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Formulation and Optimization of Mouth Dissolve Tablets Containing Rofecoxib Solid Dispersion

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ABSTRACT

The purpose of the present investigation was to increase the solubility and dissolution rate of rofecoxib by the preparation of its solid dispersion with polyvinyl pyrrolidone K30 (PVP K30) using solvent evaporation method. Drug-polymer interactions were investigated using differential scanning calorimetry (DSC), x-ray diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR). For the preparation of rofecoxib mouth dissolve tablets, its 1:9 solid dispersion with PVP K30 was used with various disintegrants and sublimable materials. In an attempt to construct a statistical model for the prediction of disintegration time and percentage friability, a 3^2 randomized full and reduced factorial design was used to optimize the influence of the amounts of superdisintegrant and subliming agent. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio was the controlling factor for dissolution improvement. FTIR spectra revealed no chemical incompatibility between the drug and PVP K30. As indicated from XRD and DSC data, rofecoxib was in the amorphous form, which explains the better dissolution rate of the drug from its solid dispersions. Concerning the optimization study, the multiple regression analysis revealed that an optimum concentration of camphor and a higher percentage of crospovidone are required for obtaining rapidly disintegrating tablets. In conclusion, this investigation demonstrated the potential of experimental design in understanding the effect of the formulation variables on the quality of mouth dissolve tablets containing solid dispersion of a hydrophobic drug.

KEYWORDS: rofecoxib, polyvinyl pyrrolidone K30, solid dispersion, solvent method, mouth dissolve tablets, factorial design.

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INTRODUCTION

Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions.[1] Chiou and Riegelman[2] outlined 6 types of drug-carrier interactions in solid-state dispersions: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates, and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. Among the carriers used in the formation of solid dispersions, polyvinyl pyrrolidone (PVP) is the most commonly used.[3] This polymer shows excellent water solubility and varies significantly in molecular weight, ranging from 10 000 to 700 000 Da. The molecular size of the polymers favors the formation of interstitial solid solutions.[4] Rofecoxib is described chemically as 4-[4-(methylsulfonyl) phenyl]-3-phenyl-2(5H)-furanone. It is a nonsteroidal anti-inflammatory drug that exhibits antiinflammatory, analgesic, and antipyretic activities in animal models. Previous attempts were made to increase the dissolution rate of rofecoxib by preparing its solid dispersions with polyethylene glycol 4000 (PEG 4000)[5] or inclusion complexes with cyclosextrins.[6] Although it was withdrawn from the market in 2004 by Merck Inc as a result of its cardiac effect, rofecoxib was used in this study as a model drug because of its poor water solubility and because the research can be applied to other products.

In recent years, the mouth dissolve tablet has attracted the interest of many researchers. Many elderly patients have difficulty swallowing tablets, capsules, or powders. To alleviate this problem, these tablets are expected to dissolve or disintegrate in the oral cavity without drinking water. The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease.[7] The basic approach used in the development of fast-dissolving tablets is the use of superdisintegrants. Another approach used in developing such tablets is maximizing pore structure of the tablets. Freeze-drying[8] and vacuum-drying techniques[9]

have been tried by researchers to maximize the pore structure of the tablet matrix. Freeze-drying is cumbersome and yields a fragile and hygroscopic product. On the other hand, vacuum-drying was adopted after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly. Therefore, it was decided to adopt the vacuum-drying technique in the present investigation.

The aim of the present study was to evaluate the physicochemical properties of solid dispersions of rofecoxib in PVP K30. In order to characterize the prepared dispersions, differential scanning calorimetry (DSC), X-ray diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR) as well as dissolution and solubility studies were performed. Moreover, a trial for the incorporation of the prepared solid dispersion in a mouth dissolve tablets was made. A 3^2 randomized full factorial design was used to study the effect of formulation variables on the performance of these tablets.

Materials and Methods

Rofecoxib, PVP K30, croscarmellose sodium, crospovidone (Polyplasdone), sodium starch glycolate, and anhydrous lactose (200 mesh) were a gift from Egyptian International Pharmaceutical Industries Co (Tenth of Ramadan City, Egypt). Dibasic potassium hydrogen phosphate (KH_2PO_4), hydrochloric acid (37%), monobasic sodium hydrogen phosphate ($Na_2HPO_4.12H_2O$), chloroform, methylene dichloride, thymol, and camphor were supplied from Elgomhoria Co (Cairo, Egypt). Magnesium stearate was supplied from October Pharma (Cairo, Egypt). Other reagents and organic solvents used were of analytical grade. Buffer and its dilutions were prepared with double-distilled water.

Preparation of Solid Dispersions and Physical Mixtures

Solid dispersions of rofecoxib in PVP K30 containing 5 different weight ratios (1:1, 1:2, 1:5, 1:7, and 1:9) were prepared by the solvent evaporation method. An appropriate amount of PVP K30 was added to a solution of rofecoxib in chloroform and dichloromethane (1:4). The solution was stirred at room temperature for 2 hours, and the solvent was removed under vacuum at 40°C in a rotary evaporator (VU 2000, Heidolph, Schwabach, Germany). Solid residue was dried in a vacuum oven (Lab-Line instruments Inc, Dubuque, IA) for 24 hours at room temperature, pulverized, and sieved using a set of sieves (Mettler Toledo, Greifensee, Switzerland). Powder samples between 420 and 200 μm were stored in a closed container away from the light and humidity until use.[10] Physical mixtures were prepared by mixing the appropriate amounts of rofecoxib and PVP K30 in a mortar. The resulting mixtures were sieved, collected, and stored in a closed container away from the light and humidity until use.[11]

Phase Solubility Study

Solubility studies were performed according to the method described by Higuchi and Connors.[12] An excess amount of rofecoxib was placed into a 25-mL glass flask containing different concentrations of PVP K30 in 20 mL distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent loss. The content of the suspension was equilibrated by shaking for 72 hours in a thermostatically controlled water bath (Julabo SW 20C, Osaka, Japan) at 25°C.[13] After attainment of equilibrium, the content of each flask was then filtered through a 0.45-μm filter (Minisart, Sartorius GmbH, Heidelberg, Germany). The filtrate was diluted and assayed spectrophotometrically (Schimadzu UV-1201, Schimadzu Corp, Kyoto, Japan) for rofecoxib content at 263 nm. All solubility measurements were performed in triplicate.

Dissolution Studies

Dissolution experiments were performed in triplicate with a Pharma Test dissolution tester (Pharma Test SP6-400, Hainburg, Germany) in distilled water at 37°C using the paddle method at a rotation speed of 100 rpm. Powdered samples of each preparation equivalent to 12.5 mg of rofecoxib were added to the dissolution medium. At appropriate time intervals, 5 mL of the mixture was withdrawn and filtered through Millipore membrane filter (Millipore Corp, Billerica, MA). The initial volume was maintained by adding 5 mL of fresh dissolution medium. The removed samples were assayed for rofecoxib content at 263 nm.[10] The dissolution profiles were examined as follows: the initial dissolution rate (IDR) was calculated as percentage dissolved of the drug over the first 20 minutes per minute, the percentage of the drug dissolved after 20 and 60 minutes (PD_{20} and PD_{60}), and the dissolution efficiency (DE%) parameter after 60 minutes. The dissolution efficiency can be defined as the area under the dissolution curve up to a certain time. It is measured using the trapezoidal method and is expressed as a percentage of the area of the rectangle divided by the area of 100% dissolution in the same time.

Fourier Transform Infrared Spectroscopy

FTIR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer (1600 series, Perkin-Elmer Inc, Norwalk, CT). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential Scanning Calorimetry

The DSC thermograms were recorded on a DSC (model 50, Shimadzu). Samples of 1.3 mg weight were heated in hermetically sealed aluminum pans over a temperature range of 30°C to 300°C at a constant rate of 10°C/min under nitrogen purge (30 mL/min).

X-ray Diffraction

XRD patterns were obtained using a Scintag XGEN 4000 powder diffractometer (XGEN 4000, advanced diffraction system, Scintag Inc, Cupertino, CA) with CuKα radiation. Diffractograms were run at a scanning speed of 8°/min over a 2θ range of 0° to 80°.

Preparation of Rofecoxib Tablets

Different rofecoxib mouth dissolve tablets were prepared according to the proportions given in Table 1. The raw materials were passed through a screen (40 mesh) prior to mixing. Powdered 1:9 solid dispersion, containing amount equivalent to 12.5 mg rofecoxib, was mixed with the other excipients and compressed on a single-punch tablet machine (Korsch Frogerais, type AO, Berlin, Germany) equipped with flat-faced 10-mm punches. The tablet weight was adjusted to ~250 mg. Sublimation of camphor was performed under vacuum from the prepared tablets at 60°C for 24 hours.

Experimental Design of Rofecoxib Mouth Dissolve Tablets

A 3^2 randomized full factorial design was used in order to investigate the joint influence of 2 formulation variables. In this design, 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations.[14] The amounts of subliming agent, camphor (X_1), and the superdisintegrant, crospovidone (X_2), were selected as independent variables. The disintegration time and percentage friability were selected as dependent variables. Checkpoint batch was also prepared to prove the validity of the evolved mathematical model. In addition, contour plots were used to graphically represent the effect of the independent variables.

Table 1. Percentages of Different Ingredients Used in Preparation of Rofecoxib Mouth Dissolve Tablets

Ingredient	% (wt/wt)
1:9 solid dispersion equivalent to 12.5 mg rofecoxib	50
Superdisintegrant	4-12
Subliming agent	0-20
Anti-adherent (talc)	2
Lubricant (Mg stearate)	1
Anhydrous lactose	to 100

Evaluation of the Prepared Tablets

The tablet geometry was determined by a means of a micrometer (Baty Co, Ltd, Sussex, England), while the tablet breaking strength (hardness) and the tablet friability were determined using Pharma Test hardness tester and Pharma Test fribilator, respectively. The disintegration and wetting times were measured according to the method described by Gohel et al.[14] Briefly, the disintegration time was 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. On the other hand, the wetting time was measured as follows: 5 circular tissue papers (10 cm diameter) to simulate the tongue conditions were placed in a Petri dish with a 10-cm diameter. Ten milliliters of water containing methylene blue, 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

Solubility Measurement

The solubility of rofecoxib in distilled water at 25°C was found to be 6.35 μg/mL. The determined solubility of rofecoxib is in agreement with the previously published value by Seedher and Bhatia.[15] The influence of PVP K30 upon the solubility of rofecoxib is presented in Figure 1. The increase in solubility was linear with respect to the weight fraction of the carrier. At 7% of PVP K30 the increase in solubility at 25°C was ~5-fold compared with pure drug. The increase in the solubility with increasing PVP K30 concentration indicates the solvent properties of PVP K30 for the drug. This behavior suggests the feature of an A_L-type solubility phase diagram 10. This finding is in accordance with Abdul-Fattah and Ghargava[16] regarding the increased solubility of Halofantrine. The increase in solubility in the presence of PVP K30 can probably be explained by increased wettability of rofecoxib. Indeed, PVP K30 causes a decrease of the interfacial tension between the drug and the dissolving solution.

Dissolution Studies

The dissolution profiles[17] were calculated and are shown in Table 2. Compared with the pure powdered drug, the presence of PVP K30 increases the dissolution of rofecoxib from the physical mixtures, which increases the dissolution rate (Figure 2). Since the release profiles of the drug from the different physical mixtures are so close to each other, they were omitted from Figure 2, and the dissolution parameters

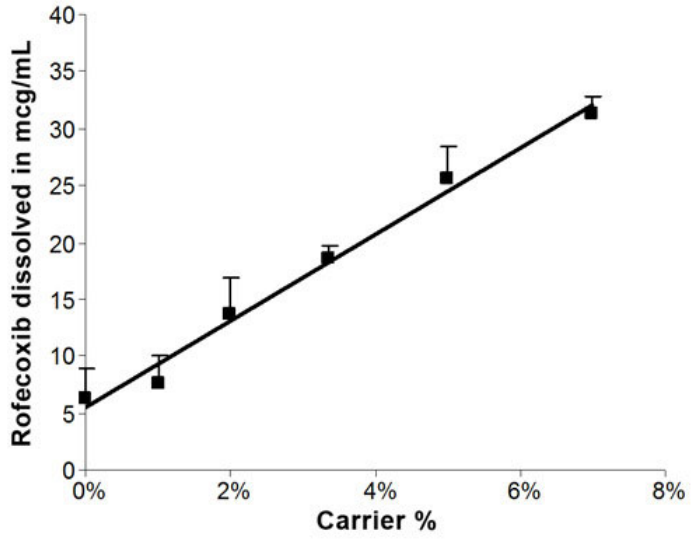

Figure 1. Phase solubility diagram of rofecoxib in water at 25°C in presence of PVP K30.

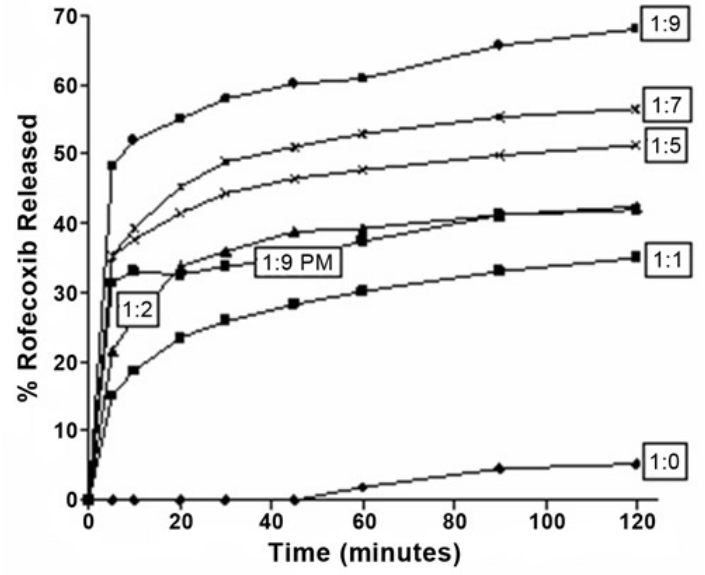

Figure 2. Dissolution profile of rofecoxib from different rofecoxib PVP K30 solid dispersions in distilled water at 37°C.

were used to indicate their characteristics (Table 2). All the release profiles showed 2 different phases of drug release. An initial rapid release phase followed by a slower one. These results could be attributed to the general phenomenon of particle size reduction during the dissolution process. PD_{20} and PD_{60} were greater in magnitude for solid dispersions than for the physical mixtures. This reduction in the time parameters in the dispersion systems preferentially occurred at low rofecoxib contents. For example, the IDR and PD_{60} of rofecoxib from 1:9 rofecoxib-PVP K30 coprecipitate were 2.75%/min and 60.97%, respectively. The IDR and PD_{60} of the corresponding physical mixture were 1.62%/min and 37.32%, respectively. Similar results were described by other authors.[18] Some authors explained this result as the dispersion effect of the hydrophilic carrier and by a possible lowering of the surface tension of the medium by PVP.[18]

Fourier Transform Infrared Spectroscopy

In order to get evidence on the possible interaction of the drug with the carrier, FTIR analysis was used. Figure 3 shows the IR spectra of rofecoxib, PVP K30, and their formulations. Pure rofecoxib displays a peak characteristic of the C-O bending vibration at 1150.5 cm^{-1} and a band with main strong peak at 1747.4 cm^{-1} indicative of the C=O stretch of the ester group. The spectrum of PVP K30 showed important bands at 2955 cm^{-1} (C–H stretch) and 1655 cm^{-1} (C=O). A very broad band was also visible at 3425 cm^{-1} that was attributed to the presence of water confirming the broad endotherm detected in the DSC experiments.[4] In spite of the broad peaks from PVP K30, the FTIR spectra of both physical mixture and solid dispersion still showed peak of the esteric C=O stretch vibration

Table 2. Dissolution Parameters (±SD) of Rofecoxib From Different Rofecoxib PVP K30 Physical Mixtures and Solid Dispersions in Distilled Water*

		IDR (%/min)			PD_{20}			PD_{60}			DE%*10^{-2}		
Rofecoxib		0	±	0	0	±	0	1.92	±	0.1	0.24	±	0.02
	1:1	1.40	±	0.1	28.13	±	1.8	36.98	±	1.3	29.04	±	0.8
	1:2	1.66	±	0.4	33.38	±	3.1	40.57	±	2.6	34.11	±	1.4
PM	**1:5**	1.64	±	0.6	32.97	±	2.1	36.29	±	3.6	31.66	±	1.9
	1:7	2.04	±	0.3	40.85	±	1.7	41.96	±	4.2	38.18	±	2.2
	1:9	1.62	±	0.6	32.55	±	2.1	37.32	±	3.6	32.6	±	1.9
	1:1	1.17	±	0.6	23.56	±	1.3	30.27	±	3.8	23.75	±	2.0
	1:2	1.68	±	0.1	33.8	±	3.0	39.4	±	2.4	32.77	±	2.4
SD	**1:5**	2.07	±	0.3	41.54	±	2.7	47.7	±	2.2	41.34	±	2.7
	1:7	2.26	±	0.3	45.34	±	2.8	53.02	±	2.3	44.95	±	1.3
	1:9	2.75	±	0.3	55.16	±	2.8	60.97	±	2.3	54.49	±	1.3

*PVP indicates polyvinyl pyrrolidone; IDR, initial dissolution rate; PD, percentage of the drug dissolved; DE, dissolution efficiency; PM, physical mixture; and SD, solid dispersion.

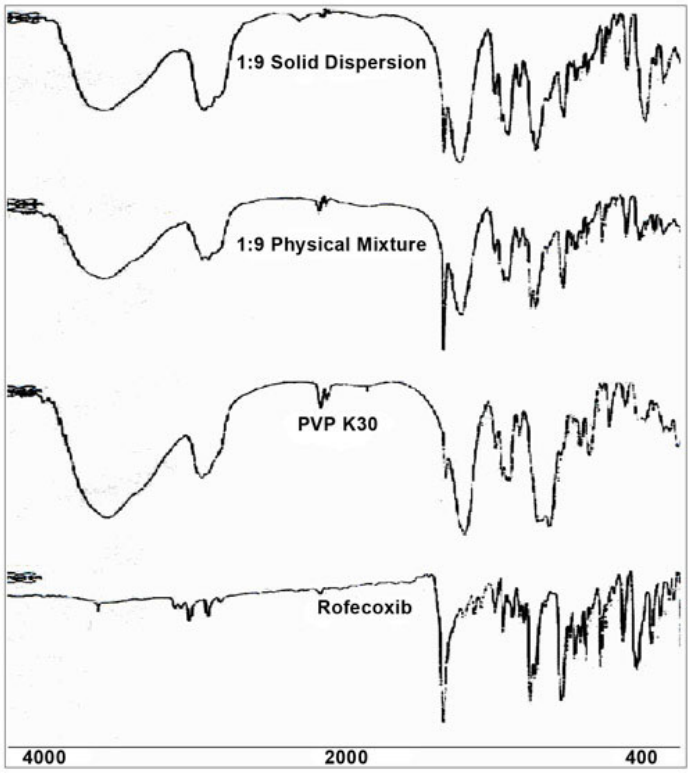

Figure 3. FTIR spectra of solid dispersions of rofecoxib and PVP K30. Pure rofecoxib, PVP K30, 1:9 physical mixture of rofecoxib/ PVP K30, and 1:9 solid dispersion of rofecoxib/ PVP K30 prepared by solvent method.

of the drug. Also a C-O vibration peak was still detected at the same position as that of drug. Consequently, the FTIR spectra of both physical mixture and solid dispersion seemed to be only a summation of drug and PVP K30 spectra. This result suggested that there was no interaction between drug and PVP K30 in their combinations.

X-ray Diffraction and Differential Scanning Calorimetry

The powder diffraction patterns of pure rofecoxib showed characteristic high-intensity diffraction peaks. The powdered PVP K30 was amorphous where it showed only few peaks with very weak intensities. The X-ray diffraction patterns of rofecoxib solid dispersion with PVP K30 showed amorphous pattern. On the other hand, the XRD pattern of 1:9 physical mixture showed partial amorphization of the drug (Figure 4). According to these results, the amorphous property of rofecoxib in its formulation with PVP K30 is considered to be mainly responsible for the dissolution enhancement. A DSC was performed on the individual components, physical mixture, and solid dispersion (results not shown), which also revealed the amorphous nature of the solid dispersion of rofecoxib. According to the FTIR and XRD results, the lower dissolution of the drug from 1:9 than 1:7 physical mixtures could be explained. In case of physical mixtures, increasing the PVP concentrations salted out the drug owing to its partial water solubility. On the other hand, in case of solid dispersions, the drug was amorphous and had higher hydrophilicity, so that PVP concentrations used (1:9) were not enough to salt out the drug. As a result, increasing the PVP loading more than 1:7 in the physical mixture led to drug precipitation; however, it was not the case for the solid dispersions.

Evaluation of Rofecoxib Mouth Dissolve Tablets

In order to select the best superdisintegrant and subliming agent, preliminary trials were conducted as shown in Table 3. All the prepared tablets are characterized by a uniform thickness, diameter, and weight. Based on the disintegration results in Table 3, the investigated superdisintegrants can be ranked according to their ability to swell in water as crospovidone > croscarmellose > sodium starch glycolate 17. Edward[19] stated that wicking and capillary action are postulated to be major factors in the ability of these superdisintegrants to function. The results shown in Table 3 indicate that camphor was more efficient than thymol in shortening both disintegration and wetting times. The porous structure of these tablets is responsible for faster

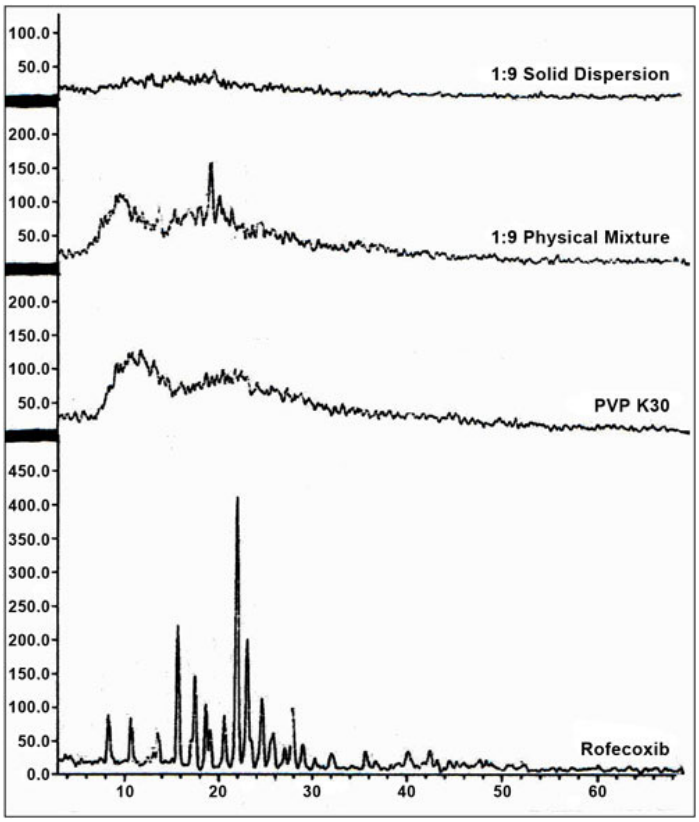

Figure 4. XRD patterns of solid dispersions of rofecoxib and PVP K30. Pure rofecoxib, PVP K30, 1:9 physical mixture of rofecoxib/PVP K30, and 1:9 solid dispersion of rofecoxib/ PVP K30 prepared by solvent method.

Table 3. Composition and Evaluation of Rofecoxib Mouth Dissolve Tablets*

Formulation	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8
1:9 Rofecoxib-PVP K30 solid dispersion	50	50	50	50	50	50	50	50
Superdisintegrants								
- Crospovidone	4	8	12	—	—	12	12	12
- Sodium starch glycolate	—	—	—	12	—	—	—	—
- Croscarmellose sodium	—	—	—	—	12	—	—	—
Subliming agents								
- Camphor	—	—	—	—	—	10	20	—
- Thymol	—	—	—	—	—	—	—	20
Lactose to	100%	100%	100%	100%	100%	100%	100%	100%
Weight (g)	0.240	0.241	0.237	0.244	0.242	0.247	0.239	0.238
Thickness (mm)	2.86	3.1	3.01	2.99	3.03	2.98	3.02	3.02
Diameter (mm)	10.01	10.02	10.02	10.01	10.03	10.05	10.02	10.01
Hardness (Kp)	5.4	4.9	5.1	5.1	5.2	5.1	5.3	5.2
Friability (% loss)	0.107	0.090	0.073	0.075	0.071	0.115	0.124	0.125
Disintegration time (seconds)	445	244	183	255	210	142	95	132
Wetting time (seconds)	402	211	151	215	180	105	60	95

*PVP indicates polyvinyl pyrrolidone; —, value of 0. All batches contained 2% talc and 1% mg stearate.

water uptake, and hence it facilitates wicking action of crospovidone in bringing about faster disintegration.[20] As a result, the batch A_7 containing both 12% crospovidone and 20% camphor exhibited faster disintegration and wetting. Hence, they were selected for further studies.

Factorial Design

In order to investigate the factors systematically, a factorial design was employed. The amount of subliming agent (camphor, X_1) and the superdisintegrant (crospovidone, X_2) were chosen as independent variables in a 3^2 full factorial design. As shown in Equation 1, a statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Yi = b_o + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_1^2 + b_{22}X_2^2, \quad (1)$$

where Yi are the dependent variables, namely, disintegration time and percentage friability; b_0 is the arithmetic mean response of the 9 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

Table 4. 3^2 Full Factorial Design Layout*

	Variables Levels		Disintegration Time	
Batch Code	X_1	X_2	(seconds) ± SD	Friability% ± SD
F_1	−1	−1	445 ± 4.1	0.107 ± 0.012
F_2	−1	0	244 ± 4.2	0.090 ± 0.015
F_3	−1	+1	183 ± 5.12	0.073 ± 0.016
F_4	0	−1	169 ± 5.1	0.150 ± 0.013
F_5	0	0	156 ± 2.31	0.120 ± 0.016
F_6	0	+1	142 ± 2.51	0.115 ± 0.018
F_7	+1	−1	133 ± 4.2	0.222 ± 0.017
F_8	+1	0	118 ± 2.6	0.142 ± 0.014
F_9	+1	+1	95 ± 1.3	0.124 ± 0.011
Checkpoint	−0.2	+0.8	133 ± 2.08	0.101 ± 0.013

	Actual Values (%wt/wt)	
Coded Values	X_1	X_2
−1	0	4
0	10	8
+1	20	12

* X_1 indicates amount of camphor (%wt/wt); X_2, amount of crospovidone (%wt/wt)

Table 5. Summary of Results of Regression Analysis*

For Disintegration Time						
Response	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
FM	141.1	−87.66	−54.5	47.33	21.83	56.00
***P* value**	—	.027	.034	.269	.577	.102
RM	187.2	−87.66	−54.5	—	—	—
***P* value**	—	.016	.045	—	—	—
For Percentage Friability						
Response	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
FM	0.1186	0.036	−0.0278	−0.002	0.0145	−0.016
***P* value**	—	.009	.0187	.8593	.2563	.117
RM	0.1270	0.0363	−0.0278	—	—	—
***P* value**	—	.0031	.0107	—	—	—

*FM indicates full model; RM, reduced model; *P* value, the significance level; —, value not calculated.

changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

The disintegration time and percentage friability for the 9 patches (F_1 to F_9) showed a wide variation from 445 to 95 seconds and from 0.222 to 0.073 percentage loss, respectively (Table 4). The data clearly indicate that the disintegration time and percentage friability values strongly depend on the selected independent variables. The fitted equations (full and reduced models) relating the responses, disintegration time, and percentage friability to the transformed factor are shown in Table 5. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (positive or negative). Table 6 shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors.[21] The high values of correlation coefficient for either disintegration time or percentage friability indicate a good fit (Table 6). Consequently, the equations may be used to obtain estimates of response as a relative small error of variance was noticed in the replicates.

Full and Reduced Models

For both disintegration time and friability, the significance levels of coefficients b_{11}, b_{12}, and b_{22} were found to be more than 0.05, hence they were omitted from the full models to generate the reduced models. On the other hand, the coefficients of b_1 and b_2 were found to be significant at $P < .05$, hence they were retained in the reduced models. The reduced models were tested in portions to determine whether the coefficients b_{11}, b_{12}, and b_{22} contribute significant information for prediction of both disintegration time and friability. The results of testing the models in portions are shown in Table 6. The calculated values of F for $\alpha = 0.05$ were less than its critical value. Consequently, it can be concluded that the terms (X_1^2, X_1X_2, and X_2^2) do not contribute significantly to the prediction of both

Table 6. Calculations for Testing the Models in Portions*

For Disintegration Time					
Regression	DF	SS × 10^3	MS × 10^3	F	r^2
FM	5	**81.9**	**16.38**	6.67	0.9175
RM	2	**63.9**	**31.97**	7.5	0.9161
Error					
FM	3	**3.37**	**2.46**	—	—
RM	6	**2.35**	**4.22**	—	—
For Percentage Friability					
Regression	**DF**	**SS**	**MS**	**F**	r^2
FM	5	0.0140	0.0028	13.04	0.9560
RM	2	0.0126	0.0063	17.97	0.9570
Error					
FM	3	0.0006	0.0002	—	—
RM	6	0.0021	0.0003	—	—

*DF indicates degrees of freedom; SS, sum of squares, MS, mean of squares, r^2, regression coefficient; FM, full model; and RM, reduced model; —, value not calculated.

disintegration time and friability and therefore can be omitted from the full model.

Concerning disintegration time, the results of multiple linear regression analysis (reduced model) showed that both the coefficients b_1 and b_2 bear a negative sign. Therefore, increasing the concentration of either camphor or crospovidone is expected to decrease the disintegration time. When higher percentage of camphor is used, higher porosity is expected in the tablets. The water uptake and subsequent disintegration are thus facilitated. On the other hand, an increase in the concentration of camphor leads to an increase in friability because the coefficient b_1 bears a positive sign. When a higher percentage of camphor is used, more porous and mechanically weak tablets are produced. As indicated by negative sign of the coefficient b_2, the increase in the incorporated amounts of crospovidone resulted in decrease in the friability. Crospovidone is known to produce mechanically strong tablets. A checkpoint batch was prepared at $X_1 = -0.2$ level and $X_2 = 0.8$. From the reduced model, it is expected that the friability value of the checkpoint batch should be 0.098% and the disintegration time should be 130 seconds. Table 4 indicates that the results are as expected. Consequently, we can conclude that the statistical model is mathematically valid. The relationship between the dependent and independent variables was further elucidated using contour plot. The effect of X_1 and X_2 and their interaction on both disintegration time and percentage friability is given in Figure 5. Analysis of contour plot reveals that the whole of the contour area has acceptable friability values. It could be seen that increasing the percentage incorporated of the subliming agent had a negative effect on the disintegration time with a positive effect on the friability. On the other hand, increasing the amount of crospovidone from −0.4 to 1 led to a decline in the disintegration time, while the friability remained within 0.9%. In industry, the total time required for manufacturing a dosage form is of prime concern. Consequently, the arbitrary selection of a batch of tablets with a desired friability and disintegration time can be done considering other aspects such as ease of manufacturing, cost, etc.

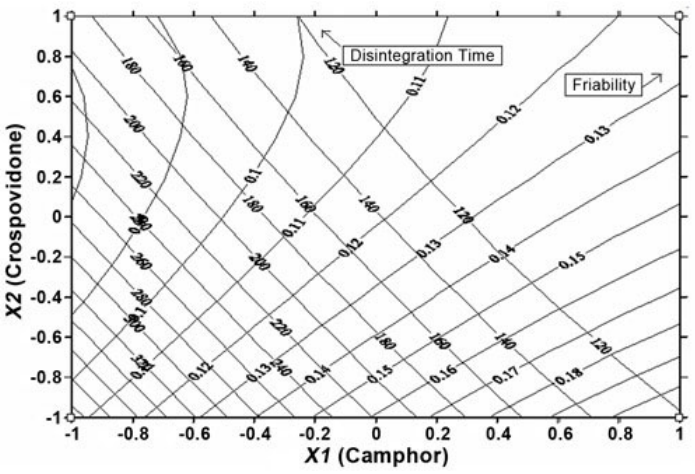

Figure 5. Combined contour plot for disintegration time and percentage friability.

CONCLUSION

The present study showed the suitability of PVP K30 as a carrier for the preparation of rofecoxib solid dispersions. As demonstrated by both XRD and DSC, the amorphization of rofecoxib offered an explanation of better dissolution rate from its solid dispersion. The significant effects of the interaction and polynomial variables on the investigated characteristics of rofecoxib mouth dissolve tablets were verified using 3^2 randomized full and reduced factorial designs. Compared with the experimental optimized preparation, the observed responses were in close agreement with the predicted values of the optimized one, thereby demonstrating the feasibility of the optimization procedure in developing rofecoxib mouth dissolve tablets.

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