

DESIGN AND OPTIMIZATION OF HYDROGEL BASED BILAYER ORAL CONTROLLED DRUG DELIVERY SYSTEM CONTAINING PARACETAMOL AND DICLOFENAC SODIUM AS A MODEL DRUG

***A. Talukdar and B. K. Dey**

Department of Pharmacy, Assam Down Town University, Panikhaiti, Guwahati, Assam, PIN-781026

**Author for Correspondence*

ABSTRACT

The aim of the present study was to prepare a bilayer hydrogel tablet formulation for controlled release of two NSAIDs namely Paracetamol and Diclofenac Sodium as a model drug. The hydrogels were prepared by using Natural polymers like Chitosan, Guar Gum, Ethyl Cellulose and synthetic polymer like PVP K30. The bilayer hydrogel tablets were prepared by conventional dry mixing and direct compression method. The concentration of polymers was varied in order to study the various preformulation parameters like angle of repose, bulk density, compressibility index and physical characteristics like hardness, friability, weight variation and drug content. The *in vitro* drug release studies were carried out in acidic buffer solution of pH 1.2 for initial 2 hours and then in phosphate buffer solution of pH 7.4 for next 10 hours. FTIR studies were carried out to find any drug and polymer interaction and polymer and polymer interaction. The optimized formula F4 showed a controlled release for both the drug as desired upto 12 hours. The drug release mechanism from the optimized formulation was found to follow diffusion control mechanism.

Keywords: NSAIDs, Bilayer, Hydrogels, PVP K30

INTRODUCTION

The Hydrogels (also known as Aqua gel) are the 3D, cross-linked polymeric networks of water absorbing polymer chains (Baek *et al.*, 2001). These hydrogels are mostly consisting of various natural or synthetic polymers. Due to the large water absorbing property hydrogels have got a wide range of uses in the field of pharmacy (Chen and Park, 2000). Thus, the hydrogels are made from water-soluble polymer, which include various chemical compositions and physical properties. The hydrogels are prepared in a form of matrix tablet, slabs, implants, micro particles, micro needle, nanoparticles, and films (Peppas *et al.*, 2006; Peppas *et al.*, 2000). The hydrogels are widely applicable in clinical practice and therapeutic purposes for a wide range of applications, including processes like genetically engineering, cellular immobilization, regenerative medicine, diagnostic tools and as a targeted drug delivery device (Patel and Patel, 2010).

Conventional tablet formulation containing paracetamol (Shirse, 2012; Rajesh *et al.*, 2012) and diclofenac sodium (Biswas and Basu, 2010; Radhakrishnan *et al.*, 2011) are commercially available in Indian market. A diclofenac sodium enteric-coated tablet is given 50 mg orally 2 or 3 times a day or 75 mg orally 2 times a day and maximum dose is 150 mg daily. In extended-release tablets 100 mg orally once a day is used (Gehanno *et al.*, 2003; Efentakis *et al.*, 2010). Paracetamol 1000 mg IV or orally every 6 hours or 650 mg IV, orally, or rectally every 4 hours and maximum Single dose is 1000 mg at every 4 hours' interval. The extended release tablet contains 1300 mg orally every 8 hourly and maximum daily dose is 3900 mg (Gehanno *et al.*, 2003; Ghosh *et al.*, 2013). The treatment of various chronic diseases in the form of a combination drug therapy is often used. The fixed-dose combination formulations become available but should be used with the aims of improving patient compliance, less frequent dosing and improved patient care. The various literature studies indicate that though the combination drug therapy is beneficial for the treatment of many patients but ultimate care should be taken in prescribing and dispensing the medicine as there may be potential drug–drug interactions, contraindications leads to hepatic or renal problems, and unnecessary drug use (Ghosh *et al.*, 2013). In the present study we have formulated a fixed dose combination of paracetamol and diclofenac sodium to obtain a controlled release upto 12 hours by formulation in a hydrogel based bilayer formulation.

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MATERIALS AND METHODS

Paracetamol and diclofenac sodium were obtained as a gift sample from Piccolo Pharma (Guwahati). Gaur gum, PVP K30, ethyl cellulose, chitosan, anhydrous dextrose, micro crystalline cellulose (MCC), talc, magnesium stearate etc was purchased from B. S. Trader, Kolkata. Throughout the experiment double distilled water was used and was obtained from the working laboratory.

The obtained tablet materials, for the further processing, were evaluated for micromeritics properties such as angle of repose, bulk density, tapped density, Carr's index and Hausner's ratios (Kasid *et al.*, 2013; Mondal *et al.*, 2008; Rao and Lakshmi, 2014).

Drug Polymer Interaction Studies

The interaction between drug-polymer was studied by FT-IR of Bruker Corporation. The samples were prepared as a disc potassium bromide and then it was scanned. The samples of pure drug and physical mixture of drug and polymer were scanned separately (Kasid *et al.*, 2013; van der Weerd and Kazarian, 2005; Mallah *et al.*, 2015).

Preparation of the Bilayer Hydrogel Tablets

The Layer-1 was prepared by using direct compression method (Dey *et al.*, 2014; Mughal *et al.*, 2011). All the required quantity of the ingredients was measured and blended properly in a V-Cone Blender for homogenous blending of drug and the excipient. The blended mixture was then passed through sieve number #60 (Rowe, 2006).

The Layer-2 was also prepared by direct compression method (Rao and Lakshmi, 2014; Sabnis *et al.*, 1997; Agnihotri and Aminabhavi, 2004). All the required quantity of the ingredients was measured and blended properly in a V-Cone Blender for homogenous blending of drug and the excipient. The blended mixture was then passed through sieve number #60 (Rowe, 2006).

Finally, for the preparation of bi-layer tablets, the physical mixtures of paracetamol were added in the die cavity of single punch tablet machine. The physical mixture diclofenac sodium layers were added over the paracetamol powder. The powder mixtures were compressed to obtain the bi-layer tablets (Gohel *et al.*, 2010). The tablets were then evaluated for various physicochemical properties.

Physicochemical Properties

The various physicochemical parameters were evaluated for the prepared bilayer tablet. The average weights of the tablets were determined by taking twenty tablets from each batch were weighed and the average weights were calculated. The prepared bilayer tablets were then evaluated for shape by examining the tablet under the magnifying lens (Lachman *et al.*, 1986; Niazi, 2016). The diameter and the thickness of the bilayer tablets were measured using a calibrated vernier caliper. For this purpose, three tablets from each batch of formulation were randomly picked and evaluated (Lachman *et al.*, 1986; Niazi, 2016). Hardness of the tablets were determined by Monsanto hardness tester and the results were expressed in kg/cm² (Lachman *et al.*, 1986; Niazi, 2016). The Roche Friabilator was used to determine the percentage of Friability (Lachman *et al.*, 1986; Niazi, 2016). The initial weight (W_1) of ten tablets from the prepared batch were taken and placed in the friabilator. The tablets were rotated for 4 minutes at 25 rpm or operated up to 100 revolutions. The weight (W_2) of the tablets after the rotation was measured and the percentage friability was then calculated. To determine the weight variation ten tablets from the batches were selected randomly and individual weight was determined. As per U.S. Pharmacopoeia $\pm 5\%$ variation was allowed for the tablet (Lachman *et al.*, 1986; Niazi, 2016). The formulations F1, F2, F3, F4, F5, F6 & F7 were then evaluated for the drug content uniformity for paracetamol and diclofenac sodium. The drug content uniformity of the prepared bilayer tablets was determined according to the IP 1996.

Preparation of Standard Curves of Paracetamol and Diclofenac Sodium

A serial dilution of concentration 2, 4, 6, 8, and 10 $\mu\text{g/ml}$ (Kasid *et al.*, 2013) of paracetamol was prepared with distilled water from the stock solution of 1000 $\mu\text{g/ml}$. The absorbance of final stock solutions was measured at 246 λ max and the values were plotted for a calibration curve between absorbance v/s concentration to get the linearity and regression (R^2).

A serial dilution of concentration 2, 4, 6, 8, and 10 $\mu\text{g/ml}$ (Manasa and Srilatha, 2014) were prepared by using distilled water from the stock solution of 1000 $\mu\text{g/ml}$ and the absorbance were measured for each

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solution at λ max of 276 nm. A calibration curve was plotted between absorbance v/s concentration to get the linearity and regression (R^2).

In Vitro Dissolution Studies

The *in vitro* drug release from the bilayer hydrogel tablet were carried out for 12 hours using USP XXIII paddle type tablet dissolution apparatus with 900 ml of dissolution medium maintained at $37 \pm 0.5^\circ\text{C}$ and the apparatus was operated at 50 rpm. For initial 2 hours, 0.1N HCl buffer solution was used as dissolution medium and then the dissolution medium was changed by replacing with pH 7.4 phosphate buffer solution for further 10 hours (Chandran *et al.*, 2008). At a fixed interval of time, 5 ml of solution was withdrawn and diluted suitably. The sample was analyzed by UV spectrophotometer (Model: SPECORD 50, Analytic Jena) at 249 nm and 276 nm for Paracetamol and Diclofenac Sodium respectively. A fresh 5 ml of dissolution medium was replaced to maintain the sink condition to the dissolution jar.

Data Analysis for the Kinetic Studies (Curve Fitting Analysis)

The various kinetic models were studied to know or predict the release of drugs from the dosage form. The study was done by plotting the release data to various mathematical equations (Higuchi *et al.*, 1993; Ghosal *et al.*, 2012). The Higuchi release kinetics was studied by plotted as a cumulative drug released versus square root of time curve which yields a straight line, indicating that the drug was released by diffusion mechanism. For the Korsmeyer and Peppas release model is plotted as Log of drug released versus Log time to obtain a straight line with a slope. The zero-order release kinetics was studied by plotting a graph as cumulative percent drug release versus time to obtain a linear straight line.

Stability Studies

Two batches of optimized formulation were taken and the selected formulation were blister packed. The tablets were then stored at $40^\circ\text{C}/75\%$ RH for 3 months and after the specified time the tablets were evaluated for physical characteristics, drug content and *In vitro* dissolution study (Hossainy and Prabhu, 2008; Beg *et al.*, 2013; Ryakala *et al.*, 2015).

RESULTS AND DISCUSSION

Pre-formulation Studies

The various parameters for preformulation studies of paracetamol and mixture of other ingredients were studied for angle of repose, bulk density, tapped density, compressibility index and Hausner's Ratio (Table 1).

The various parameters for preformulation studies of diclofenac sodium and mixture of other ingredients were studied for angle of repose, bulk density, tapped density, compressibility index and Hausner's Ratio (Table 1).

PVP K30 stands for polyvinylpyrrolidone K30, MCC stands for microcrystalline cellulose, all the quantities are in mg

Table 1: Preformulation Parameters of Paracetamol Layer

Material	Average Angle of Repose	Average Bulk Density (gm/mL)	Average Tapped Density (gm/mL)	Compressibility Index	Hausner's Ratio
Paracetamol	$34^\circ.61'$	0.412	0.588	29.93	1.43
Diclofenac Sodium	$34^\circ.90'$	0.431	0.619	30.37	1.43

Physicochemical Characteristics

The bilayer tablets were prepared by direct compression method and the polymer compositions were varied for both the layer (Table 2 and Table 3) to get the optimized drug polymer ratio. The compressed tablets were evaluated for diameter, thickness, average weight, hardness, weight variation friability and

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content uniformity. The results of various physical characteristics for formulations F-1, F-2, F-3, F-4, F-5, F-6 & F-7 were given in the Table 4.

Table 2: Composition of Layer-1 (Per Tablet in mg)

Ingredient (mg/Tablet)	F1	F2	F3	F4	F5	F6	F7
Paracetamol	1000	1000	1000	1000	1000	1000	1000
Guar Gum	50	45	40	35	30	25	20
PVP K30	5	10	15	20	25	30	35
Ethyl Cellulose	30	30	30	30	30	30	30
MCC	10	10	10	10	10	10	10
Talc	3	3	3	3	3	3	3
Magnesium Stearate	2	2	2	2	2	2	2
Total Weight of the Layer 1	700						

Table 3: Composition of Layer-2 (Per Tablet in mg)

Ingredient (mg/Tablet)	F1	F2	F3	F4	F5	F6	F7
Diclofenac Sodium	100	100	100	100	100	100	100
Chitosan	170	165	150	145	140	135	130
MCC	15	20	35	40	45	50	55
Talc	10	10	10	10	10	10	10
Magnesium Stearate	5	5	5	5	5	5	5
Total Weight of the Layer	300						

MCC stands for microcrystalline cellulose, all the quantities are in mg.

Table 4: Evaluation of Bilayer Hydrogel Tablets of Paracetamol and Diclofenac Sodium

Sl. No	Tests	F-1	F-2	F-3	F-4	F-5	F-6	F-7
1	Average weight (mg)	1003	1005	1002	999	998	998	1001
2	Thickness (mm)*	7.05	7.18	7.11	6.89	6.23	7.23	6.80
3	Hardness (kg/cm ²)*	8.9	10.8	10.2	11.3	10.2	11.1	10.7
4	Friability (%w/w)*	0.19	0.14	0.14	0.9	0.16	0.19	0.18
5	Weight variation [#]	2.1%	1.23%	2.6%	2.1%	2.4%	3.2%	1.8%
6	Content Uniformity Paracetamol (%) ^Δ	97.15	94.32	96.56	97.54	97.32	93.38	98.89
7	Content Uniformity Diclofenac Sodium (%) ^Δ	94.15	93.22	95.16	98.54	94.32	92.13	97.81

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All values are mean \pm SD, n = 5, # All values are mean \pm SD (n = 20), Δ All values quoted are average of 10 units, all values are within the limit of 90 ± 110 %

Drug Polymer Interaction

The spectrum for pure drug paracetamol was shown in figure 1 and paracetamol mixed with excipients was shown in figure 2.

The spectrum for pure drug diclofenac sodium was shown in figure 3 and diclofenac sodium mixed with excipients was shown in figure 4.

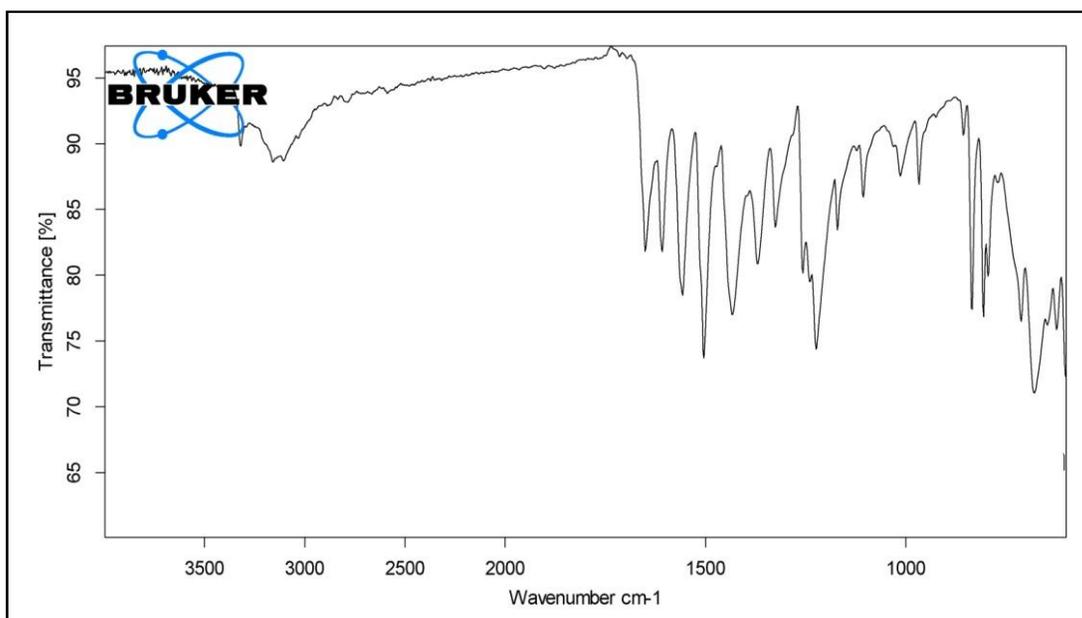


Figure 1: FTIR of Pure Drug Paracetamol

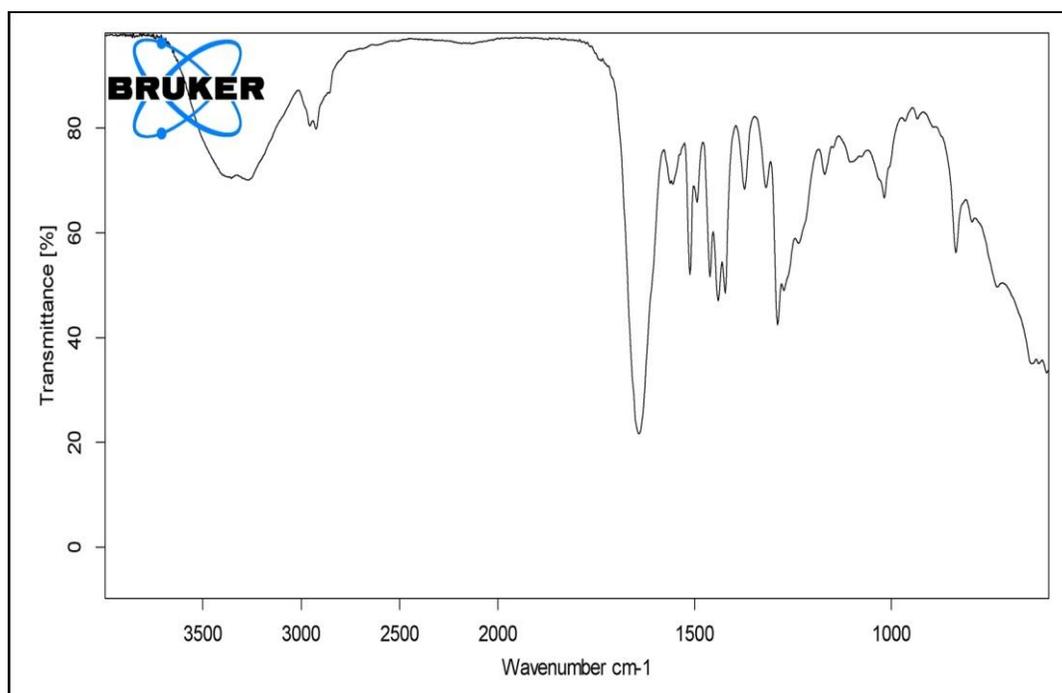


Figure 2: FTIR of Paracetamol and Physical Mixture of Polymer as per Formulation F4

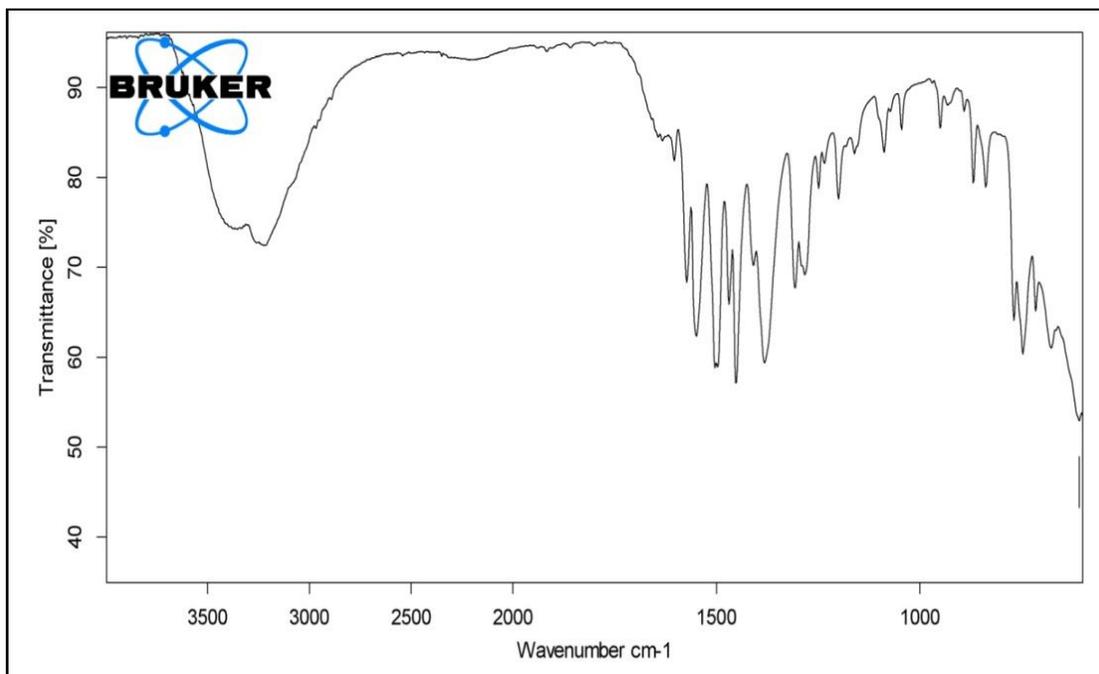


Figure 3: FTIR of Pure Drug Diclofenac Sodium

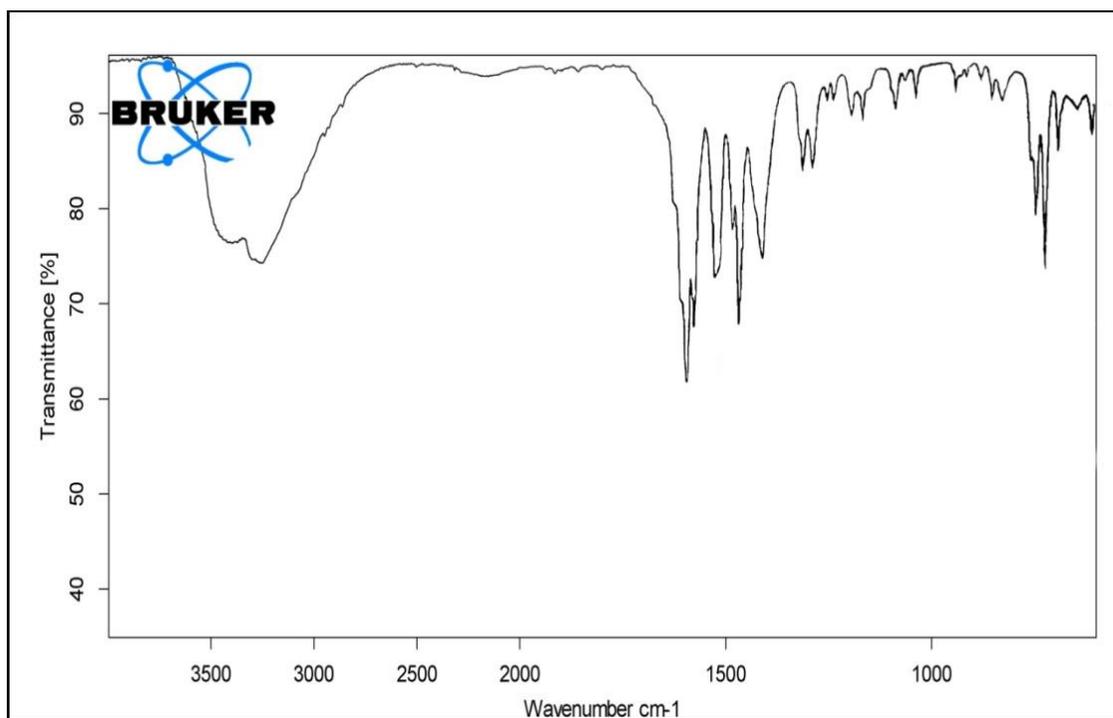


Figure 4: FTIR of Diclofenac and Physical Mixture of Polymer as per Formulation F4

In Vitro Release Studies

The calibration curve for paracetamol was plotted between absorbance v/s concentration (Table 5) to get the linearity and regression value was found to be 0.9995 (figure 5). The calibration curve for Diclofenac sodium was plotted between absorbance v/s concentration (Table 6) to get the linearity and regression value was 0.9754 (figure 6).

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The in vitro release studies were carried out for all the formulation. Initial 2 hours was done in pH 1.2 hydrochloric acid buffer and the remaining 10 hours was continued in pH 7.4 phosphate buffer. The cumulative release studies and the percentage drug release were calculated. The graphs for *In vitro* dissolution studies of paracetamol and diclofenac sodium from the bilayer hydrogel tablet were shown in figure 7 and figure 8 respectively.

Table 5: Concentration vs Absorbance of Paracetamol Tablet at Wavelength 249 nm

Concentration (mcg/ml)	Absorbance (nm)
0	0
2	0.163
4	0.356
5	0.533
6	0.727
7	0.909

Table 6: Concentration vs Absorbance of Diclofenac Sodium Tablet at Wavelength 276 nm

Concentration (mcg/ml)	Absorbance (nm)
0	0
2	0.042
4	0.097
6	0.159
8	0.223
10	0.332

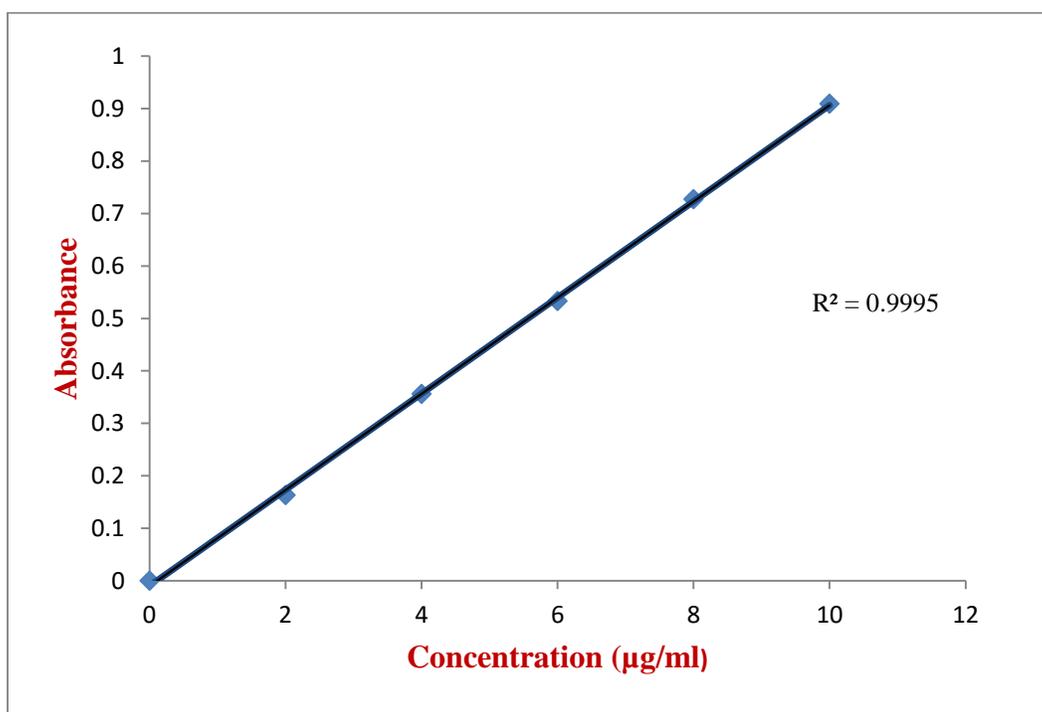


Figure 5: Standard Curve of Paracetamol (◆ Absorbance)

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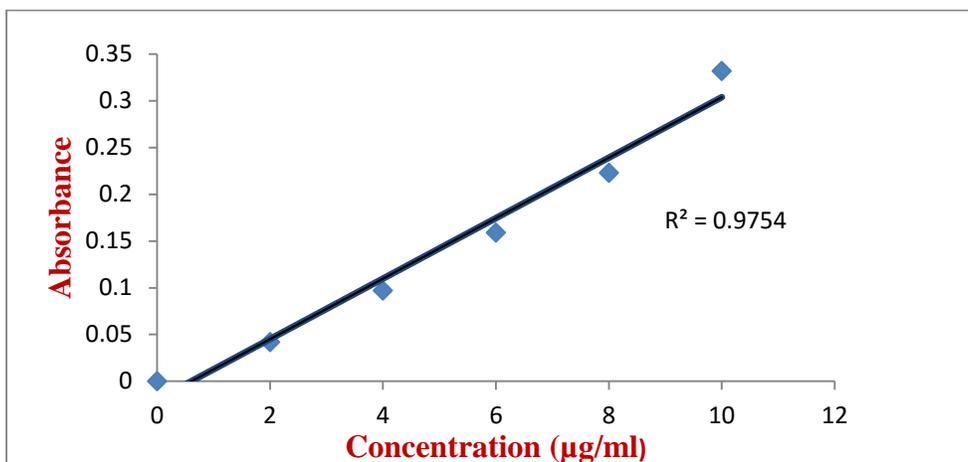


Figure 6: Standard Curve of Diclofenac Sodium (◆ Absorbance)

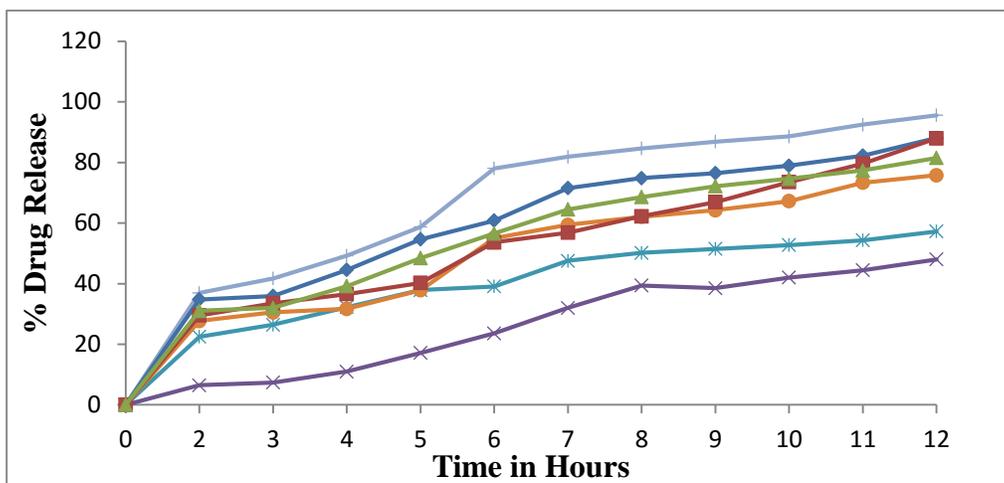


Figure 7: *In vitro* Dissolution Studies of Paracetamol from the Bilayer Hydrogel Tablet (× - F1,*- F2, ●- F3,+ - F4, ◆- F5, ■- F6, ▲- F7)

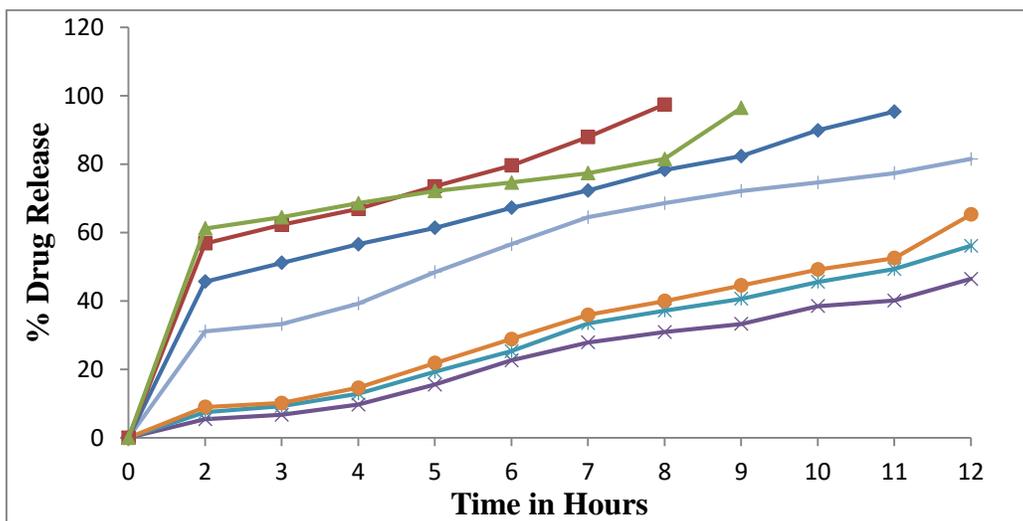


Figure 8: *In vitro* Dissolution Studies of Diclofenac Sodium from the Bilayer Hydrogel Tablet (× - F1,*- F2, ●- F3,+ - F4, ◆- F5, ■- F6, ▲- F7)

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Mathematical Model Fitting of Obtained Drug Release Data

The *in vitro* release studies data was fitted to various release mechanism equation of various mathematical models and the best-fit model was determined. The various parameters listed in Table 7 and Table 8 for paracetamol and diclofenac sodium respectively; the time exponent (n), the release rate constant (k) and the regression coefficient (R²) were also calculated. In a set of data, the model showing the highest value to R² was taken as the best-fit model. In the tables R² = regression coefficient.

Table 7: Data of Various Parameters of Model Fitting for Paracetamol for Optimized Formulation F-4

Zero Order		First Order		Higuchi		Peppas		Parameter for Korsmeyer-Peppas Equation
R ²	K	R ²	K	R ²	K	R ²	K	n
0.9712	0.6039	0.8699	-0.1443	0.9947	0.3715	0.9839	0.8784	0.1449

n is time exponent, K is release rate constant, R² is the regression value

Table 8: Data of Various Parameters of Model Fitting for Diclofenac Sodium for Optimized Formulation F-4

Zero Order		First Order		Higuchi		Peppas		Parameter for Korsmeyer-Peppas Equation
R ²	K	R ²	K	R ²	K	R ²	K	n
0.9327	0.4195	0.9851	-0.0432	0.9787	0.5203	0.9860	0.8701	0.1022

n is time exponent, K is release rate constant, R² is the regression value

Stability Studies

The stability study was carried out for batch number F4 with a batch size of 20 tablets and various parameters were evaluated for their physical appearance, drug content and *In vitro* dissolution study at specified intervals of time and the data were listed in Table 9.

Discussion

In order to achieve the development of a sustained and controlled release dosage forms, the present work was carried out by utilizing Bilayer Hydrogel technology. This formulation can be used for the treatment for antipyretic and analgesic activity. For the study, paracetamol and diclofenac sodium were used as a model drugs.

The average angle of repose for layer 1 of Paracetamol and layer 2 of Diclofenac Sodium were found good flow properties as per the pharmacopoeia. The compressibility index and Hausners ration of the physical mixture of powder for layer 1 and layer 2 were found to be within the specification limit. From all the preformulation data it was found that the ingredients were suitable for the direct compression to prepare the bilayer tablet.

The FTIR studies of the pure drug and the excipient were studied. The peaks for pure drug were compared with the peaks of drug and polymer mixtures. The results of FTIR studies did not show any major changes in peaks which indicate there was no well-defined interaction in drug and excipients. This indicates that the drugs were compatible with the formulation components.

All the batches of bilayered tablets fulfilled the official requirement of uniformity of dosage units. The average percentages of deviation of tablets weight were less than ±3%. Drug content of paracetamol layer was found to be uniform among the seven formulations. The thickness of tablet was within the ranged. The hardness and percentage friability of all batches ranged was also within the permissible value.

The formulations were prepared by varying the concentration and combination of polymer and the dissolution studies were carried out for all the formulation. The best combination of polymer was found to

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be in the formulation F4.

Table 9 Stability studies of bilayer hydrogel tablets of Paracetamol and Diclofenac Sodium at 40°C/75% RH

Tests	Limits	Initial Result	3 rd Month Result
Appearance	white, Compound Cup shaped Bilayer Hydrogel release tablets	white, Compound Cup shaped Hydrogel tablets	white, Compound Cup shaped Bilayer Hydrogel release tablets
Average weight	About 1000mg	1003mg	1006mg
Hardness	9.0-13.0kg/cm ²	9.5 kg/cm ²	10.2kg/cm ²
Thickness	6.8-7.3 mm	6.9 mm	6.9 mm
Paracetamol:			
1 hour	Between 20.0 - 40.0%	29.9% to 31.6% Avg- 30.8%	27.8% to 30.2% Avg- 29.0%
4 hour	Between 50.0 - 80.0%	68.6% to 73.2% Avg- 70.9%	72.4% to 76.8% Avg- 74.6%
8 hour	Not less than 80%	90.2% to 94.6 Avg- 92.4%	91.5% to 97.9% Avg- 94.7%
Diclofenac Sodium:			
1 hour	Between 20.0 - 40.0%	30.0% to 34.2% Avg- 32.1%	29.1% to 32.5% Avg- 30.8%
4 hour	Between 50.0 - 80.0%	68.3% to 70.1% Avg- 69.2%	73.6% to 78.4% Avg- 76.0%
8 hour	Not less than 80%	91.6% to 95.3 Avg- 92.8%	93.9% to 99.9% Avg- 96.8%
Assay:			
Paracetamol	90-110%	98.6%	97.0%
Diclofenac Sodium	90-110%	101.6%	99.2%

Batch number taken is F-4, Batch Size is 20 tablets, Packed in PVC Blister

The data obtained from *in vitro* release study were fitted to various mathematical model like zero order, first order, Higuchi model and Peppas model separately for Paracetamol and Diclofenac Sodium. The results of mathematical model fitting indicate that, the best fit model was found to be Higuchi and first order release respectively for optimized formulation (F-4).

Thus, we can conclude that the release of the drug from the formulation follows a diffusion process. The formulation F4 was charged for stability 40^o C/ 75% RH for three months and the results was found to be satisfactory.

Conclusion

In the present study, we had tried to control the release of two NSAID drug likely paracetamol and diclofenac sodium in the form of bilayer hydrogel formulation. From the present study it was concluded that the paracetamol and diclofenac sodium can be given as a bilayer hydrogel tablet as the drug release was controlled up to 12 hours and it follows the diffusion controlled release. It was also found that the drug was uniformly distributed in the formulation. Thus, we can conclude that paracetamol and diclofenac sodium can be formulated as bilayer hydrogel tablet for better patient compliances by reducing the dose frequency.

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