Enhancement of Dissolution Profile by Solid Dispersion (Kneading) Technique

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ABSTRACT

This article investigates enhancement of the dissolution profile of valdecoxib using solid dispersion with PVP. The article also describes the preparation of fast-dissolving tablets of valdecoxib by using a high amount of superdisintegrants. A phase solubility method was used to evaluate the effect of various water-soluble polymers on aqueous solubility of valdecoxib. Polyvinyl pyrrolidone (PVP K-30) was selected and solid dispersions were prepared by the method of kneading. Dissolution studies using the USP paddle method were performed for solid dispersions of valdecoxib. Infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and x-ray diffractometry (XRD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Tablets were formulated containing solid dispersion products and compared with commercial products. IR spectroscopy, XRD, and DSC showed no change in the crystal structure of valdecoxib. Dissolution of valdecoxib improved significantly in solid dispersion products (< 85% in 5 minutes). Tablets containing solid dispersion exhibited better dissolution profile than commercial tablets. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of valdecoxib.

KEYWORDS: Solid dispersion, valdecoxib, dissolution enhancement, fast-dissolving tablets.

INTRODUCTION

Valdecoxib, 4-(5-methyl-3-phenyl-4-isoxazolyl) benzenesulfonamide, a novel COX-2 inhibitor, is a potent nonsteroidal anti-inflammatory drug that is indicated for amenorrhea and various osteopathic and inflammatory conditions.[1] Although it has excellent oral bioavailability (87%), its poor aqueous solubility (10 μg/mL, 25°C) makes its absorption dissolution rate limited and thus delays onset of action. Solid dispersion, which was introduced in the early 1970s,[2] is essentially a multicomponent system, having drug dispersed in and around hydrophilic carrier(s). Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide,[3] ketoprofen,[4] tenoxicam,[5] nifedipine,[6] nimodipine,[7] ursodeoxycholic acid,[8] and albendazole.[9] Various hydrophilic carriers, such as polyethylene glycols,[10] polyvinylpyrrolidone,[11] hydroxypropyl methylcellulose,[12] gums,[7] sugar,[13] mannitol,[14] and urea,[8] have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous-soluble drugs.

Polyvinylpyrrolidone (PVP) has been used for the preparation of solid dispersion as a component of the binary system for various drugs such as sulindac,[15] fenofibrate,[16] tenoxicam,[5] tacrolimus,[17] and flurinazine.[18]

The present work aims to evaluate the potential of the solid dispersion technique for development of fast-dissolving tablets of valdecoxib using PVP as the hydrophilic carrier. Furthermore, the study undertakes to investigate kneading as a method for preparation of such binary systems, their solid-state characterization, interaction in the liquid state, and attempts to see the possible mechanism of improved dissolution rate.

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MATERIALS AND METHODS

Materials

Valdecoxib (VALD) was a gift sample from Ajanta Pharma (Mumbai, India). Polyvinyl pyrrolidone (PVP-K30) was kindly provided by BASF India (Mumbai). All reagents and solvents used were of analytical grade.

Methods

Preparation of PVP-VALD Solid Dispersion

A mixture of PVP and VALD (1:1 and 1:2 by weight) was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through sieve no. 60 and stored in a dessicator until further evaluation.

Table 1. Percentage Dissolution and Dissolution Efficiency of Valdecoxib From Different Binary Systems in Comparison With Original Drug*

System	DP_5†	DE_{15}†	DE_{60}†
VALD	10.18 ± 0.25	8.51 ± 0.74	11.89 ± 0.42
PM1	23.22 ± 1.06	23.43 ± 0.53	39.04 ± 2.42
PM2	38.48 ± 5.97	39.41 ± 3.16	62.74 ± 2.93
SD1	69.89 ± 3.42	67.46 ± 0.57	90.8 ± 0.14
SD2	86.80 ± 0.42	80.03 ± 1.39	98.53 ± 2.99

*VALD indicates valdecoxib; DP_5, % dissolved at 5 minutes; DE_{15} and DE_{60}, dissolution efficiency at 15 and 60 minutes).
†All values are mean of 3 readings ± SD.

Physical mixtures (PM) were obtained by pulverizing in a glass mortar and carefully mixing accurately weighed (1:1 and 1:2 by weight) amounts of VALD and PVP.

For convenience, all binary systems were given a code name, which is summarized in Table 1.

Solid State Studies

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Jasco FTIR-5300 spectrophotometer (Tokyo, Japan). Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed using Shimadzu-Thermal Analyzer DT 40 (Kyoto, Japan) on 2- to 8-mg samples (Sartorius BP 210 S electronic microbalance, Goettingen, Germany). Samples were heated in an open aluminum pans at a rate of 10°C per min^{-1} in a 30 to 300°C temperature range under a nitrogen flow of 40 mL/min.

X-ray Powder Diffractometry

X-ray powder diffraction patterns were recorded on a Jeol JDX 8030 x-ray diffractometer (Tokyo, Japan) using Ni-filtered, CuKα radiation, a voltage of 40 kV, and a 25-mA current. The scanning rate employed was 1° min^{-1} over the 10 to 30° diffraction angle (2θ) range.

Liquid State Studies

Phase Solubility Studies

An excess of VALD was added to screw-capped vials containing aqueous polymer solution (0.05% to 0.25% wt/vol concentration range). Vials were shaken mechanically at 25 ± 0.5°C for 24 hours. At equilibrium after 2 days, aliquots were withdrawn, filtered (0.22 μm pore size) and spectrophotometrically assayed for drug content at 244 nm (Shimadzu-UV 160A Spectrophotometer). Each experiment was performed in triplicate (coefficient of variation [CV] < 3%).

Dissolution Rate Studies

Dissolution rate studies were performed in distilled water (pH 6.8) at 37 ± 0.5°C, using 6-station USP XXII apparatus (TDT-50, Electrolab, Mumbai, India) with paddle rotating at 50 rpm. Solid products, both solid dispersions as well as physical mixtures, each containing 5 mg of drug were subjected to dissolution. At fixed time intervals, samples withdrawn were filtered (pore size 0.22 μm) and spectrophotometrically assayed for drug content at 244 nm. Each test was performed in triplicate (CV < 3%). Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time.[19]

Tablet Preparation and Characterization

Tablets containing equivalent of 10 mg of valdecoxib (SD2 product) were compressed on a 16-station single rotary tabletting press (GMC, Mumbai, India) using a 9-mm standard concave punch by direct compression technique.

Prepared tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche Friabilator), weight variation, and drug content.

In vitro dissolution studies of MD4 (tablets containing solid dispersion SD2) and 2 commercial tablets of valdecoxib (containing 10 mg), Valus (Glenmark formulations, Mumbai, India) and Valcox (Unichem Labs, Mumbai, India), respectively, were carried using 900-mL 0.1 HCl as the dissolution media.

RESULTS AND DISCUSSION

Fourier Transform Infrared (FTIR) Spectroscopy

IR spectra of VALD and its binary systems with PVP are presented in Figure 1. Pure valdecoxib spectra showed sharp characteristic peaks at 3377.6, 3250.3, 1332.9, and 1149.68 cm^{-1}. All the above characteristic peaks appears in the spectra of all binary systems at same wavenumber indicating no modification or interaction between the drug and carrier.

Differential Scanning Calorimetry (DSC)

Thermal behavior of pure drug and corresponding drug carrier system are depicted in Figure 2. The DSC curve of VALD profiles a sharp endothermic peak (Tpeak = 172.8°C)

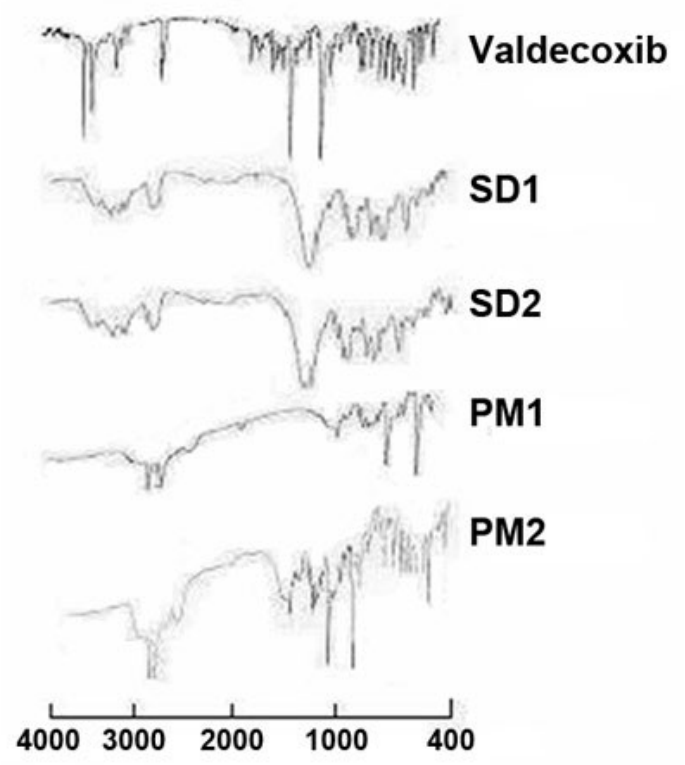

Figure 1. FTIR Spectra of valdecoxib and various binary systems with PVP.

corresponding to its melting, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted toward lower temperature, with reduced intensity, in both physical mixtures as well as solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Moreover, the data also indicate there seems to be no interaction between the components of binary system. No significant difference in DSC pattern of dispersions and physical mixture suggests that even in the kneading process could not induce interaction at the molecular level and solid dispersion formed is a physical mixture with highly dispersed drug crystals in carrier.

X-ray Diffractometry

X-ray diffracometry (XRD) spectra of pure compound and binary systems with carriers are presented in Figure 3. The x-ray diffractogram of VALD has sharp peaks at diffraction angles (2θ) 12.26°, 15.88°, 19.88°, 22.08°, and 23.92° showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of both physical mixtures and solid dispersion system. Moreover, the relative intensity and 2θ angle of these peaks remains practically unchanged. Thus it can be clearly suggestive from x-ray data that there is no amorphization of VALD and it is still in its original crystalline form. IR and DSC studies support the same hypothesis, which is confirmed by x-ray diffractometry.

Liquid State Studies

Solubility studies were performed with several hydrophilic carriers (data not shown), maximum augmentation of solubility was observed with PVP. The phase solubility diagram of the VALD-PVP system is shown in Figure 4. Intrinsic solubility of VALD is found to be 9.4 μg/mL, which is in good accordance with literature. Addition of PVP increased the solubility of drug by more than 4 times at 0.2% polymer concentration. The drug solubility increased linearly with increasing polymer concentration indicative of the A_L type of solubility phase diagram. No attempt has been made to calculate the stability constant since the exact stoichiometric ratio of drug-polymer is not known.

Dissolution Rate Studies

Dissolution profiles of original drug crystals and drug-carrier binary systems are presented in Figure 5. It is evident that the solid dispersion (SD) technique has improved

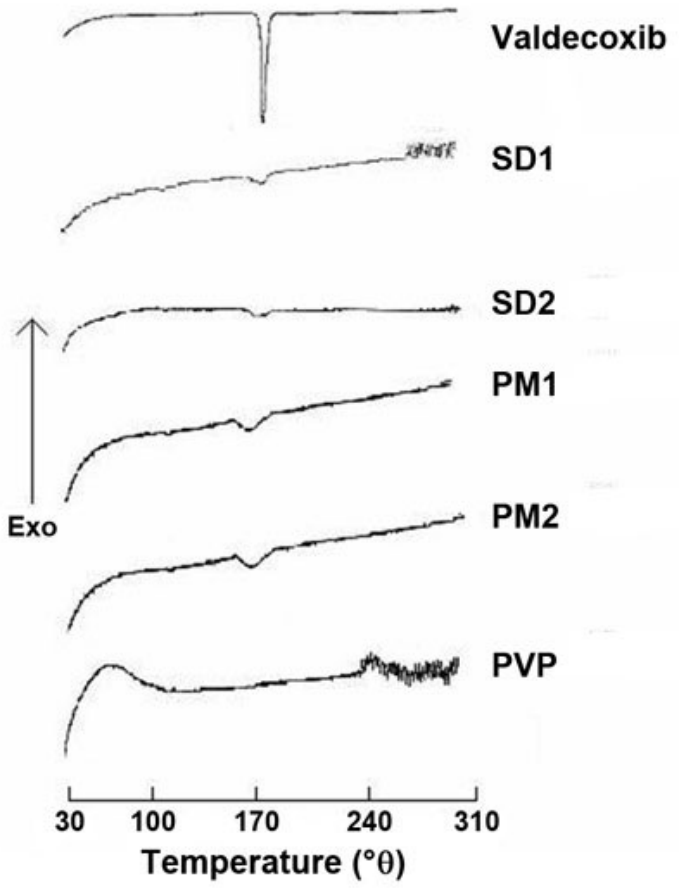

Figure 2. DSC curves of valdecoxib and various binary systems.

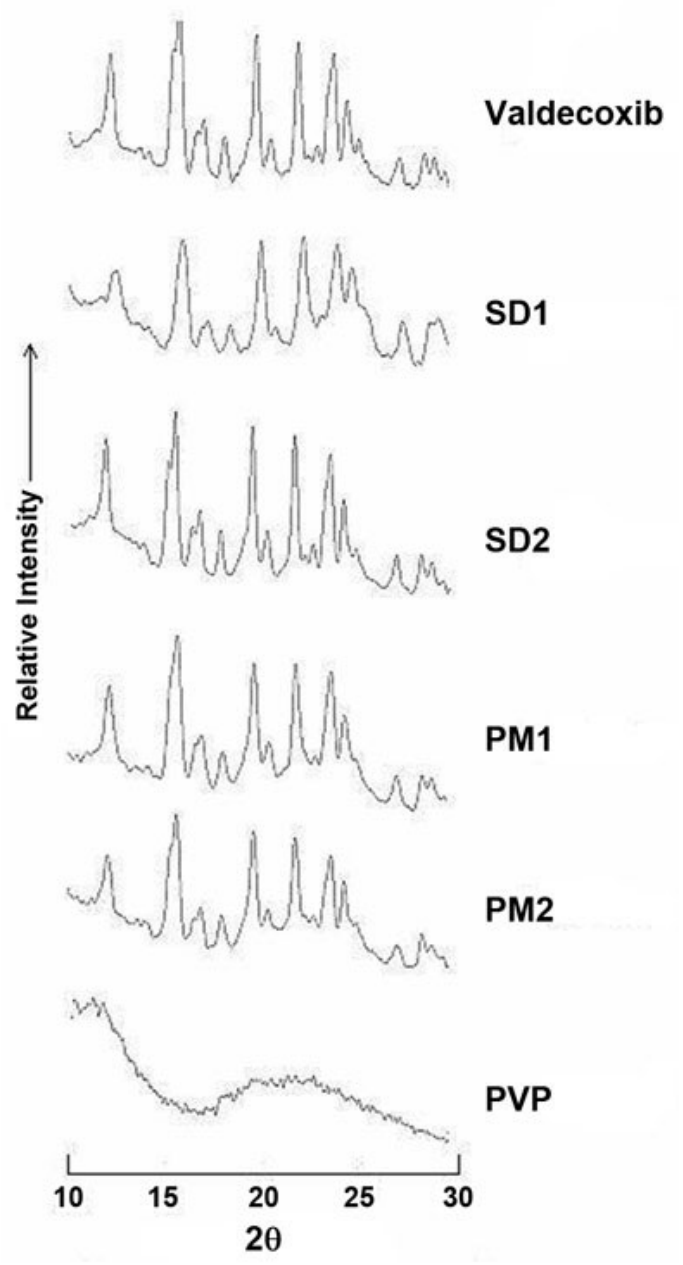

Figure 3. XRD spectra of valdecoxib and various binary systems.

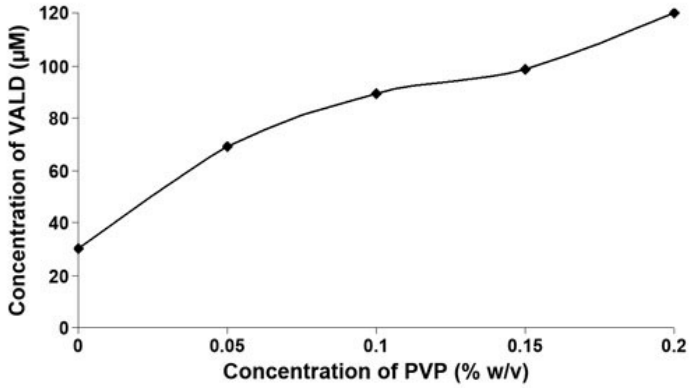

Figure 4. Phase solubility diagram of valdecoxib with PVP.

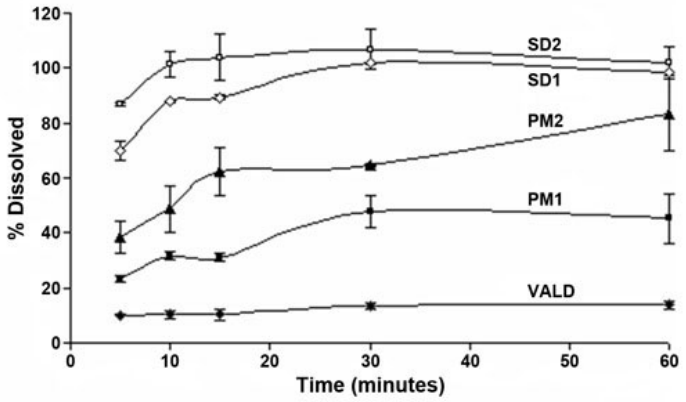

Figure 5. Dissolution profile of valdecoxib and its binary systems with PVP.

the dissolution rate of VALD to a great extent. Table 1 summarizes % drug dissolved in 5 minutes (DP_5), dissolution efficiency at 15 minutes (DE_{15}), and dissolution efficiency at 60 minutes (DE_{60}) for VALD and its binary systems with carriers. The values given in Table 2 indicate that SD2 (DE_{60} = 98%) shows maximum enhancement in dissolution rate. However, SD1 also produces comparable results on terms of dissolution efficiency (DE_{60} = 90%). Physical mixtures (PM) also improve dissolution rate by a significant extent as compared with drug alone ($P < .05$). The order of efficiencies of products based on DE values is SD2 > SD1 > PM2 > PM1 > VALD.

This enhancement of dissolution of VALD from drug-carrier systems can be ascribed to several factors. Ford[20] reviewed the mechanism of dissolution rate improvement from solid dispersion. Lack of crystallinity, ie, amorphization, increased wettability and dispersibility and particle size reduction considered to be important factors for dissolution rate enhancement. As indicative from dissolution data of physical mixtures, improvement could be attributed higher wettability and dispersibility. Dry mixing of drug with a hydrophilic carrier results in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media. During dissolution studies, it was noted that drug-carrier systems sink immediately, whereas pure drug keeps floating on the surface for a longer time interval.

Furthermore, kneading results in uniform distribution of drug in the polymer crust in a highly dispersed state. Thus,

Table 2. Formulation Variable for the SD2-containing Tablets

Ingredient	MD1	MD2	MD3	MD4
SD2	33 mg	33 mg	33 mg	33 mg
Crosscarmellose sodium	45 mg	—	—	10 mg
Sodium starch glycolate	—	45 mg	—	45 mg
Crosspovidone	—	—	45 mg	—

Each tablet contains 100 mg pharmatose, 119 mg avicel PH 200, 1.5 mg magnesium stearate, and 1.5 mg of aerosil.

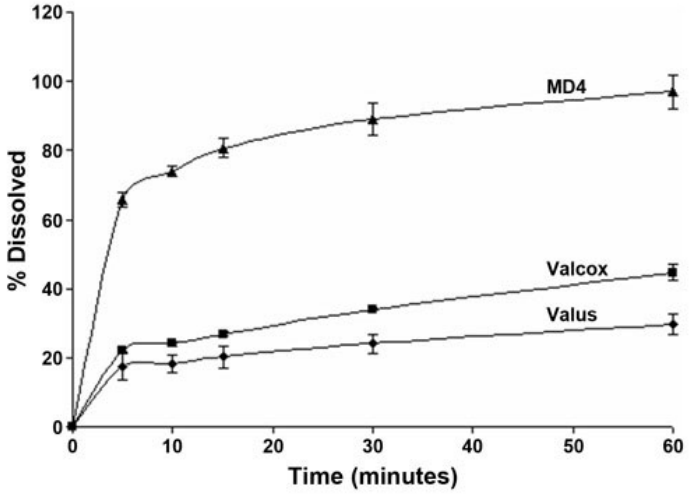

Figure 6. Dissolution profile of tablets containing solid dispersion and comparison with commercial tablets.

when such a system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increase the dissolution surface available. Moreover, other factors such as absence of aggregation and/or reagglomeration phenomenon during dissolution and particle size reduction could be attributed to a better dissolution profile.[21]

Tablet Preparation and Characterization

To formulate a mouth-dissolving tablet of valdecoxib, the SD2 binary mixture was selected based on its in vitro dissolution performance.

The use of superdisintegrants for preparation of fast-dispersing tablets is highly effective as well as commercially feasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration. This disintegration is reported to have effect of dissolution characteristics as well.

Three different superdisintegrants, crosscarmellose sodium, crosspovidone, and sodium starch glycolate, were tried to achieve fast dispersion of tablets. The formula of different tablets prepared is summarized in Table 2. However, tablets containing crosspovidone showed the fastest disintegration (48 seconds). To improve the disintegration, crosscarmellose sodium was included in the formula, which results in a very fast dispersion (15 seconds).

Table 3. Percentage Dissolution and Dissolution Efficiency of Valdecoxib from Fast-Dissolving Tablets Containing solid dispersion (MD4) and Commercial Formulation, A and B

Formulation	DP_5 (%)*	DP_{60} (%)*	DE_{60} (%)*
MD4	65.73 ± 2.29	97.01 ± 4.93	82.77 ± 1.88
Valus	17.49 ± 4.04	29.77 ± 2.88	22.79 ± 0.90
Valcox	22.12 ± 0.98	44.64 ± 2.39	32.26 ± 0.32

*All determinations are mean of 3 readings ± SD. DP_5 and DP_{60}, % dissolved at 5 minutes and 60 minutes respectively, DE_{60}, dissolution efficiency in 60 minutes.

Tablet characteristics of optimized tablet MD4 are tabulated in Table 3. In vitro dissolution studies for MD4 confirmed the results obtained with solid binary mixtures. MD4 tablets showed good dissolution efficiency (DE_{60} = 82.77%) and rapid dissolution (DP_5 = 65.73%). When compared with commercial formulations in the Indian market (Figure 6), tablets formulated with the binary mixture (SD2) clearly perform better (Table 3) and a significant enhancement in dissolution characteristics was observed ($P < .05$). Significant increase in DP_{60} (% dissolved in 60 minutes) was found with MD4 with respect to commercial formulation Valus (3.25-fold) and Valcox (2.2-fold).

CONCLUSION

The study shows that the dissolution rate of valdecoxib can be enhanced to a great extent by solid dispersion technique using an industrially feasible kneading method. Hence valdecoxib-PVP binary systems along with use of superdisintegrants could be considered for formulation of fast-dissolving tablets of valdecoxib.

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