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R E S E A R C H A R T I C L E

Dissolution Enhancement of Racecadotril by using In-situ Micronization Technique

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A B S T R A C T

The main objective of In-situ Micronisation is to enhance the rate of dissolution and absorption of poorly water soluble drugs. Racecadotril is an anti-diarrheal drug that acts by inhibiting the enzyme enkephalinase and shows anti-secretary effect. It reduces the secretion of water and electrolytes into the intestine. Racecadotril is a BCS class-II drug that has poor water solubility. The intention of the present work is to improve the solubility of drug by the formation of microcrystals. Five formulations of Racecadotril containing varying concentrations of polymer (PVPK30) were designed. The microcrystals were prepared by solvent change method and were evaluated for Percentage crystal yield, Mean particle size, Percentage Drug content, In vitro dissolution studies and also they can be characterized by FT-IR, DSC, XRD & SEM. The In-vitro dissolution studies revealed that out of five formulations, formulation F5 was found to be optimized which showed less particle size & the drug release was found 98.89% at 60min.

Keywords: In-situ Micronization, Racecadotril, Microcrystals, PVPK30, Solvent change method.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Solubility plays an important role in the success of a drug development. Compounds having low solubility can cause problems for in vitro and in vivo assays, and also for drug development. Different solubility screening requirements and methodologies have been developed to meet the needs of different stages of drug discovery and development. The

term solubility refers to the maximum amount of solute that dissolves in a definite quantity of solvent at a specified temperature[1]. In situ process has been developed to enhance the rate of dissolution and absorption of poorly water soluble drugs. Most of the techniques like pH modification, use of surfactants, the formation of solid dispersions, complexation with cyclodextrins, co-solvent and hydrotroph formation, co-crystallization techniques are commonly used to improve the dissolution and bioavailability of poorly water- soluble drugs[2]. Racecadotril is a non specific anti diarrhoeal drug which produces an anti secretory action by inhibiting the enzyme enkephalinase. Racecadotril is a BCS class-II drug that has poor water solubility. The present investigation was to prepare and characterize the microcrystals of Racecadotril, a poorly water soluble drug employing in situ micronisation technique by rapid solvent change method to enhance the solubility and dissolution rate and to optimize the solvent and antisolvent ratio (v/v) using constant stabilizer concentration in the formulation of Racecadotril microcrystals and evaluated for the percentage crystal yield, mean particle size, content uniformity & in-vitro dissolution studies . The prepared microcrystals of the optimized formulation were characterized by using various techniques like DSC, FT-IR & SEM.

2. Materials and Methods

Materials: Racecadotril is obtained from Med rich pharmaceuticals Ltd., Bangalore, PVPk30 and Methanol is brought from S.D. Fine chem. Ltd. Mumbai.

Preparation of Racecadotril Microcrystals

Raceccadotril microcrystals can be prepared by using Rapid solvent change method which involves the preparation of an organic solution of the drug by dissolving 1.76 g of drug in 10 ml of methanol. To this solution, a measured quantity of aqueous solution containing 0.1% w/v of carrier, which is anti-solvent to the drug solution, was added by continuous stirring. This results in the super saturation with respect to the drug and formation of crystal growth and nucleation. By using magnetic stirrer, the mixture was stirred for 60 min and filtered by using whattman filter paper and crystals were collected and dried in an oven at 45^0C for 2 hrs. By this method, formulations from F1-F5 were prepared by changing the solvent to anti-solvent ratios[3.] Composition of different formulations of Racecadotril (RCD) Microcrystals were mentioned in table-1

3. Results and Discussion

Evaluation of Racecadotril Microcrystals:

Percentage crystal yield

Percentage crystal yield was calculated to know about percent yield or efficiency and helps in the selection of appropriate method of formulation. The final weights of the prepared microcrystals were taken and the percentage of crystal yield was calculated[4]. Percentage practical yield of RCD microcrystals containing PVP K30 were mentioned in table-2

Mean particle size: The eye piece micrometer was calibrated by using a standard stage micrometer at 45X. Sample suspensions were prepared by using propylene glycol, mounted on a slide and placed on a mechanical stage. Around 50 particles were counted to estimate the true mean [5]. Mean particle size of RCD microcrystals Containing PVP K30 were mentioned in table-3

Percentage drug content

Prepared microcrystals containing 10 mg of drug were taken in 100 ml standard flask and volume was made up to 100 ml with methanol and suitably diluted. The absorbance of the solutions was measured at 232 nm [6]. % Drug Content of RCD Microcrystals Containing PVP K30 were mentioned in table-4

Characterization of microcrystals FT-IR Spectroscopy

Fourier Transform Infrared (FT-IR) spectral measurements for Racecadotril, PVP K30, and their microcrystals were recorded using the Thermo-IR 200 FTIR spectrophotometer by Potassium bromide pellet method. Each spectrum was derived from 16 single average scans collected in the range of 4000-400 cm^{-1} at the spectral resolution [8]. FT-IR data of RCD and RCD microcrystals was determined in table-5 and the respective graphs in Fig.1

DSC Thermal Analysis

Thermal analysis of Racecadotril and their microcrystals were recorded with Netzsch DSC 200PC. The temperature axis and cell constant of DSC were previously calibrated with Indium. A heating rate of 5^0C/min was employed over a temperature range of 25-200^0C with nitrogen purging. The sample was weighed into an aluminum pan was used as reference [9].The results obtained were depicted in Fig.2

Scanning Electron Microscopy (SEM):

Scanning electron micrographs of Racecadotril microcrystals and pure drug powder were taken using a scanning electron microscope. Samples were fixed on an aluminum stub with conductive double-sided adhesive tape and coated with gold in an Argon atmosphere (50 Pa) at 50mA for 50 sec [10]. SEM of pure Racecadotril and F5 were depicted in Fig.3

In-vitro Dissolution Studies

The USP type II apparatus (paddle type) was used for conducting the In vitro dissolution studies of pure drug and microcrystals. The dissolution studies were performed using phosphate of pH 7.4 buffer as dissolution medium at 37 ± 0.5^0C with 75 rpm speed. Samples of each preparation equivalent to 80mg of drug were added into the dissolution medium. The sample of 1ml aliquots were withdrawn periodically (15, 30, 45 and 60 min) and replaced with same quantity of fresh dissolution medium. The filtered solutions were diluted and samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 232 nm. Percent of Racecadotril dissolved at various time intervals was calculated and plotted against time [7]. Dissolution data of microcrystals of RCD was determined in atble-6.Comparative % Cumulative drug release of RCD microcrystals was depicted in Fig.4

4. Conclusion

Racecadotril is a poorly water soluble drug, an enhanced solubility was observed by the preparation of microcrystals through rapid solvent change method & PVP K30 as hydrophilic stabilizing agent. Microcrystals prepared by

using PVPK30 have shown a narrow particle size distribution and change in the crystal habit from rod type to small plate type. The FTIR results showed no chemical interaction between the drug and the stabilizer, and crystalline habit modification has occurred in the microcrystals without any polymorphic changes. The enhanced dissolution rates attributed to the reduction of the particle size, change in crystal habit, formation of hydrophilic surface and the increased wet ability and reduction in crystalline during micro-crystallization. It was concluded that the mentioned technique is a promising tool for effective microcrystal formation during pharmaceutical development in order to increase dissolution rate of poorly water soluble drugs.

Table 1: Tadalafil + Excipients compatibility study (binary mixture)

S.No	Ingrediens	Formulation Code				
		F1	**F2**	**F3**	**F4**	**F5**
1	RCD(g)	1.76	1.76	1.76	1.76	1.76
2	PVP K30(g)	0.2	0.3	0.4	0.5	0.6
3	Solvent volume (ml)	10	10	10	10	10
4	Anti-solvent volume(ml)	20	30	40	50	60

Table 2: Percentage practical yield of RCD Microcrystals containing PVP K 30

S.No.	Formulation code	% Practical yield
1	F1	87.2
2	F2	88.4
3	F3	90.2
4	F4	91.2
5	F5	95.5

Table 3: Mean particle size of RCD MIcrocrystals containing PVP K 30

S.No.	Formulation Code	Mean particle size (µm)
1	F1	19.15±0.12
2	F2	15.27±0.07
3	F3	17.31±0.22
4	F4	14.30±0.05
5	F5	11.36±0.01

Table 4: % Drug Content of RCD Microcrystals Containing PVP K30

S.No.	Formulation Code	% Drug content
1	F1	94.03±0.07
2	F2	97.02±0.17
3	F3	98.56±0.23
4	F4	95.24±0.73
5	F5	97.43±0.22

Table 5: Table.5 FT-IR data of RCD and RCD microcrystals

Functional group	Pure drug(cm-1)	F5 (cm-1)
C-H (Aromatic stretching)	3045.62	3048.51
C=C (Stretching)	1550.35	1553.24
N-H (Bending)	1636.19	1641.98
C-S (stretching)	1048.08	1055.19
C-O (Alcohol stretching)	1225.30	1233.02
O-H (Alcohol Stretching)	3640.47	3635.30

Table 6: Dissolution data of microcrystals of RCD

S.No	Time (min)	% Cumulative drug release					
		Pure Drug	F1	F2	F3	F4	F5
1	15	13.66±0.26	48.89±0.25	46.75±0.12	49.46±0.001	51.68±0.25	54.28±0.11
2	30	27.01±0.08	72.40±0.14	62.46±0.22	67.15±0.31	73.45±0.21	79.74±0.04
3	45	41.63±0.15	82.16±0.46	70.22±0.12	76.35±0.07	86.01±0.05	90.12±0.01
4	60	51.42±0.03	89.80±0.71	81.79±0.29	84.52±0.32	93.56±0.05	98.89±0.43

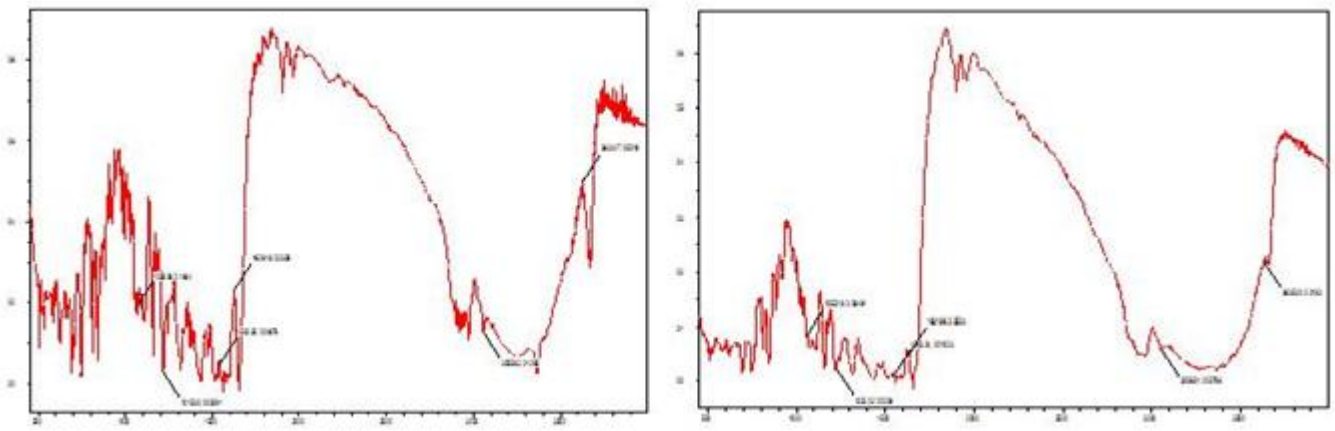

Figure 1: FT-IR spectras of RCD & F5

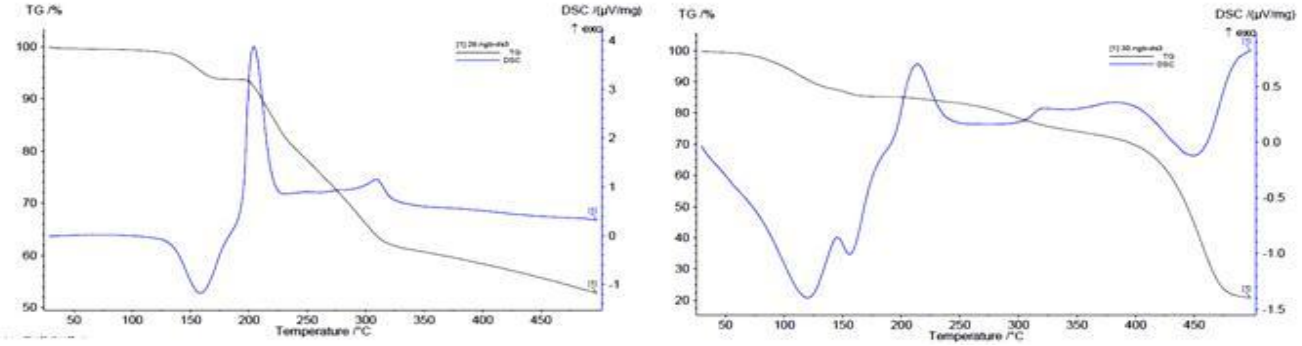

Figure 2: DSC of pure drug & F5

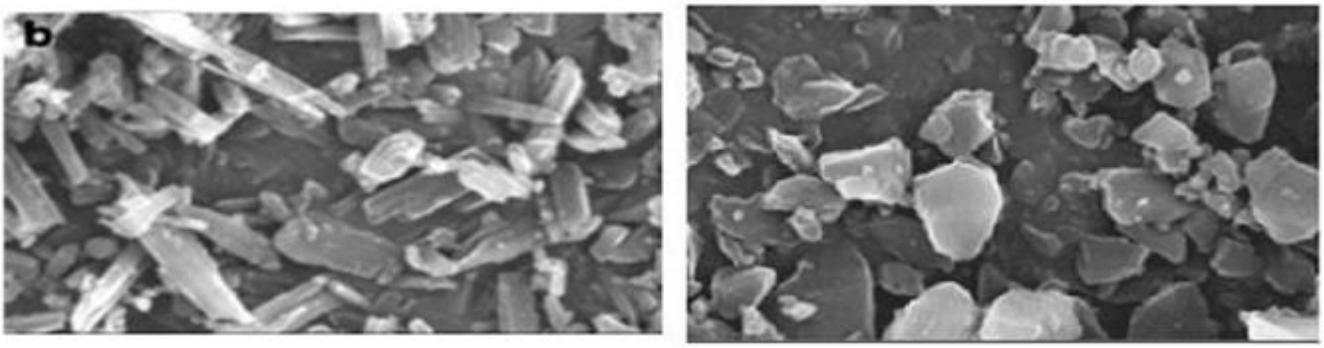

Figure 3: SEM of pure Racecadotril and F5

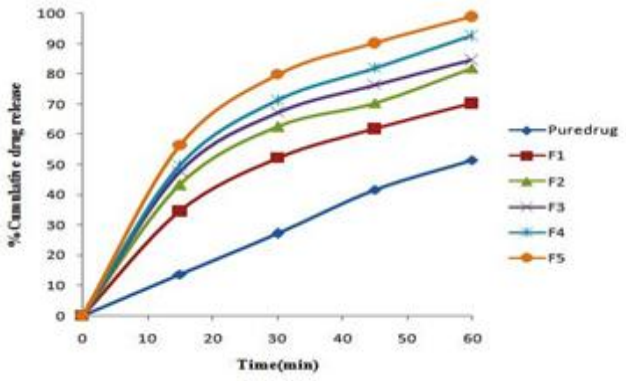

Figure 4: Comparative % Cumulative drug release of RCD microcrystals

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