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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF RACECADOTRIL BY SOLID DISPERSION METHODS

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ABSTRACT

The aim of present work was to enhance the solubility and dissolution rate of poorly water soluble drug, racecodotril by solid dispersion methods. In the present work, solid dispersion of racecadotril were prepared with a carriers like poly vinyl pyrrolidone K30 (PVP K30), polyethylene glycol 6000 (PEG6000) and poloxamer 188 by using kneading, melting, solvent evaporation, freeze drying and physical mixing methods in the 1 : 1, 1 : 2, 1 : 3, 1 : 4 ratios of drug and carrier, respectively. The formulations were further characterized for drug content, solubility, drug release studies. The interaction between drug and carrier was evaluated by using Fourier transform-infra red (FTIR) and Differential scanning calorimetry (DSC) studies. Powder X-ray diffraction (PXRD) studies were also carried out to find out the crystallinity of solid dispersion. All the prepared solid dispersions were found to be fine free flowing powders and drug content was uniform in all formulations. Solubility studies were performed using the distilled water and buffer pH 1.2. It was observed that the solid dispersions have highest solubility compared to pure drug and physical mixture in both medium. The dissolution tests were performed using the USP dissolution apparatus type-I (Basket) in acid buffer solution pH 1.2 for 1 hour. The dissolution rates of racecadotril solid dispersions were much higher than the corresponding physical mixture and pure drug. The results of FTIR revealed that there was no existence chemical interaction between the drug and carriers. The PXRD studies showed that the drug was in amorphous state completely entrapped by the carriers.

Key words: Racecadotril, Solid dispersion, Solubility, Dissolution rate, Freeze drying method, Kneading method.

INTRODUCTION

Aqueous solubility and dissolution are two of the crucial factors influencing drug absorption from the gastrointestinal tract. The solubility behaviour of a drug is the key determinant of its oral bioavailability. Potential bioavailability problems are prevalent with extremely hydrophobic drugs due to erratic or incomplete absorption from gastro intestinal tract (GIT). The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. Although salt formation, solubilisation and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs there are practical limitation of these techniques. In 1961, Sekiguchi and Obi[1] developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome. This method, which was later, termed solid

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dispersion which involved the formation of eutectic mixture of drugs with water soluble carriers by the melting of their physical mixtures. Racecadotril is the first truly intestinal anti-secretary drug treatment of diarrhoea. One of the major problems with this drug is its practically insoluble in water. In the present work undertaken was to enhance the solubility and dissolution rate of racecadotril by solid dispersion technique using water soluble carriers like PEG6000, PVP K30 and Poloxamer 188. The prepared solid dispersions were evaluated for drug content, *in vitro* dissolution rate studies, solubility studies, crystallinity studies and interactions between drug and carriers using FT-IR spectral studies.

EXPERIMENTAL

Materials and methods

Racecadotril was a generous gift from Safe Tab Life Science Laboratory, Pondicherry. PEG 6000 was purchased from S.D. Fine Chem. Ltd. Mumbai. PVP K30, Poloxamer 188 and Hydrochloric acid was purchased from Nice Chemicals, Kochi. Potassium chloride was purchased from CDH, New Delhi. Methanol was purchased from Astron Chemicals, Ahmadabad. All other chemicals used were of analytical grade.

Preformulation studies

Differential scanning calorimetry (DSC)

The possibility of drug-polymer interaction was investigated by Differential scanning calorimetry (DSC 200 TA Instruments, USA). The DSC thermograms of pure drug and the polymers were recorded to study the interactions between drug and polymers. The samples were separately sealed in aluminium cells and set in a thermal analyzer. The thermal analysis was performed at a scanning rate of 10^{o}C per minute over a temperature range of 50-200^{o}C. Alumina was employed as the reference standard.

Fourier transform-infra red (FT-IR)[18]

While studying the new formulation it is necessary to check the compatibility with the carrier or excipient used and has not undergone any degradation during storage. FT-IR spectra (Spectrum RX-1 Perkin-Elmer, German) for the drug and various physical mixtures are obtained in the transmission mode with the wave number region 4000-400 cm^{-1}. KBr pellets are prepared by gently mixing 1 mg sample powder with 100 mg KBr.

Preparation of racecadotril solid dispersion

Melting method[6]

Water soluble carriers (PEG 6000 and Poloxamer 188) are taken in a china dish and heated at 60ºC in a water bath, until the mixture melts completely. The drug (Racecadotril) is added to the molten polymer and mixed thoroughly. The dispersion is cooled to ambient condition. Solidified mass is crushed, pulverized and passed through sieve No. 120 and stored in a desiccator.

Kneading method[7]

A mixture of drug (Racecadotril) and carriers (PEG 6000, PVP K30 and Poloxamer 188) in different ratios (1 : 1, 1 : 2, 1 : 3, 1 : 4) are wetted with solvent (methanol) and water (1 : 1 ratio) and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed is dried under vacuum for 24 hours. Dried powder is scrapped, crushed, pulverized and passed through sieve No. 120 and stored in a desiccator.

Solvent evaporation method[5]

Racecadotril solid dispersions are prepared by solvent evaporation method using carrier PVP K 30 in proportions viz., (1 : 1, 1 : 2, 1 : 3 and 1 : 4). The drug and carrier are dissolved in methanol in a china dish and the mixture is heated until the solvent evaporated and clear film of drug and carrier is obtained. The resultant solid dispersion is scraped out with a spatula. Solid dispersions are pulverized in a mortar and pestle and passed through a 125 μm sieve before packing in an airtight container.

Freeze drying method[8]

Hydrophilic carrier (PVP K30) is dissolved in organic solvent (methanol), poorly water soluble drug (Racecadotril) is added to this separately and dissolved. The resulting ternary system of organic solvent, hydrophilic carrier and drug is freeze dried by filling glass vials with the solutions and positioning the vials in a lyophilizer. During operation, the freeze dried is maintained at – 45^{o}C and a compression pressure of 0.5 torr. After complete drying, the vials are taken out, and the dried products are scraped from the vials. The formulations are powdered and packaged in glass vials.

Preparation of physical mixture[9]

The physical mixture is prepared by mixing of drug and carrier in a glass mortar. Solid mass is pulverized and passed through sieve No. 120 to get uniform sized particles.

Characterization

Estimation of drug content[10]

Physical mixtures and solid dispersions equivalent to 10 mg of racecadotril are weighed accurately and dissolved in 10 mL of methanol. The solution is filtered, diluted suitably with acid buffer pH 1.2 and drug content is analyzed at 232 nm by UV-spectrophotometer.

$$\% \text{ Drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

In vitro dissolution studies[11]

Dissolution study is carried out by using USP rotating basket apparatus (Type I) for 1 hour, the stirring rate is 100 rpm. Acid buffer pH 1.2 is used as dissolution medium (900 mL) and temperature is maintained at 37 ± 0.5^{o}C. Samples equivalent to 100 mg of racecadotril is filled in hard gelatin capsules used for dissolution studies. Samples are collected at regular interval of time (5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 min). The absorbance of the samples is measured at λ_{max} 232 nm after suitable dilution using appropriate blank.

Solubility studies[11]

Solubility study is assessed out according to the method of Higuchi and Connors. The solubility of racecadotril as pure drug, physical mixture and solid dispersion (KM 7) are determined in distilled water and acid buffer pH 1.2. Samples equivalent to 10 mg of drug is taken and to this 10 mL of respective medium is being added in 250 mL conical flask, and shaken for 24 hours at room temperature on rotary flask shaker (Secor, India). The entire samples are protected from light by wrapping the flask by aluminum foil. After 24 hours samples are filtered through whatmann filter paper No. 42 and aliquots are suitably diluted and assayed by spectrophotometrically at 232 nm.

Powder X ray diffraction (PXRD) studies[2]

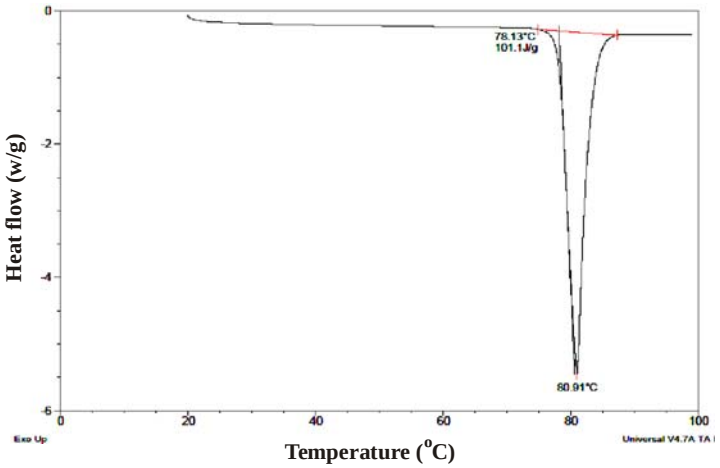
Powder X-ray diffraction patterns (PXRD) of the pure drug, physical mixture (PM7) and solid dispersion (KM7) were monitored with an X-Ray diffractometer (XD, Shimadzu, Japan) using copper as x-ray target, a voltage of 40 KV, a current of 30 mA and with 1.5404 Angstrom wavelength. The samples were analyzed over 2θ range of 7.02-59.980 with scanning step size of 0.020 (2θ) and scan step time of one second.

RESULTS AND DISCUSSION

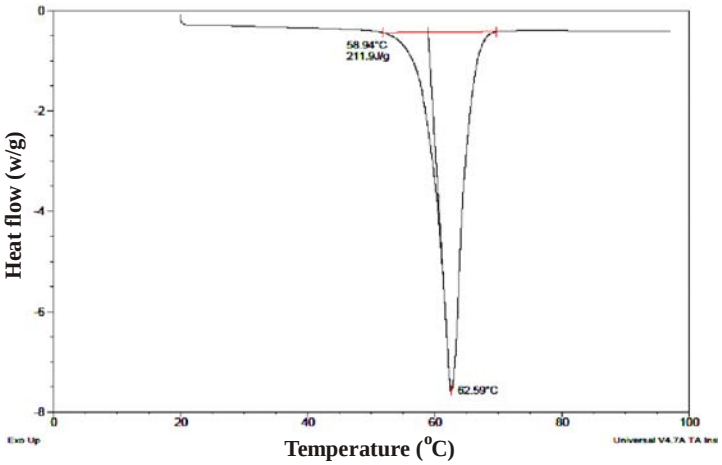
Preformulation studies

Differential scanning calorimetry (DSC)[12,16]

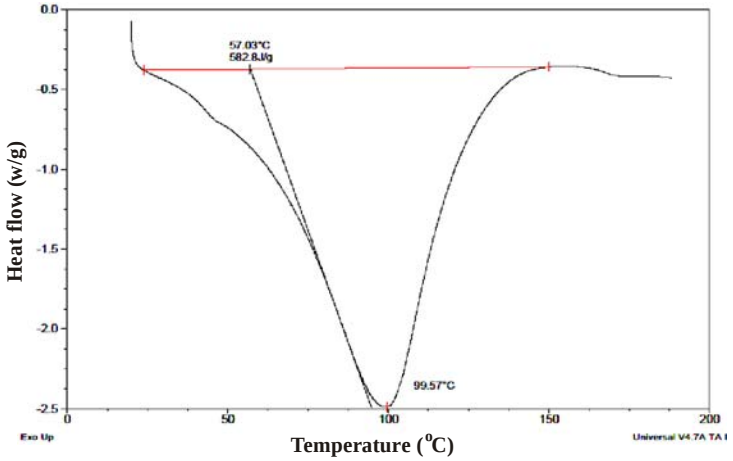
The DSC thermograms of racecadotril and of its physical mixtures are shown in Fig. 1. The sharp melting point peak of pure racecadotril appeared at 80.9°C, whereas no such peak was observed in physical mixtures (1 : 1) prepared with PEG 6000, PVP K 30 and Poloxamer 188, suggesting that racecadotril was molecularly dispersed and in an amorphous form.



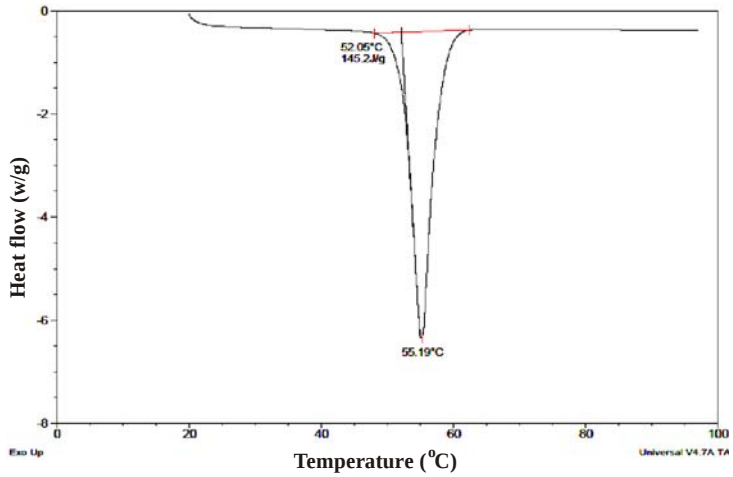
(a) Pure drug- Racecadotril



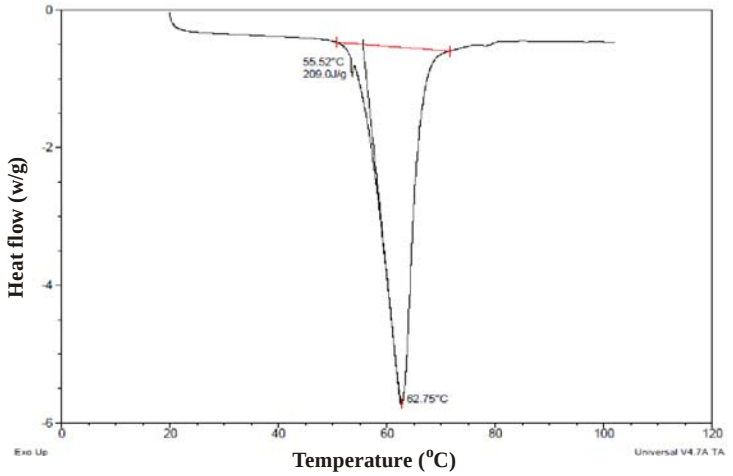
(b) PEG 6000



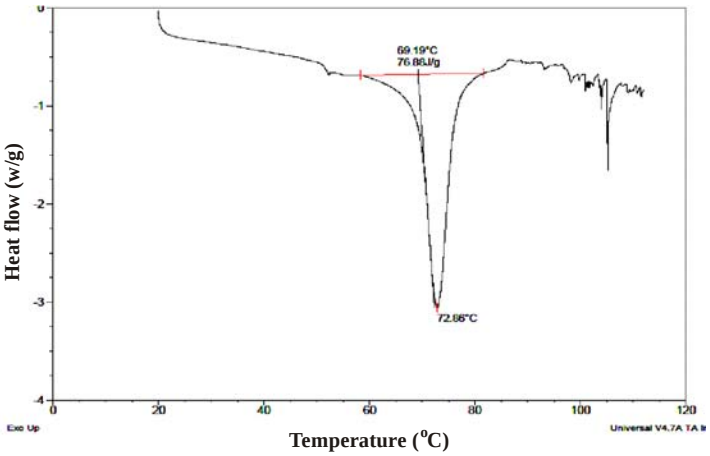
(c) PVP K30



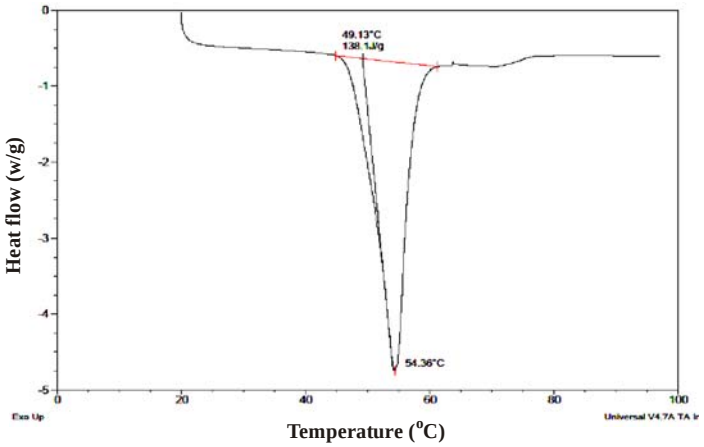
(d) Poloxamer 188



(e) Drug + PEG 6000



(f) Drug + PVP K30

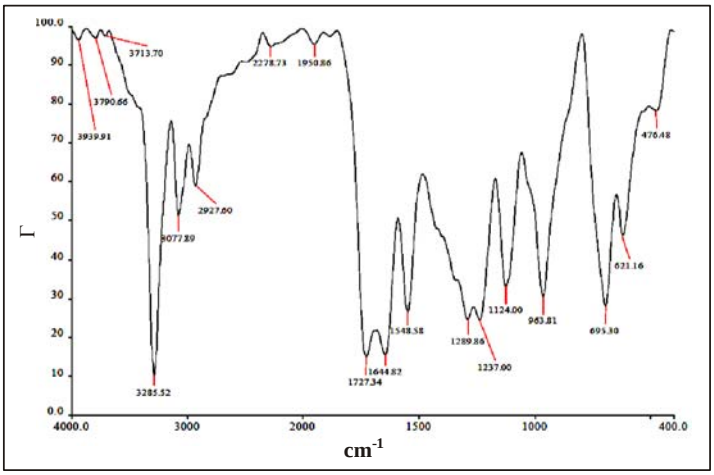


(g) Drug + Poloxamer 188

Fig. 1: DSC thermograms

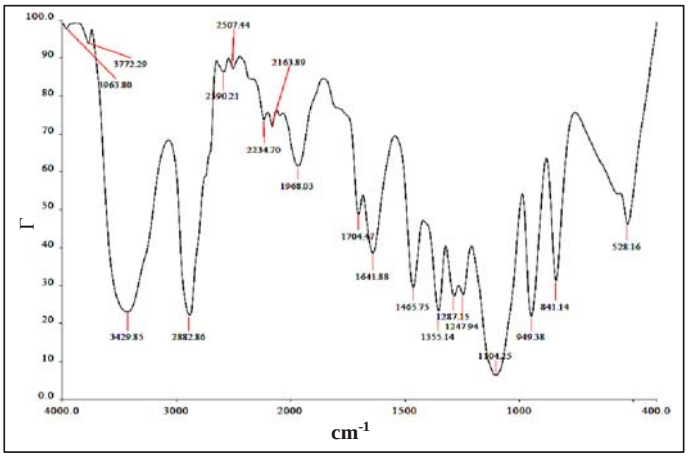
Fourier transform-infra red (FT-IR)[13]

The FT-IR spectra of racecadotril and its binary systems with PVP K30, PEG 6000 and Poloxamer 188 are present in Fig. 2.

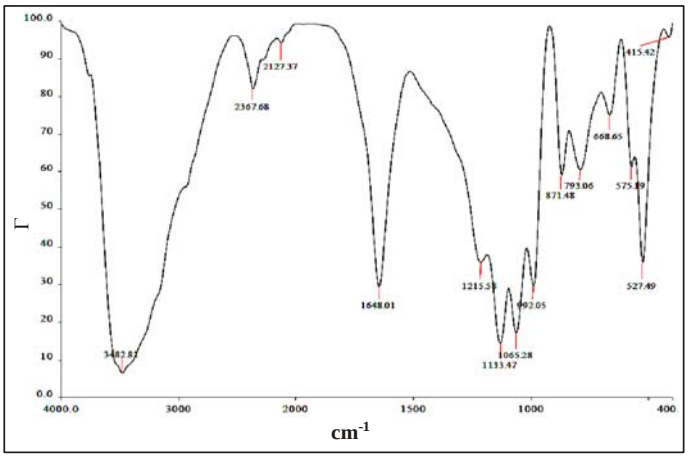


(a) Pure drug-Racecadotril

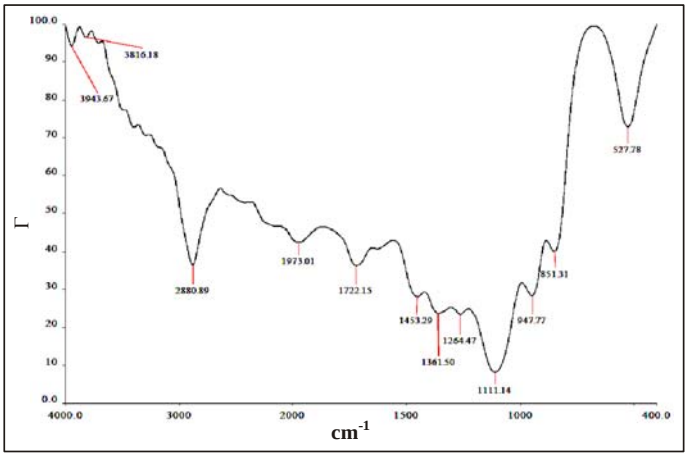
Pure racecadotril spectra showed sharp characteristic peaks at 3939.91, 3285.52, 1950.86, 1644.82, 1289.86, 695.30 cm^{-1}. All the above characteristic peaks appear in the spectra of all binary systems are within the same wave number indicating no modification or interaction between drug and carrier.



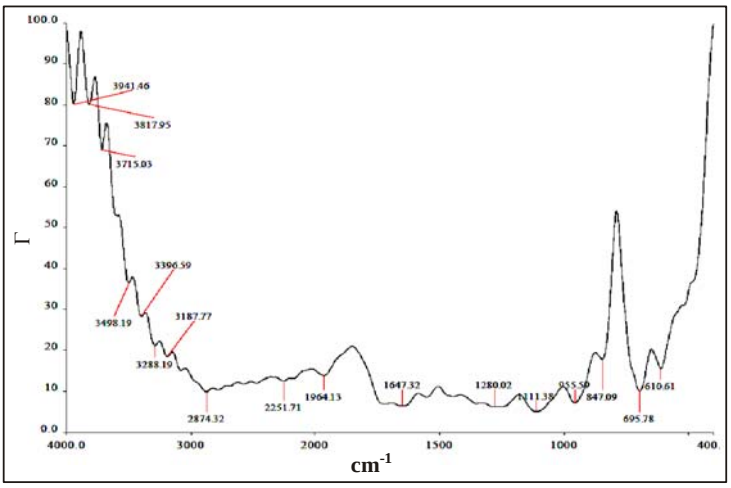
(b) PEG 6000



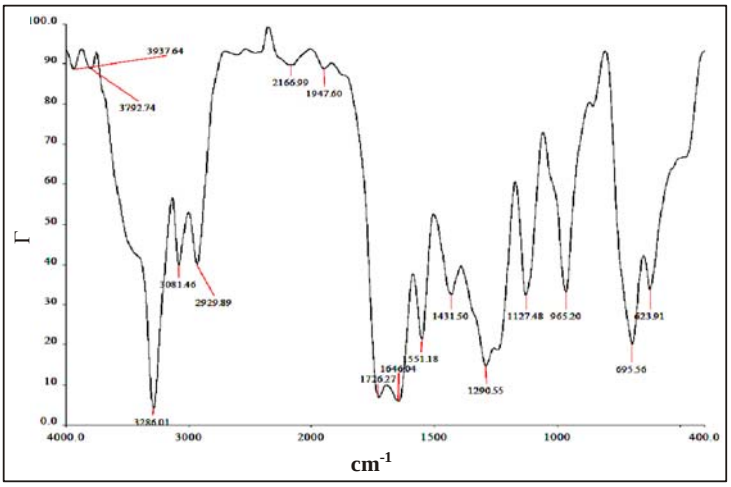
(c) PVP K30



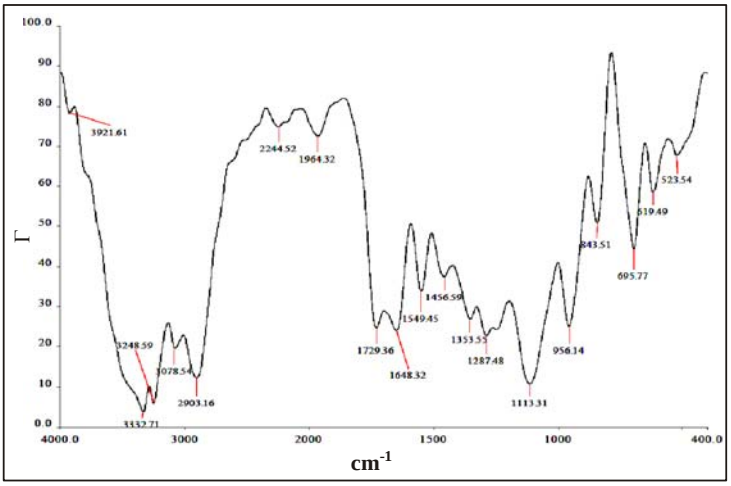
(d) Poloxamer 188



(e) Drug + PEG 6000



(f) Drug + PVP K30



(g) Drug + Poloxamer 188

Fig. 2: FT-IR spectra

Preparation of racecadotril solid dispersions[8]

In the present study, 28 formulations of racecadotril solid dispersions were prepared by using water soluble carriers like PEG6000, Poloxamer 188 and PVP K30, in the ratio of 1 : 1, 1 : 2. 1 : 3 and 1 : 4 in 4 methods (melting method, kneading method, solvent evaporation method and freeze drying method) (Table 1). The prepared solid dispersions were found to be uniform and homogeneous in appearance. PEG 6000 and Poloxamer 188 were used in the preparation of both melting and kneading method (16 formulations), but PVP K30 used in the preparation of kneading method, solvent evaporation method and freeze drying method (12 formulations), because of its hygroscopic nature.

Table 1: Preparation of racecadotril solid dispersions

S. No.	Formulation code	Composition	Ratio	Method
1	KM 1	Drug : PEG 6000	1 : 1	Kneading
2	KM 2	Drug : PEG 6000	1 : 2	Kneading
3	KM 3	Drug : PEG 6000	1 : 3	Kneading
4	KM 4	Drug : PEG 6000	1 : 4	Kneading
5	KM 5	Drug : PVP K30	1 : 1	Kneading
6	KM 6	Drug : PVP K30	1 : 2	Kneading
7	KM 7	Drug : PVP K30	1 : 3	Kneading
8	KM 8	Drug : PVP K30	1 : 4	Kneading
9	KM 9	Drug : Poloxamer 188	1 : 1	Kneading
10	KM 10	Drug : Poloxamer 188	1 : 2	Kneading
11	KM 11	Drug : Poloxamer 188	1 : 3	Kneading
12	KM 12	Drug : Poloxamer 188	1 : 4	Kneading
13	MM 1	Drug : PEG 6000	1 : 1	Melting
14	MM 2	Drug : PEG 6000	1 : 2	Melting
15	MM 3	Drug : PEG 6000	1 : 3	Melting
16	MM 4	Drug : PEG 6000	1 : 4	Melting
17	MM 5	Drug : Poloxamer 188	1 : 1	Melting
18	MM 6	Drug : Poloxamer 188	1 : 2	Melting
19	MM 7	Drug : Poloxamer 188	1 : 3	Melting
20	MM 8	Drug : Poloxamer 188	1 : 4	Melting
21	FD 1	Drug : PVP K30	1 : 1	Freeze drying
22	FD 2	Drug : PVP K30	1 : 2	Freeze drying
23	FD 3	Drug : PVP K30	1 : 3	Freeze drying
24	FD 4	Drug : PVP K30	1 : 4	Freeze drying
25	SEM 1	Drug : PVP K30	1 : 1	Solvent evaporation
26	SEM 2	Drug : PVP K30	1 : 2	Solvent evaporation
27	SEM 3	Drug : PVP K30	1 : 3	Solvent evaporation
28	SEM 4	Drug : PVP K30	1 : 4	Solvent evaporation

Characterization

Estimation of drug content[14]

The drug content in all the formulations was estimated spectrophotometrically at 232 nm (Shimadzu UV 1700, Pharmaspec, Japan). The drug content of the prepared solid dispersions was found to be in the range of 95 % to 101.3% indicating the uniform distribution of drug in the formulation (Table 2).

Table 2: Percentage drug content

S. No.	Formulation code	% Drug content (mean ± SD*)
1	KM 1	95.30 ± 2.72
2	KM 2	95.00 ± 2.40
3	KM 3	95.50 ± 3.31
4	KM 4	98.80 ± 3.67
5	KM 5	96.60 ± 1.40
6	KM 6	96.40 ± 1.04
7	KM 7	95.20 ± 2.00
8	KM 8	96.10 ± 0.37
9	KM 9	97.00 ± 2.33
10	KM 10	99.90 ± 4.83
11	KM 11	98.50 ± 0.75
12	KM 12	96.60 ± 0.99
13	MM 1	101.3 ± 1.68
14	MM 2	98.60 ± 1.68
15	MM 3	97.80 ± 2.14
16	MM 4	98.30 ± 5.80
17	MM 5	95.80 ± 1.40
18	MM 6	97.50 ± 1.30
19	MM 7	96.10 ± 2.72
20	MM 8	98.50 ± 2.72
21	FD 1	100.5 ± 1.68
22	FD 2	101.3 ± 3.69
23	FD 3	96.40 ± 3.17
24	FD 4	99.90 ± 2.89
25	SEM 1	97.20 ± 0.99
26	SEM 2	99.40 ± 1.04
27	SEM 3	99.60 ± 1.40
28	SEM 4	99.90 ± 1.34

*n=3

In vitro release studies[5,15-17]

The *in vitro* release studies were carried out for the racecadotril solid dispersions prepared by 4 methods, namely kneading, melting, solvent evaporation and freeze drying methods. In all the 4 methods the drug and polymer ratios used was 1 : 1, 1 : 2, 1 : 3 and 1 : 4.

In kneading method, 3 different carriers were used. The release profiles of PEG 6000, were found to be 44.4% (KM1), 56.5 % (KM2), 45.3 % (KM3), 47.9 % (KM4) after 1 hour (Fig. 3). From the results, it was observed that KM2 (1 : 2 ratio) exhibits maximum release of 56.5% and it was rated as the best formulation in this method. In case of PVP K30, were found to be 46.4% (KM5), 43.7% (KM6), 72.7% (KM7), 52% (KM8) after 1 hour (Fig. 4). From the results, it was observed that KM7 (1 : 3 ratio) exhibits maximum release of 72.7% and it was rated as the best formulation in this method. The release profile of Poloxamer 188, were found to be 57.5 % (KM 9), 57.3% (KM 10), 57.8% (KM11), 53.1 % (KM 12) after 1 hour (Fig. 5). From the results, it was observed that KM11 (1 : 3 ratio) exhibits maximum release of 57.8% and it was rated as the best formulation in this method.

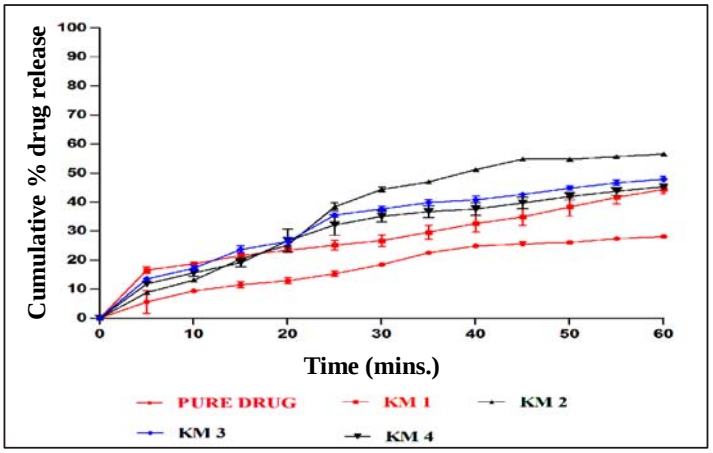


Fig. 3: Comparison of *in vitro* release profile of racecadotril using PEG 6000 by kneading method

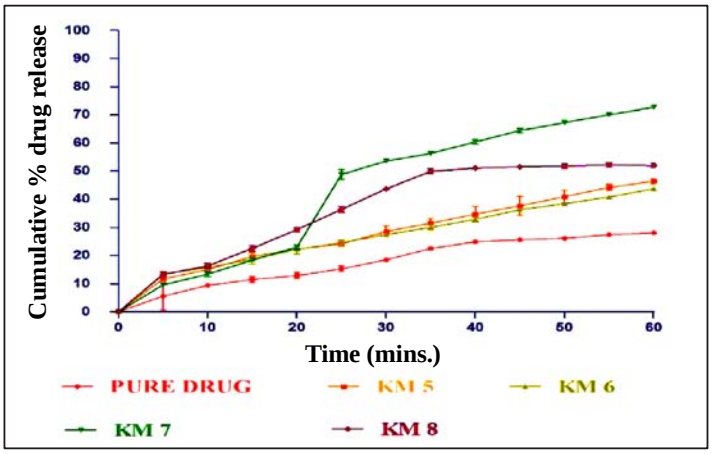


Fig. 4: Comparison of *in vitro* release profile of racecadotril using PVP K30 by kneading method

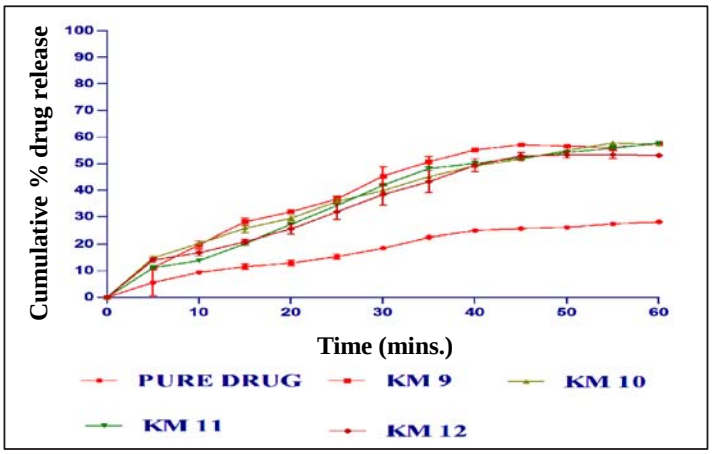


Fig. 5: Comparison of *in vitro* release profile of racecadotril using poloxamer 188 by kneading method

In melting method, two different carriers were used. The release profiles of PEG 6000, were found to be 55.8% (MM1), 59.7% (MM2), 57.7% (MM3), 46.6% (MM4) after 1 hour (Fig. 6). From the results, it was observed that MM2 (1 : 2 ratio) exhibits maximum release of 59.7% and it was rated as the best formulation in melting method using PEG 6000. In case of Poloxamer188, were found to be 55.8 % (MM5), 52.5 % (MM6), 51.3 % (MM7), 50.7% (MM8) after 1 hour (Fig. 7). From the results, it was observed that MM5 (1 : 1 ratio) exhibits maximum release of 55.8% and it was rated as the best formulation in melting method using Poloxamer 188.

In freeze drying method, PVP K30 was used as a carrier. The release profiles of PVP K 30, were found to be 47.4% (FD1), 56% (FD 2), 60.6% (FD 3), 58.2% (FD 4) after 1 hour (Fig. 8). From the results it was observed that the release profile of FD3 (1 : 3 ratio) is higher than the release profiles of other formulations in this method.

In solvent evaporation method, PVP K30 was used as a carrier. The release profiles of PVP K30, were found to be 69.4% (SEM 1), 54.2% (SEM 2), 63.2% (SEM 3), 51.3% (SEM 4) after 1 hour (Fig. 9). From the results it was observed that the release profile of SEM 1 (1 : 1 ratio) is higher than the release profiles of other formulations in this method.

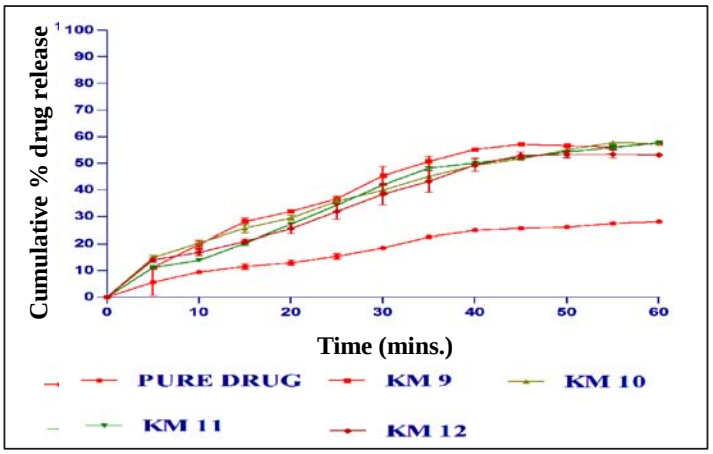


Fig. 6: Comparison of *in vitro* release profile of racecadotril using PEG 6000 by melting method

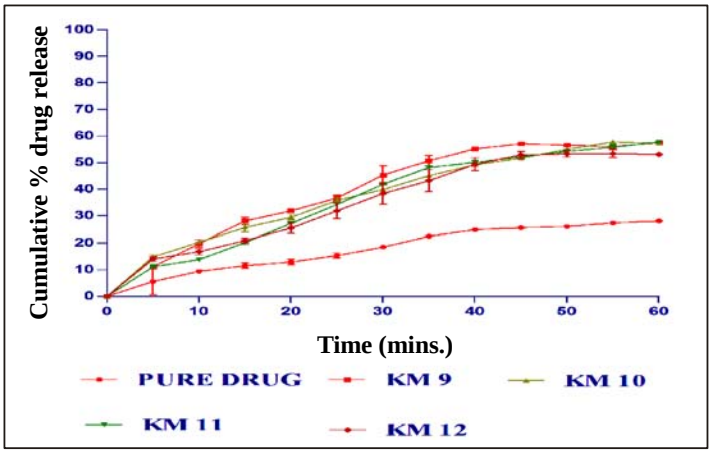


Fig. 7: Comparison of *in vitro* release profile of racecadotril using poloxamer 188 by melting method

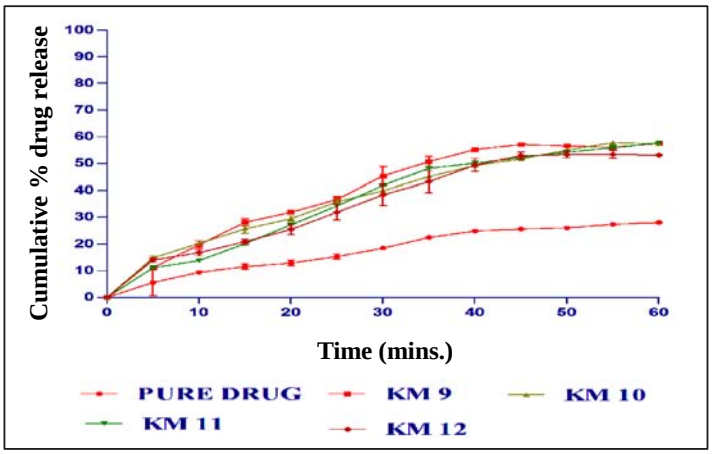


Fig. 8: Comparison of *in vitro* release profile of racecadotril using PVP K30 by freeze drying method

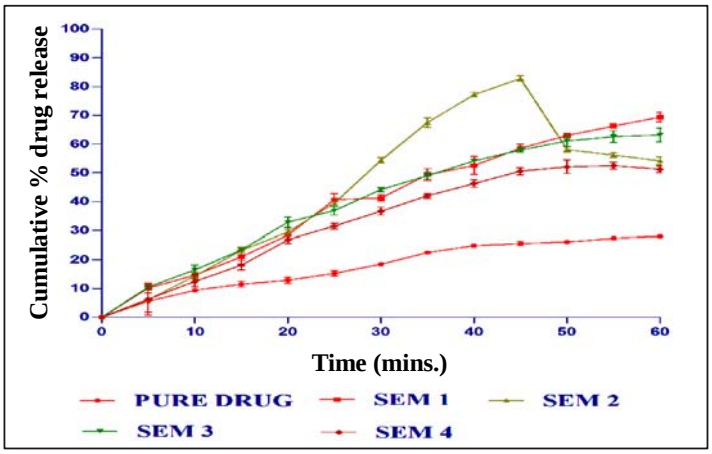


Fig. 9 Comparison of *in vitro* release profile of racecadotril using PVP K30 by solvent evaporation method

In vitro release studies reveal that there is marked increase in the dissolution rate of racecadotril from all the solid dispersions when compared to physical mixture and pure drug. From the in vitro drug release profile, it can be seen that formula KM 7 (Kneading method) containing PVP K30 (1 : 3 ratio of drug: carrier) showed higher dissolution rate 72.7% after 1hour, and so it was considered as the overall best formulation.

The increase in dissolution of the drug in both, the physical mixtures and solid dispersions was reported because of the enhanced wettability, hydrophilic nature of the carriers and possibility of reduced crystallinity of the drug in the formulations. But as the amount of PEG 6000, PVP K 30 and Poloxamer 188 were increased (1 : 4 ratio) in all formulation, the dissolution rate was decreased. This decrease in dissolution rate may be due to increased viscosity of coating materials. Drug release from the solid dispersion formulation (KM 7) was found to be significantly higher as compared with that of marketed racecadotril capsules (Fig. 10).

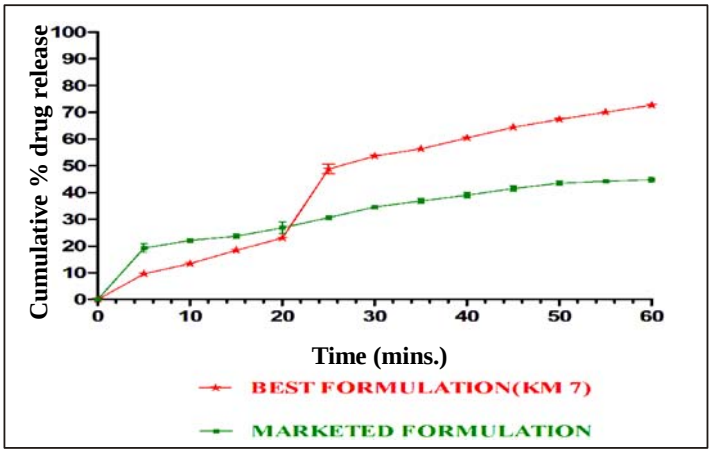


Fig. 10 Comparison of *in vitro* release profile of racecadotril marketed capsules with best formulation (KM 7)

Solubility studies[11]

The solubility study was conducted with pure drug, physical mixture and solid dispersion using distilled water and acid buffer pH 1.2 shown in Table 3. It was observed that the solid dispersion (KM 7) has highest solubility compared to pure drug and physical mixture (PM7) in both distilled water and acid buffer pH 1.2. (Fig. 11)

Table 3: Comparison of solubility study of racecadotril

S. No.	Formulation	Distilled water (mg/mL)	Acid buffer ph 1.2 (mg/mL)
1	Pure drug	0.076	0.103
2	Physical mixture	0.110	0.161
3	Solid dispersion	0.160	0.344

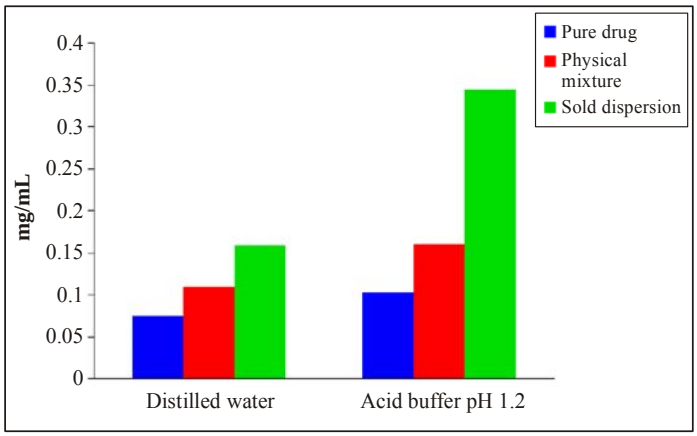
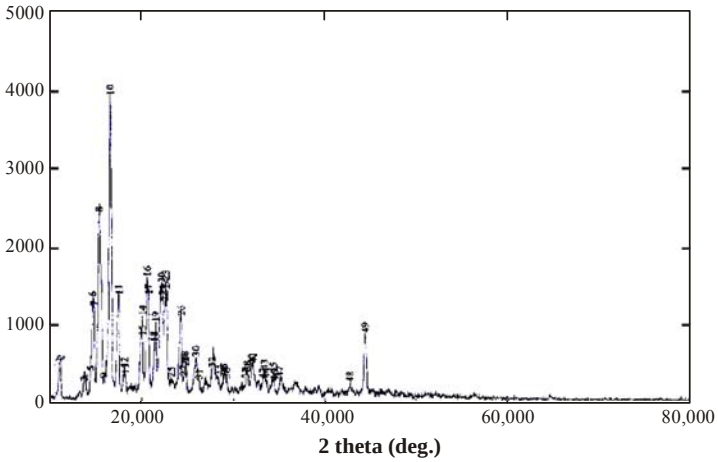


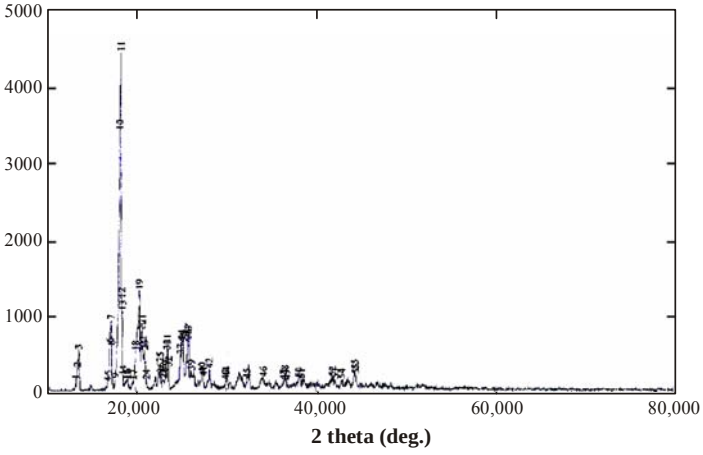
Fig. 11: Comparison of solubility study of racecadotril

Powder X-Ray diffraction (PXRD) studies[13]

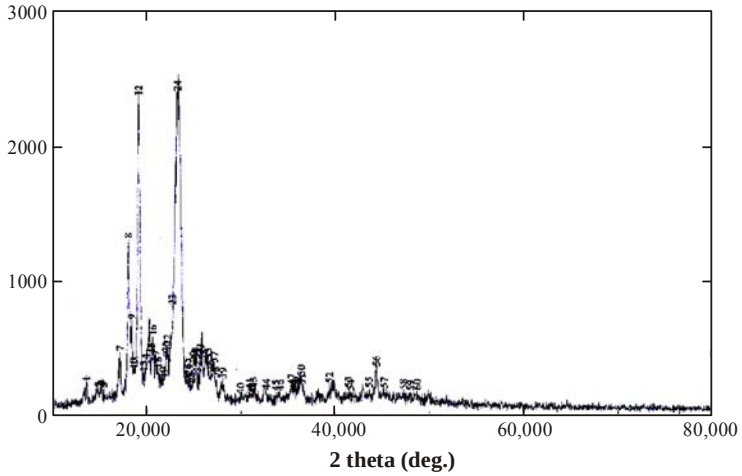
The Powder X-Ray Diffraction patterns of solid dispersion of racecadotril (KM7) with the physical mixture (PM7) and pure drug shown in Fig. 12. In the case of solid dispersion of racecadotril with PVP K30, no characteristic racecadotril peaks were observed. These results are confirmed that racecodotril was transferred from a crystal to an amorphous form upon dispersion by the kneading method.



(a) Pure drug



(b) Physical mixture (PM 7)



(c) Solid dispersion (KM 7)

Fig. 12: PXRD patterns

CONCLUSION

It was concluded that the kneading, melting, solvent evaporation and freeze drying methods are useful methods for the successful enhancement of solubility of poorly water soluble drug racecadotril with faster dissolution rate. Further, it may be assumed that the solubility and dissolution rate can be increased due to the conversion of crystalline matter into amorphous powder. Hence we can conclude that solid dispersion of racecadotri by using the water soluble carrier PVP K_{30} in the ratio 1 : 3 prepared by kneading method provide best release of drug (72.7% released in 60 min.) among all the formulations, and this ratio can be used to enhance the solubility and dissolution rate of poorly water soluble drug racecadotril.

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