Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF ASPIRIN DELAYED RELEASE TABLETS

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ABSTRACT

The main objective of this work was to formulation development of the Aspirin delayed release tablets and to understand the kinetics of drug release by applying mathematical and model-dependent approaches. Six formulations of delayed release tablets were prepared by the direct compression method and simple pan coating using Drug coat N-100 and Hydroxypropylmethylcellulose phthalate (HPMCP) as enteric coating polymers. The in vitro drug release was studied in pH 1.2 HCl and 6.8pH phosphate buffer using USP dissolution Apparatus 2 at 100 rpm. Zero-order, first-order, Higuchi, and Korsmeyer et al. models were used to estimate the kinetics of drug release. The criteria for selecting the most appropriate model were based on the goodness-of-fit test and lowest sum of squares residual. Drug release from the optimal batch was explained by the Higuchi model. The difference in percent cumulative drug release of each point was highest for the optimum batch.

Keywords: Aspirin, Delayed-Release tablet, Release Kinetics, Drug coat N-100, HPMCP.

INTRODUCTION

Aspirin's efficacy in preventing Myocardial Infraction is related to preventing thrombus formation by decreasing platelet aggregation[1]. Aspirin is a non-steroidal anti-inflammatory drug (NSAID) that permanently inactivates the cyclooxygenase (COX)-mediated activities of prostaglandins through irreversible binding[2]. There are two forms of COX: COX-1 and COX-2. COX-1 is responsible for the synthesis of thromboxane A2 in platelets and the production of prostacyclinin vascular walls[3]. Thromboxane A2 is a vasoconstrictor and platelet-aggregating agent, while prostacyclin acts as a vasodilator and platelet inhibitor[4]. The major drawback of aspirin G.I. Mucosa ulceration can be avoided by providing the Effective enteric coating. In this study, an attempt was made to formulate Aspirin delayed release tablets with the use of enteric polymer Drug coat N-100 and hydroxypropyl methylcellulose phthalate (HPMC -P) was used in combination to produce the effective enteric coating.

In order to investigate the mode of release from delayed release tablet, the release data were analyzed using following mathematical models: Zero-order kinetic (equation 1);

First-order kinetic (equation2); Higuchi equation (square-root of time equation, equation 3)[5]; and Peppas equation (equation 4)[6].

Eq.1. $Q = k_0 t$

Eq.2. $\ln (100 - Q) = \ln (Q_0) - k_1 t$

Eq.3. $Q = k_H t^{1/2}$

Eq.4. $\text{Log } (Q/100) = k_p t^n$

In equations Q, the percent of drug released is at time t, Q_0, the percent of drug remaining to release and k_0, k_1 and k_H are the coefficients of the equations. k_P is constant incorporating structural and geometric characteristics of the release device, and n is the Release exponent indicative of the mechanism of release.

MATERIALS AND METHODS

Materials

Aspirin (Alchymars ICM SM Pvt. Ltd., India), Microcrystalline cellulose (avicel) (MCC, Ming Tai Chemical Co. Ltd., Taiwan), Maize starch (Cerestar, Netherlands), HPMCP (Shin Etsu Chemical Company Ltd., Japan), Drug coat N-100 (Rohm GmbH, Germany), Magnesium stearate (BASF chemical company, Germany), Purified talc (Asian Mineral Resources Co. Ltd., Thailand), Dibutyl phthalate (Morflex Inc., USA) and other materials used were of analytical reagent grade.

Methods

Preparation of aspirin delayed release tablets

Delayed release tablets of Aspirin were prepared by using Drug coat N-100 and Hydroxypropylmethylcellulose phthalate (HPMCP) as enteric coating polymers.

Drug coat N-100: HPMCP ratios viz. 10:0, 8:2, 6:4,5:5,2:8 and 0:10. Different tablet formulations were prepared by direct compression technique and the formulations were named as F-1, F-2, F-3, F-4, F-5 andF-6 respectively. Sieve the aspirin through mesh no.16of a sifter and dried maize starch, avicel ph-102 and micro crystalline cellulose through mesh no.40 sifted material charged in to double cone blender, blend for 20 minutes add talc purified and mix for 5 minutes. Compress the granules in to tablets by tablet compression machine (Cad mach, Ahmadabad, India) with 9/32" standard concave upper & lower punches, oval shaped to a target weight of 140mg per

tablet. Prior to the compression, the granules were evaluated for several tests.

Coating with enteric polymers

The coating suspension was prepared with Drug coat N-100, Hydroxypropylmethylcellulose phthalate in different ratios, and Dibutyl phthalate as plasticizer and talc as anti adherent. 140 g core were coated using fluid bed coater (Lab coater; Umang Pharmatech, India) with enteric polymers coating suspension.

Evaluation

Evaluation of granules

Angle of Repose

The angle of repose of powdered gum was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The

Diameter of the powder cone was measured and angle of repose was calculated using the following equation [7]

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

Where h and r are the height and radius of the powder pile respectively

Bulk Density

Both bulk density (BD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas [8].

BD = Weight of the Powder/Volume of the packing

TBD = Weight of the powder /Tapped volume of the packing

Compressibility Index/ Carr's Index

The flow property was also determined by measuring the compressibility index. It is an important measure that can be obtained from the bulk and tapped densities. According to the theory, the less compressible materials are more flowable. A material having values of less than 20 to 30% is defined as the free flowing material, based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula[9]:

Compressibility Index = Tap density – Bulk density/Tap density x 100

Evaluation of Tablets

Thickness

The thickness of the tablets was determined using a thickness screw gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used and average values were calculated.

Uniformity of Weight

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Denver APX-100, Arvada, Colorado) and the test was performed according to the official method [10].

Hardness and Friability

For each formulation, the hardness and friability of tablets equivalent to 7kg/cm^2 were determined using the Monsanto hardness tester (Cad mach, Ahmadabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively[11].

Drug Content

Dissolve 2 gms of sodium 1-heptanesulfonate in a mixture of 850 ml of water and 150 ml of acetonitrile and adjust with glacial acetic acid to a ph of 3.4 is used as a mobile phase. Mixture of acetonitrile and formic acid (99:1) is used as a diluting solution. Dissolve an accurately weighed quantity of aspirin in diluting solution to obtain a solution having a known concentration of about 0.5mg per ml as a Standard 20 tablets were weighed and powdered.

Powder equivalent to about 100 mg of aspirin dissolved in 20.0ml of diluting solution. Separately Inject equal volumes (20µl) of standard preparation and sample solution, record the chromatograms and measure the responses for the major peaks. Using c^{18} column Ultra violet Detector wavelength set at 280 nm[12]. (Table 3)

Calculate Assay Contents as follows.

$$\frac{\text{Sample avg area x STD wt (in mgs) x 5 x 50 x 50 x Average Wt}}{\text{STD avg area x 50 x 50 x spl.wt (in mgs) x 5}}$$

In-Vitro Release Studies

The in vitro dissolution studies (figure 1) were carried out using USP apparatus type II (Tab Machines, Mumbai, India) at 100 rpm. The dissolution medium consisted 0.1N HCl for 2 hours after 2 hours medium is replaced with phosphate buffer pH 6.8 for 45mins (900 mL), maintained at 37°C ±0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer (Systronics UV spectrophotometer-117, Mumbai, India) at 265 nm for 0.1N HCl and 280nm for 6.8 phosphate buffer. Using Chemstation software (Agilent Technologies, New Delhi, India). It was made clear that none of the ingredients used in the formulations interfered with the assay. The kinetic data of formulated matrix tablets were shown in Table 4 and 5.

Table 1: Formula for Aspirin Tablet

S. NO	Name of ingredients	FORMULATION CODES					
		F1	F2	F3	F4	F5	F6
		Mg/tablet					
1.	Aspirin	100	100	100	100	100	100
2.	Maize starch	20	20	20	20	20	20
3.	Microcrystalline cellulose	7	7	7	7	7	7
4.	Avicel ph -102	10	10	10	10	10	10
5.	Talc	4	4	4	4	4	4
For coating solution preparation							
6.	Drug coat N-100	14	11.2	8.4	7	5.6	-
7.	HPMC-phthalate	-	2.8	5.6	7	8.4	14
8.	Acetone	105	105	105	105	105	105
9.	Isopropyl alcohol	105	105	105	105	105	105
10.	Dibutyl phthalate	2.35	2.35	2.35	2.35	2.35	2.35
11.	Sunset yellow lake	0.5	0.5	0.5	0.5	0.5	0.5
12.	Titanium Di Oxide	2.45	2.45	2.45	2.45	2.45	2.45

Table 2: Precompression parameters of aspirin delayed release tablets

S.NO	TEST	F1	F2	F3	F4	F5	F6
1	BULK DENSITY (gm/ml)	0.62	0.61	0.62	0.60	0.62	0.61
2	TAPPED DENSITY (gm/ml)	0.87	0.869	0.85	0.86	0.873	0.876
3	CARS INDEX	28.73	29.80	27.05	30.23	28.98	30.36
4	ANGLE OF REPOSE (Degrees)	25°.26’	25°.17’	25°.93’	24°.50’	24°.20’	25°.28’

Table 3: Post compression parameters of aspirin delayed release tablets

Formulations	Weight Variations (%)		Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)	Dissolution at end of 45 mins
	+	-					
F1	2.1	3.2	3.98	7	0.20	100.02	63.30
F2	2.3	3.6	4.14	6	0.19	100.11	69.15
F3	3.4	3.0	4.17	6	0.17	100.10	74.43
F4	2.5	3.1	3.92	8	0.17	100.02	84.23
F5	3.2	2.8	4.10	7	0.18	100.10	79.72
F6	3.0	3.4	4.13	6	0.19	100.03	75.76

Table 4: Correlation coefficient and constant of different kinetics models

Formulation code	Zero order		First order		Higuchi equation		Koresmayer-Peppas equation	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n
F1	0.535	0.302	0.373	0.813	0.410	3.251	0.777	0.598
F2	0.529	0.327	0.317	0.755	0.403	3.510	0.747	0.612
F3	0.522	0.350	0.266	0.702	0.397	3.750	0.728	0.608
F4	0.524	0.400	0.283	0.599	0.399	4.280	0.713	0.602
F5	0.527	0.373	0.283	0.651	0.402	3.997	0.796	0.638
F6	0.532	0.358	0.297	0.684	0.406	3.844	0.775	0.626

Figure 1: comparative dissolution profile of aspirin delayed release tablets.

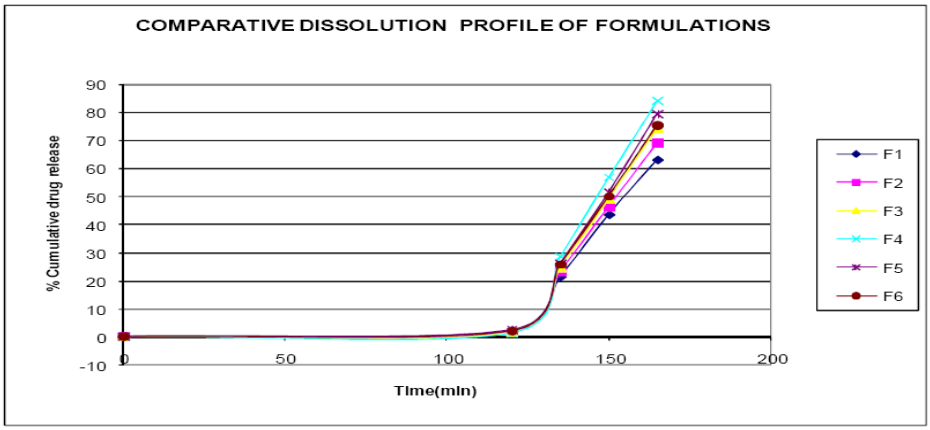


Figure 2: Infrared spectrum of pure aspirin

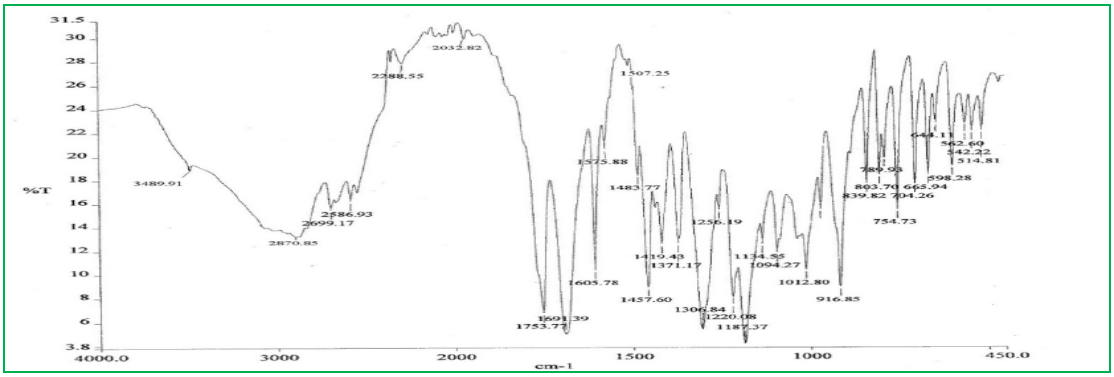


Figure 3: Infrared spectrum of Drug coat-N-100

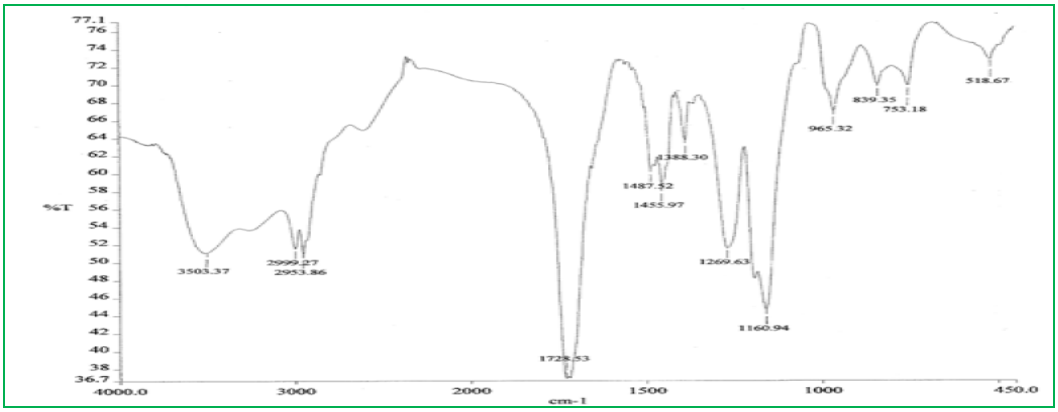


Figure 4: Infrared spectrum of HPMC-Phthalate

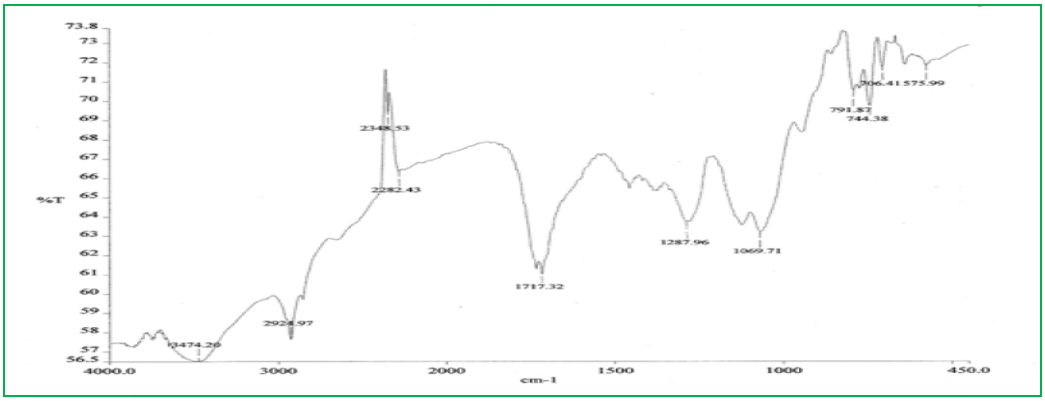
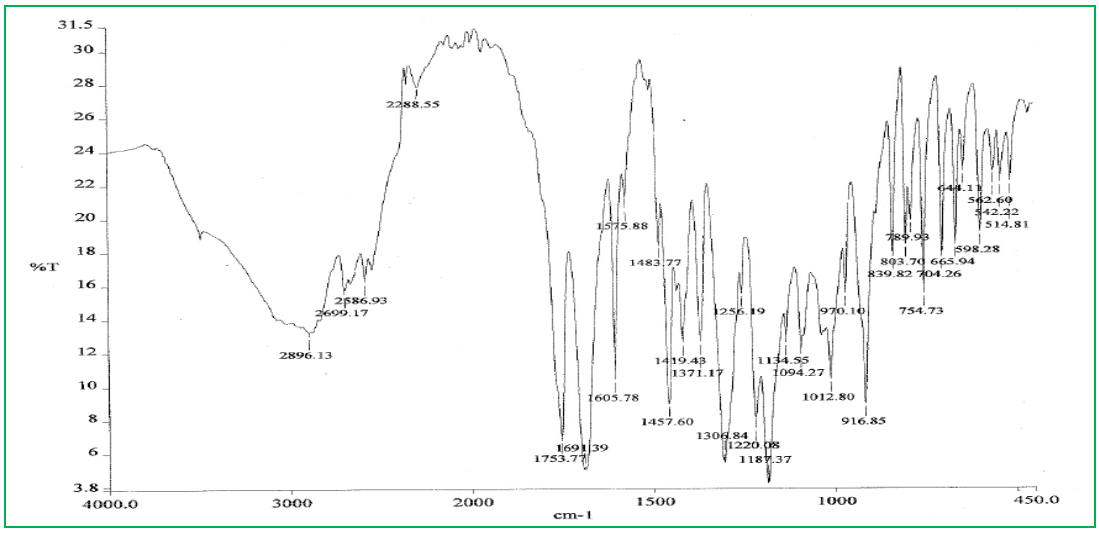


Figure 5: Infrared spectrum of Aspirin with enteric polymers



RESULTS AND DISCUSSION

Delayed release tablets, each containing 100 mg of Aspirin were prepared using Drug coat N-100 and Hydroxypropylmethylcellulose phthalate (HPMCP) as enteric coating polymers. Drug coat N-100: HPMCP ratios viz. 10:0, 8:2, 6:4, 5:5, 2:8 and 0:10 shown in table 1. Different tablet formulations were prepared by direct compression technique and the formulations were named as F-1, F-2, F-3, F-4, F-5 andF-6 respectively. Flow properties of the powder, resistance to particle to particle movement can be judged by using angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external load as might be applied in mixing and tablet compression. Values for the angle of repose were found in the range of 24.2° – 25.93°

The compressibility falls in the range of 27.05 to 30.36%. Hence prepared blends showed good flow properties. All the tablets were prepared under similar conditions and all the formulations have all the required qualities. The values of pre-compression parameters evaluated were found to be within prescribed limits indicating good flow properties shown in table 2. The data obtained for post compression parameters such as weight variation, friability, hardness, are shown in Table 3. Hardness was found to be in the range of 6-8kg/cm2 in all the formulations indicating good mechanical strength. In all the formulations the friability value is less than 1% giving an indication that tablets formulated are mechanically stable values are shown in table 3. To know the mechanism of drug release from these formulations, the data were treated using zero order, first order, Higuchi plot, and Korsmeyer Peppa's plot the values were shown in table 4. The kinetic plots were perfectly fitting to the formulated Delayed release tablets. Infrared Spectrum of Aspirin Pure drug, Infrared Spectrum of Drug coat N-100, Infrared Spectrum of HPMC-Phthalate, Infrared Spectrum of aspirin with combination of enteric polymers were shown in fig. 2, 3, 4 and 5. The graphs indicate there are no negative interactions between drug and enteric polymer material used. % weight variation was within the limits.

Drug content was known by performing assay and it was found to be between 90% to 110% and it was within the limits (shown in table 3). The dissolution of F1, F2, F3, F4, F5, and F6 showed % drug release of 63.33%, 69.15%, 74.43%, 84.23%, 79.72%, and 75.76% respectively at the end of 45 min in the phosphate buffer. The present work was made to develop delayed release tablets containing aspirin tablets. F4 batch was considered to be the best enteric formula it shows 84.23% drug release at end of 45 min in the phosphate buffer and further studies can be carried out and finally ready to be marketed.

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