Solid Dispersion by Fluidized Bed Processing: A Platform for Enhancement of Dissolution Rate of Simvastatin Poorly Water-Soluble Drug

ABSTRACT

Aim: The main objective of this work was to study the solubility and dissolution kinetics of poorly water-soluble drugs simvastatin from its solid dispersion with different carriers by using fluidized bed processing technique.

Methods: Simvastatin is BCS class- II i.e. low soluble and high permeable, which reduces its bioavailability, to overcome this problem, a solid dispersion is formed using various techniques with polymeric carrier to potentially enhance the solubility and dissolution rate such as fluidized bed processing, it will extend drug absorption, therefore the objectives were to make a comparative evaluation among different solid dispersions and to assess the effect of various carriers in solid dispersions on the drug release profile and solubility behaviours.

Results: For solid dispersion, Gelucire® 44/14, PVP-K30 and Poloxamer utilized as carrier for poorly water-soluble drugs in order to improve their bioavailability. The dissolution profiles were correlated using various mathematical models such as Zero order, first order, Higuchi and Hixon Crowell model and the Zero order kinetics model gave better correlation results than the other models.

Conclusion: Dissolution profile of SIM was significantly improved via complexation with Gelucire 44/14 as compared with the pure drug and other carriers. The binary system which was prepared using FBP showed the highest dissolution rate and solubility profile.

Keywords: Simvastatin, Solubility enhancement, Dissolution rate, Hixon Crowell, Higuchi Model.

INTRODUCTION

After administration of drug, it is usually dissolved and absorbed in the gastrointestinal tract then it reaches the target areas. In this process there are two key points one is the solubility and other is permeability in GIT. Simvastatin (SV) a lipid lowering compound and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG COA) reductase. Simvastatin comes under BCS class- II i.e. low soluble and high permeable therefore, poorly absorbed from gastrointestinal tract [1]. Solid dispersions of such drugs in hydrophilic carriers have provided a promising possibility of improving their solubility and dissolution rate. Dissolution of drugs are the most important and crucial phenomenon for all kind of dosage forms. Solid dispersion states to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug [2]. Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

In solvent evaporation method consisting of dissolved drug and the polymeric carrier in a common solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. Solvent evaporation methods show some disadvantages such as;
expensive and difficult to find common and removable solvents also difficulty in completely removing liquid solvent. In the fluidised bed processing, the carrier and the active ingredient are dissolved or suspend in a suitable solvent [3]. This solvent is evaporated by drying it to apply a stream of fluidized heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly [3,4].

In the present study solid dispersion using three carriers in different ratios were prepared by fluidized bed processing technique and solvent evaporation. SD evaluated for its saturation solubility, in vitro dissolution and dissolution kinetics.

MATERIALS AND METHODS
Simvastatin was obtained as a gift sample from Aquatic Remedies, Mumbai, MS, India. Polyvinylpyrrolidone K- 30, Gelucire 44/14, Poloxamer were purchased from Balaji Drugs, Gujrat, India. All other ingredients and reagents used in the research work were of analytical grades.

Drug Content
Solid dispersion equivalent to 20 mg was extracted into methanol and filtered. The drug content was determined by measuring the absorbance at 238nm (using UV/vis spectrophotometer, Lab India 3000+) after appropriate dilution with methanol. The drug concentration was determined using standard calibration curve [5].

Saturation Solubility Determination
Saturation solubility of Simvastatin, PMs and solid dispersions were determined in distilled water. An excess amount of pure drug, PMs and solid dispersion were added in 10 ml of distilled water [5,6]. The mixture was stirred in shaker for 24 hours, after saturation level mixture was filtered and subjected to determination of concentration of Simvastatin spectrophotometrically at 239 nm.

Preparation of Physical Mixture
Physical mixtures (PMs) were prepared by mixing Simvastatin with Gelucire 44/14, Poloxamer and PVP-K30 at different ratios (Table. 2) in V cone blender [5].

Preparation of Solid Dispersion
Solid dispersion (SDs) of Simvastatin were prepared by two methods [5,7]

Fluidized Bed Processing:
PMs containing Simvastatin and carrier (Gelucire, Poloxamer & PVP-K30) was dissolved in methanol (100 ml) to form the solution (Figure-1). After complete dissolution of PMs in methanol, the solution was sprayed on substrate lactose in fluidized bed processor (Table-2). The flow rate was set at 1.75 rpm, the inlet temperature was kept at 70 °C, product temperature was kept at 56 °C, atomization air pressure 2.25 MPa and air flow se at 1.6 Mpa (Table-1).
Table-1 Process Parameter of Fluidized Bed Processor

| Parameter                  | Values |
|----------------------------|--------|
| Spray rate (RPM)           | 1.75   |
| Inlet Temperature          | 70     |
| Product Temperature        | 56     |
| Atomization air Pressure (MPa) | 2.25   |
| Air flow control (MPa)     | 1.6    |

Optimized process parameters of FBP by top spraying drug and carrier solution on substrate lactose

Solvent Evaporation

To prepare SDs, drug and polymer were mixed in the selected ratio; 50 ml or 100 ml methanol was added portion wise with a constant stirring until the mixture completely dissolve \[20\]. The drug/polymer solution was then evaporated at 35 to 40 °C under vacuum (150 mbar) with Vacuum Oven \[8\]. The thin film was obtained in a flask and dried at 40 °C in an oven for 24 h. The resulting SD was ground in mortar and pestle (Table.2)

Table 2: Formulations of Simvastatin PMs and SDs

| Ingredients   | SSD1 | SSD2 | SSD3 | SSD4 | SSD5 | SSD6 | SSD7 | SSD8 | SSD9 |
|---------------|------|------|------|------|------|------|------|------|------|
| Simvastatin   | 200  | 200  | 200  | 200  | 200  | 200  | 200  | 200  | 200  |
| Gelucire 44/14| 200  | 400  | 600  | -    | -    | -    | -    | -    | -    |
| PVP- K30      | -    | -    | -    | 200  | 400  | 600  | -    | -    | -    |
| Poloxamer     | -    | -    | -    | -    | -    | -    | 200  | 400  | 600  |

All quantity in mg

In-Vitro Dissolution Study

The in vitro dissolution studies for pure simvastatin, PMs, SD, tablet formulations and marketed tablet were carried out using USP type-2 dissolution tester, paddle type (Electrolab, TDT 08L). samples equivalent to 20 mg simvastatin were added to 900 ml of phosphate buffer pH 7.0 and stirred at 50 rpm up to 60 min. 5 ml sample were withdrawn at 15 min, 30 min, 45min and 60 min time interval. A same volume of fresh dissolution fluid was replaced to maintain volume. The filtered samples were analysed using UV visible spectrophotometer (Lab India 3000+) at 239 nm. Each dissolution experiment was performed thrice and the mean values of simvastatin release amount with their standard deviations were calculated \[4,5\].

Tablet Dosage Form Development
Three type of tablet were prepared using 20 mg simvastatin\(^{21}\), the FBP- Solid dispersion that showed maximum drug dissolution and saturation solubility SSD3 and SD prepared by solvent evaporation method was further formulated in tablet containing SD equivalent to 20 mg, containing lactose as diluent, magnesium stearate as a lubricant and aerosol as glidant (Table 3) Using a rotary tablet press (Cemech, India), consistent pressure was applied to produce F-1 (simvastatin), F-2 (FBP-SD-3), and F-3 (SE-SD-3) tablets\(^{[7,8]}\).

| Table 3: Formulation of solid dispersion-based tablet |
|--------------------------------------------------|
| Ingredients | Formulations |
|------------|--------------|
| Simvastatin | F1 90 F2 80 F3 80 |
| Lactose    | 130 40 70 |
| MCC (Avicel) | 55 75 55 |
| Mag. Stearate | 5 5 5 |
| Croskarmellose sodium | 10 10 10 |
| Total weight | 220 220 220 |

All quantity in mg

**Dissolution Kinetics**

The in vitro drug release data obtained from the PMs, SD and marketed formulations were fitted to various dissolution kinetics models included zero order, first order, Higuchi and Hixon Crowell, in order to study the release mechanism\(^{[13]}\).

**Zero Order Kinetic Model**

To study the release kinetics, data obtained from in vitro drug release studies were plotted as the cumulative amount of drug released versus time. This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc. Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation\(^{[4,5]}\).

\[
Q_t = Q_0 + K_0 t
\]

Where, \(Q_t\) is the amount of the drug dissolved in time \(t\), \(Q_0\) is the initial amount of drug in the solution and \(K_0\) is the zero-order release constant expressed in units of concentration/time.

**First Order Kinetics Model**

This model has been used to describe absorption and/or elimination of a variety of therapeutic agents. First-order release kinetics states that change in concentration with respect to change on time is dependent only on concentration. The data obtained are plotted as log cumulative percentage of drug remaining vs. time, which would yield a straight line with a slope of \(-K/2.303\).

\[
\log Q_1 = \log Q_0 + \frac{k_1 t}{2.303}
\]

where \(Q_1\) is the amount of active agent released on time \(t\), \(Q_0\) is the initial amount of drug dissolved, and \(K_1\) is the first-order constant\(^{[4,6]}\).

**Hixon Crowell**:

Hixson and Crowell (1931) discovered that a group of particles’ regular area is proportional to the cube root of its volume. Using this relationship, they proposed an equation:
\[ \sqrt[3]{W_0} = \sqrt[3]{W_t} + K_{HC} t \]

where \( W_0 \) is the initial amount of the drug in the system; \( W_t \) is the amount remaining in the system on time \( t \); and \( K_{HC} \) is the constant of incorporation, which relates surface and volume.

The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets. To study the release kinetics, data obtained from in vitro drug release studies were plotted as the cube root of drug percentage remaining in matrix versus time \(^{[4,7]}\).

**Higuchi Model**

The first example of a mathematical model aimed to describe the drug release from a matrix system was proposed by Higuchi in 1961. The data obtained were plotted as cumulative percentage drug release versus square root of time \(^{[4,5,7]}\). It describes the drug release as a diffusion process based on the Fick’s law which is square root of time dependent.

The equation for Higuchi for release of drug is as follows:

\[ Q = K_H t^{1/2} \]

Where, \( Q \) is cumulative amount of drug release at time \( t \), \( K_H \) is the Higuchi constant and ‘t’ is time.

**RESULT AND DISCUSSION**

**Saturation Solubility Study**

Saturation solubility studies of pure simvastatin and its physical mixture and solid dispersion with Gelucire, poloxamer, and PVP- K30 were performed in distilled water by FBP and solvent evaporation technique. Maximum enhancement of solubility of simvastatin in water was obtained 260.55 \( \mu \)g/ml for solid dispersion with Gelucire 44/14 at 1:3 ratio by fluidized bed processing as shown in fig. 2. Therefore, this batch was selected for further formulation studies \(^{[22]}\).

![Graphs showing saturation solubility](image)

Fig.2: Bar graph showing saturation solubility (a) Saturation solubility of SIM and its physical mixture in water (b) Saturation solubility of SIM and its SD-FBP in water (c) Saturation solubility of SIM and its SD-SE in water
Drug Content
The solid dispersion obtained comparatively maximum solubility in water; these batches were selected for the determination of drug content. The percent drug content of simvastatin in solid dispersion with Gelucire by FBP and SE technique at 1:3 ratio was found to be 98.87 % and 97.87 % respectively.

Standard calibration curve of Simvastatin:
According to the concentration and absorbance of standard solution, a calibration curve was generated (Fig. 3) and regression coefficient and line equation calculated as follows;

\[ Y = 0.0011x + 0.0255 \quad (R^2 = 0.992) \]

Fig. 3. (a) Chemical structure of simvastatin (b) UV spectrum of pure SIM (c) calibration curve of SIM

In Vitro Dissolution Study
In vitro drug release studies have been executed using USP type II dissolution apparatus at rotation speed of 50 rpm. The cumulative drug release in phosphate buffer pH 7.0 of simvastatin pure drug, in physical mixture and in solid dispersion by FBP. PM1 to PM9 and SSD1 to SSD9 batches were shown in fig.4 and fig. 5. Drug release of pure drug after 60 minutes was found to be 39.88 %, whereas simvastatin- PM, PM1 to PM9 were found to be 50.36%, 61.85%, 67.89%, 41.36%, 52.69%, 63.45%, 55.36%, 62.45%, 64.34 % respectively and simvastatin SD, SSD1 to SSD9 was found to be 68.36%, 88.78%, 98.36%, 60.56%, 80.45%, 89.36%, 66.78%, 85.36%, 93.78 % respectively. The results show that the dissolution rate of simvastatin-SD with Gelucire 44/14 at 1:3 ratio is highest as compared to physical mixture, pure drug and carrier PVP-K30, poloxamer and it is may be due to wettability of Gelucire carrier as shown in fig. 6. Based on dissolution parameters batch of SIM-SD by FBP, SIM-SD by SE, SIM-PM with gelucire44/14 at 1:3 ratio was selected for further tablet formulation and dissolution study were executed. Tablet formulation of PM, SD-FBP and SD-SE containing 20 mg simvastatin after 60 minutes were found to be 67.89%, 98.36%, 80.48% respectively as shown in fig.6. However, we focused primarily on the effect of different structural polymers and methods of solid dispersion preparation on the solubility enhancement, dissolution mechanism and release kinetics of simvastatin from solid dispersions. These properties strongly depend upon the nature of all components, but the solubility and
dissolution rate of the drug is mainly affected by the polymer carrier\textsuperscript{[16,17,18]}. Therefore, the drug to polymer carrier ratio was fixed at 1:3.

![Fig.4 Dissolution profiles of solid dispersions of simvastatin prepared by FBP with Gelucire 44/14, PVP K-30 and Poloxamer](image_url)

![Fig.5 Dissolution profiles of physical mixture of simvastatin with Gelucire 44/14, PVP K-30 and Poloxamer](image_url)
Fig. 6 Comparative dissolution profiles of pure simvastatin, its physical mixture with gelucire 44/14 at 1:3 ratio, solid dispersion prepared by FBP with Gelucire 44/14 at 1:3 and solid dispersion prepared by SE with Gelucire 44/14 at 1:3.

Dissolution Kinetics for Simvastatin Tablet Using Different Equations

The Beer’s law standard curves for simvastatin, in the corresponding medium at the maximum absorbance, were determined using three replicates over ten concentrations within the solubility range of drug to achieve sink conditions and had shown no deviation from linearity with regression coefficient of >0.992 as shown in fig.3. The dissolution profiles of all formulations were measured and plotted in accordance with the zero-order equation (Fig. 7), the first-order equation (Fig. 8), the Higuchi square root equation (Fig. 9), and the Hixson-Crowell (Fig. 10). The release profile from SDs varied depending on the methods of preparation but there is notable improvement in release rate and the quantity of released simvastatin for all SDs over pure SIM. The release rates of SIM were found to be significantly different from each specific method and polymer. Figure 6 reveals that there was noticeable influence of polymers and preparation methods on SIM dissolution rate. It is also clear that the pure SIM had the lowest dissolution rate. As can be seen in Figure 6, the presence of Gelucire 44/14 at 1:3 ratio caused faster medium penetration, faster release and faster polymer erosion in comparison to pure SIM. The fastest SIM release, as well as its largest amount released, was observed in SD prepared by FBP this is due to incorporation or encapsulation of drug into the matrices during fluidized bed processing can affect the drug release rate. Therefore, it is clear that polymer dissolution influences the SIM release profile significantly [18,19].

The result using the zero-order equation for simvastatin tablet showed that percent of drug released from F1, F2 and F3 formulation within 60 minutes were 36.78, 98.48 and 79.49 respectively. The result indicated that there is difference in the dissolution profile for the tablet prepared by SD and pure drug. An increase in dissolution by the addition of polymer carrier Gelucire was observed. As there was an increase in dissolution related to the SD prepared by solvent evaporation method. While the dissolution from the SD tablet can be described by the zero-order equation in which the $r^2$ value was 0.9686, 0.9887 and 0.9994 respectively (Table 4). Result demonstrated using zero order kinetics from different, dissolution behaviour for the pure drug, SD- FBP and SD- SE. the result showed from the first order kinetics with
\( r^2 \) value, 0.951, 0.8607 and 0.951 respectively \([8,10,19]\). Therefore, dissolution data cannot be described by first order equation. The dissolution results were plotted in accordance with the Higuchi square root equation i.e. percent drug dissolved as a fraction of the square root of time (Fig.9) A linear relationship was obtained after an initial lag time in all formulations. The linearity of the plots indicated that the drug release process is diffusion controlled. The dissolution data were also plotted in accordance with the Hixon Crowell cube root (Fig.10) results for all formulation (F1, F2 and F3) indicated that a linear relationship was obtained.

Fig 7: A plot of percent drug dissolved versus time for the dissolution of simvastatin in accordance with the zero-order equation F1 tablet formulation containing pure simvastatin, F2 formulation containing SD by FBP and F3 formulation containing SD by SE

Fig 8. A linear plot of log (% remaining) versus time for the dissolution of simvastatin in accordance with the first-order equation F1 tablet formulation
containing pure simvastatin, F2 formulation containing SD by FBP and F3 formulation containing SD by SE

![Graph](image1)

**Fig. 9** A linear plot of percent dissolved versus square root of time for the dissolution of simvastatin in accordance with the Higuchi square root equation. F1 tablet formulation containing pure simvastatin, F2 formulation containing SD by FBP and F3 formulation containing SD by SE

![Graph](image2)

**Fig. 10** A linear plot of the cube root of the initial concentration minus the cube root of the percentage remaining versus time for the dissolution of simvastatin in accordance with the Hixson-Crowell cube root equation. F1 tablet formulation containing pure simvastatin, F2 formulation containing SD by FBP and F3 formulation containing SD by SE

**Table 4:** Dissolution rate constant and $r^2$ obtained from the application of different kinetic equations for all formulations of Simvastatin and solid dispersion
| Formulation | Zero order rate constant | First order rate constant | Higuchi square root rate constant | Hixon Crowell rate constant |
|-------------|-------------------------|---------------------------|----------------------------------|---------------------------|
| F1          | 0.5641                  | -0.0032                   | 6.4044                           | -0.0105                   |
|             | $r^2 = 0.9686$          | $r^2 = 0.951$             | $r^2 = 0.9254$                   | $r^2 = 0.9563$            |
| F2          | 1.4208                  | -0.0347                   | 16.594                           | -0.0626                   |
|             | $r^2 = 0.9887$          | $r^2 = 0.8607$            | $r^2 = 0.9995$                   | $r^2 = 0.9507$            |
| F3          | 1.1064                  | 0.0118                    | 12.818                           | -0.0308                   |
|             | $r^2 = 0.9994$          | $r^2 = 0.951$             | $r^2 = 0.9941$                   | $r^2 = 0.9898$            |

**LIST OF ABBREVIATIONS:**

- FBP: Fluidized Bed Processing
- PVP K-30: Polyvinyl Pyrrolidone K-30
- SD: Solid Dispersion
- SE: Solvent Evaporation
- PM: Physical Mixture
- MCC: Microcrystalline Cellulose
- SIM: Simvastatin
- $R^2$: Regression coefficient

**CONCLUSION**

In this study Simvastatin solid dispersion were successfully obtained using the solvent evaporation method and fluidized bed processing. Gelucire 44/14, PVP K-30, Poloxamer were used as a polymeric carrier. Therefore, the use of different techniques for solid dispersion having different properties can provide greater influence on the mechanism of the dissolution. In the case of SDs containing simvastatin prepared by fluidized bed processing, simvastatin was probably encapsulated by Gelucire, poloxamer spray drying. Zero order dissolution kinetic model was suitably used to describe the SIM release at the beginning of the dissolution experiment as well as to assess whether the release corresponds to the Higuchi model.

There was noticeable influence of polymers on SIM solubility. All solid dispersions improved the SIM intrinsic dissolution rate, however, the greatest increase in the SIM dissolution rate was obtained from SD containing Gelucire at 1:3 ratio prepared by FBP. It can also be concluded that all SDs of SIM showed considerable enhancement in dissolution rate and solubility compared to both PMs and the dissolution rate of both PMs was higher compared to the pure simvastatin.

**ACKNOWLEDGMENTS**

The authors are delighted to say thanks to the principal and management of Maulana Azad Educational Trust's Y. B. Chavan College of Pharmacy, Aurangabad, MS, India. For support and providing necessary facilities to carry out the research work successfully. Authors are also thankful to Loknete Dr. J. D. Pawar College of Pharmacy, Kalwan, Nashik for providing laboratory and necessary technical support.

**CONFLICTS OF INTEREST:** The authors declare no conflict of interest

**COMPETING INTERESTS DISCLAIMER:**
Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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