Formulation development and optimization of bilayer tablets of aceclofenac

Sanjay Dey†, Beduin Mahanti, Sudip Khila, Bhaskar Mazumder & Sadipan Das Gupta
†*Dibrugarh University, Department of Pharmaceutical Sciences, Assam, India*

Objective: The objective of the present study was to develop bilayer tablets of aceclofenac that are characterized by initial burst drug release followed by sustained release of drug.
Methods: The fast-release layer of the bilayer tablet was formulated using microcrystaline cellulose (MCC) and HPMC K4M. The amount of HPMC E4M (X_1) and MCC (X_2) was used as independent variables for optimization of sustained release formulation applying 3^2 factorial design. Three dependent variables were considered: percentage of aceclofenac release at 1 h, percentage of aceclofenac release at 12 h, and time to release 50% of drug ($t_{50\%}$). The composition of optimum formulation of sustained release tablets were employed to formulate double layer tablets.
Results: The results indicate that X_1 and X_2 significantly affected the release properties of aceclofenac from sustained release formulation. The double layer tablets containing fast-release layer showed an initial burst drug release of more than 30% of its drug content during first 1 h followed by sustained release of the drug for a period of 24 h.
Conclusion: The double layer tablets for aceclofenac can be successfully employed as once-a-day oral-controlled release drug delivery system characterized by initial burst release of aceclofenac for providing the loading dose of drug.

Keywords: aceclofenac, bilayer tablets, HPMC, MCC, optimization

Expert Opin. Drug Deliv. (2012) 9(9):1041-1050

1. Introduction

The oral route is the most convenient route most widely used for the administration of drugs. Tablets are the most popular oral formulation available in the market and preferred by patients and physicians alike. Conventional tablets are not suitable for the treatment of chronic diseases where multiple doses are required [1]. Controlled release tablets are suitable for such therapy because they offer better patient compliance, maintain uniform dose levels, reduce dose frequency and side effects [2]. In certain disease conditions, a prompt disposition of the fraction of dose should be reached in the shortest time possible to relieve the symptoms of the disease and then the continuation of the drug effect should be prolonged to optimize the therapy.

The bilayer tablet concept has long been utilized to formulate biphasic release of drugs [3,4]. Such a bilayer tablet contains a first release layer and a sustain release layer. The first releasing layer leads to prompt release of the drug, so as to reach high serum concentration in a short period of time. The sustain release layer of the bilayer tablet releases the drug for prolonged period of time to maintain the effective concentration of drug within the therapeutic index [5]. This release pattern is required for successful treatment in many therapies, primarily when maximum relief needs to be achieved as soon as possible, and is followed by a sustained release

phase to avoid repeated drug administration. It is reported that the NSAIDs are suitable candidate drugs for this type of administration [6].

Aceclofenac is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis [7]. The short biological half-life (4 h) and frequent dosing make aceclofenac an ideal candidate for sustain release dosage form [8]. Treatment of inflammation by conventional formulation is found to have many drawbacks such as adverse effects resulting from accumulation of drug in multidose therapy, poor patient compliance, and high cost.

The objective of the present study was to develop bilayer tablets of aceclofenac with a fast-release layer using sodium starch glycolate as superdisintegrant and a sustaining layer using hydroxyl propyl methylcellulose E4M (HPMC E4M) and microcrystalline cellulose (MCC) as polymeric retardant materials. Different amount of HPMC E4M and MCC were selected as independent variable for formulation of sustain release layer. The effect of independent variables on response variable like amount of aceclofenac released at 1 h (Q_1), amount of aceclofenac released at 12 h (Q_{12}), and time to release 50% of drug ($t_{50\%}$) were evaluated. Regression analysis was performed to identify the best formulation and to validate the model by comparing the experimental result with the theoretical values of the responses.

2. Materials and methods

2.1 Materials

Aceclofenac was obtained from Cipla Ltd., Mumbai, India as gift sample. HPMC (E4M and K4M) and MCC were procured from Dr. Reddy's Laboratory, Hyderabad, India. Other materials were purchased from commercial sources: sodium starch glycolate and aerosol (Nice Chemicals, Mumbai, India), magnesium stearate and polysorbate-80 (Loba Chemicals, Mumbai, India), and talc (Reidel India Chemicals, Mumbai, India).

2.2 Methods

2.2.1 Calculation of theoretical release profile of aceclofenac from sustained release tablets

The total dose of aceclofenac for once-daily sustained release formulation was calculated using available pharmacokinetic data [9] from a design of one compartment model with simultaneous release of loading dose and zero-order release maintenance dose, as described by Robinson and Erikson [10]. Pharmacokinetic studies show that 50 mg of aceclofenac produce expected therapeutic effects within 3 h with a half-life of 4.3 h. Thus, the first-order elimination rate constant, ke = 0.693/4.3 = 0.1612 mg/h. Hence, the availability rate, R_o = keD = 0.1612 × 50 = 8.06 mg/h, where D is the initial dose of drug. The maintenance dose, D_m = Rh = 8.06 × 22 = 177.32 mg, where h is the number of hours for which sustained action is desired. Thus, total dose, D_t = D + D_m = 50 + 177.3 = 227.32 mg. $D_{corrected}$ = D_t-Rt_P = 227.32-8.06 × 3 = 203.14 mg, where t_P is the time period required to achieve a peak plasma level. Hence, the matrix tablet of aceclofenac should contain a total dose of 203.14 mg (≈200 mg) and should release 25.82 ± 8.06 = 33.88 mg in 3 h like conventional tablets, and 8.06 mg/h up to 24 h thereafter.

2.2.2 Formulation of fast-release tablet

Immediate release aceclofenac tablets were prepared by dry granulation technique. All the ingredients (**Table 1**) were separately passed through sieve no. 80 to break the lumps between the particles. Here, polysorbate-80, MCC, and HPMC K4M were used as wetting agent, disintegrating agent, and binder, respectively. The specified amount of polysorbate-80 was mixed with a half portion of MCC. Then the accurately weighed quantity of drug, HPMC K4M, sodium starch glycolate, a half portion of talc, and the rest of the amount of MCC were blended together with the previous mixture homogeneously in geometrical proportion for 20 min using a laboratory glass mortar and pestle. The powder mixture was dried in a hot air oven at 40°C for 5 min. The powder blend was compressed into tablets by a 10-station tablet compression machine (Hindustan Pvt. Ltd., Ahmedabad, India). A flat-faced punch 13 mm in diameter was used for tabletting. Prepared slugs were then milled to prepare granules and passed through sieve no. 22. The granules were then mixed with the rest of the amount of talc and magnesium stearate using a laboratory glass mortar and pestle and mixed uniformly for 5 min. The lubricated granules were compressed into tablets using 9 mm circular, flat-faced punches in a 10-station compression machine (Hindustan Pvt. Ltd., Ahmedabad, India).

2.2.3 Formulation of sustained release powder blend

Aceclofenac sustained released tablets were prepared by direct compression technique. All the ingredients (**Table 2**) were separately passed through sieve no. 80 to break the lumps between particles. Drug, HPMC E4M, and MCC was weighed and mixed homogeneously in geometric proportion for 25 min. The powder blend was lubricated through mixing with talc and magnesium stearate for 5 min. The powder blend thus obtained was compressed into tablets using 9 mm circular, flat punches in a 10-station compression machine.

2.2.4 Formulation of bilayer tablet

For the preparation of quick/slow biphasic release of aceclofenac tablet, the die of the tablet machine was filled manually with a weighed amount of lubricated powder blend of sustained release component. It was compressed at a pressure of 2 – 3 kg/cm^2 for 3 s using single-punch tablet compression machine using circular, flat-faced 9 mm punch. The upper punch was raised and the lubricated granules of best formulation of immediate release component were placed on the

Table 1. Composition of 50 mg aceclofenac fast-release tablet formulations.

Ingredient*	Formulation				
	IR-1	IR-2	IR-3	IR-4	IR-5
Aceclofenac	50	50	50	50	50
Microcrysatlline cellulose	65.5	60.5	62.5	60.5	58.5
HPMC K4M	4	6	4	4	4
Polysorbate-80	-	3	3	3	5
Sodium starch glycolate	2	2	2	4	4
Aerosil	2	2	2	2	2
Talc	1	1	1	1	1
Magnesium stearate	0.5	0.5	0.5	0.5	0.5
Tablet weight	125	125	125	125	125

*HPMC K4M: Hydroxymethyl cellulose of K4M viscosity grade.

Table 2. Factor combination as per the chosen experimental design*.

Trial No	Coded Factor Levels	
	X_1	X_2
I	-1	-1
II	-1	0
III	-1	1
IV	0	-1
V	0	0
VI	0	1
VII	1	-1
VIII	1	0
IX	1	1

Translation of coded levels in actual units

Coded level	-1	0	1
X1: HPMC E4M (mg)	55	65	75
X2: MCC (mg)	37.5	45	52.5

*Each formulation contains aceclofenac (150 mg), talc (2.42 mg), and magnesium stearate (2.42 mg).

above compact. Finally, the two layers were compressed at a pressure of 6 – 7 kg/cm^2 for 15 s.

2.2.5 *Evaluation of micrometrics properties of lubricated granules/powder blend*

The micrometrics properties like bulk density, tapped density, compressibility index, and Hausner's ratio were determined for lubricated granules and powder blend. All the experiments were performed in triplicate.

2.2.6 *Experimental design*

A three-level full-factorial design consists of nine full-factorial design points; according to the model, nine experiments were conducted in total. This design generally involves dependent variables Y and independent of controlled variables X_1 and X_2. The two independent formulation variables selected for this study were X_1, amount of HPMC E4M; and X_2, amount of MCC. The levels of independent variables are shown in **Table 2**. The dependent variables were Y_1, amount release at 1 h; Y_2, amount release at 12 h; $t_{50\%}$, time to release 50%.

2.2.7 *Tablet assay and physical evaluation*

The tablets were assayed (n = 3) for drug content using methanol as extracting solvent and the samples were analyzed spectrophotometrically (Shimadzu 1700, Kyoto, Japan) at 277 nm. The drug content was determined using the equation: Absorbance = 0.045 × concentration of aceclofenac-0.002 (R^2 = 0.999). Tablets were also evaluated for hardness (n = 6), friability (n = 6), weight variation (n = 10), and thickness (n = 10).

2.2.8 *In vitro release studies of fast-release tablets*

Preliminary dissolution test under gastric condition, intended for selecting formulation with superior dissolution properties to be incorporated into the fast-release layer of bilayer tablets, were performed using United State Pharmacopeia (USP) dissolution apparatus I (Pharmatest PTW II, Pharmatest Apparatus, Hainburg, Germany) at 100 rpm. The dissolution medium consisted of 900 mL of 0.1M hydrochloric acid (pH 1.2). The release study was performed at 37 ± 0.5°C. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2 µm Whatman filter paper and analyzed after appropriate dilution by UV-Visible spectrophotometer (Shimadzu 1700, Kyoto, Japan) at 277 nm. The *in vitro* release study of all the formulations were performed in triplicate and the mean of three determinations were used in data analysis.

2.2.9 *In vitro release studies of sustained release tablets*

The release of aceclofenac from prepared bilayer tablets were performed using USP dissolution apparatus I (Pharmatest PTW II, Pharmatest Apparatus, Hainburg, Germany). Studies were carried out in 900 mL of 0.1M hydrochloric acid (pH 1.2) at 37 ± 0.5°C and at 100 rpm for a period of 2 h followed by release in phosphate buffer (pH 6.8) for another 22 h. The medium change was effected by adding 4.32 g of sodium hydroxide and 6.08 g of potassium dihydrogen phosphate dissolved in 5 ml water to the acid [11]. Aliquots of 5 mL from release medium were withdrawn and replaced with equal volumes of media to maintain sink condition. The withdrawn samples were filtered through 0.2 µm Whatman filter paper and analyzed after appropriate dilution by UV-Visible spectrophotometer (Shimadzu 1700, Kyoto, Japan) at 277 nm for first 2 h samples and at 275 nm for rest of the samples. The *in vitro* release study of all the formulation were carried

out in triplicate and the mean of three determinations were used in data analysis.

2.2.10 *In vitro release studies of bilayer tablets*

In vitro release studies of the bilayer tablets were performed using the same method used for the sustained release formulations.

2.2.11 *Curve fitting of release profile*

The *in vitro* release data were fitted to the Korsmeyer and Peppas equation [12]:

$$M_t/M_\infty = kt^n \text{ ----------(1)}$$

where M_t/M_∞ represents the fraction of drug release at time t, k is the release rate constant, and n is the diffusion coefficient. The entire curve-fitting analysis was performed using GraphPad Prism version 3.02 (GraphPad Software, Inc.) and Excel (Microsoft) software.

2.2.12 *Optimization data analysis and validation of optimization model*

Various response surface methodology (RSM) computations for the current optimization study were performed employing Design Expert software (Version 8.0.4 Trial, Stat-Ease. Inc., Minneapolis, MN) [13,14]. A statistical model incorporating interactive and polynominal terms was utilized to evaluate the response:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \text{ ------(2)}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of nine runs, and b_1 is the estimated coefficient for factor X_1. The main effects (X_1 and X_2) represent the average results of changing one factor at a time from its low value to high value. The interaction terms X_1X_2 show how the response changes when two factors are changed simultaneously. The polynominal terms (X_1 and X_2) are included to investigate nonlinearity.

Statistical validity of the polynominals was established on the basis of ANOVA provision in the Design Expert software. Subsequently, the feasibility and grid searches were performed to locate the composition of optimum formulations. The 3-D response surface graphs and 2-D contour plots were constructed in MS-Excel environment using the output files generated by the Design Expert software. Four optimum checkpoints were selected by intensive grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynominal equations. The formulations corresponding to these checkpoints were prepared and evaluated for various response properties. Subsequently, the resultant experimental data of response properties were quantitatively compared with that of the predicated values. Linear regression plots between observed and predicated values of the response properties were drawn using MS-Excel, forcing the line through origin.

3. Results and discussion

Bilayer tablet formulation is one of the novel approaches to overcome the problem of oral delivery of drug in the form of conventional tablets and as well as matrix tablet. Development of bilayer tablet for a drug is very much necessary where a prompt release of drug is required to relieve the symptoms of certain diseases (like inflammation, hypertension, etc.) as well as to maintain the appropriate serum level over the desired dosage interval. As aceclofenac is a non-steroidal anti-inflammatory drug having the less elimination half-life (4.3 h) [9], it is therefore required to develop biphasic release tablet.

At first, composition of fast-release layer is optimized as it is an important factor related to bilayer tablets to provide the loading dose of drug. The different amount of HPMC K4M (4 and 6 mg), polysorbate 80 (3 and 5 mg), and sodium starch glycolate (2 and 4 mg) were selected for the formulation of fast-release layer. The effects of above formulation variables on disintegration time and *in vitro* release of drug was observed. The lubricated granules of fast-release layer were evaluated for their flow properties (**Table 3**). Bulk density and tapped density was found within the range of 0.707 – 0.827 g/mL and 0.872 – 1.061 g/mL, respectively. Carr's index and Hausner's ratio was found to be in the range of 14.51 – 22.16% and 1.169 – 1.284. These values indicate that the prepared granules exhibit good flow properties [15].

Fast-release tablets were subjected to evaluation of different physicochemical properties (**Table 4**). Hardness was found to be within the range of 3.10 – 4.16 kg/cm^2. Friability and weight variation of the tablets were found to be within the specification limit as mentioned in official monograph, Indian Pharmacopoeia, 1996 [16]. The assayed content of drug in various formulations varied between 99.09 and 100.15%. Disintegration time of tablet in various formulations was found to be within the range of 20.33 – 124.66 s. *In vitro* release profile (**Figure 1**) of different formulation revealed that the aceclofenac release in 90 min was more in formulation IR-5 (61.52 ± 1.52%) as compared to other formulations. On the basis of disintegration time (71 s) and *in vitro* release, the composition of IR-5 formulation was selected as fast-release layer for the formulation of bilayer release tablets.

Sustained release tablets were formulated as per 3^2 factorial design and the factor amount of HPMC E4M and MCC was considered to have an important effect on the release of drug from the tablets. HPMC E4M was chosen because it is widely used as low-density hydrocolloidal system; upon contact with water, a hydrogel layer would be formed to act as a gel boundary for the delivery system, but it would fail to retard the release of drug through the matrix because of its solubility in stomach pH [17]. Microcrystaline cellulose was used in combination with HPMC E4M to slow the drug release.

The powder blend for sustained release layer were subjected to evaluation of micrometric properties (**Table 3**) like bulk

Table 3. Micrometric properties of aceclofenac immediate release lubricated granules.

Type	Formulation	Bulk Density (gm/mL)	Tapped Density (gm/mL)	Carr's Index (%)	Hausner's Ratio
Immediate Release	IR-1	0.827 ± 0.010	1.022 ± 0.016	19.11 ± 1.17	1.236 ± 0.017
	IR-2	0.821 ± 0.010	1.032 ± 0.016	20.43 ± 1.15	1.257 ± 0.018
	IR-3	0.903 ± 0.012	1.061 ± 0.017	14.51 ± 0.20	1.169 ± 0.002
	IR-4	0.707 ± 0.013	0.872 ± 0.020	18.82 ± 3.41	1.233 ± 0.051
	IR-5	0.755 ± 0.023	0.970 ± 0.038	22.16 ± 0.68	1.284 ± 0.011
Sustained Release	F1	0.515 ± 0.150	0.662 ± 0.012	22.16 ± 0.862	1.283 ± 0.014
	F2	0.531 ± 0.010	0.663 ± 0.006	19.90 ± 1.320	1.247 ± 0.021
	F3	0.543 ± 0.020	0.659 ± 0.006	17.63 ± 2.450	1.213 ± 0.035
	F4	0.491 ± 0.010	0.639 ± 0.005	23.20 ± 1.580	1.301 ± 0.027
	F5	0.507 ± 0.016	0.637 ± 0.005	20.53 ± 1.920	1.257 ± 0.030
	F6	0.520 ± 0.016	0.635 ± 0.005	18.16 ± 1.950	1.221 ± 0.029
	F7	0.471 ± 0.014	0.627 ± 0.010	24.90 ± 1.100	1.330 ± 0.020
	F8	0.489 ± 0.011	0.631 ± 0.005	22.53 ± 1.200	1.290 ± 0.020
	F9	0.498 ± 0.011	0.633 ± 0.009	21.36 ± 0.650	1.270 ± 0.010

Table 4. Physicochemical properties of immediate and sustained release tablets.

Formulation	Hardness (kg/cm^2)	Weight Variation (mg)	Drug Content (%)	Friability (%)	Disintegration Time (s)
IR-1	3.26 ± 0.11	126.33 ± 0.70	99.09 ± 1.62	0.612	124.66 ± 1.52
IR-2	4.16 ± 0.05	126.00 ± 1.05	99.39 ± 2.12	0.523	195.00 ± 1.73
IR-3	3.50 ± 0.10	128.33 ± 2.27	99.69 ± 4.44	0.509	20.33 ± 1.15
IR-4	3.96 ± 0.15	127.00 ± 1.56	99.84 ± 1.82	0.480	54.66 ± 0.57
IR-5	3.10 ± 0.17	125.66 ± 0.88	100.15 ± 1.58	0.466	71.00 ± 2.00
F1	7.33 ± 0.15	248.33 ± 1.86	99.20 ± 2.53	0.335	-
F2	7.43 ± 0.02	254.66 ± 2.58	100.55 ± 2.53	0.261	-
F3	7.23 ± 0.05	263.16 ± 1.94	99.84 ± 1.79	0.316	-
F4	7.26 ± 0.05	256.00 ± 1.67	99.28 ± 2.90	0.455	-
F5	6.80 ± 0.10	263.66 ± 2.16	99.60 ± 4.00	0.506	-
F6	7.13 ± 0.15	272.33 ± 2.33	99.88 ± 1.07	0.428	-
F7	6.16 ± 0.20	266.16 ± 1.16	98.48 ± 0.55	0.563	-
F8	6.16 ± 0.05	276.16 ± 2.04	99.92 ± 1.79	0.362	-
F9	6.43 ± 0.15	283.50 ± 1.97	98.56 ± 2.12	0.352	-

density (ranged between 0.471 and 0.543 g/mL), tapped density (0.627 – 0.663 gm/mL), Carr's index (17.63 – 24.90%), and Hausner's ratio (1.213 – 1.330). These values revealed the good flowability of powder blend.

The physicochemical properties of the sustained release tablets are shown in **Table 4**. The weight of the tablets varied between 373 and 386 mg for different formulations. The variation in weight was found to be within the range ± 5% within acceptable range as mentioned in Indian Pharmacopoeia, 1996 [16]. The thickness varied between 3.28 and 3.85 mg, hardness varied between 6.16 and 7.43 kg/cm^2, and friability ranged between 0.261 and 0.563%. The assayed content of drug in various formulations varied between 98.48 and 100.55%. The physicochemical parameters of the compressed matrices were practically within control.

Release profile of nine formulation from 32 factorial design batches are shown in **Figure 2**. The results of *in vitro* studies were depicted in **Table 5**. It is clearly indicated that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (F1 – F9). The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). The high values or correlation coefficient (**Table 6**) for the dependent variables indicate a good fit of the data with chosen experimental design. Mathematical relationship generated using multiple linear regression analysis for the studied variables are expressed as Equations 3 through 5 and the analysis of variance (ANOVA) information is shown in **Table 6**.

$$Q1 = 18.81 - 1.15X_1 + 2.08X_2 - 0.15X_1X_2 + 0.84X_1^2 - 0.31X_2^2 \quad (3)$$

$$Q12 = 68.92 - 9.26X_1 + 3.59X_2 - 0.62X_1X_2 + 5.84X_1^2 - 0.51X_2^2 \quad (4)$$

$$t_{50\%} = 5.82 + 1.36X_1 - 0.58X_2 - 0.22X_1X_2 - 0.55X_1^2 + 0.23X_2^2 \quad (5)$$

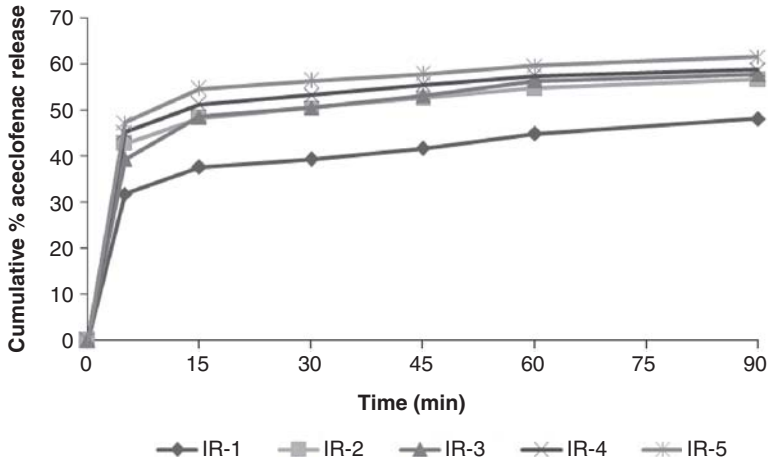

Figure 1. *In vitro* release profile of aceclofenac from fast-release tablets (n = 3).

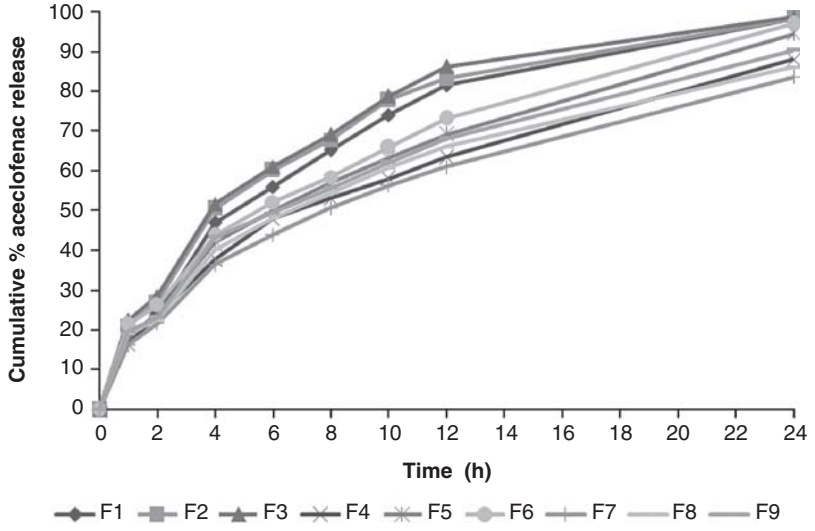

Figure 2. *In vitro* release profile of aceclofenac from sustained release tablets of factorial batches (n = 3). The mean of three determinations were presented.

Table 5. Drug release parameters of various formulations prepared as per the experimental design.

Formulation	Factor amount (mg)		Rel_{1h} (%)	Rel_{12h} (%)	$t_{50\%}$ (h)
	X_1	X_2			
F1	55	37.5	18.32	81.60	4.49
F2	55	45	21.10	83.20	3.92
F3	55	52.5	22.36	86.24	3.80
F4	65	37.5	16.40	63.44	6.60
F5	65	45	18.00	69.10	5.95
F6	65	52.5	21.41	73.20	5.38
F7	75	37.5	16.21	61.10	7.72
F8	75	45	19.02	66.14	6.50
F9	75	52.5	19.66	68.24	6.15

Table 6. Analysis of variance tables for dependent variables from full factorial design*.

Sources	Q_1 (Release at 1 h)		Q_{12} (Release at 12 h)		$t_{50\%}$	
	F	p-Value	F	p-Value	F	p-Value
Model	10.42	0.0410	59.61	0.0033	153.52	0.0008
X_1	11.56	0.0425	231.61	0.0006	607.78	0.0001
X_2	38.05	0.0086	34.81	0.0097	110.54	0.0018
X_1 X_2	0.13	0.7450	0.70	0.4632	10.60	0.0473
X_1	2.07	0.2458	30.71	0.0116	32.73	0.0106
X_2	0.29	0.6294	0.23	0.6616	5.96	0.0923
R^2	0.9456		0.9900		0.9961	

*Significant effect (p-Value < 0.5); X_1: HPMC E4M; X_2: MCC.

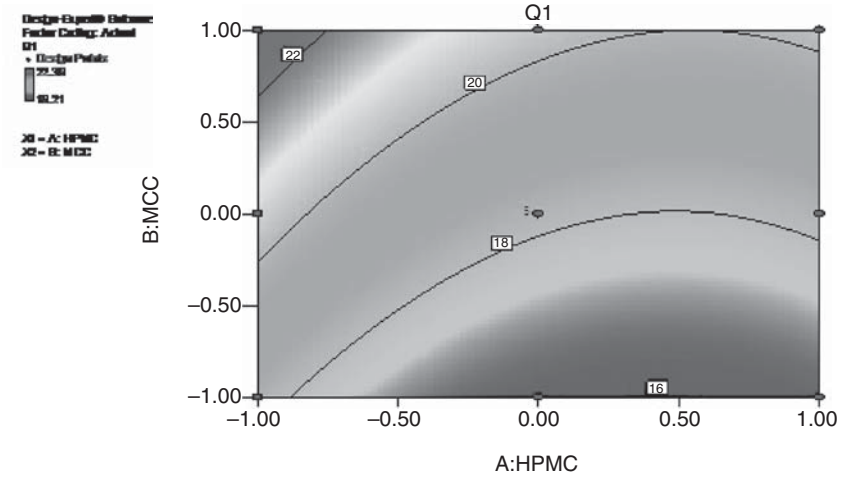

Figure 3. Contour plot showing the effect of amount of HPMC E4M (X_1) and amount of MCC (X_2) on percentage of aceclofenac released at 1 h (Q_1).

In the case of Q_1 (percentage of aceclofenac released at 1 h), coefficients b_1 and b_2 were found to be significant. In Equation 3, we can see only negative coefficient; when the HPMC E4M (X_1) was increased, aceclofenac release at 1 h decreased. Similar results were reported earlier: as the polymer concentration in the matrix system increases, the release of drug decreases [18]. The relationship between variables was further elucidated using contour plots. The effects of HPMC E4M and MCC on Q_1 are given in **Figure 3**. At low level of MCC, Q_1 did not show any significant changes when HPMC E4M increased from low level to high level. But the same Q_1 decreased from 22.36 to 16.21% when HPMC E4M was increased and the MCC was kept at the highest level. The ANOVA analysis for Q_{12} (percentage of aceclofenac release at 12 h) is shown in **Table 6**, coefficient b_1 and b_2 were found to be significant. In Equation 4, we can see only negative coefficient; when the amount of HPMC E4M (X_1) increased, concurrently decreasing the released of aceclofenac at 12 h. This finding was due to the increased strength of the gel layer; the drug diffusion was controlled by the penetration of liquid through the gel layer. The effects of HPMC E4M and MCC on Q_{12} are elucidated in **Figure 4**. As the HPMC E4M increased, the release decreased from 86.24 to 61.10% when the MCC was kept at the highest level. The model term $t_{50\%}$ (time to release 50% of aceclofenac) was found to be significant. In this case, b_1 and b_2 and the interaction were found to be significant. From Equation 5, we can see when the HPMC E4M (X_1) were increased, the $t_{50\%}$ values showed an increase, which may be due to the slower water uptake. The contour plot (**Figure 5**) indicate that as the low level of MCC, $t_{50\%}$ increased from 3.8 to 7.72 h when the HPMC E4M was increased but at the high level of MCC, there was no significant changes of $t_{50\%}$.

After generating the polynominal equation for the dependent and nondependent variables, the combination was optimized for all three responses. Upon 'trading off' various response variables, the following maximizing criteria were adopted: Q_1 in range of 16 – 18%, Q_{12} in range of 73 – 77%, and $t_{50\%}$ in between 5 and 6 h. Upon comprehensive evaluation of feasibility search and subsequent grid searches, the formulation composition with polymer levels

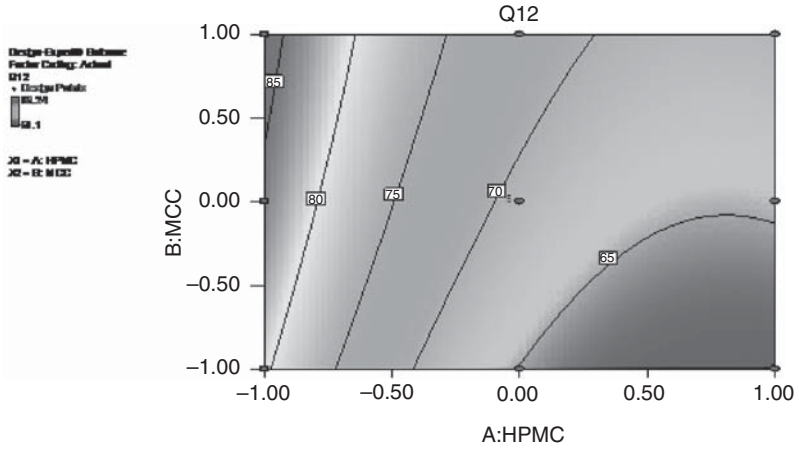

Figure 4. Contour plot showing the effect of amount of HPMC E4M (X_1) and amount of MCC (X_2) on percentage of aceclofenac released at 12 h (Q_{12}).

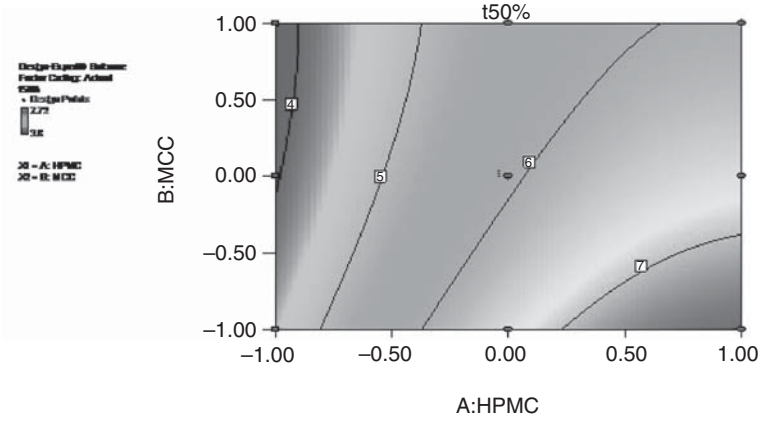

Figure 5. Contour plot showing the effect of amount of HPMC E4M (X_1) and amount of MCC (X_2) on time (h) to release 50% of aceclofenac ($t_{50\%}$).

of HPMC E4M, 62.20 mg, and MCC, 44.92 mg fulfilled maximum requisites of an optimum formulation because of better regulation of release rate. The formulation showed Q_1 as 17.84%, Q_{12} as 74.82%, and $t_{50\%}$ as 5.24 h. The results showed a good relationship between the observed and predicted response, which confirm the observed and predicted response, which confirm the practibility of the model.

Table 7 records the value of observed and predicted responses using factorial design along with the percentage-predicted errors for these four formulations. Upon comparison of the observed responses with that of predicted responses, the predicted error varied between -0.4451 and 0.9654%, with the mean ± SD of the percentage error being 0.3760 ± 0.5810%. The linear correlation plots drawn between the predicted and observed responses indicated high values of r^2 (varying between 0.943 and 0.994), indicating excellent goodness of fit.

Bilayer tablets prepared by using composition IR-5 formulation and fast-release layer and composition of optimized formulation for matrix tablet as sustained release layer were subjected to evaluation of different physicochemical parameters. The hardness, weight variation, thickness, friability, and content uniformity of the bilayer tablet were found to be 7.1000 ± 0.1732 kg/cm^2, 0.8263 ± 0.4987%, 5.28 ± 0.12 mm, 0.6823 ± 0.0002%, and 99.68 ± 1.38%.

The *in vitro* release profile of the bilayer tablets and predicted release are presented in **Figure 6**. It is clear from **Figure 6** that the formulation should be biphasic release of aceclofenac. The first fraction of the dose (the immediate dose) was released in less than 15 min, because of prompt disintegration of the fast-releasing layer. After the release of the first fraction, the release of the sustained dose depended upon the HPMC E4M:MCC ratio. The drug release from the tablets was 90% within 24 h.

Table 7. Composition of the checkpoint formulations, the predicted and experimental values of response variables, and percentage prediction error*.

Composition	Response Variables	Observed Response	Predicted Response	% Error
61.50:44.17	Q_1	17.89	17.73	0.9024
	Q_{12}	73.81	74.14	-0.4451
	$t_{50\%}$	5.26	5.28	-0.3788
60.90:43.95	Q_1	17.85	17.68	0.9615
	Q_{12}	73.48	73.28	0.2729
	$t_{50\%}$	5.42	5.38	0.7435
62.20:44.92	Q_1	17.78	17.61	0.9654
	Q_{12}	74.82	75.05	-0.3064
	$t_{50\%}$	5.24	5.19	0.3853
59.80:42.82	Q_1	17.92	17.75	0.9577
	Q_{12}	72.12	72.32	-0.2765
	$t_{50\%}$	5.52	5.48	0.7299

*Percentage Error (mean ± SD) 0.3760 ± 0.5810.

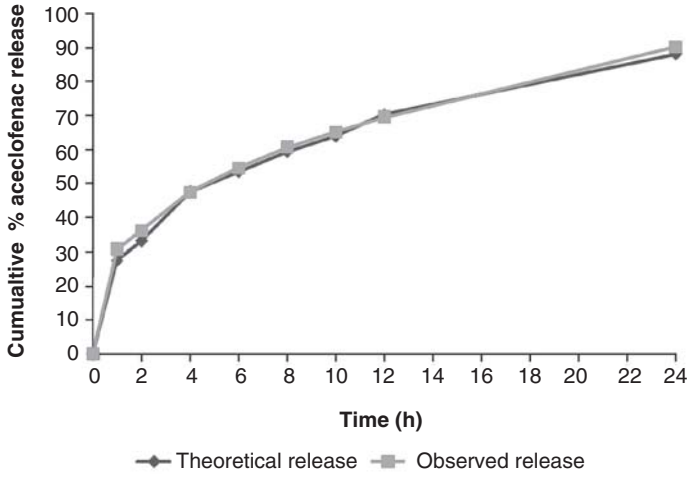

Figure 6. Comparison of the theoretical and observed aceclofenac release profile from bilayer tablet (n = 3).

The first phase of the drug release profile depended in the concentration of the drug and hence the upper surface as an immediate dose and hence followed first-order kinetics (R^2 = 0.997). In the second phase of the release (1 – 24 h), the data were fitted to Equation 1 and diffusion coefficient (n) was found to be 0.344. Based on the n value, the mechanism of aceclofenac release from bilayer tablet followed Fickian transport [19].

4. Conclusion

In the present study, the double layer tablets for aceclofenac can be successfully employed as once-a-day oral-controlled release drug delivery system characterized by initial burst release of aceclofenac for providing the loading dose of drug. The current study indicates the factor amount of HPMC E4M and MCC did significantly affect the studied dependent variables. Further *in vivo* studies are necessary to make correlation between *in vitro* and *in vivo* performance of the optimized formulation and to access the therapeutic efficacy of the bilayer tablets compared to conventional tablet.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

1. Kulkarni SV, Patel N, Rao BS, et al. Formulation and in vitro evaluation of sustained release matrix tablet of zolpidem tartarate. Int J Pharm Tech Res 2011;3:858–63
2. Yan G, Li H, Zhang R, Ding D. Preparation and evaluation of a sustained-release formulation of nifedipine HPMC tablets. Drug Dev Ind Pharm 2000;26:681–6
3. Bandari S, Eaga CM, Thadishetty A, Yamsani MR. Formulation and evaluation of multiple tablet as a biphasic gastroretentive floating drug delivery system for fenoverine. Acta Pharm 2010;60:89–97
4. Karthikeyini SC, Jayaprakash S, Abirami A, Halith SM. Formulation and evaluation of aceclofenac sodium bilayer sustained release tablets. Int J Chem Tech Res 2009;1:1381–5
5. Abraham MA, Shirwaikar A. Formulation of multilayered sustained release tablet using insoluble matrix system. Indian J Pharm Sci 1997;59:312–15
6. Lopes CM, Sousa Lobo JM, Pinto JF, Costa PC. Compressed matrix core tablet as a quick/slow dual-component delivery system containing ibuprofen. AAPS PharmSciTech 2007;8(3):E195–202
7. Insel PA. In: Goodman AG, Gilmans AG, Gilman AG, Rall T, Nies A, Taylor P, editors. The pharmacological basis of therapeutics. 9th edition. Pregamon Press; Oxford: 1922. p. 638–81
8. Trivedi P, Verma AML, Garud N. Preparation and characterization of aceclofenac microspheres. Asian J Pharm Sci 2008;2(2):110–15
9. Dooley M, Spencer CM, Dunn CJ. Aceclofenac: a reappraisal of its use in the management of pain and rheumatic disease. Drugs 2001;61:1351–78
10. Colombo P. Swelling-controlled release in hydrogel matrices for oral route. Adv Drug Deliv Rev 1993;11:37–57
11. Patel MM, Soniwala MM. Influence of release enhancer of venlafaxine HCl from glyceryl behenate matrix tablet. Indian Drugs 2008;45:98–104
12. Korsmeyer RW, Doelker GFP, Peppas NA. Mechanism of potassium chloride from compressed, hydrophilic, polymeric matrices: effect of entrapped air. J Pharm Sci 1983;72:1189–91
13. Singh B, Kumar R, Ahuja N. Optimizing drug delivery systems using systematic "design of experiments". Part I: fundamental aspects. Crit Rev Ther Drug Carrier Syst 2005;22:27–105
14. Singh B, Ahuja N. In: Jain NK, editor. Progress in controlled and novel drug delivery systems. CBS Publishers and Distributors; New Delhi: 2004. p. 22–121
15. Aulton ME, Wells TI. Pharmaceutics-the science of dosage form design. Churchill Livingstone; London, UK: 1988
16. Ministry of health and family welfare. Volume 2. Publication by Controller of Publication; Delhi: 1996
17. Pygall SR, Kujawinski S, Timmins P, Melia CD. Mechanisms of drug release in citrate buffer HPMC matrices. Int J Pharm 2009;370:110–20
18. Velasco MV, Ford JL, Rowe P, Rajabi-Siahboomi AR. Influence of drug: hydroxpropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. J Control Release 1999;57:75–85
19. Kannan S, Manivannan R, Ganesan K, et al. Formulation and evaluation of sustained release tablets of aceclofenac using hydrophilic matrix system. Int J Pharm Tech Res 2010;2:1775–80

Affiliation

Sanjay Dey[†1], Beduin Mahanti[2], Sudip Khila[3], Bhaskar Mazumder[4] & Sadipan Das Gupta[1]
[†]Author for correspondence
[1]Research Scholar,
Dibrugarh University,
Department of Pharmaceutical Sciences,
Dibrugarh-786004, Assam, India
Tel: +918900032048;
E-mail: sanju1980dey@gmail.com
[2]Calcutta Institute of Pharmaceutical Technology and Applied Health Science,
Faculty of Pharmacy, Banitabla,
Uluberia, Howrah-711316, India
[3]Student of M Pharm,
Calcutta Institute of Pharmaceutical Technology and Applied Health Science,
Banitabla, Uluberia, Howrah-711316, India
[4]Faculty of Pharmacy,
Department of Pharmaceutical Sciences,
Dibrugarh University,
Dibrugarh-786004,
Assam, India