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Dissolution enhancement of olmesartan medoxomil through polymer-based surface solid dispersion and solidified surfactant techniques

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Abstract: This study aims to formulate Olmesartan medoxomil (OM) into oral fast-dissolving tablets (FDTs) to improve its solubility and bioavailability via two different techniques; the polymer-based surface solid dispersion (SSD) technique and the solidified surfactant (SS) technique. In the first technique, two polymers were used; polyvinylpyrrolidone (PVP K90) and Poloxamer 407 (Pluronic®F127), while in the second technique the liquid Tween 80 was solidified by adsorption onto Aeroperl®300. The pre-compression and post-compression parameters of the obtained formulations were assessed. The best formulations were subjected to a taste masking evaluation and a short-term stability study. The results demonstrated that, in comparison to the pure drug, the proportion of drug released from each of the prepared FDTs considerably increased. Results of the stability studies showed that the chosen drug formulations remained stable throughout the storage period.

Keywords: Olmesartan medoxomil, fast-dissolving tablets, polymer-based surface solid dispersion, solidified surfactant.

INTRODUCTION

In the pharmaceutical industry, developing poorly soluble drugs is now a major challenge. This problem is predicted to worsen since approximately 40% or more of newly discovered chemical compounds have poor water solubility (Essa *et al.*, 2017).

For drugs with limited water solubility, a number of techniques have been developed to enhance their solubility, dissolution and bioavailability, including micronization, micro-emulsions, inclusion complexes using cyclodextrins, solid lipid nanoparticles, solid dispersions, surface solid dispersions, liquisolid technique, combining quasi-emulsion and crystallo-coagglomeration methods and nanosuspension (Essa *et al.*, 2017; Abd-El Bary *et al.*, 2014; Hasan *et al.*, 2020; Makar *et al.*, 2020; Al Ashmawy *et al.*, 2021; Jaipakdee *et al.*, 2022).

Surface solid dispersion method overcomes the limitations of solid dispersion formulated using water-soluble carriers, such as tackiness and product handling problems especially in tablet making. In this technique, the drug is deposited onto the surface of an inert carrier, which causes the drug's particle size to be reduced, allowing for rapid dissolution. In contrast to the usual solid dispersion, the carriers chosen in the surface solid dispersion are porous, insoluble in water and hydrophilic in nature. When they come into contact with water, they disperse instantly, releasing the drug particles into the medium rapidly (Abd-El Bary *et al.*, 2014; Hussein *et al.*, 2021). Various hydrophilic carriers of large surface areas can be used for drug deposition on their surfaces, including silicified microcrystalline cellulose, Explotab, Avicel, silicon dioxide, potato starch, crospovidone and croscarmellose (Lalitha and Lakshmi, 2011).

Surface solid dispersion was found to improve the solubility and dissolution rate of various poorly soluble drugs (Meka *et al.*, 2012; Hussein *et al.*,2021).

To make use of the advantages of both solid dispersion and surface solid dispersion methods, we have introduced the so-called polymer-based surface solid dispersion in which the drug is first dissolved with a water-soluble hydrophilic polymer in a common solvent, then the dissolved mixture was added to the surface of a water-insoluble hydrophilic carrier in order to achieve in a more enhancement in the drug dissolution rate in comparison to the solid dispersion or surface solid dispersion alone. This technique when coupled with product development into fast dissolving tables (FDTs) is expected to further enhance the solubility of the drug.

The liquisolid technique is one of the previously mentioned techniques which have been used for enhancement of the dissolution rate of a variety of drugs. A liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solutions in non-volatile solvents into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carrier and coating materials (Tiong and Elkordy, 2009). In the present work, such technique was modified by the

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solidified surfactant technique in which a liquid surfactant, tween 80, was mixed with an inorganic carrier, Aeroperl, till complete drying to form solidified surfactant powder. The obtained dry powder was then mixed with the drug. Thus, a free flowing and compressible powder can be obtained and a high dissolution rate of the drug is expected due to the solubilizing effect of the surfactant.

Olmesartan medoxomil (OM) is a drug approved by the FDA to selectively inhibit angiotensin II type I receptors to treat high blood pressure (Pavani and Sankar, 2021). OM is also known to have a low risk of side effects and has shown significant tolerance in a variety of patient populations over time, making it one of the safest and most effective antihypertensive drugs for long-term usage (Beg *et al.*, 2021). Despite its usefulness, OM has a challenge with its delivery via the oral route due to its low solubility, limited permeability and varying systemic availability (Beg *et al.*, 2021). The Biopharmaceutical Classification System classifies it as a Class II drug (BCS) (Dhavalkumar and Ajaykumar, 2013).

Olmesartan medoxomil is commercially available as conventional tablets having strengths of 10 and 20 mg (Moffat *et al.,* 2011).

Various techniques for improving OM solubility have been previously reported in the literature, including solid dispersion (Kala and Chinni, 2021) surface solid dispersion (Abd-El Bary *et al.*, 2014), ionic-gelation technique (Alsofany *et al.*, 2018), ternary solid dispersion (Zhang *et al.*, 2020), solid lipid nanoparticles (Pandya *et al.*, 2018), phospholipid-based nano-mixed micelles (Beg *et al.*, 2021) and formulation of nano-suspensions (Attari, 2016).

The aim of this study was to improve the solubility and rate of dissolution of OM by formulating it as fast dissolving tablets (FDTs) using two different innovative techniques: the polymer-based surface solid dispersion (SSD) technique and the solidified surfactant (SS) technique. In the SSD technique, various concentrations of PVP or Pluronic were used as hydrophilic polymers and microcrystalline cellulose (Avicel PH 101) was used as a water-insoluble hydrophilic carrier to form a polymer-based surface solid dispersion. In the SS technique, the liquid Tween was loaded onto Aeroperl, which was used as a carrier, to form solidified Tween. The powders obtained from both techniques were directly compressed into tablets, which were then assessed for thickness, weight variation, hardness, friability, wetting time, disintegration time and *in vitro* drug release. The optimum formulations were subjected to taste masking evaluation on human volunteers and a short-term stability study for three months.

MATERIALS AND METHODS

Materials

Olmesartan medoxomil (OM) was graciously donated by Sabaa International Company for the pharmaceutical and chemical industries, Egypt. Crospovidone, Aerosil and Aspartame were gift samples donated by the Sigma Pharmaceutical Industries Company, Egypt. Stevia was purchased from Toyo Sugar Refining Co., Ltd, Tokyo, Japan. Poloxamer 407 (Pluronic®F127), polyvinylpyrrolidone (PVP K90), Aeroperl®300 and tween 80 were provided as gift samples by Pharco Pharmaceutical Industries, Egypt. Orange flavor, Avicel PH 101 and mannitol were purchased from Chemical Industries Development Company (CID), Cairo, Egypt. Analytical grade was used for all other excipients, reagents and solvents.

Methods

Preparation of the polymer-based surface solid dispersion (SSD) powder

Accurately weighed amounts of PVP or Pluronic in different proportions (1, 2, 3, & 5%) were completely dissolved in the least amount of methanol with OM, then added to Avicel in a petri dish followed by continuous simple mixing for 5 minutes, then kept for 24 hours at room temperature till complete evaporation of the solvent. The obtained SSD powder was ground, passed over sieve no. 60 (250µm) and maintained for at least 24 hours in a desiccator containing anhydrous calcium chloride.

Preparation of the solidified surfactant (SS) powder

Solidified surfactant (SS) powder was prepared by thoroughly mixing the inorganic carrier Aeroperl with the surfactant tween in a mortar for 20 minutes at ratios of 50:50 and 70:30 Aeroperl: Tween respectively and kept at room temperature for 24 hours till complete drying to form solidified surfactant (SS) powder. The obtained SS dry powder was sieved with a sieve no. 60 (250µm) to obtain particles of uniform size. Accurately weighed amounts of OM and SS powder were then thoroughly mixed at ratios of 1:5, 1:10 and 1:15 respectively.

Saturated solubility testing

This test was implemented to determine the effect of PVP, Pluronic, Aeroperl and Tween on the solubility of the drug in simulated saliva. The solubility of OM in simulated saliva was determined both in its pure form and in a physical mixture in the ratio of 4:1 with PVP, Pluronic or Tween and in the ratio of 4:1:2 with PVP/ Avicel, Pluronic/Avicel or Tween/Aeroperl respectively for each mixture. Thus, excess amounts of the pure drug or mixture were added to conical flasks with a capacity of 25mL each holding 20mL of simulated saliva and maintained under magnetic stirring at 25° for 6 hours, then the flasks were removed and kept aside for 24 hours to reach equilibrium. The samples were then measured by spectrophotometric analysis at 256nm to determine the

drug dissolved after filtration and suitable dilution. Each result was recorded as the mean of three determinations (Maulvi *et al.,* 2011).

Preparation of fast dissolving tablets (FDTs) of OM

The ingredients of the prepared tablet formulations are shown in tables 1 and 2. The dry powder mixture containing the drug and all excipients other than magnesium stearate and talc powder, were thoroughly mixed in a geometric order. Magnesium stearate and talc powder were then added and blended for up to 5 minutes. Finally, the powder blend corresponding to 30 tablets of each formulation was then directly compacted into tablets in a single punch tablet machine with 8mm flat punches (Erweka, GmbH, Germany). Each tablet total weight was adjusted to 200mg and 250mg in the SSD and SS techniques respectively by varying the amount of Avicel.

Pre-compression parameters of FDTs of OM

Measurements of the repose angle, compressibility index, Hausner's ratio (Akdag *et al.*, 2020), bulk and tapped densities (Alyoussef *et al.,* 2017) were made to evaluate the powder blends.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectrophotometer (Shimadzu IR-345-U-04, Japan) was used to obtain the FTIR spectra of the pure drug, Pluronic, PVP, Aeroperl and the physical mixture of the pure drug with each excipient. The FTIR spectra were obtained by the potassium bromide disk method in a scanning range of 400 to 4000 cm^{-1} (Attari, 2016).

Differential scanning calorimetry (DSC)

DSC thermograms of the pure drug, Pluronic, PVP, Aeroperl and the physical mixture of the pure drug with each excipient were obtained using a differential scanning calorimeter (DSC-60 Shimadzu, Japan). All DSC tests were conducted under a nitrogen environment (Attari, 2016).

Powder X-Ray diffractometry (PXRD)

Using an X-ray diffractometer at room temperature, the PXRD patterns of the pure drug and the optimal formulation of the SSD and SS techniques were obtained (Brucar D8 Discover-Germany) (Zhang *et al*., 2020)

Scanning electron microscopy (SEM

Utilising a scanning electron microscope (Quanta FEG 250 FEI-USA) operating at 20 kV, the morphological characters of the pure drug powder and the best formulation of both the SSD and SS techniques were studied (Balakrishnaiah *et al.,* 2016).

Evaluation of the prepared FDTs

Tablet thickness

Ten tablets were chosen at random, their thickness was measured by a micrometer (Mitutoyo, Japan) and the average thickness was calculated (Liberman, 1991).

Weight variation

Twenty tablets were individually weighed, the average weight was calculated and the weight of each tablet was compared to the average (USP-NF24, 2000).

Tablet hardness

A tablet hardness tester (PTB 311E, Pharma Test, Germany) was used to measure the hardness of 10 tablets from each batch and the average hardness was then calculated (Liberman, 1991).

Friability

Friability was determined using a friabilator (Erweka, GmbH, Germany). Twenty tablets were weighed and placed in the friabilator. Friability was measured by calculating the percentage loss in weights (Liberman, 1991).

Content uniformity

From each formulation, 10 tablets were individually crushed and put into a volumetric flask of 100 mL capacity and containing 10mL of methanol, then the volume was completed to 100mL with simulated saliva (Balakrishnaiah *et al.*, 2016). The flask was then put on a magnetic stirrer till complete dissolution. Following filtration, the amount of OM dissolved in the filtrate was determined spectrophotometrically at 256 nm with a double beam UV-Visible spectrophotometer (Shimadzu UV spectrophotometer, Japan) by using a pre-constructed calibration curve (Liberman, 1991).

Wetting time

One tablet was put in a Petri dish containing Whatman filter paper that had been soaked in 5mL of distilled water. The wetting time was recorded as the time taken for distilled water to reach the tablet's upper surface (Sarfaraz *et al*., 2020).

In-vitro disintegration time

Six tablets from each formula were put in a disintegration tester (Erweka, GmbH, Germany). The average time needed for the tablets to disintegrate in distilled water at 37±0.5°C was recorded (Sarfaraz *et al*., 2020)..

In-vivo disintegration time

One tablet was put on the tongue of each of six volunteers, maintained till complete disintegration and the average time was calculated (Basalious *et al.,* 2013).

In-vitro drug release

The *in vitro* drug release from the produced FDTs and the pure drug were compared using a USP paddle type dissolution test apparatus (Pharma test model PT-DT40, Germany). To fulfill sink condition, 900 mL of simulated saliva solution was taken and rotated at 50 rpm at a temperature of 37±0.5°C. After 1, 3, 5, 10 and 15 minutes, aliquots of approximately 3 mL were taken and replenished with an equal volume of fresh medium. After

filtration and appropriate dilution, the quantity of drug in each sample was spectrophotometrically measured at 256 nm. To construct the drug release curves, the cumulative percent of the OM released was plotted against time (Sarfaraz *et al.,* 2020).

Taste-masking assessment

This test was done in accordance with a clinical protocol accepted by the Research Ethics Committee of the Faculty of Pharmacy, Cairo University (Approval No. PI 3103 & Approval date: 25/10/2021). Ten healthy volunteers between 25 and 35 years of age were chosen for this study. Taste-masked formulations were evaluated by putting the tablet on the volunteer's tongue, keeping it in the mouth until it disintegrated completely, spitting it out and then rinsing the mouth with 10mL of distilled water. A reference solution was made by dissolving 10mg of OM in a 25% sucrose solution to be used for comparison. On a scale ranging from 1 (the most disliked taste) to 10 (highly liked taste), volunteers were asked to figure the metallic unpleasant taste of the drug (Alayoubi *et al*., 2016).

Stability study

A short-term stability study was performed on the optimized tablet formulations (SD1 and T4). For three months, tablets were kept in small glass vials away from light in an incubator (MMM Medcenter Einrichtungen, GmbH, Germany) at 25°C and 40°C. After three months, the samples were taken and examined for appearance and *In-Vitro* drug release (Daihom *et al*., 2020).

STATISTICAL ANALYSIS

All the data were represented as the mean±standard deviation (n=3). One-way ANOVA (Tukey's multiple comparison test) was used to determine the statistical significance of the data using SPSS software (version 17.0). Significance was defined at p values≤0.05.

RESULTS

Fast dissolving tablets (FDTs) are one of the most promising novel dosage forms. They can be more effective than traditional solid dose forms. When delivered, a fast-dissolving tablet behaves as a solid dosage form when outside the body and as a solution when enters the body. As a result, convenience, patient compliance, bioavailability and time to action will all be improved (Jassem, 2022).

The direct compression method was used for preparing olmesartan medoxomil fast dissolving tablets using two different innovative techniques, the polymer-based surface solid dispersion (SSD) technique and the solidified surfactant (SS) technique, in order to enhance the solubility, dissolution rate and hence bioavailability of this poorly soluble drug.

Polymer-based Surface solid dispersion (SSD) technique

OM was previously formulated by solid dispersion (KUMAR *et al.,* 2016) and surface solid dispersion methods (Abd-El Bary *et al.,* 2014). The current research is unique in that it combines the advantages of both solid dispersion and surface solid dispersion methods by first dissolving the drug with different water-soluble hydrophilic polymers (PVP or pluronic) in methanol to improve the solubility of the drug due to the surfactant properties of the two polymers. Secondly, the dissolved mixture of OM and polymer was added to the surface of Avicel as a water-insoluble hydrophilic carrier to achieve better solubility owing to the large surface area of Avicel accessible for drug adsorption, which will result in a more enhancement in the drug dissolution rate in comparison to its previously formulated solid dispersions (Balakrishnaiah *et al.*, 2016). Moreover, improved powder flowability is anticipated, which is a key criterion for successful tablet manufacturing.

Solidified surfactant (SS) technique

Preparation of solidified surfactant is a novel strategy that has been used in the formulation of FDTs of OM to improve its solubility, rate of dissolution and therefore the bioavailability. It is a simple and convenient method and it also lowers the expense of high-priced equipment and manpower, where the liquid Tween was loaded onto Aeroperl (colloidal silica) which is highly granulated pure colloidal silicon dioxide that is used in pharmaceuticals and has a large specific surface area and a low density, making it a viable choice for the preparation of solidified surfactants (Basalious *et al.,* 2013). Its excellent adsorption, flow and compressibility features eliminated the requirement for coating materials, while also increasing the capability of loading liquids and minimizing the amount of carrier needed to achieve free-flowing particles (Cirri *et al.*, 2020). So, Aeroperl was chosen as the inorganic carrier, which was combined with Tween to form the solidified surfactant powder. Also, Crospovidone was chosen as a superdisintegrant because of its quick wetting time owing to its strong capillary action (Suryadevara *et al.*, 2017; Zayed *et al.*, 2020; KARTHICK *et al.*, 2022). Mannitol was utilized as a diluent because it has high water solubility and strong wetting characteristics that help in the tablet breakdown (Ain *et al.,* 2010; Türkmen, 2018). Avicel was used as a directly compressible vehicle owing to its high flowability and good compressibility.

Saturated solubility of OM in simulated saliva

The result of the solubility study, as shown in table 3, indicated that pure OM possesses a very low solubility in simulated saliva (0.51mg/mL). However, upon mixing the drug with PVP, Pluronic, Avicel, Aeroperl or Tween in the ratios listed in table 3, the solubility of the drug was significantly improved ($p<0.05$) to reach up to 2.81mg/mL.

It was found that the presence of Avicel with PVP or Pluronic led to a better improvement in the drug solubility than either of the two polymers alone. Thus, the solubility of the drug with PVP and Pluronic was 1.385 and 0.73mg/mL, respectively, while in the presence of Avicel, the drug solubility increased to 2.81 and 2.27mg/mL, respectively. It was noted that the effect of PVP on drug solubility was significantly higher ($p<0.05$) than that of Pluronic, Aeroperl or Tween.

Pre-compression parameters for the prepared FDTs

The powder mixtures for both techniques were measured for their angle of repose, compressibility index, bulk and tapped densities and Hausner's ratio. Table 4 shows that all of these parameters were within acceptable limits.

FTIR Spectroscopy

FTIR spectroscopy is primarily utilized to find out if there is any chemical interaction between the drug and any of the excipients utilized in its formulation.

The FTIR spectra of the pure OM, Pluronic, PVP, Aeroperl and the physical mixture of the pure drug with each excipient are depicted in fig. 1. The IR spectrum of OM exhibited the following peaks: A peak at 3394 cm^{-1} for the O-H group, a peak at 3290 cm^{-1} for N-H group, two characteristic sharp peaks at 1832 and 1708 cm^{-1} for the two C=O groups, three peaks at 1554, 1533 and 1473 cm^{-1} due to the aromatic C=C stretching and two peaks at 3040 and 3005 cm^{-1} due to the C-H stretching. It also revealed six C-O stretching peaks at 1299, 1227, 1170, 1135, 1087 and 1052 cm^{-1}. The spectra of the drug in its physical mixtures with different excipients showed the principal peaks of the drug without any shift or disappearance of any of these peaks. All of the obtained spectra can be simply regarded as the summation of the spectra of the drug and carrier, with the principal bands being identifiable.

Differential scanning calorimetry (DSC)

The DSC is a widely employed method to evaluate thermal behaviour, structural changes, drug crystallinity and any possible interactions between drugs and other chemicals. Fig. 2 exhibits the DSC thermo grams of the pure OM, Pluronic, PVP, Aeroperl and the physical mixture of OM with each of these excipients. The DSC thermogram of OM pure drug indicated a significant endothermic peak at 181.14°C, which corresponded to its melting point (Almutairy *et al.*, 2021). PVP exhibited a broad endothermic peak at 75.19°C, which corresponded to the release of adsorbed moisture, whereas Pluronic had a sharp endothermic peak at 56.82°C, which corresponded to polymer melting. Aeroperl, on the other hand, did not show any characteristic peak (data are not shown).

Powder X-ray diffraction (PXRD)

The purpose of the X-ray diffraction study was to describe the drug's physical form. The PXRD patterns of the pure drug and the best formulation of both SSD and SS techniques were represented in fig. 3. OM showed sharp diffraction peaks at 16.2°, 19.2°, 21.8° and 25.0°. On the other hand, spectra of both the solid dispersions of (OM+ PVP+ avicel) and (OM+ Pluronic+ avicel) and the solidified surfactant formulation of (OM+ Aeroperl+ Tween) showed broad diffraction patterns with no sharp peaks.

Scanning electron microscopy (SEM)

The scanning electron microscopy is a technique used for determining the drug's crystal shape, particle size and surface morphology. Fig. 4 shows the morphology of the pure drug and the optimum formulation of both SSD and SS techniques. As shown in the figure, OM was observed as plate-shaped crystals having rough surfaces. On the other hand, the SSD of (OM+ avicel+ PVP) and (OM+ avicel+ pluronic) and the solidified surfactant of (OM+ tween+ Aeroperl) were observed as amorphous particles which were irregular in shape.

Evaluation of the prepared FDTs

The direct compression method was used to prepare FDTs of OM. As depicted in table 5, all the prepared FDTs of OM passed the USP friability test with a percent weight loss of less than 1%. The OM tablets' hardness was observed to range between 1.86±0.15 and 4.06±0.15 kg/cm^2, while their thickness was found to range between 3.31±0.01 and 3.43±0.02 mm. All the tablets achieved the pharmacopeal requisites for the weight variation test as an indication of acceptable powder flowability. The calculated deviation from the mean tablet weight was found to be <1%. The drug content of all tablet formulations ranged between 95.23±1.25% and 98±1.05%.

In-vitro and In-Vivo disintegration times and wetting time

The results of the wetting and disintegration times for all of the prepared tablet formulations are shown in table 5. Non-significant differences ($p>0.05$) were found between the *In-Vitro* and *In-Vivo* disintegration times and wetting times of the tablets prepared by the SSD technique on using 1, 2 and 3% of either PVP or Pluronic.

The *in-vitro* disintegration times ranged between 13 and 19s, the *in-vivo* disintegration times ranged between 15 and 22s and the wetting times ranged between 15 and 19s, when using 1, 2 and 3% of either PVP (in formulations SD1-SD3) or Pluronic (in formulations SD5-SD7). However, increasing the concentration of both polymers to 5% led to a significant increase in all of these times ($p<0.05$), where the *in-vitro* disintegration times reached to 25 and 23s, the *in-vivo* disintegration times reached to 33 and 32s and the wetting times reached to 23 and 40s on using 5% of either PVP (formulation SD4) or Pluronic (formulation SD8) respectively. It was noteworthy that

nearly there was no difference between the results of both PVP and Pluronic.

Concerning the tablets prepared by the SS technique, the *in-vitro* and *in-vivo* disintegration times and wetting times were found to increase significantly ($p<0.05$) as the amount of the SS powder in the formula increased. Thus, in tablets containing Aeroperl (50%) and Tween (50%), the *in-vitro* and *in-vivo* disintegration times and wetting times were 30, 65 and 16s respectively, when the solidified surfactant: drug ratio was 5:1 (formulation T1). Increasing such ratio to 10:1 (formulation T2), these times jumped to 86, 120 and 26 s respectively. Further increase of the solidified surfactant: drug ratio to 15:1 (formulation T3) led to a further increase of these times to 121, 232 and 421 s respectively. Similarly, with tablets containing Aeroperl (70%) and Tween (30%), the *in-vitro* and *in-vivo* disintegration times and wetting times were 24, 47 and 11 s respectively, when the solidified surfactant: drug ratio was 5:1 (formulation T4). Increasing such ratio to 10:1 (formulation T5), these times reached 35, 83 and 18 s respectively. Further increase of the solidified surfactant: drug ratio to 15:1 (formulation T6) led to a more increase of these times to 87, 178 and 51 s respectively. It was also noted that the *in-vitro* and *in-vivo* disintegration times and wetting times decreased significantly ($p<0.05$) as the amount of Aeroperl in the formula increased. For example, comparing the two formulations T3 and T6 containing the same solidified surfactant: drug ratio of 15:1, the *in-vitro* and *in-vivo* disintegration times and wetting times were 121, 232 and 421s respectively in formulation T3 in which the Aeroperl content was 50%, while these times were only 87, 178 and 51 s respectively in formulation T6 in which the Aeroperl content was 70%. From the above results, it can be concluded that the *in-vitro* and *in-vivo* disintegration times and wetting times would decrease as the solidified surfactant: drug ratio decreased and the amount of Aeroperl in the formula increased.

In-vitro drug release studies

The goal of the *In Vitro* release studies is to anticipate the *in-vivo* behaviour of pharmaceutical preparations. Accordingly, simulated saliva was utilized in this investigation to simulate the oral cavity environment. Figs. 5 and 6 show the release profiles of all the prepared tablet formulations. It was observed that there was a marked increase in the percentage of drug released from all the prepared FDTs in comparison to the pure drug. The amount of drug released from these tablets varied between 69.83 and 96.42% after 15 minutes, while that of the pure drug was only 19.54% after the same time interval.

For tablets prepared by the SSD technique, a non-significant difference ($p>0.05$) was noticed in the percent of drug released on using 1, 2 and 3% of PVP, where the amounts of drug released were 96.04, 93.5 and 92.59% in formulations SD1, SD2 and SD3 respectively. However, increasing the polymer concentration to 5% in formulation SD4 led to a significant decrease in the percentage of drug released ($p<0.05$), where it was only 86.06%.

In tablets containing Pluronic, the percentage of drug released decreased significantly ($p<0.05$) upon increasing the concentration of the polymer, where it was 92.66, 77.61, 73.97 and 69.83% on using 1, 2, 3 and 5% of the polymer respectively (in formulations SD5-SD8).

The above results also revealed that the amounts of drug released on using PVP were higher than the corresponding amounts containing Pluronic in the same concentrations, which supported the results of the saturated solubility studies. Thus, these amounts ranged from 86.06 to 96.04% in formulations SD1-SD4 containing PVP, while they were in the range of 69.83 to 92.66% in formulations SD5-SD8 containing Pluronic.

Concerning the tablets prepared by the SS technique, a non-significant difference ($p>0.05$) was observed in the percentage of drug released as the solidified surfactant: drug ratio in the formula increased from 5:1 to 10:1. Thus, the percentage of drug released in all of these tablets ranged from 91.54 to 96.42% (in formulations T1, T2, T4 and T5). However, by increasing such ratio to 15:1, the percentage of drug released decreased significantly ($p<0.05$) to reach 85.66% in tablets containing Aeroperl (50%) and Tween (50%) in formulation T3 and 88.92% in tablets containing Aeroperl (70%) and Tween (30%) in formulation T6. It was also noticed that the percentage of drug released increased significantly ($p<0.05$) as the amount of Aeroperl in the formula increased. For example, in tablets containing the same solidified surfactant: drug ratio of 5:1, the amounts of drug released were 92.57% in formulation T1, in which the Aeroperl ratio was 50% and 96.26% in formulation T4, in which the Aeroperl ratio was 70%.

Taste-masking of OM

Olmesartan medoxomil has been reported to have a metallic, disagreeable taste. An endeavour was made to improve the solubility and dissolution rate of OM and to hide its metallic taste at the same time by preparing it as inclusion complexes with β-cyclodextrins (Sasidhar, 2013). The metallic disagreeable taste of the active ingredient was effectively masked by adding orange flavor as a flavoring agent and aspartame as a sweetener (Türkmen *et al.,* 2018). Also, stevia was used as a sweetener and a sugar substitute for diabetic and hypoglycemic patients (Alayoubi *et al.*, 2016). In this study, stevia (a natural sweetener) and aspartame (an artificial sweetener) were used as sweetening agents for masking the metallic disagreeable palate of OM and the optimum FDTs formulations were subjected to taste masking evaluation against a reference solution containing 10mg of OM dissolved in 25% sucrose solution.

It was found that the volunteers gave the optimized tablets containing either stevia or aspartame a score of 7 to 9,

indicating that the tablet formulations had a well-liked taste, while a very low score of 1-3 was given for the reference solution, indicating a disliked taste as shown in table 6.

Stability study

Optimized formulations prepared using the two techniques (SD1 and T4) were chosen for stability studies based on their cumulative % drug released. No changes were observed in both the physical appearance of the tablets and their drug release profiles upon storage for 3 months at 25°C and 40°C as depicted in fig. 7.

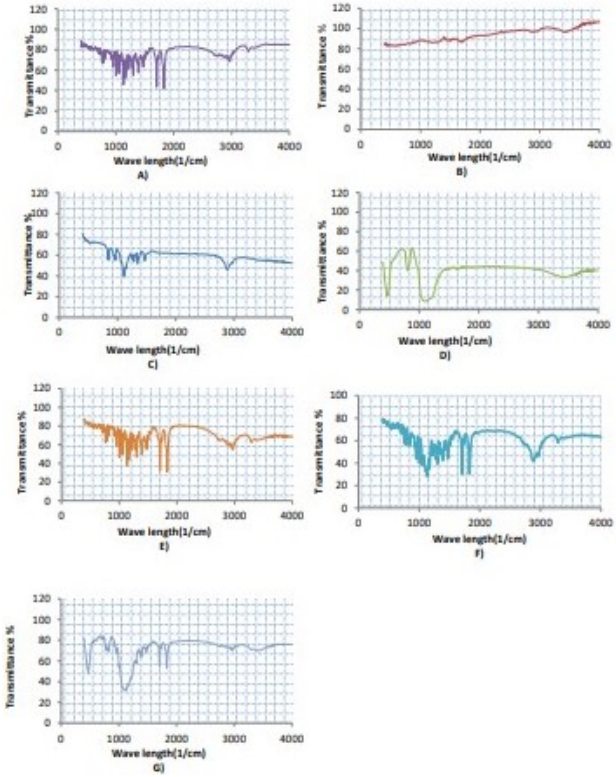

Fig. 1: FTIR spectra of: (A) OM, (B) PVP, (C) Pluronic, (D) Aeroperl, (E) physical mixture of (OM+PVP), (F) physical mixture of (OM +Pluronic) and (G) physical mixture of (OM +Aeroperl).

DISCUSSION

Saturated solubility of OM in simulated saliva

The improvement in drug solubility in simulated saliva upon mixing the drug with PVP, Pluronic, Avicel, Aeroperl or Tween could be ascribed to the decrease in particle size and the concomitant enlargement in the surface area and hence ease of wetting. Moreover, solubilization of the drug due to the surfactant properties of either the hydrophilic polymers or Tween may also contribute to the improved solubility of the drug.

The better improvement in OM solubility in presence of Avicel with PVP or Pluronic could support the superiority of the SSD approach over the conventional solid dispersion technique. In contrast to the conventional solid dispersion, the carriers utilized in the surface solid dispersion are porous, water-insoluble and hydrophilic in nature. When they come into contact with water, they disperse instantly, releasing the drug particles into the medium quickly (Abd-El Bary, Louis and Sayed, 2014). The higher effect of PVP on drug solubility than that of Pluronic, Aeroperl or Tween may be attributed to the strong crystal inhibiting effect obtained with PVP in comparison to the other formulations, as will be seen later in the X-ray diffraction studies.

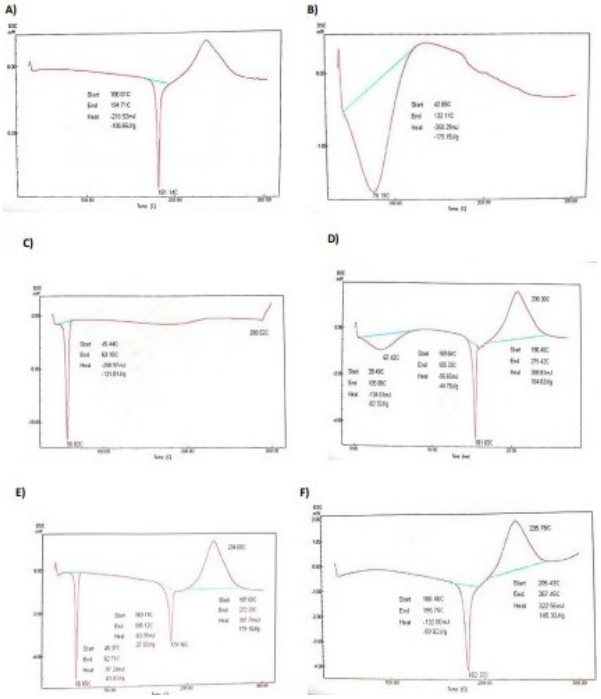

Fig. 2: DSC thermograms of: (A) OM, (B) PVP, (C) Pluronic, (D) physical mixture of (OM+PVP), (E) physical mixture of (OM+Pluronic) and (F) physical mixture of (OM +Aeroperl).

Pre-compression parameters for the prepared FDTs

All of the pre-compression parameters for the prepared FDTs were within acceptable limits, indicating that the powder mixtures had good flow properties.

FTIR Spectroscopy

The principal peaks of the drug were seen in the spectra of its physical mixtures with different excipients without any shift or disappearance of any of these peaks, suggesting the absence of any chemical interaction between OM and any of these excipients.

Differential scanning calorimetry (DSC)

DSC is a widely used method for evaluating thermal behaviour, structural changes, drug crystallinity and any possible interactions between drugs and other chemicals. Fig. 2 exhibits the DSC thermograms of the pure drug, Pluronic, PVP, Aeroperl and the drug's physical mixture

with each of these excipients. The DSC thermogram of OM pure drug indicated a significant endothermic peak at 181.14°C, which corresponded to its melting temperature (Almutairy *et al.*, 2021). The sharpness of the drug peak shown in its DSC thermogram reflects the drug's crystalline nature. The endothermic peak of the drug was not altered in the DSC thermograms of its physical mixtures as compared to the pure drug. This indicated that the drug had no interaction with any of the additives employed.

Powder X-ray diffraction (PXRD)

The purpose of the X-ray diffraction study was to characterize the drug's physical form. The PXRD patterns of the pure drug and the best formulation of both SSD and SS techniques were represented in fig. 3. The sharp X-ray diffraction peaks of the drug indicate the crystallinity of the drug. On the other hand, spectra of both the solid dispersions of (OM+PVP+avicel) and (OM+Pluronic+ avicel) and the solidified surfactant formulation of (OM+Aeroperl+Tween) showed broad diffraction patterns with no sharp peaks, indicating that the drug in these formulations has been changed from its crystalline nature to an amorphous state. It can also be observed from the figures that the strongest crystal inhibiting effect was obtained in the formulation containing PVP in comparison to the other formulations.

Scanning electron microscopy (SEM)

SEM images of the pure OM and its optimum formulation of both SSD and SS techniques suggested that OM was in a crystalline state. On the other hand, the SSD of (OM+ avicel+ PVP) and (OM+ avicel+ pluronic) and the solidified surfactant of (OM+ tween+ Aeroperl) were observed as amorphous particles which were irregular in shape. According to these findings, it was concluded that the drug had been transformed from its crystalline to an amorphous state in both the SSD and SS formulations and these findings were compatible with those of the XRD studies.

In-vitro and in-vivo disintegration times and wetting time

From the above results, it can be concluded that either the formula SD1 or SD5 containing PVP or Pluronic respectively, can be considered the best formulation among other formulations prepared by the SSD technique because both formulations presented the lowest *in vitro* and *in vivo* disintegration times and wetting times and contained the least concentration of the polymer at the same time. The superiority of either formula will be confirmed by the dissolution rate studies.

Concerning the tablets prepared by the SS technique, formulation T4, containing the higher Aeroperl ratio (70%) and the lowest solidified surfactant: drug ratio (5:1), was the best formula among other formulations prepared by the solidified surfactant technique, as it exhibited the lowest *in-vitro* and *in-vivo* disintegration times and wetting time.

In-vitro drug release studies

The marked increase in the percentage of drug released from all the prepared FDTs when compared to the pure drug might be attributed to the adsorption of drug particles on the carrier surface in an extra fine state of subdivision or molecular state. The excessive decrease in particle size and the concurrent increase in the surface area and hence ease of wetting, enhanced greatly the dissolution rate of the drug compared to the drug alone. Moreover, solubilization of the drug achieved by either the hydrophilic polymers or the surfactant Tween may also contribute to the improved drug dissolution. The enhanced drug release may also be ascribed to the change of the drug to an amorphous state, as evidenced by PXRD data, where no energy is needed to split up the crystal network, making the dissolution process energetically more favourable (Taylor & Zografi 1997).

In tablets prepared by the SSD technique using PVP, the significant decrease in the percentage of drug released upon increasing the polymer concentration to 5% was most likely owing to the elevated viscosity resulting from the high molecular mass of the polymer, in addition to the probable increased polymer chain entanglement which leads to slow motion of the drug molecules through the diffusion layer. These results, however, were in contrast to those obtained by Sui *et al*. (2020) who found that the dissolution rate of glycyrrhetinic acid from its PVP solid dispersions with 8: 1 carrier-drug ratio was faster than 4: 1 under the same PVP molecular weight condition.

In tablets containing Pluronic, the lowering in the percentage of drug released upon increasing the concentration of the polymer might be attributed to the polymer's thermo-reversible gelation phenomena. Being at saturation solubility in the diffusion layer, Pluronics may be able to form gel at the temperature of the dissolution media that would retard drug movement in the diffusion layer (HE *et al.*, 2008; Elkordy *et al.*, 2012).

The higher amounts of drug released on using PVP than the corresponding amounts containing Pluronic in the same concentrations, might be attributed to the stronger crystal inhibiting effect of PVP than that of Pluronic, as previously shown in X-ray diffraction studies. This may also be attributed to the finding that when the temperature in an aqueous medium exceeds 35°C, Pluronic produces hard-sphere micellar aggregates (Kurumada and Robinson, 2004). Therefore, it can be deduced that formulation SD1 was the best formula among other formulations prepared by the SSD technique, since it showed the highest percentage of drug released (96.04%) and contained the lowest concentration of PVP (1%) at the same time.

Table 1: Composition of FDTs of OM prepared by SSD technique

Weight (mg)	SD1a	SD1b	SD2	SD3	SD4	SD5	SD6	SD7	SD8
OM	10	10	10	10	10	10	10	10	10
PVP	2	2	4	6	10	-	-	-	-
Pluronic	-	-	-	-	-	2	4	6	10
Avicel	126	126	124	122	118	126	124	122	118
Crospovidone	10	10	10	10	10	10	10	10	10
Mannitol	40	40	40	40	40	40	40	40	40
Aspartame	4	-	4	4	4	4	4	4	4
Stevia	-	4	-	-	-	-	-	-	-
Orange Flavor	4	4	4	4	4	4	4	4	4
Mg Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

Table 2: Composition of FDTs of OM prepared by SS technique

Weight (mg)	Aeroperl.: Tween 50:50				Aeroperl: Tween 70:30		
	Drug: SS				Drug: SS		
	1:5		1:10	1:15	1:5	1:10	1:15
	T1a	T1b	T2	T3	T4	T5	T6
OM	10	10	10	10	10	10	10
Aeroperl	25	25	50	75	35	70	105
Tween	25	25	50	75	15	30	45
Avicel	128	128	78	28	128	78	28
Crospovidone	10	10	10	10	10	10	10
Mannitol	40	40	40	40	40	40	40
Aspartame	4	-	4	4	4	4	4
Stevia	-	4	-	-	-	-	-
Orange Flavor	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4
Total	250	250	250	250	250	250	250

Table 3: Saturated solubility of pure OM and its physical mixture with different excipients.

Physical mixture	Ratio	Saturated solubility in simulated saliva (mg/ml)
Pure OM	-	0.51±0.018
OM:PVP	04:01	1.385±0.047
Drug:Pluronic	04:01	0.73±0.027
Drug:PVP:Avicel PH	04:01:02	2.81±0.07
Drug:Pluronic:Avicel	04:01:02	2.27±0.032
Drug:Tween	04:01	0.86±0.02
Drug:Tween:Aeroperl	04:01:02	0.87±0.02

Data are represented as the mean ± SD (n=3). One-way ANOVA (Tukey's multiple comparison test) was used to determine the statistical significance of the data using SPSS software. Significance was defined at p values ≤ 0.05.

Table 4: Pre-compression parameters for the powder blends of FDTs formulations

	Angle of Repose (Θ)	Bulk Density(g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio
SD1	25.69±0.34	0.40±0.15	0.50±0.11	19.46±1.02	1.24±0.01
SD2	30.31±0.49	0.43±0.18	0.54±0.13	19.71±0.32	1.24±0.13
SD3	33.21±0.27	0.47±0.23	0.52±0.01	20.41±0.75	1.25±0.07
SD4	29.38±0.38	0.39±0.11	0.51±0.07	18.67±1.88	1.23±0.02
SD5	31.17±0.52	0.37±0.14	0.46±0.12	19.55±1.34	1.24±0.06
SD6	35.51±0.45	0.36±0.21	0.456±0.01	19.06±0.87	1.23±0.14
SD7	30.75±0.24	0.37±0.11	0.46±0.05	19.36±1.16	1.24±0.21
SD8	32.69±0.16	0.38±0.13	0.47±0.01	19.68±0.29	1.24±0.13
T1	32.61±1.42	0.43± 0.21	0.52±0.07	17.53±0.37	1.21±0.51
T2	32.37±1.74	0.41±0.14	0.52±0.01	20.23±0.54	1.25±0.05
T3	37.72±0.89	0.42±0.20	0.52±0.01	20.28±0.51	1.25±0.11
T4	37.49±1.26	0.38±0.15	0.45±0.01	14.28±1.71	1.17±0.02
T5	34.43±0.81	0.51±0.17	0.64±0.02	20.27±0.32	1.25±0.01
T6	31.93±0.84	0.34±0.22	0.4±0.02	15.31±0.84	1.18±0.18

Table 5: Post- compression parameters for FDTs formulations

	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Wetting time (s)	*In-Vitro* disintegration time (s)	*In-Vivo* disintegration time (s)
SD1	197.5±1.5	3.31±0.01	3.93±0.05	0.55±0.17	96.2±1.08	16.66±1.52	13±1.41	19.5±0.70
SD2	197.5±1	3.35±0.06	4.06±0.05	0.48±0.14	97.76±1.13	16±1	14.5±0.70	20±1.41
SD3	197.83±1.25	3.34±0.09	4.03±0.25	0.33±0.05	96.43±0.91	19.66±0.57	19.5±0.70	21±1.4
SD4	198.83±1.89	3.33±0.01	3.9±0.10	0.62±0.12	95.96±0.95	23±1	25.5±0.71	33.5±0.72
SD5	196.5±1.32	3.363±0.04	3.7±0.26	0.54±0.05	97.4±1.21	15±1	17±1.42	15±1.41
SD6	198±1	3.32±0.01	3.2±0.2	0.49±0.05	96.7±1.60	17±2	16.5±0.71	16.5±0.69
SD7	197.16±0.76	3.36±0.04	3.9±0.10	0.55±0.22	96.73±1	19.33±1.52	13±1.41	22.5±0.68
SD8	197±1.80	3.35±0.04	4.06±0.15	0.38±0.03	97.3±1.37	40.33±1.52	23.5±0.71	32.5±0.71
T1	248.33±1.5	3.33±0.01	2.19±0.08	0.85±0.05	95.23±1.25	16±1	30±2	65.66±1.154
T2	249.67±2.1	3.43±0.02	2±0.10	0.36±0.14	97.53±0.89	26±1	86.66±1.53	120±2
T3	250.17±2.4	3.36±0.05	1.86±0.15	0.63±0.21	97.26±0.81	421.33±1.15	121±1	232.33±2.51
T4	247.67±1.15	3.31±0.01	3.3±0.10	0.55± 0.02	96.63±1.8	11.66±1.53	24.16±1.04	47.33±1.53
T5	250.66±1.15	3.36±0.03	3.53±0.15	0.64±0.05	98±1.05	18±1	35.33±1.53	83.667±1.53
T6	248±1	3.33±0.01	2.9±0.20	0.73±0.12	97.53±0.50	51±1	87±1.73	178.33±1.52

Data are represented as the mean ± SD (n=3). One-way ANOVA (Tukey's multiple comparison test) was used to determine the statistical significance of the data using SPSS software. Significance was defined at p values ≤ 0.05.

Table 6: Results of OM taste evaluation

Volunteer No.	SD1a Containing aspartame	SD1b Containing stevia	T4a Containing aspartame	T4b Containing stevia	pure OM in sucrose solution (reference)
1	8	7	9	8	1
2	9	8	8	7	3
3	8	6	8	7	3
4	8	8	7	8	2
5	7	8	9	7	2
6	8	7	8	6	3
7	7	5	6	7	2
8	8	7	7	9	3
9	9	8	6	8	2
10	9	6	7	6	1

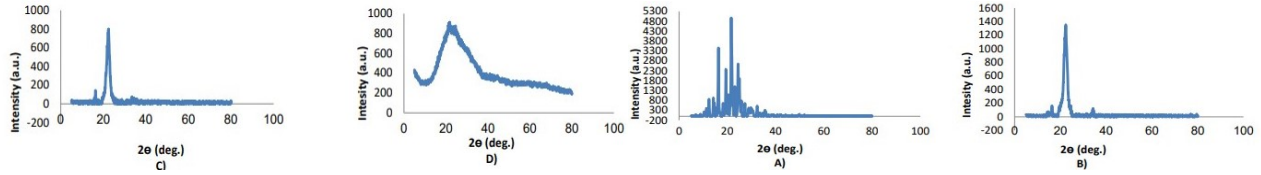

Fig. 3: Powder X-ray diffraction patterns of: A) OM, B) SSD of (OM+ PVP+ Avicel), C) SSD of (OM+ Pluronic +Avicel) and D) SS of (OM+ Aeroperl +Tween)

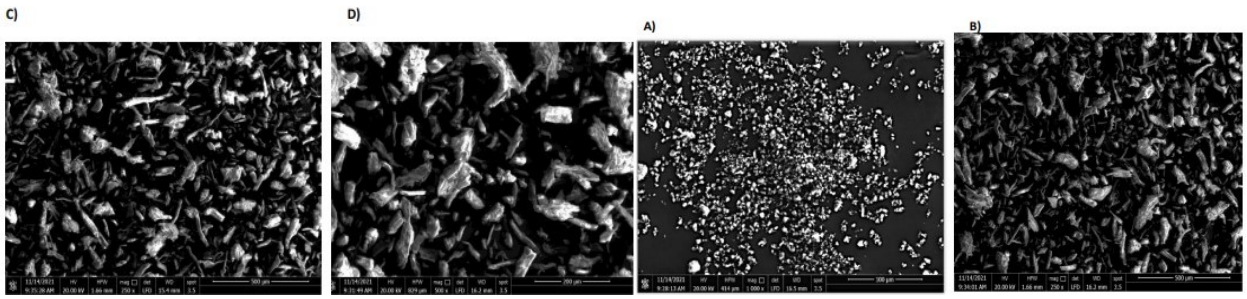

Fig. 4: SEM images of: A) OM, B) SSD of (OM+ PVP+ Avicel), C) SSD of (OM+ Pluronic+ Avicel) and D) SS of (OM+ Aeroperl+ Tween)

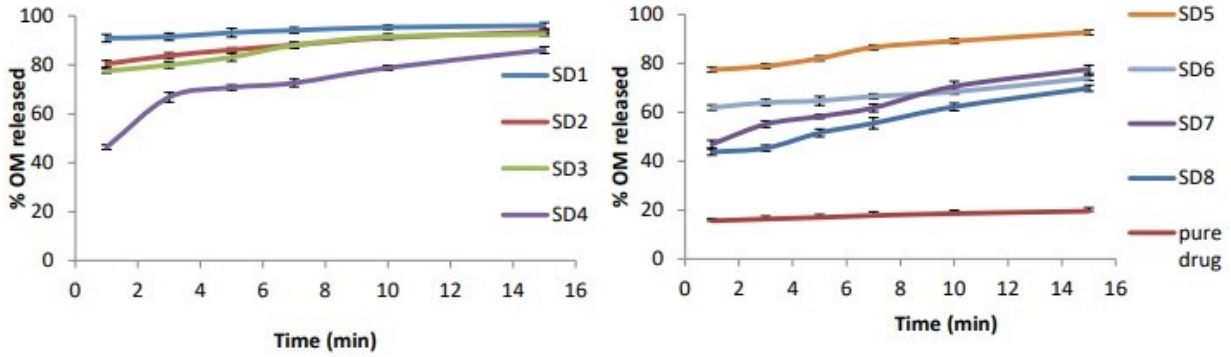

Fig. 5: OM released from its SSD formulations

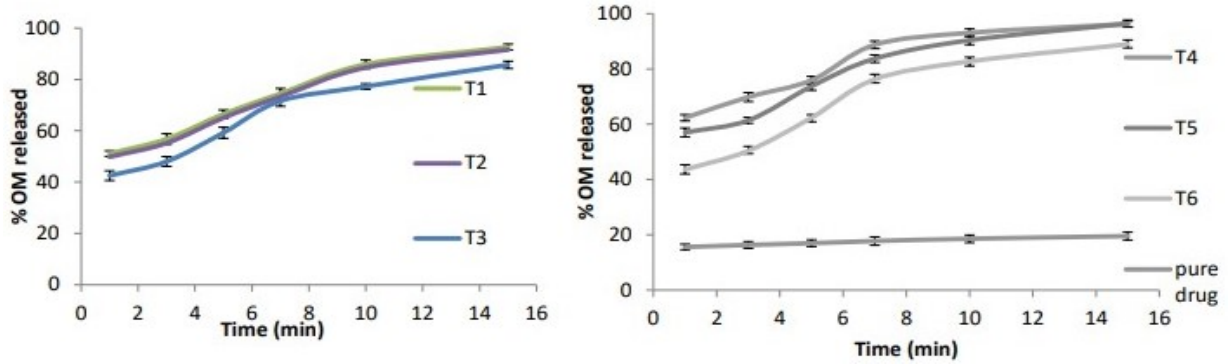

Fig. 6: % OM released from its SS formulations. Data are represented as the mean ± SD (n=3). One-way ANOVA (Tukey's multiple comparison test) was used to determine the statistical significance of the data using SPSS software. Significance was defined at p values ≤ 0.05.

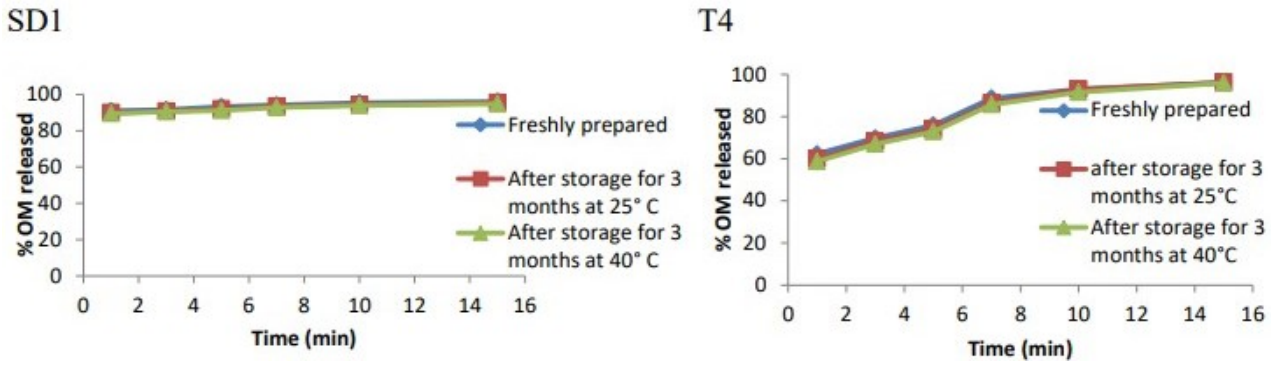

Fig. 7: % OM released from formulations SDI & T4 before and after storage at 25° & 40°C. Data are represented as the mean ± SD (n=3). One-way ANOVA (Tukey's multiple comparison test) was used to determine the statistical significance of the data using SPSS software. Significance was defined at p values ≤ 0.05.

Concerning the tablets prepared by the SS technique, the increase in the percentage of drug released as the amount of Aeroperl in the formula increased may be assigned to the fact that presence of higher amounts of Aeroperl in the formula will lead to a surfactant distribution on the large surface of such a carrier and subsequently, a more efficient solubilizing effect will be exerted on the drug, leading to an enhancement in its dissolution rate. From the above findings, it can be concluded that the percentage of drug released would increase as the solidified surfactant: Drug ratio decreased and the amount of Aeroperl in the formula increased. Thus, formulation T4 containing the higher Aeroperl ratio (70%) and the lowest solidified surfactant: Drug ratio (5:1) was the best formula among other formulations prepared by the SS technique, as it exhibited the highest percentage of drug released (96.26%) and these results were consistent with those of the disintegration times and wetting time.

Taste-masking of OM

The taste-masking experiment proved that the metallic disagreeable taste of OM was successfully masked in its optimized tablet formulations.

Although both stevia and aspartame formulations were generally satisfactory and had a pleasant mouth feel as

indicated by all of the participants, stevia is preferred as it is considered a safer sugar substitute for diabetic and hypoglycemic patients (Faleh *et al.*, 2019). Consequently, it can be concluded that natural sweeteners, rather than artificial ones, are the preferred sweetening agents for FDTs.

Stability study

Results of stability study indicated that both SD1 and T4 tablet formulations of OM were stable both physically and chemically.

CONCLUSION

The FDTs of OM prepared by both the polymer-based surface solid dispersion (SSD) and solidified surfactant (SS) techniques showed an improved dissolution rate of the drug compared to the pure drug. Therefore, FDTs of OM may be a useful alternative for treating emergency hypertension, particularly in pediatric and geriatric patients. Moreover, the proposed SSD and SS techniques are particularly favorable for industrial scale-up due to their simplicity and cost-effectiveness.

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