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FORMULATION AND EVALUATION OF BILAYER TABLETS OF A NSAID AS AN IMMEDIATE RELEASE LAYER AND SUSTAINED RELEASE LAYER

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ABSTRACT

The objective of the present study was to develop a bilayer tablet of Indomethacin by using bilayer tablet technology. Immediate release layer of Indomethacin was prepared by using crospovidone, mannitol and microcrystalline cellulose. Sustained release layer of Indomethacin was prepared by using polymers such as HPMC K4M and guar gum in different concentration ratios of [1:1], [1:0.75] & [1:0.5]. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. Tablets were evaluated for post compression parameters. *In vitro* dissolution studies were carried out using USP type II (Paddle) type apparatus using phosphate buffer pH 7.4 as a dissolution medium. In the formulations F4 & F5 drug release was found to be 90.89±0.99% & 84.43±0.38% respectively. The *in vitro* drug release data were fitted into kinetic models. It was found that the formulations F4 & F5 followed zero order kinetics. Release exponent for formulations F4 & F5 were found to be 0.279 & 0.290 respectively and thus drug release followed fickian diffusion mechanism. MDT and %DE for formulations F4 & F5 was found to be 2.6192hrs &2.8343hrs and 70.8971% & 68.5067% respectively. Selected formulations F4 & F5 showed less variation in stability studies when stored at 40 ± 2°C / 75 ± 5 % RH for 2 months. In this study the formulations F4 & F5 released the drug upto 24hrs and hence can be used for extending the drug release.

KEYWORDS: Indomethacin, Crosspovidone, HPMC K4M, Bilayer.

INTRODUCTION

The oral route of administration has received maximum attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for this route than for other routes. Patient compliance of the oral route is quite high and it is relatively safe route of administration.[1] Bilayer tablet is a new era for successful development of controlled release formulations along with various features to provide successful drug delivery. Bilayer tablets consist of two layers which are sustained release and immediate release layers.[2]

Nonsteroidal anti-inflammatory drugs (NSAIDs) have anti-inflammatory, antipyretic, and analgesic activity, and are widely used for the treatment of inflammatory diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA). NSAIDs alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own, COX enzyme synthesizes prostaglandins, creating inflammation. Indomethacin is a non-steroidal anti-inflammatory drug. Indomethacin has suitable physico-chemical properties and biological properties which help in formulation of sustained release drug delivery systems. The plasma half-life of Indomethacin is 2.6-4.5 hours. It is potent antipyretic, analgesic, and anti-inflammatory drug. Indomethacin is nonselective COX inhibitor.[3, 4, 5 & 6] An attempt was made to formulate a bilayer dosage form of Indomethacin, which could be formulated easily, using the usual tableting techniques and usual tableting ingredients, with little modification in the method of processing of the ingredients.

METERIALS AND METHODS

Indomethacin was obtained as a gift sample from Hetero labs, Hyderabad. Crosspovidone obtained from Strides technology & research, Bangalore. Microcrystalline cellulose, mannitol and magnesium stearate were obtained from S.D. Fine Chem. Ltd, Mumbai, India. Guar gum from Loba chemie Pvt Ltd, India HPMC K4M from Colorcon Asia Pvt Ltd, Goa, India All other chemicals used were of analytical grade.

Compatability Study

i) Fourier transform infra red spectroscopy (FTIR)[7]

The samples of drug, polymer and their mixture were prepared in the form of potassium bromide pellets and subjected for scanning from 4000 cm-1 to 400 cm-1 using FT-IR spectrophotometer (Shimadzu 84000S Japan).

Preparation of Bilayer tablet

Bilayer tablets consisting of Indomethacin were prepared by direct compression method. Here both IR and SR layers ingredients were accurately weighed and triturated in a glass mortar and pestle, and were lubricated with magnesium stearate and talc separately. Then, this was compressed on a single station tablet compression machine (Cadmach, Ahmedabad, India) using 11mm flat punches. First SR blend was placed into tablet machine containing 11 mm punches and dies and pressed into position by light hand pressing. Then IR layer blend poured on SR layer & compression was done using 11 mm punch.

Table 1: Composition of indomethacin immediate release layer

Formulation Ingredients Wt. in mg/tablet	**H1**
Indomethacin	25
Crosspovidone	7.2
Mannitol	45
MCC	41.8
Talc	0.5%
Mg.stearate	0.5%
Total	120

Table 2: Composition of Indomethacin bilayer tablets

Formulation Ingredients Wt. in mg/tablets	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Indomethacin	75	75	75	75	75	75	75	75
Guar gum	75	25	56.25	50	18.75	37.5	14.06	42.18
HPMC K4M	-	50	-	28.125	37.5	18.75	42.18	14.06
MCC	50	50	50	28.125	50	50	50	50
Talc	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Mg.stearate	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Formula H1	120	120	120	120	120	120	120	120
Total	321	321	302.25	302.25	302.25	302.25	302.24	302.24

EVALUATION OF TABLETS

Physical properties

Prepared tablets were evaluated for physical parameters like thickness, hardness, friability, weight variation, drug content, *in vitro* drug release studies and stability studies.

Thickness

The thickness of the tablet of each formulation was determined by using screw gauge. Thickness was determined in triplicate and mean±SD was noted (n=3).

Hardness

The hardness of the tablets of each formulation was measured by Monsanto hardness tester. Hardness was determined in triplicate and mean±SD was noted (n=3).

Friability

Friability of the tablets was determined by using Roche friabilator (Campbell electronics Mu mbai, India). Pre weighed tablets were placed in the friabilator. This was operated at25 rpm for 4 minutes. This results in the dropping of tablets at a height of 6 inches in each revolution. The tablets were then dedusted and weighed again to check the loss in its weight. Then the percentage friability was calculated using the following equation (n=3).

Weight variation test

Weight variation test was carried out by using an electronic weighing balance. 20 tablets were weighed individually and the average weight was noted, and % deviation of each tablet weight was determined by the following equation (n=3).

$$Percentdeviation(PD) = \frac{W_{avg} - W_{initial}}{W_{initial}} x\ 100$$

Where, Wavg= Average weight of tablet, W initia$_l$ = individual weight of tablet.

Drug content

The drug content was determined by crushing the 5 tablets in glass mortar and pestle and shaking the powder equivalent to weight of one tablet with 100ml of phosphate buffer pH 7.4 for 48hours and this was filtered using Whatman filter paper and suitably diluted and finally analysed using UV spectrophotometer (1601,Shimadzu, Kyoto, Japan) using suitable blank at 320nm.

***In vitro* release studies**

The drug release study was performed using dissolution test apparatus (Electro lab Mumbai, India) with a paddle speed of 50 rpm. Dissolution medium consisted of 900ml phosphate buffer pH 7.4 maintained at 37±0.5^{0}C. Then the tablet was dropped into the dissolution medium. After this the samples were withdrawn at 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 8 hours and replaced with fresh dissolution medium. Amount of drug in each aliquot was assayed on a UV-spectrophotometer (Shimadzu 1601, Japan) at 320nm using a suitable blank.

Drug release kinetics and mechanism

The *in vitro* release data of the formulations was analysed using various models to describe the kinetics and mechanism of drug release.

Zero order kinetics: Zero order was calculated by the following equation

$$Q_t = Q_0 - K_0 t$$

Where,

Q_t = Drug release at time't'.

Q_0 = Initial drug concentration

K_0 = Zero – order rate constant (hr^{-1}).

First Order Kinetics: First–order was calculated by the following equation

$$\log C = \log C_0 - K_t$$

Where,

C = Amount of drug remained at time't'.

C_0 = Initial amount of drug.

K_t = First order rate constant (hr^{-1}).

Higuchi's model: Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = Kt^{1/2}$$

The graph was plotted between square root of time and cumulative % drug release.

Korsmeyer-Peppa's model

Korsmeyer-Peppa's Model indicates the study mechanism of drug release from the matrix tablets which also describes the drug behaviour from polymeric systems.

$$M_t / M_\infty = Kt^n$$

Model independent kinetics

A. Dissolution efficiency

Dissolution efficiency is used to translate the profile difference into a single value. Dissolution efficiency was calculated by using following equation.

$$DE\ \% = \frac{\int_0^t y\, dt}{y_{100}} t \times 100$$

Where, y is the drug percent dissolved at time t.

B. Mean dissolution time

Mean dissolution time represents the mean time for drug molecules to completely dissolve. It is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of the polymer. MDT was calculated by using the following equation.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Stability study

Stability study of the optimized formulation was carried out by storing the formulations at 40 ± 2^0C / 75 ± 5 % RH for 2 month.

RESULTS AND DISCUSSION

In this investigation, an attempt was made to develop bilayer tablets containing indomethacin as a model drug.

Compatibility studies were carried out to find out compatibility between drug and excipients used in the formulations. The characteristic peaks associated with indomethacin O-H stretching at 3477.77 cm^{-1}, C-H(aromatic stretching) at 2968.55 cm^{-1}, C-H(stretching) of CH_3 2928.04 cm^{-1}, C=O (stretching) at 1705.13 cm^{-1}, C-N(stretching) at 1658.84 cm^{-1}, O-H(deformation) at 1406.15 cm^{-1}& C-O(stretching) at 1313.57 cm^{-1} 1were present in all the FTIR spectra of pure drug & formulations.. This shows that there are no considerable changes in the position of characteristic bands associated with drug and individual ingredients, thus there was no interaction between drug-polymer and polymer-polymer.

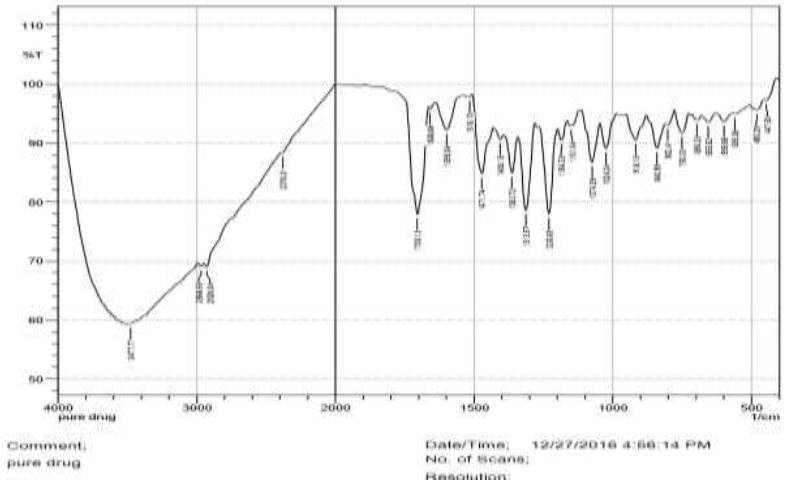

Figure 1: FTIR spectra of Indomethacin

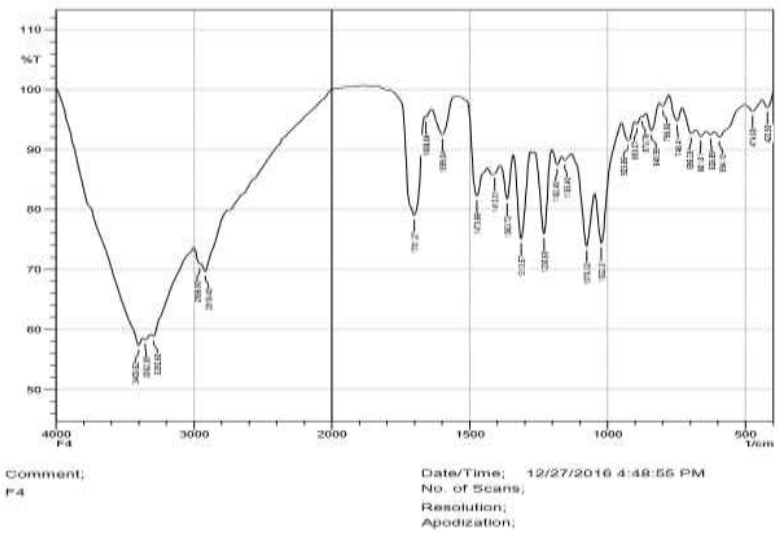

Figure 2: FTIR spectra of formulation F4.

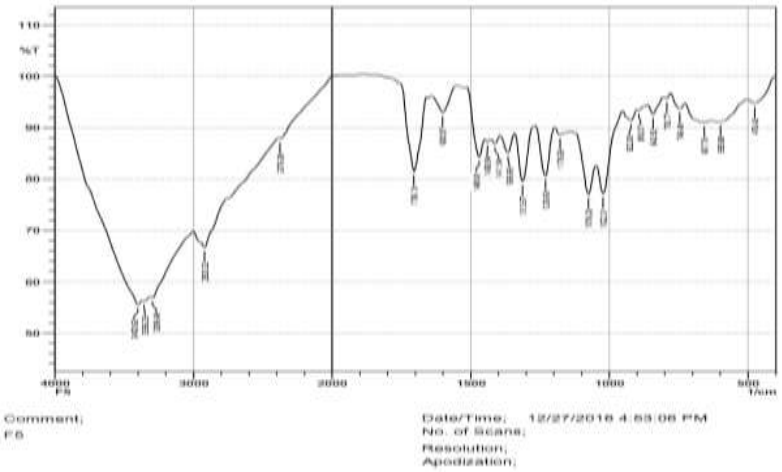

Figure 3: FTIR spectra of formulation F5.

The physical properties of tablets like hardness, friability, thickness, diameter, drug content and weight variation were found to be within limits indicating that the prepared matrix tablets were of desired specifications.

Table 3: Physical parameters of prepared tablets

Formulation code	Weight (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
F1	320.26±0.48	4.56±1.29	5.89±0.79	0.23±0.17	95.72±0.28
F2	320.64±0.83	4.83±0.73	4.89±0.23	0.38±0.02	97.41±0.79
F3	302.87±1.38	4.26±0.59	5.26±0.65	0.64±0.15	96.73±0.37
F4	301.95±0.15	4.72±0.74	5.83±0.89	0.75±0.35	96.84±0.26
F5	302.17±1.24	4.72±1.36	5.06±0.74	0.31±0.07	96.93±0.84
F6	301.85±0.69	4.16±1.24	4.96±0.34	0.55±0.6	95.34±0.24

F7	301.69±0.75	4.74±0.71	5.49±0.63	0.67±0.9	97.21±0.76
F8	302.35±0.63	4.68±1.65	6.08±0.81	0.83±0.51	96.48±0.38

The *in vitro* release of Indomethacin from immediate and sustained release layers of different formulations in phosphate buffer 7.4 at the end of 9 hr was between 64.61± 0.12% to 101.93±0.33% drug release (figure 4). Among the prepared formulations F4 & F5 showed release between 42.06±1.24% to 90.89±0.99% & 36.29±0.93% to 84.43±0.38% respectively, which were prepared by using bi-layer technique. However, formulation F4 & F5 showed highest and satisfactory drug release among the prepared formulations.

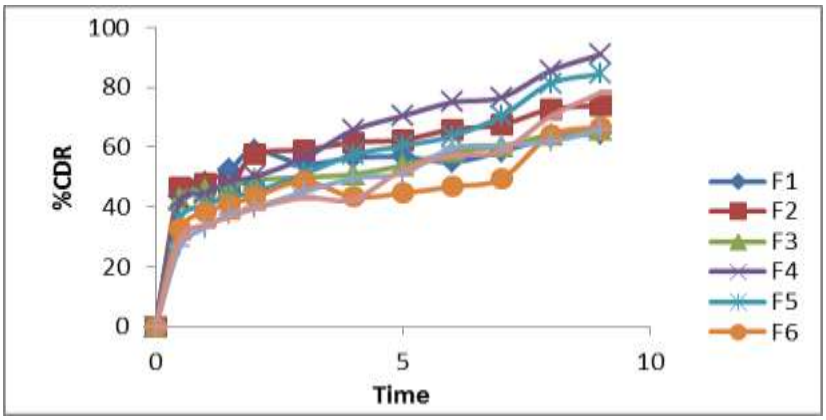

Figure 4: *In vitro* drug release profile of Indomethacin of formulations F1 to F8.

The R^2 values were found to be higher in zero order followed by Higuchi, which indicated that all the formulations followed zero order release kinetics (table 4). According to Korsmeyer-Peppas equation, the formulations F4 and F5, drug release was fickian diffusion type.

Table 4: Drug release kinetics from F1 to F12 formulations

Formulation	Correlation coefficient (r^2)			Korsmeyer-Peppa's Model (n)
	Zero order	First order	Higuchi	
F1	0.704	0.527	0.753	0.108
F2	0.931	0.796	0.949	0.171
F3	0.983	0.740	0.948	0.279
F4	0.990	0.939	0.976	0.279
F5	0.987	0.931	0.954	0.290
F6	0.800	0.74	0.756	0.192
F7	0.956	0.913	0.990	0.308
F8	0.965	0.905	0.913	0.311

Model independent parameters like MDT and % DE were evaluated for the all the formulations and results are shown in table 5. The MDT values of Indomethacin varied in the

range between 1.1203hrs to 2.8343hrs. The % DE values of Indomethacin in 9 hour varied between 63.04355 to 87.5516%. Formulations F4 & F5 prepared by bilayer technique have satisfactory %CDR, MDT and %DE. Hence formulations F4 & F5 were selected as best formulations.

Table 5: Model Independent Kinetics of indomethacin bilayer tablet

Formulation	MDT (hr)	% DE $_{9\ hr}$
F1	1.3712	84.76
F2	1.692	81.2082
F3	2.8343	68.5064
F4	2.6192	70.8971
F5	2.8343	68.5067
F6	2.7263	69.7075
F7	2.4	74.3291
F8	2.3260	63.0435

Stability study of selected formulation F4 & F5 was carried out at room temperature and at 40 ± 2°C / 75 ± 5 % RH for 2 months (table 6 & figure 5). There was less variation in physical appearance, drug content and *in vitro* dissolution profiles. It showed that the formulations were stable during the study period.

Table 6: Drug content of formulation F4 & F5

Formulation	Drug content (%) (F4)	Drug content (%) (F5)
0 month	96.8421±0.26	96.93±0.84
Room temperature (2 months)	96.1464±0.08	96.19±0.28
40±2˚C/75±5% RH (2 months)	96.1191±0.018	95.82±0.34

Values are mean ± SD, n=3

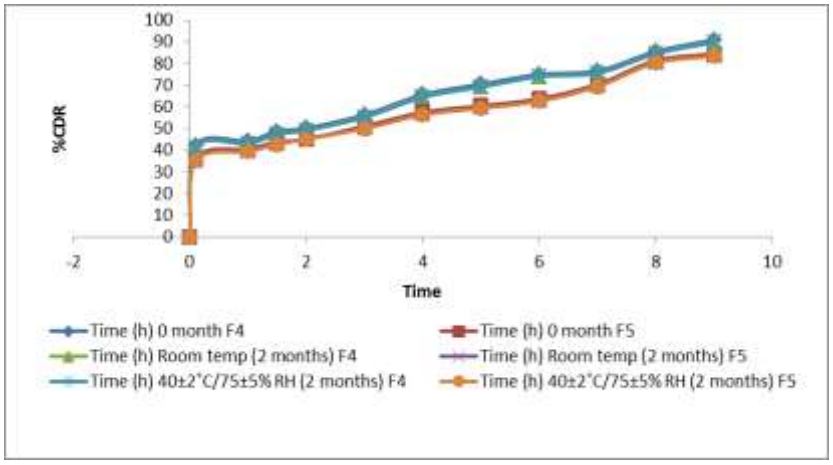

Figure 5: Comparison of *in vitro* drug release profile of F4 & F5 at 0 months, room temperature (2 months), and 40±2˚C/75±5% RH (2 months).

CONCLUSION

The present research was carried out to develop a bilayer tablet of Indomethacin using super disintegrant crospovidone for fast release layer & Guar gum and HPMC K4M for sustaining layer. Bilayer tablets showed an initial burst effect to provide the loading dose of drug, followed by sustained release for 24 hrs. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance.

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