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DESIGNING A FORMULATION TO ENHANCE SOLUBILITYAND DISSOLUTION RATE

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ABSTRACT

The present study was aimed to enhance the solubility of poorly water soluble drug Ibuprofen using solid dispersion technique and to develop solid dispersion. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. Solid dispersions of Ibuprofen were prepared by using urea, dextrose and HPMC in different weight ratios by fusion, solvent evaporation an kneading method. Drug-carrier physical mixtures were also prepared. Solid dispersions were characterized by saturation solubility, in vitro dissolution, FTIR and DSC analysis. Solid dispersion formulation prepared 1:3 ratio of drug and polymer urea was considered as the optimize formula. The prepared formulations were evaluated for in vitro dissolution studies. Solid dispersion formulation, prepared using 1:3 ratio of ibuprofen and urea showed 88.65% drug release in 90 min in 0.1HCL and considered perfect performance as required. Solid dispersions of ibuprofen using a combination of urea by may result in higher aqueous solubility of the drug.

KEYWORDS: Solid dispersion, Ibuprofen, Urea, Dextrose, HPMC, Sustained Release.

INTRODUCTION

The poor water solubility and dissolution rate of a drug is one of the biggest challenges in drug development. In particular, BCS Class II compounds that are poorly soluble and highly

permeable tend to have solubility or dissolution rate limiting absorption. Despite their high permeability, these drugs often have low oral bioavailability due to the slow and limited release of the drug into the gastrointestinal fluid.[1] One of the most successful strategies to improve the dissolution of poorly soluble drugs is the solid dispersion technique. The term solid dispersion is defined as a dispersion of a drug in an inert carrier or matrix in a solid state prepared by a solvent, melt or solvent dissolution method. Many studies have been published on solid dispersions that have demonstrated the many useful properties of solid dispersions in improving the solubility and dissolution rate of poorly water-soluble drugs. These advantages include reducing particle size, possibly to the molecular level, improving moisture and porosity, and changing the crystalline state of the drug, rather to an amorphous state.[2] Oral administration is the oldest and most convenient way of drug administration due to low treatment costs and better patient compliance. Over the past three decades, many oral drug delivery systems have been developed that can release the drug at a predetermined and controlled rate over a period of time. Sustained release, controlled release, extended release, timed release, etc. are terms used to identify a drug delivery system designed to achieve a sustained therapeutic effect by continuously releasing the drug over a long period of time after a single dose.[3] Ibuprofen, a derivative of propionic acid, is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory effects. Its pharmacological activity is due to the inhibition of COX-2, which reduces the synthesis of prostaglandins, which mediate inflammation, pain, fever and swelling. The antipyretic effect may be due to an effect on the hypothalamus, which causes an increase in peripheral blood flow, vasodilation and subsequent heat dissipation. Blocking COX-1 is thought to cause some of the side effects of ibuprofen, including gastrointestinal ulcers. Ibuprofen is a BCS class II drug and therefore has a dissolution rate limited absorption resulting in low oral bioavailability. Its biological half-life is 1.3-3 hours.[4]

MATERIALS AND METHODS

Ibuprofen was obtained as a gift sample from RESEARCH-LAB CHEM INDUSRTIES Mumbai**,** Maharashtra, India. UREA was obtained by the RESEARCH-LAB CHEM INDUSRTIES Mumbai**,** Maharashtra, India. Hpmc was obtained by the RESEARCH-LAB CHEM INDUSRTIES Mumbai**,** Maharashtra, India**,** Dextrose was obtained by the RESEARCH-LAB CHEM INDUSRTIES Mumbai**,** Maharashtra, India Methanol and ethanol was obtained by the IDEAL COLLEGE OF PHARMACY AND RESEARCH. Dichloromethane are obtained by the IDEAL COLLEGE OF PHARMACY AND

RESEARCH.

METHODS OF PREPARING IBUPROFEN SOLID DISPERSIONS

Solvent Evaporation Method

Ibuprofen solid dispersion formulations were made in a variety of carrier ratios, such as 1:1, 1:3, and 1:5 (Drug: Carrier), as indicated in Table 1. These carriers included UREA and HPMC. In a beaker of ethanol, the medication and the carriers, or polymers, were dissolved. The medication and carrier combination were put onto a Petri dish after they had fully dissolved. The mixture- containing petri dish was baked at 60°C until the solvent was totally evaporated. After being sieved using a #60 sieve, the solid dispersion was kept for later use within a desiccator.

Table 1: Formulation Of Ibuprofen Solid Dispersions By SolventEvaporation Method.

BATCHCODE	DRUG	UREA	HPMC	ETHANOL
SE-S1	100	100	-	q.s.
SE-S2	100	300	-	q.s.
SE-S3	100	500	-	q.s.
SE-S4	100	-	100	q.s.
SE-S5	100	-	300	q.s.
SE-S6	100	-	500	q.s.

Kneading method

Kneading procedure: As indicated in Table 2, formulations of Ibuprofen solid dispersions were made using carrier urea in a range of ratios, including 1:1, 1:3, and 1:5 (Drug: Carrier). To achieve a desirable slurry-like consistency, polymers were added to the mortar and pastel, and during the trituration process, a little amount of ethanol was added. The medicine is then gradually added to this slurry and trituration is carried out for an hour. After that, the resulting slurry was allowed to air dry for 24 hours at 25°C. ground, put through sieve number 100, and kept for later use in a desiccator.

Table 2: Formulation Of Ibuprofen Solid Dispersions By KneadingMethod.

BATCH CODE	DRUG	UREA	ETHANOL
K-1	100	100	q.s.
K-2	100	300	q.s.
K-3	100	500	q.s.

Fusion Method

Formulations of Ibuprofen solid dispersions were prepared using carrier Urea, in various proportions, i.e., 1:1, 1:3, 1:5 (Drug: Carrier) as shown in Table 3. Drug was added to the

vial, and heated in water bath at temp(80-90°C) until get melt then, added dextrose until clear solutionis obtained. Obtained Product is kept in desiccator.

Table 3: Formulation Of Ibuprofen Solid Dispersions By Fusion Method.

BATCH CODE	DRUG	DEXTROSE
F-1	100	100
F-2	100	300
F-3	100	500

Evaluation and Characterization of solid dispersion

All the formulations were evaluated by Physical appearance, Practical yield, drug content, saturation solubility studies.

Physical Appearance

Ibuprofen solid dispersions all batches were evaluated for appearance and color.

Percent Practical Yield (PY)

Percentage practical yield was measured to know the accuracy or efficiency of the method. Also, to know the exact yield obtained from the batch of solid dispersion helpful in selecting appropriate method for production. The practical yield (PY) was calculated using the given equation.

PY (%) = Practical Mass (SD) / Theoretical Mass (Drug + Carrier)] ×100.

Evaluation of selected solid dispersion

The selected batch of solid dispersion was subjected to In-vitro dissolution studies, FTIR, DSC, SEM and POWDER-XRD analysis.

Dissolution studies

In-vitro dissolution of drug Ibuprofen and selected Solid dispersion batch were studied using calibrated 8-station USP-II apparatus (paddle method), TDT-08L Electro lab, Mumbai, India. Samples of the drug and solid dispersions equivalent to 100 mg drug were filled in capsules and immersed in the 900 ml of different dissolution medium 0.1NHCl and Phosphate buffer pH 6.8at 75 rpm. Aliquots of 5 ml were removed at time intervals 0, 10, 20, 30, 40, 50, 60, 90, 120 mins. The samples withdrawn were then filtered using a Whatman filter paper No. 1 and analyzed at 222 nm by using UV–vis Spectrophotometer, Shimadzu, Japan. Cumulative percentages were calculated.

Fourier Transform Infrared spectroscopy

FTIR spectra of pure Ibuprofen, urea, Dextrose, Hpmc and the selected sample of solid dispersion were recorded on IR, Bruker, India, ATR pellet method. 10 mg of the solid dispersion were taken with 40-50 mg of ATR powder and filled within the pellets for scanning at range 4000 to 400 cm-1.

Differential scanning calorimetry

DSC analysis of plain Ibuprofen, urea, Dextrose, Hpmc and the selected sample of solid dispersion were performed using EX STAR DSC 6620 (Measurement and standard analysis software). Samples weighing 4 to 5 mg were heated in aluminum pans which were hermetically sealed over a temperature range of 30–300°C at a constant rate of 10°C/min under a nitrogen steam.

Scanning electron microscopy

Scanning electron microscopy: Using scanning electron microscopy (SEM), JEOL, JSM 7600F, Tokyo, Japan, the form and surface morphology of the plain fluconazole, PEG 4000, and a chosen sample of solid dispersion were examined. After the samples were put on double-sided tape that was sticky and fastened to copper stubs, a 5 kV accelerating voltage was used to examine the data.

RESULTS AND DISCUSSIONS

Physical Characteristics

Every batch that was seen had a free-flowing, white powder appearance.

Percent practical yield

Percentage yield of every Ibuprofen batch It was discovered that solid dispersions ranged from 60% to 92%. Different techniques were used to prepare the solid dispersions, as Tables 4 and 5 demonstrate. The batch SE-S2 that was made utilizing the polymer UREA and the solvent evaporation process had the greatest achievable yield, 91.5%.As a result, the procedure for creating the solid dispersion seemed repeatable, and a 1:3 drug to hydrophilic carrier ratio was chosen.

Table 4: Percent Practical Yield And Drug Content Uniformity Of Ibuprofen Solid Disersions By Solvent Evaporation Method.

Batch Code	Percentage yield
SE-S1	62.5%
SE-S2	91.5%
SE-S3	87.5%
SE-S4	58.5%
SE-S5	60%
SE-S6	69.16%
K-1	65%
K-2	72.25%
K-3	65%
F-1	76%
F-2	83.5%
F-3	77.17%

Table 5: Saturation Solubility Of Plain Ibuprofen In Different Solvents (0.1n Hcl, Buffer Ph-7.2 And Water).

PLAIN DRUG IBUPROFEN	0.1N HCL	BUFFER PH 7.2	WATER
SOLUBILITY	0.021 mg/ml	0.0083 mg/ml	0.0019 mg/ml

Table 6: Saturation Solubility Of Solid Dispersions In Different Solvents (0.1n Hcl, Buffer Ph-7. 2 And Water).

BATCH CODE	0.1N HCL	BUFFER PH 7.2	WATER
SE-S1	43.23mg/ml	42.98 mg/ml	32 mg/ml
SE-S2	49.23mg/ml	43.64 mg/ml	33.62 mg/ml
SE-S3	42.67mg/ml	39.36mg/ml	28.57mg/ml
SE-S4	43.57mg/ml	40.27mg/ml	29.35mg/ml
SE-S5	44.68mg/ml	41.64mg/ml	29.89mg/ml
SE-S6	43.56mg/ml	40.l54mg/ml	26.22mg/ml
K-1	39.27mg/ml	35.79mg/ml	25.34 mg/ml
K-2	45.32mg/ml	41.97mg/ml	31.38 mg/ml
K-3	34.3 mg/ml	33.84 mg/ml	27.67 mg/ml
F-1	42.4mg/ml	38.97 mg/ml	27.8mg/ml
F-2	47.2mg/ml	42.97mg/ml	34.67mg/ml
F-3	41.38mg/ml	39.51 mg/ml	22.43mg/ml

DISSOLUTION STUDIES

Dissolution studies in both the 0.1N HCL and pH 7.2 buffer media, batch SE-S2 released its medication at a higher pace than the pure drug, Ibuprofen. Ibuprofen's plain drug release rate in 0.1N HCL was 8.563% in 90 minutes, while batch SE-S2's solid dispersion release rate was found to be 88.65% in the same time frame. Table 7 provides the dissolving rates in 0.1N

HCL, and Figure 1 displays the dissolution profile graph. The rates of pure drug ibuprofen release in Buffer pH 7.2 was found to be 83.82% whereas in solid dispersion batch SE-S2 was found to be 98.63%. The dissolution rates in Buffer pH 7.2 is given in **Table 8** and the dissolution profile graph is shown in **Figure 2.** Hence, preparation of solid dispersions improved the dissolution rates.

Table 7: Dissolution Study Of Plain Ibuprofen And Solid Dispersion Containing Polymer Urea In 0.1n Hcl (Buffer Ph-1. 2).

Ibuprofen Capsule	
TIME IN MINS	**% CUMULATIVE RELEASE**
10	1.8%
20	1.626%
30	2.535%
40	3.089%
50	3.916%
60	6.4575%
90	8.563%
120	10.23%

Solid dispersion Capsule	
TIME IN MINS	**% CUMULATIVE RELEASE**
10	9.3%
20	24.54%
30	32.185%
40	37.76%
50	46.07%
60	59.825%
90	88.65%
120	97.2%

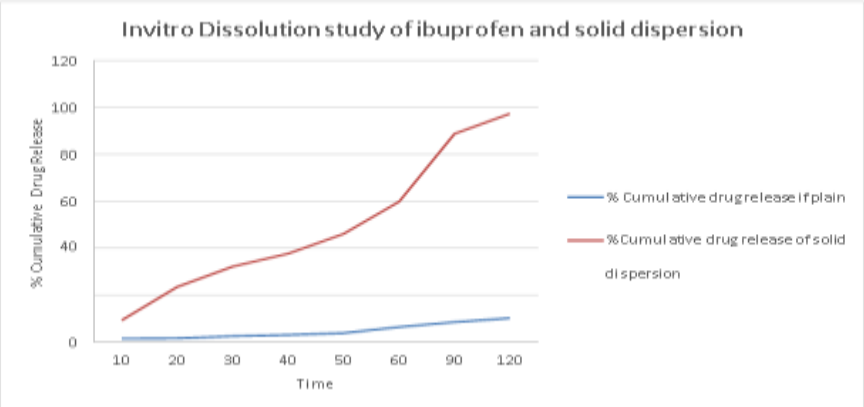

Figure 1: Drug Release Profile Of Plain Ibuprofen And Solid Dispersion Containing Polymer Urea In 0.1n H.

Table 8: Dissolution Study Of Plain Ibuprofen And Solid Dispersion Containing Polymer Urea In Buffer Ph 7.2.

Ibuprofen Capsule	
TIME IN MINS	**% CUMULATIVE RELEASE**
10	10.8%
20	18.06%
30	25.36%
40	32.7%
50	35.58%
60	62.78%
90	83.82%
120	95.76%

Solid dispersion Capsule	
TIME IN MINS	**% CUMULATIVE RELEASE**
10	18.56%
20	21.16%
30	27.183%
40	36.783%
50	45.53%
60	73.23%
90	98.63%
120	104.25%

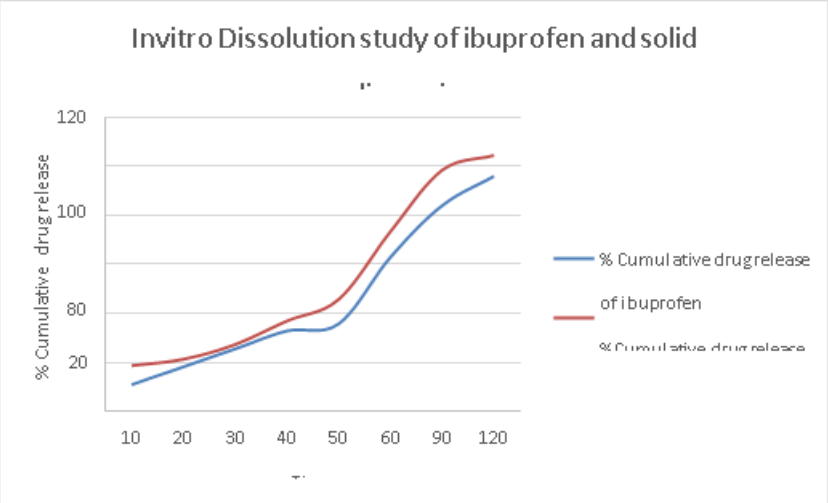

Figure 2: Drug Release Profile Of Plain Ibuprofen And SolidDispersion Containing Polymer Urea In Buffer Ph 7.

Fourier Transform Infrared spectroscopy

The FTIR spectra of pure Ibuprofen, UREA and their Solid Dispersion are shown in **Figure 3**. The FTIR studies indicated that there is no chemical interaction taking place between drug

Ibuprofen and polymer UREA during preparation of Ibuprofen solid dispersions.

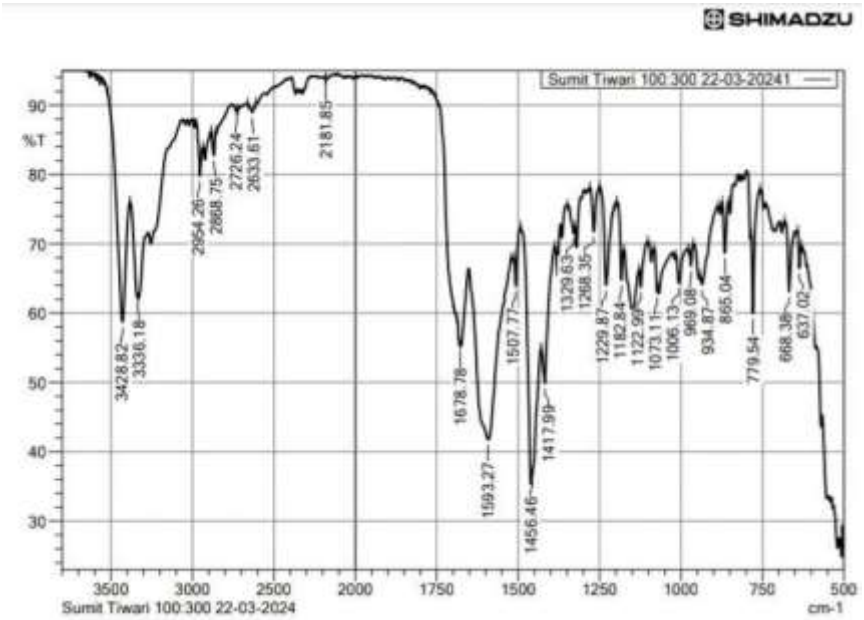

Figure 3: Ft-Ir For Plain Solid Dipersion Containing Polymer Urea.

Differential scanning calorimetry

DSC studies were carried out for plain drug Ibuprofen and Solid dispersion containing polymer Urea given in **Figure 4 and 5** indicated that ibuprofen was homogenously distributed within the carrier in an amorphous state and no drug crystallized out of solid dispersion suggesting that drug and polymer exist in a mixture rather than a reaction product.

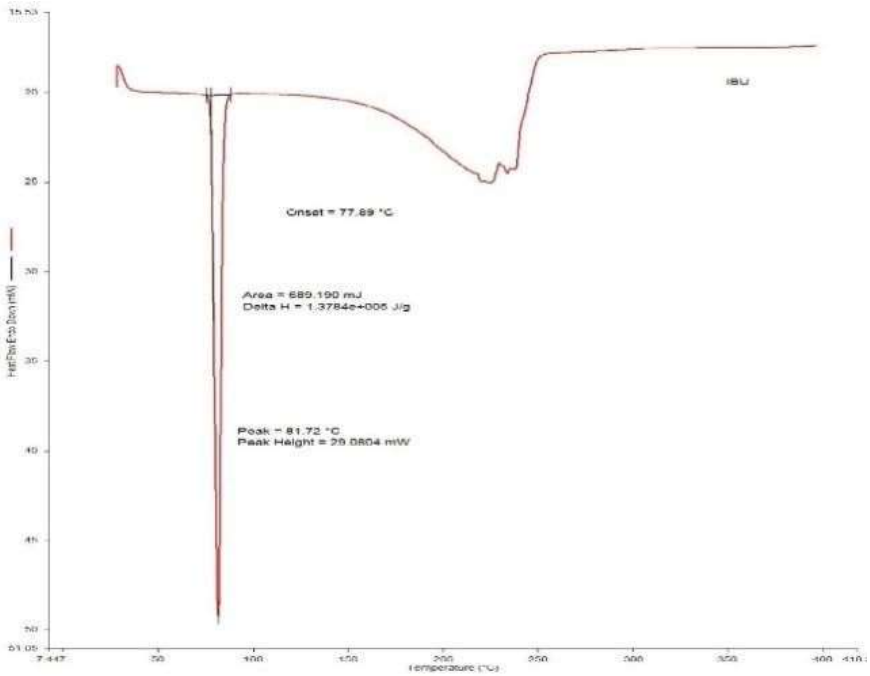

Figure 4: Dsc For Plain Drug Ibuprofen.

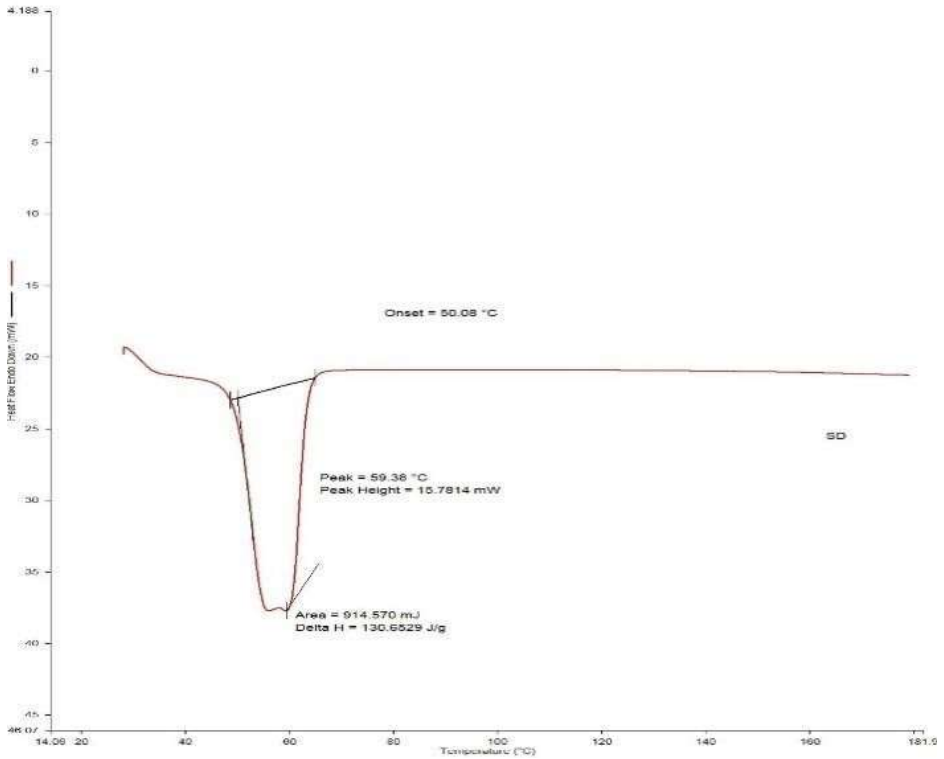

Figure 4: Dsc For Solid Dispersion Containing Urea.

Scanning electron microscopy

The SEM study was performed for plain ibuprofen, polymer UREA and Solid dispersion of selected batch SE-S2 for size and surface morphology as shown in Figure 5. The study revealed that pure ibuprofen existed in form crystals which were flat broken needles of different sizes. The polymer UREA existed in the form of irregular shaped crystals while Solid dispersion of ibuprofen existed in form compacted spherical forms. The original morphology of components disappeared stating that ibuprofen in solid dispersion was homogeneously dispersed into UREA at molecular level.

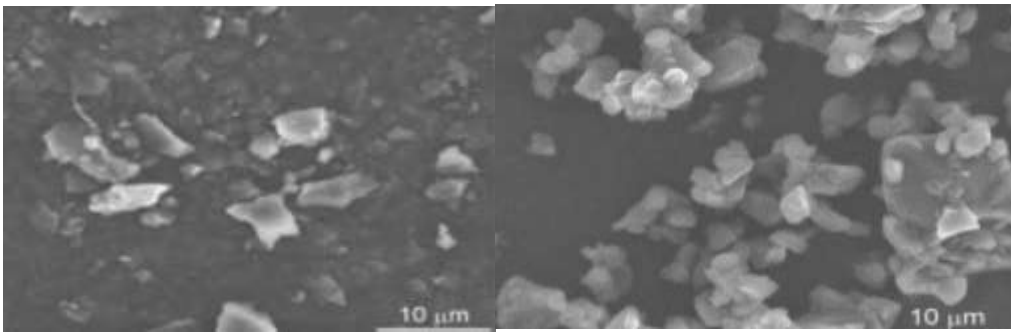

Figure 5: Sem For Plain Drug Ibuprofen And Polymer Urea.

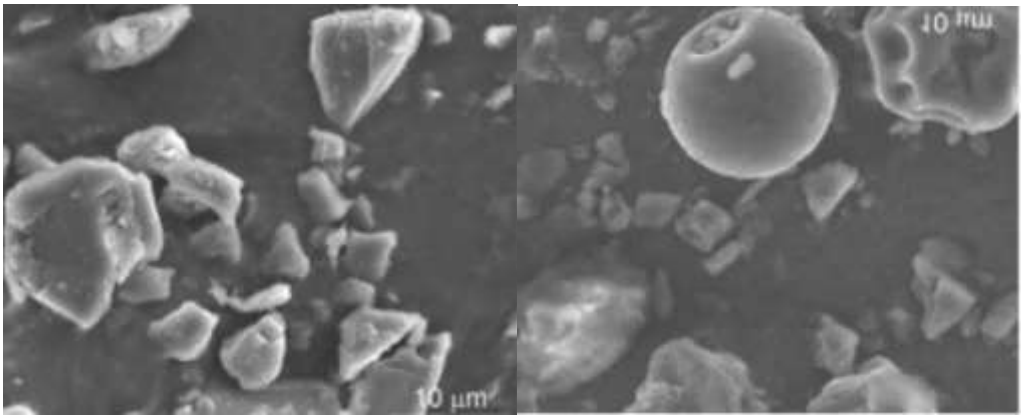

Figure 5: Sem For Solid Dipersion Containing Polymer Urea.

CONCLUSION

The results of all the studies showed that preparation of solid dispersions improved solubility, as well as dissolution rate, for poorly water-soluble drugs. Different polymers were used in the preparation of the solid dispersions, with UREA being the most effective carrier for the highest solubility levels. The solvent evaporation method yielded the highest practical yield compared to the kneading methods. The formulation of SE-S2 had the highest level of solubility as well as an increased dissolution rate compared to the plain drug.

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