Preparation and Evaluation of Delayed - Release Microparticles of Flurbiprofen

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Delayed release microparticles of flurbiprofen were formulated using an enteric polymer, cellulose acetate phthalate. The effects of various other modern enteric polymers such as hydroxypropylmethylcellulose phthalate, Eudragit L-100 and Eudragit S - 100 on the release of flurbiprofen from the CAP microparticles have been evaluated. *In vitro* release profile of flurbiprofen from microparticles showed delayed release property and concentration-dependent release. A plot of $(1-M_t/M)^{1/3}$ versus time showed linear relationship, which indicated that the drug release occurs by erosion. The study was designed in the form of a factorial design in which the effects of hydroxypropylmethylcellulose phthalate, Eudragit L-100 and Eudragit S-100 on the release rate of CAP based delayed release microparticles were calculated by using two way analysis of variance test. The results revealed that the hydroxypropylmethylcellulose phthalate exhibits positive influence whereas Eudragit L 1— and Eudragit S-100 exhibit negative effect on the drug release rate of CAP microparticles. An I.R. spectral study proved that the integrity of the drug remained unaffected in the formulation.

Flurbiprofen is an effective non-steroidal anti-inflammatory drug (NSAID), used in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gauty arthritis. It is also used as analgesic for acute tendinitis and bursitis and also for primary dysmenorrhoea[1]. The most frequent adverse side effects occurring with flurbiprofen are gastrointestinal disturbances, peptic ulceration and gastrointestinal bleeding, hence there is a potential need for an enteric coated dosage form for this drug to minimise gastric erosion side effect. It's biological half life on the other hand, is very short[2], sustaining its anti-inflammatory activity only for a few hours. Therefore, there is a need for a sustained release dosage form also, to prolong the duration of its action. The objective of the present study was to formulate a delayed release microparticular dosage form of flurbiprofen.

Flurbiprofen was obtained from Knoll Pharmaceuticals Ltd., Mumbai Cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate were procured from Tablets India Ltd., Eudragit L - 100 and Eudragit S - 100 were supplied by Sun Pharmaceuticals Ltd.

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Flurbiprofen microparticles were prepared by dissolving the drug (0.3 g) in a 10% w/v solution of cellulose acetate phthalate (in acetone:methanol 8:2 solvent mixture). The solution was then emulsified into liquid paraffin, the system was stirred continuously and the solvent was allowed to evaporate at room temperature. The microparticles were collected by filtration, washed with n-hexane and dried at room temperature.

Eight different batches were formulated according to factorial design[3] and their composition is presented in Table - 1. The morphology of the microparticles was examined by scanning electron microscopy. Size analysis study was carried out by sieving method to determine the size distribution of microparticles. The drug content in microparticles was determined (by taking three samples from each batch) and the entrapment efficiency was calculated.

In vitro release profile of flurbiprofen from microparticles was examined in pH 1.2 buffer from 0 to 2 h and in phosphate buffer of pH 7.2 from 2 to 8 h by rotating basket method specified in USP XXI at 100 rpm. Microparticles equivalent to 80 mg of flurbiprofen were accurately weighed and filled into a hard gelatin shell

TABLE 1 : COMPOSITION AND PHYSICO CHEMICAL PROPERTIES OF DIFFERENT BATCHES OF DELAYED RELEASE FLURBIPROFEN MICROPARTICLES

| Formulation Code | Composition | | | | | Angle of Repose | Drug content per 50 mg Formulation (mg) | Percentage of Drug Entrapped |
	Drug (mg)	CAP[a] (mg)	HP[b] (mg)	Eud L-100[c] (mg)	Eud S-100[d] (mg)			
F$_1$	300	1000	-	-	-	23°30'	8.9±0.21	77.39
F$_2$	300	800	200	-	-	21°29'	8.7±0.14	75.65
F$_3$	300	800	-	200	-	21°17'	11.1±0.18	96.52
F$_4$	300	800	-	-	200	22°20'	9.1±0.74	79.13
F$_5$	300	800	100	100	-	29°24'	10.7±0.52	93.04
F$_6$	300	800	-	100	100	21°29'	9.7±0.37	84.34
F$_7$	300	800	100	-	100	21°03'	10.9±0.96	94.78
F$_8$	300	800	66.66	66.66	66.66	23°09'	10.5±0.34	91.30

a) cellulose acetate phthalate, b) hydroxypropylmethylcellulose phthalate, c) Eudragit L 100, D) Eudragit S-100.

and placed in the basket. At appropriate intervals, 5 ml samples were withdrawn. The same volume of fresh test fluid was added to test medium to maintain the original volume. The samples were then analyzed at 247 nm spectrophotometrically.

In order to check the integrity of the drug in the formulation, I.R. Spectral of the pure drug and that of formulation were taken and compared.

The microparticles of all batches were found to be discrete, spherical and free flowing. Size analysis using log probability plot showed that the size distribution was log normal in all batches. The drug content analysis showed that the distribution of drug within every batch of microparticles is uniform, as it is evidenced by the least standard deviation values (Table - 1). The percentage of drug entrapped in the microparticles ranges from 75.7% to 96.5% among the eight different formulations (Table - 1).

The in vitro release data have been plotted according to the following modes of data treatment, cumulative per cent drug release vs. time, log of cumulative drug retained vs. time and erosion plot of $(1-M_t/M)^{1/3}$ vs. time. Figure 1 shows the drug release pattern of microparticles prepared with CAP and other enteric polymers. It is evident from the figure that all formulations showed delayed

release property. The drug release in the acidic medium was found to be negligible. The drug release in the alkaline medium, which simulated intestinal pH conditions was found to be sustained.

The in vitro drug release from all formulations was found to follow first order release kinetics. The linearity of the first order plots was assessed by correlation coefficient values. (Table - 2). The delayed release microparticles formulated in this study contain drug dissolved in a polymer matrix which is soluble in the dissolution medium (pH 7.2). This device may be considered as bioerodible device.

A simple expression describing release from such formulation has been described by Hopfenberg[4].

$$\frac{M_t}{M} = 1 - \left[1 - \frac{k_o t}{C_o a}\right]$$

where

M_t is mass of drug released at time 't'; M is mass released at infinite time ; and 'a' is radius of microsphere

For the purpose of data treatment, the equation can be reduced to:

$$1 - \frac{M_t}{M} = (1 - k t)^3$$

TABLE 2 : *IN VITRO* DRUG RELEASE DATA

Formulation Code	Cumulative percentage of drug released In acidic medium (pH 1.2)	Cumulative percentage of drug released In alkaline medium (pH 7.2)	Coefficient of correlation for first order kinetic model	Rate of Drug release (Percentage per hour)	Coefficient of correlation for Erosion plot	Rate of Erosion (Percentage per hour)
F_1	2.29±0.88	84.6±0.59	-0.9856	0.3595	-0.9907	0.0863
F_2	0.906±0.082	98.06±0.275	-0.9546	0.7289	-0.9899	0.1755
F_3	0.404±0.033	92.55±0.104	-0.9796	0.5096	-0.9778	0.1489
F_4	1.236±0.757	80.17±0.265	-0.9196	0.3107	-0.9787	0.0821
F_5	0.575±0.299	83.25±0.844	-0.9840	0.3480	-0.9903	0.0849
F_6	1.354±0.049	56.55±0.683	-0.9954	0.1472	-0.9933	0.042
F_7	0.306±0.049	69.4±0.520	-0.9974	0.2154	-0.9946	0.0576
F_8	2.304±.179	76.71±0.570	-0.9794	0.2434	-0.9870	0.0632

where, k is rate of erosion $\left[k = \dfrac{k_o}{C_o a} \right]$

$$\left[1 - \dfrac{M_t}{M} \right]^{1/3} = (1 - k\,t)$$

The plot of $(1-M_t/M)^{1/3}$ versus time was found to be linear for all the eight formulations, that indicates the drug release occurs mainly by erosion. The linearity of the erosion plots was assessed by correlation coefficient values (Table - 2).

The I.R. spectrum of formulation (F_8) was found to have the characteristic absorption bands as that of the I.R. Spectrum of pure flurbiprofen. (C-F-stretching band at 1127 ; C=O stretching band at 1898; O-H bending and C-O stretching at 1216 cm⁻¹ etc.,) This has proved that the drug was not chemically altered in the formulations.

In order to determine the influence of hydroxypropylmethylcellulose phthalate, Eudragit L-100 and Eudragit S-100 on drug release rate, factorial calculations were performed. The drug release rate values were tabulated in a standard order and the effect of each polymer on drug release rate were calculated by the standard method[3]. The results obtained for hydroxypropylmethylcellulose phthalate, Eudragit L-100 and Eudragit S-100 are +0.0403, -0.1033 and -0.2592, respectively. Hence, it was concluded that hydroxypropyl-
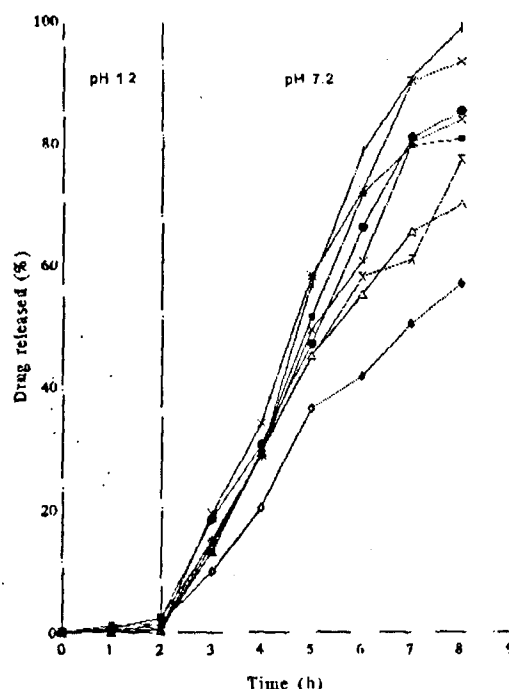

Fig. 1 : Release Profiles of Flurbiprofen

Release profiles of flurbiprofen from formulation F_1(—●—), F_2(+), F_3(—●—), F_4(—■—), F_5(—●—), F_6(—◆—), F_7(—△—) and F_8(-⦻-).

methylcellulose phthalate has an increasing effect on drug release rate, whereas Eudragit L 100 Eudragit S - 100 have decreasing effect on drug release rate. Among

the eight formulations, the formulation F_2 was considered best because, it showed delayed release and the drug release in pH 7.2 buffer was found to be almost complete (98.06%) and sustained.

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Synergestic Action of Maltose and Dextran on Extracellular Dextranase Production

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Maltose along with dextran provides a synergestic action on dextranase production by *Penicillium lilacinum*. Compared to dextran alone, dextran with maltose did not only improve the productivity and check the autolysis of cells but also cut down the period of maximum production of dextranase by two days.

Dextranase, the specific enzyme for degrading the α-1,6-glucosidic linkages in dextran (a microbiologicallly produced high molecular weight polysaccharide) is useful in medicine[1,2] and in industry[3]. In view of the potential uses of dextranase in medicine as a means for degrading dextran to molecular size-range suitable for use as synthetic blood volume expander and other useful purposes, studies on dextranase producing organisms and other parameters including different carbon sources had been performed and reported[4]. Of all organisms, *P. lilacinum* gave the maximum dextranase production in shaking condition on the 5th day at 26±2°, while maximum growth was observed on the 3rd day after which autolysis of cells would start. Among all carbon sources, only maltose other than dextran, produced dextranase in very low yield. Keeping in mind the lysis of cells and

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maltose-induced dextranse production, the present work was undertaken to investigate the synergestic action of maltose and dextran on dextranase production and other related aspects.

The *Penicillium lilacinum* (NRRL-895) strain was obtained from Common Wealth Mycological Institute, Kew, England. Dextran was a gift from Tata Fison Industries, Calcutta, India as 6% (w/v) dextran in saline. O-Toluidine was obtained from S.D. Fine Chemicals Pvt. Ltd., Mumbai, India. Maltose was procured from Merck, West Germany. All other chemicals used were standard laboratory reagents of analytical grade.

One millilitre of spore suspension (in sterile distilled water containing approximately 7x10⁷ spores/ml) from a seven day old potato corrot-agar slants was used to inoculate 50 ml of the media (0.5% dextran, 0.08% $MgSO_4$, $7H_2O$, 1.2% KH_2PO_4, 0.04% KCl, 0.05% $CaCl_2.2H_2O$,