RESEARCH PAPER

Accepted 29 January 2005
Revised 16 August 2004
Received 20 February 2004
Indian J. Pharm. Sci., 2005, 67(1): 61-65

Various Approaches in Dissolution Enhancement of Rofecoxib

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Rofecoxib is novel cyclooxygenase-2 inhibitor, which is poorly soluble in aqueous media. The aim of present study was to improve the solubility and dissolution rate of drug by formulating its solid dispersions with various hydrophilic carriers (polyethylene glycol-6000, polyvinyl pyrrolidone K-30, Eudragit E-100) and inclusion complex with β-cyclodextrin. Drug release profile was studied in 0.1 N HCl as dissolution media. Rofecoxib forms eutectic mixture with polyethylene glycol 6000 and glass solution with polyvinyl pyrrolidone K 30 and Eudragit E 100. Polyvinyl pyrrolidone K 30 was found to be more effective in increasing the drug dissolution, when compared with polyethylene glycol 6000 and Eudragit E 100. The theoretical prediction for the use of β-cyclodextrin as a dissolution enhancing agent was performed. The dissolution was obtained as high as 75% in rofecoxib:β-cyclodextrin molar ratio of 1:5 prepared by kneading method. For further dissolution enhancement the combination of two dissolution enhancing agent i.e. polyvinyl pyrrolidone K-30 and β-cyclodextrin were used. 3^2 factorial design was conducted to optimize the proportion of both the carriers.

Rofecoxib (RCB) is a non-steroidal antiinflammatory drug (NSAID) approved for the treatment of acute pain, fever, primary dysmenorrhea, rheumatoid arthritis and related disorders. RCB is specific inhibitor of cyclooxygenase-2 (COX-2)[1]. It inhibits prostanoid synthesis in cells that express COX-2, including inflammatory cells[2,3]. As cells in gastrointestinal (GI) tract principally express COX-1, a different isoform of cyclooxygenase, it is predicted that rofecoxib will have less GI toxicity than other less selective NSAID[3-6]. RCB is practically insoluble in water. In order to reach the steady plasma concentration it takes 3-4 days along with multiple dose administration of RCB (www.rxlist.com/cgi/generic/rofecox.htm 23/09/03). The pharmacokinetic characteristic like peak plasma concentration (Cmax) is influenced by its limited aqueous solubility. The rate of absorption and extent of bioavailability of such insoluble hydrophobic drug is controlled by the rate of dissolution in GI tract. The focus of the present study was to improve the dissolution of RCB. Dissolution of drug was increased by approaches like preparation of solid dispersion and inclusion complexes. Solid dispersions were prepared by solvent evaporation, while inclusion complexes were prepared by kneading method. The carriers used in the present study for dissolution enhancement of RCB were polyethylene glycol-6000 (PEG-6000), polyvinyl pyrrolidone (PVP K-30), Eudragit E-100 and β-cyclodextrin (β-CD).

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MATERIALS AND METHODS

Rofecoxib was obtained as a gift sample from Amiya Pharmaceuticals, Mumbai. PVP K-30, PEG 6000 and lactose were obtained from Laser Industries, Ahmedabad, S. D. Fine Chemicals, Mumbai and Vikas Pharma, Ahmedabad, respectively. Eudragit E-100 was obtained as gift sample from Rohm Pharma, Germany. β-cyclodextrin was procured from Roquette, France. All the reagents used in the study were of analytical grade.

TABLE 1: COMPOSITION OF SOLID DISPERSION BATCHES (PER CAPSULE)

Drug: carrier Ratio	Drug (mg)	Carrier (mg)	Lactose (mg) QS to
1:1	25	25	300
1:3	25	75	300
1:5	25	125	300
1:7	25	175	300
1:9	25	225	300

Drug: Carrier Batch Codes: RCB: PEG-6000 - PE1 to PE5, RCB: PVP K-30 - PV1 to PV5 RCB: Eudragit E-100 - E1 to E5

Preparation of solid dispersion by solvent evaporation method:

Accurately weighed RCB and the carrier (PEG-6000, PVP K-30 or Eudragit E-100) as per the ratio shown in Table 1 were dissolved in dichloromethane. The solvent was evaporated at 60° for 2 h in hot air oven. The solid dispersion was stored for 24 h in a dessicator containing fused calcium chloride as desiccating agent. The resultant solid was pulverized and then sieved through 120 #. The powder equivalent to 25 mg RCB was weighed and lactose was mixed uniformly to obtain quantity equivalent to 300 mg. It was filled in the hard gelatin capsule (size '0') by hand filling method.

Preparation of Inclusion complexes of rofecoxib with β-cyclodextrin (β-CD) by kneading method:

The required quantity of β-CD was weighed as per ratio given in Table 2 and water was added to get dough like consistency. To the mass, weighed quantity of RCB was added. The mixture was kneaded in glass mortar for 1 h and then completely dried in hot air oven at 60° for 2 h. The dried mass was sieved through 120 #. The powder equivalent to 25 mg RCB was weighed; lactose was added to obtain quantity equal to 500 mg and filled in hard gelatin capsule (Size '00').

Solubility study of RCB: β-CD complex:

Excess amount of different RCB: β-CD molar complexes (equivalent to 25 mg of RCB) were added to series of 250 ml flakes containing 50 ml 0.1 N HCl. The suspensions were shaken in water bath at 37±0.5 ° for 24 h. The samples were filtered through 0.45 μm filter and assayed for RCB content by UV spectrophotometer.

Factorial design; an optimization technique:

To achieve complete dissolution of RCB and to optimize the concentration of PVP K-30 and β-CD when used in combination, the 3^2 factorial design was adopted. The required quantity of RCB and PVP K-30, as calculated according to Table 3, were dissolved in dichloromethane. This solution was evaporated at 60° in hot air oven. The dry mass obtained was pulverized, passed through 120 # sieve and stored in airtight container. In another petridish weighed amount of β-CD was taken and water added with mixing to make a paste. To this paste weighed amount of above solid dispersion was added. The kneading of paste was continued for 1 h. Then the paste was dried in hot air oven at 60° for 2 h, pulverized and sieved through 120 #. The powder equivalent to 25 mg RCB was weighed, mixed with lactose to make quantity equivalent to 350 mg and filled in the hard gelatin capsule (size '0').

***In vitro* dissolution study:**

Dissolution study of capsule was carried out using type I (Basket type) dissolution test apparatus USP XXIII. The 900 ml of 0.1 N HCl was used as dissolution medium maintained at 37±0.5°. The stirring speed was kept at 100 RPM. Five millilitres of sample was withdrawn at time intervals of

TABLE 2: COMPOSITION OF INCLUSION COMPLEX BATCHES OF RCB: B-CD (PER CAPSULE)

Batch no.	Drug: Carrier Ratio (molar)	Drug (mg)	Carrier (mg)	Lactose (mg) QS to
D1	1.1	25	90	500
D2	1.2	25	181	500
D3	1.3	25	271	500
D4	1.4	25	362	500
D5	1:5	25	452	500

TABLE 3: COMPOSITION OF FACTORIAL DESIGN BATCHES AND DRUG RELEASE IN 60 MIN (Q_{60})

Batch Code	Real Values		Transformed Values		Percentage Drug release after 60 min (Q_{60})
	Weight ratio of Drug: PVP	Molar ratio of β-CD with respect to drug	X1	X2	
F1	1:1	1.0	-1	-1	43.979
F2	1:3	1.0	0	-1	62.035
F3	1:5	1.0	1	-1	72.368
F4	1:1	1.5	-1	0	56.716
F5	1:3	1.5	0	0	80.362
F6	1:5	1.5	1	0	86.401
F7	1:1	2.0	-1	1	66.124
F8	1:3	2.0	0	1	85.731
F9	1:5	2.0	1	1	97.917

10, 20, 30, 40, 60, 90 and 120 min and filtered through Whatman filter paper (0.7 μ size). The volume of the dissolution fluid was adjusted by replacing 5 ml of dissolution medium after each sampling. The absorbance of the withdrawn samples was measured at 284 nm and concentration of drug was calculated using standard curve equation.

RESULTS AND DISCUSSION

Pure RCB exhibited very poor dissolution and a maximum of about 17.5 % drug was dissolved during 120 min from the capsule. The poor dissolution may be attributed to low intrinsic solubility and hydrophobicity of RCB due to its chemical nature and poor wettabilility of the particles. The dissolution enhancement by PEG is contributed to the formation of eutectic mixtures as evident from fig. 1. Eutectic mixtures are not the simple physical mixtures composed of two crystalline phases but, depending on the fusion properties and heat of fusion of the pure components they have a well defined microstructure[7,8]. Fig. 1 (RCB: PEG-1: 9 ratio) shows the presence of eutectic structure, which are lamellae radiating from a central point. As the amount of RCB increases (RCB: PEG-1:1 ratio) there was progressive appearance of the pure drug crystals that hampers dissolution. Only small increase in dissolution (fig. 2) by PEG 6000 may be explained by the high melting point and high heat of fusion of RCB, which limits the dissolution of microcrystalline drug from eutectic matrix. RCB:PVP 1:1 ratio shows the partial formation of glass solution as needle shaped drug crystals were still visible. While no such crystals were detected under microscope in R:PVP, 1:5 ratio and completely plain view was seen. Thus absolute glass solution was formed in this batch and other batches with greater polymer ratio. In case of Eudragit E 100 some RCB crystals were still visible in batch of 1:9 drug: carrier ratio. From this fact the greater drug release from PVP K 30 than Eudragit E 100 can be proposed. From fig. 3, comparing the Q_{60} of PVP and Eudragit E 100 it can be assessed that PVP have greater release than Eudragit E 100. This may be due to inheritant property of the carrier used. The enhanced dissolution rate may be due to enhanced wettability, dispersibility of drug in dissolution medium and solubilization effect by the carrier.

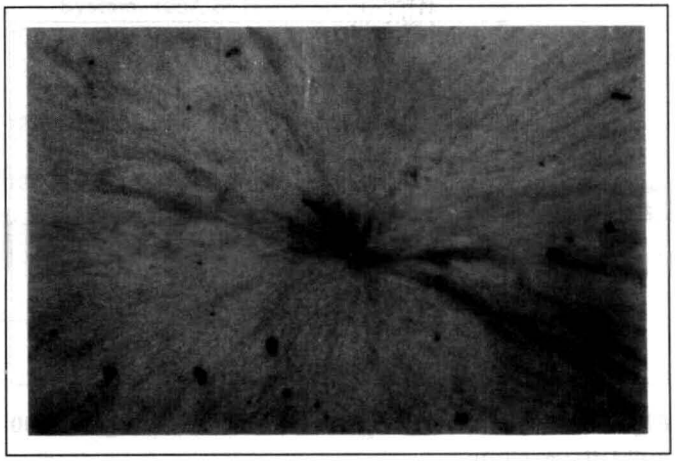

Fig. 1: Photomicrograph of RCB: PEG-6000 1:9 solid dispersion (Batch PE5) (Magnification: 150 times)

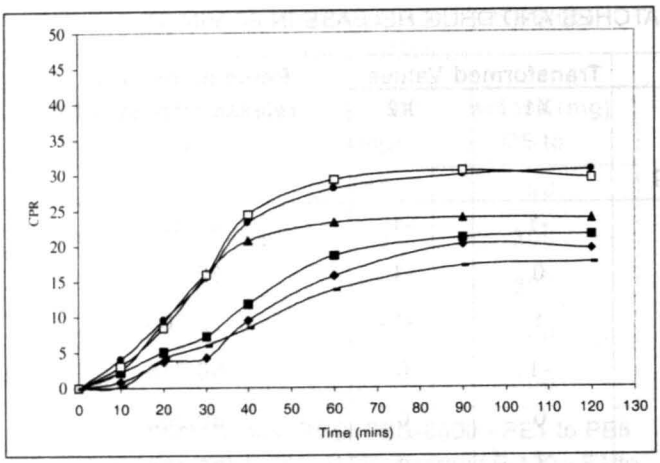

Fig. 2: Comparative *In vitro* dissolution profile of RCB: PEG 6000 solid dispersions

Pure RCB (–), Batch PE1 (◆), Batch PE2 (■), Batch PE3 (▲), Batch PE4 (●) Batch PE5 (□).

Cyclodextrins are the cyclic oligosaccharides having the ability to form inclusion complex with wide variety of compounds. Cyclodextrins can entrap poorly soluble drug molecules of appropriate size and polarity in their hydrophobic cavity to form reversible noncovalent inclusion complexes. This can improve aqueous solubility, stability and bioavailability of the drug molecule[9-11]. To judge the feasibility of the use of cyclodextrins in dissolution enhancement a number, named cyclodextrin utility number (Ucd) was introduced[12]. When the Ucd is greater than or equal to 1, complexation is sufficient for complete solubilization of drug. When Ucd is less than 1, the complexation alone is not enough for complete solubilization.

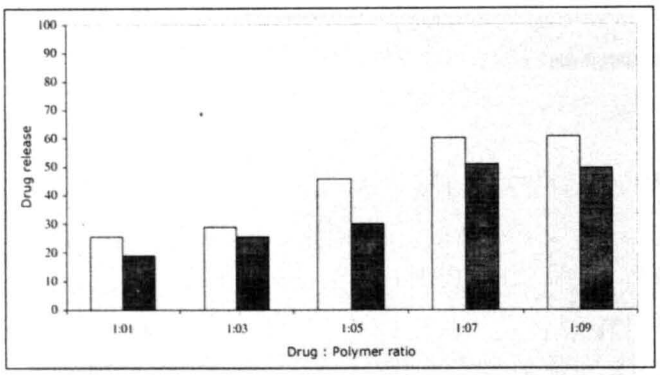

Fig. 3: Comparison of Q_{60} for PVP and Eudragit E 100 solid dispersions.

RCB: PVP K 30 solid dispersions (▢), RCB: Eudragit E 100 solid dispersions (▤)

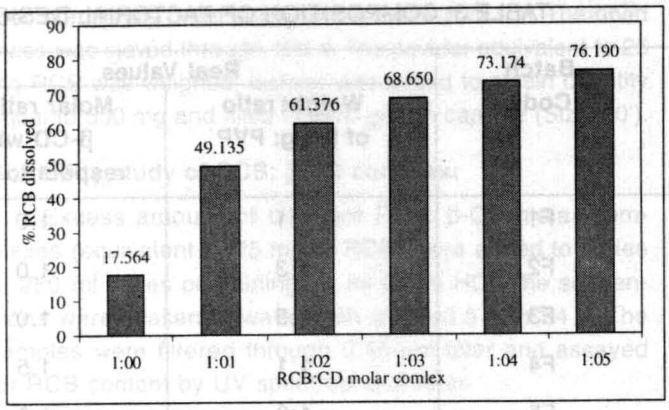

Fig. 4: Solubility of RCB from different RCB: β-CD molar complexes

The equation is given as, Ucd=[KSo/(1+KSo)]×mcd/md×MWd/MWcd, where, Ucd=cyclodextrin utility number, K=binding constant, So=aqueous solubility of pure drug in moles/l (1.52910^{-5}× M/L), md, mcd=drug dose and workable amount of CD in mg (25 and 452 mg, respectively), MWd, MWcd=molecular weight of drug (314) and β-CD (1135), respectively. When Ucd value is expected to be 1, the value of binding constant K comes to 16,330 M^{-1}. Though this value of K is high, it comes within range of K, i.e. 0-1,00,000. So β-CD can be tried for preparing inclusion complex with RCB.

The solubility of different RCB:β-CD complexes in 0.1 N HCl is shown in fig. 4. It can be observed from the figure

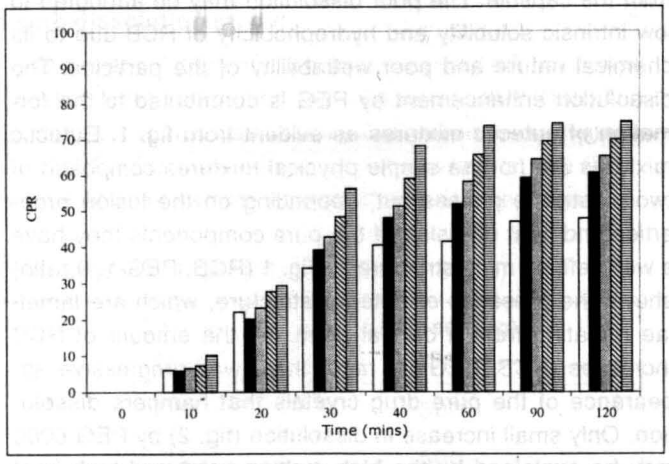

Fig. 5: Comparative dissolution profile of RCB: â-CD inclusion complex.

Batch D1 (▢), Batch D2 (■), Batch D3 (▨), Batch D4 (▩), Batch D5 (■).

that aqueous solubility of RCB increases appreciably upto 1: 3 RCB: β-CD ratio. Later, the increase in solubility of RCB with respect to increase in β-CD was not so significant. This may be due to limited solubility of β-CD in the aqueous media.

From the comparative dissolution profile of RCB: β-CD inclusion complexes (fig. 5) it was observed that as we increase the proportion of β-CD from one molar to five molar the dissolution of drug at 120 min increases from 47.7 % to 74.8 %. The weight of complex of the last batch (D5) was 477 mg. Further increase in amount of β-CD would increase bulk of tablet still higher, which was impracticable.

The reason for not achieving complete dissolution in the given molar ratio of RCB:β-CD may be the high value of K. So it can be said that β-CD alone was not sufficient for complete solubilization of this drug. Hence another carrier i.e. PVP K 30 was used along with β-CD for complete dissolution of RCB. A 3^2 factorial design was used to optimize concentration of PVP K 30 and β-CD[13]. The response studied for the evaluation of best batch among the optimization set was Q_{60} (Table 3). Q_{60} values show a variation from 43.98 % to 97.92 %, indicating that the selected variables exert considerable effect on drug dissolution. The equation for the full model and reduced model were as follows: $Y=78.131+14.98X_1+11.9X_2-5.456X_1X_1-3.131X_2X_2+0.854X_1X_2$, for full model and $Y=76.043+14.98X_1+11.9X_2-5.456\ X_1X_1$ for reduced model. The R square value for the reduced model is 0.9852, which complies with the R square value of full model i.e. 0.9951. To validate the equation, Batch F10 was prepared using level of X1=0.75 (i.e. 113 mg PVP) and X2=0.5 (i.e. 158 mg β-CD).

Predicted Q_{60} value was 91.785 % and experimental value appeared to be 92.477 %. As evident from the Factorial design the optimized batch is F9 as far as percentage drug release is concerned.

The mechanism by which combination of PVP K 30 and β-CD increases the dissolution of the RCB can be predicted. Formation of glass solution with PVP K 30 increases the initial solubility of RCB prior to complexation with β-CD. So after formation of inclusion complex there will be further increase in dissolution of RCB. PVP K 30 provides hydrophilic environment to the drug and also forms the hydrogen bonding with the hydroxyl groups on the rim of β-CD thus stabilizing the drug within cyclodextrin cavity.

From the above results it can be concluded that for the drug like RCB the true advantage of solid dispersion lies in the formation of glass solution and not in the formation of eutectic mixtures. The dissolution of RCB can be significantly improved by simultaneous use of two dissolution enhancing agent i.e. PVP K-30 and β-cyclodextrin.

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