

EFFECT OF NON IONIC SURFACTANT ON THE SOLUBILITY AND DISSOLUTION OF SIMVASTATIN

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ABSTRACT

Various investigators have been facing the problems in improving solubility, dissolution and bioavailability of poorly water soluble drugs. Solid dispersion is a unique approach to improve the solubility of poorly water soluble drugs. In the present study an attempt has been made to improve the solubility and dissolution of poorly soluble drug Simvastatin (SIM) using Poloxamer 188 (PXM) as carrier. The kneading technique was used to prepare solid dispersions in different ratios. In conclusion, solubility and dissolution enhancement of SIM was improved by preparing its solid dispersion with PXM.

KEYWORDS: Simvastatin, Poloxamer188, Solid dispersion, Kneading.

INTRODUCTION

For a drug to enter the systemic circulation to exert a therapeutic effect, it must possess some aqueous solubility¹. The improvement of solubility or dissolution has been a challenging task for the investigators for the years²⁻⁴. Recent technologies innovation of combinatorial chemistry and high throughput screening can effectively discover the seeds of new drugs, which present good pharmacological activities. However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility^{1,5}. Many methods have been reported for solubility and dissolution enhancement of poorly soluble drugs such as micronization, complexation, solid dispersions etc. Solid dispersion of many poorly water soluble drugs by incorporating them into a water soluble polymer matrix has been considered as an effective method for improving drug dissolution rate and their saturation solubility in the gastrointestinal fluids⁶.

Poloxamers are polyoxyethylene-polypropylene block copolymer nonionic surfactants that have been widely used as wetting and solubilizing agents and surface adsorption excipients⁷. Poloxamer 188 (PXM) is empirically selected to prepare solid dispersions because of its low melting point (about 56–57°C), surfactant properties, and oral safety.

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. It catalyzes the conversion of HMG-CoA to mevalonate; this conversion is an early and rate-limiting step in the biosynthesis of cholesterol. The drug is poorly absorbed from the gastrointestinal (GI) tract; therefore, it is important to enhance the aqueous solubility, dissolution rate, and bioavailability from its oral solid dosage forms⁸.

In current study, an attempt was made to increase solubility and dissolution of Simvastatin by solid dispersion technique using hydrophilic carrier such as poloxamer 188.

MATERIALS AND METHODS

Simvastatin and poloxamer 188 were generously gifted from Ind-Swift laboratories Ltd., Punjab and Signet chemical corporation Ltd., Mumbai respectively. All other chemicals were of analytical grade and were used as such.

Preparation of solid dispersions

Physical mixtures were prepared by mixing accurate weight of SIM with PXM in drug: polymer ratio of 1:2, 1:5, and 1:8 using glass mortar and pestle. The physical mixtures were kneaded for 30 minutes using a small volume of ethanol-water (1:1) solution to give a thick

paste, the wet mass was dried at 45⁰ C, pulverized, passed through 30 mesh sieve size, stored in a desiccator and then passed through 60 mesh sieve size.

Percent practical yield

Percent practical yield was determined by following formula

Practical yield (%) = practical mass (solid dispersion)/theoretical mass (drug+carrier)*100

Drug content

Solid dispersions equivalent to 10 mg of SIM were weighed accurately and dissolved in suitable quantity of methanol. The drug content was determined at 240 nm by UV spectrophotometer.

Phase solubility studies

Solubility measurements were performed in triplicate using the method reported by Higuchi and Connors⁹. An excess amount of SIM was added to 10 ml of phosphate buffer (pH 6.8) in test tubes containing increasing concentration of PXM (i.e., 0.1 %, 0.25 %, 0.5%, 0.75%, and 1% w/v) and sealed with stoppers. The test tubes were vortex-mixed for five minutes and then sonicated for 30 minutes. They were kept on constant temperature shaking bath maintained at 37±0.5⁰ C until reaching equilibrium (48h). Subsequently, the suspensions were filtered through 0.45µm membrane filter, and the filtered solutions were properly diluted. Drug concentration was determined spectrophotometrically at 240 nm.

Determination of solubility

SIM and solid dispersions equivalent to 10 mg of SIM were added to 20 ml phosphate buffer (pH 6.8) in screw-capped test tubes, vortexed for 2 minutes and shaken at 37±0.5⁰ C temperature for 24 h. Resultant samples containing undissolved solid dispersions suspended in a test medium were centrifuged at 10,000 rpm for 5 min and the clear supernatants obtained were filtered, suitably diluted and analyzed spectrophotometrically at 240 nm.

Dissolution studies

Solid dispersions equivalent to 10 mg of SIM were placed in the dissolution vessels containing 900 ml of phosphate buffer (pH 6.8) maintained at 37±0.5⁰ C temperature and stirred at 100 rpm. Samples were collected periodically and replaced with fresh dissolution medium. Concentration of SIM was determined spectrophotometrically at 240 nm. Dissolution efficiency (DE) was calculated from the area under dissolution curves at given time and expressed as a percent of the area of the rectangle described by 100 % dissolution in the same time¹⁰.

RESULTS AND DISCUSSION

Drug content

The drug content of the prepared solid dispersions was found to be in the range of 95.6-100.30 % indicating the application of present method for the preparation of solid dispersions with high content uniformity.

Percent yield

The % yield was calculated to know about % yield or efficiency of any method, which helps in selection of appropriate method of production. Initially there was observed increase in % yield as drug: carrier ratio was increased from 1:2 to 1:5 but thereafter there was observed decrease in % yield, which is attributed to difficulty of sieving when higher polymer ratio was used (fig.1).

Phase solubility studies

The solubility of SIM increased with increase in polymer concentration (fig.2) which showed that a linear increase in drug solubility with increased carrier level giving A_L type solubility diagram. Similar results have been reported with many drugs using hydrophilic carriers due to formation of soluble complexes and/or co-solvent effect of carrier¹¹.

Solubility studies

Solubility of SIM in phosphate buffer (pH6.8) was found to be 18.5±1.02 µg/ml while improvement in solubility was observed with all solid dispersions. Increase in weight fraction of surface active carrier results in increase in solubility of all solid dispersions. Maximum solubility enhancement was found in 1:8 drug polymer ratio. Solubility enhancement can be explained by its wetting and solubilizing nature.

In vitro dissolution studies

The enhanced dissolution rate with poloxamer 188 may be attributed to its surfactant activity which facilitates wetting and subsequent solubilization of drug. Poloxamer 188 has HLB value of 29 and has great tendency to solubilize the drugs.

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Table 1: Solubility of Simvastatin in phosphate buffer solution (pH6.8)

S. No	Drug: carrier ratio	Solubility(µg/ml)
1	Simvastatin	18.5±1.02
2	1:2	24.2±1.50
3	1:5	33.6±0.78
4	1:8	42.4±0.83

All results were calculated as mean± SD, n=3

Table2: Dissolution efficiency of the prepared solid dispersions

S. No	Drug: carrier ratio	% DE ₆₀
1	Simvastatin	21.25±0.92
2	1:2	32.44±0.41
3	1:5	40.75±0.74
4	1:8	42.64±0.65

All results were calculated as mean± SD, n=3

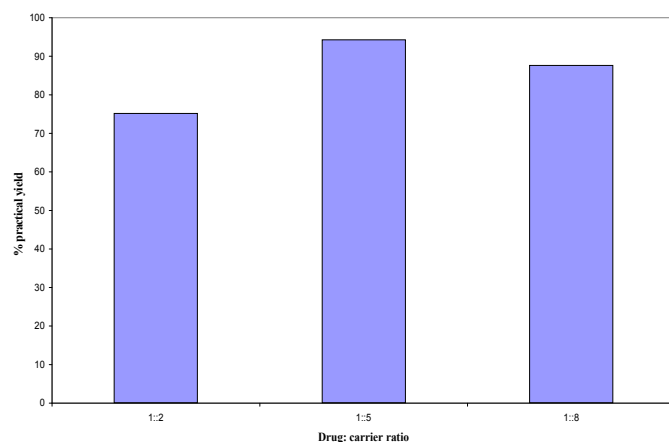


Figure1: Percent practical yield of different solid dispersions of Simvastatin

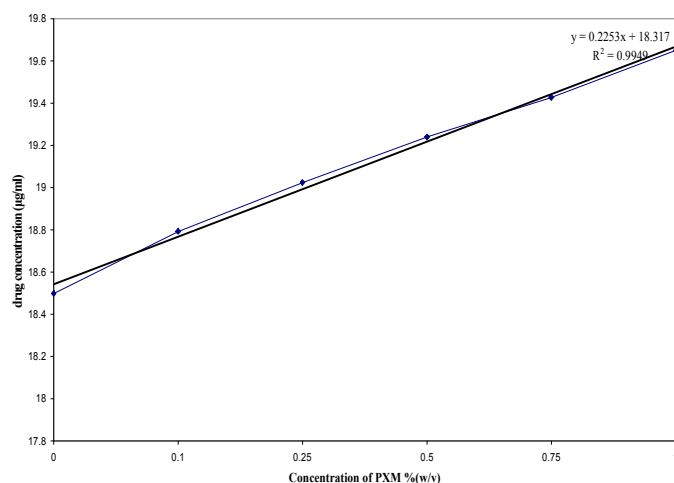


Figure 2: Effects of increasing concentration of poloxamer 188 on the solubility of Simvastatin

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