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Article

Development and optimization of cosolvent-based blended Sertraline orodispersible films - A step to personalized medicine

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Personalized medicine is gaining importance in pharmacotherapeutics as it allows tailoring the drug treatment to achieve the best patient response. Orodispersible film (ODF) is easy to formulate in hospitals, produces dose flexibility to suit an individual needs, particularly for patients suffer from swallowing issues or prohibited to take fluids. Sertraline Hydrochloride (SRT) was solubilized in several cosolvents, then different SRT ODFs based on five hydrophilic polymers namely; polyvinyl alcohol (PVA), hydroxylethyl cellulose (HEC), hydroxypropyl methylcellulose E5 LV (HPMC E5 LV), sodium alginate (NaAlg) and gelatin at two concentrations (2% and 4%) were developed and characterized. The outcomes were exposed to response surface analysis to obtain the desirability results to obtain the optimized formulation. Blended ODFs were developed from 4% PVA and 2% HEC in different blends and then potassium chloride (KCl) as a pore-forming agent was added to the best formulation to investigate its dissolution enhancement effect. F14 containing 4% PVA: 2% HEC 2:1 with 5% KCl showed best physicochemical properties of suitable pH (5.6), disintegration time (6 sec), good folding endurance which released 91 % SRT after 15 min. SRT ODF is an encouraging delivery system in the course of personalized medicine for the management of depression.

Keywords: Orodispersible films. Personalized medicine. Sertraline. Modified *in-vitro* disintegration time. Pore-forming agent.

INTRODUCTION

Dysphagia is a disease concerned with swallowing difficulties that elderly patients may suffer. Caregivers frequently try to overcome this problem by crushing the tablets or by combining the capsule content with diet or juice (Visser *et al*., 2017). Such manipulation of a dosage form may employ a danger for both patients and caregivers. Besides, these changes in the dosage forms are prone to dose inadequacy and alteration of the main targeted medicinal function as in the case of controlled release dosage forms. These manipulations may also cause stomach irritation and changes in drug absorption or instability issues (Visser *et al*., 2017). Nevertheless, there remains a serious need for a proper dosage form that may enhance the oral drug delivery for this group of patients (Abouhussein *et al*., 2019a; Slavkova, Breitkreutz, 2015; Visser *et al*., 2017) Orodispersible films (ODFs) have the advantage of instant disintegration in the oral cavity without the necessity for water and can deliver a tailored medicine to the patients. ODFs offer flexible dosing during formulation or by cutting them into the required pieces before administration (Visser *et al*., 2015). Besides, ODFs are also preferred and well accepted by children to avoid swallowing solid dosage forms (Rodd *et al*., 2011). Orlu *et al*. (2017) demonstrated the acceptability of a placebo ODFs by preschool children along with their caregivers.

ODFs are mostly manufactured by the cost-effective solvent evaporation technique through dissolving the drug

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and API in an aqueous or hydro-alcoholic solution then casting onto a surface, drying, and cutting into the preferred size (Borges *et al*., 2015; Sanghai, Nandgude, Poddar, 2016). ODFs can be easily formulated on a hospital or community pharmacy scale (Visser *et al*., 2015). If commercial products are inappropriate or not accessible, hospital pharmacists may compound their needs of medications for their patients. Many countries have issued their guidelines for compounding such formulations to ensure safe and effective products (Visser *et al*., 2020).

Sertraline hydrochloride (SRT) is a selective serotonin reuptake inhibitor (SSRI) that is used for depression and anxiety disorder management (Abouhussein *et al*., 2021; El-Bary *et al*., 2015). SRT is a BCS class II drug which is regarded by its low water solubility and good permeability (Al-Nimry, Jaber, 2017). SRT is marketed in three various concentrations: 25 mg, 50 mg and 100 mg. The frequent dose manipulated in ODFs is 25 mg/film, however, some researchers reported up to 50 mg/6 cm^2 film (Woertz, Kleinebudde, 2015). It should be noted that high drug loading could negatively affect the physical properties of ODFs like thickness, disintegration time, mechanical properties (Visser *et al*., 2015; Woertz, Kleinebudde, 2015). To overcome this drawback in the development of SRT ODFs, cosolvency technique was employed. Cosolvents have been broadly utilized for enhancing the solubility of low water-soluble drugs for being non-toxic and cost-effective technique (Amin *et al*., 2004; Yeh, Chang, Chiou, 2009). Lately, the cosolvency approach has been extended to solid dosage forms as in the formulation of inclusion complex to enhance the bioavailability of water-insoluble drugs (Li *et al*., 2018).

Therefore, the aim of our study is to assess the capability of using cosolvency approach in the formulation of ODFs enclosing the slightly water-soluble SRT using the solvent evaporation method as an easy means of applying the preparation process for small-scale production manufacturers or hospital pharmacies. Five hydrophilic film-forming polymers; polyvinyl alcohol (PVA), hydroxylethyl cellulose (HEC), hydroxypropyl methylcellulose E5 LV (HPMC E5 LV), sodium alginate (NaAlg) and gelatin at two different concentration (2% and 4%) were chosen due to their suitable film forming properties with sorbitol as a plasticizer. ODFs were plasticized by sorbitol which is a non-cariogenic sweetener that is appropriate for the administration to the oral cavity. Sorbitol can prevent dental caries by reducing the Streptococcus mutans, endorsing enamel mineralization and enhancing the salivary flow that effectively buffers any cariogenic acids (Pechová *et al*., 2018). Potassium chloride (pore-forming agent) was investigated as a dissolution enhancer.

MATERIAL AND METHODS

Materials

Sertraline HCl (SRT) kindly supplied from Adwia, Egypt. Mowiol® 4-88 (Polyvinyl alcohol 4-88) 3-5 mPas (4% in H2O, 20°C) Mw 31,000, Sigma Aldrich, Germany. HPMC E5 LV, apparent viscosity 4-6 Cps, LOBA Chemie PVT. LTD, Mumbai, India. Sodium alginate (NaALG) Fischer Scientific, UK. Hydroxyethyl cellulose (HEC) medium viscosity ~1500 mPas (5% in H_2O, 20°C) Fluka, USA. Ethanol absolute 99.8%, Propylene Glycol, ≥ 99.9%, mol wt. 76.09, PEG 400, Glycerin, Gelatin, bovine source and Potassium Chloride (99.0-100.5%), Sigma Aldrich, USA. D-Sorbitol, MW: 182.17 g/mol, Sigma Aldrich, Italy. All other reagents are of analytical grades.

Methods

Determination of saturated solubility of SRT in various cosolvents

The solubility of SRT in distilled water, simulated saliva solution (SSS) (2.38 g disodium hydrogen phosphate, 0.19 g potassium dihydrogen phosphate and 8 g sodium chloride completed to 1 L of distilled water and then adjusted to pH 6.8 ± 0.05) (Marques, Loebenberg, Almukainzi, 2011) and several cosolvents (propylene glycol, PEG 400, glycerin and ethanol) was estimated by adding an excess amount of SRT to 2 mL of each media being studied. Then, the samples were vortexed for 5 min to assist SRT solubilization utilizing a vortex mixer (Stuart, Staffordshire, UK), permitted to equilibrate for 48 h in an isothermal shaker and then were centrifuged at 7000 rpm for 10 min using Beckman Coulter Centrifuge,

Wycombe, UK. The supernatant of each tested sample was filtered to eliminate any undissolved SRT powder (Abouhussein *et al*., 2019b). Finally, SRT content was measured spectroscopically using suitable dilutions at λ 273 (Abouhussein *et al*., 2021).

Physicochemical compatibility studies of SRT with different excipients:

FTIR and DSC analysis were used for the evaluation of possible interactions that could occur between SRT and each polymer used. Analyses were carried out for drug alone and the physical mixture of SRT and each of the investigated excipient (PVA, HPMC E5 LV, HEC, sodium alginate and gelatin) in the ratio 1:1 w/w, prepared by simple and gentle perfect mixing of ingredients on a clean waxy paper.

Fourier Transform Infrared (FTIR) studies:

The tested samples (1-2 mg) compressed with potassium bromide (IR grade) into disks under vacuum and scanned from 4000 to 500 cm^{-1} with an empty pellet holder as a reference (Abouhussein *et al*., 2021; Khattab, Abouhussein, 2019).

Differential scanning calorimetric (DSC) study:

The DSC patterns of the tested samples (4-8) were measured at a scanning rate of 20 ºC/min from 10 ºC to 400 ºC at a flow rate of 40 mL/min after calibration with indium as a standard (Abouhussein *et al*., 2020; Abouhussei, *et al*., 2021).

Preparation of SRT ODFs

SRT ODFs were prepared using the solvent evaporation technique as presented in Table (I). Sorbitol was added to the solvent (preheated distilled water to 80°C). The polymer (PVA, HPMC E5 LV, HEC, sodium alginate and gelatin) using two different concentrations (2% and 4%) was dispersed in the pre-mentioned solvent mixture and stirred for two hours at room temperature till a clear solution was obtained. SRT was dissolved in the cosolvent mixture of ethanol/PG, then added to the polymer solution and stirred overnight. The solution obtained could equilibrate at room temperature to ensure clear, bubble-free solution then cast in a glass petri dish and allowed to dry in oven adjusted at 37˚C till reaching a constant weight of the film. ODFs were carefully removed from the glass petri dish and stored in a container until further use.

TABLE I - Composition and physicochemical characterization of SRT ODFs

Formulae No.	Composition of SRT ODF*	Physicochemical Characterization of SRT ODF						
	Polymer used	Colour & Homogeneity	Average weight (mg)	Thickness (mm)	In vitro Disintegration Time (sec)	pH	Folding Endurance	Drug Content Uniformity (%)
F1	2% PVA	Slightly opaque whitish, not homogenous	307±3.41	0.20±0.025	30±1.25	4.3±0.25	>300	-
F2	4% PVA	Translucent homogenous	550±3.45	0.24±0.030	48±2.36	5.0±0.23	>300	99.0±3.21
F3	2% HEC	Translucent yellowish, homogenous	275±1.59	0.15±0.015	29±1.20	4.7±0.19	>300	98.0±2.74
F4	4% HEC	Translucent yellowish, homogenous	457±4.36	0.18±0.019	50±2.21	5.7±0.43	>300	99.1±3.11
F5	2% HPMC E5 LV	Opaque white, not homogenous	302±1.25	0.24±0.020	26±1.50	5.3±0.24	6±1	-

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Formulae No.	Composition of SRT ODF*	Physicochemical Characterization of SRT ODF						
	Polymer used	Colour & Homogeneity	Average weight (mg)	Thickness (mm)	In vitro Disintegration Time (sec)	pH	Folding Endurance	Drug Content Uniformity (%)
F6	4% HPMC E5 LV	Translucent homogenous	519±3.65	0.24±0.021	74±3.58	4.6±0.36	3±1	98.5±2.36
F7	2% NaAlg	Transparent yellowish, homogenous	273±2.14	0.09±0.009	80±4.63	5.5±0.28	1±0	97.9±2.94
F8	4% NaAlg	Transparent yellowish, homogenous	430±3.22	0.12±0.010	200±5.85	5.6±0.30	1±0	98.5±3.41
F9	2% Gelatin	Slightly opaque whitish, homogenous	280±2.15	0.17±0.015	39±1.40	4.7±0.21	206±4	98.4±2.54
F10	4% Gelatin	Translucent, homogenous	532±2.85	0.26±0.020	120±4.57	5.3±0.24	>300	99.3±2.65

*Each formulation contains amount of SRT HCl equivalent to 50 mg SRT.

Statistical Design of Experiment

5 X 2 full factorial design was applied using Design Expert (Version 7, Stat-Ease Inc., MN, USA) to evaluate the effect of the investigated variables. Table (II) displays the studied parameters and responses with their targeted constrains. Two independent parameters were considered because of preliminary studies. These parameters were polymer type (X_1) which comprised five levels (PVA, HEC, HPMC E5 LV, NaAlg and Gelatin) and polymer concentration (X_2) that involved two concentrations (2% and 4%). The dependent variables were disintegration time (Y1), thickness (Y2), film homogeneity (Y3) and folding endurance (Y4). The acquired outcomes were exposed to response surface analysis followed by calculation of the desirability values to develop the optimized formulation.

TABLE II - Full factorial design used to optimize SRT sublingual ODTs

Independent Variables	**Levels**				
X1: Polymer Type	PVA	HEC	HPMC E5 LV	NaAlg	Gelatin
X2: Polymer concentration	2%			4%	
Dependent Variable	**Constraints**				
Y1: Disintegration time	Minimize				
Y2: Thickness	Minimize				
Y3: Homogeneity	Maximize				
Y4: Folding Endurance	Maximize				

Characterization of SRT casting polymer solution.

Determination of viscosity

The viscosity of all the prepared SRT polymer solutions was measured using Brookfield DV III (Abouhussein *et al*., 2018) spindle 40 at 25 °C at 25 rpm. Each reading was measured in triplicate.

Physicochemical characterization of SRT ODFs

SRT ODFs were examined for colour and homogeneity for the detection of any imperfections of the developed films.

Average weight

Three films from each formulation were weighed, and the mean weight of the three films was calculated.

Film thickness

The thickness of three films of each formulation was measured using a micrometer (model: PK-1012E, Mitutoyo, Japan) and the mean thickness was then calculated. The thickness of each film was measured at 5 different places, one of them at the center of the film, two at the axis and the other two in-betweens. The results are the average of five readings.

Drug content uniformity

SRT content in the developed ODFs was determined by solubilizing 1cm^2 of each film in 1:1 ethanol: distilled water. The solution was filtered, and SRT content was detected by measuring the absorbance spectroscopically at λ_{max} 273 nm. The results are the average of three readings.

Surface pH

The surface pH of medicated films was measured to estimate the suitability of the use of the developed formulations to the mucosae. Films were cut into uniform pieces 1cm^2 and maintained in distilled water (1 mL) for 1 h. The pH was observed utilizing a microelectrode which was brought in contact with the surface of each ODF (Abouhussein *et al*., 2020; Yasmeen *et al*., 2012). The results are the average of three readings.

Folding endurance

The elasticity is crucial to ensure the feasibility of ODF use. Folding endurance is a simple method that can be easily used in hospitals and community pharmacies to evaluate ODF. It is determined by repetitively folding the ODF at the same place until it breaks or folded to 300 times without breaking (Nafee *et al*., 2003; Nair *et al*., 2013).

Modified in-vitro disintegration time.

Concerning the disintegration test, a modified technique was accomplished. The tested ODF of a determined size was held between two clamps and fixed with a thread at the arm of the disintegration apparatus which that move up and down in SSS at 37.0±0.5°C as shown in Figure (1). The time needed to cause the ODF to disintegrate was calculated. The test was done in triplicate.

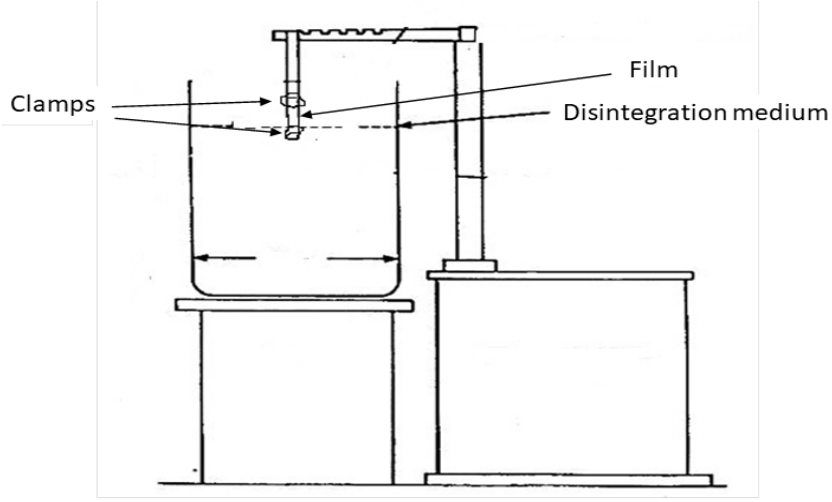

FIGURE 1 - Schematic diagram of the modified *in-vitro* disintegration apparatus.

Optimization of SRT ODFs

Mixing of polymer solutions together or blending of polymers in a melt is among the available and most convenient methods of providing polymeric materials with new functional properties (Bucknall, Paul, 2000). Consequently, the SRT/polymer solutions of the two selected formulations from the obtained desirability values were mixed in the ratio 1:1, 1:2 and 2:1 as shown in Table (III) and then stirred for 4hr.

The selected blended ODF was then optimized by adding a 5% KCl (pore-forming agent) to enhance the SRT release from the selected blended ODF.

TABLE III - Composition and physicochemical characterization of optimized SRT ODFs

Formulae No.	Composition of SRT ODF*			Physicochemical Characterization of SRT ODF						
	4% PVA	2% HEC	KCl	Colour, Transparency& Homogenity	Average weight (mg)	Thickness (mm)	In vitro Disintegration Time (sec)	pH	Folding Endurance	Drug Content Uniformity (%)
F11	33.3%	66.7%	-	Translucent yellowish, homogenous	343±2.56	0.11±0.010	8±1.0	6.6±0.52	>300	98.5±2.45
F12	50%	50%	-	Translucent yellowish, homogenous	392±2.69	0.12±0.015	6±1.5	6.6±0.36	>300	98.9±3.68
F13	66.7%	33.3%	-	Translucent yellowish, homogenous	449±3.12	0.12±0.010	6±2.0	6.7±0.95	>300	99.1±3.21
F14	66.7%	33.3%	5%	Opaque yellowish homogenous	509±2.10	0.15±0.016	6±2.4	5.6±0.26	>300	98.0±2.65

*Each formulation contains amount of SRT HCl equivalent to 50 mg SRT.

Characterization of the optimized films

ODFs were examined for its colour, homogeneity, average weight, thickness, pH, drug content and folding endurance test.

Modified in-vitro disintegration time.

The time taken for the film to disintegrate was measured using the apparatus mentioned above. The test was done in triplicate.

In-vitro dissolution of blended SRT ODFs

The percent SRT dissolved was determined using USP dissolution apparatus type 5; paddle over the disc (Hanson Research, Chatsworth, CA). SSS pH 6.8 ± 0.05 was used as dissolution medium with 50 rpm at 37˚C ± 0.5˚C (Abouhussein *et al*., 2020). Samples of 3 mL were taken at different intervals (1, 3, 5, 7, 10, 15, 20, 25, 30 min) and measured spectrophotometrically at λ_{max} 273 nm. Each formulation was tested three times and the average of the results was computed.

Scanning electron microscope imaging

The surface morphology of the selected SRT ODF was characterized by using a scanning electron microscope (SEM; Quanta FEG 250 SCM, FEI 250 SCM, FEI Quanta series, USA) at a high vacuum mode of 25 kV. SEM micrographs were recorded after fixing the selected SRT ODF on aluminum stubs then sputtering with a gold coat.

RESULTS AND DISCUSSION

Determination of saturated solubility of SRT in various cosolvents

The solubility of SRT in several cosolvents (propylene glycol, PEG 400, glycerin and ethanol) was assessed and presented in Figure (2). SRT showed a saturated solubility in ethanol and PG of 15.5 mg/mL and 14 mg/mL, respectively. However, a mixture of both cosolvents showed SRT saturated solubility of 24.5 mg/mL which is about 6 folds its solubility in water (4.14 mg/mL) and about 45.5 folds its solubility in SSS (0.538 mg/mL).

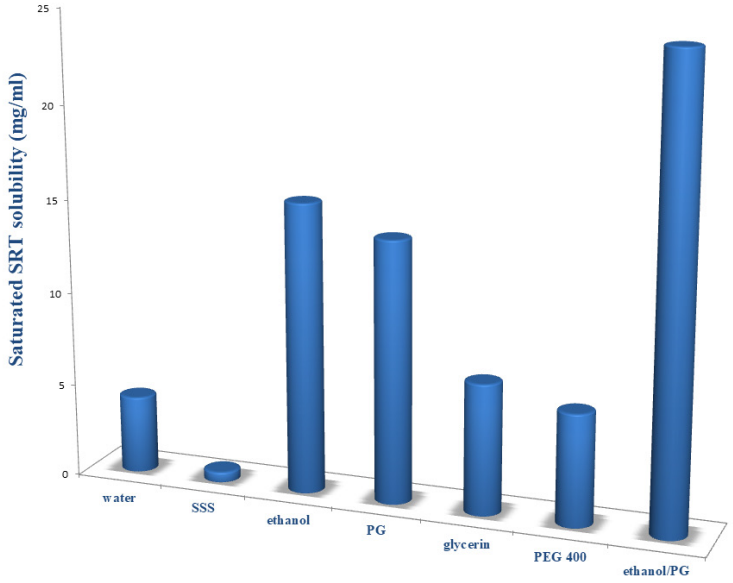

FIGURE 2 - Saturated solubility of SRT in different media and cosolvents.

Physicochemical compatibility studies of SRT with different excipients:

Fourier Transform Infrared (FTIR) studies

The FTIR spectra of pure SRT and its physical mixtures with each polymer used (PVA, HEC, HPMC LV E5, NaAlg and gelatin) are presented in Figure (3 a & b).

Figure (3-a) exhibits the FTIR charts between SRT and the inspected polymers. SRT displayed bands of υN-H at 2448 cm^{-1}, υC-C at 1583 cm^{-1}, υC-H at 1563 cm^{-1}, and υN-CH3 at 1469 cm^{-1}, in addition to symmetrical and asymmetrical bands of υC-H between 1429 and 1403 cm^{-1}. Moreover, the υN-H aliphatic amine band was observed at 1137 cm^{-1}, and those bands appeared between 1060 and 920 cm−1 were ascribed to C-H aromatic rings, while out-plane δC-H aromatic rings and the υC-Cl were positioned around 825 cm (Abouhussein *et al*., 2021)

All the characteristic functional groups in SRT were maintained in the spectrum of the physical mixtures of SRT and the tested polymers. The results indicated that no chemical interaction occurred between SRT and the polymers investigated.

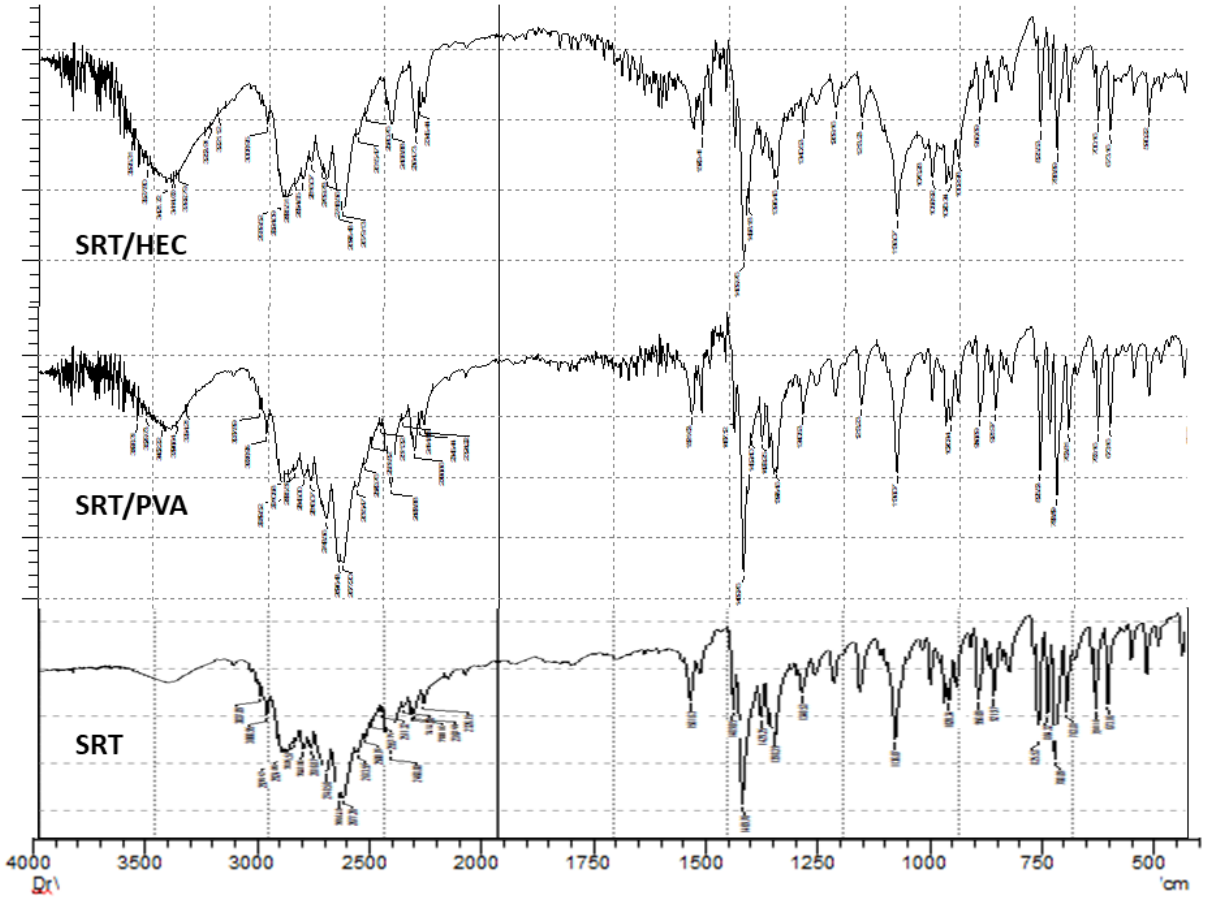

FIGURE 3 a & b - FTIR of SRT and its physical mixtures with different polymers

Differential scanning calorimetric (DSC)

DSC thermogram of SRT shows a characteristic sharp melting endothermic peak at 250.73 ºC as displayed in Figure (4). The DSC thermograms of physical mixtures of SRT and different polymers (figure 4) revealed no significant change in the melting point of SRT in the presence of the studied polymers, indicating no interaction between the examined polymers and SRT (Abouhussein *et al*., 2021).

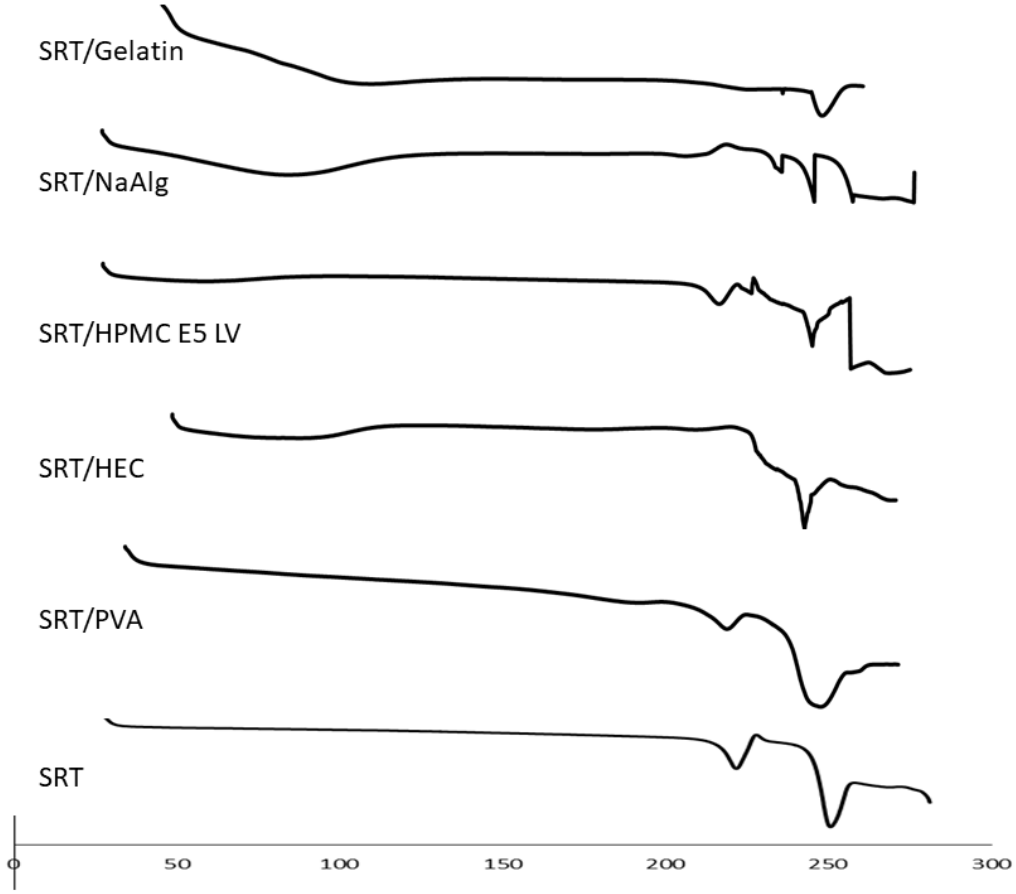

FIGURE 4 - DSC thermograms of SRT and its physical mixtures with different polymer.

Preparation of SRT ODFs

Concerning the preparation of SRT ODFs using different polymers (PVA, HEC, HPMC E5 LV, NaAlg and gelatin) at different concentrations namely 2% and 4%, all the prepared solutions gave clear solutions except NaAlg. Upon adding the SRT solution to the NaAlg solution a homogenous translucent gel was formed which was then transferred to clear film upon drying which may be due to the crosslinking of alginate salt with SRT and its incorporation in the alginate network.

Characterization of SRT casting polymer solution

Determination of viscosity

Both concentrations of HEC solutions showed the highest viscosity followed by NaAlg > gelatin > HPMC E5 LV > PVA. Alongside, increasing the polymer concentration in all polymer solutions led to an increase in the measured viscosity.

Physicochemical characterization of SRT ODFs

Table (I) shows the colour, homogeneity, average weight, thickness, disintegration time, folding endurance, drug content and pH of SRT ODFs.

Colour and Homogeneity

Polymer solutions of high viscosity led to more incorporation of SRT within the developed ODFs and resulted in a more enhanced physical appearance. HEC and NALG ODFs (showing high viscosity values) were homogenous and translucent. On the other side, 2% PVA and 2% HPMC showed non-homogenous films which may be attributed to their low viscosity polymer solution (Figure 5-A).

Together with, increasing the concentration of the used polymer led to more transparency of the prepared films which may be due to more incorporation of SRT within the polymer network.

HEC and NaAlg ODFs were yellowish while other ODFs ranged from white opaque to translucent films as shown in Table (I).

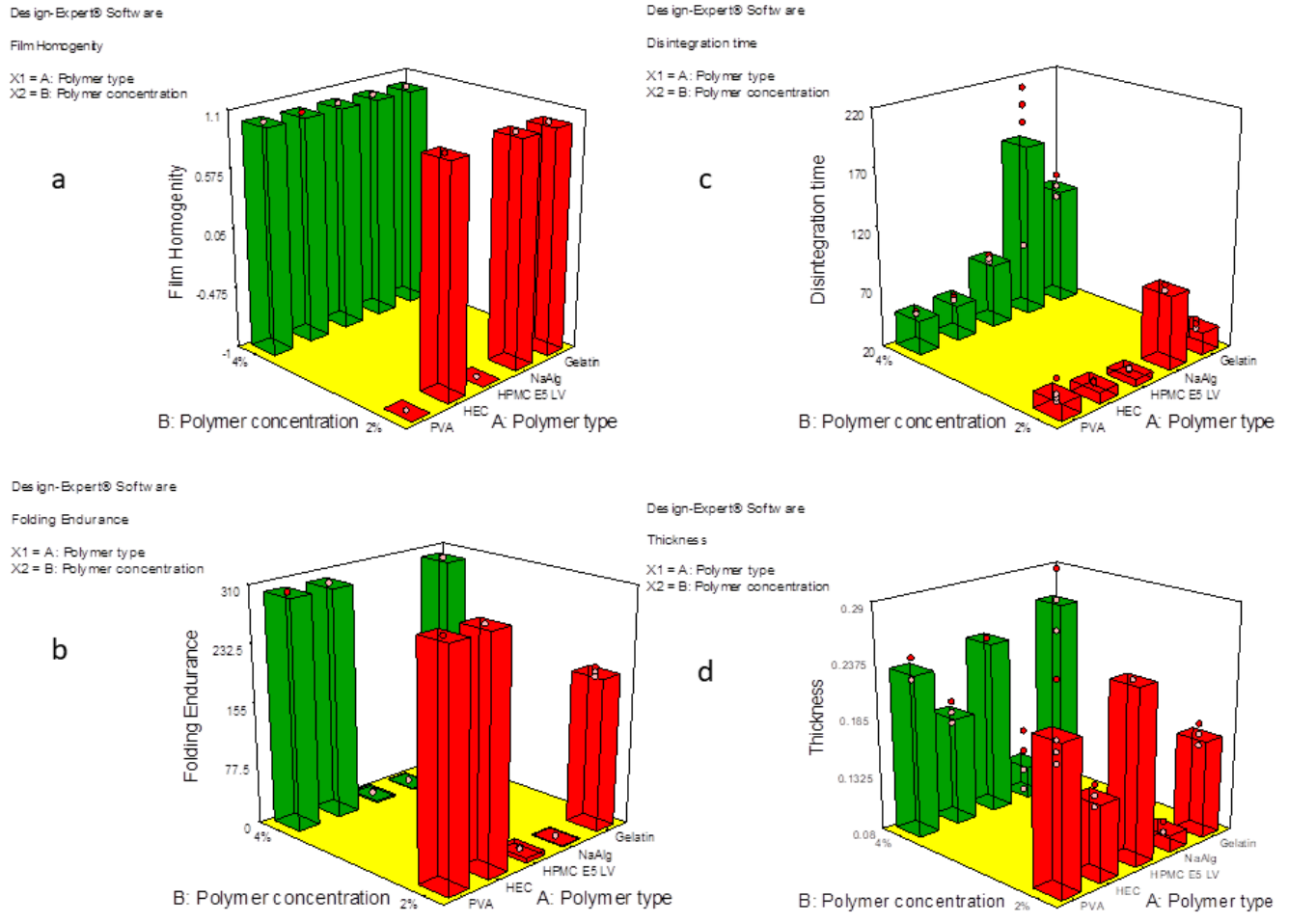

FIGURE 5 - Response surface plot for the effects of polymer type and polymer concentration on (a) film homogeneity (b) Folding endurance (c) Disintegration time and (d) Thickness of SRT ODFs.

Average weight

The average weight of PVA and HEC ODFs ranged from 307 mg to 550 mg and 257 mg to 457 mg respectively, while ODFs prepared from HPMC E5 LV varied from 302 mg to 519 mg, NaAlg ODFs from 273 mg to 430 mg and gelatin ODFs from 280 mg to 532 mg as shown in Table (I).

Thickness

The thickness of SRT ODFs ranged from 0.09 mm to 0.26 mm indicating that all films were of suitable thickness to be applied causing no inconvenience in the mouth. The film thickness varied according to the polymer type (Lakshmi, Sreekanth, Sridharan, 2014). NaAlg films showed the lowest film thickness while HPMC E5 LV showed the highest film thickness. Alongside, the film thickness increased with increasing the polymer concentration using the same polymer as displayed in Table (I) and Figure (5-D).

The ANOVA analysis showed a significant effect of the tested variables with p-values < 0.0001.

The "Pred R-Squared" of 0.8373 is in rational agreement with the "Adj R-Squared" of 0.8821. Moreover, adequate precision exhibited a value of 14.709 which indicates a satisfactory signal to noise ratio where a ratio greater than 4 is preferable. The obtained results are good indicators of the validity of the used model.

Drug Content Uniformity

All the prepared SRT OFTs with homogenous appearance gave acceptable results ranging from 97.9 - 99.3% as revealed in Table (I). The test was not done for non-homogenous films.

Surface pH

Physiological saliva pH ranges between 5.8 and 7.4, however, the pH values of ODFs that significantly differ from this physiological range may cause local irritation to the oral mucosa (Sudhakar, Kuotsu, Bandyopadhyay, 2006). Thus, pH below 5.5 is possibly not appropriate to the dental tissues (Aframian, Davidowitz, Benoliel, 2006). The measured pH values of SRT ODFs were slightly lower than the critical pH value of 5.5. The pH of F1-F10 ranged from 4.32 to 5.6 as shown in Table (I) which indicates the unsuitability for most of the prepared formulations to the buccal environment except F4, F7 and F8.

Folding endurance

All SRT ODFs prepared from PVA, HEC and 4% gelatin (F1-F4 and F10) showed good folding durability (> 300) while other formulae were not durable to folding effect as shown in Table (I) and Figure (5-B). Films prepared from HPMC E5 LV and NaAlg were brittle and not durable to folding movement. 2% gelatin ODF did not tolerate 300 folding times as it was broken after 206 folding times only.

Response surface analysis of the folding endurance results employing the suggested linear model (p-value < 0.0001) by the Design-Expert® was performed. The ANOVA analysis showed a significant effect of the polymer type with p-values < 0.0001 while displayed a non-significant effect (p< 0.869) for polymer concentration. The "Pred R-Squared" of 0.9997 is in reasonable agreement with the "Adj R-Squared" of 0.9998. Besides, adequate precision showed a value of 268.03. It indicates the signal to noise ratio where a ratio greater than 4 is preferable. All of these values were good indicators of the validity of the used model.

Modified in–vitro disintegration time.

The disintegration time is a vital parameter for the characterization of orodispersible dosage forms (Scarpa *et al*., 2018). However, there is still no official method for the determination of the disintegration time of ODFs. So, a modified method using the official disintegration apparatus was utilized.

ODFs are intended to disintegrate within seconds after their contact with saliva in the oral cavity. ODF disintegration is a significant quality and safety attribute as a film that does not disintegrate immediately can cause choking and may impact patient compliance (Preis *et al*., 2014). To ensure the rapid disintegration of ODFs,

the US FDA threshold of 30 s for orodispersible tablets (ODT) (FDA, 2008) was assumed to be appropriate when dealing with quality and safety factors of ODFs (Preis *et al*., 2014).

From Table (I) and Figure (5-C), it is shown that the disintegration time of different SRT ODFs differed with the use of different polymers. ODFs prepared from 2% HPMC E5 LV showed the lowest disintegration time (26 sec) while that of sodium alginate showed the highest disintegration time (200 sec). Increasing the polymer concentration led to an increase in the disintegration time. Most of the developed formulations displayed results above the US FDA threshold (30 sec) which necessitates the need for more work to reach more optimized formulation with more appropriate disintegration time.

The ANOVA results displayed that the studied factors (Polymer Type, Polymer concentration) at a 95% confidence level have a significant effect on the disintegration time of the SRT ODFs since $p < 0.0001$ for all the studied factors. The "Pred R-Squared" of 0.7067 is in reasonable agreement with the "Adj R-Squared" of 0.7646. Furthermore, adequate precision showed a value of 9.671 which is acceptable as it is greater than 4. All these values were good indicators of the validity of the used model. The final equation to correlate between the two independent variables and disintegration time in terms of coded factors was:

Optimization of SRT ODFs

The goal of optimization was to maximize the folding endurance and minimize both the thickness and the disintegration time within a homogenous film. Thus, the desirability values were generated by Design Expert®, and they were used as a measure to optimize the investigated responses using the achieved results. The program revealed the selection of F2 (4% PVA) and F3 (2% HEC) as they showed homogenous films with low disintegration time, highest folding endurance and relatively low film thickness as shown in Figure (6).

Thus, further optimization was approached by the development of blended films of the specified polymer concentrations at different mixing ratios (1:1, 1:2 and 2:1) as shown in Table (III). Then KCl (pore-forming agent) was selected from a previous study to be added to the best blended formulation to enhance the dissolution.

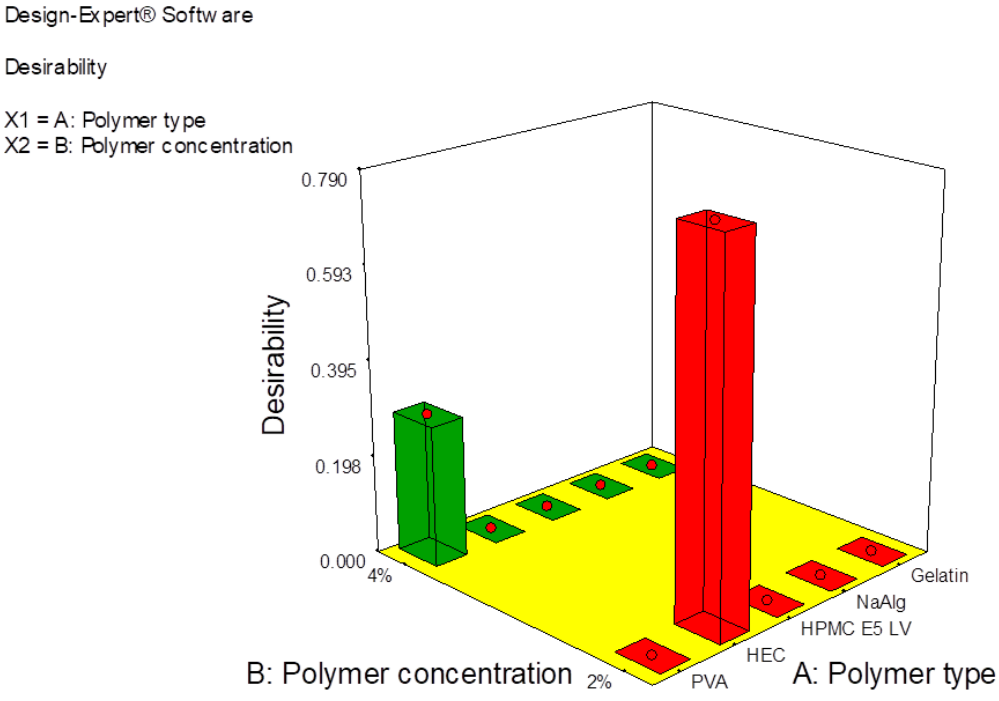

FIGURE 6 - Desirability outcomes of SRT ODFs.

Characterization of the optimized films

Table (III) shows the evaluation results of Formulations (F11-F14). All the formulations were homogenous and showed uniform SRT content. Unlike the developed ODFs from single polymers, blended ODFs showed a more suitable pH to the buccal environment as pH ranged from 5.6 to 6.75. All ODFs revealed suitable film thickness (0.11-0.15 mm).

Modified in–vitro disintegration time.

All the blended SRT ODFs showed acceptable disintegration time ranging from 6-8 sec.

In-vitro dissolution of blended SRT ODFs

As shown in Figure (7), it was observed that percent SRT dissolved was increased from ODFs formulated from blends of both HEC with PVA than from homopolymer ODFs of each of HEC and PVA. SRT dissolution rate was increased with an increase of PVA content. This may be attributed to that the high HEC amount in the ODF can retain a more durable gel structure. Accordingly, the higher PVA content resulted in a weaker gel structure and faster PVA leakage from the film. Therefore, SRT was released faster (54.78 % after 15 min) due to the breakdown of the gel framework (Tang *et al.*, 2007).

KCl enhanced the SRT dissolution rate as presented in Figure (7). KCl can increase the pressure of the film causing the formation of pores that facilitate the release of SRT from the polymer network leading to an increase of SRT dissolution (Chisca, Sava, Bruma, 2013; Yuan, Yu, Zhang, 2011).

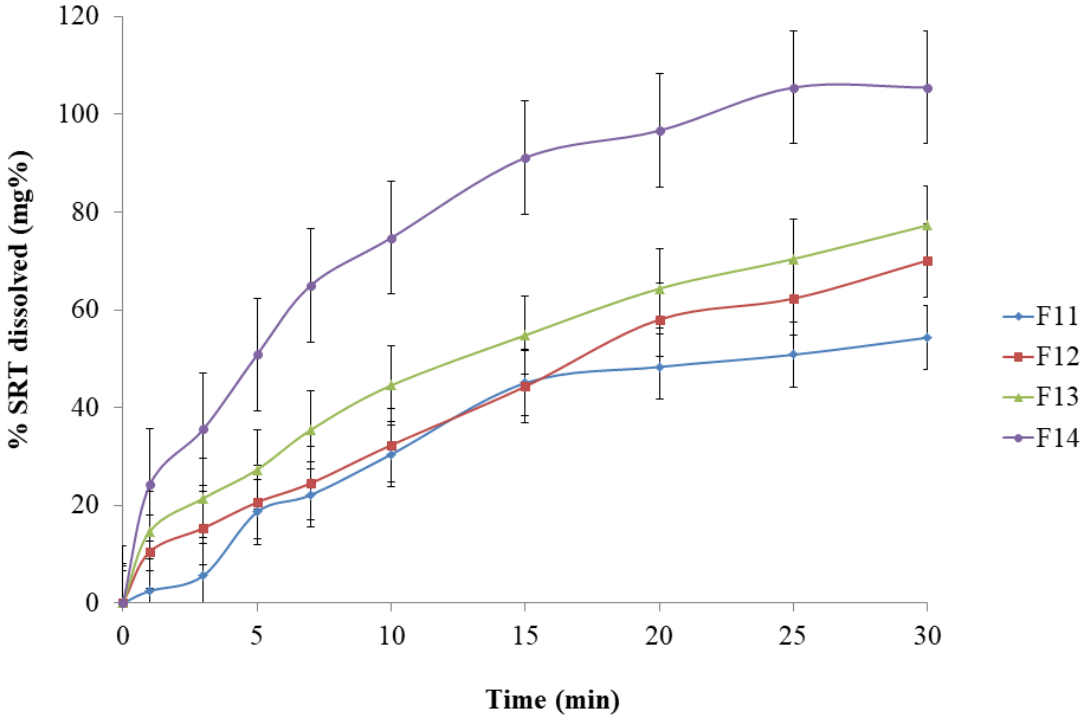

FIGURE 7 - In-vitro dissolution of SRT from the optimized SRT ODFs.

Scanning electron microscope imaging

Figure (8) shows the morphological surface images of the selected formulation (F14) containing 2:1 4% PVA: 2% HEC and 5% KCl. It was observed that F14 had a smooth porous surface with homogenous pores size (<1 μ) and distribution (Yuan, Yu, Zhang, 2011).

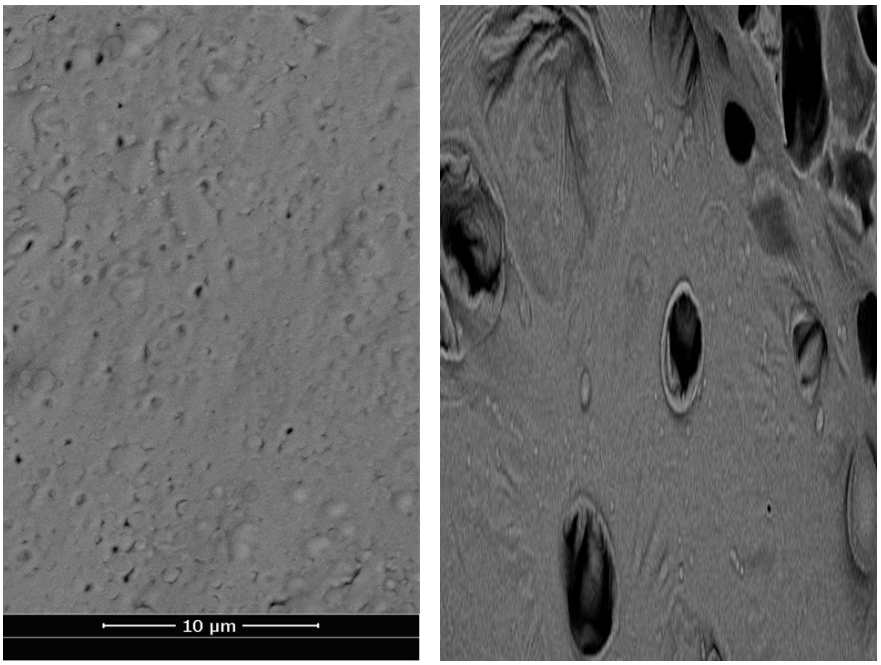

FIGURE 8 - Scanning Electron microscope of the selected SRT ODF (F14).

CONCLUSION

In our study, fourteen different SRT ODFs based on five different polymers (PVA, HEC, HPMC E5 LV, NaAlg and gelatin) plasticized with sorbitol have been developed as favorable platforms for a small-scale laboratory production of ODFs e.g., hospitals and community pharmacies. SRT ODFs based on blended polymers of both 4% PVA and 2% HEC were successfully developed and characterized. Blended SRT ODFs displayed more suitable physicochemical characterization including pH and disintegration time than homopolymer ODFs. ODF based on (2:1 4% PVA and 2% HEC & 5% KCl) showed a more enhanced dissolution rate than other films. SRT ODFs could be considered an effective pharmaceutical substitute for the conventional oral dosage forms enabling prompt management of depression episodes that can be easily formulated in hospitals and community pharmacies to be taken as a step for the implementation of personalized medicine.

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