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Research Article

IMPROVEMENT OF SIMVASTATIN SOLUBILITY USING NATURAL POLYMERS BY SOLID DISPERSION TECHNIQUE

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ABSTRACT
The solubility of the poorly soluble drugs can be improved by various techniques such as micronization[1], solubilization[2], salt formation[1], complexation[1] with polymers, change in physical form, use of prodrugs[1] and drug derivatization[1], pH alteration, addition of surfactants[3,4] , and others. Serajuadin [5] used the solid-dispersion technique for dissolution enhancement of poorly water-soluble drugs. A solid dispersion can be defined as "the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a physical mixture, melting (fusion), solvent, or melting–solvent method," while Corrigan[6] suggested it is "a product formed by converting a fluid drug–carrier combination to the solid state." Among the various approaches, the solid-dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical, and advantageous. Simvastatin (SIM), a crystalline compound, is practically insoluble in water and hence poorly absorbed from the GI tract [7,8] . It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase [9, 10], which catalyzes the reduction of HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After oral administration, Simvastatin is metabolized to its β-dihydroxy acid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in bioavailability [11]. In the present study, of solid dispersion physical mixture technique was used and solubility of drug was improved by using some natural polymers like Xanthum gum, Guar gum, Karaya gum, Chitosan and Oats powder.

KEY WORDS
Chitosan, Oats powder, Solid dispersion, Simvastatin, Oral bioavailability, Karaya Gum.

INTRODUCTION
The solubility of the poorly soluble drugs can be improved by various techniques such as micronization[1], solubilization[2], salt formation[1], complexation[1] with polymers, change in physical form, use of prodrugs[1] and drug derivatization[1], pH alteration, addition of surfactants[3,4] , and others. Serajuadin [5] used the solid-dispersion technique for dissolution enhancement of poorly water-soluble drugs. A solid dispersion can be defined as "the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by a

physical mixture, melting (fusion), solvent, or melting–solvent method," while Corrigan[6] suggested it is "a product formed by converting a fluid drug–carrier combination to the solid state." Among the various approaches, the solid-dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble, active pharmaceutical ingredients because it is simple, economical, and advantageous. Simvastatin (SIM), a crystalline compound, is practically insoluble in water and hence poorly absorbed from the GI tract [7, 8]. It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase [9, 10], which catalyzes the reduction of HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After oral administration, Simvastatin is metabolized to its β-dihydroxy acid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in bioavailability [11]. In the present study, of solid dispersion physical mixture technique was used and solubility of drug was improved by using some natural polymers like Xanthum gum, Guar gum, Karaya gum, Chitosan and Oats powder.

MATERIALS AND METHODS

Materials:

Simvastatin, Xantham gum, Guar gum, Karaya gum, Chitosan, Oats powder.

Method

SD of SIM with Xanthum gum, Guar gum, Karaya gum, Chitosan, Oats powder were prepared in the ratios of 1:1, 1:2, and 1:3 (drug–carrier). Physical mixture technique has been used for the preparation of SD in the present study. In this method, 20mg of Simvastatin was accurately weighed and physical mixtures [12] were formulated by mixing drug and carrier in geometric proportions using a spatula without applying pressure. The SD were passed through a No. 60 sieve and stored over anhydrous calcium chloride in desiccators.

EVALUATION OF SOLID DISPERSION

Drug Content:

Solid dispersions equivalent to 20 mg of SIM were weighed accurately and dissolved in 10 ml of Ethanol. The stock solutions were diluted with distilled water and analyzed by UV-Vis spectrophotometer at 238 nm.

Saturation Solubility Studies: Saturation solubility was conducted by shake-flask method [13]. Plain SIM in excess quantity was placed in separate glass-stoppered flasks containing 10 ml of distilled water. The samples were placed on a magnetic stirrer at 37 °C and at 100 rpm until equilibrium was achieved (24 hr). The aliquots were filtered through Whatman No. 41 filter paper. The filtrates were diluted appropriately with distilled water and assayed specrophotometrically at 238 nm.

pH-Dependent Solubility Studies: The pH-dependent solubility of SIM were determined in pH 1.2 and pH 7.0 buffers using similar procedure as for saturation solubility.

***In vitro* Dissolution Studies:**

The *in vitro* dissolution studies for plain SIM were carried out in Dissolution apparatus. Samples equivalent to 20 mg of SIM were added to 900 mL of 6.8 buffer at 37 ± 0.5° C and stirred at 50 rpm. Aliquots of 5 mL were withdrawn at specified time intervals and filtered through Whatman No. 41 filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed specrophotometrically at 238 nm.

Fourier Transform Infrared Spectroscopy (FTIR):

The IR spectra were recorded using an FTIR spectrophotometer with diffuse reflectance principle. The samples were scanned over the frequency range 4000–400^{-1} cm.

Scanning Electron Microscopy (SEM):

The surface morphology of samples was determined using an analytical scanning electron microscope (JSM6610). The samples were lightly sprinkled on a double-sided adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 10 Å under an argon atmosphere using a gold-sputter module in a high-vacuum evaporator. Afterwards, the stubs containing the coated samples were placed in the scanning electron microscope chamber.

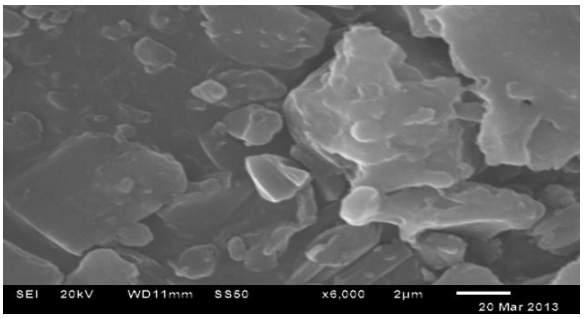


Figure: 1 SEM micrograph of solid dispersion of oats powder

Dosage Form Development:

The SD that showed maximum drug release and increase in saturation solubility was further formulated as tablets containing SD equivalent to 20 mg, lactose, Talc and magnesium stearate. The blend was formulated into tablets and evaluated for drug content uniformity.

RESULTS AND DISCUSSION

Drug Content:

Drug content in the solid dispersions was in the range of 98- 99.5% which is acceptable according to USP.

Saturation Solubility Studies, pH Solubility Profile: Simvastatin showed a solubility of 1.45 µg/mL in distilled water, 14.5 µg/mL in pH 1.2 buffer, and 24.4 µg/mL in pH 6.8 buffer. The solubility has been increased by using the natural polymers with different ratios.

SCANNING ELECTRON MICROSCOPY:

The SEM micrograph of the solid dispersion of oats powder was shown in the **Figure (1)**. The size of the dispersion ranges from 0.265µ to 0.934µ in diameter. The particles are irregular in shape and have crevices for deposition of drug.

FOURIER TRANSFORMS INFRARED SPECTROSCOPY (FTIR):

FTIR spectra data was shown in **Figure 2**. There is no significant difference in the FTIR spectra of pure drug and physical mixture. All major peaks of SIM observed at wave numbers 3550 cm-1 (free O–H stretching vibrations); 3011, 2959, and 2871 cm-1 (C–H stretching vibrations); and 1725 cm^{-1} (stretching vibration of ester and lactone carbonyl functional groups) were retained in physical mixtures and solid dispersions, which clearly indicate that no interaction was

observed between pure drug and polymers in solid dispersions.

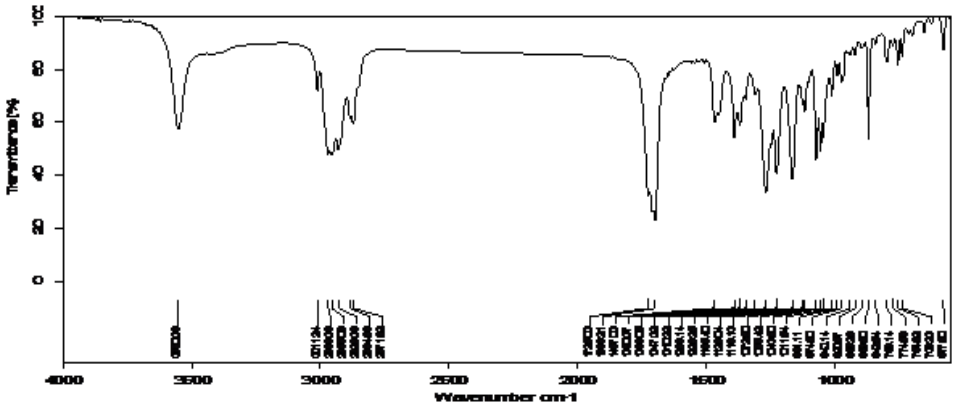
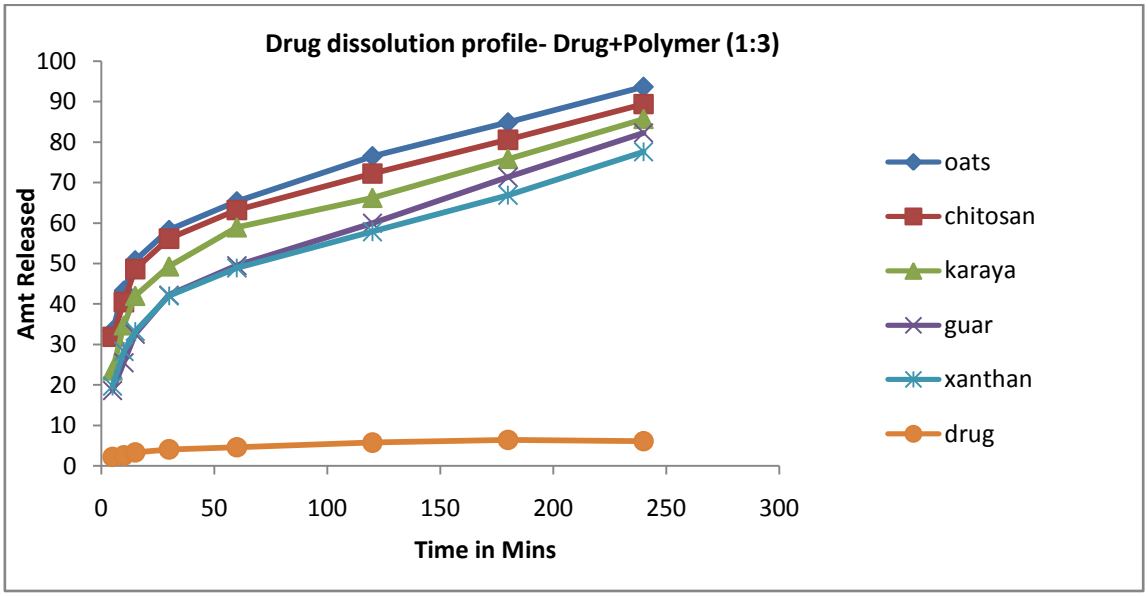


Figure: 2 FTIR image of solid dispersion of simvastatin with oats powder

***In Vitro* Dissolution Studies:**

The dissolution profiles of the solid dispersions were shown in **Graph (1)**. The dissolution rate of Simvastatin solid dispersions was higher for all the carriers when compared with the pure drug. Pure drug (Simvastatin) showed a poor dissolution profile (i.e., only 30% of drug was released at the end of 240 min, 7mg out of 20mg), whereas physical mixtures had shown improved dissolution profiles. Solid dispersion with oats powder shown almost 93.64% drug release within 240 min, whereas others chitosan 89.35%, karaya gum 85.71% guar gum 82.28% and Xanthum gum 77.57% within 240 min. The tablet dosage form also shown a better dissolution profile; 90.21% and 92.3 % (1:2, 1:3, Drug + Oats powder) of drug was released within 240 min. The improved dissolution could be attributed to a reduction in particle size of the drug, its deposition on the carrier, and improved wettability. Amount of drug release for each formulation was depicted in **Table-1.**



Graph: 1 Drug dissolution profile of drug and polymer (1:3)

Table-1: Amount of drug release from different solid dispersion formulations

S.No	Formulation	Amount release	S.No	Formulation	Amount release	S.No	Formulation	Amount release
1	F1	30.42	7	F7	70.90	13	F13	82.28
2	F2	61.07	8	F8	75.85	14	F14	85.71
3	F3	67.50	9	F9	82.71	15	F15	89.35
4	F4	73.28	10	F10	84.85	16	F16	93.64
5	F5	75.64	11	F11	89.35	17	F17	90.21
6	F6	80.35	12	F12	77.57	18	F18	92.30

F1-drug, F2-Drug+Xanthum gum 1:1, F3-Drug+Guar gum 1:1, F4-Drug+Karaya gum 1:1,F5-Drug+Chitosan1:1, F6-Drug+Oats1:1 , F7-Drug+xanthum gum 1:2, F8-Drug+Guar gum 1:2, F9-Drug+Karaya gum 1:2, F10-Drug+Chitosan 1:2, F11-Drug+oats 1:2, , F12-Drug+xanthum gum 1:3, F13-Drug+Guar gum 1:3, F14-Drug+Karaya gum 1:3, F15-Drug+Chitosan 1:3, F16-Drug+oats 1:3, F17- SD of oats powder tablet 1:2, F18 SD of oats powder tablet 1:3.

CONCLUSION

The present study reported that the solubility of Simvastatin was enhanced by using polymers. This was the first report on oats powder and chitosan used in solid dispersions. Oats powder consists of beta glucan, which is acting as a natural gum. Beta glucan might enhance the solubility of simvastatin. Simvastatin is used for the treatment of hypercholesterolemia and dyslipidemia. Oats powder is also helpful to lower the levels of cholesterol, so there may be potentiating effect to reduce levels of cholesterol.

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