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# FORMULATION AND EVALUATION OF MOUTH DISPERSIBLE TABLETS OF SIMVASTATIN USING NOVEL EXCIPIENTS

**Alaa F. Abouzeid*, Ebtessam A. Essa and Esmat E. Zin Eldin**

Department of Pharmaceutical Technology, Pharmacy College, Tanta University, Egypt.

***Corresponding Author: Dr. Alaa F Abouzeid**
Department of Pharmaceutical Technology, Pharmacy College, Tanta University, Egypt.

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## ABSTRACT

**Introduction:** Novel excipients are necessary for the development of modern and advanced drug delivery systems. Soluplus® is a newly introduced hydrophilic polymer specially designed for hot melt extrusion technique, Objectives: The aim of this work was to study the potential of using Soluplus® in enhancing dissolution rate of simvastatin (SIM), a poorly water soluble drug. The goal was extended to develop and evaluate orodispersible tablets (ODT). Methods: The drug and polymer were dissolved in ethanol in absence and presence of Aerosil 200 as solid carrier. Simultaneous precipitation was achieved by evaporation of the solvent. In addition, the drug and polymer were subjected to ethanol assisted wet co-grinding. The optimized formulation was used to prepare ODT tablets using Pharmaburst® 500 and Ludiflash® as new ODT fillers. Results: Co-precipitated products showed significant improvement in drug dissolution compared to raw SIM. Presence of Aerosil further improved dissolution parameters. Solid state characterization indicated drug-polymer compatibility and reduction in crystalline nature of SIM. Co-precipitation was superior to kneading technique. The optimized co-precipitated formula was successively used to prepare ODT. Based on the quality control studies, tablets prepared using Pharmaburst® 500 were better to those prepared using Ludiflash® concerning dissolution parameters. Conclusion: The study introduced Soluplus® as promising dissolution enhancer with Pharmaburst® 500 as new filler for tablet manufacture.

**KEYWORDS:** Soluplus®, simvastatin, oral dispersible tablets, kneading, Pharmaburst® 500.

## INTRODUCTION

The development of a successful and effective oral medicine is often confronted with many obstacles. One such obstacle is that the drug bioavailability is considerably affected by its aqueous solubility, rate of dissolution and gastrointestinal permeability.[1] Bioavailability is becoming very important due to the increased number of new chemical entities with poor water solubility. Many potentially clinically important drugs will not reach the market pipe line unless their oral bioavailability is improved. Various strategies have been evolved in trials to overcome the dissolution problem of hydrophobic drugs such as, formation of inclusion complexes[2,3]; particle size reduction by micronisation or nanonisation [4,5]and formation of self-emulsifying drug delivery systems [6]

Solid dispersion is one of the most effective strategies to improve the solubility and dissolution rate for many drugs[7] However, a major limitation of solid dispersion is the thermodynamic unstablity problem of amorphous drug leading to re-crystallization during storage, especially in presence of residual traces of drug crystals. Therefore, complete transformation of crystalline drug to amorphous form and/or inhibition of recrystallization process are the key point to improve physical stability of solid dispersions.[8,9]

The majority of published research data or marketed solid dispersion products are based on hydrophilic polymeric carriers like polyvinylpyrrolidone, polyethylene glycol or hydroxypropyl methylcellulose or their combinations.[10] Others used solubilizing agents such as Poloxamer polymers.[11,12]

Soluplus®, Polyvinylcaprolactam–polyvinyl acetate–polyethylene glycol graft copolymer, is a new polymer with amphiphilic properties. This polymer performs the two functions; matrix former and solubilizer through micelle formation in water.[13] It was initialy designed for hot melt extrusion process. Solid dispersion of drug in Soluplus® was recognized as the fourth generation of solid dispersions.[14] Being non-ionic in nature, its solubility is not affected throughout the gastrointestinal tract. Due to its low glass transition temperature (around 70°C), Soluplus® could be used in both solvent evaporation as well as melting method for production of drug dispersions. Therefore, the dissolution rate of

several drugs in aqueous media was improved by Soluplus® using hot melt extrusion techniques.[15]

The present work has been performed to study dispersions of SIM in the newly introduced grafted copolymer, Soluplus®, with the aim of producing oral dispersible tablets (ODT).

Simvastatin (SIM) is a 3-hydroxy-3- methylglutaryl-coenzyme, a reductase inhibitor which is mostly used in the treatment of hypercholesterolemia. [16] As a BCS (Biopharmaceutics Classification System) class II drug, it is water-insoluble [17] and shows dissolution rate-limited absorption with low oral bioavailability.[18,19] Being a BCS Class II drug, the dissolution is a rate-limiting step that controls its oral absorption and high variability in pharmacological effects is expected[20] There are many investigations conducted to improve SIM dissolution via solid dispersion techniques using traditional hydrophilic polymers.[11,21]

The study, therefore, investigated the use of Soluplus® as solid matrix former for SIM adopting two industrially scalable techniques; solvent evaporation and kneading methods. The effect of addition of Aerosil 200 as third component to provide large surface area upon which drug/polymer composite would interact was also evaluated. The optimized solid dispersion formulation was used to prepare tablets for intraoral administration, using new co-processed ODT bases, in comparison to the traditional excipients.

## MATERIALS AND METHODS

### Materials

Simvastatin (SIM) was a generous gift from Sigma Co., Egypt. Soluplus® and Ludiflash® were provided by BASF (Ludwigshafen, Germany). Pharmaburst® 500 was obtained from SPI Pharma, New Castle, USA. Aerosil 200, Mannitol, crosspovidone and magnesium stearate were kindly supplied by Sigma Co., Egypt. All other chemicals were of analytical grade.

### Methods

#### Construction of the Calibration Curve

Calibration curve of Simvastatin in ethanol was constructed by preparing serial dilutions from ethanolic stock solution of the drug (1000 µg/ml) to obtain concentrations in the range of 2-12 µg/ml. The prepared samples were analyzed spectrophotometrically at λ max of 238nm using UV- spectrophotometer (Thermo, Evo300pc, USA). The obtained absorbance were recorded and plotted versus concentration. The standard curve was linear ($R^2$=0.996) over the range of concentrations determined.

#### Preparation of SIM-Soluplus® solid dispersions

Solid dispersion was prepared adopting two techniquess: solvent evaporation and kneading technique using different SIM: Soluplus® ratios, in presence and absence of Aerosil (Table 1).

##### *Solvent evaporation method*

Table (1) shows the composition of different formulations prepared by drug precipitation by evaporation of organic solvent in absence (F1- F3) and presence (F4-F6) of Aerosil as carrier. In a clean and dry mortar, the calculated amount of SIM and Soluplus® were dissolved in the least amount of ethanol to obtain a clear solution. Aerosil, if present, was then dispersed and ethanol was allowed to evaporate by the aid of continues trituration using a pestle at ambient temperature. The obtained coprecipitate particles were kept in a desiccator overnight and then stored in air-tight containers till use.[21]

**Table 1: The composition of different solid dispersion formulations of simvastatin (SIM), with dissolution parameters represented as percentage amount drug released after 5 minutes (Q5) and percentage dissolution efficiency (%DE).**

| Code | Drug | Soluplus® | Aerosil | Q5 | DE (%) |
|---|---|---|---|---|---|
| Pure SIM | | | | 6.62± | 9.70 |
| F1 | 1 | 1 | --- | 19.5± | 38.5 |
| F2 | 1 | 3 | --- | 35.0± | 58.9 |
| F3 | 1 | 5 | --- | 81.2± | 94.2 |
| F4 | 1 | 1 | 0.5 | 26.8± | 44.6 |
| F5 | 1 | 3 | 0.5 | 47.6± | 75.8 |
| F6 | 1 | 5 | 0.5 | 92.7± | 95.0 |
| F7 | 1 | 1 | --- | 16.2± | 33.3 |
| F8 | 1 | 3 | --- | 33.4± | 53.9 |
| F9 | 1 | 5 | --- | 41.8± | 57.2 |
| F10 | 1 | 1 | 0.5 | 21.2± | 40.2 |
| F11 | 1 | 3 | 0.5 | 36.6± | 56.9 |
| F12 | 1 | 5 | 0.5 | 46.9± | 62.7 |
| PM | 1 | 5 | 0.5 | 30.5± | 53.2 |

*PM: physical mixture*

***Kneading method***

Table (1) shows the composition of formulations prepared in absence (F7-F9) and presence of Aerosil (F10-F12). The required amount of SIM was dissolved in the least volume of ethanol to obtain clear solution. This solution was poured onto Soluplus® and Aerosil (if present), triturated with a pestle till evaporation of the solvent and drying to form flowable powder.[22] The product was kept in a desiccator overnight and then stored in air-tight container till use.

**Preparation of physical mixtures**

The physical mixture of selected formulation was prepared by geometric mixing using mortar and pestle (Table1).

**Drug content**

The drug content was determined for formulations by dissolving an amount equivalent to 20 mg of the drug in a 20 ml ethanol. The resultant liquid was centrifuged for 10 minutes at 2000 rpm. The clear solution was suitably diluted with ethanol before spectrophotometric determination of the drug concentration.

**Solid state characterization**

***Differential thermal analysis (DTA)***

The thermal behavior of unprocessed SIM, Soluplus®, Aerosil 200 and selected formulations was investigated. The study employed differential thermal analyzer (PerkinElmer STA 6000 module, Waltham, MA). Each powder sample (about 5mg) was placed in aluminum pan which was carefully crimped. The thermal analysis of each sample was conducted at the temperature range of 25 to 400 ºC with the samples being heated at a rate of 10$^{o}$C per minute. The recorded data were analyzed using Pyris software.

***Fourier–transform infrared spectroscopy (FTIR)***

FTIR spectra of unprocessed SIM, Soluplus®, Aerosil 200 and selected formulations were recorded using FTIR system (Bruker Tensor 27, Ettlingen, Germany). Each test powder was mixed with potassium bromide (spectroscopic grade) before compressing into disk which was subjected to scanning from 5000 to 400 $cm^{-1}$.

***Powder X-ray diffraction (PXRD)***

The crystalline structure of unprocessed and processed SIM, Soluplus® and Aerosil was conducted using powder diffractometer (Crystal Impact, Bonn, Germany). Data collection was conducted at ambient temperature, using 2theta scan axis. This utilized continuous scanning mode (step size of 0.03˚) and scan range of 3–65˚.

**Preparation of Oral Dispersible Tablets (ODTs)**

Solid dispersion formulation showed the best dissolution parameters were used to prepare ODT by direct compression technique. The selected solid dispersion was mixed with readily made filler. Two different fillers specially designed for ODT were used, namely Ludiflash® and Pharmaburst® 500. For comparison, control tablets containing unprocessed drug and conventional ODT excipients were prepared. Each tablet was prepared to contain an amount equivalent to 20 mg of the drug. Preparation of tablets involved mixing the tablet ingredients according to the formulations presented in Table (2). Mixing operation was achieved according to geometric order strategy in glass bottle. The mixtures were compressed by 10 mm punch into tablets of suitable hardness (4-5 kp). This was achieved using single punch tablet press (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India).

**Table 2: The master formula used for the preparation of oral disintegration tablets.**

| Ingredients (mg/tablet) | Cont tab. | Ludif tab. | Pharmb tab. |
|---|---|---|---|
| SIM or an equivalent weight of F6 | 20 | 132.6 | 132.6 |
| Ludiflash® | - | 217.4 | - |
| Pharmaburst® 500 | - | - | 217.4 |
| Mannitol (granular) | 311 | - | - |
| Crospovidone | 17 | - | - |
| Magnesium stearate | 2 | - | - |
| Total weight | 350 | 350 | 350 |

*-The amount of solid dispersion is equivalent to 20 mg simvastatin based on the recorded drug content*.

**Flow properties of the powder blends**

Flowability studies were conducted for each tablet powder mixture prior to compression to ensure acceptable flow characteristics to ensure dose uniformity among the tablet batches. This was conducted by measuring Carr's compressibility index (CI) and Hausner ratio (HR).

The bulk density ($D_b$) was determined by pouring a weighed amount of each powder blend (M) into a graduated cylinder and the bulk volume ($V_b$) was determined. The bulk density was calculated by dividing M over $V_b$. The tapped density ($D_t$) was determined through tapping the measuring cylinder containing the powder for 15 minutes or until fixed volume is obtained. The volume occupied ($V_t$) in the cylinder was measured and the tapped density was calculated by dividing mass M over $V_t$. For each sample, Carr's compressibility index (CI) was calculated according to the following equation: CI =100 ($D_t$ - $D_b$ / $D_t$). Additionally, Hausner ratio (HR) was also calculated using the following equation: HR= $D_t$ / $D_b$. [23]

**Evaluation of Oral Dispersible Tablets**

***Tablet Hardness***

The average hardness of 10 randomly selected tablets was determined using Erweka hardness tester.

***Tablet friability***

This test utilized Erweka friability tester (Heusenstamm, Germany). The weight of 10 tablets was recorded before and after being subjected to 100 rotations. The percentage loss was calculated and was taken as a measure for the friability with the tablets being accepted if the friability not exceeding1%.[24]

***Disintegration test***

The in vitro disintegration test was carried out using 6 tablets using disintegration apparatus (Copley Scientific, Nottingham, UK). Distilled water warmed to 37 °C was used as disintegration medium. [24]

***Wetting time***

Wetting time is closely related to tablet porosity and/or the hydrophilicity of the excipients. A piece of folded filter paper was placed in a Petri dish and wetted with 6 ml of water. Allura red dye was sprinkled on the tablet surface before placing on the wetted filter paper. The time required for developing a red color on the surface of tablet was recorded and taken as the wetting time.[25]

**In vitro Dissolution studies**

The dissolution rate of SIM from different formulations (micro-particles, physical mixtures and Tablets) was determined using the USP dissolution apparatus type II (Copley, NG 42 JY, Nottingham, UK). The dissolution medium was distilled water containing 0.1% w/v sodium lauryl sulphate maintained at 37 ºC $\pm$0.5 ºC. The paddle rotation was adjusted to 50 rpm.[21]

For the prepared solid dispersions, an amount equivalent to 20 mg of SIM was used. For comparison, 20mg of raw drug was taken as control. For oral dispersible tablets, one tablet (containing 20mg of SIM or its equivalent) was loaded per dissolution vessels. Samples of 5 ml each were taken at predetermined time intervals for 60 minutes and immediately replaced with fresh dissolution medium. The samples were filtered through 0.45 mm Whatman membrane filter before spectrophotometric analysis for drug content, after suitable dilution when necessary. The cumulative amount of SIM dissolved (expressed as % of the labeled amount) was plotted as a function of time to produce the dissolution profiles. The dissolution parameters were extracted from each profile and expressed as percentage amount liberated in the first 5 minutes (Q5) and the dissolution efficiency (DE) expressed as percentage.

**Statistical Analysis**

All experiments were conducted in triplicates and statistical analysis employed Student *t*-test. Results were quoted as significant when $P < 0.05$.

**RESULTS AND DISSCUSION**

**Solid state characterization of the prepared formulations**

The drug content values of the prepared formulations were in the range of 96.4 – 99 % w/w, indicating good recovery of the drug after processing.

**Differential thermal analysis (DTA)**

Thermal analysis was employed to investigate the crystalline nature of the drug before and after processing. Thermograms of raw SIM, Soluplus®, Aerosil 200 and selected formulations (F6, F12 and physical mixture SIM/ Soluplus®/Aerosil 1:5:0.5) are shown in Figure 1.

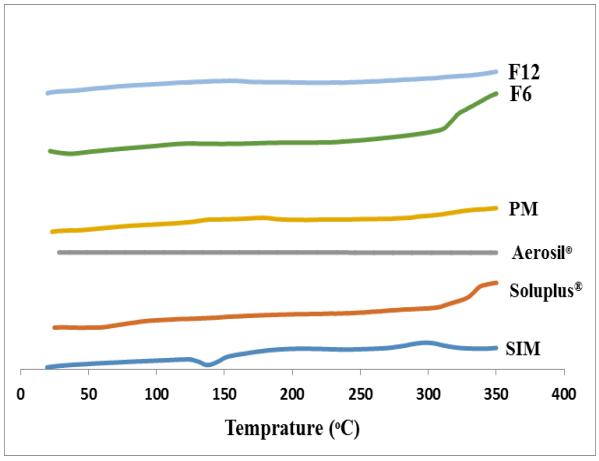


**Figure 1: DTA thermograms of raw simvastatin(SIM), Soluplus®, Aerosil 200, solid dispersion formulations F6 and F12 and Physical mixture (PM). For detailed formulations refer to Table 1.**

The DTA traces of unprocessed SIM were characterized by broad endothermic peak with an onset of 118.8°C, endset of 155°C and Tm of 137.6°C. This endotherm corresponds to the melting transition of SIM and can be taken as indication of its crystalline nature. This thermal event is similar to that reported by other investigators.[11,21] In addition to the main endothermic peak, the thermogram showed very broad enodtherm at 311.5°C that can be taken as a thermal event of drug decomposition. The thermogram of Soluplus® showed a broad melting transition peak at with a Tm of 66.3°C. Another broad exothermic peak with Tm of about 340°C could be taken as, polymer decomposition. [26]

For Aerosil, the thermogram showed the characteristic behavior of an amorphous substance with no endothermic or exothermic peak being recorded. This pattern agrees with published data for the same material.[27]

The tested formulations showed complete disappearance of the drug main transition suggesting conversion of crystalline drug into amorphous form or eutectic mixture formation with the polymer, regardless of the adopted

technique of preparation This requires further confirmation by X-ray diffraction.[28]

Unexpectedly, the melting transition of SIM was hardly detectable for physical mixture (SIM/ Soluplus®/Aerosil 1:5:0.5). This could be due to possible drug solubility in the molted Soluplus® that melts are lower temperature. Analogous phenomena have been previously reported by other investigators and were similarly explained.[29,30]

**Fourier–transform infrared spectroscopy**

FTIR spectroscopy was used to study the possible interaction between SIM, Soluplus® and Aerosil. FTIR spectrum of pure SIM shows peaks of free OH stretching vibration at 3590 $cm^{-1}$, CH stretching vibrations appears at 3011, 2959, 2872 $cm^{-1}$. For the ester and lactone carbonyl functional group, stretching vibration is noted at 1714 $cm^{-1}$. Similar spectrum of the same drug was reported.[11,21]

For Soluplus®, the spectrum showed OH stretching vibration as 3448 $cm^{-1}$, aromatic CH stretching at 2927.98 $cm^{-1}$. The spectra also show two peaks at 1735 $cm^{-1}$ and 1635 $cm^{-1}$for CO stretching vibration. Similar spectrum was reported by other investigators.[26]

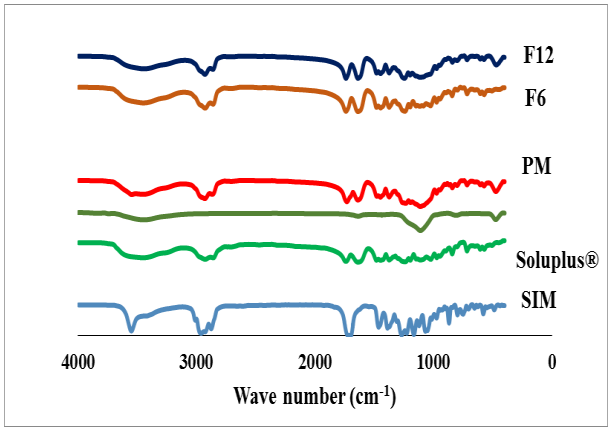


**Figure 2: FTIR spectra of of raw simvastatin(SIM), Soluplus®, solid dispersion formulations F6 and F12 and Physical mixture(PM). For detailed formulations refer to Table 1.**

The spectrum of Aerosil showed very broad absorption band in the range of 3700 and 3100 $cm^{-1}$. This peak corresponds to hydrogen bonding of the adsorbed water or water of crystallization and oxygen of the silica. The Si-O group stretching appeared at about 1200 $cm^{-1}$. Similar spectrum was recorded by other investigators with peaks being assigned similarly.[31]

FTIR spectrum of the selected formulations (F6 and F12) revealed reduction in the carbonyl functional group at 1714 $cm^{-1}$. This may be attributed to possible interaction between the SIM and Soluplus® copolymer leading to formation of hydrogen bonding as shown by broadening of the OH peak. Also the conversion of SIM from the crystalline form to the amorphous form in the solid dispersion that made the peaks of SIM become weaker and more broaden. Physical mixture showed compromised spectra of both materials, indicating no interaction.

**Powder X-ray Diffraction study**

The X-ray powder diffractogram of the raw SIM demonstrated its crystalline nature as shown by its various sharp peaks at 2θ values of 27.0°, 21.4°, 19.2°, 17.5°, 16.9°,13.8°, and 10.3° (Figure 3). These values are in good agreement with published data for the same drug[11,21]. For physical mixture, the characteristic peaks of SIM can be detected with reduced intensity. This confirms our previous assumption for the DTA that SIM endothermic peak disappearance was due to its dissolution in the melted base and not due to amorphous formation. For the tested solid dispersion formulations, the drug characteristic diffraction peaks has completely disappeared indicating transformation to amorphous form. These findings agree with the results of the DTA data.

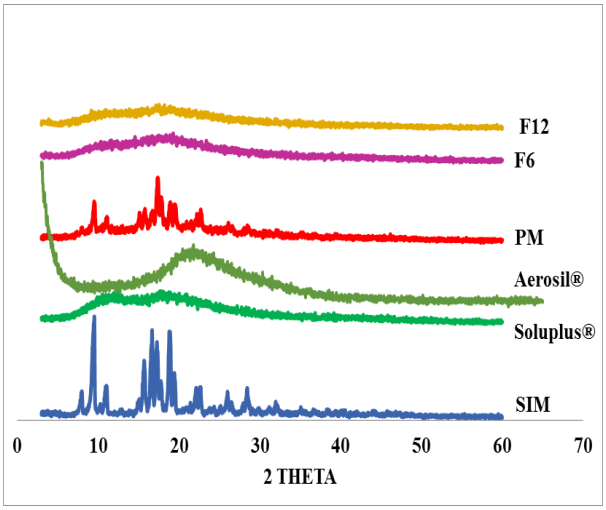


**Figure 3: X-ray diffraction pattern of of raw simvastatin(SIM), Soluplus®, Aerosil 200, solid dispersion formulations F6 and F12 and Physical mixture(PM). For detailed formulations refer to Table 1.**

**In vitro drug release from prepared formulations**

The main aim of this study was to improve the aqueous solubility of SIM using hydrophilic polymer in order to prepare oral dispersible tablets. Soluplus® is one of the recently introduced co-processed polymers used to improve drug dissolution. Soluplus® is considered as one of the fourth generation of solid dispersions matrix and reported to achieve a high degree of dissolution enhancement of poorly water soluble drugs as well as stabilizer for the solid dispersion.[13,26] According to the manufacturer, this grafted copolymer consists of polyvinyl caprolactam30%, polyvinyl acetate 13% and polyethylene glycol 6000 57%.[32] For these reasons, Soluplus® was selected as matrix former and stabilizer for SIM. Solid dispersion of drug:Soluplus® microparticles were prepared by solvent evaporation and

kneading techniques. The microparticles were prepared in presence and absence of Aerosil 200.

The dissolution profiles of SIM from the raw powder and the prepared formulations are shown in Figure 4.The dissolution parameters represented as the percentage drug released after 5 min ($Q_5$) and dissolution efficiency (DE) are present in Table 1. The latter was calculated using the trapezoidal rule and presented as the area under the dissolution profile at time t relative to the area of the rectangle described by 100% dissolution in the same time.[33]

The dissolution profile of pure SIM showed poor dissolution pattern as reflected by Q5 of only 6.6% (Table 1). The dissolution efficiency value of 9.7% indicates its poor dissolution due to poor solubility of the lipophilic drug. Similar findings were previously reported.[11,21]

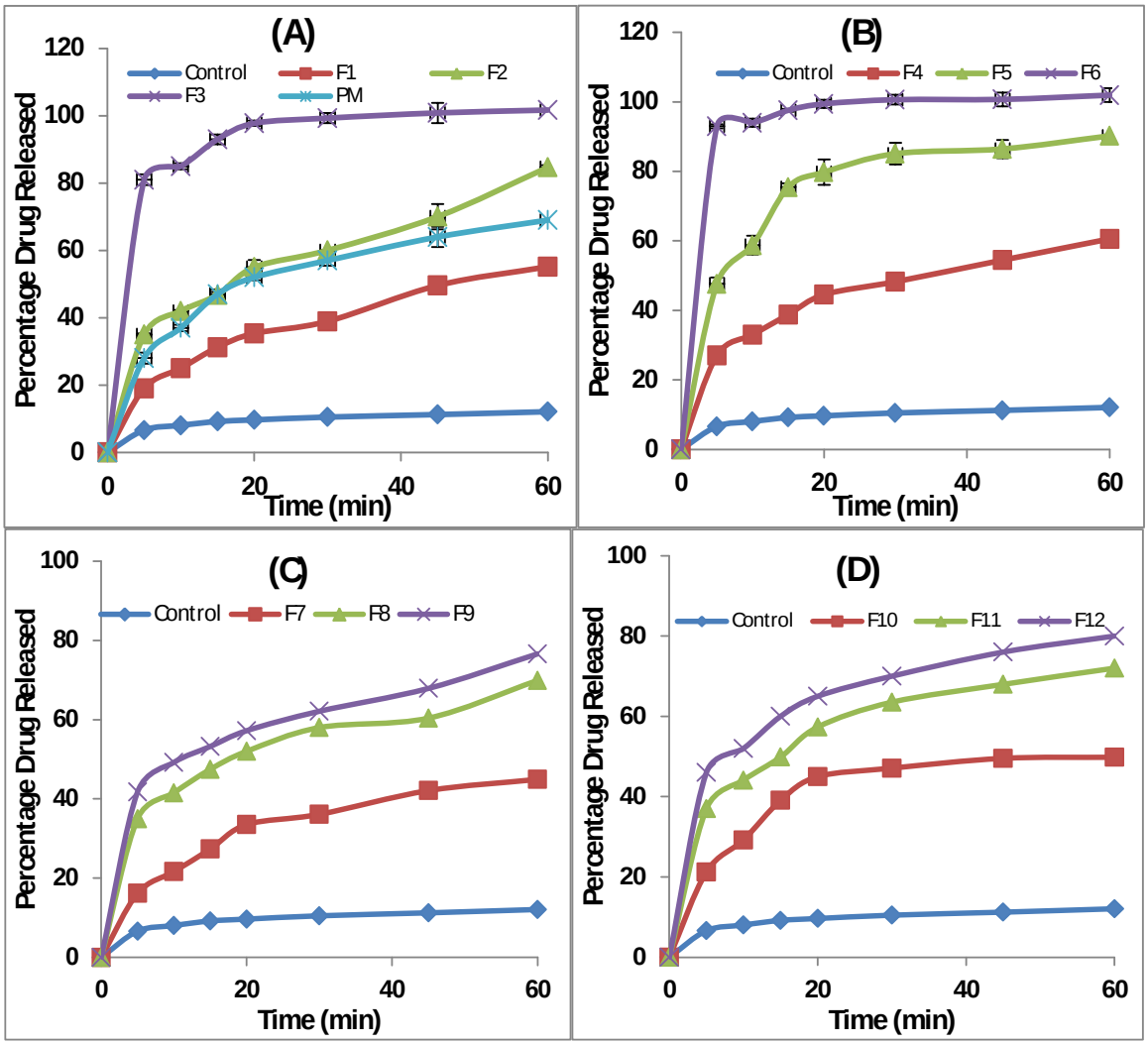


**Figure 4: In vitro dissolution of simvastatin from solid dispersion formulations prepared using solvent evaporation technique in absence (A) and presence (B) of Aerosil 200, as well as Solid dispersion prepared by kneading technique in absence (C) and presence (D).of Aerosil 200. For detailed formulations refer to Table 1.**

Preparation of SIM by solvent evaporation technique produced drug microparticles with significantly higher dissolution rate compared to the unprocessed one (Figure 4A and B). At low Soluplus® concentration (F1), about 20% of the loaded dose was liberated after 5 minutes, with similar improvement in dissolution efficiency (Table 1). Increasing Soluplus® concentration had substantial effect on drug release rate with the dissolution parameters being highest in F3 (1:5 drug:Soluplus®) with the release of 81% of the loaded dose after 5 minutes (Table 1). Such rapid release pattern is advantageous for poorly soluble drugs, especially those suffering from first pass metabolism. The significant increase in SIM dissolution could be attributed to the presence of SIM in an amorphous state as evidenced from the DTA and X-ray diffraction data. Therefore, there was no energy needed to overcome the lattice structure of drug crystals. Moreover, drug wettability increased due to the hydrophilic polymer with hydrogen bonding playing significant role in increasing drug solubility as evidenced by the FTIR data. Polymeric

micellar solubilization due to Soluplus® could be another contributing factor.[34]

Incorporation of Aerosil as third component to drug/polymer composite had a significant impact on drug dissolution (Figure 4B). Formulation F4, F5 and F6 showed Q5 of about 27, 47 and 93, respectively. The dissolution efficiency values were similarly increased (Table 1). Presence of Aerosil during evaporation of the organic solvent provided large surface area upon which drug and polymer would precipitate as thin film around the carrier particles. This will increase the surface area with the drug dissolution rate increasing accordingly.

The dissolution profiles of SIM from formulation prepared by kneading technique are presented in Figure 4 C and D. Though drug dissolution was improved relative to control, however it was to a lesser extent compared to same compositions prepared by solvent evaporation method, this due to kneading method consume only few drops of organic solvent but in solvent evaporation, more organic solvent were added to ensure the solubilization of soluplus and simvastatin. consequently,Solid dispersions produced by solvent methods tend to have a highly porous structure induced by the fast solvent removal and leading to increased drug dissolution rate.[35]

The percentage drug released after 5 minutes was 16, 33 and 42 for F7, F8 and F9, respectively. The total drug released and dissolution efficiency was increased in the same manner (Table 1). It worth nothing that addition of Aerosil during the kneading process did not show considerable impact on drug dissolution (Figure 4D). There was a slight improvement in dissolution parameters for F10 through F12, that were statistically non-significant ($P>0.05$) compared to those prepared in absence of the carrier (Table 1). This would suggest that Aerosil plays a considerable role only in solvent evaporation.

The results reveal that formulations prepared by solvent evaporation technique were superior to those prepared using kneading method. Among the tested formulations, F6 (SIM/soluplus®/Aerosil in 1:5:0.5 weight ratio) was selected as the optimum formulation. For comparison, the physical mixture of the same components of formula F6 was prepared. The dissolution profile of SIM from the physical mix (Figure 4A) showed slight improvement in SIM dissolution rate that was significantly ($P > 0.05$) less than F6. Such improvement could be due to increased drug wettability due to Soluplus®. Additionally, reduced drug particle size, as evidenced by X-ray data, is also a potential reason.

**Preparation of the powder blends for oral dispersible tablet**

Based on the recorded dissolution results, F6 were selected to prepare the oral dispersible tablets. The study employed two different ODT co-processed fillers namely pharmaburst®500 and ludiflash®. Pharmaburst®500 was found to be significantly more compactable, less friable, and more rapidly disintegrating. Pharmaburst®500 is a co-processed excipient system which allows rapid disintegration and low adhesion to punches. It has smooth and creamy mouth feel and helps to mask taste and grittiness of the medicaments. Main advantages Pharmaburst®500 is highly compatible, rapid disintegration and cost effective. [36,37]

Ludiflash is filler which designed for fast disintegrating dosage forms. It disintegrates readily within a few seconds in oral cavity with pleasant mouth feel. It gives extremely fast release rate. It has neutral to mildly sweet, pleasant taste and sugar free composition.[38]

Tablets were formulated to contain 20 mg of unprocessed drug (control tab) or an equivalent amount of solid dispersion formula F6. Ludiflash Tab and Pharmaburst Tab prepared solely of co-processed fillers ludiflash® and pharmaburst®500 respectively, while Cont Tab prepared to contain traditional excipients for ODT (Table 2). Tablets were prepared by direct compression method, after using suitable formulation aids, according to compositions shown in Table (2). During compression, it was noticed that Pharmaburst®500 was more compactable compared to Ludiflash®.

Prior to compaction, flow properties of different tablet formulations were tested to ensure the attainment of dose uniformity. Carr's compressibility index and Hausner ratio were determined and results are shown in Table 3. For good powder flowability the bulk density and tapped density should be close in value, indicating low inter-particular interactions. All formulations, showed an acceptable powder flow properties and compactability and were suitable for manufacture of tablets for Pharmaburst Tab powder and Ludiflash Tab powder with Hausner ratio of less than 1.25, this could be due to presence of Aerosil. Regarding Cont Tab, powder blend showed slightly higher values. Results of Carr's compressibility indices correlate well with Hausner ratio values. The superiority of Pharmab powder blend could be due to inclusion of Aerosil as one of the components of the filler. Aerosil may improve flow properties by decreasing the electrostatic interaction between powder particles. [39]

The recorded friability values were in the range of about 0.17 –0.9%. This is acceptable according to the acceptance criteria of the US Pharmacopea.[24] For wetting time was 30, 35 and 40 seconds for Pharmb, Ludifl and Cont tablets, respectively (Table 3).

The recorded disintegration time values for Pharmab, Ludifl and Cont tablets were 25, 46 and 42 seconds, respectively. These values are acceptable for Pharmab tablets taking into consideration the FDA specification of orodispersible tablets recommending a disintegration time of less than or equal to 30 seconds when determined

according to USP method.[24,39] This could be due to the fact that upon compression, pharmaburst®500 granules converts to microparticles which increase tablet porosity and consequently disintegration.[37] Tablet hardness ranged from 4.2Kp to 4.8Kp which is acceptable for oral dispersible tablets.

The dissolution profiles of tablets are presented as cumulative percentage drug released versus time plots in Figure 5. Tablets prepared to contain raw SIM showed slow drug release with Q5 of only 10% with the overall amount released after 60 minutes of 28%. This release behavior could be attributed to the hydrophobic nature of the drug. Tablet batches prepared using co-processed fillers showed better performance with improved dissolution parameters compared to Cont Tab. Tablets prepared using Pharmaburst®500 showed a rapid release of 83% of the loaded dose in the first 5 minutes. This value was significantly higher ($P < 0.05$) than that for Ludiflash® Tab that liberated about 70% of labeled dose. The dissolution efficiency values were 22, 74 an 87% for Control, Ludiflash and Pharmaburst tablets, respectively. This indicates the superiority of ODT fillers as base for oral disintegrating tablets.

**Table 3: Results of powder flowability, tablet quality control study, and in vitro dissolution parameters of different oral dispersible tablets represented as percentage drug released after 5 min (Q5) and% dissolution efficiency DE (%).**

| | Powder flowability | | Hardness | Friability | Wetting time (sec) | Disintegration (sec) | Q5 | DE(%) |
|---|---|---|---|---|---|---|---|---|
| | Hausner ratio | Carr's Index% | | | | | | |
| Pharmab Tab | 1.13 | 12 | 4.5±0.3 | 0.7% | 30± 2 | 24± 0.8 | 83±2.6 | 87.2 |
| Ludifl Tab | 1.24 | 19.7 | 4.8±0.5 | 0.2% | 35 ±4 | 46± 1.3 | 70± 1.5 | 74.4 |
| Cont Tab | 1.26 | 21.4 | 4.4±0.5 | 0.9% | 40± 6 | 42± 0.9 | 10.4±0.5 | 22.1 |

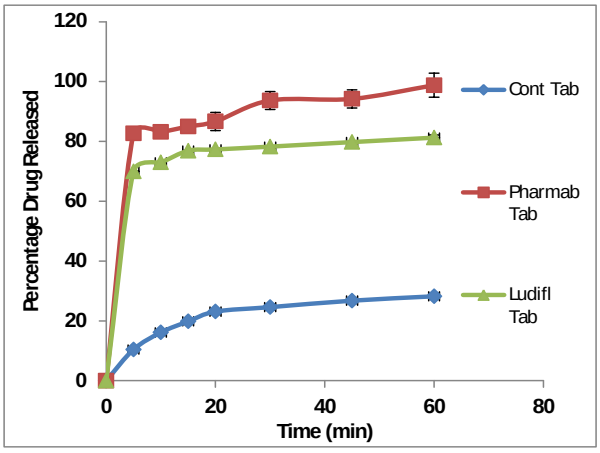


**Figure 5: In vitro dissolution of simvastatin from oral dissolution tablets. Detailed formulations are presented in Table 2.**

According to the manufacturer specifications Ludifalsh® contains Kollicoat SR 30D (polyvinyl acetate) up to 5%. This may resulted in the slow tablet disintegration due its binding properties that affected the overall tablet properties. In adittion to Pharmaburst® contain three superdisintegrants crospovidone, croscarmellose sodium and sodium starch glycolate but Ludiflash® contains only crospovidone as a super disintegrant.[37,38]

These findings are in good agreement with other investigations where Ludifalsh® decreased carvedilol release from oral dispersible tablets relative to Pharmaburst®500.[26]

## CONCLUSION

Soluplus®, a hydrophilic polymer initially designed for hot melt extrusion, was investigated to increase dissolution of simvastatin using solid dispersion techniques. Drug polymer composite was prepared by solvent evaporation and kneading techniques. Aerosil 200 was included as third component in some formulations, providing large surface area. Drug dissolution was greatly enhanced from co-precipitated micrparticles relative to those prepared by kneading; the enhancement was even greater in presence of Aerosil 200. The best formula was successively utilized to develop oral dispersible tablets using new ODT fillers. Tablets prepared using Pharmaburst®500 was superior to those prepared using Ludiflash®.

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