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FORMULATION STRATEGY FOR DISSOLUTION ENHANCEMENT OF SIMVASTATIN

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ABSTRACT

The present work aim was "Formulation Strategy for Dissolution Enhancement of Simvastatin". Simvastatin is lipid lowering drug which is known as HMG CoA reductase. The objective of this study was to increase the solubility of poorly water soluble drug, namely simvastatin, by the formation of solid dispersion and complex and also using the microwave induction technique on these formations. For solid dispersion method dispersion carrier used were poloxamer 407 and gelucire 44/14. The fusion method was used to prepare the dispersions. For inclusion complexation method β-cyclodextrin derivative of cyclodextrin was used to prepare complex with drug. Kneading method was used for formulation. After completion of these two techniques these polymers were used for the microwave induced fusion method. All the ratio of drug and polymer were used to heat for different time interval. These samples were used for solubility measurement. In the solid dispersion technique, simvastatin show higher increase in solubility with gelucire 44/14 in the ratio of 1:5 as compare to poloxamer 407. In the microwave induced fusion method simvastatin show higher solubility with simvastatin with gelucire 44/14 after 10 mins time interval as compare to poloxamer 407 and β-cyclodextrin. Solubility of simvastatin increased higher with gelucire 44/14 by using microwave induced fusion method as compare to other technique. By using gelucire 44/14 with simvastatin it show 94% increase in solubility of simvastatin as compare to pure drug in water.

INTRODUCTION: Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.

Oral drug delivery is the simplest and easiest way of administering drugs due to its convenience, good patient compliance, greater stability, accurate dosage and easy production [1].

The rate and extent of dissolution of active ingredient from any solid dosage form determines the rate and extent of absorption of drug. The bioavailability of drug depends more often in its rate of dissolution in case of poorly water soluble drug where dissolution is rate limiting step for absorption [2].

Poor water-solubility of drugs has been one of the major problems in drug formulation and drug absorption these drugs often require high doses in order to reach therapeutic plasma concentrations after

oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds [3].

Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity [4].

The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form. The drug solubility in saturated solution in a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate. It is important to improve the solubility and/or dissolution rate for poorly soluble drugs because these drugs possess low absorption and bioavailability [5].

A number of methodologies can be adapted to improve Solubilization of poor water soluble drug and further to improve its bioavailability. Solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc.

Two main strategies can be observed in enhancing the solubility of poorly water-soluble drugs. On the one hand, the drug is pre-solubilized in a liquid dosage form, like in self-emulsifying drug delivery systems or microemulsions. When such formulations are released into the lumen of the gut, they disperse to form a fine emulsion, so that the drug remains in solution. Thus, the dissolution step, which often limits the rate of absorption of the drug, can be avoided [6, 7].

On the other hand, the drug is transferred into its amorphous state, or dispersed on a molecular basis in solid dosage forms, maximizing the surface area that comes into contact with the medium during dissolution. Thus, the solubility of the drug is improved, but the drug is not prevented of precipitation [8].

Simvastatin (SIM) is a cholesterol lowering agent, which is a white, non-hygroscopic, crystalline powder having poor aqueous solubility and bioavailability. SIM is a potential inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase. Simvastatin is selective hydroxyl methyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitor, an enzyme which is responsible for the conversion of HMG-CoA to mevalonate, a precursor of cholesterol synthesis, Inhibition of this enzyme by Simvastatin results into decrease in cholesterol synthesis and decreased blood cholesterol level which would be an effective step in the treatment of patients with hypercholesterolemia and mixed dyslipidemia and in the treatment of homozygous familial hypercholesterolemia.[9]

MATERIALS AND METHODS:

Materials: Simvastatin was obtained as gift sample from Intas Pvt. Ltd, India. Gelucire 44/14 and poloxamer 407 were purchased from Gattefosse, France. β-cyclodextrin was purchased from Sunrise Remedies, Pvt. Ltd, India.

Methods: Solubility of pure drug: 100 mg of drug was taken in 50 ml of water. This sample was kept on magnetic stirrer for 24 hour. This solution was filtered through the whatman filter paper. Absorbance of solution was taken by U.V spectroscopy at 237nm and calculates the concentration.

Preparation of simvastatin solid dispersion with polymer: simvastatin and polymer were taken in the ratio of 1:1, 1:2, 1:3, 1:4, 1:5 respectively. This physical mixture was triturated appropriately in the mortar pestle. After that they were directly melted in the porcelain dish and cooled. Keep this mixture for 24 hour. This mixture sieved for fine powder. These fine powder used for the solubility measurement.

Preparation of simvastatin complex with β-cyclodextrin: Simvastatin and β-cyclodextrin were taken in the ratio of 1:1, 1:2, 1:3, 1:4, 1:5 respectivly. Triturated this mixture in mortar pestle to mix drug properly with polymer. Then dispense these mixtures in the porcelain dish respectively.

Water was used as a solvent to prepare the complexation. Add proper amount of solvent in the mixture to mix drug with polymer. Keep these mixtures for 24 hour. These complexes were used for the solubility measurement.

Preparation for Microwave Induction Fusion Method: Microwave induction of simvastatin with polymer: Simvastatin and polymer were taken in the ratio of 1:1, 1:2, 1:3, 1:4, and 1:5 respectively. These mixtures were properly triturated in mortar pestle to get fine powder. Microwave induction was done for 2, 4, 6, 8 and 10 min on individual physical mixture. Keep the mixture in microwave oven for its respected time period. Cool for 24 hour. These samples were used for the solubility measurement.

Method for Solubility measurement: Prepared mixtures were kept on magnetic stirrer by adding water as solvent. Keep stirring for 24 hour. Filter the mixture. Measure the absorbance of each mixture in UV and calculate the concentration. This method was done for each ratio of mixture.

RESULT AND DISCUSSION: In the present study, solubility of simvastatin was increased by different techniques of solubility enhancement with three different polymers. For that study preformulation parameter was studied like FTIR, SEM, and DSC.

Fourier transform infrared spectroscopy:

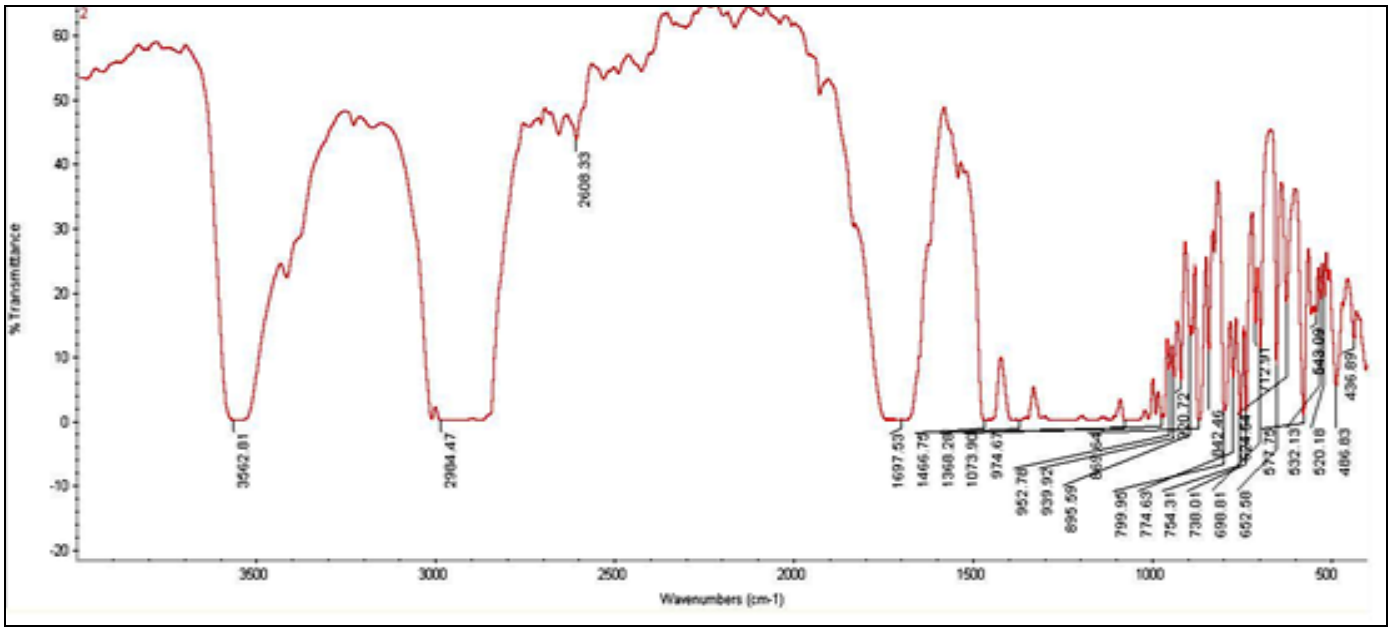

FIGURE: 1 FTIR SPECTRA OF SIMVASTATIN

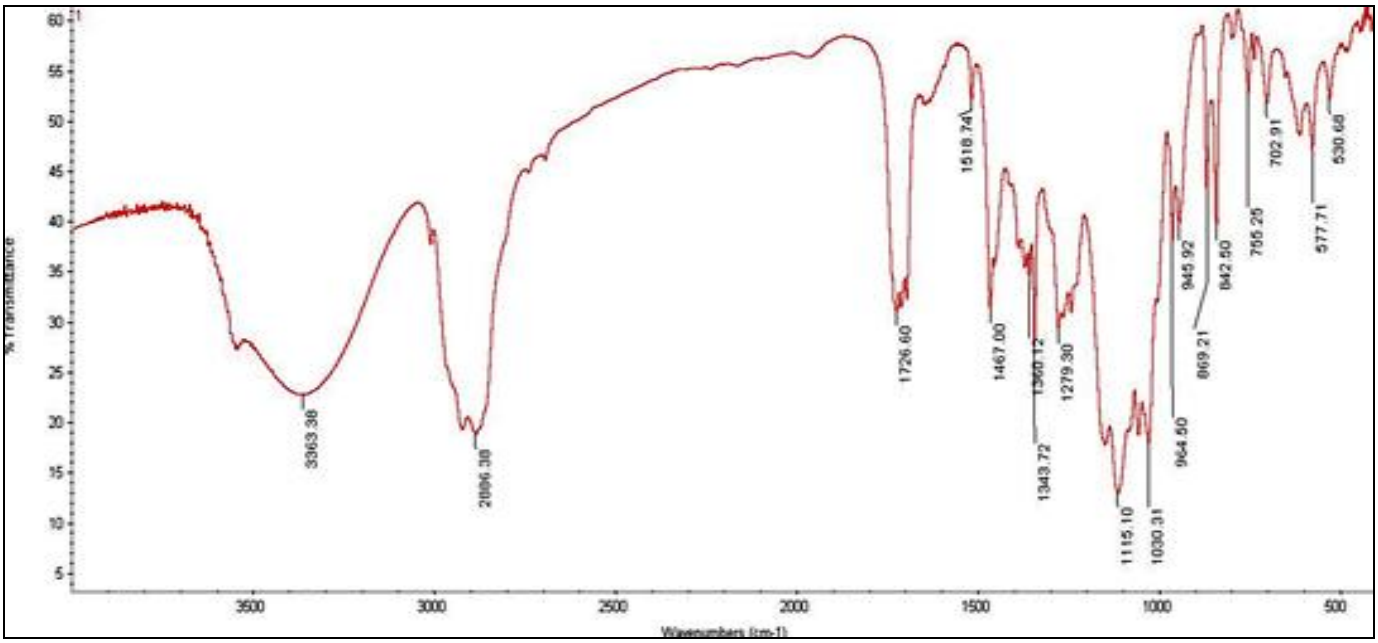

FIGURE: 2 FTIR SPECTRA OF PHYSICAL MIXTURE OF SIMVASTATIN WITH POLYMERS

Graph 1 and 2 show FTIR spectrum of simvastatin and simvastatin with polymers. Spectra of simvastatin show peak at 1697.53 cm^{-1} (C=O), 1073.9 cm^{-1} (C-O), 3562 cm^{-1} (OH bonded). All above peak appear in drug with polymers mixture. It indicates that there was no interaction between drug and polymers.

Differential Scanning Colorimetry:

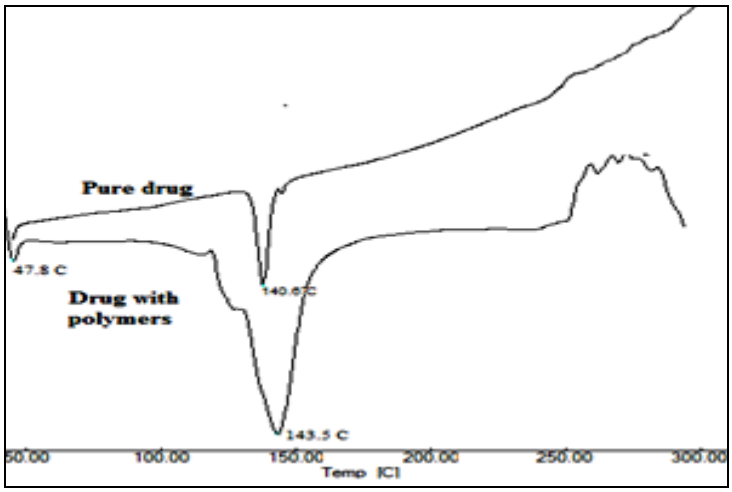

FIGURE 3: DSC GRAPH OF DRUG AND DRUG WITH POLYMERS

Above **figure 3** show DSC study of simvastatin and simvastatin with polymers. In this, simvastatin exhibit peak at 140°C. Mixture of drug and polymers show peak at 143.5°C. This entire peak indicates that there was no interaction between drug and polymers.

Calibration curve of simvastatin: Standard curve of simvastatin was taken in 0.1 N HCL in the range of 5 to 25 µg/ml and in methanol in the range of 1 to 6 µg/ml.

It has shown good linearity with regression co-efficient of 0.9983 in 0.1N HCL and 0.999 in methanol. Other resulted data are tabulated as below.

TABLE 1: OBSERVATION OF SIMVASTATIN 1.0N HCl AND METHANOL

OBSERVATION	0.1N HCL	In methanol
R square	0.9983	0.999
Slope of regression line	0.0048	0.0675
Intercept of regression line	0.001	0.0033
Equation	y = 0.001x + 0.0048	y = 0.0675x - 0.0033

Solubility of pure drug:

Solubility of pure simvastatin in water: 0.010 mg/ml

Evaluation of Methods: Three techniques were selected for solubility measurement that are solid dispersion, inclusion complexation, microwave induced fusion method.

Solid dispersion: Solid dispersion was prepared by fusion method using two polymers that are poloxamer 407 and gelucire 44/14. Observations of the solubility measurement are tabulated as below.

TABLE: 2 OBSERVATION OF SIMVASTATIN WITH DIFFERENT RATION OF POLOXAMER 407 AND GELUCIRE 44/14

Ratio of drug: polymer	Simvastatin: poloxamer 407	Simvastatin: gelucire 44/14
1:1	0.011	0.0129
1:2	0.012	0.0138
1:3	0.013	0.0144
1:4	0.0138	0.0158
1:5	0.014	0.0165

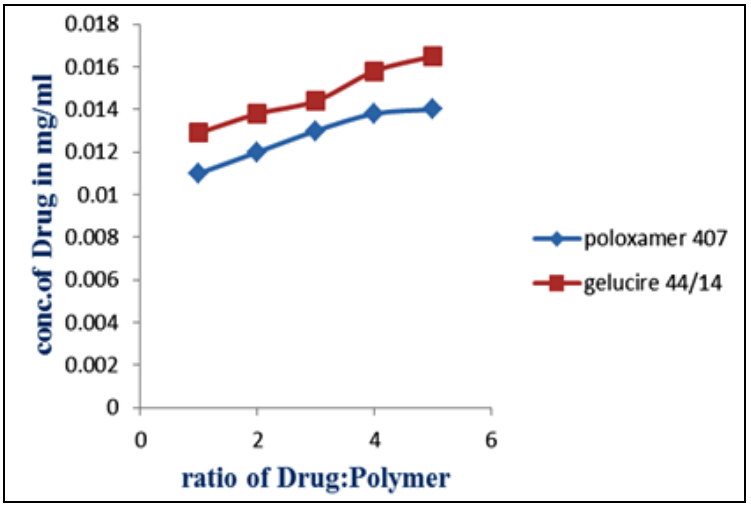

FIGURE 4: SOLUBILITY OF SIMVASTATIN WITH POLYMER

Observed data show that by using gelucire 44/14 solubility of simvastatin increase higher as compare to poloxamer 407.

Inclusion complexation: β-cyclodextrin used for this method. Kneading method used to prepare the complex of drug and polymer. Observation of solubility measurement as tabulated below.

TABLE 3: OBSERVATION OF SIMVASTATIN WITH β-CYCLODEXTRIN

Simvastatin:β-cyclodextrin	Conc. of drug, mg/ml
1:1	0.0114
1:2	0.0119
1:3	0.0122
1:4	0.0127
1:5	0.0132

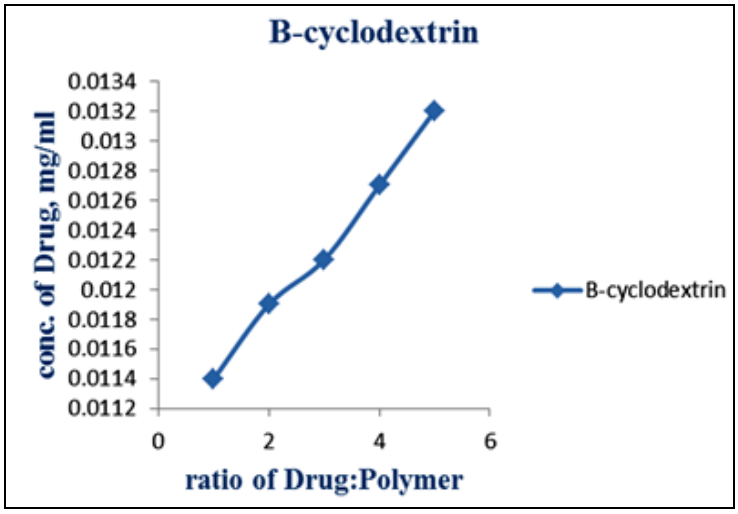

FIGURE: 5 SOLUBILITY OF SIMVASTATIN WITH β-CYCLODEXTRIN

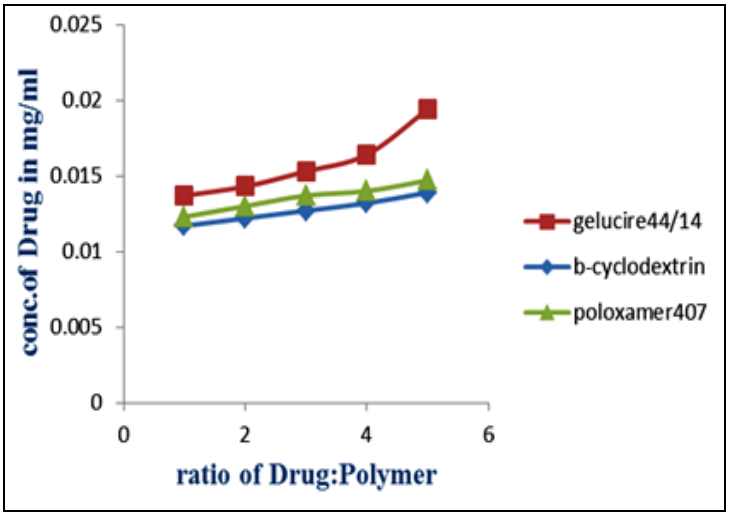

FIGURE 6: SOLUBILITY OF SIMVATATIN WITH THREE POLYMERS

Microwave induced fusion method: Poloxamer 407, gelucire 44/14, β-cyclodextrin are used for this method. Among these polymers gelucire 44/14 provide maximum solubility of simvastatin. Observed data are tabulated below.

From the observation, is it concluded that solubility of simvastatin increased higher with gelucire 44/14 as compare to other polymers. Mixture of simvastatin and gelucire 44/14 in the ratio 1:5 was used for different time interval. it shown different solubility of drug at different time interval. Observed data are tabulated below.

TABLE 4: OBSERVATION OF DRUG RELEASED WITH THREE POLYMERS

Ratio of drug: polymer	Conc. of drug with β-cyclodextrin	Conc. of drug with gelucire 44/14	Conc. of drug with poloxamer 407
1:1	0.0117	0.0137	0.0123
1:2	0.0122	0.0143	0.013
1:3	0.0127	0.0153	0.0137
1:4	0.0132	0.0164	0.014
1:5	0.0139	0.0194	0.0147

Microwave induced fusion method: Poloxamer 407, gelucire 44/14, β-cyclodextrin are used for this method. Among these polymers gelucire 44/14 provide maximum solubility of simvastatin. Observed data are tabulated below.

TABLE 5: OBSERVATION OF SIMVASTATIN WITH GELUCIRE 44/14 AT DIFFERENT TIME INTERVAL

Simvastatin : Gelucire	Time interval	Conc. of drug, mg
1:5	2	0.0176
1:5	4	0.0177
1:5	6	0.0180
1:5	8	0.0191
1:5	10	0.0194

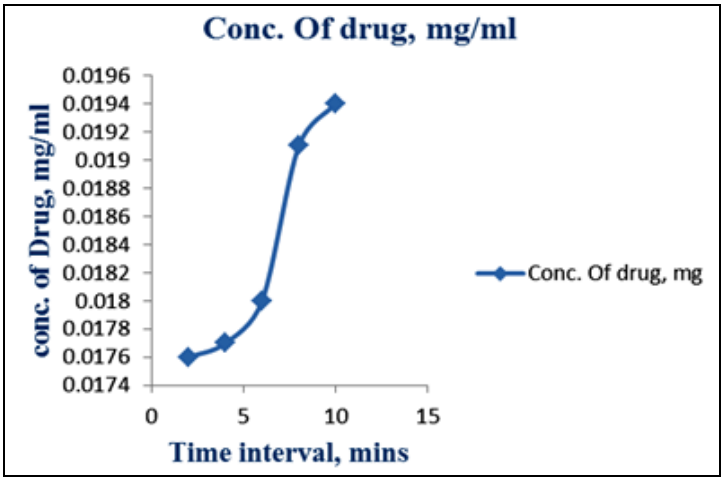

FIGURE 7: SOLUBILITY OF SIMVASTATIN WITH GELUCIRE 44/14

CONCLUSION: From the observed data it was concluded that simvastatin increased higher solubility with gelucire 44/14 by microwave induced fusion method. Solubility of simvastatin increased 94% with gelucire 44/14 by microwave induced fusion method.

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