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Pharmaceutical and Analytical Evaluation of Prolonged Release Rosuvastatin-Ca Buccoadhesive Tablets

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Authors' contributions

This work was carried out in collaboration between all authors. Author MAM and SAAR designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author MMS managed the analyses of the study and performed the statistical analysis. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Rosuvastatin-Ca was prepared in solid dispersion as buccoadhesive tablets to increase its bioavailability and the release of the drug from its buccoadhesive formulae due to its poor aqueous solubility. The solid dispersions were prepared using β-cyclodextrin, polyethylene glycol 6000 and polyethylene glycol 4000 by kneading and solvent evaporation methods and were characterized by differential scanning calorimetry (DSC). They were also prepared using poloxamer 407 as a biocompatible and mucoadhesive carrier by freeze drying method. The buccoadhesive tablets of the drug were formulated using sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose and sodium alginate by direct compression method. The prepared tablets were evaluated for their physical, dissolution, mucoadhesive and swelling properties. An in-vitro release study showed slow and prolonged release of the drug from tablets as compared to marketed formulation. Five formulae were selected for applying the recently reported analytical methods and results were compared statistically with a compendial one.

Keywords: Rosuvastatin-ca buccoadhesive tablets; in vitro study.

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1. INTRODUCTION

Therapeutic agents administered through buccal mucosa enter directly to the systemic circulation and thereby circumvent the first-pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route. Among these the buccal mucosa has several advantages like excellent accessibility, good permeability, less enzymatic activity and suitability for the administration of retentive dosage forms [1-4]. Since, the buccal route is an attractive site for administration of drugs asbuccal tablets which are small, flat and intended to be held between the cheek and teeth or in the cheek pouch [5]. An ideal buccal adhesive system must have certain properties as adherence to the site of attachment for few hours, release of the drug in controlled manner and providing the drug release in a unidirectional way into the mucosa [6].

Rosuvastatin-ca is a poorly water-soluble 3-hydroxy3-methyl glutryl CoA (HMG-CoA) reductase inhibitor, used as antihyperlipidemic agent. It is incompletely absorbed from the GIT due to its low aqueous solubility that results in a low bioavailability of about 20% [7]. Also it undergoes first-pass hepatic metabolism, thus it is beneficial to administer it as buccoadhesive tablets.

The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier. There are a number of materials used for developing such systems [8]. The most studied materials are the polymers derived from cellulose, such as hydroxyethylcellulose and carboxymethylcellulose, alginates, and poloxamers.

The aim of the present work is to prepare rosuvastatin-Ca as sustained released buccoadhesive tablets with improving drug release by solid dispersion technique to increase solubility and enhance its low bioavailability.

2. MATERIALS

Pure Rosuvastatin- Ca, B.N. RCM2MHAO2A, was kindly supplied by Hikma Pharmaceutical Company, Egypt with purity of 99.20% according to manufacturer specification.Suvikan® Tablets, B.N. 003, labelled to contain 20 mg rosuvastatin-Ca per tablet, a product of Hikma Pharmaceutical Company, Egypt, were purchased from local market. Hydroxypropylmethyl cellulose (HPMC 4000) and β-cyclodextrin (β-CD), (Sigma, USA), sodium carboxymethyl cellulose (NaCMC) and sodium alginate (Memphis, Egypt), poloxamer-407 (EIPICO, Egypt), polyethylene glycol 4000 (PEG 4000) and polyethylene glycol 6000 (PEG 6000), (BDH. Laboratory, United Kingdom) were used.Talc and magnesium stearate (ADWIC, Egypt), Avicel (NF 18/USP23 M 101, TongSing Chemicals Co., Taiwan). KH_2PO_4, NaOH and anhydrous Na_2SO_4 (EL-Nasr Co., Egypt) were also used.Phosphate buffer solution (pH 6.8) was prepared by mixing 50 mL of 0.2M KH_2PO_4 with different volumes of 0.2 M NaOH and diluting to 200 mL with water. Methanol, acetonitrile and chloroform (Sigma – Aldrich, USA) were used. Dichloro-dicyanobenzoquinone and Tetracyanoquinodimethane, (DDQ and TCNQ, Merck, Germany), 0.15% and 0.2% solutions were prepared in acetonitrile. Dichlorophenol indophenol, (DCPI, Winlab, U.K.), 0.1% solution was prepared in chloroform by dissolving 0.1gm of its sodium salt in 30 mL water,the solution was quantitatively transferred to a separator, rendered acidic with 5 mL 2N HCl and extracted with three successive 25 mL portions of chloroform, pooled through anhydrous Na_2SO_4 into a 100 mL volumetric flask and diluted to volume with chloroform.

3. METHODOLOGY

3.1 Solubility Studies

Five milligrams of rosuvastatin-Ca were weighed and were added to 10 mL distilled water containing different concentrations of PEG 6000, PEG 4000 and poloxamer 407. These mixtures were shaken in a shaker (Oscilllating thermostatically controlled water bath shaker, Gallemtkamb, England) at 37±0.5ºC until equilibrium was achieved (2 days). Then, mixtures were filtered through (pore size 0.45µm) and the obtained solutions were measured spectrophotometrically at 240nm (Shimadzu UV/Vis spectrophotometer PC – 1601, Tokyo, Japan).

Samples containing 5 mg of rosuvastatin-Ca in 10 mL of distilled water containing (0-10 mmol/L) of β-CD and were treated as mentioned above by shaking at 37±0.5ºC for 72 hours and measuring absorbance at 240nm. Phase solubility diagram was constructed using Higuchi and Connors method [9] from which apparent 1:1 stability constant of drug -β-CD complex was calculated.

3.2. Preparation of Rosuvastatin-Ca Solid Dispersion

3.2.1 Solvent evaporation method [10]

Co-evaporated products were prepared by dissolving rosuvastatin-Ca, PEG 6000 and PEG 4000 in a ratio of 1:1 in a minimum volume of methanol at room temperature. The solvent was evaporated under vacuum in a rotary evaporator at 45°C and the residues were dried under vacuum at room temperature up to a constant weight. The solid masses were pulverized using pestle and mortar and sieved. Sieve fractions of (50 – 200 µm) were used for all subsequent studies.

3.2.2 Kneading method [11]

Rosuvastatin-Ca and β-CD in a molar ratio of 1:1 were mixed manually and wetted with the minimum volume of water. Then were ground thoroughly with a pestle to obtain a paste which was then dried under vacuum at room temperature up to a constant weight. Sieve fractions of (50 – 200 µm) were used for all subsequent studies.

3.2.3 Freeze drying method (lyophilization) [12]

Rosuvastatin-Ca and poloxamer 407 in a ratio of 1:1 was prepared by dispersion of drug into 100 mL of poloxamer 407 solution with the help of a magnetic stirrer (Magnetic stirrer, Thermolyne corporation, Dubuque Lowa, U.S.A). Liquid ammonia 25% was added dropwise and stirred until a clear solution was obtained. The sample was freezed to a temperature of -40ºC (Freezer) and then lyophilized in a freeze dryer at a temperature of - 40ºC and vacuum of 90×10^{-3} Mbar (Freeze dryer, Vertis Sentry, Freeze Mobile, 25SL, Gardiner, NY, USA). The freeze dried mass was then sifted through 60 mesh sieve and stored in air-tight containers until further evaluation.

3.3 Buccoadhesive Tablets Preparation [13]

An amount of rosuvastatin-Ca solid dispersions with PEG 6000, PEG 4000, β-CD or poloxamer 407 equivalent to 20 mg of the drug were mixed with buccoadhesive polymers (NaCMC, HPMC 4000and Na. alg.) in a ratio 1:1 together with other additives like Avicel pH-101, magnesium stearate and talc using a mortar and a pestle and were tableted by direct compression (Tablet compression machine, with flat faced single punch no. 8, Erweka, Type EK: 0, Erweka apparatus, Germany) to achieve a total weight of 140 mg. Twelve different formulae were prepared together with tablets without any polymer as control.

3.4 *In vitro* Release Study

Using the USP I (rotating basket method)(Dissolution Test Apparatus, USP standard, DA-6D, Bombay 400-069 India),each of the prepared bioadhesive tablet was fixed in a petri dish using wax which coats all sides of the tablet except the upper side allowing the release of rosuvastatin-Ca from one side [14,15]. The dissolution media consisting of 900 mL of phosphate buffer of pH 6.8 (Jenco pH meter (608) with jenway double junction glass electrode, England)and was maintained at 37°C±0.5°C for 5 hours and the basket was rotating at 100 rpm. At appropriate time intervals, 5 mL of each sample was taken and filtered through a 0.045 µm Millipore filter. The sample taken off was then replaced with equivalent amount of fresh dissolution fluid to maintain a constant volume. The samples were then analyzed spectrophotometrically at 240 nm. The mean of three determinations were used to calculate the drug release from each of the formulations.

3.5 Evaluation of Rosuvastatin-Ca Buccoadhesive Tablets [16]

3.5.1 Drug content

Ten of the prepared buccoadhesive tablets were powdered and mixed. An amount equivalent to 20 mg of rosuvastatin-Ca was taken and dissolved in 100 mL of methanol, then was filtered. The absorbance of the collected solution was measured at 243 nm and the mean drug content of 10 tablets and the standard deviations were calculated.

3.5.2 Uniformity of weight, thickness and hardness

Ten of the prepared buccoadhesive tablets were randomly selected for analysis. The mean weight, thickness (Tablet thickness apparatus, Plainimeter, India) and hardness (Tablet hardness tester, Model: T H-16, China)of tablets were calculated.

3.5.3 Friability

Twenty of the prepared buccoadhesive tablets were randomly selected and brushed. They were accurately weighed and placed in the drum of the friabilator (Digital tablet friability test apparatus, Model: F T-2D, VEEGO, Progressive Insturments, India), that rotated at 100 rpm, for 4 minutes. Then tablets were removed, carefully brushed and reweighed. The percent loss in weight was taken as a measure of tablet friability and mean friability (%w/w) was calculated.

3.5.4 Disintegration time

Six of the prepared buccoadhesive tablets were randomly selected and the disintegration time (Tablet Disintegration test apparatus, VEEGO Model: VTD-3D, India) for each tablet in distilled water at 37°C was recorded in min. and mean disintegration time was calculated.

3.6 Bioadhesive Forces of Rosuvastatin-Ca Buccoadhesive Tablets [17,18]

The tensile strength required to detach the bioadhesive tablet from the mucosal surface was applied, as a measure for the bioadhesive performance of the tablets.

- The rabbit intestinal mucosa was selected as the model mucosal membrane. Male rabbits (1.0-1.5 kg) were sacrified and their intestine (jejunum parts as their pH starts from 6.5) were carefully washed with normal saline to remove any loose material. Then frozen at -20°C until required. At time of use, the tissue was allowed to thaw at 4 °C, cut into 3 cm length, opened longitudinally to expose the inner mucosal surface and mounted securely in place with mucosal side upwards.
- The apparatus used for the determination of the bioadhesive force was locally designed. It was composed mainly of two arms balance. The left arm of the balance was replaced by a tablet holder that composed of a small platinum lamina, which was vertically suspended through a wire. At the same side a movable platform was maintained in the bottom in order to fix the model mucosal membrane. A glass beaker was placed on the right pan of the balance and a burette was fixed near the right arm to allow water to fall in the beaker at a constant rate.
- For the determination of the bioadhesive force, the tablet was glued to the platinum lamina using cyanoacrylate adhesive (Amir alpha). A piece of rabbit intestinal mucosa of 3 cm in length was also glued to the platform. The exposed tablet surface was moistened with 15 µl of phosphate buffer (pH6.8) and left for 30 sec for initial hydration and swelling. The platform was then raised upward until the hydrated tablet was brought into contact with the mucosal surface. A preload of 50 gm was placed over the platinum lamina for 3, 10 and 15 min as the initial pressure. The preload was then removed and water was allowed to fall in the beaker at a constant rate. Increasing the weight of water added would gradually stretch the tablet from the mucosal surface till complete detachment of the adhesive bond and finally the separation of tablet from mucosa. The water in the beaker was weighed and the bioadhesive force was calculated per unit area of the tablet as follows:

$$F = (W_w \times g) / A \quad \text{……..……..} \quad (1)$$

Where F: is the bioadhesive force in (dynes/ cm^2), $W_{w:}$ is the weight of water collected in the beaker in (gm), g: is the acceleration due to gravity in (cm/ sec^2) = 981 cm/ sec^2 and A: is the surface area of the tablet in (cm^2) = πr^2 = 22/7× (0.8^2) = 2.01cm^2.

3.7 Swelling Properties of Rosuvastatin-Ca Buccoadhesive Tablets [19]

For each formulation, three tablets were weighed separately (W1). Each tablet was placed in a petri dish, 4 mL of phosphate buffer (pH 6.8) was added and placed in an incubatorat 37°C (Electric oven, Heraeus, UT 5060 E, Germany). At time intervals of 0.5- 5 h, excess buffer was carefully removed and the swollen tablets were weighed (W2). The swelling index was determined from the equation:

Swelling index= (W2- W1) / W1…… (2)

3.8 Microenvironment Ph Studies of Rosuvastatin-Ca Buccoadhesive Tablets [19,20]

The microenvironment pH of the prepared bioadhesive tablets was determined to evaluate the possible irritation effects on the mucosa. The tablets were left to swell in 4 mL of the phosphate buffer of pH 6.8 in small beakers and the pH was measured at time intervals of 2.5 h and 5 h by pH meter (Jenco pH meter (608) with jenway double junction glass electrode, England) in contact with the microenvironment of the swollen tablets. The average pH of six tablets was calculated.

3.9 Application of the Proposed Analytical Methods to Rosuvastatin-Ca Buccoadhesive Tablets

Atomic absorption spectrometry (AAS) and charge transfer complexation with dichloro-dicyanobenzoquinone (DDQ), tetracyanoquinodimethane (TCNQ) and dichlorophenol indophenols (DCPI) [21] were applied to analyze five chosen formulae of prepared rosuvastatin-Ca buccoadhesive tablets (F2, F3, F6, F10 and F12).Twenty tablets of each formula were weighed and finely ground. An amount of fine powder equivalent to 100 mg of rosuvastatin-Ca were weighed in a beaker and extracted by sonication with 70 mL H_2O or methanol for about 10 min, respectively then filtered in a 100- mL volumetric flask and completed to volume with the same solvent. The clear aqueous filtrate labeled to contain 1.0 mg mL^{-1} of rosuvastatin-Ca was analyzedby AAS (Perkin-ElmerA/Analyst 400 atomic absorption spectrometer, USA)and the methanolic filtrate was analyzed Vis-spectrophotometery through charge transfer complexation (Shimadzu UV/Vis spectrophotometer PC – 1601, Tokyo, Japan) as previously reported [21].

4. RESULTS AND DISCUSSION

Absorption spectra of rosuvastatin-Ca in phosphate buffer pH 6.8 showed λ_{max} at 240nm.

4.1 Solubility Studies

It was found that the solubility of drug in buffer pH 6.8 is 1.8mg/ml, in methanol is 24mg/ml while in water was 1.1 mg/ml. Due to the low solubility of drug in aqueous media so a carriers were tried to increase its solubility. The solubility of the drug in PEG 6000, PEG 4000 and poloxamer 407 were presented in Fig. 1 which illustrated a linear increase in the solubility of the drug with increasing polymer concentration.

The phase solubility diagram for drug with β -CD presented in Fig. 2 showed that aqueous solubility of drug increases linearly as a function of β -CD concentrations which can be classified as AL type of Higuchi [9] and might be ascribed to the formation of rosuvastatin-calcium - β –CD complex in the molar ratio of 1:1. The calculated apparent stability constant (Kc) for the prepared solid dispersion of rosuvastatin-Ca was 460 M^{-1} for (drug- β -CD) according to the equation mentioned by Higuchi and Connors [9] that found to be within the ideal range reported (100 and 1000 M^{-1}).

Kc= slope / [intercept (1- slope)] [9]…….. (3)

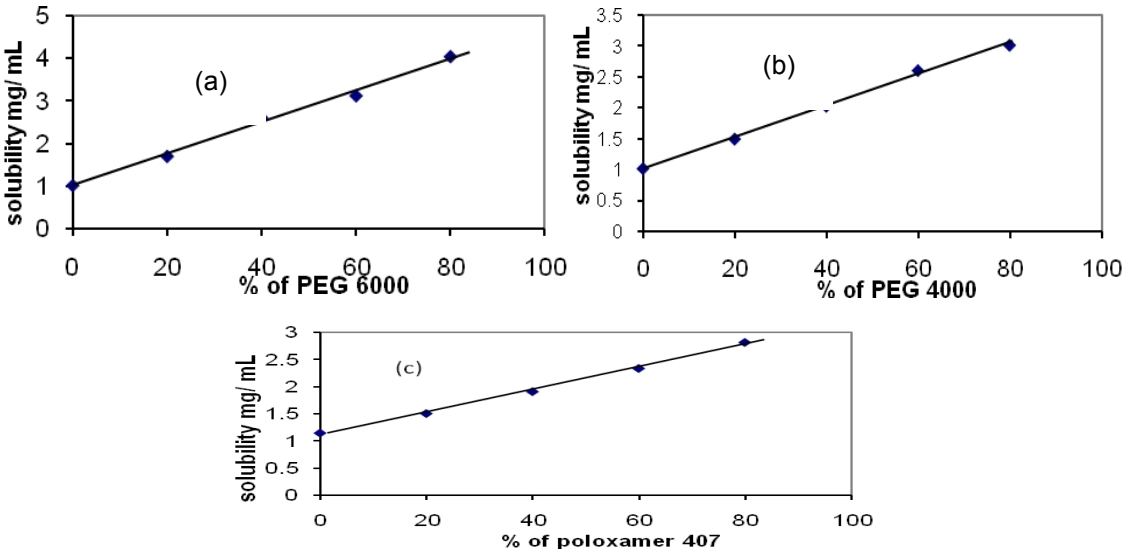

Fig. 1. Solubility diagram of rosuvastatin-Ca: (a) in PEG 6000,(b) in PEG 4000 and (c) in poloxamer 407

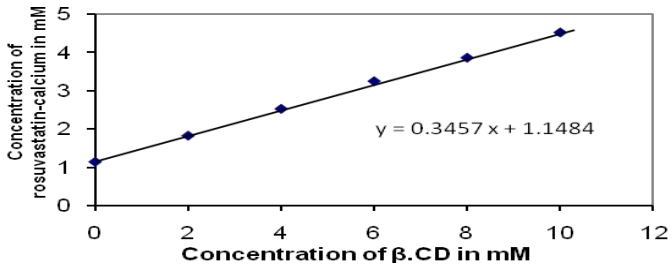

Fig. 2. Phase solubility diagram for rosuvastatin-Ca with β-CD

4.2 Characterization of Rosuvastatin-Ca Solid Dispersion

DSC thermograms illustrated that rosuvastatin-Ca shows two endothermic peaks at 86.03 °C and 279.89°C that disappeared in the thermograms of solid dispersions of drug with PEG 6000, PEG 4000, β-CD and its freezedried complex with poloxamer 407; proving complexation of drug with the four polymers, Fig. 3.

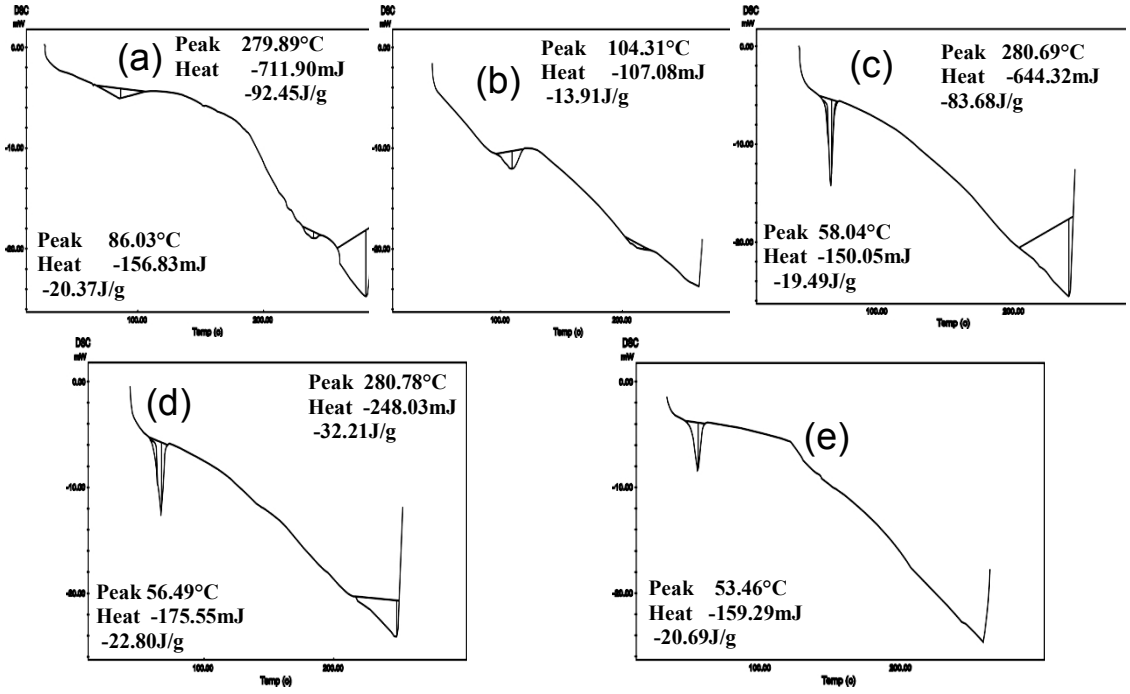

Fig. 3. DSC thermograms of (a) Rosuvastatin-Ca, (b) Rosuvastatin-Ca - β-CD, (c) Rosuvastatin-Ca - PEG6000, (d) Rosuvastatin-Ca - PEG4000, and (e) Rosuvastatin-Ca Poloxamer 407 solid dispersions

4.3 Buccoadhesive Tablets Preparation [13]

Rosuvastatin-Ca buccoadhesive tablets were prepared by direct compression using buccoadhesive polymers as NaCMC, HPMC 4000, Na alginate and poloxamer-407, avicel PH-101 as diluents and magnesium stearate and talcas lubricants. The dose of drug was 20mg, mixed with the buccoadhesive polymer in a ratio 1:1 to obtain total weight of each tablet of 140 mg; Table 1.

4.4 *In vitro* Release Study [14,15]

Using the USP I (rotating basket method) a slow and prolonged release of the drug was observed from the prepared buccoadhesive tablets was observed in comparison with market product (Suvikan® tablets). An improvement in the total amount of drug release from the solid dispersion was observed which might be indicative to the formation of inclusion complexes between rosuvastatin-Ca and the hydrophilic carriers used that were previously confirmed by DSC analysis. Regarding the % drug release profile of the prepared buccoadhesive tablets F2 showed highest drug release (75.4% in 300 min); Fig. 4.

Table 1. Composition of the prepared buccoadhesive rosuvastatin-calcium tablets

Formula	Drug	polymer	Drug- polymer complex equivalent to 20 mg drug	Talc	Magnesium stearate	Avicel	Total weight
Rosuvastatin-calcium plain	20 mg	—	—	0.7 mg	0.7 mg	118.6 mg	140 mg
F1(drug+NaCMC)	20 mg	20 mg	—			98.6 mg	
F2(drug +NaCMC+β-CD)	—		82.4 mg			36.2 mg	
F3(drug +NaCMC+ PEG6000)	—		53.56 mg			65.04 mg	
F4(drug +NaCMC+ PEG4000)	—		55.32 mg			63.28 mg	
F5(drug +HPMC)	20 mg		—			98.6 mg	
F6(drug +HPMC+ β-CD)	—		82.4 mg			36.2 mg	
F7(drug +HPMC+ PEG6000)	—		53.56 mg			65.04 mg	
F8(drug +HPMC+ PEG4000)	—		55.32 mg			63.28 mg	
F9(drug +Na.alg)	20 mg		—			98.6 mg	
F10(drug + Na.alg +β-CD)	—		82.4 mg			36.2 mg	
F11(drug + poloxamer 407)	20 mg		—			98.6 mg	
F12(drug + poloxamer 407 freeze drying)	—	—	76.75 mg			61.85 mg	

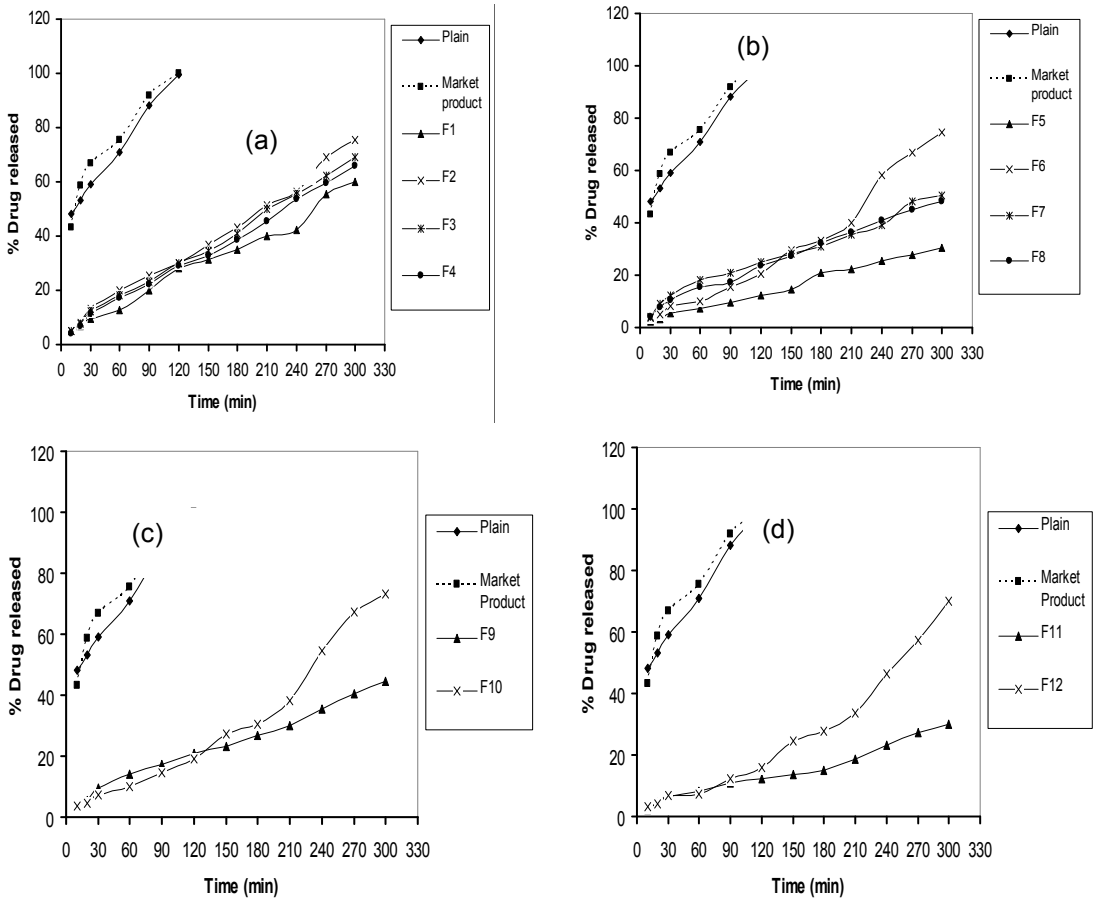

Fig. 4. In vitro-release study of Rosuvastatin-Ca from (a) NaCMC, (b) HPMC, (c) Na alg. and (d) Poloxamer 407 buccoadesive tablets

4.5. Evaluation of Rosuvastatin-Ca Buccoadhesive Tablets [16]

4.5.1 Quality control testing

The assayed mean content of drug in the prepared buccoadhesive tablets were calculated to be 95.57% - 101.72% ± 0.85-2.29.The mean weights of all tablets were in the range of 138.06 - 139.70 mg ± 0.17-0.79, thickness was ranged between 2.46 and 2.52 mm ± 0.04-0.09 and hardness between 3.22 and 4.67 kg ± 0.10-0.27 . The percent weight loss in the friability test was found to be 0.13-0.45% ± 0.03-0.12 and disintegration time was 55.4-86.0 min ± 0.27-0.84.Thus all the physical parameters of the compressed tablets prepared were practically within the acceptable limits as indicated in Table 2.

4.6 Bioadhesive Forces of Rosuvastatin-Ca Buccoadhesive Tablets [17,18]

Fig. 5 shows the effect of contact time on the bioadhesive force. It was clear that increasing the contact time significantly increased the bioadhesion properties for all formulae except F12, where a mean contact time of 10 min showed highest bioadhesive force for most formulations. These hydrophilic bioadhesive materials only become adhesive on hydration to form a tacky film. It is also interesting to note that after a certain time, there is a decrease of the adhesion properties indicating the possible further water diffusion towards the rest of the dry disc and the drying out of the bioadhesive interface as for the rest of formulae [20].

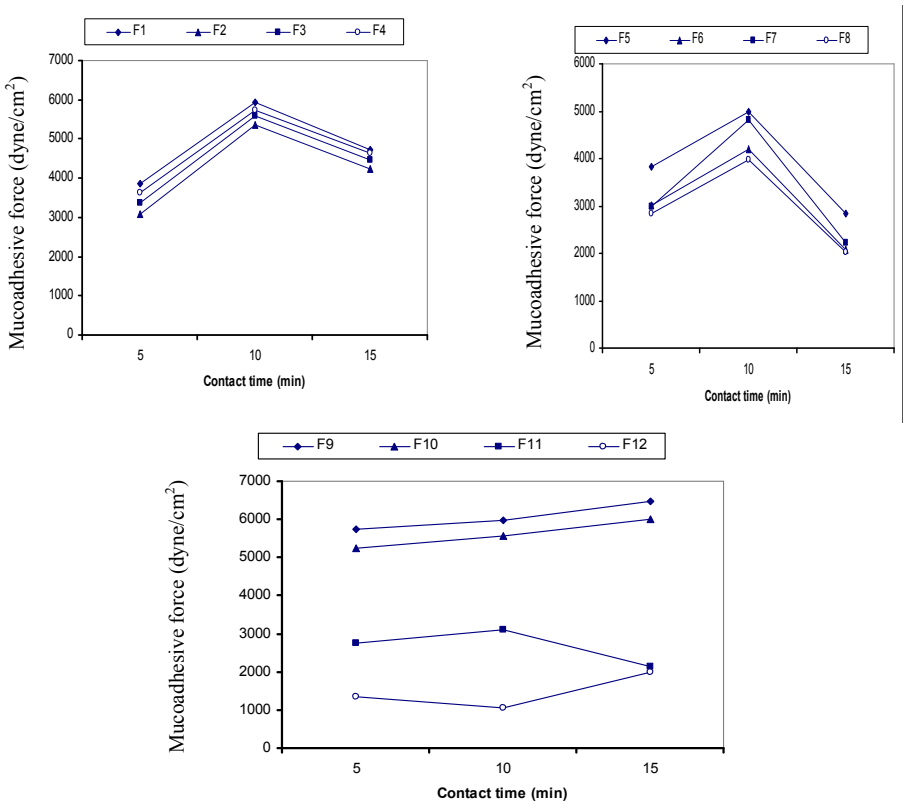

Fig. 5. Bioadhesive force (dyne/cm2) of (a) NaCMC, (b) HPMC and (c) Na.alg and poloxamer 407 containing tablets after different contact times (minutes)

Table 2. Evaluation of rosuvastatin-Ca buccoadhesive tablets

Formulae	Drug content% Mean %±SD	Weight uniformity(mg) Mean %±SD	Thickness (mm) Mean %±SD	Hardeness (Kg) Mean %±SD	Friability (%w/w) Mean %±SD	Disintegration time (min) Mean %±SD
F1	101.55±0.85	139.70±0.23	2.51±0.06	4.59±0.27	0.14±0.03	60.5±0.27
F2	97.45±1.08	138.06±0.22	2.50±0.07	4.63±0.20	0.14±0.03	55.4±0.34
F3	98.30±1.27	138.35±0.17	2.46±0.05	4.65±0.21	0.13±0.04	58.4±0.34
F4	97.19±1.46	138.95±0.17	2.52±0.06	4.67±0.21	0.13±0.03	57.4±0.34
F5	95.57±2.29	139.03±0.42	2.49±0.05	3.76±0.13	0.31±0.10	77.9±0.80
F6	97.98±0.98	139.45±0.54	2.51±0.07	3.59±0.17	0.26±0.09	72.5±0.30
F7	96.69±1.84	139.53±0.60	2.51±0.09	3.66±0.12	0.26±0.07	71.4±0.33
F8	97.91±1.14	138.99±0.73	2.52±0.07	3.61±0.13	0.31±0.12	71.0±0.80
F9	98.04±1.65	139.80±0.25	2.51±0.04	3.74±0.20	0.28±0.06	85.4±0.32
F10	101.62±0.97	138.83±0.36	2.46±0.07	3.64±0.21	0.33±0.06	84.5±0.34
F11	97.84±1.92	139.19±0.79	2.49±0.07	3.22±0.10	0.39±0.05	86.0±0.74
F12	101.72±0.89	139.09±0.57	2.51±0.07	3.22±0.10	0.45±0.06	83.9±0.84

4.7 Swelling Properties of Rosuvastatin-Ca Buccoadhesive Tablets [19]

Fig. 6 shows swelling indices as a function of time of all prepared formulae that reflect the water uptake of the matrices. The swelling index after 2 h. was chosen as the mean swelling value. NaCMC containing formulae showed the highest swelling value due to presence of more hydroxyl group in the NaCMC molecules which hold more amount of water in their network.

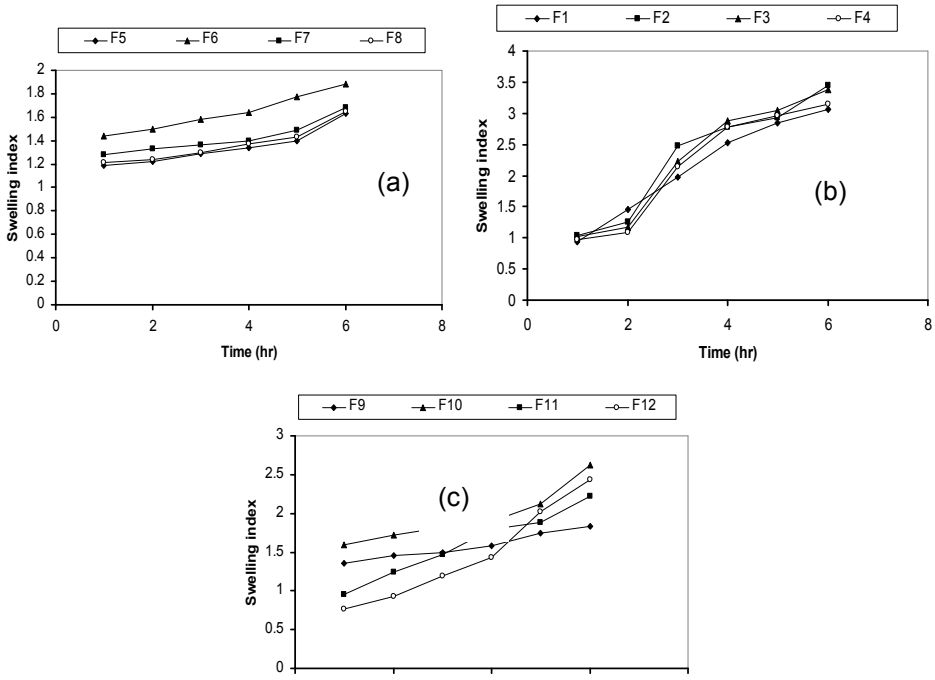

Fig. 6. Swelling indices of the prepared rosuvastatin-Ca tablets containing (a) HPMC, (b) Na CMCand (c) Na alg. and poloxamer407

4.8 Microenvironment pH Studies of Rosuvastatin-Ca Buccoadhesive Tablets [19]

The microenvironment pH of the prepared rosuvastatin-Ca buccoadhesive tablets was determined in order to investigate the possibility of any side effects in-vivo. As the acidic or alkaline pH may cause irritation to the buccal mucosa. Table 3 shows the microenvironment pH values after 2.5 and 5 h. The microenvironment pH value was chosen after 2.5 h. as mean value, where poloxamer 407 containing formulae (F12) showed the highest pH value of 6.44.

In calculating the rank order of in-vitro release, bioadhesive force, swelling index and microenvironment pH of the prepared rosuvastatin-Ca formulae, the prepared formulae were arranged in a descending order. So, the best five formulae containing different polymers used were F2, F3, F6, F10 and F12 [21].

Table 3. Micro environment pH of the prepared rosuvastatin-Ca buccoadhesive tablets

Formulae	Approximate microenvironment pH	
	2.5 h	5 h
	6.32	6.47
F2	6.36	6.48
F3	6.34	6.48
F4	6.33	6.49
F5	6.41	6.36
F6	6.43	6.43
F7	6.39	6.39
F8	6.40	6.40
F9	6.35	6.36
F10	6.37	6.39
F11	6.42	6.34
F12	6.44	6.32

Table 4. Statistical analysis of the results obtained by proposed and reported methods [22] for analysis of F2 and F3 buccoadhesive tablets

Parameter	F2					F3				
	AAS	DDQ	TCNQ	DCPI	Reported method [22]	AAS	DDQ	TCNQ	DCPI	Reported method [22]
Linearity range ($\mu g\ mL^{-1}$)	100-500	40-160	5-50	10-80	2-18	100-500	40-160	5-50	10-80	2-18
N	5	5	5	5	4	5	5	5	5	4
Mean %	91.75	89.71	89.81	89.51	90.61	101.10	101.53	99.39	99.44	100.38
S.D.	1.41	0.90	0.62	1.41	0.81	0.82	1.07	0.86	1.46	1.52
Variance	1.99	0.81	0.38	1.99	0.66	0.67	1.14	0.74	2.13	2.31
t-test (2.36)	1.43	1.56	1.68	1.38	-	0.92	1.34	1.24	0.94	-
F-test (6.60)	3.03	1.23	1.71	3.03	-	3.44	2.02	3.12	1.08	-
Standard addition (Mean±SD)	-	96.89±1.24	96.20±0.92	96.07±0.89			100.10±1.35	101.24±1.40	99.08±1.37	

-Figures in parenthes are the theoritical t- and F- values at P=0.05.Ref [22] : UV measurement of the drug solution in methanol at 243 nm.

Table 5. Statistical analysis of the results obtained by proposed and reported methods [22] for analysis of F6 and F10 buccoadhesive tablets

Parameter	F6					F10				
	AAS	**DDQ**	**TCNQ**	**DCPI**	**Reported method [22]**	**AAS**	**DDQ**	**TCNQ**	**DCPI**	**Reported method [22]**
Linearity range (µg mL^{-1})	100-500	40-160	5-50	10-80	2-18	100-500	40-160	5-50	10-80	2-18
N	5	5	5	5	4	5	5	5	5	4
Mean %	95.14	92.73	92.94	91.97	93.25	97.00	96.69	96.78	95.84	95.44
S.D.	1.53	0.74	1.00	1.07	0.63	1.13	0.88	0.81	1.43	1.15
Variance	2.34	0.55	1.00	1.14	0.40	1.28	0.77	0.66	2.04	1.32
t-test (2.36)	2.29	1.12	0.54	2.10	-	2.04	1.86	2.06	0.45	-
F-test (6.60)	5.90	1.38	2.52	2.88	-	1.04	1.71	2.02	1.55	-
Standard addition (Mean±SD)	-	96.81±1.16	96.72±0.76	96.15±0.79	**-**	**-**	98.93±1.04	97.46±0.72	96.43±0.79	**-**

-Figures in parenthes are the theoritical t- and F- values at P=0.05.Ref [22] : UV measurement of the drug solution in methanol at 243 nm.

Table 6. Statistical analysis of the results obtained by proposed and reported methods [22] for analysis of F12 buccoadhesive tablets

Parameter	F12				
	AAS	**DDQ**	**TCNQ**	**DCPI**	**Reported method [22]**
Linearity range (µg mL^{-1})	100-500	40-160	5-50	10-80	2-18
N	5	5	5	5	4
Mean %	98.70	96.18	96.00	96.40	2-18
S.D.	0.84	0.54	0.61	1.03	4
Variance	0.71	0.29	0.37	1.06	97.57
t-test (2.36)	1.55	2.14	2.34	1.48	1.35
F-test (6.60)	2.58	6.25	4.90	1.72	1.82
Standard addition (Mean±SD)	-	97.11±1.22	97.82±0.77	97.28±1.02	**-**

-Figures in parenthes are the theoritical t- and F- values at P=0.05. Ref [22]: UV measurement of the drug solution in methanol at 243 nm.

4.9 Application of the Reported Analytical Methods to Rosuvastatin-Ca Buccoadhesive Tablets

The recently reported AAS and charge transfer complexation procedures [21] were successfully applied for the determination of rosuvastatin-Cain the chosen formulae (F2, F3, F6, F10 and F12), where no interference from excipients and additives were observed except F2 and F6 which showed somewhat low mean % recoveries that might be due to presence of buccoadhesive polymers. The mean recoveries±SD were ranged between 89.51±1.41 and 101.53±1.07. These results were compared with those obtained by a compendial UV method [22] for the same formulae where no significant difference was observed with respect to accuracy and precision; above Tables 4-6.

5. CONCLUSION

Rosuvastatin-Ca buccoadhesive tablets were found to fulfill almost of the required parameters like drug release, bioadhesive strength, content uniformity, swelling index, microenvironment pH, friability, hardness, thickness and weight uniformity. Development of mucoadhesive buccal drug delivery of rosuvastatin-ca is alternative route of administration to avoid problems associated with conventional oral route, improve bioavailability and sustain release. In this study, calculation of the rank order of in vitro release, bioadhesive force, swelling index and microenvironment pH of the prepared rosuvastatin-Caformulae indicated that the best five formulae were F2, F3, F6, F10 and F12, which were used for applying the recently proposed new analytical methods [21] as compared with a reported method.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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