

Formulation, Characterization, and Optimization of Fast-Dissolve Tablets Containing Celecoxib Solid Dispersion

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ABSTRACT

Celecoxib is a poorly water-soluble drug, and bioavailability from its crystalline form is very low. The purpose of the present investigation was to increase the solubility and dissolution rate of celecoxib by preparing a solid dispersion with polyvinyl pyrrolidone K30 (PVP-K30) using a solvent-evaporation method. The dissolution profiles of developed formulations in distilled water containing 1% SLS were studied. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). For the preparation of celecoxib fast-dissolve tablets, a 1:2 solid dispersion with PVP-K30 was used with croscarmellose sodium as a superdisintegrant and Pearlitol 200SD (pearlitol) as a pore-forming agent. A 3² full-factorial design was employed to study the effect of independent variables, the amounts of croscarmellose sodium (X_1) and pearlitol (X_2), on dependent variables, disintegration time, percentage friability, wettability, and percentage of drug released after 20 min (Q_{20}). The results show that a dispersion of the drug in polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio is the controlling factor for dissolution improvement. FTIR spectra show no chemical incompatibility between the drug and PVP-K30. FTIR and DSC data indicate that celecoxib was in the amorphous form, which explains the faster dissolution rate of the drug from its solid dispersions. Concerning the optimization study, multiple regression analysis reveals that an optimum concentration of croscarmellose sodium and a higher percentage of pearlitol are required for obtaining rapidly disintegrating tablets.

INTRODUCTION

Oral drug administration is perhaps the most appealing route for drug delivery (1). Of the various orally administered dosage forms, the tablet is one of the most preferred (2, 3). In recent years, the task of developing rapidly disintegrating tablets has been accomplished by using suitable diluents and superdisintegrants.

Celecoxib is a new non-steroidal, anti-inflammatory drug (NSAID) that acts by inhibiting the activity of the enzyme cyclooxygenase-2 (COX-2) (4–7). It is used mainly for osteoarthritis, rheumatoid arthritis, and dysmenorrhea (8–10). Celecoxib is practically insoluble in water (0.003 mg/mL), and peak blood levels are reached between 2 and 3 h after oral administration. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/mL at 37 °C) due to erratic or incomplete absorption from the GIT (11).

Techniques that have been used to improve dissolution and bioavailability of poorly water-soluble drugs include micronization, use of surfactants, and the formation of solid dispersions (12, 13). Among the carriers used in the

formation of solid dispersions, polyvinyl pyrrolidone (PVP-K30) is most commonly used (14). This polymer shows excellent water solubility and varies significantly in molecular weight, ranging from 10,000 to 7,00,000 Da (15, 16).

Full-factorial experimental design is one of the best tools for studying the effect of different variables on the quality determinant parameters of any formulation. In the present study, independent variables were assigned to the amounts of croscarmellose sodium (X_1) and pearlitol (X_2) at three different levels, whereas responses or dependent variables were assigned to disintegration time, percentage friability, wettability, and percentage of drug release after 20 min (Q_{20}). Multiple linear regression analysis of the results gave equations that adequately describe the influence of the independent variables on the selected responses.

The aim of the present study was to evaluate the physicochemical properties of solid dispersions of celecoxib in PVP-K30. To characterize the prepared dispersions, differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR), as well as dissolution studies, were performed. A 3² randomized full-factorial design was used to study the effect of formulation variables on the performance of these tablets.

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MATERIALS AND METHODS

Materials

Celecoxib and croscarmellose sodium (Ac-di-sol) were obtained as gift samples from Cadila Pharmaceutical Ltd., Ahmedabad, India. Pearlitol 200SD was obtained as a gift sample from Roquette Chemicals Ltd., France. Polyvinyl pyrrolidone (PVP-K30) was obtained as a gift sample from S.D. Fine Chemicals Ltd., Mumbai, India.

Preparation of Solid Dispersions of Celecoxib with PVP-K 30

In this method, accurately weighed quantities of celecoxib and PVP-K30 in proportions of 1:1, 1:2, 1:3, and 1:4 were dissolved in petri dishes containing methanol. Methanol was evaporated at room temperature for 2 h. The solidified mass obtained in each case was scraped, crushed, pulverized, and passed through an 80-mesh sieve. All the solid dispersions were preserved in well-closed glass containers until use.

Dissolution Studies

Dissolution experiments were performed using USP Apparatus 2 (Electrolab, TDT-06-T, Mumbai, India) in distilled water containing 1% SLS at 37 °C with a rotation speed of 50 rpm. Powdered samples of each preparation equivalent to 100 mg of celecoxib were added to the dissolution medium. At appropriate time intervals, 5 mL of the mixture was withdrawn and filtered. The initial volume was maintained by adding 5 mL of fresh dissolution medium. The samples were assayed for celecoxib content by UV spectrophotometry at 254 nm.

DSC Analysis

DSC scans of the samples (8–10 mg) were recorded using a Shimadzu 60 DSC with TDA trend line software under dry air (100 mL/min) between 50 and 300 °C at a scanning rate of 10 °C/min.

FTIR Analysis

FTIR spectra of moisture-free samples were obtained using a spectrophotometer (FTIR-8300, Shimadzu Co., Kyoto, Japan) by the potassium bromide (KBr) pellet method (2 mg sample in 200 mg KBr).

Preparation of Celecoxib Tablets

Celecoxib fast-dissolve tablets were prepared according to the proportions given in Table 1. The raw materials were passed through a 40-mesh screen before mixing. A powdered 1:2 solid dispersion containing an amount of celecoxib equivalent to 100 mg was mixed with the other excipients and directly compressed on a RIMEK rotary tablet machine using 12-mm diameter flat-face round punches (Karnavati Eng. Pvt. Ltd, Ahmedabad). The tablet weight was adjusted to approximately 500 mg.

Table 1. Ingredients Used for Preparation of Celecoxib Fast-Dissolve Tablets

Ingredient	Amount
1:2 solid dispersion equivalent to 100 mg celecoxib	60% (w/w)
Superdisintegrant (croscarmellose sodium)	0.5–4% (w/w)
Pearlitol (pore-forming agent)	7–9% (w/w)
Antiadherent (talc)	2% (w/w)
Lubricant (magnesium stearate)	1% (w/w)
Lactose monohydrate	q.s.
Total weight of tablet	500 mg

Experimental Design of Celecoxib Fast-Dissolve Tablets

A 3² randomized full-factorial design was used to investigate the joint influence of formulation variables. In this design, two factors were evaluated, each at three levels, and experimental trials were performed at all nine possible combinations (18). The amounts of superdisintegrant, croscarmellose sodium (X_1), and pore forming agent, pearlitol (X_2), were selected as independent variables. Disintegration time, percentage friability, wettability, and Q_{20} were selected as dependent variables (response, Y). The methods for the preparation and evaluation of the tablets and the amount of celecoxib were kept constant for all the trials.

Evaluation of the Prepared Tablets

Tablet-breaking strength (hardness) and tablet friability were determined using a hardness tester and a friability test apparatus (Monsanto, Hicon, India), respectively.

The disintegration and wetting times were measured according to the method described by Gohel et al. (18, 19). The disintegration times were measured using a modified disintegration method. For this purpose, a petri dish (10-cm diameter) was filled with 10 mL of water. The tablet was carefully put in the center of the petri dish, and the time for the tablet to disintegrate completely into fine particles was noted.

Wetting time was measured as follows. Five circular tissue papers of 10-cm diameter were placed in a 10-cm diameter petri dish. Ten milliliters of water containing eosin (0.01%), a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

RESULTS AND DISCUSSION

Dissolution Studies

Dissolution studies of pure celecoxib and all prepared solid dispersions were carried out in distilled water

Table 2. Q_{20} and Q_{60} from Pure Celecoxib and Solid Dispersions

	Drug/PVP-K30				
	1:1	1:2	1:3	1:4	Celecoxib
Q_{20}	16.85 ± 0.2	36.23 ± 1.1	31.68 ± 0.8	32.14 ± 0.5	6.54 ± 0.4
Q_{60}	52.64 ± 3.4	85.69 ± 1.9	79.48 ± 2.6	62.35 ± 1.5	20.08 ± 0.8

containing 1% SLS. Q_{20} and Q_{60} values are shown in Table 2. From these data, it is evident that the onset of dissolution of pure celecoxib was very low. The drug released from pure celecoxib was only 20.08% in 1 h during the in vitro dissolution study, suggesting a strong need to enhance the dissolution of celecoxib.

The presence of PVP-K30 increases the dissolution rate of celecoxib up to a drug-to-polymer ratio of 1:2. Q_{20} and Q_{60} for PVP-K30 1:2 were 36.23% and 85.69%, respectively, whereas Q_{20} and Q_{60} for PVP-K30 1:4 were 32.14% and 62.35%, respectively. This might be due to the formation of a viscous boundary layer around the drug particles, leading to a decrease in the dissolution rate (Table 2).

DSC Analysis

The possible interaction between the drug and the carrier was studied by DSC (Figure 1). Pure celecoxib powder showed a melting endotherm at 165.3 °C, whereas the scan of PVP-K30 showed a broad endotherm ranging from 80 to 120 °C due to the presence of residual moisture.

The DSC scan of the final formulation shows a melting endotherm between 100 and 250 °C, due to loss of water from PVP-K30, and the absence of a drug peak. The absence of a celecoxib peak indicates that celecoxib is amorphous or is present as a solid solution inside the PVP-K30 matrix. According to these results, the amorphous property of celecoxib in the formulation with PVP-K30 is mainly responsible for the dissolution enhancement.

FTIR Analysis

The IR spectrum of celecoxib (Figure 2) shows medium absorption bands at 3160 and 3260 cm^{-1} , which were assigned to the drug –NH symmetric and asymmetric stretching vibrations, respectively. The other characteristic bands may be attributed to the following group vibrations: 1150 and 1340 cm^{-1} (S=O symmetric and asymmetric stretching, respectively), 1560 cm^{-1} (NH bends), and 780 cm^{-1} (aromatic –CH bend). The spectrum of PVP-K30 showed, among others, important bands at 2925 cm^{-1} (C–H stretch) and 1652 cm^{-1} (C=O). A very broad band at 3300 cm^{-1} , which was attributed to the presence of water, was also visible, confirming the broad endotherm detected in the DSC experiments.

The solid dispersion prepared at a 1:2 ratio using the solvent evaporation method showed a decrease in band

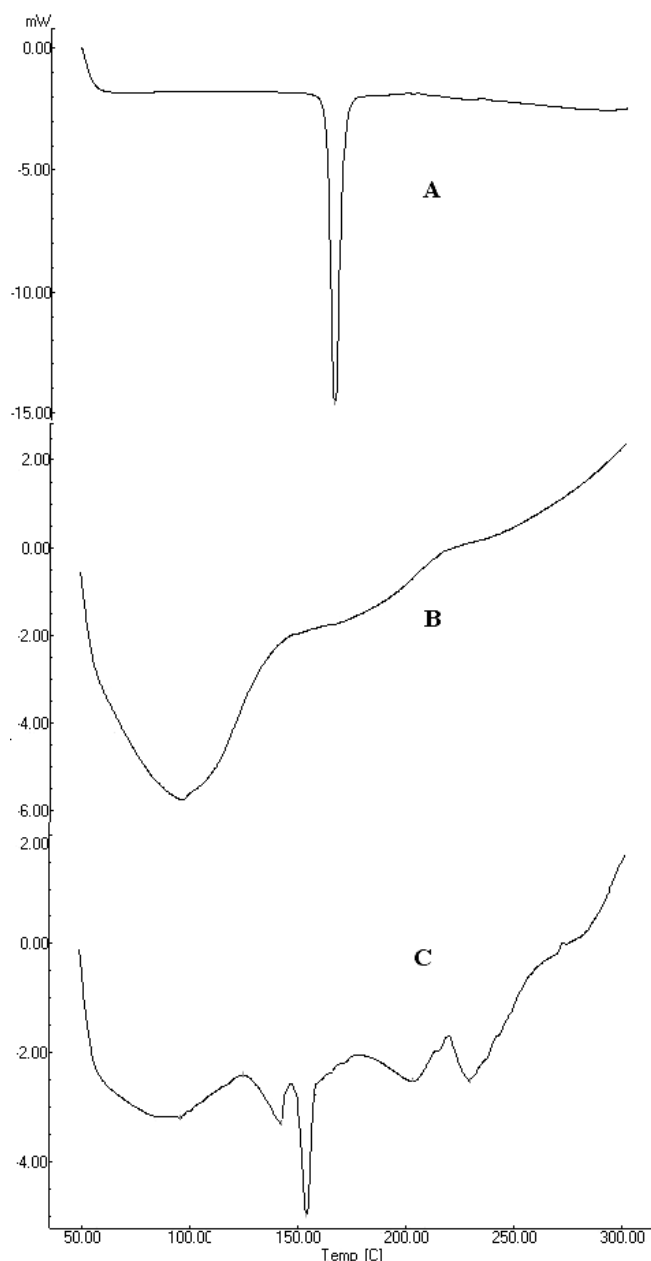


Figure 1. DSC scans of (A) pure celecoxib, (B) PVP-K30, and (C) batch H₆.

intensity and a shift to higher wave numbers. This finding suggests that there might be molecular interaction between the drug and PVP-K30 in a solid dispersion. Croscarmellose sodium, PVP-K30, and pearlytol show interaction with each other and with pure drug in final formulations prepared with pure celecoxib drug.

Evaluation of Celecoxib Fast-Dissolve Tablets

Rudnic et al. (19) postulated that wicking and capillary action are major factors in the ability of superdisintegrants to function. To select the amounts of superdisintegrant and pore-forming agent, preliminary trials were conducted as shown in Table 3. All the prepared

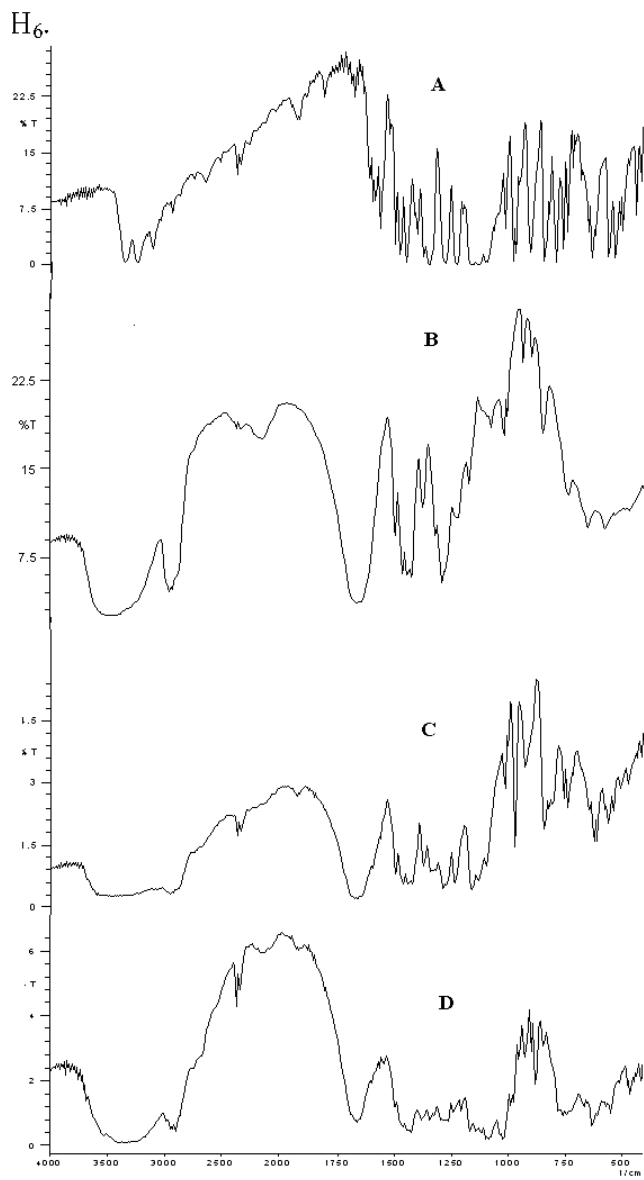


Figure 2. FTIR spectra of (A) celecoxib, (B) PVP-K30, (C) 1:2 solid dispersion, and (D) batch H_6 .

tablets were characterized by weight, uniform thickness, diameter, hardness, friability, disintegration time, and wetting.

As a result, the tablet containing croscarmellose sodium showed the longest time for wetting, because the major mechanism of disintegration for croscarmellose sodium is swelling, whereas tablets containing pearlitol showed a quicker water uptake rate and less time for wetting (Table 3). Batch A_8 , which contained both 20 mg of croscarmellose sodium and 45 mg of pearlitol, exhibited faster disintegration and wetting.

Experimental Design of Celecoxib Fast-Dissolve Tablets

To investigate the factors systematically, a factorial design was employed (Table 4). As shown in eq 1, a

statistical model incorporating interactive and polynomial terms was used to evaluate the responses:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

where Y is the dependent variable, namely disintegration time, wettability, friability, and Q_{20} ; b_0 is the arithmetic mean response of the nine runs; and b_1 and b_2 are the estimated coefficients for the factors X_1 and X_2 , respectively. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value.

The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The fitted equations (full models) relating the responses to the transformed factor are shown in Table 5. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., positive or negative). The high values of the correlation coefficients (Table 5) for the dependent variables indicate a good fit.

Concerning disintegration time, the results of multiple linear regression analysis show that both the coefficients b_1 and b_2 are negative. Therefore, increasing the concentration of either croscarmellose sodium or pearlitol is expected to decrease the disintegration time. Four percent (wt/wt) croscarmellose sodium, which showed a minimal disintegration time of 108 sec, was selected as the optimum concentration. It was observed that a further increase in the concentration of croscarmellose sodium led to an increase in disintegration time. This delay in disintegration may be caused by the increased water requirement of a larger amount of croscarmellose sodium, which was consequently transformed into swelling force for rapid disintegration of the tablets. When a higher percentage of pearlitol is used, tablets with a higher porosity are expected. Water uptake and subsequent disintegration are thus facilitated.

On the other hand, an increase in the concentration of pearlitol leads to an increase in friability because the coefficient b_2 is positive. When a higher percentage of pearlitol is used, the tablets that are produced are more porous and mechanically weak. As indicated by the negative sign of the coefficient b_1 , an increase in the incorporated amounts of croscarmellose sodium resulted in a decrease in friability.

Concerning Q_{20} , the results of a multiple linear regression analysis showed that coefficients b_1 and b_2 bear an opposite sign. In vitro dissolution after 20 min varied from 77.6% to 85.92% and showed good correlation (0.9109). Amounts of croscarmellose sodium greater than its optimum concentration retarded drug release because of swelling action; therefore, increasing the concentration of croscarmellose sodium is expected to decrease drug release after 20 min. From the multiple regression analysis, both coefficients b_1 and b_2 are negative for tablet wettability.

Table 3. Preliminary Trials of Celecoxib Fast-Dissolve Tablets

Ingredients/Properties	Formulation*							
	A ₁	A ₂	A ₃	A ₄	A ₅	A ₆	A ₇	A ₈
Celecoxib (mg)	100	100	100	100	100	100	100	100
PVP-K30 (mg)	200	200	200	200	200	200	200	200
Ac-di-sol (mg)	–	–	–	5	15	20	15	20
Pearlitol (mg)	–	35	40	–	–	–	42.5	45
Talc (mg)	10	10	10	10	10	10	10	10
Mg stearate (mg)	5	5	5	5	5	5	5	5
Lactose (mg)	185	150	145	180	170	165	127.5	120
Weight (g)	0.498	0.495	0.496	0.497	0.495	0.493	0.497	0.496
Thickness (mm)	3.02	3.03	3.02	2.99	3.1	3.01	3.03	3.02
Diameter (mm)	11.05	11.0	11.05	11.07	11.06	11.09	11.04	11.01
Hardness (g/cm ²)	3.3	3.2	3.0	3.2	3.3	3.4	3.5	3.2
Friability (% loss)	0.06	0.38	0.34	0.32	0.24	0.26	0.2	0.5
Disintegration time (sec)	212	182	188	148	165	173	132	124
Wetting time (sec)	110	72	79	80	88	95	72	70

* All batches contained 2% talc and 1% magnesium stearate.

Table 4. 3² Full-Factorial Design Layout

Batch	Variable Level in Coded Form		Independent Variables			
	X ₁	X ₂	Disintegration time (sec)	Wettability	Friability	Q ₂₀
H ₁	–1	–1	178	125	0.46	77.60
H ₂	–1	0	163	105	0.42	78.4
H ₃	–1	1	158	93	0.40	78.74
H ₄	0	–1	142	88	0.38	79.94
H ₅	0	0	124	75	0.36	82.25
H ₆	0	1	108	70	0.36	85.92
H ₇	1	–1	112	78	0.34	84.74
H ₈	1	0	114	79	0.35	85.77
H ₉	1	1	119	79	0.31	85.60
Variables Level			Low(-1)	Medium(0)	High(+1)	
Amount of Ac-Di-Sol (X ₁)			3%	4%	5%	
Amount of Pearlitol (X ₂)			6%	8%	10%	

As the amount of croscarmellose sodium or pearlitol was increased, the wetting period of the tablets decreased. That means that increasing the concentration of superdisintegrant agent or pore-forming agent decreases the wetting time. Croscarmellose sodium 4% (wt/wt) and pearlitol 10% (wt/wt) were selected as the optimum concentrations that showed a minimal wetting time of 70 sec with 85.92% drug release in 20 min.

CONCLUSION

The present study concluded that PVPK-30 is a suitable carrier for the preparation of celecoxib solid dispersions. As demonstrated by DSC, the amorphization of celecoxib offered an explanation of better dissolution rate from its solid dispersion. In the FTIR spectra, most of the characteristic polymer peaks were present, but the characteristic peaks of celecoxib were absent. This indicates that celecoxib was trapped inside the polymer matrix. Experimental design provided a better understanding of the effect of formulation variables on the quality of fast-dissolve tablets containing a solid dispersion of a hydrophobic drug. The optimal batch exhibited a disintegration time of 108 sec, a percentage friability of 0.3%, a wettability of 70 sec, and a Q₂₀ of 85.92%.

Table 5. Summary of Regression Analysis Results

Coefficients	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
Disintegration time	139.43	-37.19	-13.52	11.29	4.86	2.86	0.9877
Wetting time	76	-19.5	-8.17	8.25	10.5	2.5	0.9965
Friability	0.355	-0.0505	0.019	0.005	0.0115	0.016	0.9700
Q_{20}	82.72	-3.56	1.32	-0.07	-0.875	-0.06	0.9109

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