DOI: https://doi.org/10.31351/vol34iss4pp33-43

Solubility and Dissolution Rate Enhancement of Simvastatin by Adsorption on Magnesium Aluminum Silicate

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Received 31/1/2024, Accepted 11/7/2024, Published 20/12/2025

Abstract

Simvastatin (SIM), is an inactive lactone, anti-hyperlipidemic drug. According to the Biopharmaceutical Classification System (BCS), SIM is classified as class II drug with low solubility, which results in low bioavailability. Adsorption technique is a highly effective approach for increasing the solubility and dissolution rate of poorly soluble drugs. The goal of this research is to use such approach to increase the solubility and dissolution rate of SIM by using magnesium aluminum silicate (MAS) as adsorbent, Soluplus® and poloxamer 407 as surfactants. By the use of solvent evaporation method all the MAS loaded SIM formulations were prepared in different drug: adsorbent: surfactant weight ratios, then evaluated for their percentage yield, drug content, water solubility, dissolution, crystal lattice using X-ray powder diffraction (XRD) and Differential Scanning Calorimetry (DSC) studies. Fourier Transform Infrared Spectroscopy (FTIR) was used for the determination of drug- excipient interaction. All formulas exhibited an increase in drug solubility. The formula F8 (SIM: MAS: Soluplus® 1:6:3) gave the best results, as it showed 91.3% yield, 85.5±0.19 % drug content,178.3 -fold increased solubility compared to that of pure drug and 1.6 -fold as compared to F6(without Soluplus®) and 85.5 % of drug released within 30 minutes with complete amorphization that confirmed by DSC and XRD. while the FTIR confirmed the adsorption process. Therefore, the adsorption technique can be considered as an efficient method for enhancing the solubility and dissolution rate of SIM.

Keywords: Simvastatin, Adsorption Technique, Magnesium Aluminum Silicate, Soluplus®, Poloxamer 407

Introduction

Aqueous solubility and intestinal permeability are the two most crucial characteristics of drugs for oral administration. According to the Biopharmaceutical Classification System (BCS), most of drugs are BCS class II and IV, which have low solubility. Drugs must dissolve in gastrointestinal fluids after oral administration in order to be absorbed and produced their therapeutic effect [(1)]. Solubilization approaches, such as solid dispersion systems, particle size reduction, salt formation, prodrug, liposomes, etc., can be used to overcome the problem of low solubility. Solubility can be enhanced by amorphization whereby the crystalline drugs undergo transformation into their highly energetic amorphous state, showing enhanced solubility when compared to their original form [(2)]. Adsorption on porous materials is an amorphization method. It is the phenomenon by which the molecules of drug spontaneously concentrate at a contacting surface, thereby forming a surface or interfacial layer [(3,4)]. Layered silicates have a capability to act as carrier for different drugs due to their large surface area and expandable interlayer space. Magnesium aluminum silicate (MAS) is an example of layered silicate [(5)]. It was documented that, MAS has the pore volume of approximately 4000 mm^3/g, and surface area of 300 m^2/g by BET analysis indicating MAS has a great adsorption capacity so it was used for this technique, and , due to its high biocompatibility, it is a useful excipient for drug administration[(6)]. In addition, the crystallinity and melting point of the drug would be decreased by its entrapment into porous structure of silica [(7)]. Simvastatin (SIM), an inactive lactone, it is a synthetic lipid-lowering agent generated from an *Aspergillus Tereus* fermentation product. Following oral consumption, SIM hydrolyzes to yield the corresponding β-hydroxy acid form. This is a crucial metabolite and a blocker of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the enzyme that catalyzes the rate-limiting step in the production of cholesterol by converting HMG-CoA to mevalonate. SIM has a formula of $C_{25}H_{38}O_5$ as shown in Figure 1. It is a crystalline, white , non-hygroscopic powder with log P = 4.4[(8)].

It has low aqueous solubility and therefore low oral

bioavailability of about 5%. Being categorized as a Class II drug. SIM often shows dissolution rate-limited oral absorption and high variability in pharmacological effect [9]. Solid dispersion, cyclodextrin complexation, and nanoparticle formulations were among the techniques used to improve its solubility [10-12]. The main objective of this research is to use MAS as adsorbent to enhance the solubility of SIM as a preliminary study to formulate the drug as oral tables with immediate release.

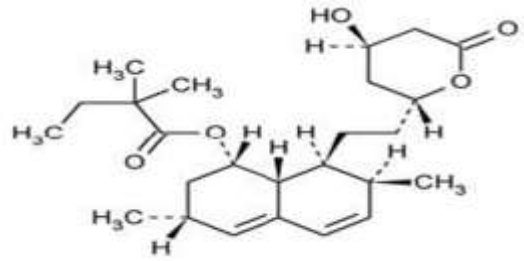

Figure 1. Structure of simvastatin [8]

Materials and Methods

Materials

Simvastatin and Magnesium aluminum silicate (MAS) were purchased from Hangzhou, Hyperchem. China. Soluplus ®, poloxamer 407 were purchased from CDH, India. The remaining materials were all analytical in nature.

Methods

Preparation of MAS loaded SIM

Solvent evaporation method was used to adsorb SIM on MAS. SIM (500 mg) and surfactants (if any) was dissolved in 30 ml of ethanol. Required weight of MAS (according to the ratios in Table 1) was dispersed in drug solution with stirring by magnetic stirrer for 1 hour. Then the solvent was allowed to evaporate completely in the oven at 40 °C for 24 hours. The resulting dry solid mass was then pulverized and passed through a #60 mesh sieve to get homogenized product and then placed in desiccators containing $CaCl_2$ and kept there for further studies [13].

Preparation of physical mixture (PM)

Physical mixture was prepared by geometric mixing of drug, MAS and the selected surfactant in the same ratios as that of the selected formula by using mortar and pestle with gentle mixing. This mixture was passed through a sieve of #60 mesh size and then kept in desiccators at room temperature for further studies [14].

Evaluation of MAS loaded SIM

Determination of percentage yield

The percentage yield (PY) was calculated practically for all the prepared formulas to determine the suitability of the technique. The PY was obtained by dividing the formula's actual mass by the theoretical mass by using the following equation [15]

$$\text{Yield (\%)} = \frac{\text{Actual wieght of dry product}}{\text{Theoretical weight of drug+ carrier(s)}} \times 100 \ldots\ldots \text{eq 1}$$

Determination of % drug content

A precisely weighed amount of product corresponding to 10 mg of SIM, was dissolved in 10 ml of ethanol and stirred for a duration of one hour. The volume was then completed up to 50 ml. The resulted mixture was filtered through a filter paper. The drug solution was analyzed by using UV-spectrophotometer at λ max of 237 nm [16].

Determination of saturation solubility

An excess amount SIM and the obtained formulas were added individually to 10 mL distilled water, the samples were then incubated for 48 hours at 25 ˚C in a water bath shaker. after centrifuging. the samples were filtered using filter paper and diluted if needed [17]. The amount of SIM dissolved in the diluted samples was measured using a UV spectrophotometer set at 238 nm [18]. This test was carried out in triplicate for each sample.

In-vitro dissolution studies

The in vitro dissolution studies for pure SIM and formulas with highest solubility were carried out according to USP monograph where apparatus II was used. Accurately weighed samples equal to 10 mg of SIM have been added in 900 mL of 0.01 M phosphate buffer (pH 7.0) with 0.5% sodium dodecyl sulfate (SDS) at 37 ± 0.5°C and rotated at 50 rpm. At predetermined intervals, 5 mL aliquots were withdrawn and filtered through a 0.45 µm filter membrane. To keep the volume of dissolution medium constant, same volume of a fresh dissolution medium was added. Then spectrophotometric analysis for SIM at 238 nm, was performed on the filtered samples [19,20]. This test done in triplicate.

Selection of the best formula

The formula with high percentage yield, high drug content, highest solubility, and the fastest dissolution rate was chosen for more characterizations.

Characterization of the best formula

X-ray powder diffraction (XRD)

The XRD was used to detect any alteration in the crystalline structure of the drug. The X-ray diffractograms of the drug, MAS, selected surfactants, selected formula and its PM, were achieved with the use of an X-ray diffractometer (Shimadzu, Japan) [21]. The rate of scanning was 5°/min over a 2 theta range of 5–80°, voltage and current of 30 kV and 30 mA, respectively.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry of SIM, MAS, selected surfactants, optimized formula and, and its PM were done using DSC60 (Shimadzu, Japan). Sample's thermal behavior was examined at a scanning rate of 10 ˚C/min in an inert environment

that was being flushed with nitrogen at a rate of 20 ml/min, which includes a temperature range of 20 – 200 ˚C [22]

Fourier transform infrared (FTIR)

The FTIR of pure SIM, MAS, selected surfactant, selected formula and its PM were carried out in order to detect drug-excipient interaction. Using an FTIR Shimadzu 8000 Japan, the samples were compressed using potassium bromide in the form of a disc; the scanning area of the obtained spectra spanned between wave numbers 4000-400 cm^{-1}[23].

Scanning Electron Microscopy (SEM)

The surface morphology of SIM, MAS, F8 and its PM were determined using an analytical scanning electron microscope (Axia Chemise, Netherlands) employed a secondary detector with varying magnification and acceleration voltage [24]. The samples were gently spreading onto on double-sided carbon tape and coated with a very thin layer of gold at 20k .

Statistical analysis

A similarity factor (*f2*) was employed for statistically comparing the dissolution profiles. The range of values for this factor is 0–100. When the *f2* values are greater than 50 (50–100), the two dissolution profiles are regarded as identical; on the other hand, when *f2* values less than 50 suggest that the comparing profiles are not identical. The subsequent equation defined the similarity factor (f2) [25].

$$f2 = 50 \cdot \log\left\{100 \cdot \left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5}\right\} \quad (3)$$

The number of dissolution time points is represented by (n). The reference and test dissolution values are expressed as percentages at time (t) and (Rt), respectively.

One way ANOVA (Graph Pad Prism) was used to analyze the values of the other results, and a p-value of 0.05 was chosen as the level of significance.

A p-value of greater than 0.05 was regarded as non-significant. A p value less than 0.05 was to regarded be significant.

Results and Discussion

Drug content and percent yield

The results of PY and % drug content are shown in Table 1. The PY of the prepared formulas was found to be in the range of 79.4-93.5 %. Demonstrating the applicability of the technique. Whereas the drug content of all the ten formulations was in the range of 29.7 - 85.5 % .Since it is expected there was no free drug, the observed low drug content can be explained as that, the loaded drug molecules were tightly bound to the silica surface or attached deeply to pores which were unable for ethanol to extract them [26]. The increased value of drug content by increasing MAS may be due to adsorption of drug on the surface that can be easily extracted by the solvent. Addition of surfactants have different effect. Soluplus® with large molecule (mwt=90,000 - 140,000 g/mole) can adsorb onto silica surface may alter the wettability, porosity, or surface energy of silica particles, which may enhance the displacement of SIM from the surface and pores of silica, so it can be easily extracted by ethanol [27,28]. On the other hand, polxamer407 with smaller molecule (12600 g/mole) [29] may block the pores and imped the extraction of the drug by ethanol resulted in low observed drug content.

Table 1. Formulas' composition with varying MAS and surfactant ratios with percentage yield and drug content of the prepared formulas

Formula No.	Drug	MAS	Surfactants		Percentage yield (PY)	Drug content (w/w) (%) (Mean ±SD), n=3
			Soluplus®	poloxamer 407		
F1	1	1	…	…	79.4	58 ±0.1
F2	1	2	…	…	93.5	69.8 ±0.07
F3	1	3	…	…	88	71.9±0.14
F4	1	4	…	…	91	77±0.3
F5	1	5	…	…	90	70±0.02
F6	1	6	…	…	90	73.3±0.32
F7	1	6	1	…	90.3	80.4±0.04
F8	1	6	3	…	91.3	85.5±0.19
F9	1	6	…	1	90.5	29.7±0.57
F10	1	6	…	3	92.4	59.2±0.14

Saturation solubility

All of the prepared formulas showed a significant ($p<0.05$) enhancement in their solubility in water when compared to that of pure SIM. The solubility of formulas F1-F6; increased as the ratio of SIM:MAS increased as shown in Table 2 and Figure 2, this result may be attributed to the adsorption of drug molecules at the surface of MAS and inside its pores by diverse forces, including hydrophobic interactions, dispersive forces and hydrogen bonding. Hydrogen bonding is the major force for this type of adsorption. The proportion of hydrogen bonding is directly correlated with the number of silanol groups present at the surface of MAS and the functional groups of the drug molecules. Such adsorption provides a large surface area for drug loading, so a large, exposed surface area of the drug for the solvent greatly enhances drug saturated solubility [7,30].

Table 2. The saturated solubility of MAS loaded SIM developed with various Drug: Adsorbent: Polymers weight proportions at 25˚C in distilled water.

Formula code	Saturation Solubility mg/ml (Mean ±SD), n=3	Formula Number	Saturation Solubility mg/ml (Mean ±SD), n=3
Pure SIM	0.0074±0.00	**F6**	0.845±0.074
F1	0.188±0.04	**F7**	0.96±0.09
F2	0.213±0.008	**F8**	1.32±0.204
F3	0.289±0.014	**F9**	0.468±0.02
F4	0.430±0.02	**F10**	0.85±0.107
F5	0.694±0.07		

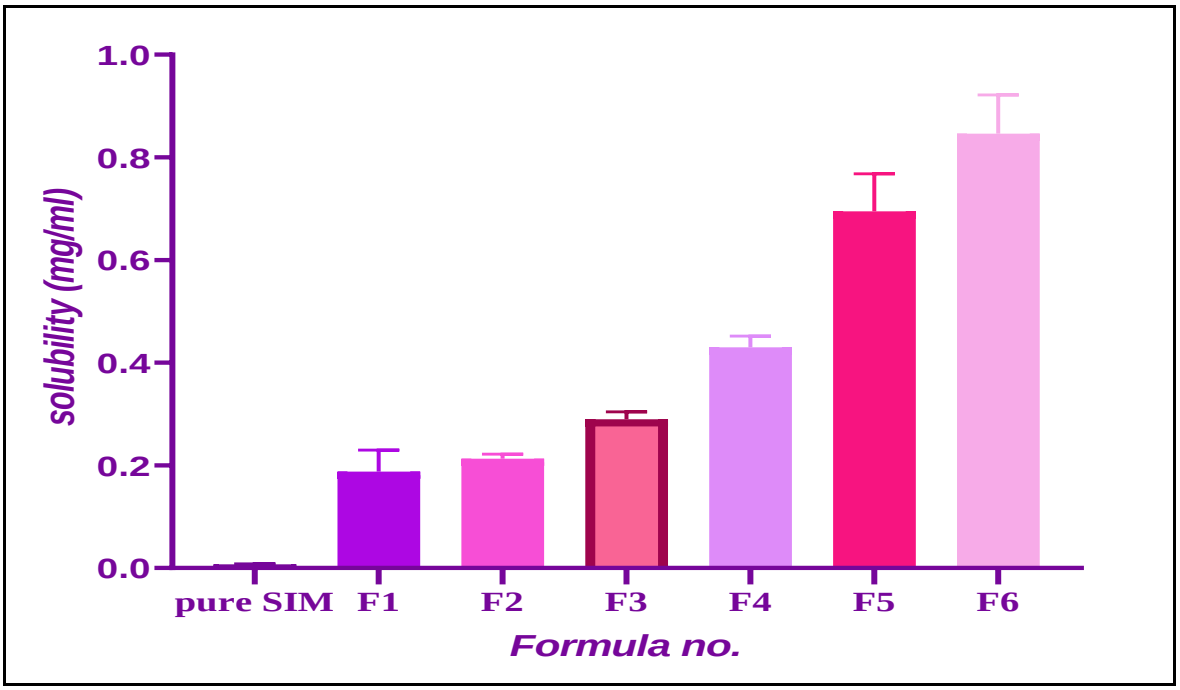

Figure 2. Effect of MAS on the solubility of SIM in distilled water at 25°C.

Formulas F7-F10 show the effect of Soluplus® and poloxamer 407 on the solubility of SIM (Table 2 and Figure 3). The further improvement of SIM solubility in presence of surfactants might belong to the ability of these surfactants to improve wettability properties of the hydrophobic drug. So, the presence of these wetting agents markedly strengthened the solubilizing power of MAS toward the drug [26]. F8 (1:6:3 SIM: MAS: Soluplus®) exhibited the maximum solubility 1.32±0.204 mg/ml indicating that this combination enhances the solubility by 178.3- folds in comparison with the drug's original form and (1.6 - fold) as compared to F6 without Soluplus®.

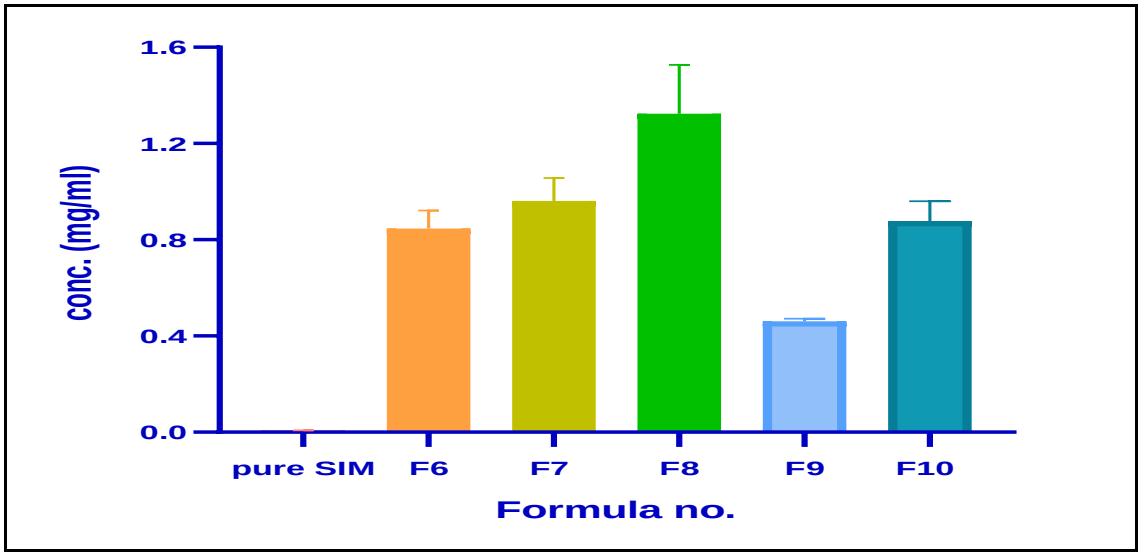

Figure 3. Effect of surfactants on solubility of MAS loaded SIM

In-vitro dissolution studies

The dissolution study was carried on F6, F8 and F10 which showed highest solubility. Figure 4 demonstrates that F6 (1:6 SIM: MAS) improved dissolution rate of SIM in phosphate buffer (pH 7.0) in comparison with the pure drug (*f2*=46.3). Moreover, Figure 4 demonstrates that, presence of Soluplus® (F8) enhanced the dissolution rate of SIM in contrast to the effect poloxamer 407 (F10) which decreases it. The reason behind this result, is that, Soluplus® is an amphiphilic co-polymer, it enhances the access of dissolution medium to drug binding sites by its adsorption to the silica surface and improves wetting, resulting in less drug retention and enhanced dissolution in comparison with pure drug (f_2=38.9)[31]. In contrast, the low drug release for F10 may suggest adsorption of PXM407 molecules onto the silica surface and deposit in the silica pores and block them so it also imped the release of drug from these pores, while the increased release of SIM by PM (Figure 5), to a level similar to its release from F8 (*f2*=62.9) may be considered as false positive result explained by the interactions between SDS (the anionic surfactants in dissolution medium) and the free nonionic surfactant (Soluplus®), which form complexes via the adsorption of SDS clusters on the hydrophobic segments of the Soluplus® chain , this complex may encapsulate the SIM and enhance its dissolution[32]. Similar results were obtained by Sheng Qi *etal* were the dissolution Etravirine is increased by the presence of SDS and nonionic hydrophilic polymer in the dissolution media [33].

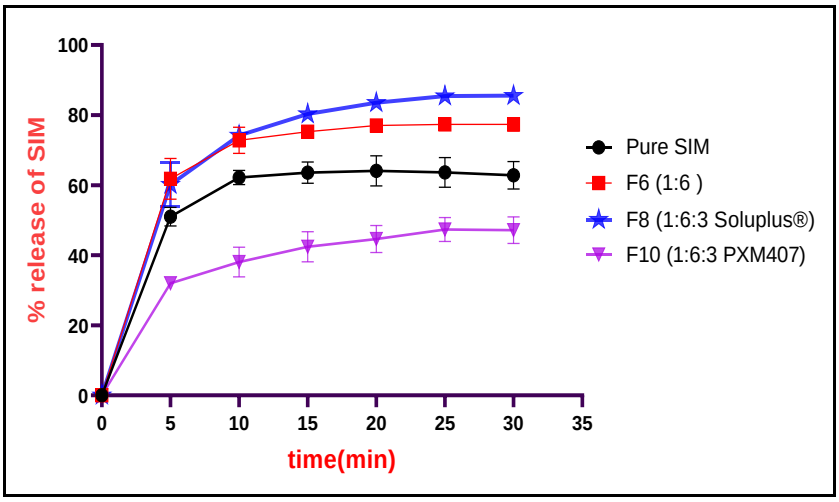

Figure 4. Effect of surfactant types on the in-vitro dissolution of in 0.1 M phosphate buffer pH 7.0 with 0.5% SDS at 37±0.5°C.

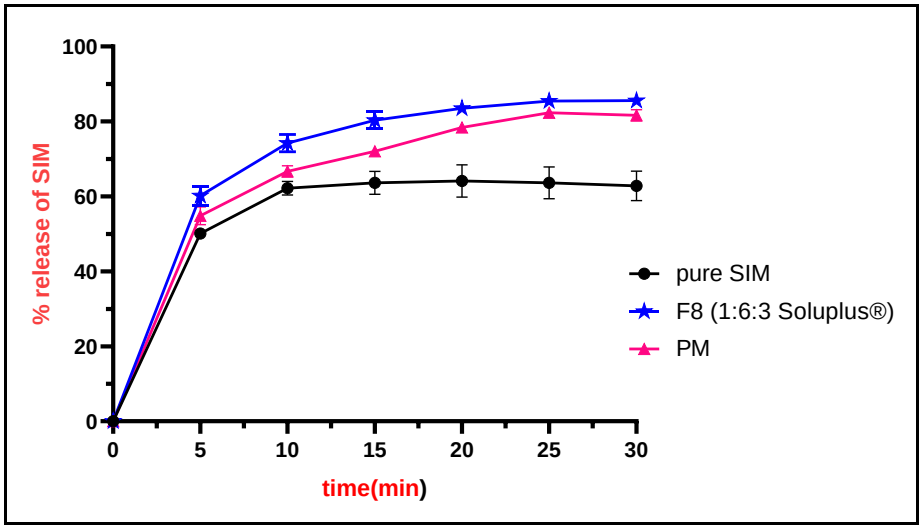

Figure 5. In vitro dissolution of the pure SIM, F8(1:6:3) Soluplus®(SOLU) and its physical mixture (PM) in in 0.1 M phosphate buffer pH 7.0 with 0.5% SDS at 37±0.5°C.

Selection of the best formula

From the above results F8 was chosen as the optimal formula since it possessed high PY%, drug content, highest solubility and fastest dissolution rate so it was subjected to further studies.

Differential scanning calorimetry (DSC)

The DSC thermograms of SIM, MAS, F8 and its PM are seen in Figure 6. The DSC curve of SIM exhibits a prominent endothermic peak at its melting point of 144 ˚C. This result confirms the purity and crystallinity of the used SIM [34]. A broad endothermic peak was seen by Soluplus®, indicating its amorphous nature with corresponding glass transition temperature (Tg) around 70°C [35]. However, the DSC of MAS showed a broad, gradually occurring dehydration peak that ranged between 100.6 to 140.1°C [36]. Regarding PM, the melting point of the SIM peak dropped to 141.2°C with decreased intensity due to dilution with other components. The thermogram of F8 revealed the absence SIM peak which could be explained to complete adsorption and conversion of the drug from crystalline to amorphous state.

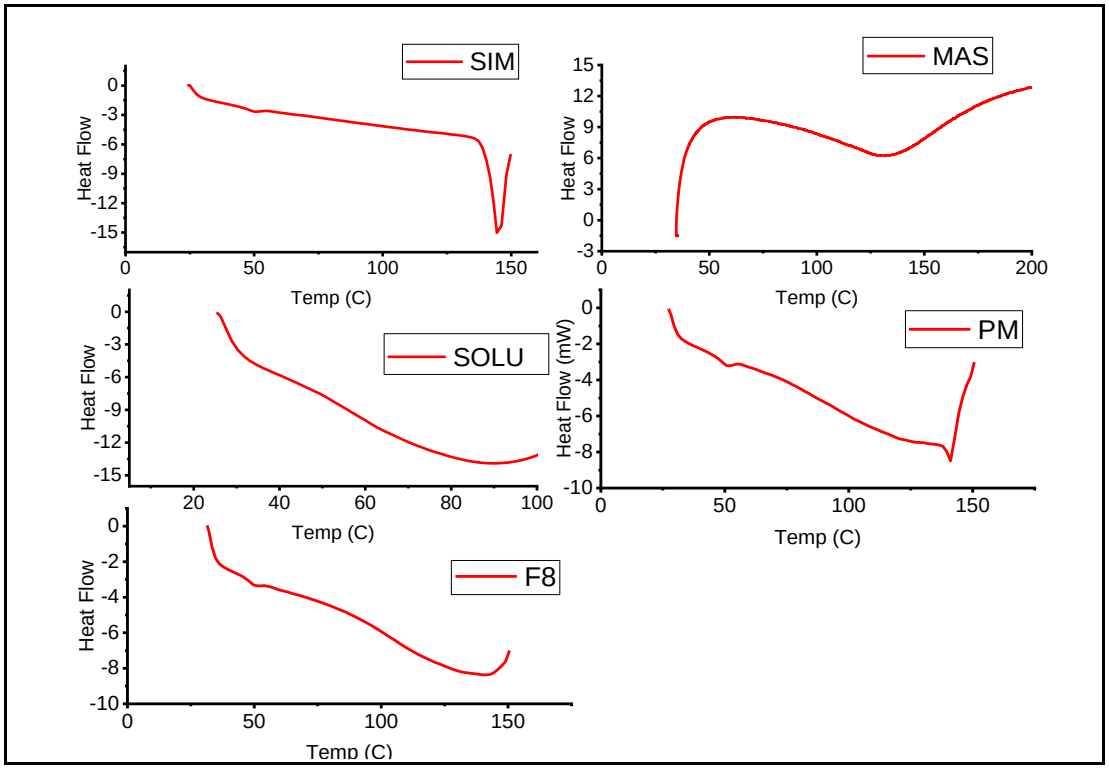

Figure 6. DSC thermograms of SIM, MAS, Soluplus®, F8 and its PM

X-ray powder diffraction (XRD)

The XRD diffractogram of SIM, PM, F8, Soluplus® and MAS are shown in Figure 7. In the X-ray diffractogram of SIM, Braggs peaks were detected at 2θ of 9.5°, 11.1°, 15.8°, 16.6°, 17.3°, 17.8°, 18.9°, 19.5°, and 22.6° indicating the crystalline nature of SIM. These numbers were in range with the previously published article [37]. The Soluplus® pattern in the presence of halo, indicating its amorphous nature [38]. XRD pattern of MAS showed characteristic peak at 2θ of 7.5°, 20.3°, 22.0°, 28.9°, and 36.7°, with low intensity indicating it is relatively having low crystallinity [39,40]. Physical mixture's pattern showed the peaks of drug were decreased in their intensity and masked by the high amount of MAS. The characteristic peaks of SIM were not detected in optimized formula (F8) XRD patterns, but the peaks that corresponded to the MAS still visible, revealing the main impact of the high concentration of the carrier in this formula. A decline or disappearance of the prominent peaks of SIM in F8, confirming the amorphous form is predominating. This amorphous state may assist to increase solubility as this form is more easily soluble than the crystalline form. This result supported the DSC result.

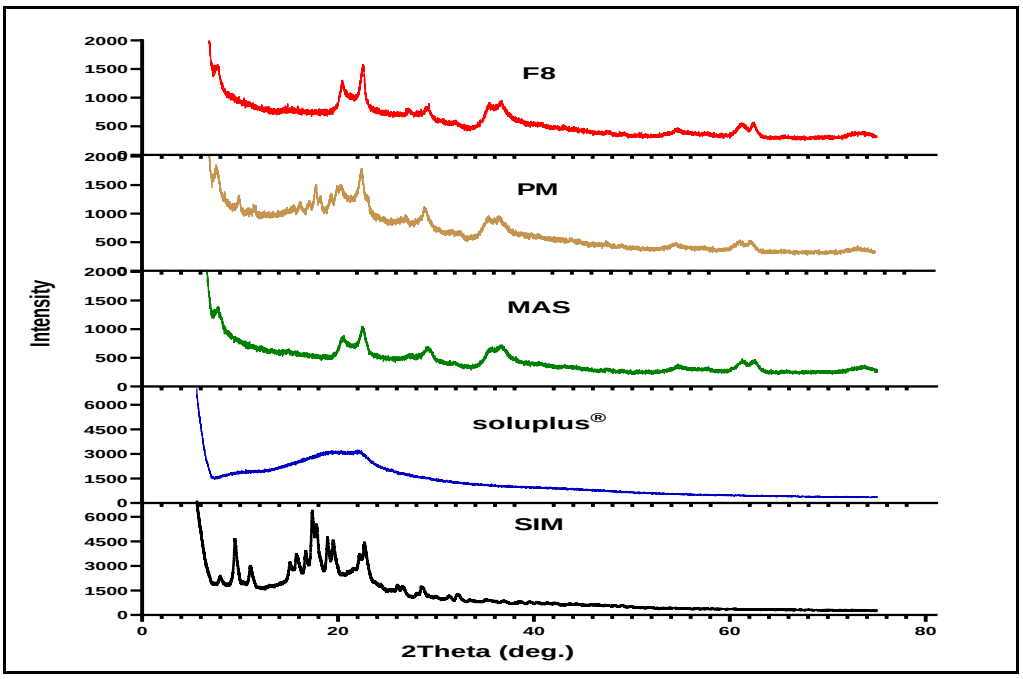

Figure 7. X-ray diffractograms of SIM, PM, MAS, Soluplus®, selected formula(F8).

Fourier transform infrared (FTIR)

The distinctive peaks of SIM were observed at 3547 cm^{-1} (free O–H stretching vibration), 2951 cm^{-1} (methyl C–H stretching vibration), 1699 cm^{-1} (stretching vibration of C=O for ester), 1266 cm−1 (C–O stretching vibration) as shown in Figure 8 which are in agreement with the previous study [41]. The spectrum of the MAS shows its characteristic bands, that are hydroxyl stretching of Si–OH at 3612 cm^{-1}, hydroxyl stretching at 3445 cm^{-1}, hydroxyl bending at 1634 cm^{-1} and the stretching of Si–O–Si at 1010.4 cm^{-1} which are in line with the previous results [42]. Whereas, FTIR result of Soluplus® show the characteristic broad peak of hydroxyl group at 3437 cm^{-1} (O-H stretching). Peaks at 1741 cm^{-1} and 1633 cm^{-1} are attributed to C=O stretching of ester group and tertiary amide group, respectively are consistent with previous study [43]. The FTIR Spectrum of PM showed the characteristic peak of SIM with low intensity indicating the predominant effect of the adsorbent. The spectrum of the optimized formula showed O–H stretching peak of SIM shifted from 3547 to cm^{-1} to lower wavenumber. whereas the O–H stretching peak at 3612 cm-1 of Si-OH group of MAS appeared as a shoulder at 3622 cm^{-1} that may be due to the formation of a hydrogen bond between silanol group on the surface of MAS and hydroxyl group and ester group of SIM [44]. The carboxyl stretching peaks at 1699 cm^{-1} shifted to higher wavenumber 1734 cm^{-1} and presented lower intensity in formula indicating an electrostatic interaction of carboxyl group of SIM with the positively charged sites in the edges of MAS structure. The most characteristic peaks of SIM are still present but some decrease in intensity and shifting of some peak. These results confirm the adsorption process.

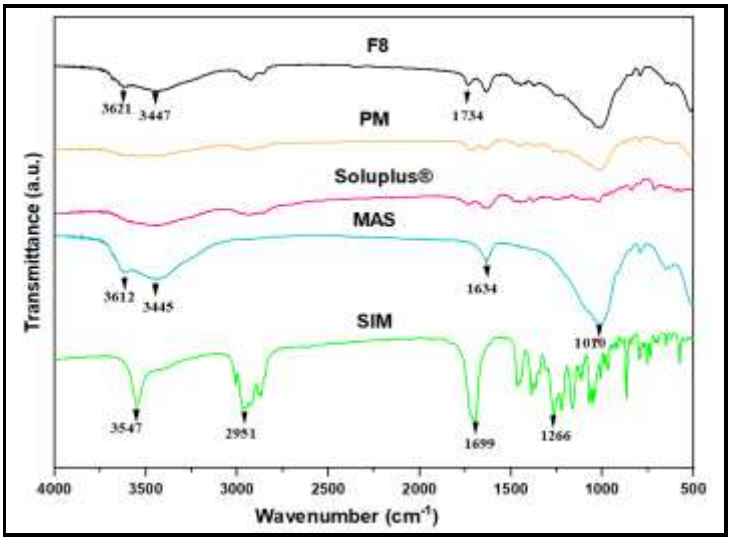

Figure 8. FTIR spectrum of SIM, MAS, Soluplus®, PM, F8

***Scanning Electron Microscopy (SEM*)**

SEM images of SIM, MAS, F8 and its PM are presented in Figure 9. The SEM images of SIM particles exhibit crystalline structure appeared as rod-shaped that align with the previous study [24, 45]. Surface morphology of MAS resembling thin, flat layers this is arises from the layered arrangement of the aluminum silicate structure [46]. While the surface morphology of PM revealed rough surface with particles of different size according to the components of the mixture. On the other hand, F8 surface morphology appeared smooth and lack of any aggregated of particles, which may be due to incorporation of SIM or/and Soluplus® inside the tiny pores or in between the layers of MAS

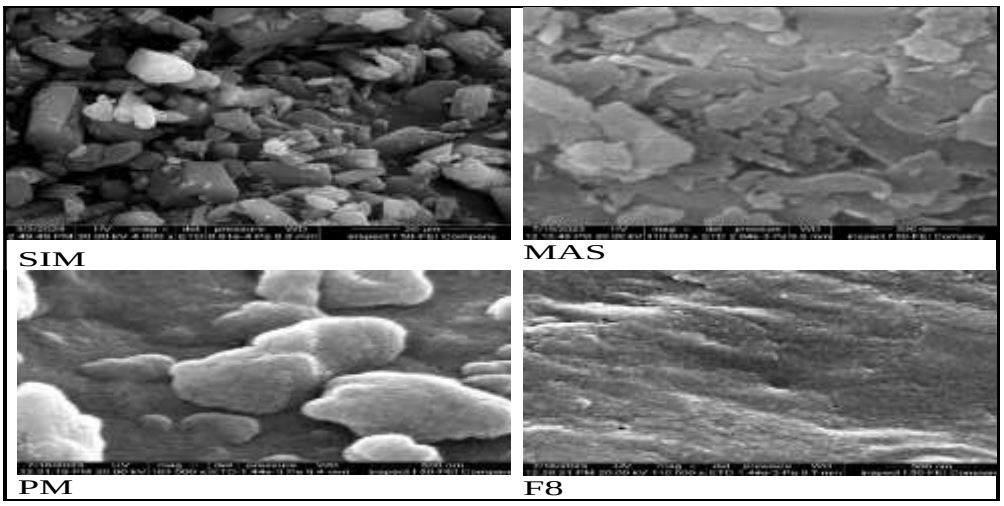

Figure 9. Particle and surface morphology of SIM, MAS, F8 and its PM.

Conclusion

Adsorption technique was successful in enhancing the solubility and dissolution rate of SIM using MAS as adsorbent. Further enhancement was obtained by addition of Soluplus® as a hydrophilic polymer. The adsorption process was responsible for conversion the drug into amorphous form with improved solubility as confirmed by DSC and XRD. Further confirmation about the adsorption was obtained by FTIR and SEM.

Acknowledgment

The authors are very thankful to the College of Pharmacy, University of Baghdad for providing the necessary facilities to carry out this work.

Conflicts of Interest

None

Funding

Self-funding

Ethics Statements

The research is an in vitro study so it does not require ethical approval from an ethics committee.

Author Contribution

The authors confirm their contribution to the manuscript as follows: study conception and design: second author, data collection: firs author. Both authors participate in writing, reviewing and approved the final version of the manuscript.

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تحسين الذوبانية وسرعة التحرير للسمفاستاتين بواسطة الامتزاز على سليكات الالمنيوم المغنيسيوم

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الخلاصة

السيمفاستاتين، هو لاكتون غير نشط ، دواء مضاد لارتفاع الدهون في الدم. ينتمي الدواء إلى الفئة الثانية وفقا لنظام تصنيف المستحضرات الصيدلانية الحيوية مع انخفاض التوافر البيولوجي بسبب انخفاض قابليته للذوبان. تقنية الامتزاز هي تقنية فعالة لتحسين قابلية الذوبان ومعدل ذوبان الأدوية ضعيفة الذوبان وتعتبر السيليكا المسامية واحدة من الممتزات الفعالة. تهدف الدراسة الحالية إلى تعزيز قابلية الذوبان ومعدل ذوبان السيمفستاتين باستخدام تقنية الامتزاز باستخدام سيليكات الألومنيوم المغنيسيوم كممتز الى جانب السولبلس و البولوكسامر ٤٠٧ كمواد خافضة للتوتر السطحي. تم تحضير جميع تركيبات السيمفستاتين الممتزة على سيليكات الألومنيوم المغنيسيوم بطريقة تبخر المذيبات في نسب مختلفة من وزن الدواء: الممتز:خافض التوتر السطحي ، ثم تم تقييم هذه التركيبات من حيث النسبة المئوية لإنتاجيتها ، ومحتوى الدواء ، والذوبان في الماء ، وتحرر الدواء، والشبكة البلورية باستخدام حيود الأشعة السينية و مسعر المسح التفاضلي والتحليل الطيفي بالأشعة تحت الحمراء لتحديد التوافق بين الدواء والمضافات الأخرى .أظهرت جميع الصيغ المعدة تحسنا في قابلية ذوبان الدواء و تم الحصول على أفضل نتيجة من الصيغة رقم ٨ (دواء: سيليكات الألومنيوم المغنيسيوم: سولبلس بنسبة ١:٦:٣) بنسبة انتاج ٩١,٣٪ و محتوى دواء بنسبة ٨٥,٥٪ و زيادة ١٧٨,٣ ضعفا في الذوبان مقارنة بذوبان الدواء النقي و ١,٦ ضعف مقارنة بالصيغة رقم ٦ (بدون سولبلس) و تحرر ٨٥,٥٪ من الدواء خلال ٣٠ دقيقة مع عدم تبلور كامل والذي أكده امسعر المسح التفاضلي و حيود الاشعة السينية. اما التحليلي الطيفي بالأشعة تحت الحمراء فقد أكد عملية الامتزاز . و بذلك يمكن اعتبار ان تقنية الامتزاز وسيلة فعالة في زيادة الذوبانية و تحرر دواء السيمفستاتين.

الكلمات المفتاحية: سيمفاستاتين ، تقنية الامتزاز ، سيليكات الألومنيوم المغنيسيوم ، سولبلس ،بولكسامر ٤٠٧