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FORMULATION, EVALUATION AND DEVELOPMENT OF BILAYER TABLET

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ABSTRACT

Bilayer tablet of diclofenac sodium and paracetamol was formulated with diclofenac as sustained release formulation. In the same sustained release layer of diclofenac sodium, an immediate layer of paracetamol was optimized separately and then constituted in bilayer tablet using the amount of polyethylene glycol, microcrystalline cellulose and crospovidone as independent variables for fabricating paracetamol tablets. Diclofenac sodium tablets were prepared using hydroxypropyl methylcellulose as a matrixing agent. Effect of these polymers concentration and different diluents were studied and was evaluated by dissolution studies of prepared bilayer formulations along with friability, hardness, content uniformity

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Key Words

Bi-layer tablet, diclofenac sodium, paracetamol , test batch study

INTRODUCTION

Combination therapy have various advantages over monotherapy such as problem of dose dependent side effects is minimized, a low dose combination of two different agent reduces the dose related risk, the addition of one agent may counteract some deleterious effect of other using low dosage of two different agents minimize the clinical and metabolic effects that occur with maximal dosage of individual component of combined tablet.

Paracetamol is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer). It is commonly used for the relief of headaches, other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. Paracetamol is used for the relief of and pains associated with many parts of the body. It has analgesic properties comparable to those of aspirin, while its anti-inflammatory effects are weaker. It is better tolerated than aspirin in patients in whom excessive gastric acid secretion or prolongation of bleeding time may be a concern.

Prolonged daily use increases the risk of upper gastrointestinal complications such as stomach bleeding,] and may cause kidney or liver damage Paracetamol is metabolized by the liver and is hepatotoxic; side effects may be more likely in chronic alcoholics or patients with liver damage

Diclofenac is a non steroidal anti inflammatory drug (NSAID). This medicine works by reducing substances in the body that cause pain inflammation. Diclofenac is used to treat pain or inflammation caused by arthritis or ankylosing spondylitis. Diclofenac is used to treat a migraine headache attack. Diclofenac may cause life-threatening heart or circulation problems such as heart attack or stroke, especially if you use it long term. Diclofenac may also cause serious effects on the stomach or intestines, including bleeding or perforation (forming of a hole).

Conventional formulations containing paracetamol and diclofenac sodium are commercially available in Indian market. The conventional formulations containing 100 mg of diclofenac sodium are used in arthritis, spondylitis, post-operative pain management and other chronic inflammatory

conditions, at a dosing schedule of 3 to 4 times a day. The modified release (MR) tablets of diclofenac sodium containing 100 mg of diclofenac sodium are prescribed as once a day formulations. The major benefits of modified release diclofenac sodium tablets over conventional diclofenac sodium tablets includes reduced dosing frequency and decreased incidence of gastrointestinal side effects. The modified release diclofenac sodium tablets provide analgesic activity for a prolonged duration of time, whereas the combination of conventional paracetamol with MR diclofenac sodium can provide analgesic and anti-pyretic effect. This combination formulation is also beneficial for the patients who are on multiple drug therapy requiring both anti-pyretic and analgesic activity]. Dose skipping will be reduced with these types of dosage forms. The objective of the present investigation was to develop a combination dosage form (bi-layer tablet) containing paracetamol and diclofenac sodium.

MATERIALS AND METHODS

Paracetamol, diclofenac sodium, Cab-O-Sil M5 and microcrystalline cellulose (Avicel PH 102) were received as gift samples from Green Pharmaceuticals (India), Helios Pharmaceuticals Limited (India), Cabot Sanmar Limited (India) and Zydus Cadila (India), respectively. Polyvinylpyrrolidone (PVP K30), crospovidone and hydroxypropylmethylcellulose (HPMC K4M) were received as gift samples from Torrent Pharmaceuticals (India). Polyethylene glycol 6000 (PEG 6000) and magnesium stearate were purchased from S. D. Fine Chemicals Private Limited (India) and Laser Laboratories (India), respectively. Voveran® SR tablets were purchased from a local pharmacy. The other chemicals used were of reagent grade

Preparation of Microcrystalline Cellulose Granules:

Microcrystalline cellulose was granulated using 5% w/v aqueous PVP K30 solution. The wet mass was passed through a 20# sieve to obtain granules. The granules were dried at 60° in a tray drier. The 20/40 mesh cut granules were used for preparing paracetamol tablets.

Preparation of Paracetamol Tablets:

Paracetamol, PEG 6000 and intragranular fraction of crospovidone (half of the total amount of crospovidone) were heated ($60\pm 5^\circ$) in a porcelain dish. The heated mass was passed through a 20# sieve. The granules were allowed to cool to room temperature and

Table No.1 Formulation of Paracetamol Tablet

INGREDIENTS	BATCH CODE		
	F1	F2	F3
Paracetamol	500	500	500
PEG600(mg)	100	80	50
crospovidone	6	6	5
Cab-o –sil	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5
Microcrystalline cellulose granules	110	110	110

blended with extra granular fraction of granular microcrystalline cellulose (MCC), crospovidone, Cab-O-Sil and magnesium stearate. The tablets were prepared on a single station tablet press (Cad mach Machines Ltd., India). The tablets were evaluated for percentage friability, crushing strength and disintegration time.

EVALUATIONS OF PARACETAMOL TABLETS :**Hardness:**

The tablet crushing strength was tested by commonly used Pfizer tablet hardness tester. A tablet is

Table No. 2 Hardness Showing Tablet Crushing Strength

No. of Tablet	F1	F2	F3
1	4.2	4.5	5
2	4.8	4.7	4.6
3	5.3	4.8	4.8
4	4.3	4.5	5.2
5	5.6	4.6	5.1

placed between the anvils and the crushing strength, which causes the tablet to break, is recorded.

Friability:

Tablet strength was tested by Roche friabilator. Pre weighed tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets

Table 3: Friability of Tablets

Tablets	% loss
F1	0.3
F2	0.5
F3	0.2

Uniformity of weight:

Randomly selected twenty tablets from all the three formulations were weighed individually and together in a single pan balance. The average weight was noted .

Table no. 4 Uniformity Of Weight Of Paracetamol Tablets :

No. Of Tablets	Weights of Tablets(Mg)	No. of Tablets	Weights of Tablets(Mg)	Average Weight Of Tablets(Mg)
1	715	11	713	
2	712	12	716	
3	722	13	720	
4	720	14	720	
5	716	15	719	717.2
6	715	16	716	
7	714	17	717	
8	714	18	722	
9	718	19	720	
10	720	20	715	

Disintegration time :

Disintegration time was determined using the disintegration apparatus in phosphate buffer pH 6.8 maintaining the temperature at $37 \pm 2^\circ\text{C}$.

Table No. 5 Disintegration Time

Tablets	Disintegration time(minutes)
F1	11
F2	8
F3	4

IN VITRO RELEASE OF OPTIMIZED BATCH:

In vitro drug release of paracetamol was performed in phosphate buffer (pH 7.4, $37 \pm 0.5^\circ$) in USP XXIII paddle apparatus (Model TDT-00T, Electrolab, Mumbai, India), at a rotational speed of 50 rpm. Paracetamol contents were estimated by UV/Vis spectroscopic method (Model UV-1700, Pharmaspec, UV/Vis Spectrophotometer, Shimadzu, Japan) at 243 nm after suitable dilution of the samples.

Table No. 6 Dissolution Test For Optimized Batch Of Paracetamol**PREPARATION OF DICLOFENAC SODIUM TABLETS:**

Sr.no.	Time	Absorbance	Conc./ml	Conc./900ml	Conc.(mg/ml)	%DR
1	0	0	0	0	0	0
2	10	0.980	2.45	220	0.220	49
3	20	1.28	3.20	288	0.288	64
4	30	1.723	4.30	387	0.387	86

Mixture of diclofenac sodium and HPMC K4M (1:1, 1:0.75, 1:0.6, and 1:0.5) were granulated using a blend of water (1 part) and isopropyl alcohol (9 parts). The wet mass was passed through a 20# sieve. The granules were dried at 55° for 15 min in a tray drier. The 20/40

mesh cut granules were used for preparing modified release diclofenac tablets. Cab-O-Sil and magnesium stearate, each at 0.5% w/w, were sequentially mixed with the granules and the tablets were compressed on a single station tablet press (Cadmach Machines Ltd.,

India). Diclofenac sodium tablets were characterized for release. percentage friability, crushing strength and *in vitro* drug

Formulation of diclofenac tablet

Table no. 7 Formulation of diclofenac tablet

Ingredient	Batch code			
	D1	D2	D3	D4
Diclofenac sodium (mg)	100	100	100	100
HPMC K4M (mg)	100	75	60	50
Cab-o-sil	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5

EVALUATIONS OF DICLOFENAC TABLETS:

Hardness:

The tablet crushing strength was tested by commonly used Pfizer tablet hardness tester. A tablet is

placed between the anvils and the crushing strength, which causes the tablet to break, is recorded.

Table No. 8 Hardness Showing Tablet Crushing Strength

No. of Tablet	D1	D2	D3	D4
1	4.6	4.1	3.6	4.3
2	4.3	4.3	3.8	3.7
3	3.6	4.6	3.9	3.6
4	3.8	4.2	4.5	3.9
5	3.9	4.1	4.2	4.2

Friability :

Tablet strength was tested by Roche friabilator. Pre weighed tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets

Table 9: Friability Of Tablets

Tablets	% loss
D1	0.4
D2	0.6
D3	1.2
D4	1.1

IN-VITRO DISSOLUTION TEST FOR OPTIMIZED BATCH

Table No.10 Dissolution Test For Optimized Batch Of Diclofenac

Sr.no	Time	Absorbance	Conc./ml	Conc./900ml	Conc.(mg/ml)	%DR
1	0	0	0	0	0	0
2	15	0	0	0	0	0
3	30	0	0	0	0	0
4	60	0	0	0	0	0
5	120	0	0	0	0	0
6	180	0.04	0.15	135	0.135	15
7	240	0.092	0.32	288	0.288	32
8	300	0.118	0.41	369	0.369	41
9	360	0.138	0.48	432	0.432	48

10	420	0.176	0.61	449	0.449	61
11	480	0.208	0.72	648	0.648	72
12	540	0.242	0.84	756	0.756	84
13	600	0.271	0.94	846	0.846	94

PREPARATION OF BI-LAYER TABLETS:

For the preparation of bi-layer tablets (batch D5), the granules of the optimized batch of paracetamol (722 mg, batch AF4) were added in the die cavity of single punch tablet machine. The granules of optimized batch

of diclofenac sodium s(177 mg, batch D2) were added over the granules of paracetamol. The granules were compressed to obtain bi-layer tablets The tablets were evaluated or percentage friability, crushing strength and *in vitro* drug release.

Evaluation of Bilayer Tablet

Table No.11 Evaluation Of Bilayer Tablet

Sr.no	Parameter	Result
1	Thickness	5.3
2	Friability	0.7
3	Hardness	4.7
4	Weight variation	98 %
5	%DR	92

IN VITRO DISSOLUTION TEST

Table No. 12 In Vitro Dissolution Test For Bilayer Tablet

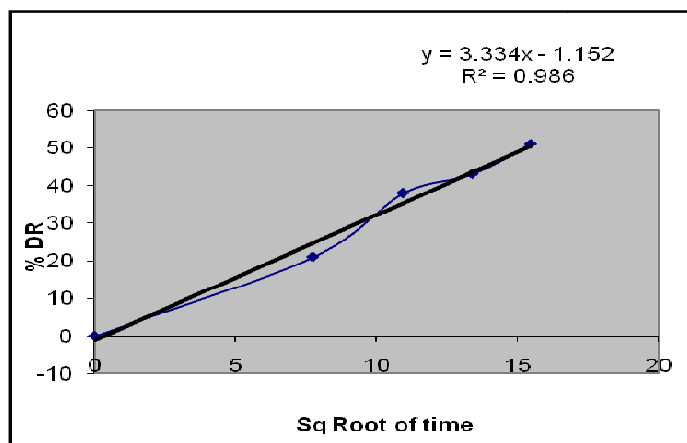
Sr.no	Time	Absorbance	Conc./ml	Conc. /900ml	Conc. (mg/ml)	%DR
PARACETAMOL						
1	0	0	0	0	0	0
2	10	0.991	2.55	2295	2.295	51
3	20	1.08	2.80	2520	2.520	56
4	30	1.45	3.75	3375	3.375	75
DICLOFENAC						
5	60	0.060	0.21	189	0.189	21
6	120	0.109	0.38	342	0.342	38
7	180	0.124	0.43	387	0.387	43
8	240	0.147	0.51	459	0.459	51
9	300	0.173	0.60	540	0.540	60
10	360	0.190	0.66	594	0.594	66
11	420	0.208	0.72	648	0.648	72
12	480	0.225	0.78	702	0.702	78
13	540	0.248	0.86	774	0.774	86
14	600	0.265	0.92	828	0.828	92

ANALYSIS OF RELEASE PROFILES

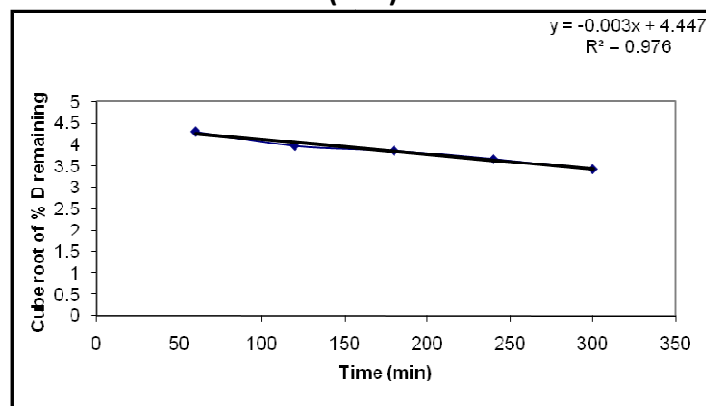
The rate and mechanism of release of bilayer tablet was analyzed by kinetic model such as

Higuchi plot

Graph no: 01 % drug release v/s square root of time

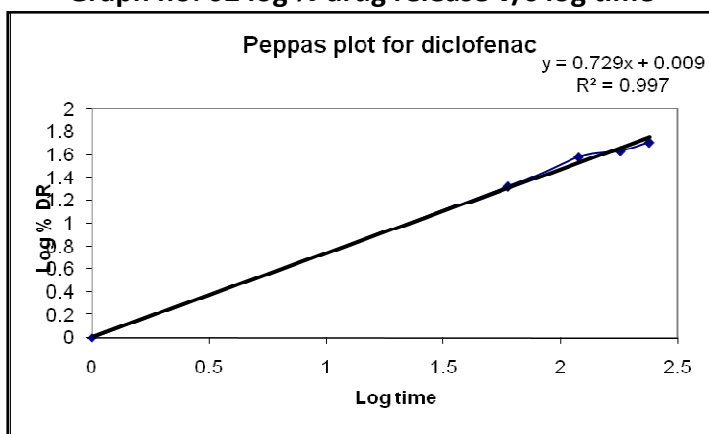


Graph no: 03 cube root of % drug remaining v/s time (min)



Pappas Model

Graph no: 02 log % drug release v/s log time



Hixson Crowell cube root model

Kinetic Model Describing Equvation And R² Value

Kinetic model	Regression coefficient and equation
Higuchi model	$Y=3.33x-1.152$ $R^2=0.986$
Pappas model	$Y=0.729x+0.009$ $R^2=0.997$
Hixson crowell cube model	$Y=-0.003x+4.447$ $R^2=0.976$

From above kinetic model Pappas model was best fitted for release kinetics of bilayer tablet.

RESULT AND DISCUSION

Crospovidone exhibits high capillary activity and pronounced hydration capacity when it comes in contact with aqueous fluids. Microcrystalline cellulose is a compressible hydrophilic excipient and it also works as an auxiliary disintegrating agent. Hence, granules of MCC were added extragranularly.

The disintegration time of paracetamol tablets can be tailored by selecting optimum amount of PEG 6000, MCC and crospovidone. The disintegration time was less than 11 min due to incorporation of disintegrating agent(MCC) in the tablets. percentage friability of tablet of batches F1-F3 was within the acceptable limits (<1%). Friability of the tablets ranged from as low as 0.2 to as high as 0.5. The Hardness of the formulated

paracetamol tablets (batches F1-F3) ranged from 4 to 6 kg. Considering the results of disintegration time, crushing strength and friability, batch F2 was ranked as the optimized batch and subjected to *in vitro* drug release study. more than 75% of paracetamol was released within 30 min from the tablets of batch F2 and hence, batch F2 was used for the preparation of bi-layer tablets.

Four batches of diclofenac sodium tablets were prepared using varying ratio of drug to HPMC (1:1, 1:0.75, 1:0.6 and 1:0.5). The drug was released over 10 h from the tablets batch D2 containing 1 part of drug and 0.75 parts of the matrixing agent. Time required to release 90% of drug ($t_{90\%}$) was 600 min.

Tablets of batches D3 and D4 were not subjected to *in vitro* drug release since the friability was greater than 1%. Hence, considering the results of friability and *in vitro* release, batch D2 was ranked as an optimized batch and used for the preparation of bi-layered tablet.

The bi-layer tablets were prepared by using composition of batches F2 and D2. The bi-layer tablets showed acceptable friability (0.7%) and crushing strength

(4.7 Kg). The *in vitro* drug release data of bilayer tablet was analyzed for establishing kinetics of drug release.

From above kinetic model Pappas model was best fitted for release kinetics of bilayer tablet. The bi-layer tablets showed immediate release of paracetamol and modified release (up to 10 hrs) of diclofenac sodium. The dosage form is patient friendly since the dosing frequency will be reduced. Moreover, the tablets will be easy to swallow, as the tablet weight was less than one gram.

CONCLUSION

From all above studies, we concluded that, by using HPMC, we can modify sustained release of diclofenac and modify paracetamol release by using microcrystalline cellulose as disintegrating agent. Hence bilayer tablet of paracetamol and diclofenac is prepared.

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