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Research Article

Formulation and Evaluation of Modified release Bilayer Tablet of Paracetamol and Diclofenac sodium

Shailendra S Tomar[*1], Ashwani Mishra and Anupam Pathak

Department of Pharmacy, Barkatullah University, Bhopal (M.P.) 462026

***Correspondence Info:**
Shailendra Singh Tomar
Department of Pharmacy
Barkatullah University, Bhopal
(M.P.) 462026 India
E-mail:
singhtomarshailendra@gmail.com

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Abstract

The main objective of this research work is to develop a stable formulation of a NASAID by formulating bilayer tablet having one immediate release layer of Paracetamol and sustain release layer of Diclofenac sodium and to evaluate their pre-compression and post-compression parameters A bilayer tablet comprises first layer of instant release of the paracetamol and a second layer for sustain release Diclofenac sodium. The formulation was initiated with preparing granules of both the drug individually by wet granulation method and then then they were compressed to prepare bilayer tablet. The compressed bilayer tablets were evaluated for weight variation, thickness, hardness, friability, *in-vitro* drug release using USP dissolution apparatus and interaction study by DSC. The optimized Formulation table of formulations F5 formulation was found to be acceptable because it release drug up to 82.11 % of drug release for bilayer Tablet and this batch passed all the evaluation parameters.

1. Introduction

Oral route is the most widely employed route of drug administration. This route remains the preferred mode. The popularity of the route is due to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and normally improved shelf-life of the product. Sustained release systems have also been administered through this route because of flexibility in dosage forms design [1]. The concept of bilayer tablet has been introduced to attain sustain release of drug which refers to tablet containing subunits that's either may be same (homogenous) or different (heterogeneous). Bilayer tablet preferred when the release profile of the drugs are different from each other or for two separate incompatible substances.[2-3] Usually conventional dosage form produces fluctuations in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. The problems of repetitive dosing and unpredictable absorption of the Drug led to us to the concept of controlled drug delivery system. The goal behind these delivery systems is to reduce the frequency of dosing to increase effectiveness of the drug by localization of the drug at the site of action which in turn reduces the dose requirement and thus provides uniform drug delivery. The rational of sustained drug delivery is to ensure safety and to improve effectiveness of drug and thus improve patients compliance.[4-5]

Non steroidal anti-inflammatory drugs are important for the treatment of rheumatic arthritis and for reducing pain and inflammation. The NSAID's requires higher dose for efficacy in arthritis. At higher doses, they show many side effects like gastric irritation, abdominal pain, ulcerative stomatitis and dizziness [6]. Even sustained and immediate release bilayered drug delivery system containing a suitable NSAID and H_2 receptor antagonist having absorption in the upper part of gastrointestinal tract to maintain plasma concentration with in therapeutic range for prolonged period of time, improves bioavailability, thereby reduces dosing frequency and improves patient compliance.

2. Material and Methods

Paracetamol and Diclofenac Sodium obtained from gift sample from Brothers Pharmaceutical Rajasthan HPMC K4M, Polyvinyl pyrrolidone K30, MCC, Magnesium Stearate, Talc, Polyethylene Glycol 6000 were purchased Central drug laboratory Delhi (CDH). All other chemicals were used of Analytical grade.

2.1 Method of Granule preparation

2.1.1 Immediate Release layer granule Preparation

Granules were prepared by wet granulation method. Microcrystalline cellulose and paracetamol powder were mixed homogeneously using glass mortar and pestle. Polyvinyl pyrrolidone solution (5%) was used as granulating agent. Granules were prepared by passing the wet coherent mass through a #20 sieve. The granules were dried in hot air oven at a temperature of $50^0C \pm 0.5^0C$ for 15 min. Dried granules sieved through #40 sieves and mixed with sodium starch glycolate and polyethylene glycol-6000 then magnesium Stearate and talc was added before compression.

2.1.2 Sustained Release layer granule Preparation

Granules were prepared by wet granulation method. Polymer hydroxypropyl methyl cellulose k4M and Diclofenac sodium mixed homogeneously using glass mortar pestle and Isopropyl alcohol and water (9:1) was used as granulating agent. Granules were prepared by passing the wet coherent mass through a #20 sieve. The granules were dried in hot air oven at a temperature of $50^0C \pm 0.5^0C$ for 15 min. Dried granules sieved through #40 sieves and mixed with lubricating agent magnesium stearate and talc 4-5 minute before compression

2.2 Formulation of Different Batches

2.2.1 Immediate release layer

Table 1: Shows different batches prepared by taking super disintegrating agents in different concentration for immediate release layer

Ingredient (mg)	Fi 1	Fi 2	Fi 3	Fi 4	Fi 5
Paracetamol	500	500	500	500	500
Microcrystalline Cellulose	80	80	80	80	80
Polyethylene 6000	50	50	50	50	50
Sodium starch Glycolate	10	15	20	25	30
Magnesium stearate	0.5	0.5	0.5	0.5	0.5
PVP K-30 (5%)	q.s	q.s	q.s	q.s	q.s
Talc	0.5	0.5	0.5	0.5	0.5

2.2.2 Sustained release layer

Table 2: Shows different batches prepared by taking polymers in different Concentration for Sustained Release layer

Ingredients	Fs1(mg)	Fs2(mg)	Fs3(mg)	Fs4(mg)	Fs5(mg)
Diclofenac Sodium	100	100	100	100	100
HPMC K4M	20	30	40	50	60
Isopropyl alcohol &	9:1	9:1	9:1	9:1	9:1
Water	0.5	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5	0.5

2.3 Evaluation of Flow Properties of Granules

2.3.1 Angle of repose

5g Granules were poured through the walls of a funnel, which was fixed at a position by clump with stand such that its lower tip was at a height of exactly 2cm. above from plan surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel.

$$\Theta = \tan^{-1}(h/r)$$

Θ= angle of repose, h = height of the heap, r = radius of the heap

2.3.2 Bulk density and Tapped density

Granules were poured gently through a glass funnel into a graduated cylinder. The cylinder was then tapped from a height of 2.0 cm. until the time when there was no more decrease in the volume. Bulk density and Tapped density was calculated.

Bulk density = Weight of sample in g/final volume in cm^3 of the sample contained In cylinder

Tapped density=Weight of sample in g/final volume in cm^3 after tapped in cylinder

2.3.3 Carr's compressibility index (C.C.I.): Used for compare the bulk Density and tapped density.
Carr's compressibility index=Tapped density--bulk density/tapped densityX100

2.3.4 Hausner ratio: Hausner ratio= Tapped density/Bulk density

Table 3: Different Pre-compression parameters of both the layer of bilayer tablets

Formulation Code	Angle of Repose (Ɵ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carrs Index (%)	Hausner Ratio
F1 Paracetamol	28.12,	0.325,	0.302	13.617	1.16
F1 Diclofenac Sodium	29.34	0.485	0.422	14.521	1.05
F2 Paracetamol	24.42,	0.382	0.315	15.368	1.18
F2 Diclofenac Sodium	26.45	0.477	0.413	14.230	1.08
F3 Paracetamol	22.64,	0.380	0.326	16.666	1.15
F3 Diclofenac Sodium	23.43	0.483	0.435	14.237	1.06
F4 Paracetamol	23.24,	0.396	0.338	12.968	1.09
F4 Diclofenacsodium	25.22	0.410	0.379	14.312	1.03
F5 Paracetamol	25.62	0.370	0.332	14.270	1.13
F5 Diclofenac Sodium	27.84	0.422	0.389	15.211	1.11

2.4 Evaluation of prepared Tablets

2.4.1 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.

2.4.2 Hardness and Friability

Hardness of tablets measured by Monsanto hardness tester. A pre-weight tablets sample is placed in friabilator which is then operated for 100 revolutions for 4 minutes. After test tablets that lose less than 1.0 % of their weight are generally considered acceptable.

Table 4: Comparison of physical parameters of tablet obtained by wet granulation techniques

Formulation Code	Friability (%)	Hardness (kg/cm^2)
F1	0.88	4.8
F2	0.84	4.6
F3	0.79	4.3
F4	0.81	4.2
F5	0.84	4.0

2.5 *In -Vitro* Dissolution Studies for Immediate Release layer (Paracetamol)

The *in vitro* release study for all the formulations was carried out by USP dissolution test apparatus Type-2.The temperature of dissolution medium (6.8 pH Phosphate buffer, 900 ml) was maintained at 37^0C with a stirring rate of 50 rpm.

This study was 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. The temperature of dissolution medium (6.8 pH Phosphate buffer, 900 ml) was maintained at 37^0C 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.

Table 5: *In- vitro* drug release study of immediate release layer of F5

S. No	Time (minutes)	% CDR
1	0	0
2	5	49
3	10	64
4	15	86

Table 6: *In vitro* Drug Release Studies of F5 of Diclofenac Sodium

S. No	Time(hr)	%CDR
1	1	05.29
2	2	19.58
3	3	34.04
4	4	42.66
5	5	53.45
6	6	63.95
7	7	71.42
8	8	74.82
9	9	78.12
10	10	82.11

Table 7: Regression co-efficient (r^2) values of different kinetic models for formulation F5.

Release kinetics Model	Regression value (r^2)
Zero order	0.992
First order	0.981
Higuchi	0.997
Peppas	0.968

2.7 Thermal analysis

It comprises a group of techniques in which a physical sample property is measured as a function of a temperature, while the sample is subjected to a predefined heating or cooling programme. The related technique of differential scanning calorimetric (DSC) relies on difference in energy required to maintain the sample and reference at an identical temperature. Differential Scanning Calorimetric (DSC) monitor heat effect associated with phase transition and chemical reaction as a function of temperature. In a DSC the difference in heat flow to the sample and reference at the same temperature, is recorded as a function of temperature. The DSC of formulation F5 is done by Instrument Name: Jade DSC, Instrument Type: Pyris 6. This study was performed by increasing the temperature from 1^0C to 400^0C at heating rate of 10/ min in a nitrogen environment.

3. Result and Discussion

3.1 Evaluation of Flow Properties of Granules of Immediate Release Layer (Paracetamol) And Sustained Release Layer (Diclofenac sodium)

Prepared granules of immediate layer were evaluated for their flow a property is Angle of repose (θ) ranged from 22.64 to 28.12 with granules prepared by wet granulation technique. It shows good flow property of prepared granules. Carr's index (CI) obtained were in the range of 12.968 to 16.66 and Hausner ratio (HR) observe in the ranged from 1.09 to 1.18 for granules in the different formulations. These value show good flow property of prepared granules. Prepared granules of Sustained release layer were evaluated for their flow properties as given table no.6.9 that is Angle of repose (θ) ranged from 23.43 to 29.34 with granules prepared by wet granulation technique. It shows good flow property of prepared granules. Carr's index (CI) obtained were ranged of 14.230 to 15.211 and Hausner ratio (HR) observe in the ranged from 1.03 to 1.11 for granules in the different formulations. These value show good flow property of prepared granules.

3.2 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.

3.3 Hardness:

The hardness of all formulations was observed and it revealed in the range from 4 to 5kg/cm^2.

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

3.5 (a) In Vitro drug release of Immediate release layer:

By increase the concentration of super disintegrating agent the % drug release (Paracetamol) is increased. F5 has highest 86% of Paracetamol release so It was considered as best optimized formulation.

3.6 (b) In Vitro drug release of Sustained release layer:

The *in-vitro* drug release study revealed that formulation F5 showed Diclofenac Sodium release of 82.11% up to 10 hrs. In formulation F5 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.

3.7 Thermal analysis by DSC:

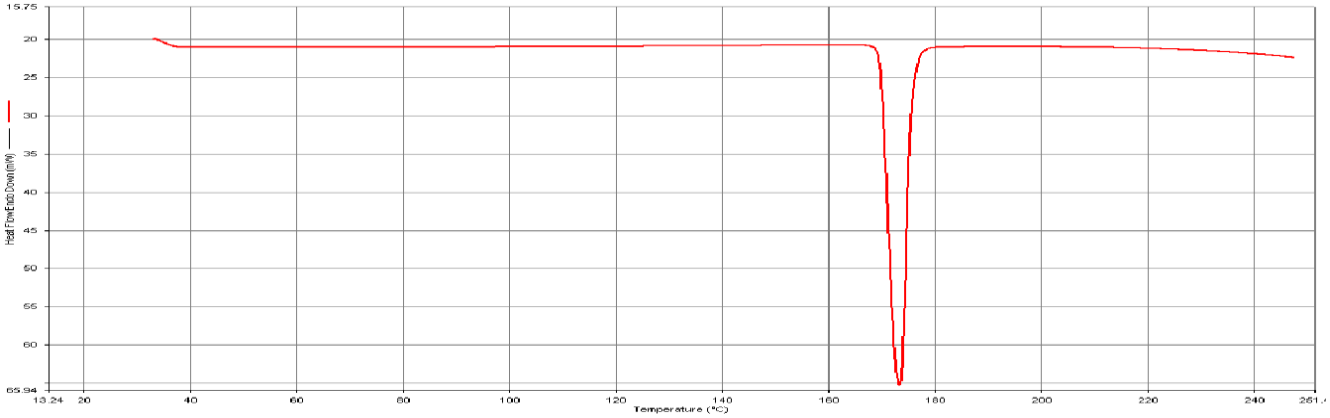

Figure 1: D.S.C. of Paracetamol

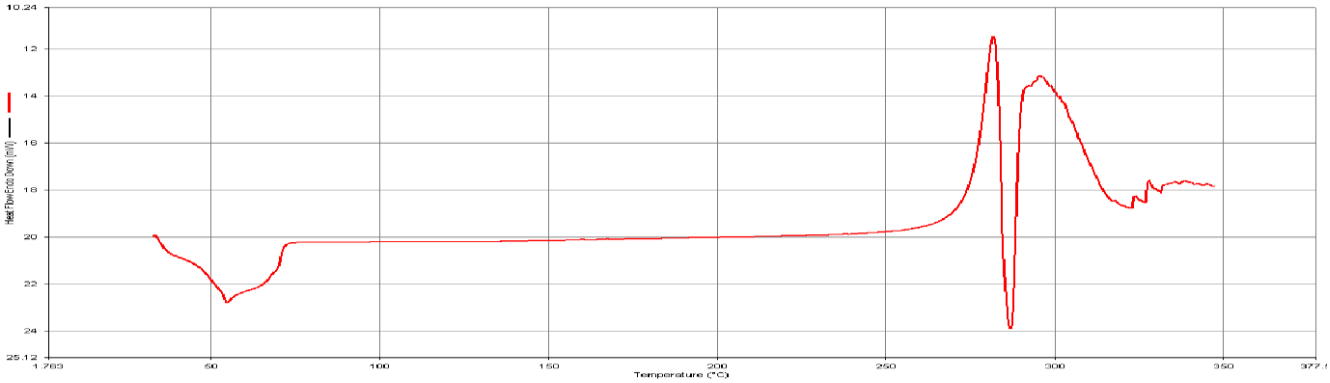

Figure 2: D.S.C. of Diclofenac Sodium

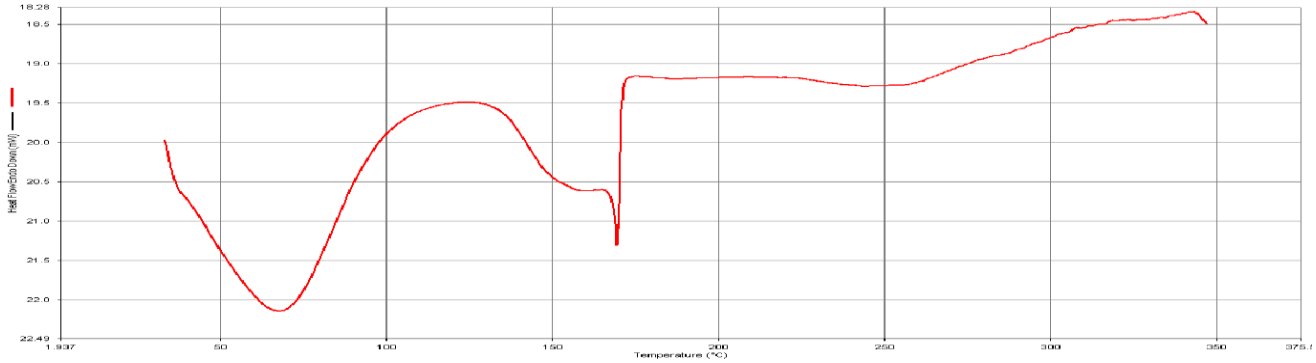

Figure 3: D.S.C. of HPMC K4M

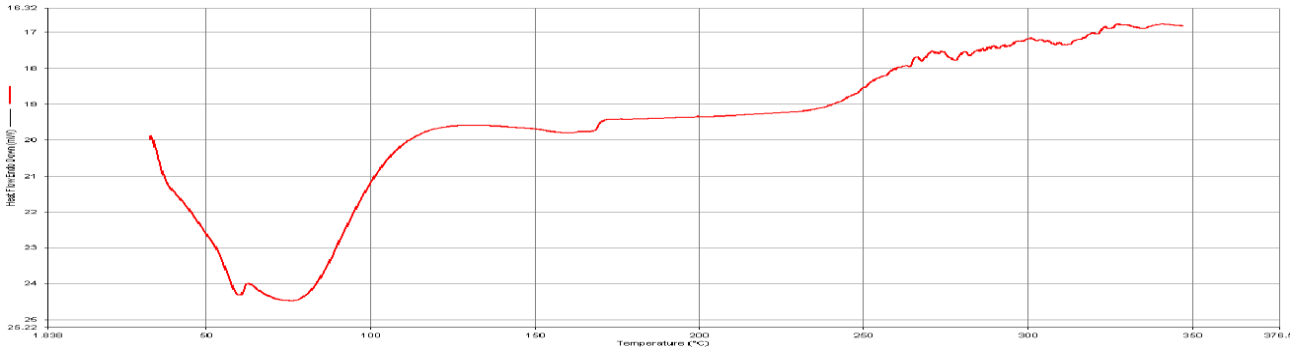

Figure 4: D.S.C. of formulation

Figure no 1 is DSC thermogram of pure drug Paracetamol showed sharp endothermic peak between 170 to 175°C which is the glass transition temperature of the Paracetamol. Figure number 2 is a DSC thermogram of Diclofenac Sodium which showed two endothermic peaks one at 52 to 57°C which could be because of the hydrate form of drug with the drug and other peak was at 275 to 285 °C which is the glass transition temperature of the Drug. Figure 3 was a thermogram of Polymer HPMC which also showed two endothermic peaks one is between 60 to 70°C this is because of the presence of moisture and the other is between 170 to 180°C which exhibited glass transition temperature of Polymer. In figure 3 few sharp endothermic peaks were obtained during exotherm this is due to "experimental phenomena" this could be because of rapid volatilization of gases trapped in the material can cause sharp peaks, as can rapid volatilization of gases trapped in apartially sealed hermetic pan. Figure no 4 showed thermogram of Blend of formulation an endothermic peak between 170 to 175°C which is the glass transition temperature of the Paracetamol. Few weak endothermic peaks were also obtained between 260 to 285°C These Endothermic peak exhibited melting point of Diclofenac Sodium as well as experimental phenomena" this could be because of rapid volatilization of gases trapped in the material can cause sharp peaks, as can rapid volatilization of gases trapped in a partially sealed hermetic pan till 350°C.

4. Conclusion

The overall result of the present work shows that this formulation also provide Paracetamol as immediate release layer which help to treat pain management simultaneously with Diclofenac Sodium. The various concentration of HPMCK4M was used to formulate a formulation which sustained the release of Diclofenac Sodium for 10 hrs. The reason behind choosing the HPMC K4Mpolymer 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 K 4M 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 releaseas 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.

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