Solid Dispersion of Rebamipide for Enhancement of Solubility

Parul Nigam

Assistant Professor, Rama University, Kanpur

Abstract: The limited solubility of Rebamipide, a therapeutic agent used for treating gastrointestinal disorders such as peptic ulcers, often restricts its bioavailability. This study focuses on enhancing the solubility of Rebamipide through the development of solid dispersions using polyethylene glycol 4000 (PEG-4000) and polyvinylpyrrolidone K-30 (PVP K-30) as hydrophilic carriers. Various formulation techniques, including solvent evaporation, co-precipitation, and melt extrusion, were employed to prepare these solid dispersions. Comprehensive physicochemical characterization was performed to assess the properties of the formulated dispersions. The study found a marked increase in the solubility and dissolution rate of Rebamipide in the solid dispersions compared to its pure form. The optimized solid dispersion formulation, particularly with PEG-4000 and PVP K-30, exhibited enhanced bioavailability in pharmacokinetic evaluations. These findings suggest that the use of PEG-4000 and PVP K-30 in the formulation of solid dispersions for Rebamipide can significantly improve its solubility, thereby offering a promising avenue for more effective treatment of gastrointestinal disorders.

Keywords: *Rebamipide, Solid Dispersion, PEG-4000, PVP K-30, Solubility Enhancement, Bioavailability, Gastrointestinal Disorders, Solvent Evaporation, Co-precipitation, Melt Extrusion.*

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Corresponding Author- parulnigamm@gmail.com

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Introduction

In present scenario, tablet is considered as one of the best solid dosage forms due to its easy preparation method and administration[1]. From all the types of tablet, the oral disintegration form is the most acceptable and suitable for all the age-group of patients. With the help of saliva in the mouth these can easily be disintegrate and

dissolved[2]. This class is also useful for sustained action treatments, for example in case of dysphagia. If the solubility of such class of drug has been increased, it will be more useful and acts more rapidly[3]. To increase the disintegration and pharmacokinetics of this class of drugs, solid dispersion technique has been used. By performing this technique, not only the dissolution rate of drug increases but also the chances of toxicity will get reduced[4].

Solid dispersion has been defined as "Dispersion of one or more active substances in a hydrophilic transport or substrate generated by fusion, solvent, or melting solvent technique in a solid state." Solid dispersion increases porosity of the drug and hence, solubility also increases. It is also responsible for transforming insoluble drugs into an amorphous state, which allows for greater solubility[5]. Enhancing the wetting properties of the substances surface, as well as particle size reduction and improving the interfacial area accessible for drug dissolution, can help increase drug dissolution rates from a solid dispersion[6].

Materials and Methods

Rebamipide was purchased from Global Scholar Scientific Solutions, (Lucknow); Polyvinyl Pyrrolidone K-30 from Yarren Chem Products, (Mumbai); Poly-ethylene glycol 4000 from S.D. Fine-Chem, Ltd, (Mumbai); Potassium dihydrogen phosphate from Merck Ltd., (Mumbai); Ethanol from Changshu Hongsheng Fine Chemical co. Ltd.; Sodium hydroxide pellets and Hydrochloric acid from Thermo Fisher Scientific Pvt. Ltd. (Mumbai).

Methodology

The methodology comprises of following steps-

- Preparation of Calibration Curve-
- Preparation of std. curve in phosphate buffer
- Preparation of std. curve in 0.1N Hcl
- Preparation of Solid dispersion by solvent evaporation method

Preparation of Calibration curve

The preparation of calibration curve of pure drug was performed with the help of UV spectroscopy.

- Preparation of standard curve in phosphate buffer (pH 6.8)

10 mg of drug Rebamipide was accurately weighed and placed in a100 ml volumetric

flask containing some amount of solvent then made the volume up to 100ml with phosphate buffer. The standard stock solution thus obtained was then serially diluted with phosphate buffer to get 2,4,6,8,10µg/ml.The absorbance of the solution was determined using phosphate buffer as blank,at 226nm.The absorbance value was plotted against concentration to obtain the calibration curve.

- Preparation of standard curve in 0.1 N HCl

10 mg of drug Rebamipide was accurately weighed and placed in a100 ml volumetric flask containing some amount of solvent then madethe volume up to 100ml.The standard stock solution thus obtained was then serially diluted with 0.1 N HCl to get 2,4,6,8,10µg/ml.The absorbance of the solution was determined using 0.1N HCl as blank,at 224nm.The absorbance value was plotted against concentration to obtain the calibration curve.

Preparation of solid dispersion by solvent evaporation method

Rebamipide solid dispersion were prepared by solvent evaporation method. Different carriers(PVP K-30, PEG-4000) used in different ratio as shown in table (1). The drug and carrier were taken separately in different ratio(1:1, 1:2, 1:3) wt:wt and transferred into motar pestle and triturate to form a mixture. Add 25 ml of ethanol and mix properly. The content transfer into a beaker and heat for 5-10min at 30-40˚C.The solvent was removed by leaving it for 24 hr .The dried solidifing mass were scraped,crushed and grinded in mortar and pestle and pass through sieve no 60 and store in closed container.

Formulation table:

Formulation code	Drug(Rebamipide)	PEG-4000	PVP K-30
F1	200mg	-	200mg
F2	200mg	-	400mg
F3	200mg	-	600mg
F4	200mg	200mg	-

F5	200mg	400mg	-
F6	200mg	600mg	-

Characterization of solid dispersion

(a) Partical size determination

The particle sizewas determined using optical microscopy. A tleast 100 particles of solid dispersion were counted for precise size distribution.

(b) Determination of production yield

The production yield of solid dispersion of various batches were calculated using the weight of final product with respect to the initial total weight of the drug and polymer used and percent production yield were calculated as per the formula mentioned below-

Percentage yield = Practical yield/ Theoretical yield*100

(c) Determination of drug content

A sample of dried 10 mg of solid dispersion was taken in a 10 ml volumetric flask containing some amount of phosphate buffer pH6.8 and made up volume up to 10 ml with phosphate buffer.Filter it through the whatman filter paper.Drug content was determined by UV spectrophotometer at 226nm.

(d) Solubility studies

An excess amount of pure drug and prepared solid dispersion were placed in contact with 10 ml of 0.1 N HCl and phosphate buffer in a closed container. The suspension were sonicated for 15 min and kept at constant temperature (37±0.5˚C) in a water bath. After 72hr. the suspension were filtered and diluted appropriately and quantified by UV spectroscopy at 226nm.

Spectrophotometric study

Standard solution of Rebamipide was prepared by dissolving 10 mg of drug in 100ml of 0.1 N HCl .The final concentration after dilution was 10µg/ml.The λ-max of Rebamipide was to be found 224nm.

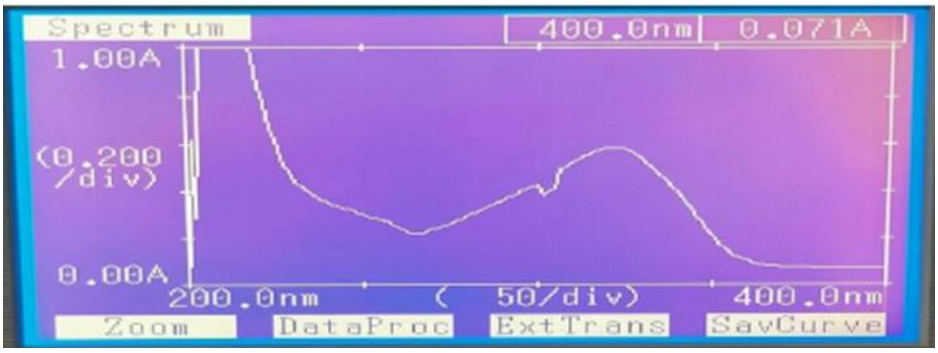


Figure 1- UV analysis of Rebamipide

Calibration curve of Rebamipide in 0.1N HCl

STOCK SOLUTION (1) - 10 mg of Rebamipide dissolve in 100 ml of 0.1 N HCl to get the solution of 100µg/ml.

STOCK SOLUTION (2) - From stock solution (1),we take 10 ml and dilute up to 100ml with 0.1 N HCl to get the solution 10 µg/ml. From stock (2) we take 2,4,6,8,10ml and transfer to the 10 ml volumetric flask and final volume made with same solvent, then we get drug concentration 2,4,6,8,10µg/ml. The absorbance value of respective concentration at the wave length 224nm and plot the calibration curve.

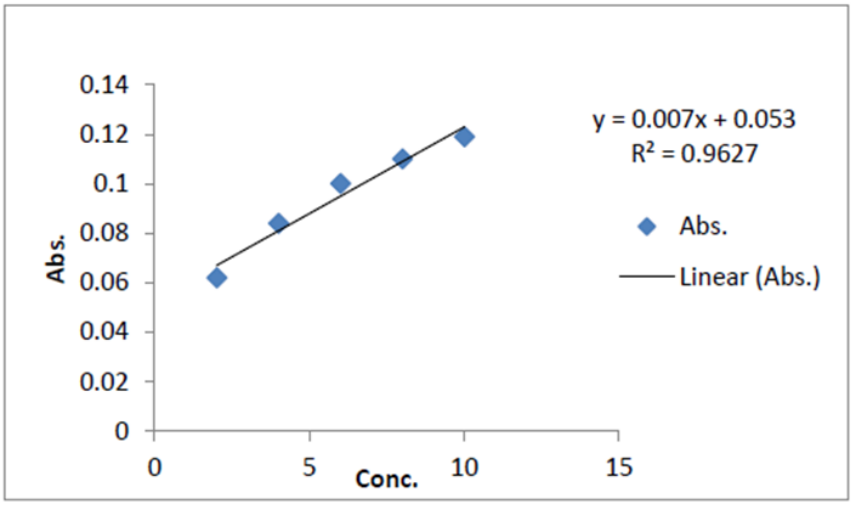
Conc.(µg/ml)	Abs.
2	0.062
4	0.084
6	0.10
8	0.11
10	0.119

Calibration curve of Rebamipide in Phosphate buffer pH6.8

STOCK SOLUTION (1) - 10 mg of Rebamipide dissolve in 100 ml of phosphate buffer to get the solution of 100µg/ml.

STOCK SOLUTION (2) - From stock solution (1),we take 10 ml and dilute up to 100ml with phosphate buffer to get the solution 10 µg/ml. From stock (2) we take 2,4,6,8,10ml and transfer to the 10 ml volumetric flask and final volume made with same solvent,then we get drug concentration 2,4,6,8,10µg/ml.The absorbance value of respective concentration at the wave leanth 224nm and plot the calibration curve.

Conc.(µg/ml)	Abs.
2	0.026
4	0.035
6	0.059
8	0.064
10	0.080



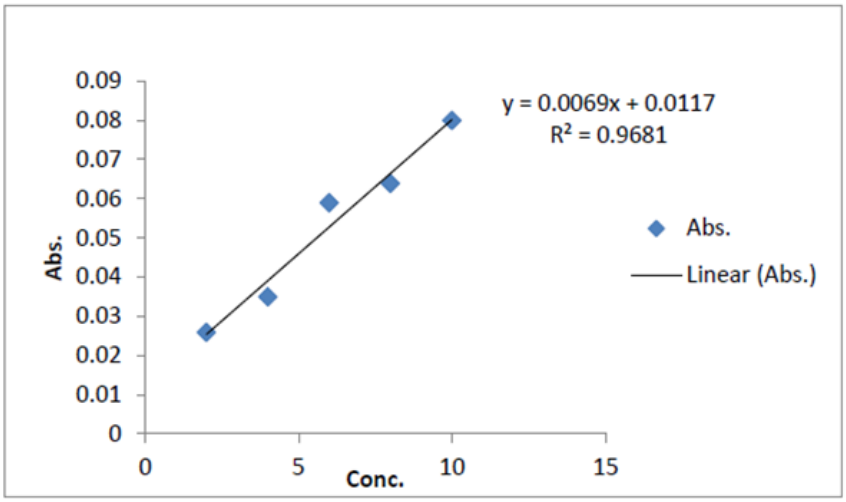


Figure 2- Standard plot of Rebamipide in phosphate buffer

Particle size analysis

Particle size was determined using optical microscope. At least100 particles of solid dispersion were counted for precise size distributation. The particle size distribution of solid dispersion of F1 to F6 was found to be 70µm, 65µm, 45µm, 67µm, 63µm, 37µm respectively.

Production yield

Production yield of solid dispersion determined for all formulation F1 to F6 70.1% to 85%.It was indicated that the formulation F4 has higher production yield.(shown in below table)

F1	0.30 gm	75%
F2	0.421gm	70.1%
F3	0.612gm	76.5%
F4	0,340gm	85%
F5	0.49gm	81.6%
F6	0.584gm	73%

Drug content studies

The drug content studies was determined in phosphate buffer through UV-spectometer at λ-max 224 nm. The percentage drug content shown in below table:

Formulation	Absorbance	Concentration	%drug content
F1	0.044	4.68 mg	93.6
F2	0.036	3.52 mg	105.6
F3	0.027	2.21 mg	88.4
F4	0.039	3.95 mg	79
F5	0.038	3.81 mg	110
F6	0.031	2.79 mg	101

Solubility studies

The solubility studies of Rebamipide and all the formulation was studied in both solvent (i.e. 0.1 N HCl and Phosphate buffer pH 6.8).

In 0.1 N HCl the formulation F3 shown good solubility while in solvent phosphate buffer the formulation F5 show good solubility.

Solubility data in 0.1N HCl :

Formulation	Abs.	Conc./ml
Rebamipide	0.069	250µg
F1	0.208	1987µg

F2	0.493	5550µg
F3	0.817	9600µg
F4	0.229	2250µg
F5	0.101	650µg
F6	0.079	375µg

Solubility data in Phosphate buffer (pH 6.8):

Formulation	Abs.	Conc./ml
Rebamipide	0.325	4540µg
F1	0.393	5526 µg
F2	0.382	5366 µg
F3	0.389	5468 µg
F4	0.252	3482 µg
F5	0.551	7815 µg
F6	0.435	6134 µg

IR Spectroscopy

IR spectra are important record which gives sufficient information about the structure of a compound. FTIR spectra of solid dispersion (Rebamipide and poly ethylene glycol 4000) were obtain using FTIR spectrometer.

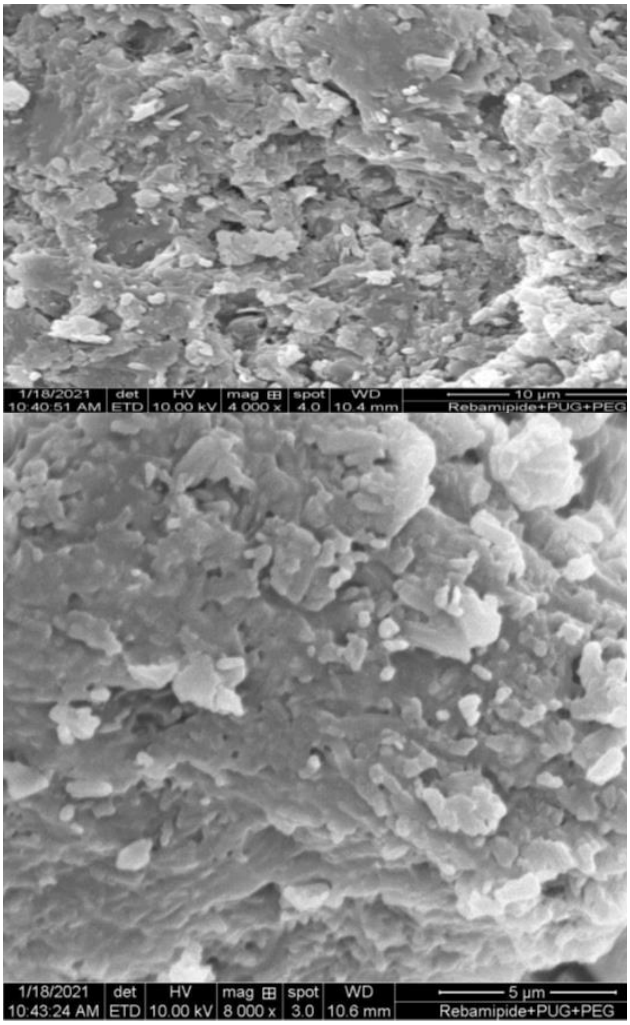
FTIR Spectral data of solid dispersion

Frequency(cm-1)	Functional group
3269	O-H stretching carboxylic acid
2881	N-H stretching amine
1725	C=O stretching aldehyde
1643	C=C stretching alkene
1540	N-O stretching nitro compound
1466	C-H bending alkane
1422	O-H bending carboxylic acid
1279	C-O stretching aromatic ester
757	C-Cl stretching

Scanning electron microscopy (SEM)

SEM pictures of selected formulation (F5) was presented in below figure. It showed irregular shaped glassy appearance in addition to size reduction. The smaller

particle size lead to great the wetted area, and hence the better solubility.



Conclusion

The drug (Rebamipide) have potent anti-ulcer property but fails to show the desired action due to less oral bioavailability.

The physiochemical evaluation of drug concludes that it belong to BCS-IV system i.e. low solubility low permeability and among the present conventional drug delivery system the solid dispersion was found as one of the best carrier system for the delivery of drug through oral route.

As per the data obtain from the evaluation study it was found that among the prepared set of formulations F1, F2 ,F3, F4, F5, F6 the formulation F5 possess best result in reference to estimation of drug content, formulation F3 possess good solubility in .1N HCL, Formulation f 5 showed better solubility in PBS (6.8) as compare to pure drug.

The above experiment conclude that the incorporation of drug within the system enhances the solubility of drug molecule.

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