	40	60	-	-	-	-	-	-
Carbopol	-	-	-	10	20	40	-	-	-
Precirol	-	-	-	-	-	-	40	60	80
PVP K 30	10	10	10	10	10	10	10	10	10
DCP	143	123	103	153	143	123	123	103	83
Mg. Stearate	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	200	200	200	200	200	200	200	200	200

RESULT:

The results of evaluation parameters of formulations F1-F8 were calculated and described in this.

Precompression parameters such as Angle of Repose, Loose Bulk Density, Tapped Bulk Density, Hausner's Ratio, and Carr's Index. Values are listed in Table 5.

Table 5: Pre compression study of immediate release layer tablets

Batches	Bulk Density gm. cm^{-3} ($\pm$S.D) (n=3)	Tapped density gm. cm^{-3} ($\pm$S.D) (n=3)	Carr's Index ($\pm$ S.D) (n=3)	Hausner's ratio ($\pm$S.D) (n=3)	Angle of repose (Θ^o) ($\pm$S.D) (n=3)
F1	0.29$\pm$ 0.058	0.36$\pm$ 0.07	12.1$\pm$ 0.12	1.13$\pm$ 0.22	28.45$\pm$ 0.02
F2	0.30$\pm$ 0.06	0.33$\pm$ 0.06	9.09$\pm$ 0.18	1.11$\pm$ 0.222	27.36$\pm$ 0.01
F3	0.33$\pm$ 0.066	0.4$\pm$ 0.08	17.5$\pm$ 0.01	1.21$\pm$ 0.24	30.49$\pm$ 0.05
F4	0.24$\pm$ 0.048	0.43$\pm$ 0.086	14.5$\pm$ 0.11	1.18$\pm$ 0.23	31.27$\pm$ 0.03
F5	0.29$\pm$ 0.058	0.31+0.062	12.1$\pm$ 0.08	1.13$\pm$ 0.22	30.72$\pm$ 0.02
F6	0.30$\pm$ 0.06	0.37$\pm$ 0.074	6.09$\pm$ 0.09	1.14+0.23	29.45$\pm$ 0.06
F7	0.35$\pm$ 0.07	0.48$\pm$ 0.096	17.5$\pm$ 0.16	1.24$\pm$ 0.25	28.12$\pm$ 0.01
F8	0.33$\pm$ 0.066	0.4$\pm$ 0.08	16.3$\pm$ 0.13	1.20$\pm$ 0.24	30.80$\pm$ 0.08

Table 6: Pre compression study of sustained release layer tablets

Batches	Bulk Density gm cm^{-3} ($\pm$S.D (n=3)	Tapped density gm cm^{-3} ($\pm$S.D) (n=3)	Carr's Index ($\pm$ S.D) (n=3)	Hausner's ratio ($\pm$S.D) (n=3)	Angle of repose (Θ^o) ($\pm$S.D) (n=3)
F1	0.24$\pm$ 0.04	0.63 $\pm$ 0.12	15.85 $\pm$0.12	1.18 $\pm$0.23	29.19 $\pm$0.02
F2	0.28$\pm$ 0.05	0.62 $\pm$ 0.124	17.74 $\pm$0.18	1.21 $\pm$ 0.24	29.65 $\pm$0.05
F3	0.30$\pm$ 0.06	0.54 $\pm$ 0.108	21.62 $\pm$0.04	1.19 $\pm$0.23	27.34 $\pm$0.42
F4	0.29$\pm$ 0.058	0.64 $\pm$ 0.128	14.06 $\pm$0.05	1.16 $\pm$0.232	29.62 $\pm$0.31
F5	0.32$\pm$ 0.064	0.52 $\pm$ 0.10	20.63 $\pm$0.07	1.26 $\pm$ 0.25	28.51 $\pm$0.25
F6	0.38$\pm$ 0.07	0.58 $\pm$ 0.11	17.74 $\pm$0.01	1.21 $\pm$ 0.24	27.19 $\pm$0.43
F7	0.34$\pm$ 0.068	0.62 $\pm$ 0.12	19.62 $\pm$0.21	1.20 $\pm$0.24	28.37 $\pm$0.67
F8	0.40+0.066	0.58 $\pm$ 0.11	22.66 $\pm$0.08	1.15 $\pm$0.23	26.34 $\pm$0.26
F9	0.48$\pm$ 0.09	0.62 $\pm$ 0.12	21.62 $\pm$0.07	1.28 $\pm$ 0.25	25.26 $\pm$0.05
F10	0.31+0.062	0.54$\pm$ 0.10	18.53 $\pm$0.11	1.12$\pm$ 0.22	29.57$\pm$ 0.91
F11	0.42$\pm$ 0.084	0.46$\pm$0.09	20.12$\pm$ 0.07	1.24$\pm$ 0.25	30.12$\pm$ 0.02
F12	0.37$\pm$ 0.074	0.48$\pm$00.096	16.61$\pm$ 0.05	1.14$\pm$ 0.23	24.28$\pm$ 0.85
F13	0.35$\pm$ 0.07	0.44$\pm$0.08	11.23$\pm$ 0.13	1.18$\pm$ 0.23	30.64$\pm$0.12
F14	0.32$\pm$ 0.064	0.50$\pm$0.1	15.67$\pm$ 0.04	1.15$\pm$ 0.23	31.05$\pm$0.21
F15	0.47$\pm$0.09	0.51$\pm$ 0.10	16.67$\pm$ 0.15	1.14$\pm$0.22	29.42$\pm$ 0.88

The results of evaluation parameters of formulations F1-F15 were calculated and described in this. Precompression parameters such as Angle of Repose, Loose Bulk Density, Tapped Bulk Density, Hausner's Ratio, and Carr's Index. Values are listed in Table 6. It was found that granules of all batched of wet granulation were found having fair-passable flow property.

The result of post compression evaluation parameters of formulations F1-F15 such as hardness, friability, weight variation and drug content is given in table no 7.

**Table 7: Post compression study of bilayer layer tablet**

Batches	Hardness (kg cm^{-2}± S.D) (n=3)	Friability (%)	Weight variation Avg weight (mg)(S.D $\leq$ 10%)	% Drug Content (S.D)
F1	6± 0.42	0.61 ± 0.12	300± 0.04	100± 0.01
F2	5± 0.39	0.66 ± 0.13	301± 0.09	101± 0.08
F3	7± 0.35	0.38 ± 0.07	300± 0.10	101± 0.10
F4	6± 0.46	0.33 ± 0.06	301± 0.14	99.98± 0.15
F5	7± 0.50	0.26 ± 0.05	299± 0.18	98.87± 0.17
F6	5± 0.59	0.37 ± 0.07	304± 0.13	100± 0.09
F7	7± 0.46	0.49± 0.09	301± 0.43	99.52± 0.13
F8	6± 0.57	0.20 ± 0.04	298.8± 0.36	99.48± 0.11
F9	7± 0.62	0.57 ± 0.11	297± 0.21	97.39± 0.04
F10	5± 0.21	0.36± 0.07	300± 0.38	99.19± 0.17
F11	6± 0.53	0.29± 0.05	301±0.09	100± 0.15
F12	7± 0.60	0.64± 0.12	299.8± 0.9	100± 0.06
F13	7± 0.76	0.52± 0.10	299.6± 0.38	99.53± 0.25
F14	5± 0.66	0.41± 0.08	300± 0.44	99.89± 0.12
F15	7± 0.95	0.50± 0.1	301± 0.32	99.54± 0.24

In-Vitro Drug Release data of batch F1 to F15 were shown in figures given below.

6.   In Vitro Dissolution Study
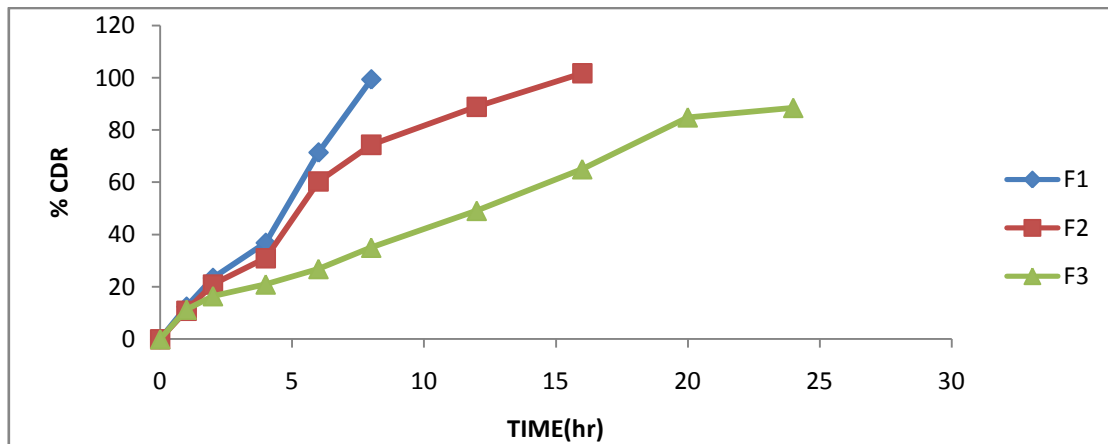
Figure 2: In Vitro Dissolution Study of Immediate release layer tablet F1 to F3
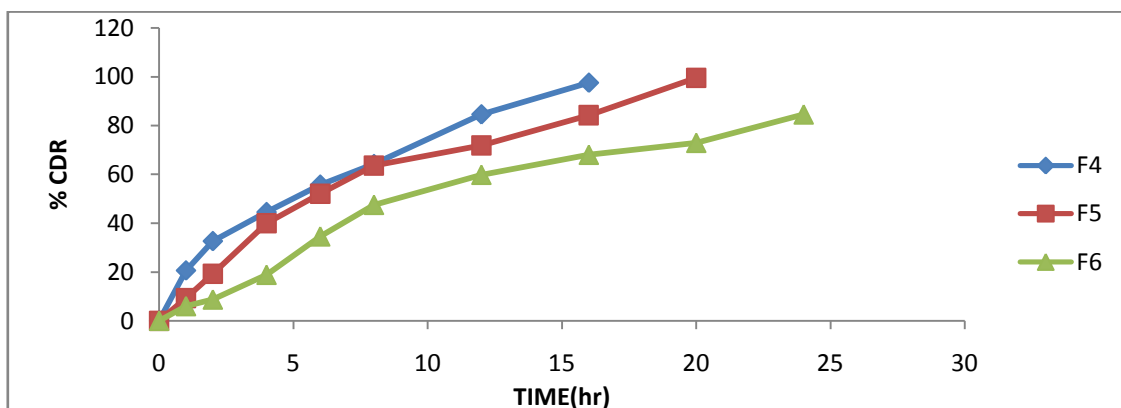
Figure 3: In Vitro Dissolution Study of Immediate release layer tablet F5 to F6
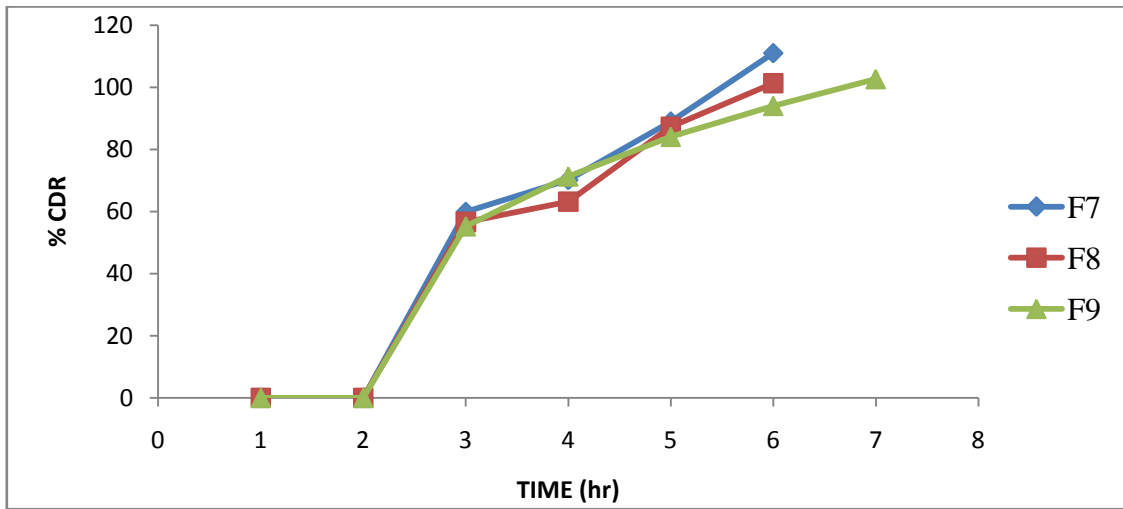
Figure 4: In Vitro Dissolution Study of Sustained release layer tablet F7 to F9
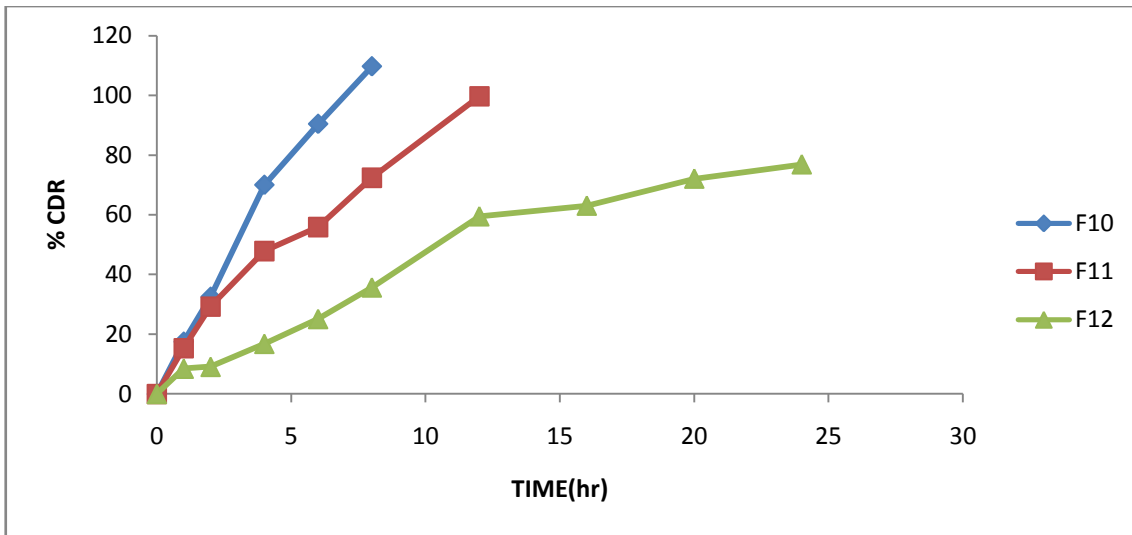

Figure 5: In Vitro Dissolution Study of Sustained release layer tablet F10 to F12
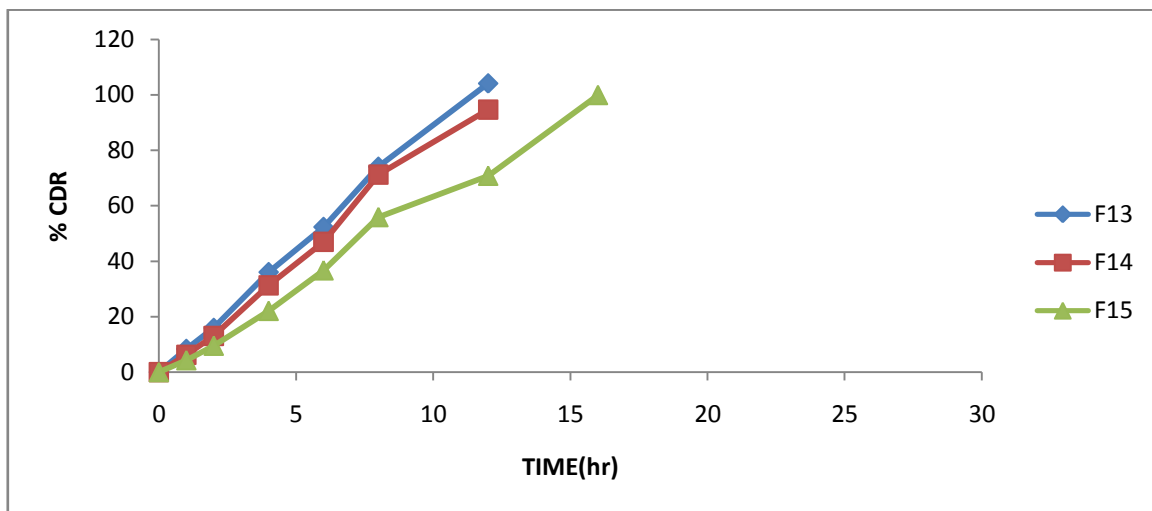

Figure 6: In Vitro Dissolution Study of Sustained release layer tablet F7 to F9

DISCUSSION

In Bilayer tablet of Baclofen immediate release layer was prepared by direct compressionand sustained release was prepared by wet granulation method. The Tablets Containing PEO WSR 303 polymer showed the desired sustained action. Formulations **F6** releases up to 24 hours and it shows good sustained action. In all the formulations an initial burst release was seen to provide the loading dose of the drug, followed by the controlled release. From these results it clearly indicates that the prepared formulations are potential of the Baclofen bilayer matrix tablet as an alternative to the conventional dosage form. Batch F7-F9 containing ethyl cellulose not shows the retardation of drug at lower concentration. Ethyl cellulose shows sustain action up to 8 hrs.   HPMC different viscosity grades, PEO WSR 303 and Carbopol 934 shows retardation of drug. A higher viscosity polymer shows desired retardation up to 24 hr.

CONCLUSION:

In vitro release studies demonstrated that the release of Baclofen from the prepared bi-layer matrix tablets were dependent on polymeric level. When we increased the polymeric concentration, due to this increased concentration of sustained release polymers drug release was retarded up to 24 hr. In all the formulations an initial burst release was seen to provide the loading dose of the drug, followed by the controlled release for 24 hr From these results it clearly indicates that the prepared formulations are potential of the Baclofen bi-layer matrix tablet as an alternative to the conventional dosage form.

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