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Naproxen-Eudragit microspheres: screening of process and formulation variables for the preparation of extended release tablets

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The objectives of the present study were to screen the formulation and process variables for the preparation of extended release naproxen tablets with Eudragit L100-55. The tablets were prepared by compression of microspheres that were obtained by a coprecipitation technique. The process involved dissolution of naproxen and Eudragit L 100-55 in alcohol USP followed by the addition of an aqueous solution containing a surfactant and deaggregating agents. The mixture was stirred for a specified time period to obtain microspheres, which were filtered and air-dried to a constant weight. The microspheres were then compressed to obtain plain tablets with a diameter of 12 mm. A 7-factor 12-run Plackett-Burman screening design was employed to evaluate the main effects of homogenization time (X1), rate of water addition (X2), amount of polymer (X3), amount of precipitating solution (X4), concentration of electrolytes (X5), compression pressure (X6), and the concentration of lubricant (X7) on the rate of drug release. The response variable was cumulative percent of naproxen dissolved in 12 h in simulated intestinal fluid with constraints on responses that included percent yield, hardness, thickness, and the angle of repose. Mathematical relationship for percent of naproxen dissolved in 12 h (Y5) with various factors yielded the following polynomial equation; Y5 (% dissolved in 12 h) $= 95.48 + 0.53\ X_1 + 3.51\ X_2 + 3.84\ X_3 - 3.80\ X_4 - 2.46\ X_5 - 2.90\ X_6 - 3.91\ X_7$. The results showed that all the seven factors affected, with varying order, the release of naproxen from its compressed tablets.

1. Introduction

Naproxen is a potent non-steroidal anti-inflammatory drug (NSAID), used in the treatment of rheumatoid arthritis, osteoarthritis, acute gout and as analgesic and antipyretic. However its use is frequently limited because of significant gastrointestinal side effects. Aabakken et al. have reported the gastroduodenal side effects of two forms of oral naproxen formulations through endoscopic findings [1]. Long acting naproxen formulations in polyorganophosphazene microspheres were tested for *in vitro* and *in vivo* drug release [2]. The *in vitro* naproxen release from microspheres prepared by spray drying was very rapid (2 h), independently of the polymer used and the amount of entrapped drug. On the other hand, the release from microspheres prepared by solvent evaporation was slow and was related to drug loading and polymer composition. The present investigation was directed towards the development of sustained release tablets of naproxen by compressing its microspheres with Eudragit polymer L100-55. Coprecipitation technique reported by Simonelli et al. [3] and Khan et al. [4] was used to prepare indomethacin micromatrices. Coprecipitates of poorly water soluble drugs have been extensively studied to improve their dissolution and bioavailability [4–6]. However, the recent trend is to modify this technique to sustain the release of therapeutic agents [7–10]. The method of microsphere preparation involves the solubilization of drug and polymer mixture in an organic solvent and adding a non-solvent with agitation. The product obtained is filtered and dried. Coprecipitate of ibuprofen using different acrylate polymers have been prepared and characterized [11]. In the present study naproxen was used as a model drug as it has a short half life, gastrointestinal effects, is soluble in alcohol and practically insoluble in water. Eudragit L100-55 was used as it yields microspheres without any need of additives. The micromatrices obtained may have different water permeability due to changes in pore size and structure of polymers separated during their manufacturing [12]. Factors such as stirring speed, the solvent and non-solvent used, drug-polymer ratio and compression pressure should be evaluated to control these properties. These factors could provide information helpful in defining conditions for the design and production of microspheres with oral sustained release properties. Statistical experimental designs are frequently used in developing micromatrices and studying the formulation and process variables on its characteristics. Screening designs help in identifying important factors that affect the final product. Factors not significant can be fixed or eliminated in further optimization experiments. In the present investigation, 12-run Plackett-Burman screening design (Tables 1, 2) was employed to evaluate the main effects of homogenization time, rate of water addition, amount of polymer, amount of precipitating solution, concentration of electrolytes, compression pressure and concentration of lubricant on cumulative percent of naproxen dissolved in 12 h in simulated intestinal fluid.

2. Investigations, results and discussion

The observed properties of microspheres and the compressed tablets are shown in Table 3. As shown in the Table, the hardness ranged from 2.25 to 10 kp suggesting that tablets of appropriate hardness (4–8 kp) could be obtained without the need of any binder. Similarly the thickness range was found to be 3.6 to 5.59 mm, angle of repose range was found to be 29.05 to 36.87, and the percent yield of the drug in microspheres was found to be between 72.73 to 99.87. These results suggest that by a careful evaluation of process and formulation variables,

Table 1: Factors in the Plackett-Burman screening design

Independent Factors
X1 = homogenization time (min.)
X2 = Rate of addition of water (ml/min)
X3 = Polymer : Drug ratio (Eudragit L100-55 : Naproxen)
X4 = Amount of precipitating water (ml)
X5 = Concentration of electrolyte (%)
X6 = Compression pressure (kg)
X7 = Concentration of lubricant (%)

Table 2: Plackett-Burman screening design with seven variables (randomized runs)

Form	X1	X2	X3	X4	X5	X6	X7
1	8	200	1.5	150	1.5	1500	1
2	8	50	3	150	1.5	500	1
3	4	200	3	150	0.5	500	1
4	8	200	3	50	0.5	500	3
5	8	200	1.5	50	0.5	1500	1
6	8	50	1.5	50	1.5	500	3
7	4	50	1.5	150	0.5	1500	3
8	4	50	3	50	1.5	1500	1
9	4	200	1.5	150	1.5	500	3
10	8	50	3	150	0.5	1500	3
11	4	200	3	50	1.5	1500	3
12	4	50	1.5	50	0.5	500	1

suitable tablets can be obtained from the microspheres. However, it is important that they have suitable drug release characteristics.

The dissolution profiles of formulations 1–6 and 7–12 are shown in Figs. 1 and 2 respectively. As shown in these figures, the dissolution range at the end of 12 h was found to be 82% (formulation 7) to complete dissolution (formulations 2, 3, 4, and 5). Other formulations had the dissolution between 82 and 100%.

Table 3: Properties of naproxen tablets and microspheres

Form	Thickness	Hardness	Angle of repose	% Yield
1	3.6	10	35.54	99.63
2	4.58	2.25	33.11	86.99
3	5.59	7.5	35.54	72.73
4	5.59	5	34.22	73.32
5	4.35	10.5	29.05	81.86
6	4.22	3.5	34.29	96.14
7	3.7	10	36.87	99.22
8	4.57	9	35.311	78.21
9	4.1	8.5	30.96	97.8
10	4.17	7	35.54	88.79
11	4.63	8	34.215	78.64
12	4.1	6	36.87	99.87

Table 4: Analysis of variance for Y5

Source	Df	SS	MS	F-Ratio
Total (corrected)	11	902		
Regression	7	858.8	122	11.36
Residual	4	43.22	10.8	

Standard deviation about the regression = 3.287
Explained variation about the mean = 95.2
Confidence that the regression equation predicts the observed values better than the mean = 98.3

Table 5: Observed and predicted values of the response (Y5)

Form	Observed (h)	Predicted (h)	Residuals
1	87.67	90.43	−2.76
2	99.36	96.92	2.44
3	107.7	107.78	−0.08
4	108.8	108.61	0.19
5	105.7	102.94	2.76
6	88.92	89.00	−0.08
7	81.99	79.44	2.55
8	98.16	97.65	0.51
9	87.74	87.34	0.40
10	85.65	88.20	−2.55
11	96.32	96.83	−0.51
12	97.79	100.67	−2.88

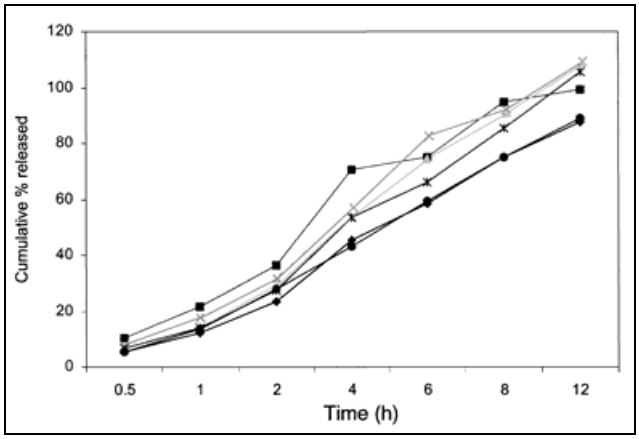

Fig. 1: Dissolution profile of naproxen microsphere tablet formulations in pH 7.5 phosphate buffer media. (◆) ms1, (■) ms2, (▲) ms3, (×) ms4, (*) ms5 and (●) ms6

In order to understand the relationship between dependent (Y1 to Y5) and independent (X1 to X7) variables, a polynomial equation was obtained for Y5. This equation is: $Y5 = 95.48 + 0.53\ X_1 + 3.51\ X_2 + 3.84\ X_3 - 3.80\ X_4 - 2.46\ X_5 - 2.90\ X_6 - 3.91\ X_7$. The regression coefficient obtained for Y5 was 0.95 and the analysis of variance of the model parameters are shown in Table 4. The test indicated a significant ($P < 0.05$) effect of factors on responses [F_{model} ($11.36 > F_{crit}$ (6.09)]. By inserting the values of X1 and X7 in the polynomial equation, predicted values of Y5 for all the 12 experiments could be obtained. The observed and predicted values are shown in Table 5, which are found to be in close agreement. The magnitude and direction of each significant effect can be estimated from the model independently of each other by averaging all the differences of responses with high factor values and low factor values for every factor from X1 to X7.

The main effects of all the independent variables are shown in Table 6. A positive value denotes an increase in dissolution with an increase in factor and a negative value denotes an increase in dissolution with a decrease in the factor. Therefore, the factors, X1 through X3 have a positive influence on Y5 whereas the factors X4 through X7 have a negative influence.

From these results it can seen that the lubricant concentration (X7) has inverse effect on the response (Y5). This

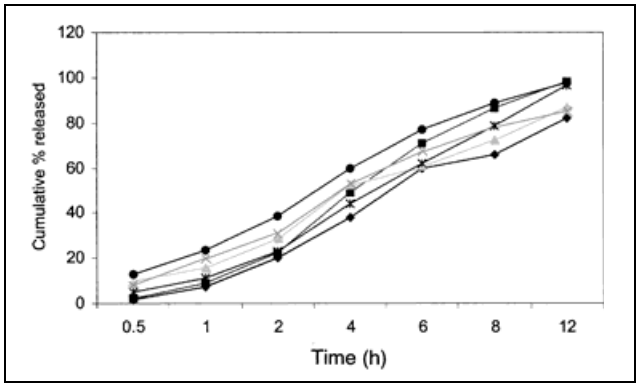

Fig. 2: Dissolution profile of naproxen microsphere tablet formulations in pH 7.5 phosphate buffer media. (◆)ms7, (■)ms8, (▲)ms9, (x)ms10, (*)ms11 and (●)ms12

Table 6: Magnitude and direction of the variables on the response Y5

Factors	Main Effects (Y5)
X1	1.18
X2	7.02
X3	7.7
X4	−7.61
X5	−4.91
X6	−5.8
X7	−7.82

could be explained by the fact that the hydrophobic nature of magnesium stearate which form a layer on the outer surface of the tablet fills the pores which may present, and create a difficulty for the dissolution medium to penetrate the tablet and dissolve the drug. On the other hand, increasing the polymer concentration (X3) increased the amount of drug released after 12 h. This may be due to the chemical nature of Eudragit L100-55 and the method of its preparation. Eudragit L100-55 contains a high percent of methacrylic acid (46–50.6%) which increases its solubility in water above pH 5.5, and it is prepared by spray drying of Eudragit L 30D-55 and contains emulsifiers [13]. These characters increase the wettability and encourage the dissolution of naproxen tablet. Also it was observed that an increase in the amount of precipitating water decreased the amount of drug released after 12 h. This is because the increase in solubility of drug increased the amount of drug escaped during filtration. This explanation is supported by the results showing the effect of rate of water addition (X2) on the release. Increasing the rate of addition (decreasing the time of addition) is followed by rapid precipitation of polymer encapsulating the drug, meanwhile increasing the concentration of drug inside the microspheres which appear later in the dissolution medium. From Table 6, it can also be seen that increasing the compression pressure (X6) decreased the amount of drug released after 12 h. These results are not surprising because increasing the force of compression may destroys the matrix structure and form hard compact mass which delay or may even hinder the release of drug. The electrolyte concentration (X5) showed inverse effect on Y5. The reasons are not clear but it may be due to efficient microsphere formation and increased compressibility of the formulation. The least effect on Y5 was observed with the homogenization time. Increasing the homogenization time increased the shear on the micromatrices which results in higher Y5 value.

In conclusion controlled release naproxen microspheres have been formulated by using a simple and practical technique that eliminated the use of toxic organic solvents or heating to prepare extended release preparations. The naproxen microspheres showed good flowability and drug-loading efficiency, and were successfully compressed to obtain tablets of acceptable hardness, thickness and dissolution behavior.

All the seven factors affected the release of naproxen tablets obtained from the microspheres of naproxen : Eudragit L100-55 coprecipitates. The main effects decreased in the order, lubricant concentration $(-7.82) >$ Eudragit L100-55 : drug ratio $(7.70) >$ amount of precipitating water $(-7.61) >$ rate of addition of water $(7.02) >$ compression pressure $(-5.8) >$ concentration of electrolyte $(-4.91) >$ homogenization time (1.18). Out of these seven factors, two or three most significant factors can be judiciously used in a further optimization study with quadratic response surfaces to obtain naproxen controlled release tablets with predicted drug release profiles. The quadratic response surface methodology will also help in the understanding of interaction effect between the variables.

3. Experimental

3.1. Chemicals

Naproxen was purchased from Sigma chemicals, and Eudragit L100-55 was gift from Röhm Pharma (Weiterstadt, Germany). Alcohol and other chemicals were used as received. Water used was deionized and distilled.

3.2. Screening design

Preliminary range finding experiments were carried out before developing the screening design. Observations obtained helped in deciding the factors and their levels in the design to allow production of microspheres with predicted responses. The formulation and process variables studied on the responses are shown in Table 1. A seven-factor twelve run Plackett-Burman screening design at two levels was set up (Table 2) using X.STAT® statistical experiment design software.

3.3. Preparation of microspheres

Batches were prepared with the formulation and process variables as per the Plackett-Burman design (Table 2). For each batch, the amount of naproxen was fixed at six grams. All the Eudragit L100-55 (as per the design) was completely dissolved in alcohol USP. To the alcoholic solution, six grams of naproxen was added and dispersed uniformly by using magnetic stirrer. To the alcoholic dispersion, a predetermined amount of water (as per the design) maintained at 4 °C containing 0.25% Tween 20 and $CaCl_2$ (X5) as deaggregating agent was added. Water addition was at specific rate (X2) under constant stirring speed for specific homogenization time (X1) using a PRO 250 homogenizer (Monroe, CT USA). The resultant microspheres were filtered using Buchner funnel with Whatman #4 qualitative filter paper and vacuum pump if necessary. The microspheres remaining on the filter paper were collected and dried at 40 °C for 24 h. The dried microspheres were then passed through #20 mesh.

3.4. Drug loading efficiency

An accurately weighed microsphere sample (30–50 mg) was dissolved in phosphate buffer solution (pH 7.5), sonicated for 30 min and assayed spectrophotometrically for naproxen at 332 nm. The polymer and other additives did not interfere at this wavelength. The drug concentration was calculated and expressed as % yield value. The yield value was obtained by the formula,

$$\% \text{ yield value} = \frac{\text{weight of dissolved drug in ms sample X 100}}{\text{weight of theoretical drug in the sample}}$$

3.5. Angle of repose measurement

This was carried out for different batches of microspheres by obtaining the Tan of the angle formed by a heap of powder with the table surface after dropping from a funnel.

3.6. Preparation of tablets

Microspheres corresponding to 500 mg in weight of naproxen were mixed with magnesium stearate (X7) as lubricant and compressed with 12 mm standard plain punches using a Carver press at specified compression pressure, (X6) as shown in Table 2. The Carver press used (model C, Carver, Inc., USA) was attached to a semiautomatic compression assembly (model 2826, Carver, Inc., Wabash, Indiana USA). The dwell time used for compression was 3 s.

3.7. Dissolution studies

Dissolution experiments were performed using 900 ml of phosphate buffer pH 7.5 in dissolution beakers maintained at 37 ± 1 °C and stirred at 50 rpm using an automated dissolution apparatus (Vankel VK7000 with an autosampler VK8000. Vankel Industries, Inc., Cary NC). The dissolution system was programmed to collect 5 ml samples automatically through full flow filters (Vankel Industries) at specified time intervals for 12 h. The samples collected were analyzed spectrophotometrically at 332 nm to obtain the cumulative percent of naproxen dissolved. All the experiments were performed in duplicate.

3.8. Hardness and thickness measurements

The compressed tablets were tested for their hardness and thickness using Stokes hardness-tester and Dial thickness gauge (Lux Scientific instrument Corp., Japan), respectively. The experiments were performed in duplicate.

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