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Research Article

Formulation and *in vitro* evaluation of bi-layer tablet of cyclobenzaprine hydrochloride ER and diclofenac potassium IR – A novel fixed dose combination

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ABSTRACT

The aim of this study was to prepare bi-layer tablet of Diclofenac Potassium (DP) and Cyclobenzaprine Hydrochloride (CBH) for the effective treatment of severe pain due to inflammation and muscle spasm. DP and CBH were formulated as immediate and extended release layer respectively. DP was formulated as immediate release layer (IR) using excipients like microcrystalline cellulose and maize starch in different drug to excipient ratio keeping other excipients as constant. DP granules was prepared by wet granulation method using purified water and mixed with extragranular excipients. CBH was formulated as extended release (ER) layer using hydrophilic matrix (hydroxypropylmethylcellulose [HPMC K100MCR]). The effect of concentration of hydrophilic matrix (HPMC K100MCR) on CBH release was studied. The dissolution study of extended release layer showed that an increasing amount of HPMC results in reduced CBH release. The rationale for formulation of bi-layer tablet of these two drugs in combination was (1) to reduce the manufacturing cost and time (2) to reduce the dosing frequency and thereby improve the patient compliance.

Keywords: bi-layer tablet; hydroxylpropyl methylcellulose; diclofenac potassium; cyclobenzaprine hydrochloride; extended release; immediate release; FDC; stability.

INTRODUCTION

Bi-layer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose (Gunsel W.C., 1989).

Cyclobenzaprine is a muscle relaxant medication used to relieve skeletal muscle spasms and associated pain in acute musculoskeletal conditions. The mechanism of action for cyclobenzaprine is unclear. Studies from the 1980s in rats indicate that cyclobenzaprine activates the locus ceruleus in the brain stem, leading to an increased release of norepinephrine in the ventral horn of the spinal cord and the subsequent inhibitory action of norepinephrine on alpha motor neurons (Commissiong J.W. et al.1981).

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in conditions such as arthritis or acute injury. It can also be used to reduce menstrual pain, dysmenorrhea. The name is derived from its chemical name: 2-(2,6-dichloranilino) phenylacetic acid. Diclofenac originated from Ciba-Geigy (now Novartis) in 1973 and was first introduced in the UK in 1979 (Salmann, A.R., 1986).

Obviously, the aim of present study was to develop a bilayer tablet for a novel fixed dose combination which is comparable to stand alone marketed formulations and thereby improve patient compliance and reduction of manufacturing cost. Formulated investigational bilayer tablets were subjected to evaluation for physical properties, *in vitro* release studies during pre and post stability studies.

EXPERIMENTAL

Materials

Diclofenac potassium, Cyclobenzaprine hydrochloride and HPMC K100MCR were obtained as a gift sample from M/s. Ranbaxy Research Labs Ltd., Gurgaon. Skelebenz ER Capsules 30mg [Sun pharmaceuticals Ltd.], Voltaflam IR Tablets 50mg [Novartis (India) Ltd.] Calcium carbonate, Lactose monohydrate (DCL11), Magnesium stearate, Maize Starch, Red iron oxide [Central drug house (P) Ltd.], Colloidal silicone dioxide, Croscarmellose Sodium [E.Merk (India) Ltd.], Povidone K30 [Lobachemie (P) Ltd.] were obtained from commercial

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Table 1: Composition of different investigational bilayer tablets

Composition of Cyclobenzaprine HCl ER Layer						
Batch no.		C1D1	C2D2	C3D3	C4D3	C5D3
S.No.	Ingredients	mg/tab				
Intragranular						
1	Cyclobenzaprine HCl	30.0	30.0	30.0	30.0	30.0
2	HPMC K100MCR	4.5	7.5	10.5	25.5	40.5
3	Povidone K30	15.0	15.0	15.0	15.0	15.0
4	Lactose DCL11*	98.5	95.5	92.5	77.5	62.5
5	Isopropyl Alcohol**	q.s.	q.s	q.s	q.s	q.s
Extragranular						
6	Magnesium stearate	2.0	2.0	2.0	2.0	2.0
Layer wt.		150.0	150.0	150.0	150.0	150.0
Composition of Diclofenac Potassium IR Layer						
Intragranular						
1	Diclofenac potassium	50.0	50.0	50.0	50.0	50.0
2	Maize starch	40.0	60.0	75.5	75.5	75.5
3	Calcium carbonate*	99.5	76.0	30.0	30.0	30.0
4	Microcrystalline cellulose (Avicel PH101)	-	-	30.5	30.5	30.5
5	Red iron oxide	2.0	2.0	2.0	2.0	2.0
6	Purified water**	q.s	q.s	q.s	q.s	q.s
Extragranular						
7	Colloidal Silicon Dioxide (Aerosil 200)	2.5	2.5	2.5	2.5	2.5
8	Croscarmellose Sodium (AcDisol)	4.0	4.0	4.0	4.0	4.0
9	Microcrystalline cellulose (Avicel PH102)	-	3.5	3.5	3.5	3.5
10	Magnesium stearate	2.0	2.0	2.0	2.0	2.0
Layer wt.		200.0	200.0	200.0	200.0	200.0
Total tablet wt.		**350.0**	**350.0**	**350.0**	**350.0**	**350.0**

* Filler; ** Lost during process; q.s.- qty sufficient

sources. All reagents and chemicals used were of analytical grade only.

Drug Excipient Compatibility Study by FTIR

The mixture contains drug and respective excipients proposed for both immediate release and extended release layer were evaluated for drug excipient compatibility study. These individual mixtures were taken on an agate pestle and triturated with 100mg of potassium bromide. The mixture was then compressed into a pellet and then introduced into the instrument (schimadzu model) for analysis. The spectrum was recorded between 500 and 4000 cm^{-1}.

Preparation of Diclofenac potassium IR Layer Blend

As per table 1 the calculated quantity of DP and Intragranular excipients were sifted through #25 BSS sieve and mixed with red iron oxide (pre-sifted through #100 BSS sieve) and was granulated using starch paste as binder in a stainless steel bowl manually. Wet mass was dried in hot air oven and milled through #22 BSS sieve. Colloidal silicone dioxide (Aerosil 200), Croscarmellose Sodium (AcDisol) and microcrystalline cellulose (Avicel PH102) were sifted through #25 BSS sieve and then added to dried granules and mixed for 5 minutes in a polybag and then lubricated with magnesium stearate (pre-sifted through #60 BSS sieve) and labeled.

Preparation of Cyclobenzaprine Hydrochloride ER Layer Blend

As per table 1 the weighed quantity of CBH, Hypromellose (K100MCR) and Lactose monohydrate (DCL11) were sifted through #25 BSS sieve and mixed together in a polybag manually. Povidone (K30) was dissolved in Isopropyl alcohol in a glass beaker. Blend of the drug and excipients was granulated using the binder solution in a stainless steel bowl manually. Wet mass was dried in hot air oven and milled through #25 BSS sieve and then lubricated with magnesium stearate (pre-sifted through #60 BSS sieve) and labeled.

Compression of Bilayer Tablet & Physical Evaluation

The final blends of bilayer tablets as per table 1 were compressed in to tablets using 12.5 x 6.5mm oval shaped standard concave, plain punches & corresponding die fitted in single punch tablet machine. Tablets were evaluated for weight, thickness, hardness and friability and disintegration time of IR layer.

***In vitro* Release Studies**

Dissolution study of Cyclobenzaprine HCl ER layer

The *in vitro* dissolution studies were carried out by using USP type II (Paddle) at 50 Rpm. Dissolution medium (900 ml) consists of 0.1N hydrochloric acid was maintained at 37± 0.5 °C. The In-vitro release study was up to 16hrs; 10ml of samples were withdrawn at predetermined time intervals and further diluted with medium after filtered through 0.45µm filter. The amount of $C_{20}H_{21}N$•HCl dissolved was determined by measuring UV absorbance at 290nm.

Dissolution study of Diclofenac potassium IR Layer

The *in vitro* dissolution studies were carried out by using USP type II (Paddle) at 50 Rpm. Dissolution medium (900 ml) consists of Simulated Intestinal Fluid (without enzyme)was maintained at 37± 0.5 °C in line with USP32. The *in vitro* release study was carried out up to till 90 minutes; 10ml of samples were withdrawn at predetermined time intervals further diluted with medium after filtered through 0.45µm filter. The amount of $C_{14}H_{10}Cl_2KNO_2$ dissolved was determined by measuring UV absorbance at 276nm using concurrent placebo as blank.

Dissolution study of Marketed Stand-alone Formulations

Voltaflam 50 (DP) Tablets (IR) manufactured by Novartis Ltd. and Skelebenz30 (CBH) Capsules (ER) manufactured by Sun pharma Ltd., were also evaluated for *in vitro* release studies using respective dissolution method.

Selection of best formulation

Different dissolution profiles were compared to establish the effect of formulation on the drug release. The dissolution similarity was assessed using the FDA recommended approach (f2 similarity factor). This model independent mathematical approach was described by Moore and Flanner (1996):

$$f2 = 50 \cdot \log\{[1 + (1/n)\sum_{t=1}^{n}(Rt - Tt)^2]^{-0.5} \cdot 100\}$$

where *Rt* and *Tt* are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. When the two profiles are identical, f2 value should in between 50 and 100. An average difference of 10% at all measured time points results in an f2 value of 50 (Shah V.P. et al., 1998).

Release Kinetics

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics (Hadjiioannou et al., 1993; Bourne, 2002; Higuchi, 1963; Korsmeyer et al., 1983). The following plots were made: 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).

Stability Studies

The selected formulations were packed in amber-colored bottles, tightly plugged with cotton and capped. They were then stored at Accelerated /ACC (40°C ± 2°C/75% RH ± 5% RH) and long term/CRT (25°C ± 2°C/60% RH ± 5% RH) conditions up to the period of three months by kept at respective desiccators. Stability samples were evaluated for physical appearance, drug content and *in vitro* release studies at 1 month, 2 month and 3 month time intervals and compared with its initial data.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Study by FTIR

Table 2: FTIR peaks of CBH and CBH + Excipients

CBH		CBH + Excipients	
Peak No.	**Characteristic peaks (cm^{-1})**	**Peak No.**	**Characteristic peaks (cm^{-1})**
19	1160.94	15	1167.69
23	1018.23	20	1034.62
9	1593.88	8	1655.59
4	2957.30	2	2917.77
28	855.28	24	876.49

Table 3: FTIR peaks of DP and DP + Excipients

DP		DP + Excipients	
Peak No.	**Characteristic peaks (cm^{-1})**	**Peak No.**	**Characteristic peaks (cm^{-1})**
25	765.6	14	766.57
2	3247.54	1	3422.06
7	1577.46	3	1577.49
4	2972.73	2	2918.73
12	1381.75	7	1381.75
18	1088.62	11	1081.87

Compatibility studies of DP and CBH with respective excipients were determined by FTIR scan of each sample at the range of 500-4000 cm^{-1}.

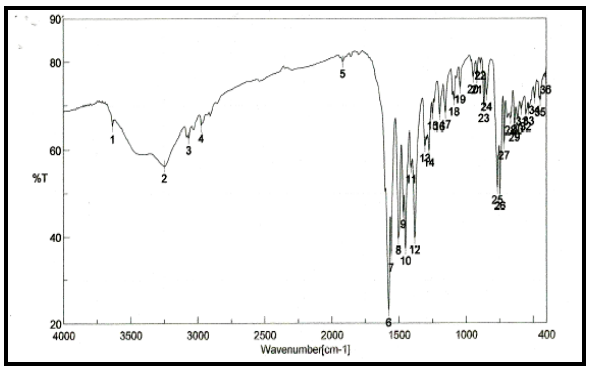

Figure 1: FTIR spectra of pure drug DP

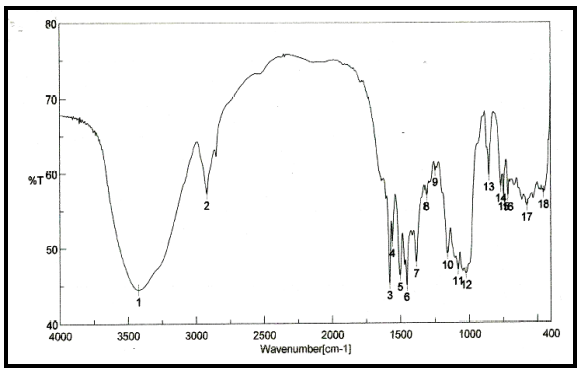

Figure 2: FTIR spectra of DP + Excipients

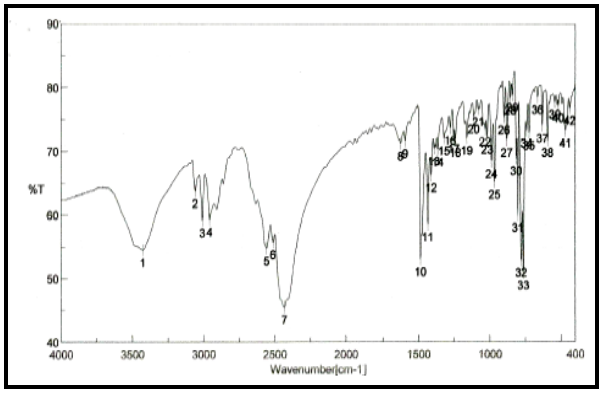

Figure 3: FTIR spectra of pure drug CBH

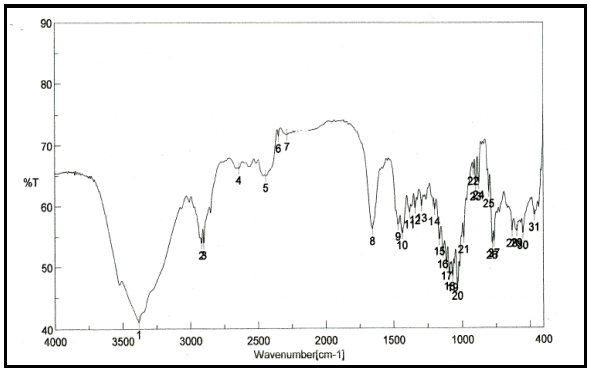

Figure 4: FTIR spectra of CBH + Excipients

The IR spectra of all the tested samples showed in table 2 & 3 and figure 1, 2, 3 & 4 the prominent characterizing peaks of pure Diclofenac Potassium & Cyclobenzaprine HCl which confirm that interactions between the drug, polymers and excipients were unlikely to occur.

Evaluation of Physical characterization of the bilayer tablets

All the batches were produced under similar conditions to avoid processing variables. As per table 4, the results are found to be satisfactory with respect to description, average weight, thickness, hardness, friability, disintegration time of IR layer and drug content.

***In vitro* Release Studies & selection of best formulation**

The *in vitro* dissolution data was analyzed by plotting the cumulative percent drug released vs. time for both DP and CBH. Based on the results shown in table 5 and figure 5 it was decided to select the composition of investigational batch no. C3D3 with respect to DP immediate release layer as it meets both USP criteria and similarity factor f2 (against marketed product i.e., Voltaflam IR Tablets 50mg).

As per figure 6 the simple visual observation of the plot shows that the formulations (C1D1, C2D2 & C3D3) with low concentration of hydrophilic polymer (HPMC K100MCR), an initial rapid release (≈34% & above) of CBH was observed within the first one hour of the dissolution study. This initial fast drug release rate can be attributed the availability of drug at outer surface where the drug molecules needs to pass through minimum diffusion path length. The swelling index increased with an increase in the content of HPMC (Kailasam et al., 2010), results in increase the diffusion path length. This in turns retard the drug release as the diffusion path length of drug is now longer, resulted in controlled release. Further release of CBH was studied for 16 h.

Based on the results summarized in table 6 it seems that two investigational batches i.e. C4D3 and C5D3 are significantly similar to the marketed formulation (Skelebenz ER Capsules 30mg) with respect to dissolution profiles of Cyclobenzaprine HCl which is reflected by its f2 values.

But at the same time, the dissolution profile of investigational batch C4D3 was significantly similar to that of marketed formulation (Skelebenz ER Capsules 30mg) which is reflected by highest f2 value (84.0). Hence, considering the results of *in vitro* release, batch C4D3 was ranked as an optimized batch in comparison with batch C5D3 (where as the f2 value is 59.3) and was subjected to kinetic release study and stability study.

In this selected formulation, the calculated regression coefficients for Higuchi, Zero order and First order models were 0.9588, 0.7855 and 0.9499 respectively

Table 4: Physical characterization of investigational bilayer tablets

Test parameters	Observations				
	C1D1	C2D2	C3D3	C4D3	C5D3
Description	Oval shaped pink and white colored uncoated bilayer tablets				
Thickness (mm)*	3.04±0.03	3.08±0.03	3.11±0.02	3.09±0.03	3.14±0.06
Hardness (kg/cm2)*	6.90±0.36	6.98±0.28	6.97±0.23	6.90±0.28	7.12±0.36
Friability (%w/w)*	0.42±0.14	0.31±0.08	0.19±0.07	0.16±0.06	0.11±0.03
Average Wt (mg)*	353.20±5.14	351.90±4.25	351.70±5.25	353.70±6.17	353.70±2.79
D.T. range of IR Layer (min.sec)	12.40- 16.10	10.15- 13.45	5.37-7.12	6.37-8.25	6.10-8.12
Assay of DP (%)	98.12	97.34	97.65	99.30	96.80
Assay of CBH (%)	99.10	96.40	96.90	97.80	97.21

*Each value represents mean ± SD (n=10)

Table 5: *In vitro* release profile of DP from investigational bilayer tablets

Time (min)	Cumulative Drug Released (%) ± SD (n=6)			
	Voltaflam	C1D1	C2D2	C3D3
0	0±0	0±0	0±0	0±0
10	46±4.21	14±4.74	25±2.97	43±4.21
20	63±3.60	27±3.59	35±1.97	53±3.6
30	73±2.36	40±2.16	47±2.72	68±2.36
45	83±1.82	51±5.01	57±1.63	76±1.82
60	96±2.24	62±3.35	70±3.15	89±2.24
90	97±1.19	80±2.07	84±3.26	95±1.19
	f2	**23.8**	**29.7**	**58.9**

Table 6: *In vitro* release profile of CBH from investigational bilayer tablets

Time (Hr)	Cumulative Drug Released (%) ± SD (n=6)					
	Skelebenz	C1D1	C2D2	C3D3	C4D3	C5D3
0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
1	29±2.55	80±1.37	57±2.98	34±3.35	28±0.86	22±1.47
2	35±1.20	100±2.82	80±2.14	59±4.66	36±2.99	33±4.71
3	45±1.32	98±1.89	100±2.82	77±3.17	46±1.14	45±1.64
4	63±1.23	98±2.05	97±1.79	95±5.26	62±2.95	54±2.05
5	70±2.19	98±1.84	98±2.17	95±2.21	69±1.37	61±0.71
6	76±1.66	97±2.07	97±1.87	96±3.36	76±6.37	69±2.01
7	80±2.99	98±1.07	99±2.17	97±1.73	81±1.08	72±1.66
8	84±2.80	99±1.81	98±1.66	98±1.20	86±6.16	77±2.46
12	94±0.92	98±2.05	99±2.07	99±1.33	90±1.57	91±3.61
16	97±1.93	99±2.04	99±2.07	100±1.51	100±2.82	99±8.00
f2		**22.5**	**26.4**	**34.6**	**84.0**	**59.3**

(table 7). Therefore, the release seems to fit the Higuchi model (Figure 9). To explore the release pattern, results of the *in vitro* dissolution data were fitted to the Korsmeyer and Peppas model which characterizes the transport mechanism. The value of release exponent (n) for the optimized formulation C4D3 was 0.5581, indicating release governed by non-Fickian diffusion (Figure 10).

Stability Studies

At the end of the testing period, the bilayer tablets were observed for changes in description, hardness, drug content and *in vitro* drug release studies. Based on the results in table 8 & 9 no significant changes in the description, hardness and drug content of the bilayer tablets (C4D3) were observed at the end of the storage period. The result of the stability study (table 10 - 13 & figure 11 - 14) does not highlight any significant alteration in the *in vitro* release pattern of the drug in optimized formulation C4D3 before and after stability study for DP and CBH indicates that the formulation could provide a minimum shelf life of 2 years. However, a detailed investigation is necessary to determine the exact shelf- life.

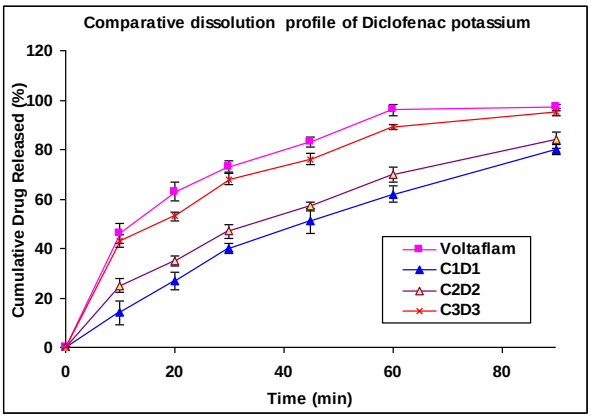

Figure 5: Comparative dissolution profile of DP of investigational bilayer tablets

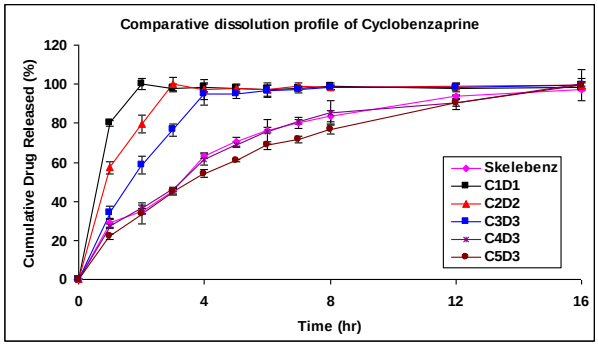

Figure 6: Comparative dissolution profile of CBH of investigational bilayer tablets

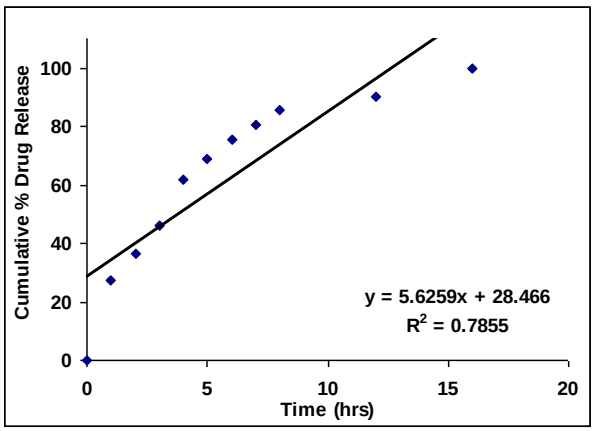

Figure 7: Zero order release model of CBH of C4D3

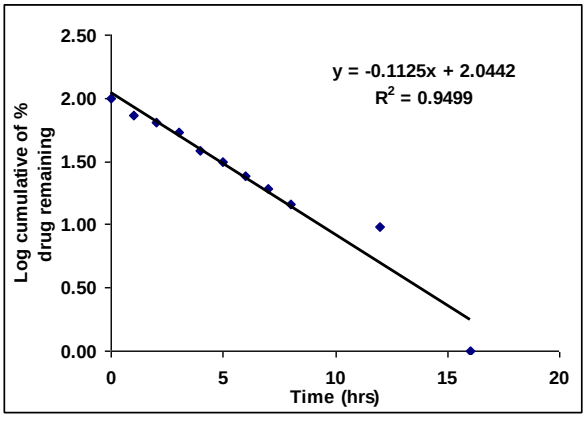

Figure 8: First order release model of CBH of C4D3

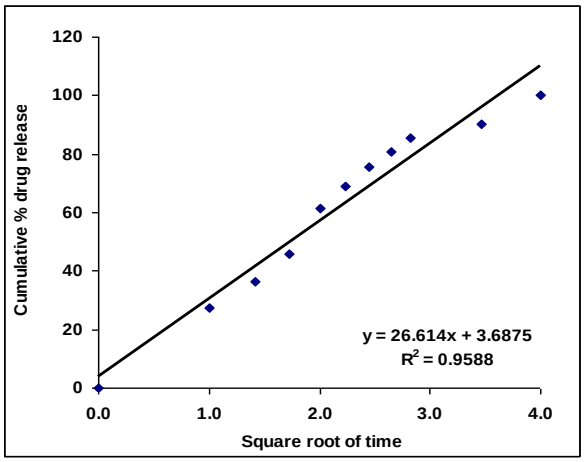

Figure 9: Higuchi release model of CBH of C4D3

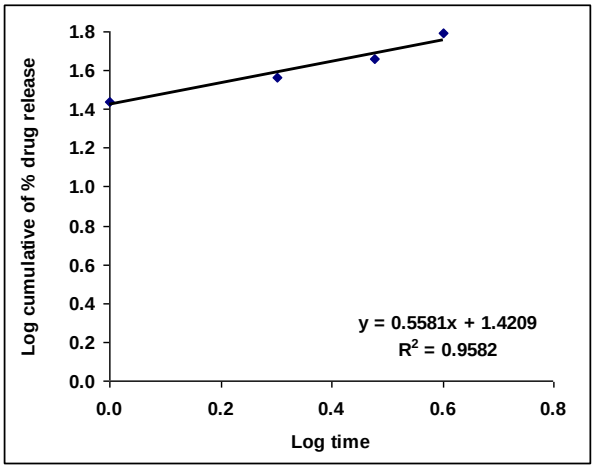

Figure 10: Korsmeyer– Peppas Model for mechanism of drug release

Table 7: Mathematical modeling and drug release mechanisms of optimized formulation (C4D3)

Regression coefficient (r^2)			Korsmeyer-Peppas	
Zero Order	**First Order**	**Higuchi Equation**	***r²***	***n value***
0.7855	0.9499	0.9588	0.9582	0.5581

Table 8: Physical characterization of the bilayer tablets C4D3 (CRT)

Test parameters	Observations			
	Initial	**1M -CRT**	**2M -CRT**	**3M -CRT**
Description	Oval shaped pink and white colored uncoated bilayer tablets			
Hardness (kg/cm2) *	6.90±0.28	6.97±0.37	6.76±0.50	7.01±0.65
Assay of DP (%)	99.30	98.4	97.8	98.1
Assay of CBH (%)	97.80	98.1	97.4	97.6

*Each value represents mean ± SD (n=10)

Table 9: Physical characterization of the bilayer tablets C4D3 (ACC)

Test parameters	Observations			
	Initial	1M -ACC	2M -ACC	3M -ACC
Description	Oval shaped pink and white colored uncoated bilayer tablets			
Hardness (kg/cm2)*	6.90±0.28	6.05±0.75	5.97±0.79	6.28±0.48
Assay of DP (%)	99.30	99.2	98.1	97.8
Assay of CBH (%)	97.80	98.2	98.5	98.0

*Each value represents mean ± SD (n=10)

Table 10: *In vitro* release profile of DP (C4D3) on stability (CRT)

Time (min)	Cumulative % Drug Release (DP) (%) ± SD (n=6)			
	Initial	1M – CRT	2M - CRT	3M – CRT
0	0±0	0±0	0±0	0±0
10	43±4.21	43±2.26	41±3.75	46±2.27
20	53±3.6	53±2.42	52±4.09	49±3.71
30	68±2.36	68±3.72	72±2.90	77±2.41
45	76±1.82	76±1.72	78±3.11	80±1.97
60	89±2.24	89±2.59	86±2.46	89±3.25
90	95±1.19	95±1.58	95±2.92	102±3.52

Table 11: *In vitro* release profile of DP (C4D3) on stability (ACC)

Time (min)	Cumulative % Drug Release (DP) (%) ± SD (n=6)			
	Initial	1M – ACC	2M - ACC	3M - ACC
0	0±0	0±0	0±0	0±0
10	43±4.21	36±2.34	37±2.61	35±2.17
20	53±3.6	48±1.74	48±2.94	52±3.88
30	68±2.36	64±2.25	58±2.65	62±3.88
45	76±1.82	75±2.28	75±3.97	69±4.79
60	89±2.24	85±1.01	82±7.17	78±5.81
90	95±1.19	94±1.50	97±3.92	96±3.81

Table 12: *In vitro* release profile of CBH (C4D3) on stability (CRT)

Time (Hrs)	Cumulative % Drug Release (CBH) (%) ± SD (n=6)			
	Initial	1M–CRT	2M-CRT	3M-CRT
0	0±0.00	0±0.00	0±0.00	0±0.00
1	28±0.86	25±0.86	23±1.71	26±0.96
2	36±2.99	34±2.99	32±1.69	32±0.93
3	46±1.14	43±1.14	41±2.16	43±0.75
4	62±2.95	57±2.97	55±1.96	58±0.80
5	69±1.37	67±1.37	65±0.9	67±2.24
6	76±6.37	70±6.37	68±0.91	71±1.86
7	81±1.08	76±1.08	75±0.72	79±1.55
8	86±6.16	81±6.16	80±1.2	85±3.05
12	90±1.57	95±1.57	93±2.91	95±1.37
16	100±2.82	98±2.82	94±3.22	97±2.07

Table 13: *In vitro* release profile of CBH (C4D3) on stability (ACC)

Time (Hrs)	Cumulative % Drug Release (CBH)(%) ± SD (n=6)			
	Initial	1M–ACC	2M - ACC	3M - ACC
0	0±0.00	0±0.00	0±0.00	0±0.00
1	28±0.86	25±0.86	24±1.44	23±1.47
2	36±2.99	31±2.99	32±1.49	29±1.89
3	46±1.14	43±1.14	40±2.37	42±1.96
4	62±2.95	56±2.95	52±1.38	51±1.59
5	69±1.37	65±1.37	64±1.30	63±2.55
6	76±6.37	73±6.37	69±2.55	69±4.09
7	81±1.08	79±1.08	75±1.46	75±1.70
8	86±6.16	83±6.16	82±2.52	80±4.81
12	90±1.57	94±1.57	93±2.25	91±2.43
16	100±2.82	98±2.82	95±1.44	95±2.41

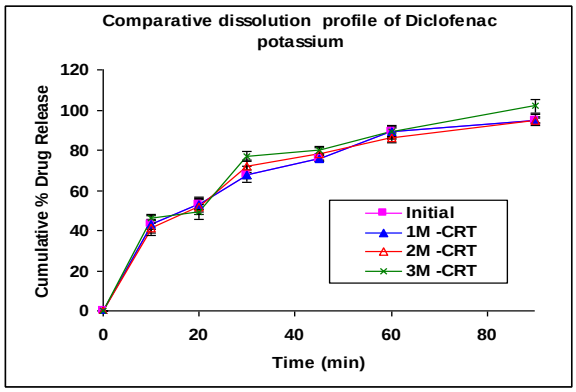

Figure 11: Comparative *in vitro* release profile of DP (C4D3) on stability (CRT)

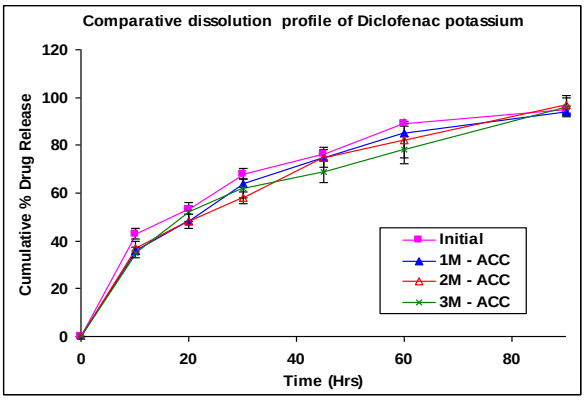

Figure 12: Comparative *in vitro* release profile of DP (C4D3) on stability (ACC)

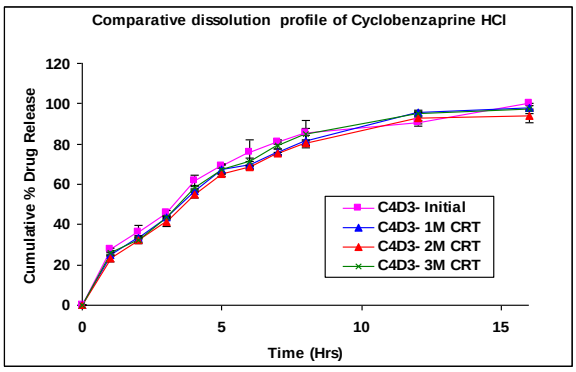

Figure 13: Comparative *in vitro* release profile of CBH (C4D3) on stability (CRT)

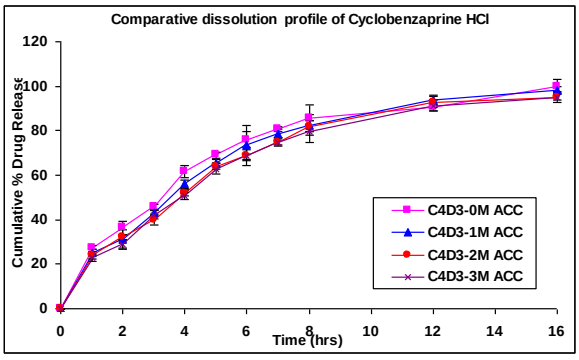

Figure 14: Comparative *in vitro* release profile of CBH (C4D3) on stability (ACC)

CONCLUSION

HPMC K100MCR was used in different ratio to optimize the formulation with desired release of Cyclobenzaprine HCl up to 16 hrs which is comparable to stand alone marketed product. Different ratio of Maize starch, Calcium carbonate, MCC (PH101) and MCC (PH102) were used in immediate release layer. The optimized bilayer tablet C4D3 consists of immediate and extended release layer shows desired release rate, which is significantly comparable to respective stand alone marketed products i.e., Voltaflam IR Tablets 50mg manufactured by Novartis (India) Ltd., India and Skelebenz ER Capsules 30mg manufactured by Sun Pharmaceuticals Ltd., India respectively and therefore this formulation was subjected to stability studies. Hence, bi-layer tablet comprising Diclofenac potassium IR and Cyclobenzaprine hydrochloride ER is indicating a promising potential of FDC as an alternative to stand alone formulations for the treatment of severe pain due to muscle spasm and inflammation thereby improve the patient compliance.

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