

Formulation and evaluation of simvastatin buccal film

Gamal M El-Maghraby, Mona M Abdelzاهر*

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

ARTICLE INFO

Article history:

Received on: 12/11/2014

Revised on: 11/12/2014

Accepted on: 19/01/2015

Available online: 27/04/2015

Key words:

Simvastatin, Buccal film,
Solvent casting,
Carboxymethyl cellulose,
Polyvinylpyrrolidone.

ABSTRACT

The aim of this work was to develop and evaluate a buccal film for delivery of simvastatin. Buccal films containing carboxymethyl cellulose (CMC) with and without Polyvinylpyrrolidone (PVP) as polymers were prepared. Tween 80 was included with and without propylene glycol (PG) to modulate the characteristics of the films. The films were prepared by solvent casting with drug concentration being maintained at 2.5 mg/cm². In absence of Tween and PG, the films were opaque due to precipitation of drug. PG reduced the swelling index and increased the thickness of the film due to shrinkage. Incorporation of PVP into the films increased the bioadhesion force and time. The rate of drug release depended on the composition of the film with the presence of PVP increasing the release efficiency compared to the corresponding PVP free films. Similarly, incorporation of PG increased the drug release efficiency. Thermal analysis indicated the presence of the drug in amorphous form or as a solid solution in the film components. The developed films are promising for buccal administration of simvastatin.

INTRODUCTION

Simvastatin belongs to the statins which is lipid lowering group. They act by inhibiting the 3-hydroxy3-methylglutaryl coenzyme A (Schachter, 2004). In the past few years, several novel indications for statin therapy was emerged (Paraskevas *et al.*, 2008). It was shown to reduce vascular inflammation, attenuate myocardial injury (Tandon *et al.*, 2005), decrease the incidence of Alzheimer's disease and dementia (Fassbender *et al.*, 2001), limit the progression of inflammatory diseases (Christensen *et al.*, 2006), and treat chronic periodontitis (Pradeep and Thorat, 2012). Simvastatin is water insoluble crystalline powder (Ungaro *et al.*, 2010). It undergoes extensive first pass metabolism in the liver which results in very low and variable oral bioavailability. The properties of drug like short half-life (2-3 hour), small dose size (5-80mg) and low molecular weight (418.57) makes it suitable candidate for administration by buccal route (Hiremath, 2009). This route of administration is expected to overcome the problem of poor oral bioavailability by at least avoiding the presystemic metabolism of the drug.

In addition, buccal delivery can be useful in treatment of chronic periodontitis. Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally (Vishnu *et al.*, 2007). The recent years saw the introduction of a number of mucoadhesive dosage forms for buccal drug delivery. These include buccal tablets, discs, films, and semisolid products such as gels. Of these systems, buccal films are preferable over tablets and discs in terms of patient comfort and flexibility with high potential for accurate drug dosing and longer residence time compared to semisolid formulations (Verma *et al.*, 2011). Accordingly, the objective of this work was to develop and evaluate a buccal film for delivery of simvastatin.

MATERIALS AND METHODS

Materials

Simvastatin (SIM) and carboxymethyl cellulose (CMC) were obtained as a gift sample from Sigma Pharmaceutical Company, Quesna, Egypt. Polyvinylpyrrolidone K40 (PVP K40) was purchased from Sigma Chemical Co., Steinheim, Germany. Propylene glycol (PG) was purchased from BDH chemical Ltd., Poole, England. Tween 80 (TW) was purchased from El Nasr Pharmaceutical Chemicals Co., Cairo, Egypt.

* Corresponding Author

Mona M Abdelzاهر, Department of Pharmaceutical Technology,
College of Pharmacy, University of Tanta, Tanta, Egypt
Email: monam.abdelzاهر@gmail.com

Preparation of simvastatin buccal films

Table 1 presents the composition of different buccal films. The buccal films were prepared by solvent casting method (Mahajan *et al.*, 2011) in which the polymers were dissolved in water to form a clear solution. The drug was dissolved in ethanol before mixing with the polymer solution. Tween 80 and/or propylene glycol were added to the mixture. The solution was casted into a petri dish (78.6 cm²) and dried. The dry film was cut into square shaped sections (4 cm²).

Evaluation of simvastatin films

Weight uniformity

The individual weight of 3 samples (4 cm²) of each formulation was determined using an electrical balance (Semalty *et al.*, 2008). The results were analyzed for mean and standard deviation.

Thickness uniformity

The thickness of 3 samples (4 cm²) of each formulation was determined using the Vernier Caliber (Giradkar *et al.*, 2010). The results were analyzed for mean and standard deviation.

Folding endurance

Folding endurance was determined by repeatedly folding the film at the same place till it broke or folded up to 200 times without breaking (Khairnar *et al.*, 2009).

Drug content uniformity

The medicated film (4 cm²) which is expected to contain 10mg of simvastatin theoretically was dissolved in 50 ml ethanol. The solution was suitably diluted with ethanol before determination of the drug concentration spectrophotometrically at a λ_{max} of 238 nm (Hiremath, 2009) using UV spectrophotometer (Thermo Fisher Scientific, Madison, USA). The experiment was performed in triplicate and the drug content was expressed as percentage of the labeled using the following equation:

Drug content (%) = (Experimental drug content / Theoretical drug content) x 100

Microenvironment pH

The microenvironment pH of the prepared buccal films was determined to ensure palatability of the film. A combined glass electrode was used for this purpose. The films (4 cm²) were soaked in 5ml of distilled water for 1hr at ambient temperature. The surface pH was recorded by mounting the electrode on the surface of the swollen film and allowing it to equilibrate for 1 minute (Khairnar *et al.*, 2009). The experiment was performed in triplicate.

Swelling index

The film sample (1 cm²) was placed in a pre-weighed stainless steel basket of the dissolution apparatus. The loaded basket was weighed before being submerged into 200ml phosphate

buffered saline (PBS, pH 7.4). The loaded basket was taken out of the bath and reweighed after careful removal of any surface moisture by gentle wiping with tissue paper. The increase in the weight of the film was determined at each interval (5, 10, 15, and 30) and the experiment was continued until a constant weight was observed. The swelling index was calculated using the formula (Koland *et al.*, 2010):

$$\text{Swelling index} = (W_t - W_0) / W_0$$

Where W_t is the weight of the film at time t and W_0 is the weight of the film at zero time (before coming into contact with PBS).

In vitro bioadhesion strength

The bioadhesive strength of the prepared simvastatin films was measured using rabbit intestine as a model mucosal membrane (Nafee *et al.*, 2003). The animals were sacrificed immediately before the start of the experiment. The rabbit intestine was excised and washed gently with phosphate buffer pH 6.6. The intestine was cut longitudinally to expose the mucosal surface. This was cut into rectangular pieces (4cm²). These were glued with cyanoacrylate adhesive on the ground surface of a holder made of cellulose acetate plastic film so that the mucosal surface is uppermost. The buccal film (4cm²) was glued to another holder of the same size. The surface of the rabbit intestine was moistened with phosphate buffer pH 6.6. The two holders with rabbit intestine and buccal film were put in contact with each other with uniform and constant light pressure between fingers for one minute (preload time) to facilitate adhesion bonding. The upper tissue holder was allowed to hang on an iron stand with the help of an aluminum wire fastened with a hook fixed on the back of the holder. A pre-weighed light weight polypropylene bag was attached to the hook on the backside of the lower film holder with aluminum wire. After a pre-load time of one minute, water was added to the polypropylene bag using a burette adjusted to deliver water at a rate of 2.0 drops per second until the film was detached from the tissue. The collected water in the bag was measured and expressed as the weight (gram) required for the detachment (bioadhesive strength) (Alanazi *et al.*, 2007). The force of adhesion and bond strength was calculated according to the following equations (Habib *et al.*, 2010):

$$\text{Force of adhesion (N)} = (\text{Bioadhesive strength (g)} \times 9.81) / 1000$$

$$\text{Bond strength (N m}^{-2}\text{)} = \text{Force of adhesion} / \text{film surface area}$$

In vitro bioadhesion time

The *in vitro* residence time of simvastatin films was evaluated by assessing the time required for these films to detach from rabbit intestinal mucosa (Singh *et al.*, 2008). The rabbit intestinal mucosa was fixed with mucosal side facing up on the surface of a glass slide cover slips using cyanoacrylate glue. The mucosa was moistened with phosphate buffer solution (pH 6.6). The film (1 cm²) was wetted with the same buffer and was pasted to the rabbit intestinal mucosa by applying a light force with fingertip for one minute. The whole assembly was placed in the dissolution vessel so that the film is facing up and the glass side is down before adding 250ml of phosphate buffer pH 6.6 previously

equilibrated at 37 ± 0.5 °C. The dissolution paddle was rotated at a rate of 50 rpm. This stirring rate is believed to simulate the environment of the buccal cavity. The time taken for the film to completely erode or detach from the mucosa was recorded as the *in vitro* mucoadhesion time (Hassan *et al.*, 2011).

In vitro release studies

The drug release from the films was studied using USP rotating paddle dissolution test apparatus. The dissolution medium consisted of 250 ml phosphate buffer pH 6.6 containing 0.15% sodium dodecyl sulfate. The later was included to ensure sink conditions. The release studies were performed at 37 ± 0.5 °C, at a stirring rate of 50 rpm. Buccal film (4cm²) which contains 10mg of simvastatin was glued to a glass slide with cyanoacrylate adhesive from one side to ensure unidirectional drug release. The glass slide was placed in the bottom of the dissolution vessel so that the film remains on the upper side of the slide. Samples (5ml) were withdrawn at predetermined time intervals (15, 30, 45, 60, 90, 120, 150, 180, 210, 240, 270, 300 min) and replaced with equal volume of fresh dissolution medium. The samples were filtered and analyzed by UV spectrophotometer at 238 nm. The amount of drug released at each time interval was calculated and the cumulative amount of drug released was calculated as a function of time to construct the drug release profile (Hiremath *et al.*, 2009). The drug release efficiency (RE) was calculated from the area under the dissolution curve at time t (determined using the nonlinear trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (El Maghraby and Alomrani, 2009).

Compatibility studies of simvastatin with the formulated additives

To investigate any possible interactions between the drug and other ingredients of the formulation, differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FTIR) were used.

Differential scanning calorimetry

These studies involved recording the thermograms of the samples (simvastatin, the selected polymers and their films in presence and absence of Tween 80 and/or propylene glycol) using a differential scanning calorimetry (DSC) (DSC-60, Shimadzu, Japan). Samples equivalent to approximately 2 mg of the drug were loaded into aluminum pans before crimping the lids using a Shimadzu crimper. The thermal behavior of each sample was investigated at a heating rate of 10 °C/min, covering temperature ranges of 25–300 °C. The instrument was calibrated with an indium standard. Data analysis was conducted using the TA-60WS thermal analysis software. The transition midpoint (T_m) of the drug was recorded.

Fourier Transform infrared spectroscopy

The Fourier transform infrared (FTIR) spectra of simvastatin, the selected polymers and their films in presence and

absence of Tween 80 and/or propylene glycol were recorded using FTIR spectrophotometer (FTIR- Spectrometer, Tensor 27, Bruker, USA). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000 to 600 cm⁻¹.

RESULTS AND DISCUSSION

Physicochemical characteristics of simvastatin buccal bioadhesive films

Table 1 presents the composition of the successful formulations which produced acceptable simvastatin buccal films after solvent casting. The prepared films were transparent, smooth, uniform and flexible. It should be noted that initial studies utilized a formulation similar to F1 but without Tween 80. This produced opaque film which can be attributed to possible precipitation of the drug. This problem was eliminated after addition of Tween 80 to produce F1 which resulted in an acceptable film. It was thus decided to incorporate Tween 80 as a basic component in all formulations. Preparation of PVP-based films F3 was initially prepared in absence of CMC. This resulted in a transparent film which was difficult to remove from the petri dish due to the stickiness of PVP. Accordingly, CMC was combined with PVP and Tween 80 to produce F3 (Table 1) which produced an acceptable film. Incorporation of propylene glycol into the CMC or PVP based films produced plasti films but the films suffered some shrinkage. The same polymers were successfully utilized to prepare buccal films for various drugs. PVP and CMC were incorporated in ketorolac buccal film (Alanazi *et al.*, 2007). Other investigators employed CMC in combination with carbopol to develop clotrimazole buccal film (Singh *et al.*, 2008), with PVP being utilized in combination with hydroxyl propyl cellulose in glibenclamide buccal film (Goudanavar *et al.*, 2010).

Table 1: Composition of different formulae of simvastatin buccal films.

Formulae	SIM (mg/cm ²)	CMC (mg/cm ²)	PVP (mg/cm ²)	TW (mg/cm ²)	PG (mg/cm ²)
F1	2.5	7.5		3.8	
F2	2.5	7.5		3.8	20.2
F3	2.5	5.63	1.87	3.8	
F4	2.5	5.63	1.87	3.8	20.2

SIM is simvastatin, CMC is carboxymethyl cellulose, PVP is Polyvinylpyrrolidone, K40, TW is tween 80, and PG is propylene glycol.

The physical characteristics of the films are presented in Table 2. The data revealed the formation of thin films with the thickness being increased in case of films containing PG. The increase in thickness can be attributed to the shrinkage of the films. The increase of film thickness was associated with an increase in the weight of the film (Table 2). The recorded values of the thickness and weight are comparable to published data on miconazole buccal film (Rasool and Khan, 2010). Due to the shrinkage of the film the drug content of the shrunked films was more than that of non-shrunked ones. The data in the Table reveal low values of the SD in all parameters which indicates the reproducibility of the method of preparation. The folding and endurance study revealed high flexibility of the films which is

indicated from the ability of the films to tolerate folding for more than 200 times without cracking. The microenvironment pH of different batches ranged from 6.05 to 6.84 so they were expected to be palatable.

Swelling index

The swelling index values are in the following order F1> F3> F2> F4 (Table 2). These results suggested that the presence of CMC resulted in stronger water absorption power. This absorption power and hence the swelling index were decreased in presence of propylene glycol and/or PVP. These findings agree with the previously recorded results on similar films (Basu *et al.*, 2010) (Anjankumar, 2011).

Table 2: Physicochemical characteristics of the prepared simvastatin buccal films.

Characteristics Formulae	Thickness (mm)	Weight (mg/4cm ²)	Drug content (mg/4cm ²)	Folding endurance	pH	Swelling index
F1	0.133 (0.006)	58.33 (1.15)	10.63 (0.02)	>200	6.32 (0.02)	12.88 (1.15)
F2	0.283 (0.006)	98.66 (1.16)	12.45 (0.24)	>200	6.05 (0.03)	4.28 (0.29)
F3	0.163 (0.006)	61.33 (0.58)	10.65 (0.14)	>200	6.85 (0.14)	7.75 (1.74)
F4	0.233 (0.006)	99.33 (0.58)	13.15 (0.72)	>200	6.49 (0.27)	3.04 (0.31)

Values between brackets are SD, n = 3. The swelling index was calculated as the maximum increase in weight relative to the initial weight of the film. The maximum increase in weight was reached after 30, 15, 15 and 10 minutes for F1, F2, F3 and F4, respectively.

Bioadhesion strength and residence time

The bioadhesion strength and time are presented in Table 3. The bioadhesion strength of the prepared film depended on the composition of the film. Films containing PVP showed greater bioadhesion strength compared to the corresponding films in absence of PVP.

Table 3: Bioadhesion parameters of the prepared simvastatin buccal films.

Formulation	Bioadhesive strength (g)	Force of adhesion (N)	Bond strength (Nm ⁻²)	Bioadhesion time (min)
F1	3.31 (1.08)	0.032	8.12	57.3 (15.75)
F2	3.13 (1.78)	0.031	7.68	67.3 (13.01)
F3	5.63 (0.62)	0.055	13.81	65.3 (1.15)
F4	3.63 (1.14)	0.035	8.89	156.3 (35.47)

Values between brackets are SD, n = 3.

Thus F3 was better than F1 and F4 was better than F2 with respect to the bioadhesive strength. Similar finding was recorded after incorporation of PVP in CMC films (Perioli *et al.*, 2004). With respect to the effect of propylene glycol on bioadhesion its effect was contrary to that of PVP. This can be explained on the base that the bioadhesion strength depends on the charge density which is higher in case of PVP with incorporation of propylene glycol reducing such density (Habib *et al.*, 2010). It

should be noted that the data of bioadhesion time did not correlate with that of the bioadhesion strength (Table 3). This can be attributed to the fact that both parameters depend on different factors with the bioadhesion strength depending on the electrostatic interaction and the bioadhesion time (residence time) being affected by the dissolution rate of the film (Habib *et al.*, 2010).

In-vitro release studies

The in vitro drug release from the prepared films was determined at conditions mimicking the buccal cavity. The release profiles are shown in Figure 1. The kinetics of drug release was determined by fitting the release profiles to the zero-order, first-order and Higuchi diffusion model. Linear regression was then performed and the correlation coefficient (R²) values were recorded and used for determination of the best fit. These values are presented in Table 4. For CMC based films (F1 and F2) the release pattern followed a zero order kinetics providing constant rate of drug release irrespective to the remaining drug in the film. Incorporation of PVP in the films resulted in films (F3 and F4) which produced initial rapid release followed by slower release rate and the profile followed Higuchi diffusion kinetic model (Table 4).

Table 4: Kinetics of simvastatin release of different formulae according to different kinetic models, and the release efficiency.

Formulae	Correlation coefficient (R ²)			Release efficiency
	Zero-order	First-order	Higuchi	
F1	0.9779 (0.01)	0.9344 (0.017)	0.9586 (0.017)	39.92 (1.8)
F2	0.9505 (0.021)	0.8523 (0.055)	0.9429 (0.035)	42.55 (2.99)
F3	0.9449 (0.047)	0.8147 (0.054)	0.9716 (0.019)	53.78 (5.15)
F4	0.9224 (0.046)	0.7195 (0.056)	0.9727 (0.024)	62.45 (3.69)

Values between brackets are SD, n = 3.

Similar release pattern was recorded for films containing PVP and/or CMC. For example zero order release pattern was recorded for clotrimazole film in which CMC was used as the polymer (Singh *et al.*, 2008) with CMC/PVP combination producing a film which released ibuprofen according to Higuchi diffusion system (Perioli *et al.*, 2004). The release efficiency was calculated with the goal of investigating the effect of film composition on the release rate of the drug. The calculated release efficiencies are presented in Table 4. Incorporation of PVP in the mucoadhesive films increased the release rate as indicated from the release efficiency values (Table 4). This effect can be attributed to the ability of PVP to increase the wetting and penetration of water into the film matrices with subsequent increase in the diffusion of the drug (Koland *et al.*, 2012). With respect to the effect of incorporation of propylene glycol, its presence increased the release rate which is manifested as an increase in the release efficiency. This can be explained on the base of the solubilizing effect of propylene glycol on simvastatin which can result on faster drug release (Kang *et al.*, 2004).

Another possible explanation depends on the humectant nature of the propylene glycol which leads to hydration of the film. This will result in more rapid drug release as the release is known to be proportional to the amount of water absorbed into a film (Rasool and Khan, 2010).

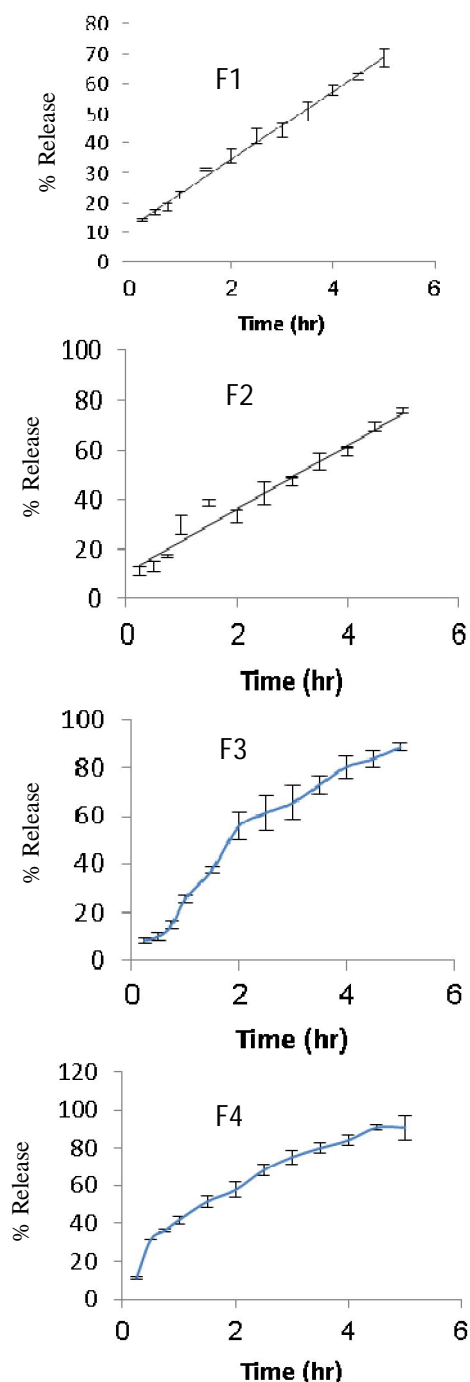


Fig. 1: Release profiles of simvastatin from different mucoadhesive films.

Compatibility studies of simvastatin with formulated additives Differential scanning calorimetry

Figures 2 and Figure 3 show representative thermograms for the simvastatin, the selected polymers and their films, in presence and absence of Tween 80 and/or propylene glycol. Pure

simvastatin produced sharp endothermic peak at 139 °C corresponding to the melting transition of the drug. This reflects the crystalline nature of the drug.

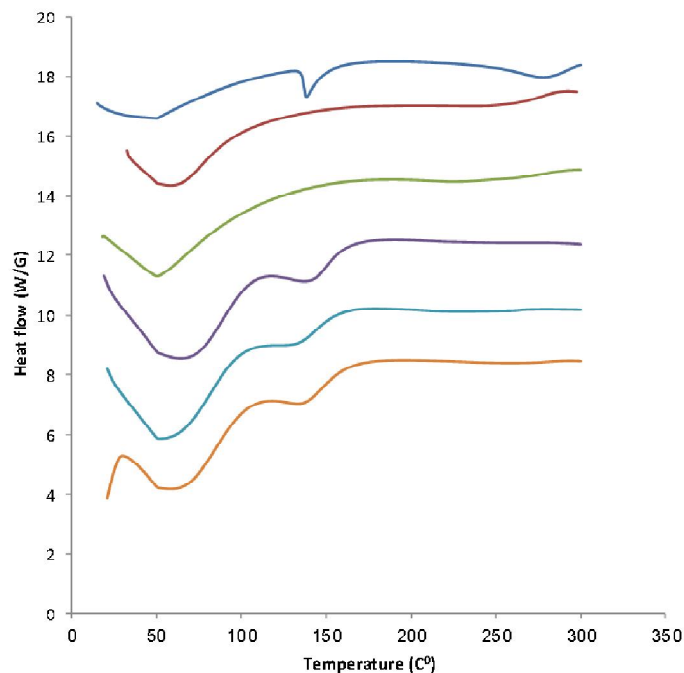


Fig. 2: DSC thermograms of simvastatin, carboxymethyl cellulose and their films in presence and absence of Tween 80 and/or propylene glycol. The curves from top to bottom are pure drug (SIM), pure polymer (CMC), a film composed of (SIM, CMC, and TW), a film composed of (SIM, CMC, and PG), a film composed of (SIM, CMC, TW, and PG), and a film composed of (CMC, TW, and PG).

This is in good agreement with previous findings on the thermal analysis of simvastatin (Hiremath *et al.*, 2009). Carboxymethyl cellulose produced broad endothermic peak around 58.315 °C. This broad peak can be attributed to evaporation of the bound water. This thermogram is similar to the previously reported data for the same polymer (Mekaway *et al.*, 2013). Presence of this endotherm in the thermograms of the films indicates evaporation of the bound water or sorbed moisture. As for CMC, Polyvinylpyrrolidone produced broad endothermic peak at 60 °C. This can be also attributed to evaporation of bound water. This is supported by previous reports on the same polymer (Giri *et al.*, 2010).

Incorporation of the drug in either CMC/Tween or CMC/PVP/Tween films resulted in complete disappearance of the endothermic peak of the drug. This can be attributed to transformation of the drug into amorphous structure or presence of the drug as solid solution in the film. Both films showed the broad endotherm corresponding to evaporation of the bound liquid (Figures 2 and 3). Incorporation of propylene glycol in simvastatin films resulted in the appearance of additional broad endothermic peak with a T_m being recorded in the range of 125 to 134 °C. This broad endotherm can be attributed to evaporation of the propylene glycol which is more viscous liquid. To confirm this explanation, plain films comprising CMC, Tween and propylene glycol with or

without PVP were prepared and subjected to DSC study. The resulting thermograms (Figures 2 and 3) revealed the broad endothermic peaks which were detected in the medicated film. This confirms that the second broad peak corresponds to propylene glycol evaporation. Overall, the recorded DSC data explain the good release rate of such lipophilic drug even in small amount of dissolution medium.

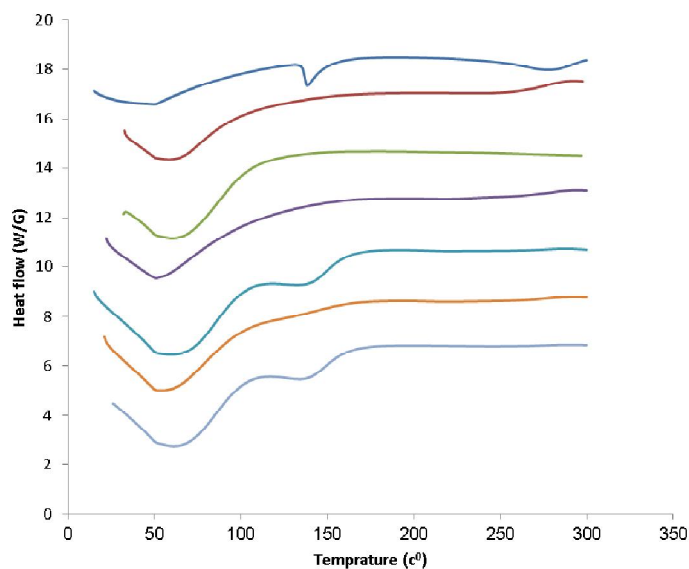


Fig. 3: DSC thermograms of simvastatin, carboxymethyl cellulose, Polyvinylpyrrolidone, and their films in presence and absence of Tween 80 and/or propylene glycol. The curves from top to bottom are pure drug (SIM), pure polymer (CMC), pure polymer (PVP), a film composed of (SIM, CMC, PVP, and TW), a film composed of (SIM, CMC, PVP, and PG), a film composed of (SIM, CMC, PVP, TW, and PG), and a film composed of (CMC, PVP, TW, and PG).

Fourier Transform infrared spectroscopy

Figures 4 and 5 show The FTIR spectra of simvastatin, the selected polymers and their films in presence and absence of Tween 80 and/or propylene glycol. Pure simvastatin showed the characteristics peaks at 3550 which corresponds to the free OH stretching vibrations, 2969 which corresponds to methyl C-H asymmetric stretching, 1699 which is due to the ester C=O stretching and 1269 which is due to lactone -C-O-C stretch. The recorded spectrum is similar to the previously recorded for the same drug (Pandya *et al.*, 2008).

The spectra of pure CMC showed characteristics peaks at 3441.96 which corresponds for the O-H stretching, 2924 which is due to C-H stretch, 1629 corresponding to the anti-symmetric vibration of COO⁻ groups, 1429.49 and 1326.55 due to symmetrical deformations of CH₂ and COH groups and at 1056.77 which is due to CH-O-CH₂ stretching.

This pattern is in good agreement with the previously recorded spectrum for the same polymer (Tongdeesoontorn *et al.*, 2011). Pure PVP spectrum showed characteristics peaks at 2994, 2929 and 2835.82 due to CH stretching, at 1692.41 due to C=O stretching, 1319.16 due to CN stretching, with the peak recorded between 1290.53 and 1017.65 being attributed for the C-H stretching vibration. In addition the spectrum revealed a broad

band at 3442.31 which reflects the hygroscopic nature of the polymer. This is similar to the previously recorded spectrum (Giri *et al.*, 2011) (El Maghraby and Elsergany, 2014). It is important to note that the critical function groups (carbonyl and hydroxyl groups) are existing in the drug as well as in the tested polymer.

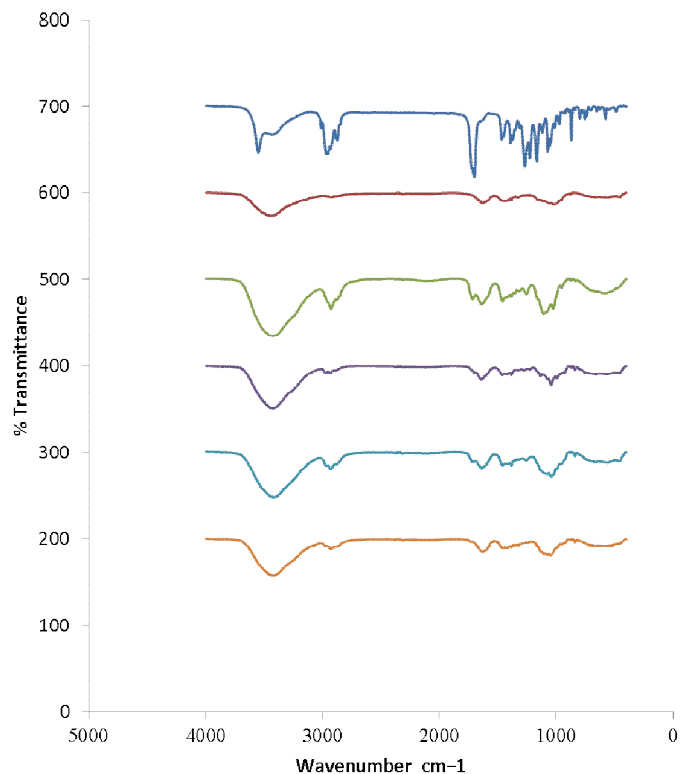


Fig. 4: FTIR spectra of samples (simvastatin, carboxymethyl cellulose and their films in presence and absence of Tween 80 and/or propylene glycol). The curves from top to bottom are pure drug (SIM), pure polymer (CMC), a film composed of (SIM, CMC, and TW), a film composed of (SIM, CMC, and PG), a film composed of (SIM, CMC, TW and PG), and a film composed of (CMC, TW, and PG).

This may make identification of interaction a difficult task. Looking at the spectra of the prepared films, it can be noted that the position of the carbonyl group is in between that of the drug and that of the polymer with the peak becoming broader. Taking into consideration the fact that the concentration of polymer predominate in the film composition, the recorded peak of carbonyl group in the film can be considered as the summation of the peaks of the drug and the polymers.

With respect to the OH stretching vibration of the drug, the recorded band in the films was overshadowed by the corresponding broad bands in the polymers. Overall, the recorded spectra for the prepared films did not reflect significant interaction between the drug and the polymers although it did not exclude possible hydrogen bonding. It should be noted that the release experiments reflected the liberation of the drug from the films suggesting that the presence of hydrogen bonding (if any) is not deleterious for the drug.

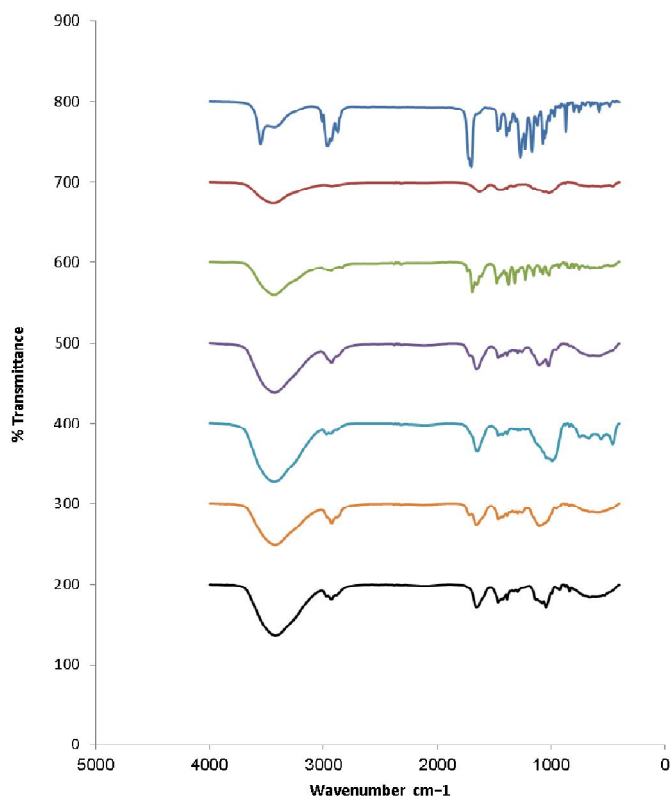


Fig. 5: FTIR spectra of samples (simvastatin, carboxymethyl cellulose, Polyvinylpyrrolidone and their films in presence and absence of Tween 80 and/or propylene glycol). The curves from top to bottom are pure drug (SIM), pure polymer (CMC), pure polymer (PVP), a film composed of (SIM, CMC, PVP, and TW), a film composed of (SIM, CMC, PVP, and PG), a film composed of (SIM, CMC, PVP, TW, and PG), and a film composed of (CMC, PVP, TW, and PG).

CONCLUSION

Preparation of CMC film in absence of Tween and propylene glycol resulted in opaque films due to precipitation of the drug. Incorporation of Tween produced clear film due to solubilization of the drug. Incorporation of PVP into the films increased the bioadhesion force and time. The rate of drug release from the films depended on their composition with presence of PVP increasing the release efficiency compared to the corresponding PVP free films. Similarly, incorporation of PG increased the drug release efficiency. The developed films included the drug in amorphous form or as a solid solution. The developed films are promising for buccal administration.

REFERENCES

- Alanazi FK, Abdel Rahman AA, Mahrous GM, Alsarra IA. Formulation and physicochemical characterization of buccoadhesive films containing ketorolac. *J. Drug Del. Sci.*, 2007; 17 (3):183-192.
- Anjankumar PB. Design and evaluation of buccal patches of valsartan. *IJPI's Journal of Pharmaceutics and Cosmetology*, 2011; 1 (2):50-55.
- Basu B, Garala K, Thimmasetty J. Formulation and evaluation of pimozone buccal mucoadhesive patches. *International Journal of Pharmaceutical Sciences and Nanotechnology*, 2010; 2 (4):739-748.
- Christensen M, Su A, Snyder R, Greco A, Lipschutz J, Mandaio M. Simvastatin protection against acute immune-mediated glomerulonephritis in mice. *Kidney international*, 2006; 69:457-463.

El Maghraby GM, Alomrani AH. Synergistic enhancement of itraconazole dissolution by ternary system formation with pluronic F68 and hydroxypropylmethylcellulose. *Sci. Pharm.*, 2009; 77:401-417.

El Maghraby GM, Elsergany RN. Fast disintegrating tablets of nisoldipine for intra-oral administration. *Pharmaceutical development technology*, 2014; 19 (6):641-650.

Fassbender K, Simons M, Bergmann C, Stroick M, Lutjohann D, Keller P, Runz H, Kuhl S, Bertsch T, Bergmann KV, Hennerici M, Beyreuther K, Hartmann T. Simvastatin strongly reduces levels of Alzheimer's disease beta amyloid peptides AB42 and AB40 *in vitro* and *in vivo*. *PNAS J.*, 2001; 98 (10):5856-5861.

Giradkar KP, Channawar MA, Kajale AD, Sirdhar E, Kambel RS, Bakde B. V, Chandewar AV. Design, development and *in vitro* evaluation of bioadhesive dosage form for buccal route. *IJPRD*, 2010; 2 (6).

Giri N, Natarajan RK, Gunasekaran S, Shreemathi S. ¹³C NMR and FTIR spectroscopic study of blend behavior of PVP and nano silver particles. *Archives of Applied Science Research*, 2011; 3 (5):624-630.

Giri TK, Badwaik H, Alexander A, Tripathi DK. Solubility enhancement of ibuprofen in the presence of hydrophilic polymer and surfactant. *International Journal of Applied Biology and Pharmaceutical Technology*, 2010; 1 (2):793-800.

Goudanavar PS, Bagali RS, Patil SM, Chandashkhara S. Formulation and *in-vitro* evaluation of mucoadhesive buccal films of glibenclamide. *Der Pharmacia letter*, 2010; 2 (1):382-387.

Habib F, Abdel Azeem M, Fetih G, Safwat M. Mucoadhesive buccal patches of lornoxicam. *Bull. Pharm. Sci.*, 2010; 33(1):59-68.

Hassan MA, Barakat NS, El-Badry M, Shehata MS. Formulation and *in vitro* / *in vivo* evaluation of naproxen mucoadhesive buccal patches for local effect. *J. Drug Del. Sci. Tech.*, 2011; 21 (5):423-431.

Hiremath JG, Sarfaraz MD, Hiremath D, Sarudkar SA. Preparation and physicochemical characterization of simvastatin loaded mucoadhesive bilayered tablet. *Indian Journal of Novel Drug Delivery*, 2009; 1(1):18-24.

Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, Lee HB, Cho SH. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *International Journal of Pharmaceutics*, 2004; 274:65-73.

Khairnar A, Jain P, Baviskar D, Jain D. Development of mucoadhesive buccal patch containing aceclofenac: *in vitro* evaluations. *International Journal of PharmaTech. Research*, 2009; 1(4):978-981.

Koland M, Charyulu RN, Vijayanarayana K, Prabhu P. *In vitro* and *in vivo* evaluation of chitosan buccal films of ondansetron hydrochloride. *International Journal of Pharmaceutical Investigation*, 2012; 1(3):164-171.

Mahajan A, Chhabra N, Aggarwal G. Formulation and characterization of fast dissolving buccal films: A Review. *Der Pharmacia Letter*, 2011; 3(1):152-165.

Mekkawy A, Fathy M, El-Shanawany S. Formulation and *in-vitro* evaluation of fluconazole topical gels. *British Journal of Pharmaceutical Research*, 2013; 3 (3): 293-313.

Nafee NA, Boraie NA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. *Acta Pharm.*, 2003; 53:199-212.

Pandya P, Gattani S, Jain P, Khirwal L, Surana S. Co-solvent evaporation method for enhancement of solubility and dissolution rate of poorly aqueous soluble drug simvastatin: *In vitro - In vivo* evaluation. *AAPS PharmSciTech*, 2008; 9(4): 1247-1252.

Paraskevas KI, Stathopoulos V, Mikhailidis DP. Pleiotropic effects of statins: implications for a wide range of diseases. *Current vascular pharmacology*, 2008; 6 (4):237-239.

Perioli L, Ambrogi V, Angelici F, Ricci M, Giovagnoli S, Capuccella M, Rossi C. Development of mucoadhesive patches for buccal administration of ibuprofen. *Journal of Controlled Release*, 2004; 99:73-82.

Pradeep AR, Thorat MS. Clinical effects of sublingually delivered simvastatin in the treatment of patients with chronic

periodontitis: A Randomized clinical trial. J periodontal, 2010; 81(2):214-222.

Rasool BK, Khan S. *In-vitro* evaluation of miconazole mucoadhesive buccal films. Int. J. Appl. Pharm, 2010; 2 (4):23-26.

Schachter M. Chemical pharmacokinetic and pharmacodynamic properties of statins: an update. Blackwell publishing fundamental and clinical pharmacology, 2004; 19:117-125.

Semalty M, Semalty A, Kumar G, Juyal V. Development of mucoadhesive buccal films of glipizide. Ind. J. Pharm. Sci., 2008; 1 (2):184-190.

Singh S, Jain S, Muthu MS, Tiwari S, Tilak R. Preparation and evaluation of buccal bioadhesive films containing clotimazole. AAPS PharmSciTech, 2008; 9 (2):660-667.

Tandon V, Bano G, Khajuria V, Parihar A, Gupta S. pleiotropic effects of statins. Indian J Pharmacol., 2005; 37 (2):77-85.

Tongdeesontorn W, Mauer L, Wongruong S, Sriburi P, Rachtanapun P. Effect of carboxymethyl cellulose concentration on physical properties of biodegradable cassava starch-based films. Chemistry Central Journal, 2011; 5 (6):1-8.

Ungaro F, Giovino C, Catanzo O, Miro A, Mele A, Quaglia F, La Rotonda MI. Use of cyclodextrins as solubilizing agents for simvastatin: effect of hydroxypropyl- β -cyclodextrin on lactone/hydroxyacid aqueous equilibrium. International J of Pharmaceutics, 2010; 404:49-59.

Verma S, Kaul M, Rawat A, Saini S. An overview on buccal drug delivery system. International Journal of Pharmaceutical Sciences and Research, 2011; 2 (6):1303-1321.

Vishnu VY, Chandrasekhar K, Ramesh G, Madhusudan Rao Y. Development of mucoadhesive patches for buccal administration of carvedilol. Current Drug Delivery, 2007; 4:27-39.

How to cite this article:

El-Maghraby G. M., Abdelzاهر M. M. Formulation and evaluation of simvastatin buccal film. J App Pharm Sci, 2015; 5 (04): 070-077.