International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 13, Issue 7, 2021

Original Article

FORMULATION OF SOLID DISPERSIONS FOR ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF SIMVASTATIN

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Received: 23 Feb 2021, Revised and Accepted: 29 May 2021

ABSTRACT

Objective: The objective of the present work was to formulate the solid dispersions of simvastatin for enhancement of its aqueous solubility and dissolution rate.

Methods: In the present study, solid dispersions of simvastatin were prepared by Kneading and Solvent evaporation methods. The polymeric carriers like Polyethylene glycol (PEG) 6000 and Polyvinyl Pyrrolidone (PVP) K30 were used in different ratios (ratio of drug: carrier was 1:1, 1:2) to formulate solid dispersions. The prepared solid dispersions were characterized by differential scanning calorimetry (DSC), Fourier transforms infrared spectroscopy (FTIR), and evaluated for drug content, percentage yield, saturation solubility, *in vitro* dissolution studies. The best formula of the solid dispersion was selected according to the solubility and dissolution data.

Results: The F7 formulation was found to be an optimized formulation containing PVP K30 in the ratio 1:1 prepared by solvent evaporation technique. The Drug content was found to be higher i.e. 94.89 in the F7 batch. The FT-IR spectra revealed that there was no interaction between drugs and carriers. DSC thermogram indicated entrapment of simvastatin in PVP K30 and the conversion of crystalline simvastatin into an amorphous form. The F7 formulation showed maximum drug release i.e. 98.60% in 60 min which is 2 times greater than pure drug making it an optimized formulation.

Conclusion: The solubility of simvastatin was successfully enhanced through the solid dispersion technique. Solid dispersions prepared with solvent evaporation method were more soluble than solid dispersions prepared with kneading method with carrier PVP K30.

Keywords: Simvastatin, Polymeric carriers, Solid dispersion, Polyvinyl Pyrrolidone K30, Solvent evaporation method, Solubility enhancement

DOI: https://dx.doi.org/10.22159/ijpps.2021v13i7.41205. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

Near about 35-40% of new chemical entities possess the problem of low aqueous solubility that affects drug absorption in the gastrointestinal tract (GIT) which leads to lower bioavailability, high inter and intrasubject variability, dose dumping chances, reduction in the effectiveness of the medication, and lastly, formulation development get collapsed [1]. In such cases, scientists look for better formulations that will improve solubility and thus dissolution and bioavailability get improved. Various strategies involved are micronization, salt formation, solubilization, self-micro emulsifying drug delivery system, complexation, prodrug approaches, dendrimers formation, spray drying, solid solution/solid dispersion with hydrophilic carriers, nano-particular systems [2].

According to the Biopharmaceutical Classification System (BCS), oral medications are classified into four classes based on their solubility and permeability characteristics. Out of the four classes, class II and class IV possess the problem of low aqueous solubility, so there is a need to improve solubility by using different solubility enhancement techniques to improve *in vitro* dissolution and bioavailability of medications [3]. Solid dispersion is gaining more focus in few decades. Solid dispersion is defined as a group of solid products consisting of at least two components, hydrophobic drug, and hydrophilic carrier. The term dispersion means a hydrophobic drug is dispersed in an inert hydrophilic matrix [4].

Simvastatin is a Cholesterol-lowering, hydrophobic drug having a log P value of 4. It is a BCS Class II drug with low aqueous solubility (30 µg/ml). It is a white crystalline powder. It acts as a specific potent inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase which reduces HMG CoA to mevalonate thus blocking vital steps for cholesterol biosynthesis in the liver, so it is extensively employed in the treatment of hypercholesterolemia and dyslipidemia. The structure of simvastatin is shown in fig. 1 [5, 6].

In the present research, trials were taken to improve the solubility and thus dissolution rate of simvastatin by formulating its solid dispersions. Different concentrations of carriers were used for preparing solid dispersions and prepared free-flowing dispersions then evaluated for Solubility, FT-IR, and DSC analysis.

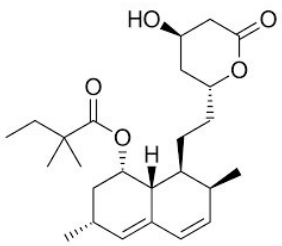

Fig. 1: Structure of simvastatin

MATERIALS AND METHODS

Materials

Simvastatin gift sample was obtained from Cipla Pvt. Ltd. (Mumbai). Polyvinyl pyrrolidone K30 has been purchased from Loba Chemie Pvt. Ltd. Mumbai. Polyethylene glycol 6000, Ethanol was obtained from Research Lab Fine Chemical Industries Pvt. Ltd. (Mumbai). Other chemicals and reagents were of analytical grade.

Methods

Physicochemical characterization of drug

The Drug was identified by various physicochemical properties such as Color, Odour, Melting point, DSC analysis, and FT-IR spectroscopy [7].

Determination of saturation solubility of simvastatin

Solubility of simvastatin was determined by the shake flask method in different solvents like water, ethanol, methanol, chloroform, phosphate buffer pH 6.8, and phosphate buffer pH 7.4. Saturated solutions of simvastatin were prepared in different solvents and were stirred for 24 h using a rotary shaker. The solution was then filtered through Whatmann filter paper. The concentration of simvastatin was determined using a UV spectrophotometer against the respective solvent as blank at λmax of drug [8].

Preparation of calibration curve in ethanol

The stock solution was prepared by taking accurately weighed 100 mg of simvastatin in a 100 ml volumetric flask and dissolving it in ethanol and volume made up to the 100 ml mark. The concentration of the solution was 1000 µg/ml. From the stock solution, 1 ml was pipetted in a 10 ml volumetric flask and the volume was made up to mark with distilled water to obtain the concentration of 100 µg/ml. This was a working standard solution. from this solution, 0.5, 1, 1.5, 2, 2.5 and 3 ml were pipetted in separate 10 ml volumetric flasks and diluted up to mark with distilled water to get final concentrations of 5,10,15,20,25,30 µg/ml. The Samples were measured spectrophotometrically at λmax of a drug against ethanol as a blank. Absorbance values were plotted against concentrations of the drug to obtain a calibration curve [9].

Preparation of solid dispersions (SDs)

Solid dispersions of simvastatin were prepared using kneading and solvent evaporation methods employing PEG 6000 and PVP K30 as carriers. Prepared solid dispersions (SDs) were compared with pure drug and physical mixtures of drug and polymer.

Physical mixture

Simvastatin and carriers (PEG 6000, PVP K30) were mixed in mortar and pestle to obtain physical mixtures.

Kneading method

Drug and carriers (PEG 6000 and PVP K30) were mixed in different ratios i.e. 1:1, 1:2. A small amount of solvent (ethanol) was added into the mixture of drug and carrier until the formation of paste. Then that obtained paste was kneaded for few minutes and dried in an oven at 40 °C. The dried mass was then ground and sieved through sieve No. 80. The formulations were encoded as F1, F2, F3, and F4. F1 and F2 for PEG SDs and later for PVP SDs [10].

Solvent evaporation method

Solid dispersions of simvastatin in PEG 6000 and PVP K30 prepared by solvent evaporation method with ratios 1:1 and 1:2 were denoted by F5, F6, F7, and F8 respectively. The required amount of carrier dissolved in a sufficient quantity of ethanol. To this, the solution of the drug was added with continuous stirring until the formation of a clear solution. The solvent then evaporated leaving behind solidified mass. The mass was dried, grounded, and sifted through sieve No. 80. The prepared dispersions were then characterized [11].

Characterization of solid dispersions

Saturation solubility determination

The Shake flask method was used for the determination of the solubility of prepared solid dispersions. The excessive quantity of prepared SDs was added in a glass stoppered flask containing 25 ml of solvent and flasks were shaken for 24 h at 37±0.5 °C. After 24 h, the solution was filtered, diluted appropriately and absorbance was taken at the λmax of a drug. Analysis of each sample was carried out in triplicate. The Change in solubility value was compared with pure drug solubility.

Determination of percentage yield

The Percentage yield of F1 to F8 formulations was calculated by using the following equation [12]. Determination was carried out in triplicate

$$\% \text{ yield} = \frac{\text{Actual weight of solid dispersion}}{\text{Total weight of drug and carrier}} \times 100$$

Estimation of drug content

The Solid dispersion equivalent to 10 mg of drug was dissolved in 10 ml of ethanol, filtered, diluted, and drug content was determined using UV spectrophotometer at λmax of a drug against ethanol as a blank. Analysis of each sample was carried out in triplicate [13].

Fourier transform infrared spectroscopy

By using FT-IR Spectrophotometer (FT-IR 8400S, Shimadzu), compatibility studies of drugs and carriers were carried out. FTIR spectra of SDs and physical mixture were obtained by the potassium bromide method in which powder is scanned in the range of 4000-400 cm^{-1} with resolution 1 cm^{-1} [14].

DSC analysis

DSC thermographs of the physical mixture, solid dispersion were obtained using the Mettler-Toledo instrument. Samples were sealed in pierced aluminum pans and heated to a scanning rate of 10 °C/min over the temperature range of 40-350 °C. The inert atmosphere in the chamber was maintained by providing nitrogen gas at a flow rate of 40 ml/min [15].

In vitro dissolution studies

The *in vitro* Dissolution data was obtained by using USP Type II (Paddle type) dissolution apparatus with a rotating speed of 100 rpm and the media used was 900 ml phosphate buffer pH 6.8 maintained at 37±0.5 °C. Sample equivalent to 40 mg added in dissolution media. At specific time intervals i.e. after every 10 min, a 5 ml sample was pipetted, and an equal amount of fresh media was added. Pipetted samples were filtered, diluted, and analyzed by UV spectrophotometer at λmax of drug [16]. Analysis of each sample was carried out in triplicate.

RESULTS AND DISCUSSION

The Drug was found to be in solid, off-white powdered form. The melting point was determined by the capillary method and it was found to be in the range of 138-140 °C which is the same as the standard reported melting point [17].

Being a class II drug, simvastatin having low aqueous solubility. Solubility was found to be 0.028 mg/ml in distilled water, 0.125 mg/ml in ethanol, 0.118 mg/ml in methanol, 0.619 mg/ml in chloroform, 2.418 mg/ml in phosphate buffer 6.8 and 0.865 mg/ml in phosphate buffer 7.4.

The calibration curve was done by using a UV–spectrophotometer. Absorbance maxima (λmax) was found to be at 238 nm, so the calibration curve was prepared in ethanol at 238 nm. [18]. The plot had a correlation coefficient (R^2) of 0.996, a slope of 0.022, and a C-intercept of–0.012. These results indicated that there is a linear relationship between concentration (5–25 µg/ml) and absorbance, as shown in fig. 2. As per the literature survey, it is confirmed that simvastatin show linearity in the concentration range of 5 to 30 µg/ml when ethanol is used as a solvent and also as a blank.

The Solubility of solid dispersions was determined and compared with that of pure drug solubility in distilled water. It was found to be an increase in solubility of all the prepared solid dispersions as shown in table 1. The maximum increase in solubility was found in the F7 formulation that was prepared by solvent evaporation technique employing PVP k30 as a carrier in the ratio of 1:1 with the drug. So, here it can be said that PVP k30 is the more effective carrier in preparing SDs than PEG 6000. Literature also supports the enhancement of solubility of solid dispersions is better with the hydrophilic carrier PVP K30 than the PEGs by the solvent method. This improved solubility can be attributed to the solubilization effect of the carrier, which increases the wetting property of the drug [14].

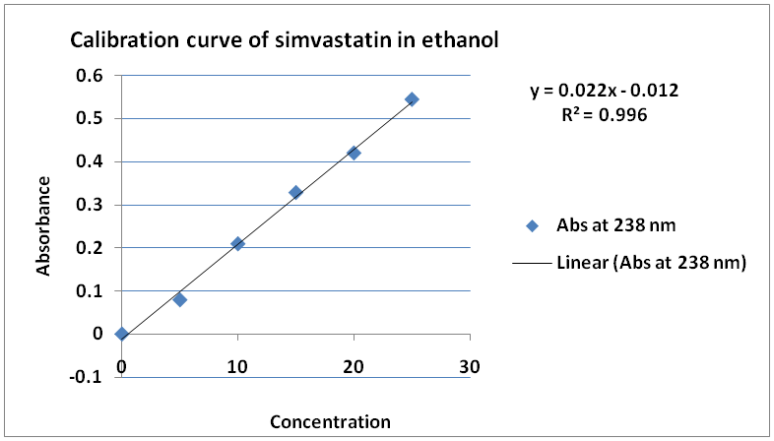

Fig. 2: Calibration curve of simvastatin

Table 1: Solubility data of pure drug and prepared solid dispersions

Formulation code	*Solubility (mg/ml)
Pure drug	0.028±0.20
F1	0.814±0.19
F2	1.643±0.32
F3	3.651±0.18
F4	5.815±0.65
F5	3.246±0.45
F6	4.974±0.22
F7	8.982±0.51
F8	7.489±0.21

*Data expressed as mean±standard deviation (SD), n=3

The percentage yield and drug content for different ratios of drug and carrier were calculated by using formula and values are shown in table 2. The percentage yield values were found to get decreased at the higher ratios of the carrier due to the difficulty during sieving. Drug content values are found to in the range of 88.75 to 94.89%. Low standard deviation between values indicated uniformity of drug content in all formulations [19]. In Percentage yield values, the yield was high in the F3 batch i.e. 95.23% but drug content was 90.26%. In F7 formulation, though the yield is 93.18%, actual drug content was found to be higher i.e. 94.89.

Table 2: Percentage yield and drug content of prepared solid dispersions

Formulation code	*Percentage yield	*Drug content
F1	92.11±0.961	89.22±0.003
F2	92.87±1.023	88.75±0.017
F3	95.23±1.104	90.26±0.012
F4	89.08±0.025	93.83±0.007
F5	92.01±0.725	90.81±0.013
F6	90.27±1.621	92.48±0.003
F7	93.18±1.321	94.89±0.002
F8	91.09±0.984	93.14±0.006

*Data expressed as mean±standard deviation (SD), n=3

FT-IR spectrum of simvastatin showed peaks of characteristic functional groups at wavenumbers 3549.14 cm^{-1} (free O–H stretching vibrations), 1705 cm-1 (stretching vibration of ester and lactone carbonyl functional groups), and 2877 cm^{-1}, 2955 cm^{-1} (C–H stretching vibrations) as shown in fig 3. FT-IR spectrum of PVP K30 is shown in fig. 4. The major peaks of simvastatin were retained in the physical mixture and solid dispersions as shown in fig. 5 and fig. 6, respectively. Peaks of-OH Stretch (3566.85 cm^{-1}), carbonyl group (1697.47) are observed to be shifted by some difference. The possible reason for shifting is intermolecular hydrogen bonding. But, no major difference was observed which indicates the compatibility of drug and PVP K30 in solid dispersion. In Solid dispersions, the possibility of hydrogen bonding between simvastatin and PVP is due to PVP. As PVP has two groups =N, =O that can potentially form a hydrogen bond with the drug [15].

The DSC Thermogram of simvastatin showed a sharp endothermic peak at 140 °C temperature as shown in fig. 7. The sharp, intense peak indicates the pure crystalline nature of the drug. PVP K30 showed a wide endotherm in the temperature range of 56-95 °C which can be attributed to loss of water due to hygroscopic nature [20]. In the physical mixture, both endotherms were observed indicating compatibility of drug and PVP K30. Lastly, in SD Thermogram, a less sharp peak of the drug was seen or can be said to be disappeared as compared to the thermogram of pure drug, but a wide endotherm at the range of 50-95 °C indicates entrapping of simvastatin in the carrier and confirms the amorphous nature of solid dispersion. A decrease in the intensity of the sharp peak of simvastatin can be attributed to increased dissolution or entrapment of simvastatin in the PVP K30 [21].

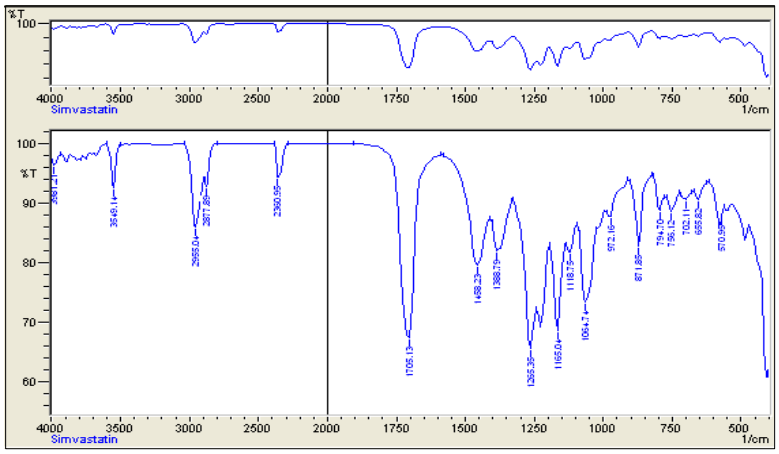

Fig. 3: FTIR spectrum of simvastatin

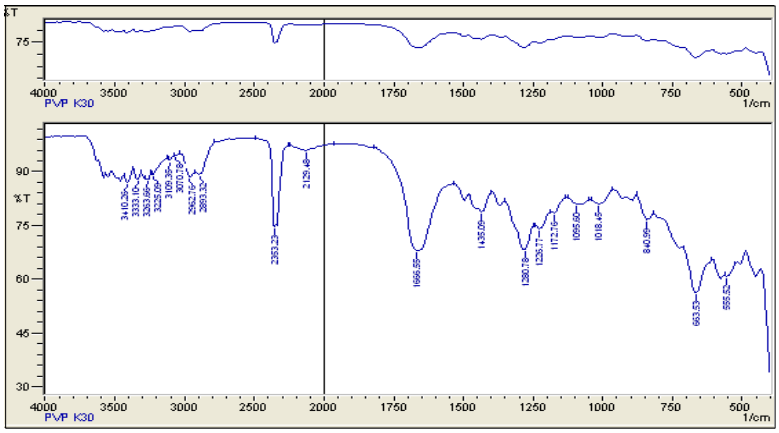

Fig. 4: FTIR spectrum of PVP K30

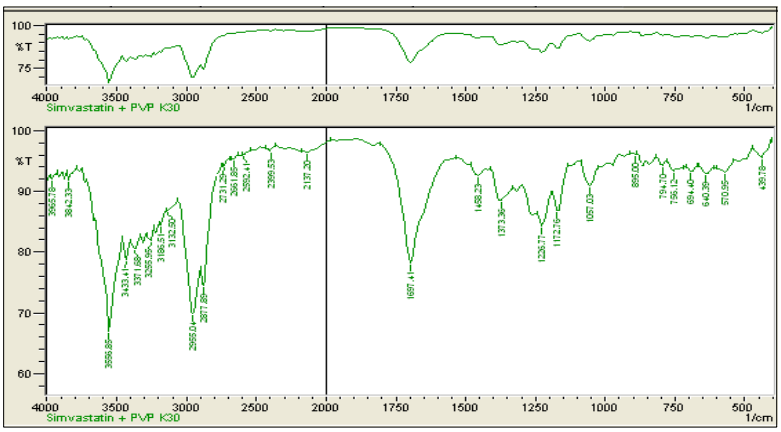

Fig. 5: FTIR spectrum of physical mixture of simvastatin and PVP K 30

The *In vitro* dissolution studies of pure drug, physical mixture, and SDs were carried out in phosphate buffer pH 6.8 up to 60 min. The pure drug showed 48.41% drug release in 60 min which indicates a poor dissolution profile. The formulations F1 to F4 which were prepared by the kneading method showed drug release from 84.73 to 93.20% in 60 min which indicated enhanced dissolution profile as compared to pure drug. The formulations F5 to F8 showed drug release from 94.72 to 98.60% drug release. F7 formulation showed maximum drug release i.e. 98.60% in 60 min which is 2 times greater than pure drug. This marked increase in dissolution and solubility can be attributed to the reduced, uniform particle size and hydrophilic nature of PVP K30. Thus from the above data, it can be said that simvastatin PVP SDs show better dissolution profiles compared to that of PEG 6000, even at the lowest PVP ratio i.e. (1:1) by solvent evaporation method [22].

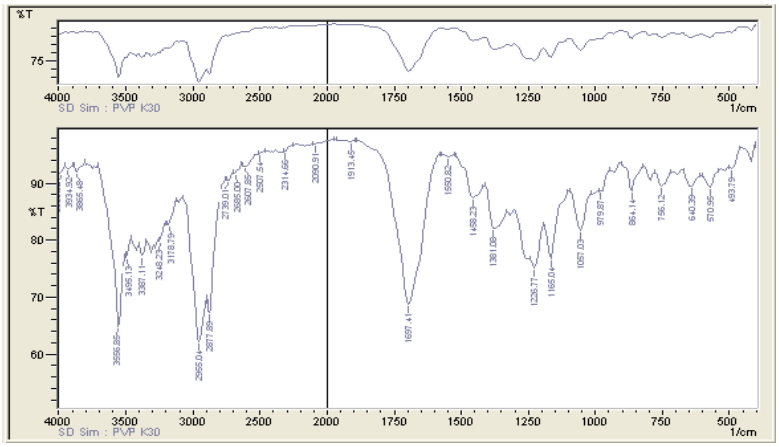

Fig. 6: FTIR spectrum of solid dispersion of simvastatin and PVP K30 (F7 formulation)

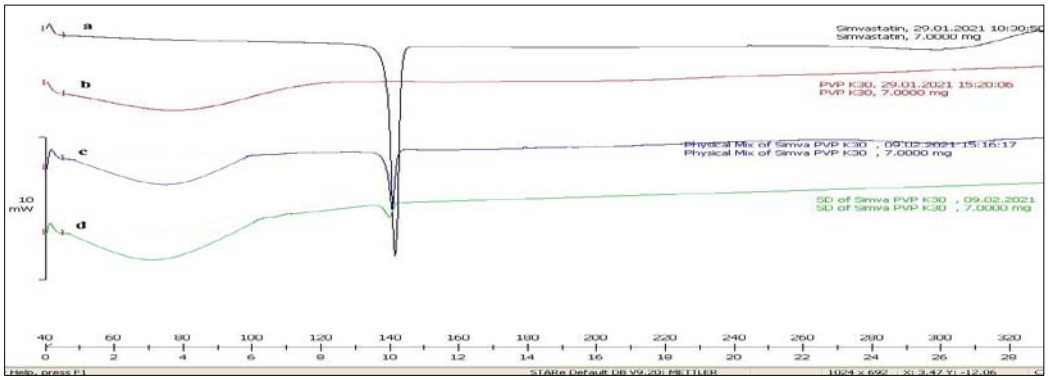

Fig. 7: Overlay of DSC thermograms of (a) Simvastatin, (b) PVP K30, (c) Physical mixture of simvastatin and PVP K30, (d) Solid dispersion of simvastatin and PVP K30 (1:1)

Table 3: Dissolution data of prepared solid dispersions

Time (in min)	*Percentage (%) drug release								
	Drug	F1	F2	F3	F4	F5	F6	F7	F8
0	1.088±1	1.914±1	1.783±2	2.871±1	3.362±1	1.726±1	1.669±2	8.762±1	7.862±1
5	2.299±1	3.051±2	3.984±1	8.181±2	9.981±2	6.676±2	6.520±1	20.23±1	16.38±1
10	3.878±1	6.054±1	9.154±1	16.99±1	21.11±1	18.42±1	19.05±2	31.83±2	27.58±2
20	7.601±2	14.90±2	21.53±2	30.83±1	33.40±2	31.27±1	34.48±1	43.88±2	39.94±2±
30	16.16±2	30.39±2	36.85±2	48.16±2	47.06±2	44.51±2	50.61±2	56.46±2	52.60±1
40	26.60±1	46.21±2	51.00±1	67.27±2	64.33±3	60.09±2	68.27±1	69.56±2	66.62±1
50	37.35±1	65.13±2	67.97±1	87.04±2	82.97±2	77.17±2	86.71±2	86.48±1	80.91±2
60	48.41±1	84.73±1	86.43±1	90.69±1	93.20±2	95.81±1	94.72±1	98.60±1	96.48±1

*Data expressed as mean±standard deviation (SD), n=3

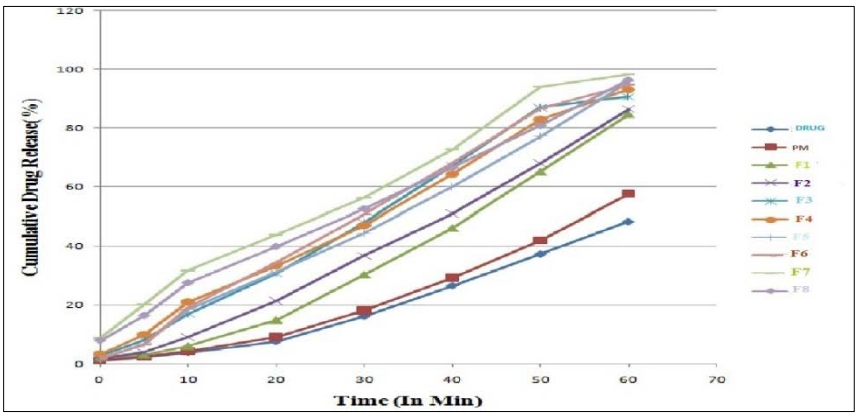

Fig. 8: *In vitro* dissolution profile of a pure drug, physical mixture, and solid dispersions (F1 to F8)

The *in vitro* dissolution data is given in table 3. By using Dissolution data, a graph is plotted between Cumulative % drug release and time which is shown in fig. 8. As per solubility and dissolution data, it can be confirmed that solvent evaporation is the best method as compared to kneading and the physical mixture method for the preparation of solid dispersions. In fig. 9, dissolution profiles of pure drug, physical mixture, F3, and F7 formulations are shown which indicates enhancement of simvastatin dissolution rate by a solvent evaporation method (F7 formulation dissolution profile). In the literature review of cefixime solid dispersions, the maximum increase in the dissolution rate was obtained with the dispersions prepared through the solvent evaporation method than the kneading method, and comparatively faster dissolution rates were obtained than that of the pure drug [23].

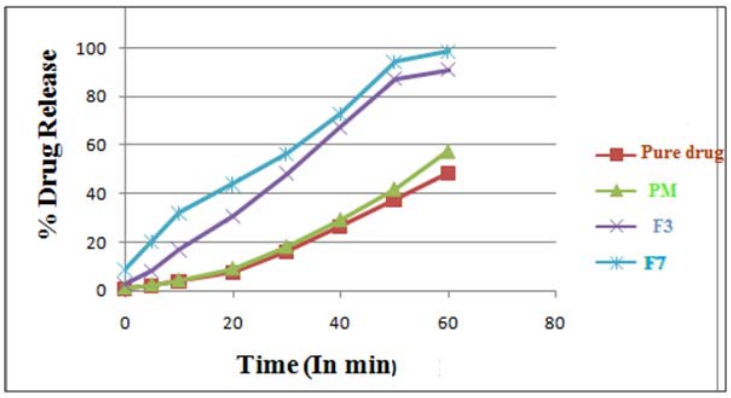

Fig. 9: *In vitro* dissolution profile of a pure drug, physical mixture, F3 and F7 formulation

F7 was found to be the best formulation so drug release kinetics was obtained from *in vitro* dissolution data and shown in table 4. It was found to follow a zero-order kinetic model with an $R^2$of 0.986 as shown in fig. 10.

Table 4: Correlation coefficient values for optimized formulation

Formulation code	Correlation coefficient (r^2) values				
	Zero order model	Korsemeyer peppas model	Higuchi model	Hixson crowell model	First order model
F7	0.986	0.982	0.970	0.965	0.937

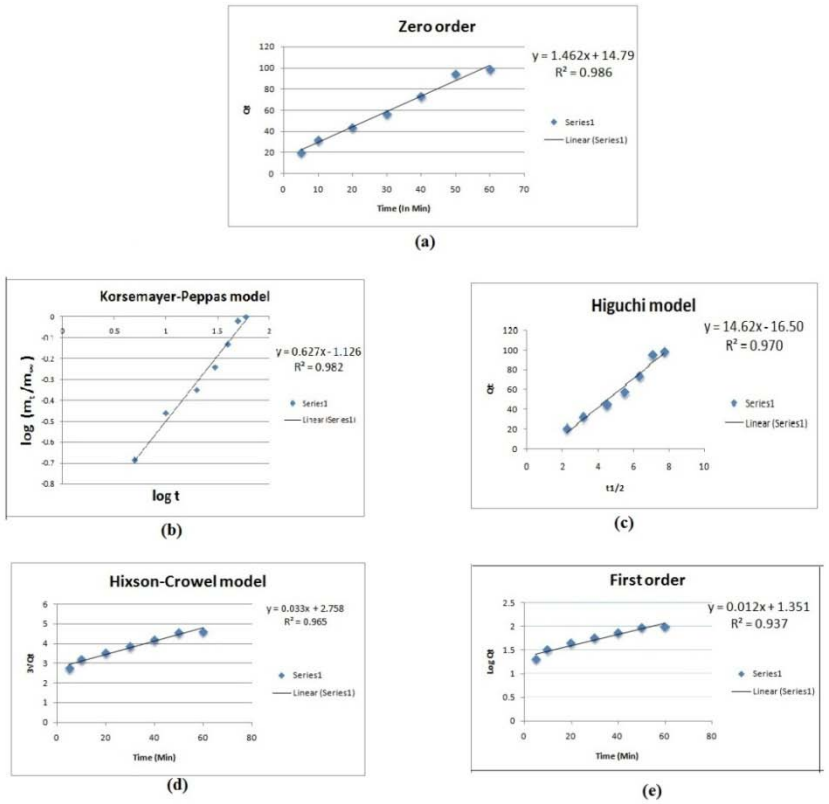

Fig. 10: Dissolution release kinetics (a) Zero-order model, (b) Korsemeyer peppas plot, (c) Higuchi model, (d) Hixson crowell model, (e) First order model

CONCLUSION

The solid dispersions of simvastatin prepared by kneading and solvent evaporation method with two different carriers (PEG 6000, PVP K30) showed considerably higher drug dissolution in comparison with pure drug. The result showed that the solid dispersions prepared with the solvent evaporation method give a higher dissolution rate than the kneading method. Amongst the carrier used, PVP K30 showed significant enhancement in solubility and dissolution. SD of drug and PVP K30 in the ratio of 1:1 gave a higher intrinsic dissolution rate. The DSC Thermogram of optimized solid dispersion batch (F7) showed entrapment of drug in a carrier matrix and confirmed amorphous nature. PVP K30 does not show any incompatibility with simvastatin and that was confirmed by FT-IR analysis. Thus, the present research concluded that solid dispersion technology can be used effectively to enhance the solubility and also dissolution rate of the poorly water-soluble drug simvastatin.

FUNDING

This study was not funded.

AUTHORS CONTRIBUTIONS

All authors in the present research study have contributed their equal parts. Payal D. Borawake has collected the data, designed the study, and performed the experimental work. Kauslya Arumugam has interpreted the data. The research was guided and supervised by Jitendra V. Shinde. All authors contributed to the manuscript writing.

CONFLICT OF INTERESTS

None

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