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RESEARCH PAPER

Development of Diclofenac Sodium Controlled Release Solid Dispersion Powders and Capsules by Freeze Drying Technique Using Ethylcellulose and Chitosan as Carriers

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ABSTRACT

Controlled-release, solid dispersions of diclofenac sodium (DS) were prepared by freeze-drying technique, using ethylcellulose (EC) and chitosan (CS) as single and combined carriers. Factorial design was applied as an experimental design to study the main and interactive effects of EC and CS on drug dissolution from the controlled release solid dispersion. All DS solid dispersions showed slower drug dissolution than did DS powder. The equations of dissolution parameters as functions of EC and CS contents were established through multiple regression. The contour plots of the established equations were constructed. The 10:(2.4 + 0.05) DS:(EC + CS) solid dispersion was prepared and developed into a capsule dosage from, using lactose as diluent. The effect on capsule dissolution of a disintegrant, sodium starch glycolate (Explotab®), in concentrations of 2%, 5%, and 8% was studied. The solid-dispersion capsule containing 5% Explotab was found to provide the most similar dissolution profile to the one obtained with the 10:(2.4 + 0.05) DS:(EC + CS) solid-dispersion powder. The dissolutions of the 10:(2.4 + 0.05) solid-dispersion powder and capsules were closer to a first-order model than to a zero-order or diffusion control model.

INTRODUCTION

Dissolution retardation through the solid dispersion technique has become a field of interest in recent years. Shaikh et al. (1) prepared prolonged-release solid dispersions of acetaminophen and theophylline by a simple evaporation method, using ethylcellulose (EC) as a water-insoluble carrier. A diclofenac sodium (DS) controlled-release solid dispersion was also developed by spray-drying, and was formulated into a tablet dosage

form with chitosan and EC as single and combined insoluble carriers (2,3). Other insoluble carriers, such as methacrylic acid copolymer (Eudragit®) and carnauba wax, were also investigated in preparing controlled-release solid dispersions (4,5). In general, solid dispersions can be prepared by various techniques, such as simple evaporation, spray drying, and freeze drying (6). Recently, a fast-release, solid dispersion system of indomethacin was successfully prepared by freeze-drying (7). It therefore seemed interesting to attempt to apply this process in preparing controlled release solid dispersions.

In this investigation, controlled-release solid dispersions of diclofenac sodium (DS) were developed by a freeze-drying process, using ethylcellulose (EC) and chitosan (CS) as single and combined carriers. The dissolution-retarding effects of both carriers were investigated. The relationships between drug dissolution and the contents of the two carriers were established by multiple regression. The contour plots of the established relationships were drawn, and the optimum amounts of the two carriers for the maximum required drug dissolutions were predicted.

The next stage of investigation was to formulate the prepared controlled release solid-dispersion system of DS into a capsule dosage form. This part of the study was intended to investigate the influence of a disintegrant, Explotab®, on the capsule prepared from the DS:(EC + CS) solid dispersion powder with lactose as diluent. The optimum concentration of Explotab to be employed in the capsule was then investigated.

MATERIALS

The following chemicals were obtained from commercial sources: DS (Batch No. DFDH 045, CFS PTE Ltd., Switzerland), EC (Ethocel 20 cps, Dow Chemical Company, Midland, MI), chitosan (Unicord PCL Ltd., Thailand). Lactose, sodium starch glycolate (Explotab), and silicon dioxide (Aerosil®) were supplied by Pharmaceutical Science Ltd., Thailand.

METHODS

Preparation of DS: Single-Carrier Solid Dispersions

The ratios of 10:3 DS:EC and 10:0.1 DS:CS were selected because of the high dose of DS for sustained release (8). DS and EC were dissolved separately in absolute ethanol, while CS was dissolved in 1% acetic acid.

Table 1

The Ratios of Diclofenac Sodium, Ethylcellulose, and Chitosan Used in Prepared DS Solid Dispersions According to Two Level Full Factorial Design

	Ratio of			Level of	
Formulation	DS	EC	CS	EC	CS
I	10	1	0	−1	−1
II	10	3	0	1	−1
III	10	1	0.1	−1	1
IV	10	3	0.1	1	1

The mixture formed by adding the polymer solution to the DS solution, was poured into an aluminum tray and placed on a shelf within a chamber of a freeze dryer (Labconco Corp., Model Lyph-Lock 12L, Kansas City, MO). The freeze-drying process was run until a dry, solid dispersion of DS was obtained. The obtained dispersion was then screened through a 40-mesh standard sieve and stored in a desiccator.

Preparation of DS:Combined-Carrier Solid Dispersions

EC as an insoluble polymer, and CS as a polymer that would swell, were used as combined carriers. The DS:(EC + CS) mixture was prepared by adding the polymer solutions to the ethanolic drug solution. According to a full factorial experimental design of two levels (−1 and 1), the ratios of DS:EC:CS used in preparing solid dispersions of DS are given in Table 1. For 10 parts of DS, the −1 level corresponded to 1 part of EC and 0 part of CS, while the 1 level represented 3 parts of EC and 0.1 part of CS, respectively.

Validation of DS:(EC + CS) Solid-Dispersion System

In order to validate the predicted equation of drug dissolution from the DS:(EC + CS) solid-dispersion system, a solid dispersion of 10:(2.4 + 0.05) DS:(EC + CS) was prepared by the same procedure as described above.

Preparation of DS Solid-Dispersion Capsules

The 10:(2.4 + 0.05) DS:(EC + CS) solid dispersion was developed into capsule dosage forms according to

Table 2

Formulations of DS Solid Dispersion Capsules Prepared from 10: (2.4 + 0.05) DS:(EC + CS) Solid Dispersion

Formulation	I	II	III	IV
DS solid dispersion (mg)	124.5	124.5	124.5	124.5
Lactose (mg)	287.1	279.9	269.8	260.7
Explotab® (%)	—	2	5	8
Aerosil® (%)	0.5	0.5	0.5	0.5

the formulations listed in Table 2. Lactose was used as the capsule diluent, while various concentrations of a disintegrant, Explotab (2%, 5%, and 8%) were used in the capsule formulations. Silicon dioxide (Aerosil) was used as a glidant in the capsules. A control capsule containing 0% Explotab was also prepared.

Dissolution Studies

Dissolution studies of DS powder, DS solid-dispersion powders, and DS solid-dispersion capsules equivalent to 100 mg drug were performed according to Method A described under Drug Release in USP XXIII (9), using the USP type II dissolution apparatus (Pharma Test Apparatebau GmbH, Model TW II, Hainburg, Germany) at a stirring rate of 50 rpm. The tests were performed in 0.1 N HCl for 2 hr and in pH 6.8 phosphate buffer solution for a further 10 hr. Sample solutions in acid and buffer media were assayed spectrophotometrically (Milton Roy Company, Ivyland, PA, Spectronic 3000 Array) at 274 nm and 277 nm, respectively, for DS content. The dissolution studies were conducted on six samples obtained with DS powder, each solid dispersion system, and each DS capsule formulation.

Disintegration Studies

Disinegration studies of the DS controlled release solid dispersion capsules were performed by a USP type disintegrator (K.S.L. Engineering Co., Ltd., USP type, Thailand) according to USP XXIII (9), using distilled water as medium. Average disintegration time of a capsule formulation was obtained from six capsules.

RESULTS AND DISCUSSION

Solid Dispersion Systems with Single Carriers

The dissolution profiles of DS powder and of 10:3 DS:EC and 10:0.1 DS:CS solid dispersions are presented in Fig. 1. Because DS dissolved poorly in acid medium (10), the very low percentages of dissolved drug were observed in the first 2 hr. All of the DS solid-dispersion systems exhibited slower dissolutions than did the DS powder. The 10:3 DS:EC solid dispersion exhibited slower drug dissolution than did the 10:0.1 DS:CS solid dispersions.

The dissolution profile of the 10:0.1 DS:CS solid dispersion indicated that CS was not suitable as a single carrier for preparing controlled-release dispersions of DS since its dissolution profile was too fast in the initial period and less than 80% drug dissolution was achieved. The dissolution-retarding effect of chitosan was derived from the swelling action of chitosan upon contact with the acid medium (11). As chitosan swelled, it provided a viscous environment around the drug molecules or colloids, causing slow diffusion of the drug into the surrounding medium, and hence slow drug dissolution.

EC seemed to be more suitable as single carrier for solid dispersions of DS. However, the dissolution profile

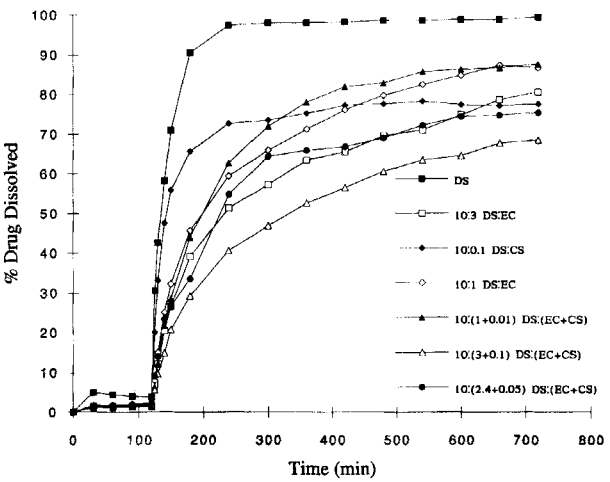

Figure 1. Dissolution profiles of diclofenac sodium powder and diclofenac sodium solid dispersions.

of the 10:3 DS:EC solid dispersion was too slow in the final stage.

The use of EC and CS as combined carriers was an effort to obtain a more suitable dissolution profile for the controlled release DS dispersion. By combining two mechanisms of controlling drug release—dissolution-retarding effects caused by slow release of drug through the viscous environment and by narrow pathway for drug diffusion—an the improvement in the dissolution profile of the DS solid dispersion was expected.

Solid Dispersion Systems with Combined Carriers

For the solid dispersion systems prepared according to the factorial design, the 10:(3 + 0.1) DS:(EC + CS) solid dispersion exhibited the slowest drug dissolution, followed by the 10:3 DS:EC, 10:1 DS:EC, and 10:(1 + 0.1) DS:(EC + CS) dispersions, respectively (Fig. 1).

It was clear that changing the ratio of DS:EC from 10:1 to 10:3 resulted in slower drug dissolution. For a solid dispersion system, the dissolution-modifying effect of a carrier depended on its content. With greater amounts of the carrier, a greater dissolution-modifying effect was expected (12). Dangprasirt and Ritthidej (2) revealed that the greater amount of EC used in preparing spray-dried DS–EC solid dispersions resulted in slower drug release. Increasing the amount of EC in acetaminophen-EC solid dispersion systems prepared by a simple evaporation technique also caused a greater dissolution-retarding effect (1). A greater amount of an insoluble carrier, EC, in the solid dispersion resulted in less pathway available for penetration of dissolution medium and drug diffusion. Thereby, greater retardation in drug dissolution was achieved in the solid dispersion of higher EC content.

Dissolution profiles of the DS:(EC + CS) solid dispersions revealed that the EC:CS ratio was an important factor in controlling the dissolution of the solid dispersion. By comparing dissolution profiles of the 10:1 DS:EC and 10:(1 + 0.1) DS:(EC + CS) solid dispersions, it was evident that the use of combined carriers did not provide a greater dissolution-retarding effect than did the use of single carrier. However, the dissolution profile of the 10:(3 + 0.1) DS:(EC + CS) solid dispersion was slower than the dissolution profile of the 10:3 DS:EC solid dispersion. This result indicated that the dissolution-retarding effect of CS, on the DS:(EC + CS) solid dispersion, due to its viscosity-inducing effect, depended on the amount of EC in the system. Hence, the interactive effect of CS and EC was expected.

In order to identify the interactive effect, the dissolution data for the prepared solid dispersions of DS were subjected to multiple regression, using a statistical computer program. Since the release profile of the ideal controlled release dispersion of DS should follow zero-order kinetics, we set a zero-order dissolution rate constant (K^0) of 0.139 mg/min and the correlation of linearity of dissolution profile (R^2) of the highest value as the ideal criteria for development of the controlled release solid dispersion of DS having an optimum dissolution profile (2). The dissolution profiles of the prepared DS:(EC + CS) solid dispersions were analyzed by linear regression. Their K^0 and R^2 values were computed as listed in Table 3.

By multiple regression, the relationships between K^0 or R^2 and the two variables, the levels of EC (X_1) and CS (X_2) used in preparing the solid dispersions, were established. The K^0 and R^2 equations as functions of the two variable levels were derived and described as follows:

$$K^0 = -0.012899X_1 - 0.005763X_1X_2 - 0.002578X_2 + 0.133273 \quad (r^2 = 1.000) \tag{1}$$

$$R^2 = 0.019151X_1 + 0.008953X_1X_2 + 0.003990X_2 + 0.852938 \quad (r^2 = 1.000) \tag{2}$$

Table 3

K^0 and R^2 of DS:(EC + CS) Solid Dispersions

Ratio of		Level of Reduced Variables			
EC	CS	X_1	X_2	K^0 (mg/min)	R^2
1	0	−1	−1	0.142987	0.838751
3	0	1	−1	0.128715	0.859147
1	0.1	−1	1	0.149357	0.818823
3	0.1	1	1	0.112032	0.885033
2.4	0.05	0.60	0	0.124732	0.829421

Validation of the Predicted Equations

According to the predicted K^0 and R^2 equations, the solid dispersion system of 10:(2.4 + 0.05) DS:(EC + CS), consisting of an X_1 of 0.4 and an X_2 of 0.5 would yield a K^0 of 0.125672 mg/min and R^2 of 0.864384, respectively. The prepared 10:(2.4 + 0.05) DS:(EC + CS) solid dispersion was found to yield a K^0 of 0.124732 mg/min and R^2 of 0.829421. Therefore, the predicted and observed values of K^0 and R^2 were similar, indicating the validity of the predicted equations.

Optimization of the DS:(EC + CS) Solid Dispersions

The contour plots of K^0 and R^2 equations were drawn as shown in Figs. 2(a) and 2(b). From Fig. 2(a) it was shown that the effect of CS (X_1) on K^0 was prominent at higher levels of EC (X_2). When EC was fixed at a high level, increasing CS from −1 to 1 in the DS:(EC + CS) solid-dispersion system resulted in a higher degree of dissolution retardation than when EC was fixed at a low level. The effect of CS on R^2 was also more prominent at a high EC level than at a low EC level.

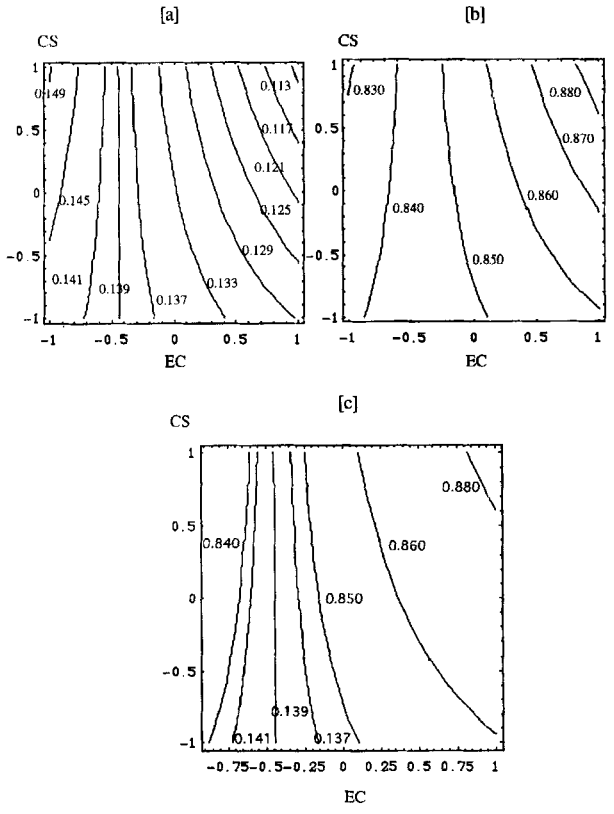

Figure 2. Contour plots of (a) K^0 and (b) R^2 as function of EC and CS levels. (c) Superimposed contour plots of K^0 and R^2 equations as functions of EC and CS.

Superimposition of the contour plots, as demonstrated in Fig. 2(c), revealed a restricted area containing the K^0 values of 0.137 to 0.141 mg/min and R^2 values of 0.840 to 0.850. Within this area, the levels of X_1 and X_2 yielding the required K^0 of between 0.137 to 0.141 mg/min and the required highest R^2 value could be selected. From this superimposed contour plot, the dissolution profile yielding the required K^0 with the highest R^2 could be obtained from various sets of X_1 and X_2 levels. From the contour line of 0.137 mg/min (K^0), it was shown that if EC and CS levels were set at −0.15 and −1 (EC:CS = 1.85:0), respectively, then increasing the CS level to 1 and decreasing the EC level to −0.35 (EC:CS = 1.65:0.1) would result in the same K^0 of 0.137. Thus, the a smaller amount of EC could be used in order to obtain the same K^0 by adding a small amount of CS into the solid-dispersion system. From Figure 2(c) it was also seen that changing the EC:CS ratio from 1.85:0 to 1.65:0.1 did not result in a significant change in the R^2 value.

Development of DS Controlled Release Capsules

The prepared 10:(2.4 + 0.05) DS:(EC + CS) solid dispersion was developed into a capsule dosage form. A water-soluble diluent, lactose, was selected because of its hydrophilicity, which would impart little dissolution-retarding effect to the solid dispersion with packing into capsules. The 10:(2.4 + 0.05) DS:(EC + CS) solid dispersion was chosen as a model solid dispersion to be developed into a capsule formulation because its dissolution profile lay between the profiles of the 10:0.1 DS:CS and 10:3 DS:EC solid dispersions. The effect of the disintegrant Explotab was studied by varying its concentration (0%, 2%, 5%, and 8%) in the capsule formulations. The goal of the investigation was to develop a solid-dispersion capsule having the closest dissolution to the solid-dispersion powder being encapsulated. Therefore, a dissolution parameter indicating the characteristic of the dissolution profile had to be established.

Figure 3 illustrates dissolution profiles of the DS controlled-release solid-dispersion capsules as compared to that of the solid dispersion powder. Table 4 shows the r^2 values (correlation coefficients) of the plots between time and log-percentage of drug remaining undissolved (first-order model) as compared to the plots between time and percentage of drug dissolved (zero-order model) and between the square root of time and percentage of drug dissolved (diffusion control model) for the 10:(2.4 + 0.05)

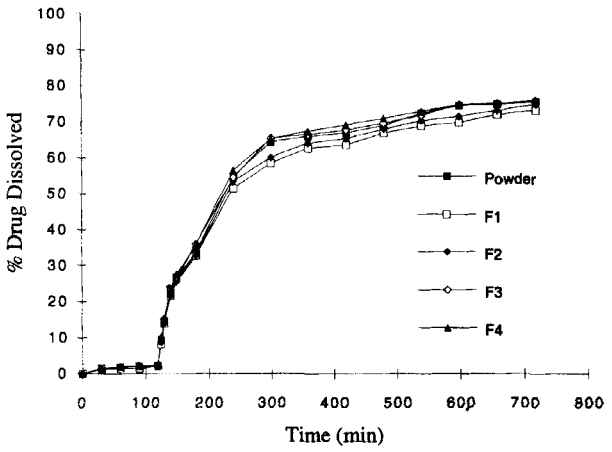

Figure 3. Dissolution profiles of the 10:(2.4 + 0.05) DS:(EC + CS) controlled-release solid-dispersion capsules as compared to the profile of the solid dispersion powder.

DS:(EC + CS) solid dispersions and capsules from 2 to 12 hr. The plots for the zero-order model and diffusion control model were found to yield a smaller r^2 than the plot of the first-order model. Therefore, the dissolutions of the solid-dispersion powder and capsules were found to follow the first order model rather than the zero-order or diffusion control model. Hence, the first-order dissolution rate constant (K^1) from 2 to 12 hr was chosen as the dissolution parameter in determining the dissolution rate of the solid dispersion powder and capsules. The K^1 values of the 10:(2.4 + 0.05) DS:(EC + CS) solid-dispersion and capsules are listed in Table 4.

Since the K^1 of the solid-dispersion powder was 0.000950 min^{-1}, a capsule having a K^1 of 0.000950 min^{-1} was the prime target of capsule formulation development. As shown in Fig. 3, the capsules containing 5% Explotab exhibited the most similar dissolution profile to the solid-dispersion powder. The dissolution profiles of the capsules with 0% and 2% Explotab were comparable, and the dissolution profiles of the capsules of 5% and 8% Explotab were similar. The capsule of 8% Explotab showed the fastest dissolution, followed by the capsules of 5%, 2%, and 0% Explotab, respectively. Hence, increasing the Explotab concentration resulted in faster capsule dissolution. The capsules of 0% Explotab provided less drug dissolution than did the solid-dispersion powder. Thereby, the incorporation of the solid-dispersion powder into capsules, using lactose as diluent, resulted in less drug dissolution. The use of the disintegrant Explotab in the capsule was proven to help in restoring drug dissolution; however, an adequate concentration of the disintegrant was needed.

Disintegration times (DTs) of DS controlled-release solid-dispersion capsules are shown in Table 4, and ranged from 1.98 to 3.67 min. Since lactose was a water-soluble diluent, it provided no disintegration-retardation effect. All of the capsule formulations provided similar dissolution profiles during their initial stages of drug dissolutions and the capsule disintegration times were therefore not responsible for the differences in the capsule dissolutions. As the capsules disintegrated, they yielded coarse powder agglomerates of small size, which could pass through the 10-mesh sieve of the disintegrator within a short period of time. The coarse agglomerates then disintegrated further into fine powders. The effect of Explotab as a disintegrant was not significant in the initial stage of capsule disintegration. However, its influence was more significant in the latter stage of powder-agglomerate disintegration. Faster disintegration of the powder agglomerate resulted in faster drug dissolution, owing to a greater surface area available for the dissolution process. This was responsible for faster capsule dis-

Table 4

DT, K^1 (2 to 12 hr), and r^2 of Dissolution Data (2 to 12 hr) as Zero-Order or First-Order or Diffusion Control Model of 10:(2.4 + 0.05) DS:(EC + CS) Solid Dispersion Powder and Capsules

Preparation	Explotab® (%)	K^1 (per min)	r^2 Zero-Order	r^2 First-Order	r^2 Diffusion Control	DT ± SD (min)
Powder	—	0.000950	0.783137	0.875900	0.859146	—
Capsule	0	0.000870	0.801407	0.891200	0.874577	3.67 ± 0.26
Capsule	2	0.000910	0.796768	0.888879	0.870930	2.94 ± 0.11
Capsule	5	0.000950	0.778432	0.869865	0.855588	2.60 ± 0.15
Capsule	8	0.000970	0.769042	0.859686	0.848104	1.98 ± 0.15

solution as the Explotab concentration in the capsule was increased.

The relationship between K^1 and the Explotab concentration (%) for the DS controlled-release solid-dispersion capsules was derived with a statistical computer program and represented by the following second-order polynomial equation.

$$K^1 = 0.000022X - 0.000001X^2 + 0.000870 \quad (r^2 = 0.999911) \qquad (3)$$

From the predicted equation, the 4.6% concentration of Explotab needed to yield the required K^1 of 0.000950 min^{-1} was computed. This meant that the use of 4.6% Explotab in the 10:(2.4 + 0.05) DS:(EC + CS) solid-dispersion capsule would provide the drug dissolution most similar to the 10:(2.4 + 0.05) DS:(EC + CS) solid-dispersion powder. By varying the Explotab concentration from 0% to 8%, the 10:(2.4 + 0.05) DS:(EC + CS) controlled-release solid-dispersion could be developed into capsules with various dissolutions, ranging from a K^1 of 0.000870 min^{-1} to a K^1 of 0.000970 min^{-1}. Therefore, the DS controlled-release solid-dispersion capsule with a particular required dissolution (K^1 of 0.000870 to 0.000970 min^{-1}) could be formulated from the 10:(2.4 + 0.05) DS:(EC + CS) solid dispersion by choosing an optimum concentration of Explotab.

CONCLUSION

This study demonstrated the application of a freeze-drying technique in preparing DS controlled release solid dispersions. The use of EC and CS as single and combined carriers was proven useful in retarding drug release from the DS solid dispersions. In the solid-dispersion system consisting of EC in a high ratio, the use of EC and CS as combined carriers yielded a greater dissolution-retarding effect than the use of each polymer as a single carrier. By using multiple regression and contour plots, the ratio of EC:CS that would yield the solid dispersion with the most optimum dissolution profile could be chosen. The freeze-dried DS:(EC + CS) solid dispersion could be developed into a capsule dosage form without altering drug dissolution, by using lactose as diluent and an optimum amount of Explotab as disintegrant.

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