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Research Article

Enhancing the Solubility, Dissolution Rate and Oral Bioavailability of Poorly Water-soluble Drug, Satranidazole by Solid Dispersion prepared by using β-Cyclodextrin as a Carrier

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ABSTRACT

The present work aims to prepare and characterize solid dispersions of Santranidazole using β-Cyclodextrin to improve its aqueous solubility and dissolution with the aid of solvent evaporation technique. Solid dispersions showed marked improvement in the solubility behavior and stepped forward for drug launch. From all the formulations, F2 becomes an optimized method based on the characterization, solubility and dissolution studies. The enhancement of dissolution depends upon the nature and quantity of the carrier. The rise in the dissolution rate may be attributed to; the reduced particle size of drug deposited at the carrier's floor and the enhanced wet capacity of the drug debris by the carrier. The optimized formulations have been evaluated through Differential Scanning Calorimetry (DSC), Fourier remodel infrared spectroscopy (FTIR) and Scanning electron microscopy (SEM).

Introduction

The variety of drug molecules with poor aqueous solubility and dissolution rate has grown gradually over the past so many years because of the use of high throughput and combinatorial screening tools during the drug discovery and choice phase.[1] Development of oral bioavailability of poorly water-soluble drug remains one of the toughest elements of drug improvement. Many approaches, along with salt formation, solubilization and particle length discount have normally been used to boom dissolution rate and thereby oral absorption and bioavailability of such tablets.[2] However, all these strategies have ability limitations. All poorly soluble drugs are not appropriate for enhancing their solubility by means of salt formation. Using co-solvents or surfactants to improve dissolution charge poses troubles and decreasing particle length will increase solubility, but there is negative wetting and float.[3-6] Solid dispersions can overcome these troubles. Many providers used in strong dispersions also cause troubles because of their hygroscopic nature. Therefore, continuously looking for new carriers and strategies goes on with the purpose to be useful for massive scale production. Studies for alternative carriers have been increasing to match for the industrial packages in addition to reduce the production cost and toxic effects. Many polymers have boundaries in enhancing solubility of poorly soluble drugs due to their excessive viscosity. The use of polymers with low viscosity and excessive swelling

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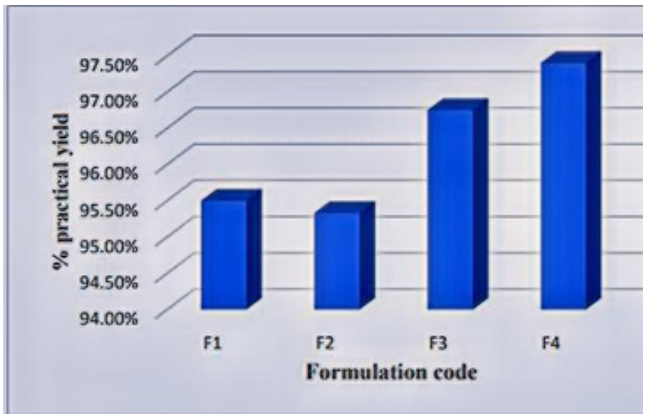

Fig. 1: %Yield of solid dispersion.

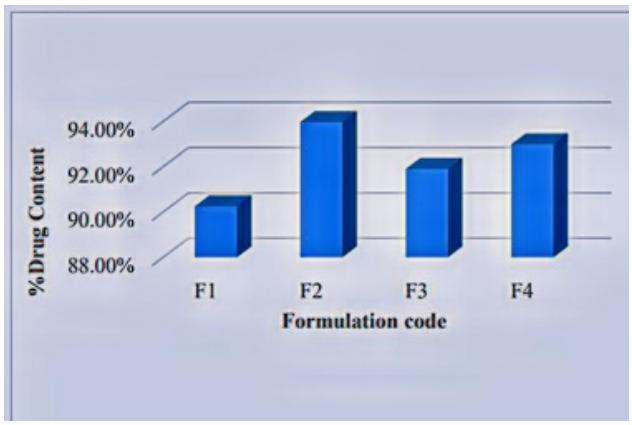

Fig. 2: Drug content of satranidazole in solid dispersion.

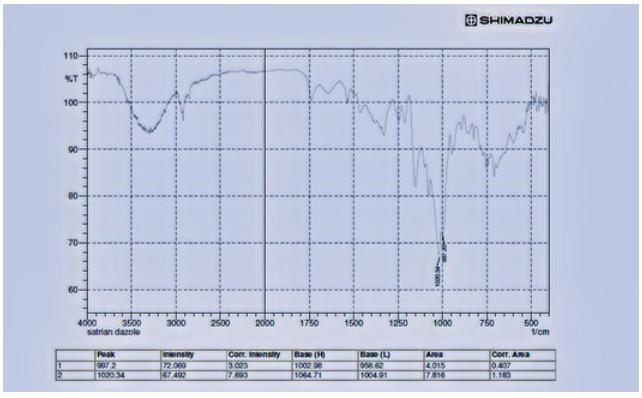

Fig. 3: FTIR spectra of satranidazole.

capacity offers a higher opportunity for those varieties of polymers. Use of natural polymer is extra useful because of their low fee, biocompatibility, and biodegradability[7] value powerful pharmaceutical excipients are continually appropriate. Pharmaceutical excipients developed from herbal sources are financial. Contemporary consumers look for natural ingredients in meals, drugs and cosmetics as they believe that something herbal may be safer and without facet outcomes.[8,9] Herbal excipients shows less toxicity, good availability and economic considerations

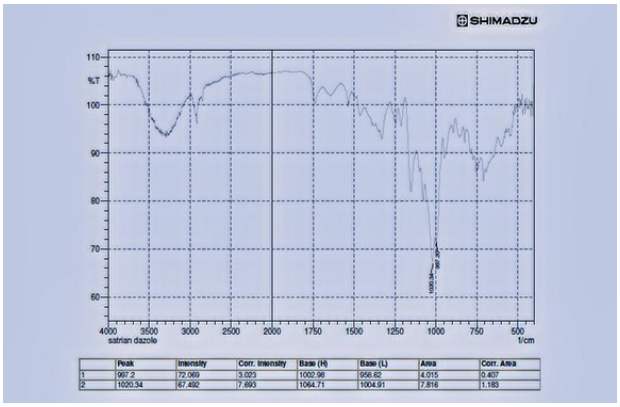

Fig. 4: FTIR spectra of physical mixture.

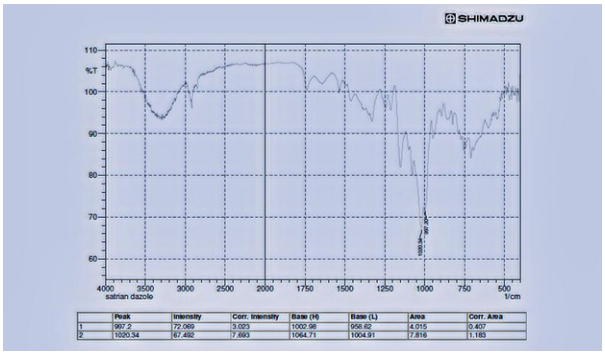

Fig. 5: FTIR spectra of satranidazole solid dispersion.

in pharmaceutical industry compared to their synthetic counterparts obviously, derived excipients have proven promising results within the change of drug release from the formulations. [10-13]

The poor aqueous solubility of the drug may lead to dissolution-related bioavailability problems. β-cyclodextrin plays a pivotal role in the development of dosage form due to their impact on solubility, dissolution charge, chemical stability, and drug absorption. Various attempts have been made to enhance the drug solubility of poorly aqueous soluble amongst them solid dispersion has proven to be a successful technique. B-CDs are used to increase the solubility of water-insoluble drugs, through the formation of inclusion complexation. Generally, the small drug molecules, and those compounds with the lowest water solubility showed a preferential increase in solubility as a function of CD concentration. Therefore, β-CD has been given much priority for their use in pharmaceutical preparations to increase the stability and bioavailability of poorly water soluble drugs such as Satranidazole. Satranidazole falls under class II compounds as per biopharmaceutical classification system. Satranidazole is a systemically acting drug which is twice as effective as other nitroimidazoles. It is successfully used in the treatment of some parasitic diseases. Satranidazole exhibits a low bioavailability which is related to its poor aqueous solubility.

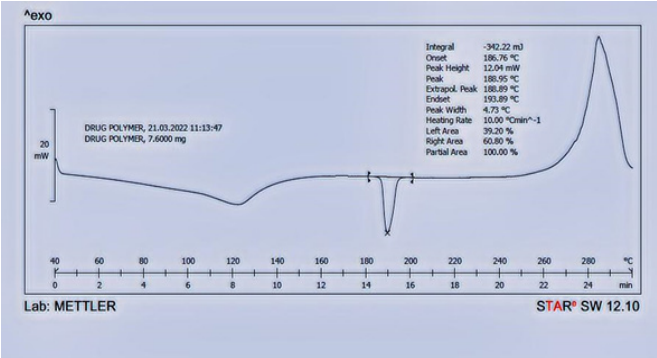

Fig. 6: DSC of satranidazole.

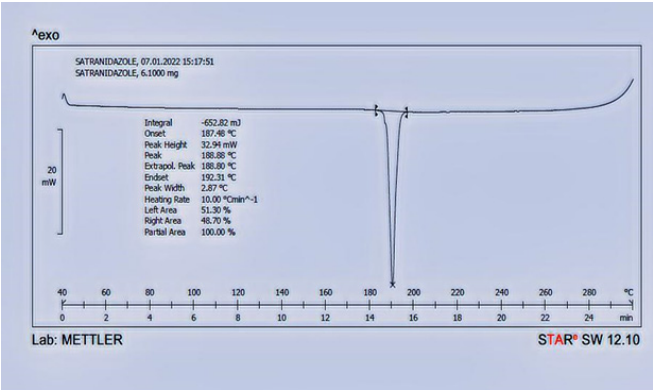

Fig. 7: DSC of physical mixture.

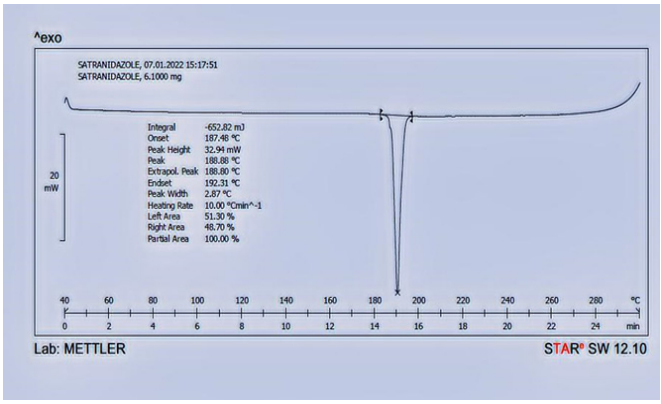

Fig. 8: DSC of satranidazole solid dispersion.

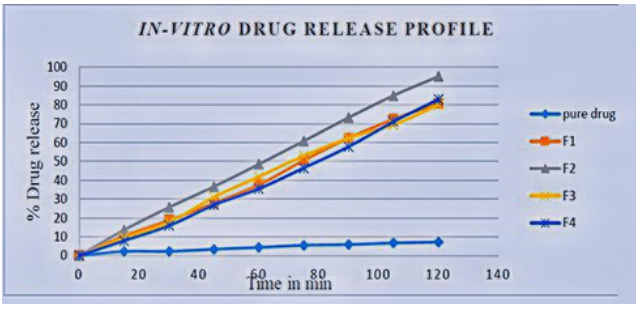

Fig. 9: Comparative *in-vitro* drug release profile of pure drug and all formulation.

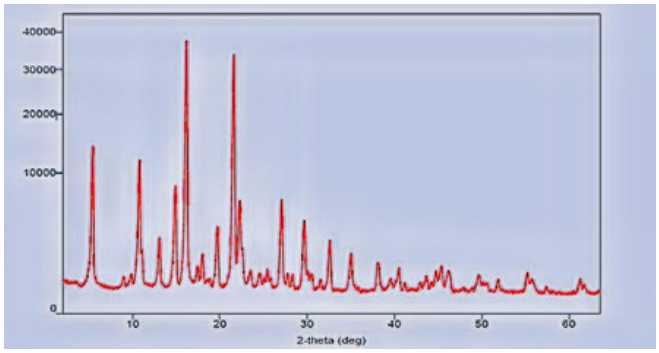

Fig. 10: X-ray diffractogram of satranidazole solid dispersion.

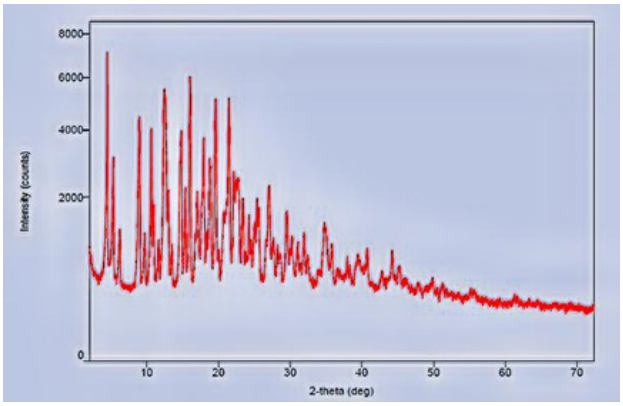

Fig. 11: X-ray diffractogram of satranidazole solid dispersion.

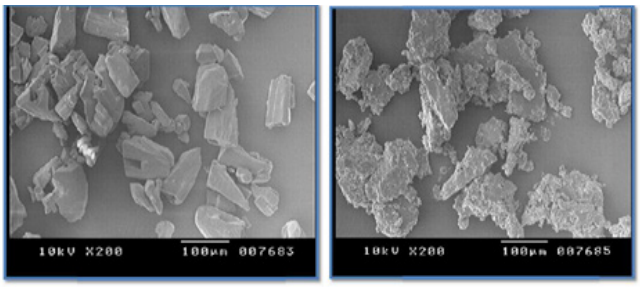

Fig. 12: SEM images of pure satranidazole (A) and (B).

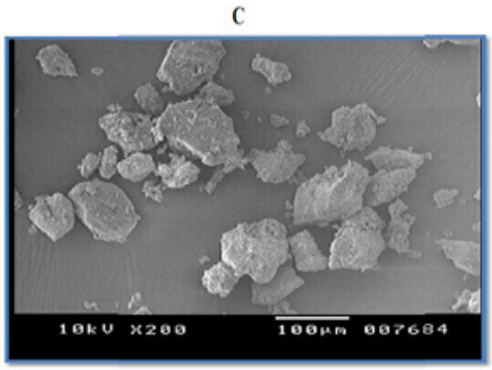

Fig. 13: SEM images of satranidazole solid dispersion C.

Table 1: Formulation design of solid dispersion of santranidazole

S. no	*Formulation code*	*Polymer*	*Drug: polymer Ratio*	*Method*
1.	F1	β-cyclodextrin	1:1	Solvent evaporation method
2.	F2		1:2	
3.	F3		1:3	
4.	F4		1:4	

*One part is equal to 100 mg.

Table 2: *In-vitro* dissolution studies of solid dispersion of santranidazole

Formulation	*Dissolution Media*	*Paddle speed (rpm)*	*Bath temperature*	*UV analysis*	*Time (minutes)*
Solid dispersion	0.1N HCl	100	37 ± 0.5°C	318nm	15–120

Table 3: Characterization of drug

S. no.	*Properties*	*Nature*
1	Physical state	Crystalline
2	Colour	Yellow
3	Solubility	Poorly soluble in water, Soluble in methanol, Chloroform, Acetonitrile, DMSO etc.

Table 4: Estimation of %practical yield of satranidazole solid dispersion

S. no	*Formulation code*	*%Practical yield of solid dispersion (%)*
1	F1	95.50
2	F2	95.33
3	F3	96.75
4	F4	97.40

Table 5: Estimation of drug content

S. no.	*Formulation*	*%Drug content*
1	F1	90.25
2	F2	93.27
3	F3	91.20
4	F4	92.99

The purpose of this work was to formulate Santranidazole stable dispersions with the aid of solvent evaporation technique using β-cyclodextrin as carrier to enhance its solubility, dissolution and *in-vitro* bioavailability. All the solid dispersions showed appreciably better dissolution, whereas F2 is the optimized one. Solid dispersion have been subjected to distinctive studies along with Differential scanning Calorimetry, FTIR, X-ray powder diffractometry, and Scanning electron microscopy.

Materials And Methods

Material

Santranidazole pure drug was gift sample from Alkem Laboratories, New Mumbai India. β-cyclodextrin was obtained from Merk chemicals, Mumbai. All other chemicals used were of analytical grade.

Table 6: Micromeritics properties of satranidazole solid dispersion

Sample	*Bulk density (gm/cm^3)*	*Tapped density (gm/cm^3)*	*Hausner's ratio*	*Carr's index (%)*	*Angle of repose (0)*
Pure drug	0.360	0.545	1.61	34.85	410.36
F1	0.479	0.537	1.12	12.54	220.13
F2	0.502	0.531	1.10	7.51	230.12
F3	0.472	0.539	1.09	10.42	250.10
F4	0.439	0.536	1.11	9.52	240.14

Table 7: *In-vitro* drug release of Satranidazole solid dispersion compared with pure drug

S. no	*Time (min)*	*0*	*15*	*30*	*45*	*60*	*75*	*90*	*105*	*120*
1	Pure drug	0	2.22	2.28	3.39	4.37	5.50	5.89	6.71	7.23
2	F1	0	10.37	18.74	27.88	37.58	50.48	62.44	72.32	80.82
3	F2	0	13.62	25.65	36.95	48.54	60.83	73.32	85.01	94.18
4	F3	0	9.27	17.70	31.03	41.87	52.96	62.40	69.54	79.99
5	F4	0	7.91	15.91	26.88	35.53	46.53	57.87	71.10	83.01

Method

Saturation solubility and phase solubility study: Solubility is an important consideration. The solubility of Santranidazole was tested in various solvents such as Water, methanol, Chloroform and Acetonitrile etc.

Preparation of Solid Dispersions and Physical Mixtures

Preparation of Solid Dispersion by Solvent Evaporation Method

Santranidazole and β-Cyclodextrin were triturated in ratio 1:1, 1:2, 1:3, and 1:4. w/w with addition of few drop of methanol to form a paste in a separate china dish. The solvent allowed 40°C to evaporate to form a dry stable mass that is beaten into high-quality debris, passes through sieve No.60 for further use, and is held in a desiccator.

Evaluation Parameters

Percentage yield

The well dried solid dispersion was collected and weighed accurately. The percentage yield was calculated by using formula given below.

$$\text{Percentage Yield} = \frac{\text{Actual weight of Product}}{\text{Total Weight of Drug and Polymers}} \text{ X } 100$$

Drug Content

To examine the amount of drug included inside the stable dispersion, Santranidazole was extracted from the solid dispersion by dissolving them in 25 mL methanol. The ensuing solution became filtered via Whatman clear out paper. The Santranidazole content inside the methanolic extract was analyzed with the aid of spectrophotometrically by using UV-seen spectrophotometer at a wavelength 254 nm. (UV – JASCO V 530) in opposition to methanol as clean.

$$\% \text{ Drug Content} = \frac{Wa}{Wt} \text{ X } 100$$

In-vitro Dissolution Studies

In-vitro dissolution study of Santranidazole and all prepared formulations were carried out by using USP type II paddle apparatus (LABINDIA DS 8000). The dissolution medium was (900 ml) 0.1 N HCL (pH 1.2) and temperature was maintained at 37 ± 0.5°C. The oar was turned at 100 rpm. At suitable time intervals 15, 30, 45, 60, 75, 90, 105, 120 (minutes). 5 mL of sample was taken and filtered through Whatman filter paper. The dissolution medium was supplanted by 5 mL of new dissolution medium to keep up a sink condition. After dilutions, the examples at that point examined spectrophotometrically at 318 nm utilizing UV-visible spectrophotometer.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy (NOVA NANO SEM-450) used to examine particle size and floor topography is operated at 25 kV acceleration voltage.

The surface morphology of Santranidazole and prepared system of strong dispersion and together with complicated, had been tested via scanning electron microscopy (NOVA NANO SEM-450). The usage of a scanning electron microscope running at 25 kV, electron micrographs of substances, strong dispersion and inclusion complexes were obtained. Till remark, the samples were located on a glass stub with double-sided adhesive tape and vacuum coated with gold in an argon atmosphere. To analyze the morphological and surface characteristics of the individual components, solid dispersion and inclusion complexes, micrographs with various magnifications have been recorded.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra approach was used for detecting any possible physicochemical interaction between A.P.I. and excipients used in formulation. A 1:2 physical drug and excipient mixture was prepared and combined with the required amount of potassium bromide. The 100 mg mixture was compressed using a hydraulic press at a pressure of 6 tons to form a transparent pellet. FTIR spectra was recorded in the wavelength region of 4000–400 cm^{-1} in FTIR spectrophotometer. FTIR spectra of pure drug compared with A.P.I. and excipient and matching were done to detect any presence or absence of peaks. This study was done by using (BRUKER TENSOR 37) spectrophotometer.

Differential Scanning Colorimetry (DSC)

The DSC curve of Santranidazole and physical mixture were obtained using differential scanning colorimeter by increasing heating rate at 10°C/min and heated over temperature range of 50 to 250°C in an atmosphere of nitrogen (20 mL/min). 1-mg of the sample was taken in a hermetically sealed, flat bottom aluminum sealed pan and placed at sample stage, thermogram was recorded. This study was recorded using (DSC60 SHIMADZU).

Powder X-ray Diffractometry (XRD) Study

X-ray diffractometry used to determine inclusion complexation in solid state. Liquid drug sample not own diffraction pattern. The diffraction pattern of newly formed substance clearly differs from that solid dispersion. Difference between diffraction patterns indicates complex formation. If the drug substance is solid, the comparison must be made between the diffractogram of the assumed complex and the mechanical mixture of drug and polymer. A physical mixture diffraction pattern is always the sum of those of each component, while complex diffraction patterns are obviously different from each component and

lead to a new solid phase with distinct diffractograms. The dynamic formation of solid dispersion medicine changes the pattern of diffraction.

Result And Discussion

Pre-formulation Evaluation

Physical Characterization of the Drug

The drug was evaluated for physical state, color, odour was noted down.

Determination of λ_{max}

The UV-visible spectrum of Satranidazole in methanol is λ_{max} shown at maximum corresponding to 318 nm wetting property of drug.

Percentage Yield

Percentage yield was calculated to know about percentage yield or efficacy of any method. The practical yield increases as polymer concentration increases. The highest practical yield is 97.40%, and minimum practical yield is 95.50%.

Drug Content

The drug content material changed into within the variety of 90.25 to 93.97. All solid dispersion confirmed presence of high drug content material and low well-known deviation effects. It's far indicated that drug is uniformly dispersed within the powder formulation.

Micromeritics Studies

In these studies, the flow properties of pure drug and solid dispersion studied and the obtained results are as shown in Table 6.

FTIR Study

FTIR studies were done to distinguish the potential cooperation's between the Satranidazole and bearer. It was uncovered that there was no distinction in the places of the retention groups, consequently giving proof to the nonappearance of communication in the strong state among Satranidazole and bearer. Every single trademark pinnacle shows up in the spectra of all strong scattering at same wave number, demonstrating no change or collaboration between the medication and polymer.

DSC Study

The DSC curve of pure drug and drug with carrier was carried out by Mettler Toledo diffractometer. DSC spectra of pure Satranidazole, physical mixture and solid dispersion obtained.

Interpretation

The DSC of Satranidazole API shows a sharp endothermic peak at 165.41°C. Indicated purity of drug Satranidazole.

In-vitro Dissolution Studies

Interpretation

In-vitro drugs release all components of strong dispersion compared to pure drugs. Dissolution studies have been carried out in 0.1 N HCL.

- Dissolution of natural Satranidazole changed into located drug release minimal 2.22 and maximum 7.23%.
- The in-vitro dissolution look at all formula having β-Cyclodextrin showed the cumulative %drug launch of batch F3 is 79.99% and batch F2 is 94.18% at the give-up of 120 minutes.
- The end result indicated that F2 has higher cumulative release of drug with β Cyclodextrin. possible mechanism of 94.18% dissolution rate of drug in solid dispersions because of wettability and disposability of drug from the dispersion, solubilization impact of provider, absence of drug aggregation, reduction in drug crystallinity and conversion of drug in an amorphous state.

Interpretation

From Figs. 10 and 11 graph it indicated that API Satranidazole shows sharp peak. While XRD of solid dispersion showed less intense peak, indicating the conversion of crystalline from into amorphous form. The diffraction pattern of pure Satranidazole showed its highly crystalline nature. The diffraction pattern of Satranidazole: β-cyclodextrin solid dispersion shows less intense the peak of Satranidazole with reduction in peak intensities indicating that conversion of crystalline to partial amorphous form.

Scanning Electron Microscopy (SEM)

The Fig. 12 of A and B SEM micrographs of Satranidazole powder showed irregular shaped crystalline particles. On Fig. 13 C, Formulation F2 was spherical in shape and smooth morphology.

The SEM micrographs of Satranidazole powder showed irregular shaped particles, whereas Fig. 13, formulation F2 was spherical in shape and smooth morphology.

Conclusion

The drug has been categorized under BCS Class II. Its low aqueous solubility and dissolution rate may be enhanced by using solid dispersion technology by encapsulating drug with β-cyclodextrin. It has been reported that usage of hydrophilic carriers leads to an increase in the dissolution rate of poorly soluble drugs and bioavailability. Solid dispersions come in contact with the aqueous media, the carrier gets dissolved and the drug gets released as fine particles, providing larger surface area for the dissolution rate and bioavailability. A recent study shows that the dissolution rate, bioavailability and solubility of poorly

soluble drug satranidazole improved by preparing its slid dispersion with the aid of solvent evaporation method by using β-cyclodextrin. Solid dispersion prepared by means of solvent evaporation technique shows suitable drug content material and in-vitro drug release. The result of IR and DSC shows the compatibility of drug and polymer with no interactions.

It has been concluded that β-Cyclodextrin are employed as polymer for oral drug transport to effectively deliver drugs by encapsulating in it. Solid dispersion of Satranidazole has increased solubility and dissolution rate of drug.

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