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Development of modified porous starch as a carrier to improve aqueous solubility

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ABSTRACT

The objective of this work was to improve aqueous solubility of poorly water soluble drugs by a modified porous starch as solid dispersion carrier. The yield of the porous starch was found to be 80%. The flow property of the prepared porous starch was found to be good, with good compressibility index. The particle size of the prepared porous starch were found to be in the range of 53–130µ. There was no possible interaction between prepared porous starch and metronidazole in the solid state, as confirmed by FT-IR spectra and. DSC thermograms. Drug content of all the formulations were found to be in the range between 97-100%. The dissolution profile showed that in solid dispersions prepared by physical mixing process and solvent evaporation method, the dissolution of pure metronidazole is high in comparison with the solid dispersion samples. Whereas in solid dispersions prepared by kneading method, dissolution of pure metronidazole is very low in comparison with the solid dispersion samples of drug with porous starch due to co-habitation of carriers with metronidazole that improved the dissolution rate of the drug. The predicted drug release mechanism for kneading method was by peppas model where the drug release could be by diffusion process. Thus this study confirmed that a porous starch can be developed and utilized as a carrier to improve the aqueous solubility of poorly water soluble BCS class II drugs thereby improving its dissolution rate and bioavailability.

Keywords: Porous starch, metronidazole, solid dispersion, solubility.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion but it is problematic if the drug is poorly soluble or poor membrane penetrability [1,2]. When a drug is administered orally in solid dosage form such as tablet, capsules, or suspension it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. The bioavailability of many poorly water-soluble drugs is limited by their dissolution rates [3]. There are several ways to increase the bioavailability of drugs which include micronisation, use of salt forms, use of metastable polymorphs, selective adsorption onto insoluble carriers, solute solvent complexation, complexation with cyclodextrins and solid dispersion [4]. Solid dispersion is a multicomponent system having drug dispersed in and around hydrophilic carriers. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting (fusion), solvent, or melting solvent method and they are used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs of BCS class II and III drugs [5,6]. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrolidone and polyethylene glycol are used as carriers for solid dispersions [7-9]. Starch is a carbohydrate consisting of a large number of glucose units joined together by glycosidic bonds. It consists of two types of molecules: the linear and helical amylose and the branched amylopectin. Depending on the plant, starch generally contains 20 to 25% amylose and 75 to 80% amylopectin [10]. Porous starch is a biodegradable starch that has great potential as a solid dispersion carrier for oral poorly water soluble drugs. Porous starch has a nano-porous structure, low density, high specific surface area and pore volume; its distinctive advantages include nontoxicity, biocompatibility, and biodegradability [11]. Traditionally porous starch has been prepared by swelling or by heat assisted microwave technique [12]. Metronidazole is a white or yellowish crystalline powder slightly soluble in

water, in ethanol (95 percent), in acetone and in dichloromethane; very slightly soluble in ether [13]. This work was aimed at exploring the possibility of improving solubility and dissolution rate of poorly water soluble drug metronidazole using the prepared porous starch as solid dispersion carrier.

MATERIALS AND METHODS

Metronidazole was obtained from Yarrow Chem Products, Mumbai. Starch was purchased from Swastik pharmaceuticals, Mumbai. Ethanol and acetone were purchased from S.D.Fine chemicals, Mumbai. All other reagents used were of AR grade.

Preparation of porous starch

Porous starch was prepared by the method reported earlier [14] with some modifications. A 10%w/w of starch was prepared in hot water, heated to 100^0C for 30 minutes under constant stirring in a reaction vessel. The temperature was then lowered to 85^0C and then poured into a petridish. The resulting slurry was kept in a refrigerator overnight to facilitate gelation. The gelled product was scrapped and transferred to 50 ml of 90% ethanol and kept for 24 hours in order to maintain the porous structure of gel, whereby ethanol displaced the water in aqua gel. It is then dried in direct sunlight for 2 hours and then kept in vacuum drier, which is maintained at 60^0C for 6 hours. The dried product is powdered and then passed through sieve no.60 and stored in a dessicator till further use.

Characterization of prepared porous starch

1. **Solubility:** Solubility of porous starch was tested in water, aqueous buffers of pH 1.2, 4.5, and 7.4 and organic solvents such as alcohol, dichloromethane, chloroform, acetone and petroleum ether.
2. **pH:** The pH of 1% w/v slurry was measured using a digital pH meter
3. **Melting Point:** Melting point was determined by using melting point apparatus
4. **Viscosity:** Viscosity of 1% dispersion in water was measured using Brookfield viscometer (Model DV-II) spindle no.2 at varying rpm.
5. **Swelling Index:** Prepared porous starch (200 mg) was added to 10 ml of water and light liquid paraffin taken in two different graduated test tubes and mixed. The dispersion in the tubes was allowed to stand for 12 h. The volumes of the sediment in the tubes were recorded. The swelling index of the material was calculated as follows.

$$S.I\ (\%) = \frac{VW - VL}{VL} \times 100$$

Where, VW – volume of sediment in water
VL – volume of sediment in liquid paraffin
S.I – swelling index

6. **Test for gelling property:** The gelling property was evaluated by heating a 1% w/v dispersion in water at 100°C for 30 min.
7. **Particle size:** The particle size was determined using optical microscope (Olympus LITE image). Sample powder was taken on a slide and spread into a thin film. A total of 100 particles are counted and their size is determined. The average particle size in micrometers was determined.
8. **Surface morphology:** The surface morphology of the prepared starch was determined using optical microscope (Olympus LITE image).
9. **Bulk density:** Bulk density (g/cc) was determined by three tap method in a graduated cylinder.
10. **Angle of repose:** Angle of repose was measured by fixed funnel method.
11. **Compressibility index:** Compressibility index (CI) was determined by measuring the initial volume (Vo) and final volume (V) after hundred tappings of a sample of starch phosphate in a measuring cylinder. CI was calculated using equation

$$Carr's\ index = \frac{Vo - V}{Vo} \times 100$$

Where, V_0 = initial volume
V = final volume after tapping

Preparation of solid dispersions

Solid dispersions of metronidazole with the prepared porous starch in varying ratio as mentioned in Table 1 were prepared by following methods.

1. Solid dispersions prepared by the solvent evaporation method
Solid dispersions of metronidazole with the prepared porous starch were prepared in the ratios of 1:1 and 1:2. Accurately weighed quantity of porous starch and drug was dissolved in acetone. After complete dissolution, the solvent was evaporated under reduced pressure at 60°C in a dessicator. Subsequently, a uniform mixture was obtained that was sieved and stored in glass vials at room temperature until use.
2. Solid dispersions prepared by physical mixing method
Solid dispersion of metronidazole was prepared in the ratio of 1:1 and 1:2 by physically mixing both carrier and drug using a glass mortar and pestle thoroughly until a uniform mixture is obtained. The mixture obtained was passed through sieve no.100 and stored in a glass vial until use.
3. Solid dispersions prepared by kneading method
Solid dispersions of metronidazole were prepared in the ratio of 1:1 and 1:2. Required quantity of starch was taken in a mortar. To this 5ml of 50 % alcohol was added and triturated to form a paste. Then, drug is added slowly into the paste and triturated continuously for 1 hour. The paste was air dried at 25^0C for 12 hours. The mixture was then size reduced by passing through sieve no.100 and stored in a glass vial until use.

Evaluation of solid dispersions

1. **Fourier Transform-Infra Red Spectroscopy**: Compatibility studies of pure drug, porous starch and the physical mixture of both drug and porous starch were carried out using Fourier Transform Infrared Spectrophotometer (Shimadzu FT-IR 8400-S) in the range of 400-4000cm^{-1} by KBr disc method.
2. **Differential Scanning Calorimetric analysis**: The pure drug, porous starch and physical mixtures of drug and porous starch were subjected for DSC studies using differential scanning calorimeter (Mettler-7, Germany). 5mg of samples were weighed into aluminium pans and sealed and the samples were run at a heating rate of 10°/min over a temperature range of 25-300° in atmosphere of nitrogen.
3. **Estimation of metronidazole**: From the prepared solid dispersion samples amount
equivalent to 100mg of metronidazole was taken in a 100ml volumetric flask and the volume was made up to the mark with phosphate buffer (pH 7.4). The dispersion was vortexed, filtered, diluted suitably with buffer and the drug content was estimated at 223 nm using UV-visible spectrophotometer (UV-1601, Shimadzu).
4. **In-Vitro Dissolution studies**: Dissolution studies were carried out using the rotataing basket method (USP apparatus II). Solid dispersions equivalent to 100 mg of pure drug were filled into the capsules (size no:1) and placed in the baskets that is immersed in 900ml of pH 7.4 phosphate buffer as dissolution medium, maintained at 37±0.5ºC and rotated at 100rpm. At designated time intervals, 5 ml samples were withdrawn, and replaced with 5 ml of fresh dissolution medium. The samples were filtered, diluted suitably and analyzed spectrophotometrically at 320 nm using pH 7.4 phosphate buffer as blank. The dissolution experiments were performed for pure drug also in triplicate for each sample. The same dissolution study was carried out for a marketed product as well to compare the drug release profile of the prepared formulations.
5. **Kinetic modeling of drug release mechanism:** The dissolution data of all formulations were fitted to zero-order, first-order, Hixson-Crowell, Higuchi and Korsemeyer and Peppas models to predict the drug release mechanism.

RESULTS AND DISCUSSION

Solvent exchange method was used to prepare this modified porous starch, where alcohol used as exchange solvent to avoid contraction and collapse of aquagel due to direct air drying. The yield of the porous starch was found to be 80%. Prepared porous starch were tested for their pH, melting point, viscosity, particle size, flowability and compressibility and the results are shown in table 2. The flow property of the prepared porous starch was found to be good, with good compressibility index thereby confirming that this starch can be used as an excipient in formulation of tablets. The pH of 1% solution was found to be 6.8. No gelling and the swollen particles of prepared porous starch separated from water. The particle size of the prepared porous starch was measured by using optical microscope for about 100 particles and the particle size were found to be in the range of 53–130 µ. The photomicrograph image of the porous starch was shown in figure1. Viscosity of 1 % w/v dispersion of modified porous starch in water was found out using Brookefield's viscometer at varying rpm using spindle 2. It was showing shear thinning behavior as viscosity was found decreasing with increasing rate of shear.

In order to study possible interaction between carriers and metronidazole in the solid state, FT-IR spectra were recorded. The FT-IR spectra of metronidazole, prepared porous starch powder and physical mixture of porous starch with metronidazole in the ratio 1:1 and 1:2 were recorded. The IR spectral studies of metronidazole showed sharp peaks at 3033.82cm^{-1} (for O-H stretching), 2879.52cm^{-1}(for C-H stretching), and 1483.16cm-1 (for N-O stretching attached to the asymmetric carbon in the ring). Similar identical peaks were observed in physical mixture of metronidazole with porous starch, in both 1:1 & 1:2 ratio, thereby confirming the absence of drug-carrier interaction (Fig 2-5). DSC thermograms of metronidazole, porous starch and physical mixture of drug with porous starch in the

ratio 1:1 and 1:2 were shown in Fig. 6-9. DSC thermogram of metronidazole showed sharp endothermic peak at 160.88°C, which was around its actual melting point 160°C. The DSC thermogram of the porous starch showed a peak at 207°C. The thermograms of physical mixture in the ratio 1:1 and 1:2 also showed the peak near to its melting points 161.2°C and 160.98°C respectively indicating that drug was stable within the polymer matrix and absence of any interaction between the drug and the polymer. This result of DSC supports the results obtained from IR spectra.

Drug content of all the six formulations were carried out using UV spectrophotometer at 320 nm. The results indicated that the drug content of all the six formulations was found to be in the range between 97-100%. The dissolution behavior of metronidazole from solid dispersions and pure drug were analyzed in pH 7.4 phosphate buffer. The dissolution profiles of all the prepared formulations by different methods namely physical mixing, kneading and solvent evaporation at pH 7.4 phosphate buffer are shown in Figures 10, 11 and 12 respectively. From the solid dispersions prepared by physical mixing process, it was evident that the dissolution of pure metronidazole is high in comparison with the solid dispersion samples of drug with porous starch prepared by physical mixing method. In this case, co-habitation of carriers with metronidazole retarded the dissolution rate of the drug when the ratio of drug to carrier was 1:1 and 1:2. From the solid dispersions prepared by kneading method, it was evident that the dissolution of pure metronidazole is very low in comparison with the solid dispersion samples of drug with porous starch. 38.45% of drug was released in 90 minutes. In this case, co-habitation of carriers with metronidazole clearly improved the dissolution rate of the drug when the ratio of drug to carrier was 1:1 and 1:2. These results conformed that the dissolution rate of solid dispersion prepared by kneading method is higher than the pure metronidazole. From the solid dispersions prepared by solvent evaporation method, it was evident that the dissolution of pure metronidazole is high in comparison with the solid dispersion samples of drug with the porous starch prepared by solvent evaporation method. In the case of solvent evaporation method, co-habitation of carriers with metronidazole retarded the dissolution rate of the drug when the ratio of drug to carrier was1:1 and 1:2. On comparison of the above three methods, kneading method was found to enhance drug release significantly than physical mixing, solvent evaporation methods.

Parallely a marketed product was subjected to dissolution studies using phosphate buffer pH 7.4 as dissolution medium. During this study, it was found that 104% of drug from marketed product was released in 50 minutes in comparison with the solid dispersions prepared by kneading method using porous starch, which showed 95 and 98 % drug release respectively for the drug and carrier ratio 1:1 and 1:2 at the end of 90 minutes. The predicted drug release mechanism by PCP Disso V3 software indicated that all the prepared solid dispersion formulations showed R^2 value between 0.9108–0.9881. Formulation F1K showed R^2 value of 0.9635 and k value of 48.02, whereas formulation F2K showed R^2 value of 0.9108 and k value of 81.10. This predicted that the drug release mechanism was by peppas model where the drug release could be by diffusion process. Formulation F1P (prepared by physical mixing method) showed R^2 value of 0.9609, whereas formulation F2P showed R^2 value of 0.9881 which confirmed that the drug release was by first order and matrix respectively. Similarly formulations F1S and F2S (prepared by solvent evaporation method) showed R^2 values of 0.9571 and 0.9525, which predicted the drug release mechanism by zero order and first order respectively.

Table 1: Formulation of solid dispersions

S. No	Ingredients in mg	Formulation code					
		F1K	F2K	F1P	F2P	F1S	F2S
1	Metronidazole	100	100	100	100	100	100
2	Modified porous starch	100	200	100	200	100	200

Table 2: Characterization of Modified porous starch

S. No	Parameters	Observed values*
1	pH of 1% solution	6.8±0.01
2	Melting point	207±1^{0}C
3	Viscosity at 20 rpm	3.56±1.2cps
4	Swelling index	200±1.3%
5	Particle size	53-130µm
6	Bulk density	0.623±0.05g/ml
7	Angle of repose	13^{0}89±0.55´
8	Compressibility index	6.315±0.2%

** - Average of three determinations*

Fig.1: Optical photomicrograph of the prepared porous starch

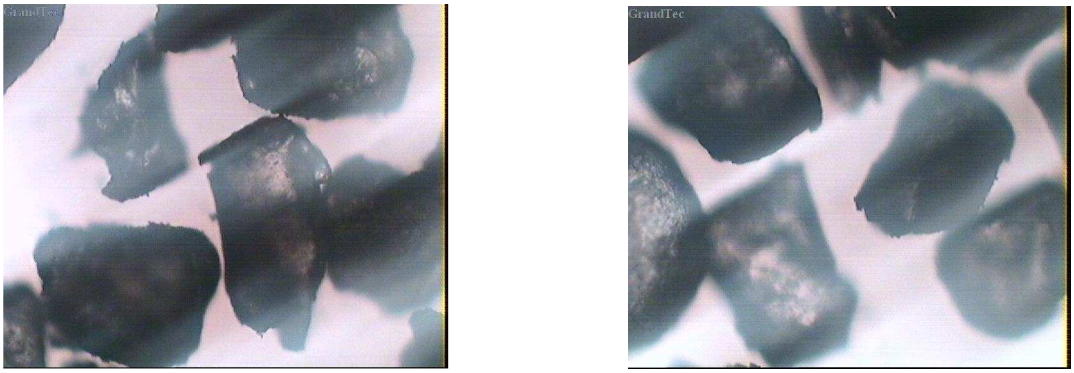


Fig.2: Infra red spectra of pure drug metronidazole

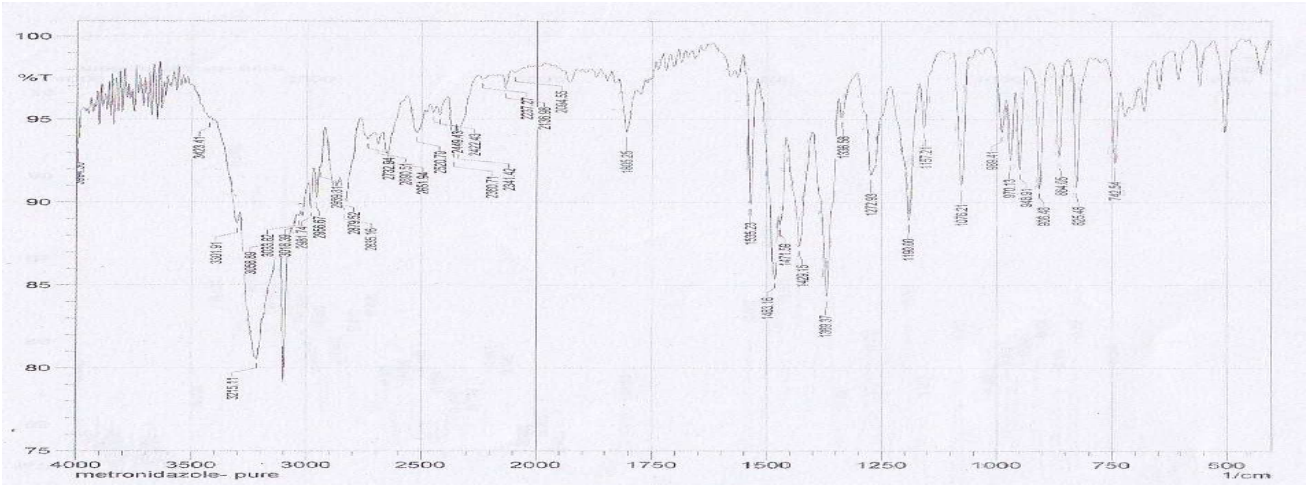


Fig.3: Infra red spectra of biodegradable porous starch

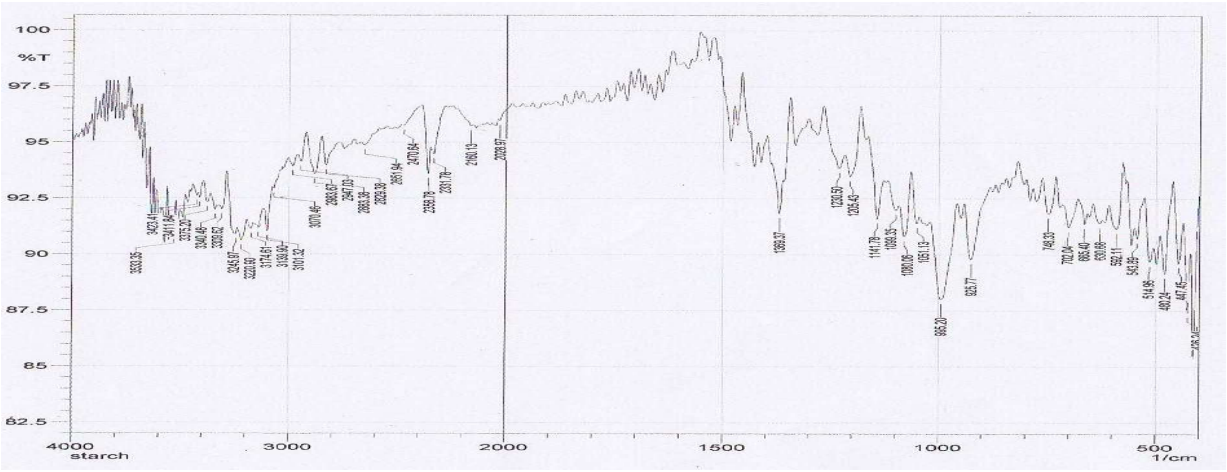


Fig.4: Infra red spectra of physical mixture of metronidazole with starch (1:1)

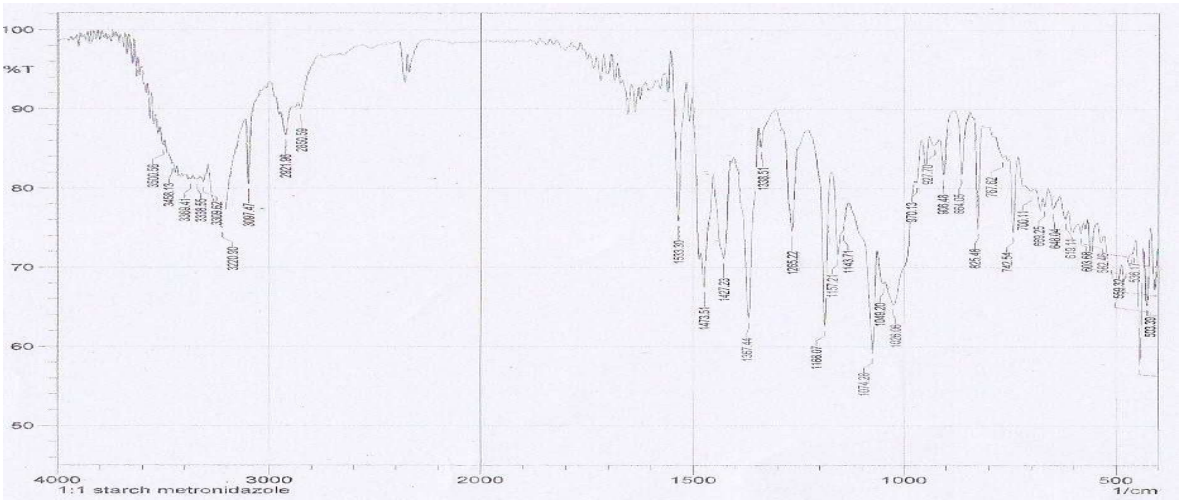


Fig.5: Infra red spectra of physical mixture of metronidazole with starch (1:2)

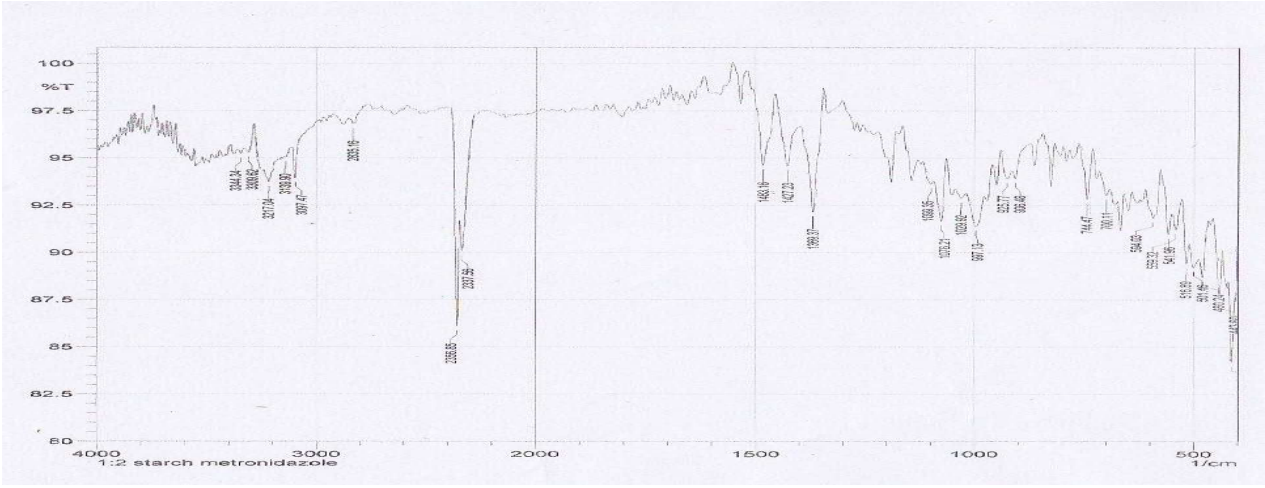


Fig.6: DSC thermogram of pure drug metronidazole

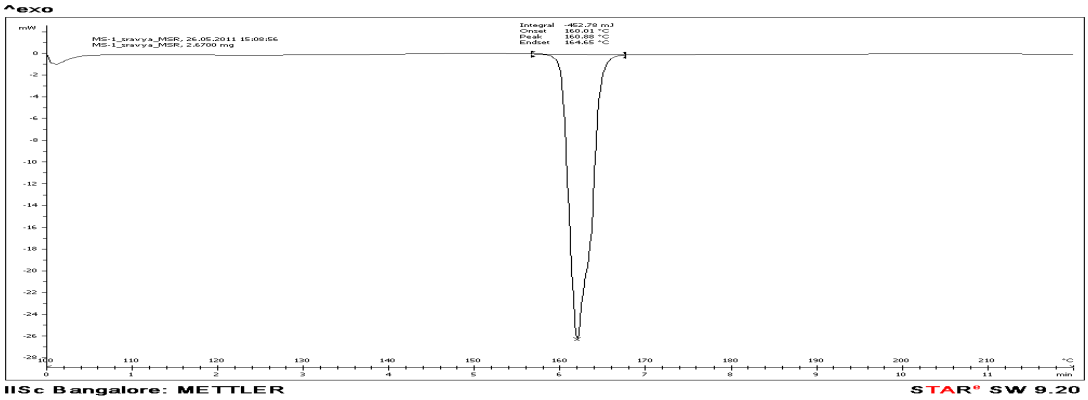


Fig.7: DSC thermogram of biodegradable porous starch

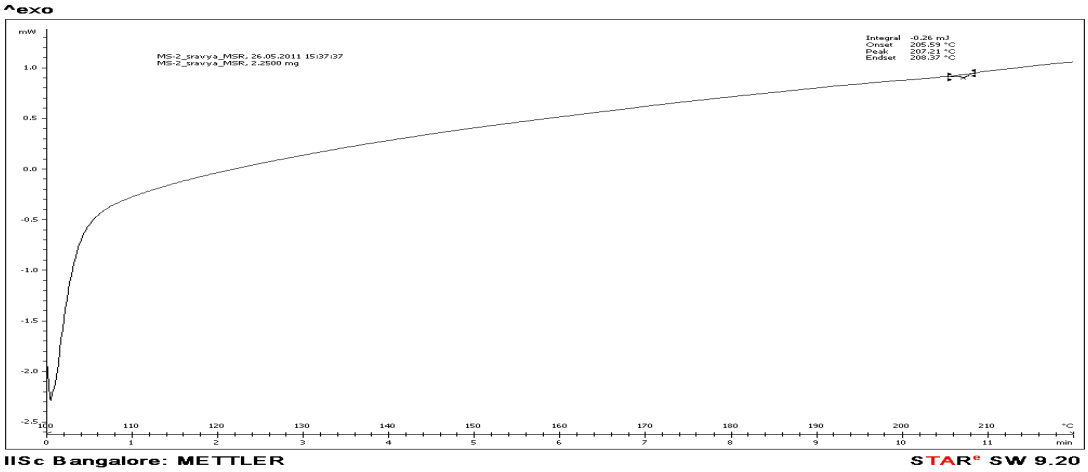


Fig.8: DSC thermogram of mixture of metronidazole with porous starch (1:1)

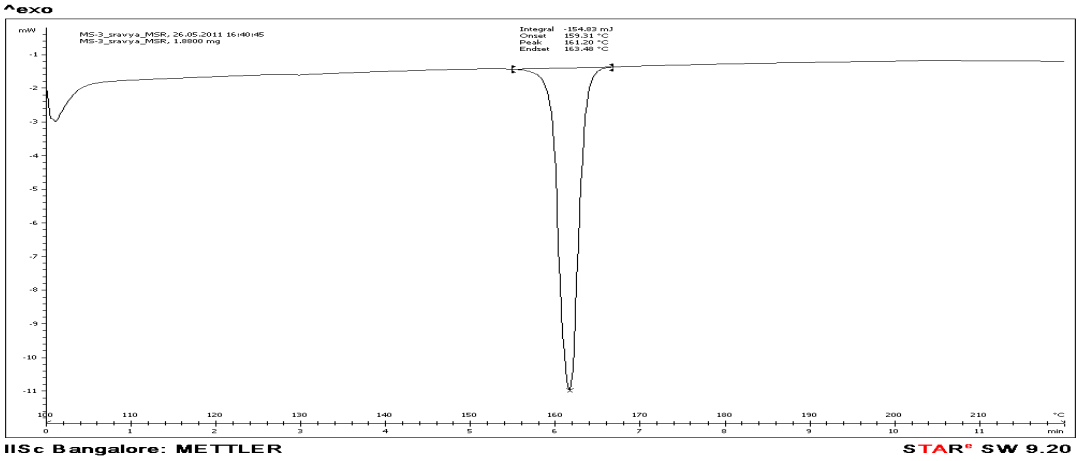


Fig.9: DSC thermogram of mixture of metronidazole with porous starch (1:1)

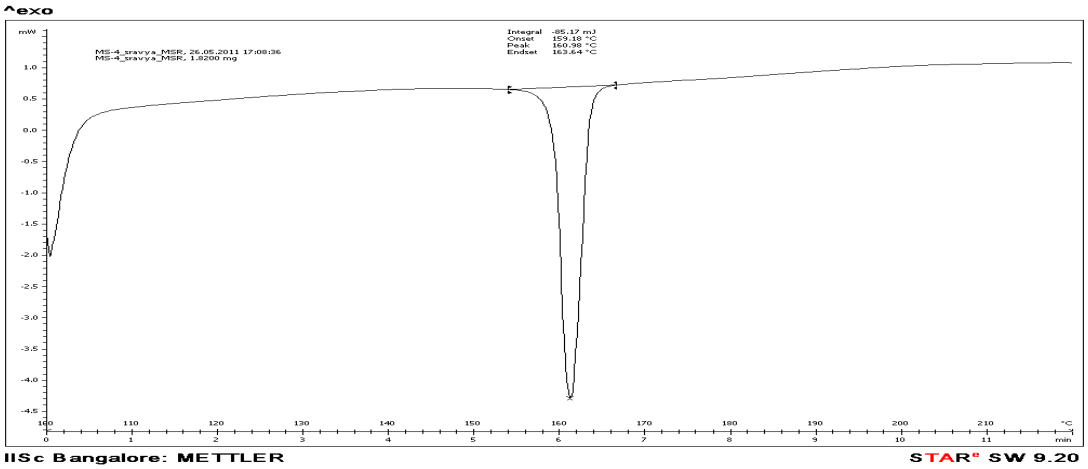


Fig.10: Dissolution profile of solid dispersions prepared by physical mixing

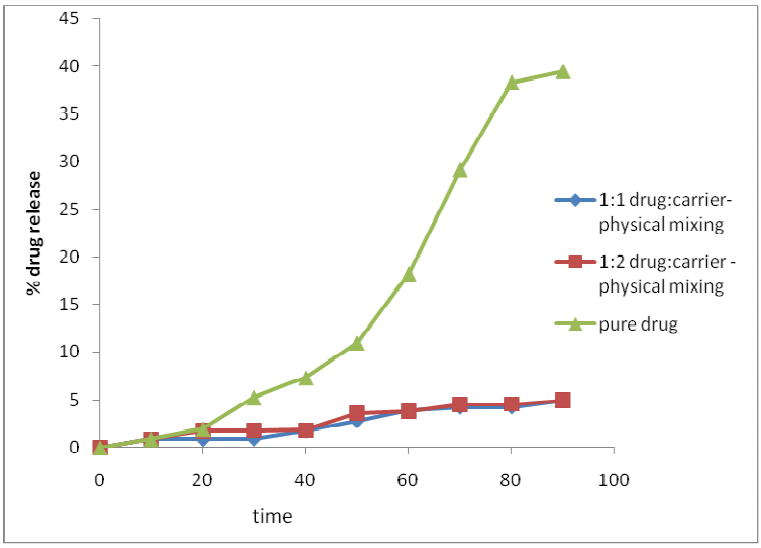


Fig.11: Dissolution profile of solid dispersions prepared by kneading

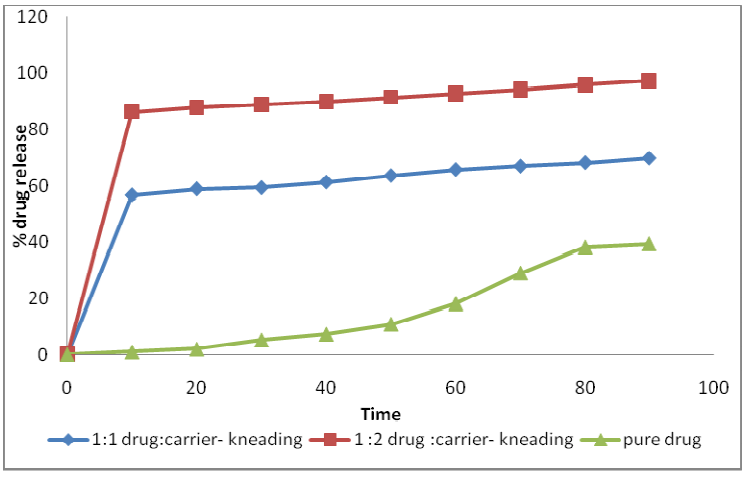
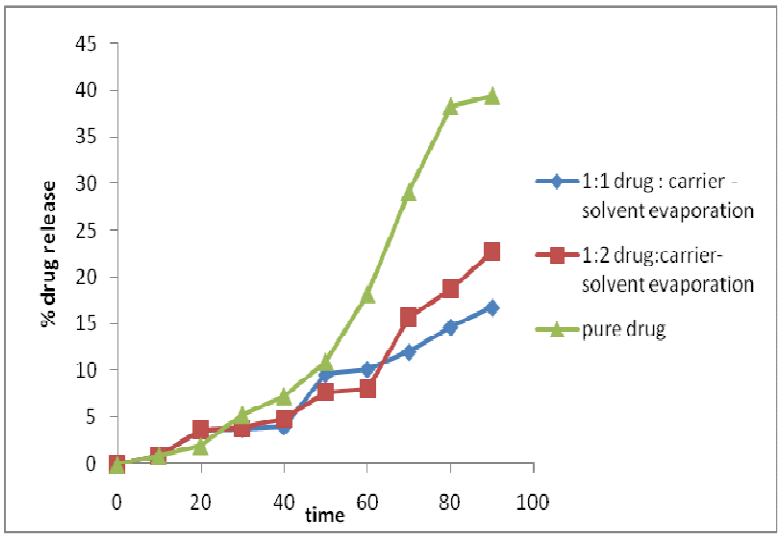


Fig.12: Dissolution profile of solid dispersions prepared by solvent evaporation



CONCLUSION

This study confirmed that a porous starch can be developed and utilized as a carrier to improve the aqueous solubility of poorly water soluble drugs thereby improving its dissolution rate and bioavailability. This may be applied as an alternative to other methods that are currently available to improve the aqueous solubility of BCS class II drugs, which has low solubility and high permeability.

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