IJBPAS, June, 2023, 12(6): 2661-2672

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

FORMULATION AND EVALUATION OF BILAYER TABLET OF CONVENTIONAL RELEASE PARACETAMOL AND MODIFIED RELEASE DICLOFENAC SODIUM

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Received 15th July 2022; Revised 20th Aug. 2022; Accepted 5th Oct. 2022; Available online 1st June 2023

https://doi.org/10.31032/IJBPAS/2023/12.6.7188

ABSTRACT

The present study deals with formulation and evaluation of bilayer tablet of paracetamol and diclofenac sodium to provide control release of drug and to maintain the drug concentration. The major ingredients are paracetamol granules and diclofenac sodium granules and were prepared separately by wet granulation method. Paracetamol, PEG6000 and intergranular fraction granules were cooled and blended with microcrystalline cellulose, crosscarmellose, magnesium stearate and mixture of diclofenac sodium and HPMC K100 were granulated using water and isopropyl alcohol. The wet mass is passed through a 20# sieve and dried. The granules of optimized batch of paracetamol and diclofenac sodium were compressed to obtain bi-layer tablet. The tablets were evaluated for percentage friability, crushing strength and in-vitro drug release. Totally 3 formulations for paracetamol and 2 formulations of diclofenac were prepared and studied for their various parameters. The formulation F2 for paracetamol showed in-vitro drug release of 82% and exhibited satisfactory results in all parameters and subjected to stability studies. And the formulation D2 showed in-vitro drug release of 86.11% and exhibited satisfactory results. Thus formulation F2 for paracetamol and D2 for Diclofenac was found to be successful conventional release and modified release bi-layer tablet and can be manufactured with reproducible characteristics from batch to batch.

Keywords: HPMC K100, Paracetamol, Microcrystalline Cellulose

INTRODUCTION:

Drugs can be introduced through a variety of ways, including oral, submucosal, percutaneous, pulmonary, parenteral, etc., to treat diseased conditions. The oral route is regarded as the most convenient and frequently used method of medication administration **[1]**. The most common and standard dosage form is a tablet. Conventional tablets are not appropriate when multiple medications are required for the treatment of chronic medical conditions and the medications are not compatible. In these cases, bi-layer tablets are the best dosage form to use for delivering incompatible medications in a single dose **[2]**.

Bi-layer tablets are the type of tablets made by compressing different granulations fed into one die in succession, one on top of the other, in layers. Every layer comes out from a separate feed frame with individual weight control **[3]**. The setup of rotator tablets can be of two or three layers. More layers are possible but the design becomes very special **[4]**. Ideally, by applying a slight compression of each layer and individual layer ejection permits weight checking for control purposes **[5]**. The drug substances contained in an conventional release pharmaceutical composition are suitably a drug substance which has a very low solubility under acidic conditions, under conditions similar to those present in the stomach and/or drug substances which have a pKa value below about 5.5 such as in a range of from about 4 to about 5 **[6]**. The compositions that have been designed is in such a manner that two important requirements will be obtained, one of which is that the pharmaceutical composition releases the active drug substance very fast under acidic conditions whereby the drug substance will dissolve and readily become available for absorption almost immediately upon entrance into the stomach **[7]**. The mechanical strength of a composition according to the invention is quiet sufficiently high to withstand the normal handling of a pharmaceutical composition and to enable the composition to be coated using the various traditional coating equipment also well known by a person skilled in the art **[8]**. A modified release dosage form is one for which the drug release characteristics of time course and/ or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments or promptly releasing dosage form. Delayed release and extended release are two types of modified release dosage forms **[9]**. Delayed release dosage form is the one that releases the active ingredient or drug at a targeted time other than promptly after administration **[10]**. Extended release dosage form is one

that allows at time least a two-fold reduction in dosage frequency or significant increase in patient compliance or therapeutic performance as compared to that presented in conventional dosage form. Biological factors influencing oral sustained-release dosage form design **[11]**.

Paracetamol, also known as acetaminophen or APAP, is a medication used to treat pain and fever. It is typically used for mild to moderate pain. The evidence for fever relief in children is very poor though **[12]**. It is often sold or prepared in combination with other ingredients **[13]**. It can be used in combination with opioid as a pain medication, paracetamol is also used for more severe pain such as cancer pain and after surgery **[14]**. It is typically used either by oral route or rectally but is also sometimes administered intravenously **[15]**. Paracetamol is generally safe at recommended doses. In those patients with severe liver disease, it may still be used, but in very low doses **[16]**.

Diclofenac on the other hand is a nonsteroidal anti-inflammatory drug (NSAID) taken or applied to reduce inflammation and as an analgesic re ducing pain in certain conditions **[17]**. The name "diclofenac" derives from its chemical name: 2-(2,6-dichloranilino) phenyl acetic acid **[18]**. The use of this drug in animals is controversial due to its high toxicity which can rapidly kill scavenging birds that may eat the dead animals. It has also been banned for veterinary use in various countries **[19]**.

The goal of the current study is to develop and evaluate a bilayer tablet containing paracetamol and diclofenac sodium to control drug release and maintain drug concentration. The objective of the study is to increase therapeutic efficacy by providing prompt pain relief with lower toxicity.

MATTERIALS AND METHODS:

Material used:

Paracetamol API was purchased from SD fine chemical limited, All are chemicals and reagent used are of analytical grade.

METHOD:

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 and dried at 60°c in a tray drier. The 20/40 mesh cut granules were used for preparing paracetamol tablets **[20]**.

Table 1: List of the ingredients used

S. No.	INGREDIENTS	CATEGORY
1	Paracetamol	AIP
2	PEG 6000	Polymer
3	MCC PH101	Diluent
4	Magnesium stearate	Glidant
5	Talc	Lubricant/glidant

6	Lactose	Filler/diluents
7	Hydroxylpropyl cellulose L.F	Disintegrating agent
8	Calcium carbonate	Bulking agent
9	Diclofenac sodium	AIP
10	Stearic acid	lubricant
11	PVV K 90	Binder
13	Crosscarmellose sodium	Disintegrating agent

Preparation of Paracetamol tablets (Figure 1): Paracetamol, PEG6000 along with the intragranular fraction granules were cooled and then blended with microcrystalline cellulose, croscarmellose, Cab-O-Sil and magnesium stearate. The tablets were prepared on a single station tablet press and evaluated for percentage friability, crushing strength and disintegration time **[21]**.

Table 2: Formulation table for conventional release layer

Ingredients (mg)	Quantities(mg/tab)		
	F 1	F 2	F 3
Paracetamol	500	500	500
PEG 6000	30.00	25.00	20.00
Water	q.s	q.s	q.s
MCC PH101	60.00	80.00	50.00
Magnesium stearate	1.00	1.00	1.00
Talc	2.00	3.00	2.50
Lactose	20.00	20.00	20.00
Hydroxylpropyl cellulose LF	2.00	1.50	1.50
Calcium carbonate	40.00	30.00	35.00
Croscarmellose sodium	25.00	20.00	30.00
Total weight(mg/tab)	680	680.50	660

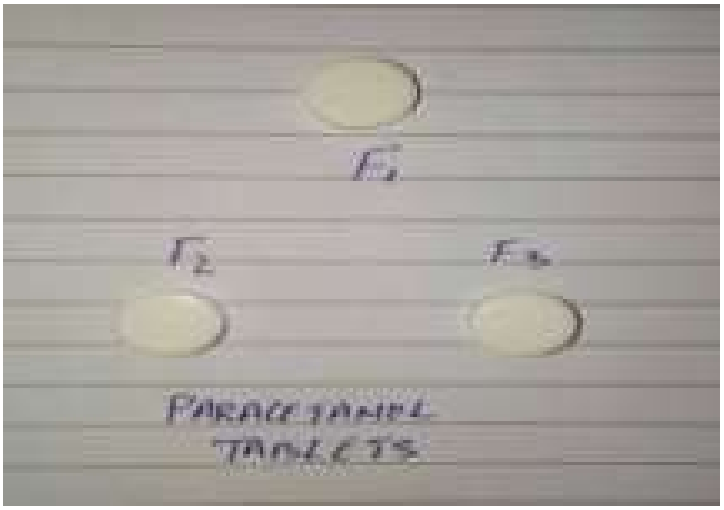

Figure 1: Paracemaol Tablet

Preparation of Diclofenac Sodium tablets (Figure 2):

Mixture of diclofenac sodium and HPMC K4M were granulated using water (1part) and isopropyl alcohol (9parts) **[22]**. The wet mass passed through a 20# sieve and dried at 55°C for 15 min in tray drier. Cab-O-Sil and magnesium stearate, each at 0.5% w/w were mixed with the granules. The tablet were prepared on single station

tablet press and evaluated for percentage friability, crushing strength and in vitro drug release **[23]**.

Table 3: Formulation table for Diclofenac sodium

Ingredients	Quantity in mg		
	D1	D2	D3
Diclofenac sodium	100	100	100
HPMC K 100	90.00	80.00	70.00
PVP K 90	87.00	85.00	65.00
Stearic acid	35.00	45.00	50.00
Total weight(mg/tab)	312	310	285

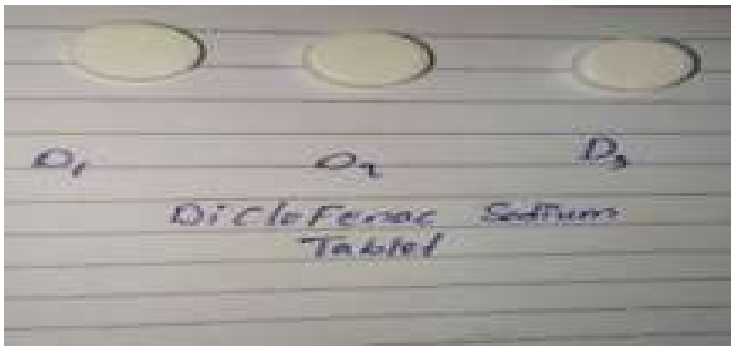

Figure 2: Diclofenac tablet

Preparation of Bi-Layer tablet (Figure 3):

The granules of optimized batch of Paracetamol were added in the die cavity of single punch tablet machine. The granules of optimized batch of Diclofenac sodium were added over the granules of paracetamol. The granules were compressed to obtain bi-layer tablet. The tablets were than evaluated for the percentage friability, crushing strength and in vitro drug release **[24]**.

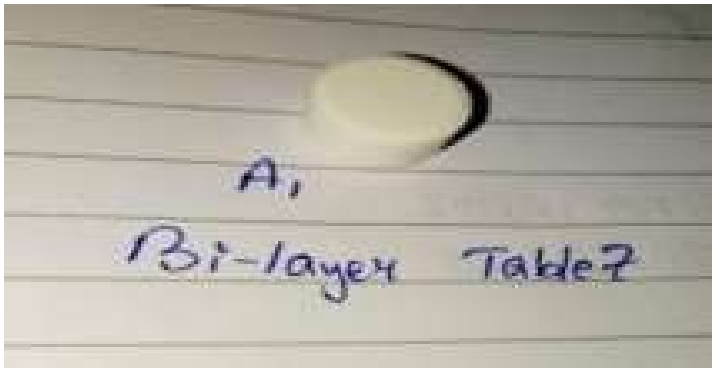

Figure 3: Bilayer tablet

Evaluation of prepared tablets:

Weight Variation: The USP provides the weight variation test by weighed 20 tablets individually, calculated the average weight and compared the individual tablet weights to the average. The tablets meet the USP

test if no more than 2 tablets are outside the % limit and if no tablet differs by more than 2 times the % limit. Drug content twenty tablets were weighed individually, and the drug was extracted in water. The range of content uniformity is 90 % -110 %.

Hardness: The hardness of 20 tablets was determined using the Monsanto hardness tester and the average values were calculated. 4 kg/ cm2 is considered to be minimum for a satisfactory tablet.

Thickness: The thickness of the tables was determined by using Vernier calipers. 20 tablets were used, and average values were calculated.

Tablet friability: The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W0) or a sample of 20 tablets are deducted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

Disintegration test: The disintegration test was carried out by use of Disintegration test apparatus. Were 6 tablet was subjected in the apparatus and shown in the minute and average value was calculated.

In -Vitro Dissolution Studies:

The in vitro release study for all the formulations was carried out by USP dissolution test apparatus Type-2.The temperature of the dissolution medium (6.8 pH Phosphate buffer, 900 ml) was strictly maintained at 37^0C with a stirring rate of 50 rpm **[25]**. This process was than done for 30 min. The tablet was placed inside the dissolution vessel.At time of 5, 10, 15, 20 and min, 5 ml of aliquots were withdrawn. The volume of dissolution fluid was adjusted every time to 900 ml by adding fresh buffer media. Sample were suitably assayed spectrophotometrically at λ max=242 nm in a double beam UV and visible spectrophotometer (Jasco double beam) against blank. The drug concentration was calculated using standard calibration curve. 2.6 In -Vitro Dissolution Studies for Sustained Release layer (Diclofenac Sodium) The in vitro release study for all the formulations were carried out by USP Dissolution apparatus Type -2 **[26]**. The temperature of dissolution medium (6.8 pH Phosphate buffer, 900 ml) was maintained at 370C with a stirring rate of 50 rpm. This study was done for 10 hrs. The tablet was placed inside the dissolution vessel. At time of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 hr, 5 ml of samples were withdrawn. The volume of dissolution fluid was adjusted every time to 900 ml by adding fresh buffer media. Sample were suitably assayed spectrophotometrically at λ max=202 nm in a double beam UV and visible spectrophotometer (Jasco double beam) against blank. The drug

concentration was calculated using standard calibration curve **[27]**.

RESULTS AND DISCUSSION

Weight variation: The weight variation was observed for different formulations with low standard deviation value, including uniformity of weight. The variation was carried when it was range of ± 5 % complying with pharmacopoeia specification (Indian Pharmacopoeia 1996). All tablets passed weight variation test.

Hardness: The hardness of all formulations was observed and it revealed in the range from 4 to 5kg/cm2.

Friability: The percentage friability of all formulations were observed and it was in the range from 0.77 % to 0.88%

In Vitro drug release of Immediate release layer: By increase the concentration of super disintegrating agent the % drug release (Paracetamol) is increased. F2 has highest 86% of Paracetamol release so It was considered as best optimized formulation.

In Vitro drug release of Sustained release layer: The in-vitro drug release study revealed that formulation D2 showed Diclofenac Sodium release of 82.11% up to 10 hrs. In formulation F2 was found to be acceptable because it release drug up to 82.11 % On the basis of in-vitro drug release study. By taking the optimized concentration of high viscosity polymer HPMC K4Mand it was selected as a best formulation.

Table 4: Evaluation of Paracetamol

Test	F_1	F_2	F_3
Hardness ($kg/cm^{2)}$	4.8	4.3	4.6
Thickness(mm)	6.2	6.43	6.39
Friability	0.22	0.59	0.61

Table 5: Evaluation of diclofenac sodium

Test	D_1	D_2
Hardness (kg/cm^2)	8.30	8.41
Thickness (mm)	7.31	7.09
Friability (%)	0.44	0.39

Table 6: In vitro drug release study of F2 of Paracetamol

Time	% CDR
0	0
5	27
10	40
15	54
20	66
25	74
30	87

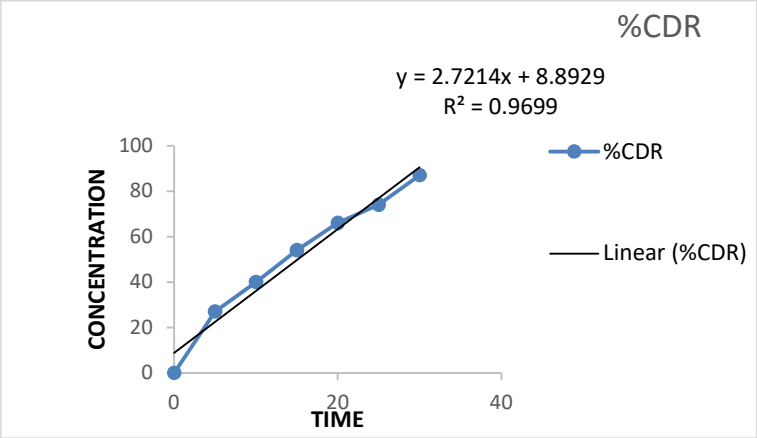

Table 7: In vitro drug release study of D2 of Diclofenac sodium

S. No.	Time (hr)	% CDR
1	0	0
2	2	06.29
3	4	34.04
4	6	53.45
5	8	76.77
6	10	81.01

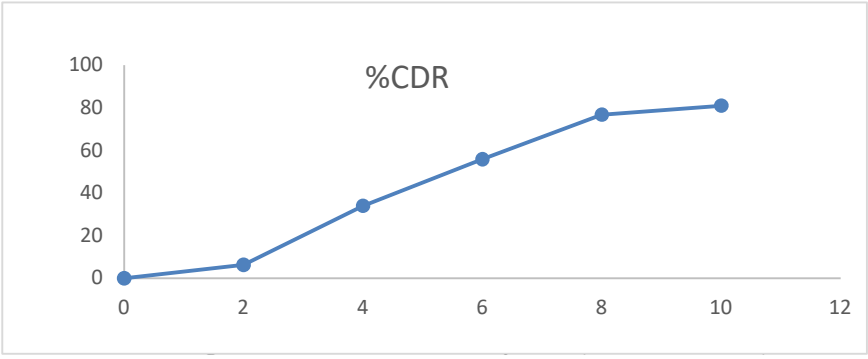

Table 8: Evaluation for Paracetamol and Diclofenac sodium bilayer tablet

Parameters	B1
Hardness (kg/cm^2)	9.20
Thickness (mm)	7.44
Friability (%)	0.11
Disintegration time (min)	382

Table 9: in vitro dissolution study of Bi-layer tablet (Diclofenac sodium)

Sl. No.	TIME (min)	CONC
1	0	0
2	15	23.354
3	30	39.21
4	60	53.45
5	120	71.24
6	180	84

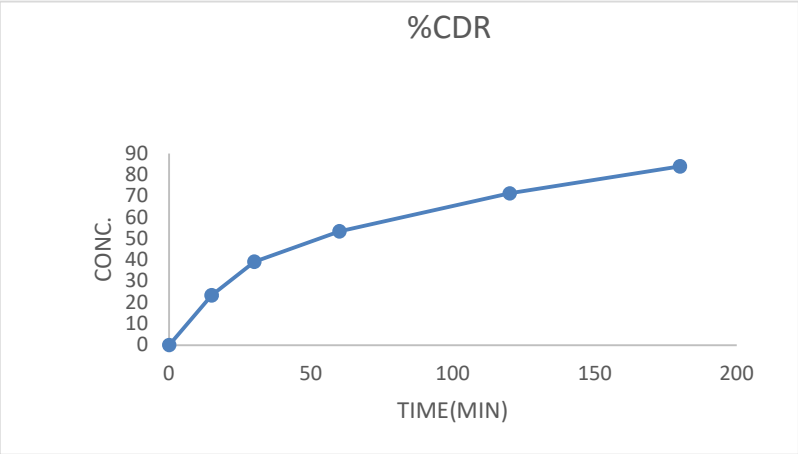

Figure 5: Drug release of Paracetamol Bi-layer tablet with respect to time

Table 10: In-vitro dissolution study of bi-layer tablet (Paracetamol)

S. No.	TIME(min)	CONC.
1	0	0
2	15	25
3	30	39
4	60	53
5	120	72
6	180	84

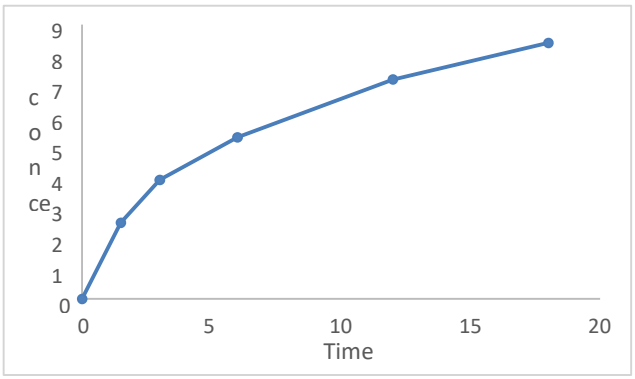

Figure 6: Drug relase of Diclofenacl Bi-layer tablet with respect to time

CONCLUSION

The overall result of the present work shows that this formulation also provide Paracetamol as conventional release layer which help to treat pain management simultaneously with Diclofenac Sodium. The various concentration of HPMCK100 was used to formulate a formulation which sustained the release of Diclofenac Sodium for 10 hrs. The reason behind choosing the HPMC K100 polymer was its low density hydrocolloid system which upon contact with water form hydrogel layer which act as a gel layer boundary for the delivery system, HPMC K100 provide several advantages i.e. sustained release, good stability in varying pH values and moisture levels. This could be concluded after

performing all the evaluations that if we formulate bi-layer tablet of Paracetamol & Diclofenac Sodium by varying its mode of release as per the biopharmaceutical property of both the drug. We can increase the bioavailability of the formulation. At the End of the of the dissertation work A bilayer tablet of Paracetamol and Diclofenac sodium is the best promising mode of delivery by getting good pain management.

5. ACKNOWLEDGEMENTS

The authors are thankful to Assam down town University (AdtU), for providing laboratory and the basic facilities for carrying out experimental workas well as other research facilities.

6. CONFLICT OF INTERESTS

Authors have declared that no competing interests exist.

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