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Studies in Formulation of Orodispersible Tablets of Rofecoxib

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Orodispersible tablets are better choice for the pediatric and geriatric patients. Present study demonstrates the use of factorial design in the formulation of orodispersible tablets of rofecoxib. Preliminary screening of three superdisintegrants namely sodium starch glycolate, crospovidone and croscarmellose sodium was carried out (batches AA1 to AA9) and crospovidone was found most effective giving lowest disintegration time and wetting time. Batches AA10 to AA12 were prepared to optimize the amount of crospovidone and the optimum concentration of crospovidone was found to be around 10%. Mannitol was incorporated as a diluent to improve palatability and to impart sweet taste as well as to keep the tablet weight (100 mg) constant in all the batches. From the preliminary results, a 3^2 full factorial design was employed for preparation of tablets possessing optimized characteristics (batches AA13 to AA21). The percentage of crospovidone (X_1) and mannitol (X_2) were selected as independent variables. Wetting time and disintegration time were selected as dependent variables (response; Y). Full and refined models were derived for the prediction of the response variable Y. Based on the results of multiple linear regression analysis, it was concluded that lower disintegration time and wetting time could be obtained when X1 is kept at high level and X2 is kept at low level. Promising batch (batch AA18) was compared with two marketed samples (brand A and B) of rofecoxib tablets for *in vitro* drug release after 30 min in three dissolution media. Tablets of batch AA18 exhibited better drug dissolution after 30 min than the tablets of brand A and B in all the dissolution media.

Tablets hold premier position among all dosage forms. Elderly persons have poor physiological and physical abilities due to increase in age. Hence, many elderly persons will have difficulties in taking conventional oral dosage forms such as solutions, suspensions, tablets, and capsules because of hand tremors and dysphagia. Young individuals suffering from under-developed muscular and nervous systems have problem of swallowing. It is difficult to administer tablets or capsules to patients who are uncooperative, on reduced liquid-intake plans or are nauseated. To overcome these problems, mouth dissolving tablets or dispersible tablets are good option. Since, they disintegrate and dissolve rapidly in saliva without the need for drinking water. The development of a fast-dissolving tablet also provides an opportunity for a line extension in the marketplace. A wide range of drugs (neuroleptics, cardiovascular drugs, analgesics, antihistamines, and drugs for erectile dysfunction) can be considered candidates for this dosage form. Fast dispersing tablets are prepared by technique like tablet molding[1], spray drying[2], lyophilization[3], sublimation[4] or addition of disintegrants[5]. Some of the patented technologies for preparation of fast dissolving tablets are, Zydis[6,7], OraSolv[8], DuraSolv[8], Flash Dose[7], Wowtab[9] (With Out Water) and Flashtab[10].

Rofecoxib is a non-steroidal antiinflammatory, water insoluble, tasteless drug. Hence, it was selected as a model drug for the preparation of orodispersible tablets. In the present study solid deposition method on disintegrant was

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adopted. Disintegrant also helps in dispersing the drug particles. To impart mouth feel mannitol was selected as a diluent due to its negative heat of solubilization. Present work was undertaken to study the effect of variables on the characteristics of orodispersible tablets utilizing the factorial design.

MATERIALS AND METHODS

Rofecoxib, sodium starch glycolate (Primogel; SSG), crospovidone (Polyplasdone XL; CRP), croscarmellose sodium (Ac-Di-Sol; CCS), mannitol (Perlitol), and sodium lauryl sulphate (SLS) were received as gift samples form Zydus Cadila Healthcare Ltd., Ahmedabad. All the other reagents were of pharmaceutical grade and were used as received.

Selection of superdisintegrant:

Preliminary study was carried out for screening of three superdisintegrants namely sodium starch glycolate (SSG), crospovidone (CRP) and croscarmellose sodium (CCS). Mannitol was incorporated as a diluent to improve palatability and to impart sweet taste as well as to keep the tablet weight (100 mg) constant in all the batches.

Granulation:

Granulation was carried out by solid deposition method[11]. Superdisintegrant (SSG, CRP or CCS) was mixed with mannitol. The powder blend was mixed and kneaded with purified water to obtain coherent damp mass. Rofecoxib was mixed with wet mass for 5 min. The damp mass was passed through a 40 mesh. The wet granules were dried in a hot air oven at 60° for 1 h. The dried granules were reshifted through a 40 mesh and retained on a 100 mesh. The granules (40/100 mesh) were stored in a tightly closed glass container until further use (Batch AA1 to AA12). The granulation method was kept constant for all the batches. Composition of the batches is shown in the Table 1.

Preparation of tablets:

The granules of batch AA1 to AA12 were mixed with talc (2%) for 2 min and magnesium stearate (1%) for 1 min. This blend was compressed into tablets using 8/32 inch diameter flat face round tooling on a Rimek-I rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad). Tablet weight was kept 100 mg and hardness between 2.5 and 3 kg/cm^2.

TABLE 1: COMPOSITION AND RESULTS OF BATCHES AA1 TO AA12 PREPARED FOR THE SELECTION OF DISINTEGRANT.

Batch	Disintegrant	Disintegrant (%)	Mannitol (%)	Disintegration Time (s)	Wetting Time (s)	Residue remain on screen
AA1	CCS	20	60	23.33	110	Yes
AA2	CCS	40	40	46.33	90	Yes
AA3	CCS	60	20	139.00	150	Yes
AA4	CRP	20	60	8.33	4.3	Yes
AA5	CRP	40	40	6.66	5.3	Yes
AA6	CRP	60	20	6.33	8	Yes
AA7	SSG	20	60	62.33	135	Yes
AA8	SSG	40	40	57.33	115	Yes
AA9	SSG	60	20	100.33	188	Yes
AA10	CRP	0	80	9.66	12.3	No
AA11	CRP	10	70	3.66	4	No
AA12	CRP	20	60	8.33	4.3	Yes

Note: All the batches contain 20 % w/w of Rofecoxib. Batch AA12 is repetition batch of AA4. CCS: Croscarmellose sodium, CRP: Crospovidone, SSG: Sodium starch glycolate.

The tablets were stored in tightly closed glass container and evaluated for following parameters in triplicate.

Evaluation of wetting time, disintegration time[13] and uniformity of dispersion[14] of tablets:

Filter paper was kept in a petridish (diameter 9.5 cm) containing purified water (15 ml). A tablet having small amount of amaranth powder on the upper surface was placed on the filter paper. Time require to develop red color on the upper surface of the tablet was recorded as wetting time[12]. One tablet was placed in each tube of disintegration apparatus (model ED2, Electrolab). Disintegration test[13] was carried out using distilled water as a disintegrating media at 24±2°. The tablet should disintegrate within 3 min to pass the test. Two tablets were kept in 100 ml water and gently stirred for 2 min. The dispersion was passed through 22 mesh. The tablets were considered to pass the test if no residue remained on the screen.

Optimization of formulation variables:

From the preliminary results, a 3^2 full factorial design was adopted to optimize the variables[15]. Percentage crospovidone (X_1) and % mannitol (X_2) were selected as independent variables. Wetting time and disintegration time were selected as dependent variables (response; Y). The preparation and evaluation methods for tablets and amount of rofecoxib were kept constant for all the trials as mentioned above. The composition of batches AA13 to AA21 is shown in Table 2.

***In Vitro* drug release[16,17]:**

The *in vitro* dissolution study was performed using a USP dissolution apparatus- II (model TDT-60T, Electrolab) at 100 rpm, using 1%w/v SLS in water or distilled water or isopropyl alcohol: water mixture (40:60) as a dissolution medium[18,19] maintained at 37°. Samples (5 ml) were withdrawn at 30 min, filtered through a 0.45 micron membrane filter, diluted and assayed at 237 nm using a UV/VIS double beam spectrophotometer (Shimadzu, model-1601).

RESULTS AND DISCUSSION

Batches AA1 to AA9 were prepared to select the disintegrant. From the results shown in Table 1, it can be concluded that the tablets containing crospovidone (batch AA4 to AA6) exhibit quick disintegration time and wetting time followed by tablets containing croscarmellose sodium and sodium starch glycolate. The probable reason for delayed the disintegration and wetting of the tablets might be slow water uptake or more gelling tendency of croscarmellose sodium and sodium starch glycolate than crospovidone. Hence, crospovidone was selected as a disintegrant for the further studies. Among the three batches containing crospovidone (AA4 to AA6), batch AA4 exhibited lowest disintegration time and wetting time. The tablets granules failed to separate and hence, small core remains even after wetting of the tablet. This may be due to formation of network of wetted particles of disintegrant that counteract the disintegration force. From these results it is obvious that the optimum concentration of crospovidone might be less than 20%.

Batches AA10 to AA12 were prepared to optimize the amount of crospovidone. The composition and results of batches AA10 to AA12 are shown in Table 1. Batch AA10 and AA11 exhibited decrease in disintegration time but batch AA12 exhibited increase in disintegration time. While slight increased wetting time was also noticed at 20% crospovidone than 10% crospovidone (Table 1). Hence, it can be concluded that the optimum concentration of crospovidone is around 10%.

All the tablets exhibited disintegration time between 3 and 8 sec indicating very rapid disintegration. From the results depicted in Table 2, it can be concluded that batches containing medium level of mannitol exhibits lowest disintegration time at all the concentration of crospovidone. While, batches containing higher amount of mannitol exhibited highest disintegration time in their treatment group. This might be due to competition between mannitol and crospovidone for water. The results of batches AA13 to AA21 were subjected to multiple linear regression analysis. The output of multiple linear regressions is shown as full model (Eqn. 1). The terms showing p-value greater than 0.05, were dropped to generate reduced model (Eqn. 2). The value of correlation coefficient (R^2) greater than 0.9 indicates good agreement between the dependent and independent variables. From the reduced model generated for disintegration time it can be concluded that, % of crospovidone (X_1) had negative effect while concentration of mannitol (X_2) had positive effect on disintegration time. It means that as the amount of crospovidone is increased disintegration time decreases while as the amount of mannitol is increased the disintegration time increases. So, high level of crospovidone and low level of mannitol should be selected for the rapid disintegration of the tablets.

Full model (disintegration time)$=3.22-0.58X_1+0.83X_2-0.083X_1^2+3.16X_2^2+0.25X_1X_2$ (Eqn. 1). Reduced model (disintegration time)$=3.17-0.58X_1+0.83X_2+3.16X_2^2$ (Eqn. 2).

TABLE 2: COMPOSITION AND RESULTS OF BATCHES AA13 TO AA21 PREPARED USING 3^2 FULL FACTORAL DESIGNS.

Batch	Variable Level in Coded Form		Disintegration time	Wetting time
	X_1	X_2	(s)	(s)
AA13	-1	1	8	6.33
AA14	0	1	7	6.33
AA15	1	1	6.5	5.33
AA16	-1	0	3	5.33
AA17	0	0	3	5
AA18	1	0	3.5	4.33
AA19	-1	-1	6.5	4
AA20	0	-1	6	4
AA21	1	-1	4	4
Independent Variables			Real Values	
% Crospovidone (X_1)	4		8	12
% Mannitol(X_2)	80		85	90

Tablets of batches AA13 to AA21 exhibited wetting time between 4 and 7 sec. From the results depicted in Table 2, it can be concluded that wetting time increased from low to high level of mannitol in respective treatment group. At medium to high level of factor X_2 disintegration time decreased with increase in % crospovidone. From the results of multiple linear regression analysis it can be concluded that factor X_1 has inverse effect on wetting time while factor X_2 has positive effect (Eqn. 3 and 4). High level of X_2 should not be selected for low wetting time. The value of correlation coefficient (R^2) greater than 0.9 indicates good agreement between the dependent and independent variables.

Full model (wetting time)=$5.04-0.33X_1+1.0X_2-0.22X_1^2+0.11X_2^2-0.25\ X_1X_2$ (Eqn. 3).

Reduced model (wetting time)=$4.96-0.33X_1+1.00X_2$ (Eqn. 4).

From the above discussion, batch AA18 (disintegration time 3.5 s and wetting time 4.33 s) was selected as a promising batch. It was compared with two marketed samples (brand A and B) of rofecoxib tablets for amount of *in vitro* drug release after 30 min in three different dissolution media. Three different media were selected to get discrimination in dissolution of Rofecoxib. The person good at the art of dissolution study will appreciate the selection of three different categories i.e. with surfactant (SLS), hydroalcoholic (IPA:water) and distilled water. Rofecoxib follows Lambert-Beer's law in a concentration range 1-11 μg/ml in all the

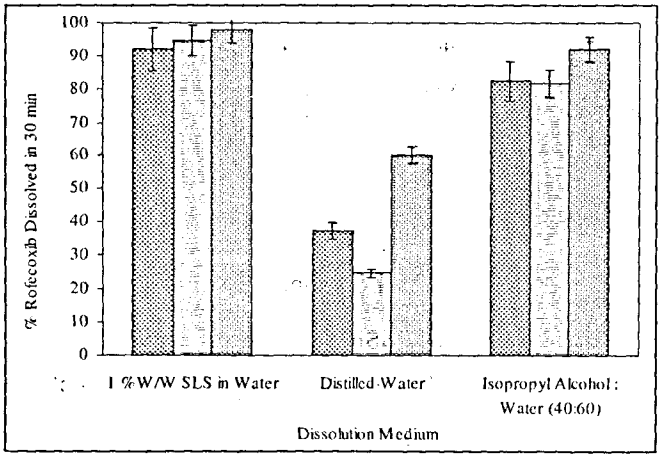

Fig. 1: Comparison of promising batch with marketed tablet samples.

Comparison of Batch AA18 ☐ with marketed tablet samples brand A ▨ and Brand B ☐ of rofecoxib for % rofecoxib dissolved in 30 min.

dissolution media. All the media exhibits good correlation (R^2 greater than 0.97). From the results shown in fig 1, it can be concluded that the tablets of batch AA18 exhibits better *in vitro* drug dissolution after 30 min than the tablets of brand A and B in all the media.

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