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Anionic polymers based buccoadhesive wafers controlled the release of anticandidal drug miconazole nitrate

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ABSTRACT: Oropharyngeal candidiasis, an opportunistic fungal infection, is caused by Candida albicans. Conventional formulations of antifungal drug, miconazole nitrate (MN), have limited retention on the infected oral mucosa, leading to its rapid clearance from the affected site. Aim of present study was to design and optimize MN buccal mucoadhesive wafer formulation for enhanced retention time as well as controlled drug release. Varying ratios of anionic, cationic and nonionic polymers were used to prepare wafers by freeze-drying method. Drug excipient interaction studies were performed by fourier transform infrared (FT-IR) and differential scanning calorimetry (DSC) analysis. Formulations were further evaluated by various wafer quality assessment parameters. Scanning electron microscopy (SEM) analysis and X-ray diffraction (XRD) studies were performed for surface analysis and solid state characterization, respectively, of prepared formulations. *In vitro* drug release studies of optimized formulations were performed and release kinetics was evaluated. Wafer formulations with anionic polymers exhibited acceptable results of swelling, adhesiveness and folding endurance analysis. Optimized formulations showed controlled release of MN by non-Fickian diffusion. Results suggest that buccoadhesive wafer formulated by anionic polymers may be utilized to achieve desired therapeutic effects of MN.

KEYWORDS: Mucoadhesive; polymer; antifungal; formulation; release kinetics

1. INTRODUCTION

Oropharyngeal candidiasis (OC) is a local fungal infection affecting the oral mucosa. It is characterized by removable white-colored thick patches and primarily it is caused by the fungus Candida albicans (CA) [1]. CA is normally present in the oral cavity, however, it is infectious when there is a disturbance of the normal oral microbial population [1–3]. Topical therapy should be the preferred treatment of OC to avoid adverse effects and possible microbial resistance development associated with systemic administration of drug [4]. Drug delivery to the oral mucosa by conventional formulations (e. g., gel) have drawbacks such as rapid clearance of drug due to continuous secretion of saliva leading to repeated administration and inconvenience to the patient. Therefore, localized drug delivery of antifungal drugs [(e. g., miconazole nitrate (MN)] to the oral mucosa is the most appropriate treatment of OC [5].

MN is a safe and effective synthetic broad-spectrum antifungal imidazole analog. It is used for topical as well as systemic fungal infections since more than 40 years [6, 7]. Marketed MN gel formulations are currently available, but their residence time at the infection site is limited, and therefore, repeated application of the formulation is necessary for the therapeutic efficacy of the drug. Gel preparation exhibits peak saliva concentrations shortly after application, but the drug eliminates rapidly from the oral cavity thereafter [5, 8].

Mucoadhesion is defined as the ability of natural or synthetic polymers to adhere to biological tissue [9]. Buccal mucoadhesive dosage forms may exist in solid, semi-solid or liquid form possessing the property of adhesion to the buccal mucosa. Mucoadhesive drug delivery prolongs the contact of formulation at the site of application to increase the therapeutic efficacy of the drug by controlling its release. This leads to improved patient compliance and reduced dosing frequency [10, 11].

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Mucoadhesive polymers usually possess hydrophilic functional groups such as carboxyl, hydroxyl, amine and sulphate. Hydration of mucoadhesive polymers by sufficient water causes exposure of adhesive sites for secondary bond (mainly hydrogen bond and van der Waals attraction) formation and mobilization of flexible polymer chains for interpenetration into mucus macromolecules [12–14]. Mucoadhesive formulations obtained from single polymers usually exhibit inadequate capability. Two or more polymers may be blended and optimized to obtain a mucoadhesive formulation with satisfactory mechanical, mucoadhesion and release features [15].

Wafer is a thin porous polymer film usually obtained by freeze-drying. Wafer drug delivery systems may possess mucoadhesive properties based on the type of polymer used for its preparation. Wafers are an appropriate dosage form for controlled release applications in the buccal cavity [16]. Apart from adequate mucoadhesive capability (for longer residence time and controlled release of drug), a buccoadhesive wafer should be soft and resilient [17, 18]. Buccal mucoadhesive tablets of MN, Oravig™ and Loramyc®, are already approved in the USA and Europe, respectively [19]. However, buccal mucoadhesive wafer formulations have more patient compliance because of their flexible and thin nature.

The present study was designed for development of buccoadhesive wafer formulations of MN by using mucoadhesive anionic polymers such as sodium carboxy methyl cellulose (NaCMC) and sodium alginate (SA), cationic polymer (i. e., chitosan) and non-ionic polymer [i. e., hydroxyethyl cellulose (HEC)]. The mucoadhesive wafer formulations were designed with the purpose of prolonged residence in the oral cavity along with the controlled release of MN for therapeutic effect on the infected area.

2. RESULTS

2.1. Optical microscopy

A photograph of the optimized wafer formulation W8 obtained from optical microscopy is shown in Figure 1. The micrograph revealed a porous interconnecting polymeric network.

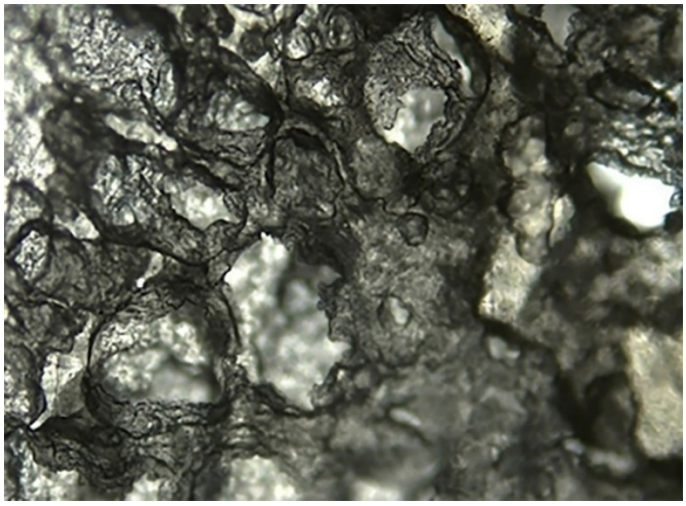

Figure 1. Optical microscopy structure of wafer formulation W8 (100X).

2.2. Scanning electron microscopy (SEM) analysis

SEM images (100X magnification) of the optimized wafer W8 showed a desirable porous and crosslinked structure of the polymers (Figure 2). The figure shows presence of pores (i. e., 136.4 µm, 185.5 µm and 229.9 µm diameter) on the surface of wafer formulation W8.

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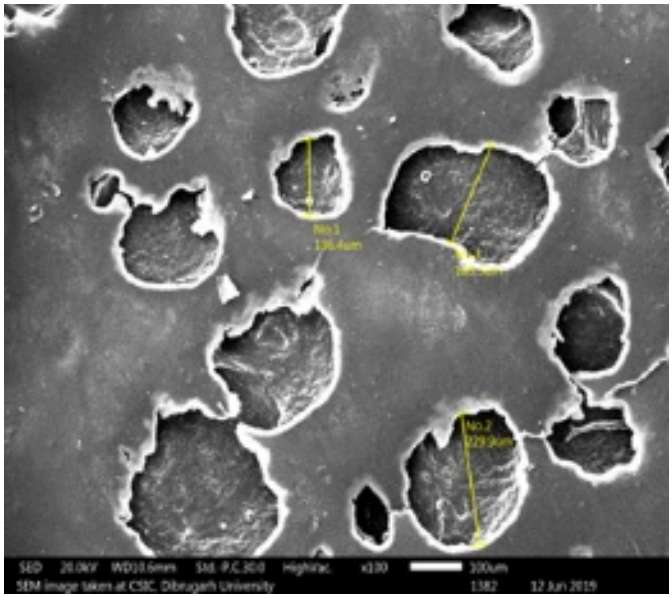

Figure 2. SEM image of wafer formulation W8 (100X).

2.3. Surface pH analysis

Surface pH of various MN wafer formulations is mentioned in Table 1.

Table 1. Physical characteristics of buccoadhesive wafer formulations (Data expressed as mean ± SD, n = 3)

Formulation code	Surface pH	Wafer thickness (mm)	Folding endurance	Swelling index (%)	Adhesiveness (mJ/cm²)
W1	7.0±0.10	0.10±0.02	154±2.54	21.47±0.40	23.76±3.41
W2	6.9±0.10	0.11±0.03	150±4.45	23.24±1.23	43.87±4.15
W3	7.0±0.11	0.14±0.05	168±2.34	25.39±0.94	76.37±4.43
W4	6.9±0.10	0.16±0.04	178±4.30	27.34±0.43	67.56±4.17
W5	7.1±0.10	0.20±0.05	180±3.67	39.23±1.39	24.66±2.04
W6	7.1±0.10	0.23±0.05	169±4.76	28.25±0.67	42.11±3.12
W7	7.1±0.11	0.27±0.05	>200	51.62±0.44	82.76±4.65
W8	6.9±0.10	0.27±0.04	>200	53.80±0.39	143.23±5.14
W9	7.1±0.10	0.28±0.03	177±4.51	43.37±1.52	62.54±3.76
W10	7.1±0.10	0.30±0.04	>200	52.04±0.68	92.59±4.35

2.4. Folding endurance

Flexibility of wafers was evaluated to estimate the folding endurance. Flexibility is an imperative physical factor of a wafer for ease of application on the site. Significantly ($p < 0.05$, detailed statistical analysis presented in supplementary file) higher folding endurance was exhibited by W7, W8 and W10 formulations, which remained intact for 200 foldings.

2.5. Swelling index

Swelling characteristic is an important property of buccoadhesive system for controlled release of drug and effective mucoadhesion. Swelling behavior analysis exhibited that wafers containing NaCMC, SA and HEC (formulations W7, W8 and W10) showed significantly ($p < 0.05$, detailed statistical analysis shown in supplementary file) higher swelling index as compared to other developed formulations (Table 1). The porous surface of wafer (as shown in Figure 2) facilitated the absorption of water for swelling. Surface wettability of the wafer increased by increasing the concentration of anionic (i. e, NaCMC and SA) and non-ionic (i. e., HEC) hydrophilic polymers, which led to increased water permeation inside matrix. However, the presence of water-insoluble cationic polymer chitosan in the formulation showed limited wafer swelling behavior as compared to formulations W7, W8 and W10. Formulation W8 showed maximum swelling.

2.6. Adhesiveness

In vitro adhesiveness analysis of different wafer formulations is shown in Table 1. Formulation W8 showed maximum adhesiveness followed by W10 and W7. This indicates that formulations comprising a higher concentration of anionic polymers (i. e., NaCMC and SA combination) presented good adhesive properties. Chitosan containing formulations showed a lower extent of adhesiveness as compared to formulations W7, W8 and W10. Formulation W8 exhibited significantly ($p<0.05$, statistical analysis is reported in supplementary file) higher adhesiveness property in comparison to all other developed formaulations. However, there was no significant difference among adhesiveness values of formulation W7 and W10.

2.7. Fourier transform infrared (FT-IR) analysis

FT-IR spectroscopy of MN, physical mixture (drug with excipients, 1:1) and formulation W8 are shown in Figure 3. FT-IR spectra of MN (Figure 3c) show the characteristic peaks at 759.54, 820. 55, 1011.68, 1084.50, 1319.22, 1471.52 and 1586.39 cm^{-1}. These peaks may be assigned to C-Cl stretching in chloride substituted in benzene, bending of C-H in 1,3-disubstituted benzene, bending of C-H in $-CH_2$, C-O stretching in CH_2-O-CH_2, stretching of C-C in two degree aromatic amine, stretching of C-C in C=C-C and stretching of C=N in imidazole ring, respectively [20]. Physical mixture of MN with excipients exhibited peaks of NaCMC at 1588. 25 and 1404.58 cm^{-1} for asymmetric and symmetric carboxylate groups, respectively [21]. These peaks were also present in the FT-IR spectra of formulation. As shown in Figure 3a, presence of broad peak at 3283.01 cm^{-1} is a typical characterisitic exhibited by stretching vibration of O–H group of SA [22]. The same peak is also visible in the spectra of physical mixture of MN and excipients.

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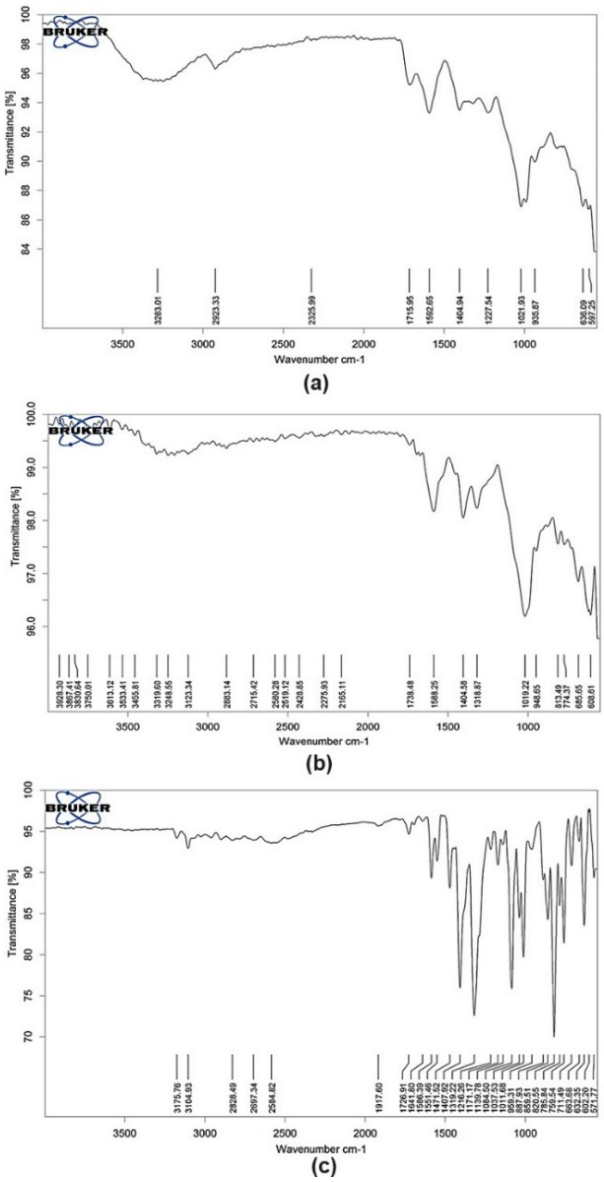

Figure 3. FT-IR spectra of (a) MN loaded wafer formulation W8, (b) physical mixture of MN with excipients and (c) MN.

2.8. Differential scanning calorimetry (DSC) analysis

DSC thermograms of MN, physical mixture of MN with excipients (1:1) and wafer formulation W8 are shown in Figure 4. A typical endothermic peak at 185 °C and an exothermic peak at 201 °C is visible in MN thermogram (Figure 4c), which corresponds to the melting point of MN. Physical mixture of MN with excipients (Figure 4b) showed a broad melting endothermic peak at 124 °C, which can be a result of excipient mixture melting. The presence of melting endotherm peak in the thermogram of physical mixture (Figure 4b) and formulation W8 (Figure 4a) at 192 °C and 208 °C indicates a higher value of melting enthalpy of MN because of a highly ordered lattice arrangement [23].

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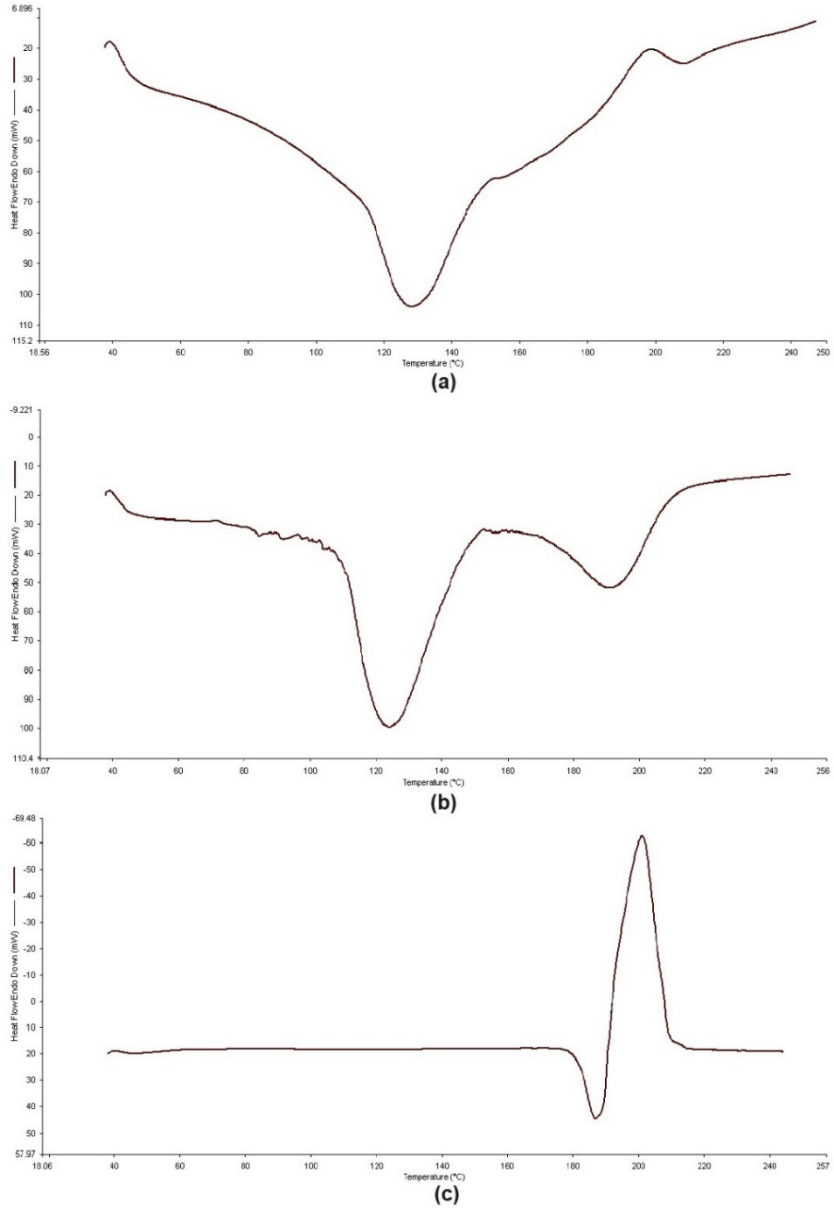

Figure 4. DSC analysis of (a) MN loaded wafer formulation W8, (b) physical mixture of MN with excipients and (c) MN.

2.9. X-ray diffraction (XRD) analysis

XRD analysis of MN (Figure 5c) showed high peaks with sharp intensity. It suggests that the drug is crystalline in nature. Diffraction pattern in the XRD spectra of MN physical mixture with excipients (Figure 5b) indicated its highly amorphous nature. XRD spectra of formulation (Figure 5a) revealed a reduction in the number of typical MN peaks indicated that the drug availability as molecular dispersion in the wafer formulation.

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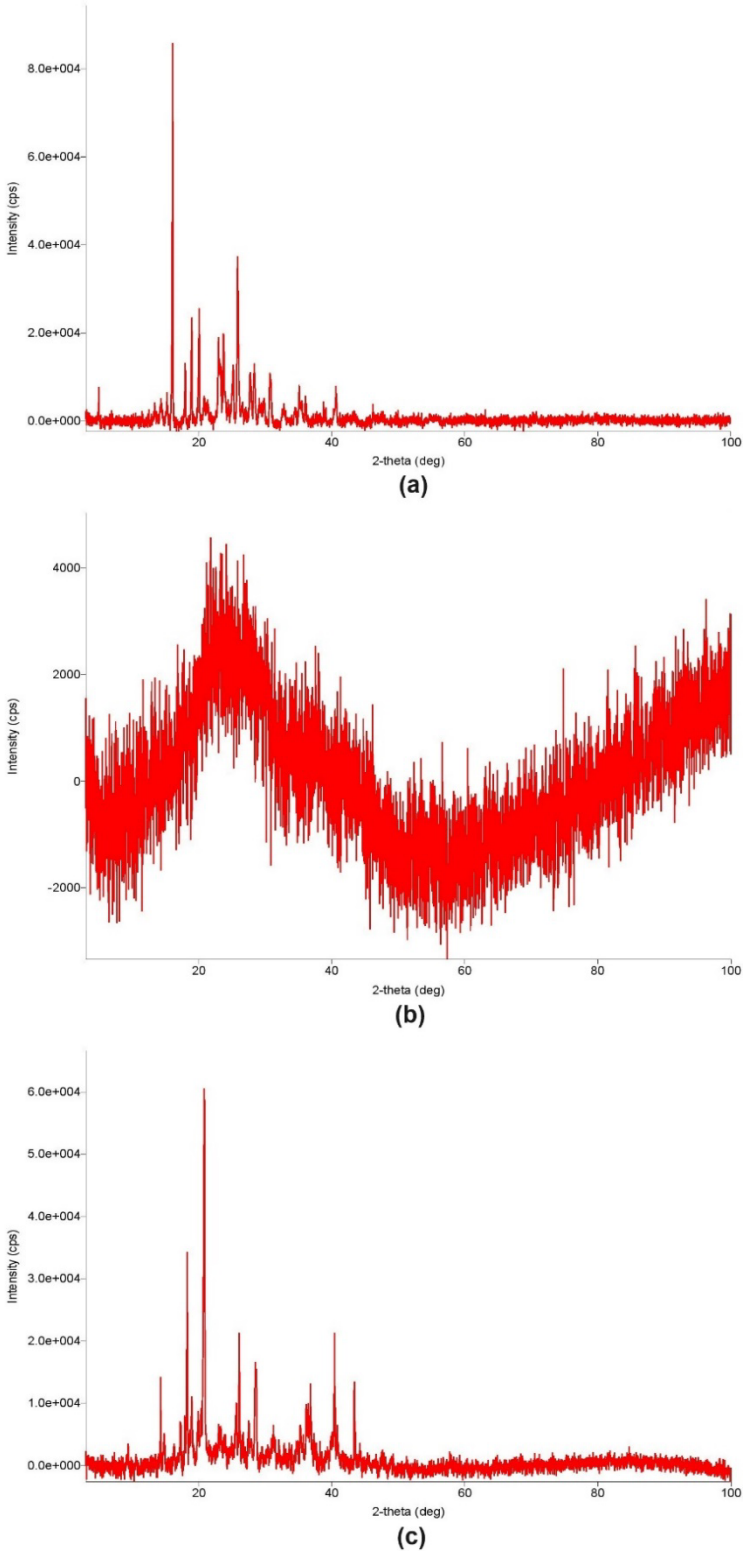

Figure 5. XRD pattern of (a) MN loaded wafer formulation W8, (b) physical mixture of MN with excipients and (c) MN.

2.10. *In vitro* drug release studies

Drug release profile of MN from W7, W8 and W10 wafer formulations is given in Figure 6. Based on the results of various evaluation parameters depicted in Table 1, formulations W7, W8 and W10 were selected for *in vitro* drug release studies. Wafer formulation W8 exhibited 85.39 % of cumulative drug release over a period of 8 h, which could be attributed to its higher degree of swelling.

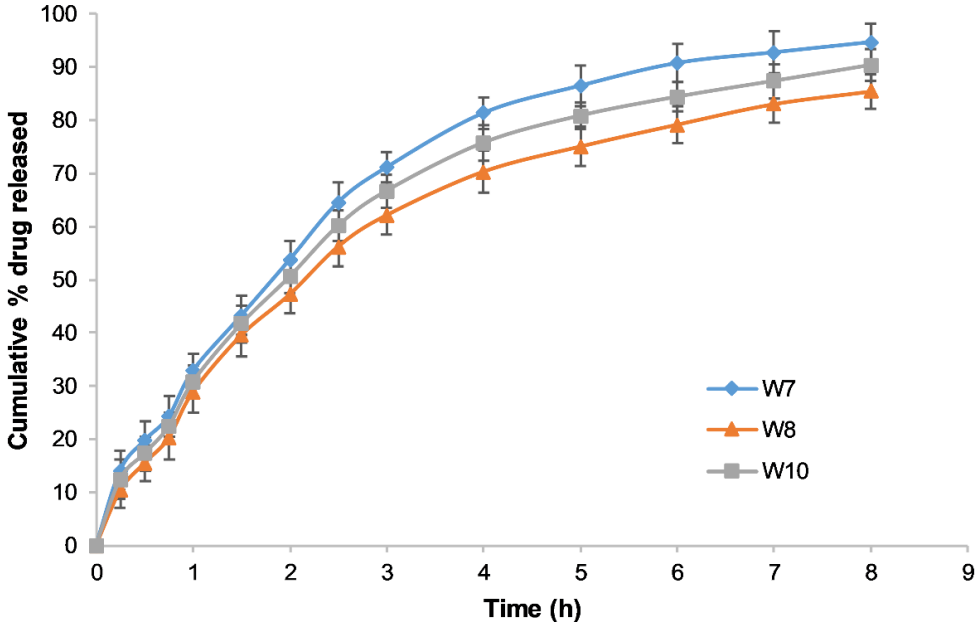

Figure 6. *In vitro* release profile of wafer formulations W7, W8 and W10 in phosphate buffer (pH 6.8) (Data expressed as mean ± SD, n = 3)

2.11. Drug release kinetics

Korsmeyer-Peppas drug release model exhibited the highest coefficient of determination (R2) for wafer formulations W7, W8 and W10 (Table 2). The value of n obtained from Korsmeyer-Peppas model revealed anomalous release profile of MN, which indicated the drug release by diffusion and swelling behavior of wafer.

Table 2. Kinetic modelling data of wafer formulations W7, W8 and W10 based on *in vitro* drug release profiles.

Formulation Code	Zero Order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n
W7	0.8719	0.1779	0.9311	0.0041	0.9623	4.93	0.9858	0.6762
W8	0.8808	0.1613	0.8995	0.0045	0.9693	4.4624	0.9926	0.7562
W10	0.8765	0.1691	0.9186	0.0043	0.966	4.6818	0.9868	0.7108

3. DISCUSSION

Presence of pores on the wafer surface in SEM study confirms its ability of wafer to absorb water on the mucosal site and adhere to the site of application for drug release in a controlled manner.

Mucosal irritation and discomfort to the patient may be caused by the acidic or alkaline pH of the wafer, which may further lead to mucosal damage. Therefore, pH measurement of the wafer surface is an important criterion to assess its side effects. Wafer surface film pH should be nearer to pH of the buccal cavity (6.8-7.2). All the wafers showed compatible pH to the buccal cavity. No significant ($p > 0.05$) difference was observed among surface pH of developed formulations. Hence, it is believed that the prepared wafer formulations will not irritate the mucosa for a long duration [24].

Swelling behaviour of wafer supports the controlled release of drug [25]. A remarkable increase in the surface area while swelling can encourage drug release, conversely an increased diffusion path of the drug delay the release [26]. Rise in polymer hydrophilicity results in a higher rate of hydration. Usually, absorption of aqueous medium from the site of application starts upon application of a bioadhesive wafer, which leads to hydration of the wafer. Swollen wafer forms strong hydrogen bond at the site resulting into an effective bioadhesion.

Data presented in Table 1 exhibits that the presence of non-ionic polymer such as HEC in formulation W10 and W7 could have a contributory adhesive effect. However, formulation W8 (with anionic polymers and without HEC) presented significantly higher adhesiveness values. This indicates presence of HEC in W10 and W7 could not significantly enhance adhesive property. Additionally, literature suggests

that chitosan has limited mucoadhesive strength and limited water solubility [27]. Therefore, chitosan containing formulations (W2, W3, W6 and W9) exhibited comparatively lower adhesiveness.

In the FT-IR spectrum of formulation W8, corresponding peaks of MN are not visible or hidden in the peaks of various excipients indicating entrapment of MN in the polymer matrix. Moreover, comparison of FT-IR spectra showed that typical peaks of NaCMC and SA are visible in the FT-IR spectra of MN physical mixture as well as formulation (W8), indicating least possibility of a strong interaction among drug and excipients. There were no clear typical peaks of MN were visible in the DSC results of formulation and physical mixture. Presence of broad endothermic peaks due to amorphous polymers in DSC thermograms of MN physical mixture and formulation (W8) signifies that the drug is present within polymer matrix, which is in agreement with FT-IR results. Regarding the results of XRD analysis, it was observed that physical mixture of MN with excipients was amorphous, while the formulation exhibited some signals, which could be due to rearrangement of molecule in the formulation or partial solubilization of MN by propylene glycol (PG) could have converted the drug into a molecular dispersion in the polymer matrix.

Strong anionic charge of the polymer is one of the important favorable property of mucoadhesive formulation [28, 29]. In agreement with this, anionic hydrophilic polymers (i. e., NaCMC and SA) in formulation W8 could have caused controlled swelling, mucoadhesion and sustained drug release of MN.

Formulations W7 and W10 showed 94.66 % and 90.33 % cumulative drug release, respectively, in 8 h. Presence of HEC in formulations W7 and W10 helped sustain the drug release, however, there was no significant ($p = 0.2260$) difference was detected in cumulative % of drug released by them in 8 h. No statistically significant ($p = 0.3002$) difference of cumulative % of drug released was observed among formulation W8 and W10. Presence of HEC in formulation W10 could not significantly differentiate the cumulative % of drug released as compared to formulation W8 (without HEC). Significantly ($p = 0.0291$) higher cumulative % of drug released exhibited by formulation W7 as compared to formulation W8 (85.39 %) in 8 h. This could be accredited to a comparatively lower concentration of SA and NaCMC (e. g., hydrophilic polymers) in formulation W7, which led to reduced swelling and a gradual increase in the erosion of the formulation [30, 31].

Analysis of drug release kinetics exhibited that a blend of higher concentrations of anionic hydrophilic polymers (i. e., NaCMC, SA) caused an increase in water uptake and wetting in W7, W8 and W10 formulations. The early presence of water in/around the wafer and higher content of crosslinked polymers in the formulation led to an increase in swelling behavior. This outcome reflected a decrease in MN release rate. Formulation W8 showed the most sustained release.

4. CONCLUSION

Buccoadhesive wafers of anticandidal drug MN were successfully developed. Formulations W7, W8 and W10 were mainly based on anionic polymer and they exhibited desirable surface pH, wafer thickness, folding endurance, swelling index and adhesiveness. FT-IR and DSC analysis exhibited that any significant drug-excipient interaction was absent. *In vitro* drug release profile of prepared wafers revealed that formulations could prolong the drug release for 8 h. Release kinetics analysis showed drug release by diffusion and swelling. Therefore, MN-loaded wafer formulation could be a favorable drug delivery technique for the management of oropharyngeal candidiasis.

5. MATERIALS AND METHODS

5.1. Materials

MN was supplied by Ajanta Pharma Ltd., Mumbai, India. NaCMC, SA and citric acid anhydrous (CAA) were received from Sisco Research Laboratories Pvt. Ltd., India. HEC, propylene glycol (PG) and medium molecular weight chitosan were procured from Sigma Aldrich, USA. NaCMC is a negatively charged polymer widely used in drug formulation and it has an excellent swelling property. SA is the sodium salt of alginic acid obtained from brown algae and it is classified as negatively charged polymer. Chitosan is a versatile biodegradable polymer used in drug delivery and it possesses positive charge. HEC, a neutral polymer, is obtained from chemical modification of natural polysaccharide cellulose.

5.2. Formulation of mucoadhesive wafers

Lyophilization method was used for the preparation of mucoadhesive wafers. CAA and PG were added as cross-linking agent and plasticizer, respectively. Initially, MN was dissolved in methanol. SA, NaCMC, HEC, PG and CAA were dissolved in distilled water at 60±2°C followed by dispersion of chitosan into it. The blend was then added into the vortex of vigorously stirred MN solution to produce a uniform

mixture. Final volume of the mixture was made up by distilled water. The resultant mixture was sonicated for 15 min at room temperature. Wafers were obtained by overnight freeze-drying of mixture on an aluminium tray in a lyophilizer. Composition of wafers with different concentrations of polymers is shown in Table 3.

5.3. Optical microscopy

The wafer sample was observed by using an optical microscope at 100X magnification for the study of morphological characteristics of the formulation.

5.4. SEM analysis

The exterior morphology and cross-sections of the optimized wafer were examined by SEM (JSM-IT 300LV, JEOL, India). Double-sided adhesive carbon tape was used to place the sample on labeled stainless steel stubs. The wafers were coated with gold sputtering in argon atmosphere and images captured.

Table 3. Composition of various wafer formulations.

Code	NaCMC (%)	SA (%)	Chitosan (%)	HEC (%)	PG (%)	CAA (%)	MN (%)
W1	0.5	0.5	-	0.5	1	1.5	5
W2	1	-	0.5	-	1	1.5	5
W3	1.5	-	1	0.5	1	1.5	5
W4	2	1	-	0.5	1	1.5	5
W5	2.5	1.5	-	1	1	1.5	5
W6	-	1.5	2.5	-	1	1.5	5
W7	3	2	-	0.5	1	1.5	5
W8	3.5	2.5	-	-	1	1.5	5
W9	3.5	2	1	-	1	1.5	5
W10	4	3	-	1	1	1.5	5

5.5. Surface pH analysis

Surface pH was analyzed by allowing wafer to swell in phosphate buffer, pH 6.8. Thereafter, wafer was removed from buffer solution and wiped by using a tissue paper. Then electrode of pH-meter was brought in contact with wafer surface and left to equilibrate for measurement of pH [32].

5.6. Thickness analysis

Wafer thickness was determined using the digital vernier caliper (Insize Electronic Callipers). Each wafer was measured from at least five different locations (four corners and center) and mean thickness was examined.

5.7. Folding endurance

Wafer (~2 cm X 2 cm) was repeatedly folded at 180° angle from the same place for 200 times or until it broke. Number of times wafer folded without breaking was counted and the value was reported as folding endurance value [33].

5.8. Swelling index

The wafer sample (1 cm^2) was weighed initially and submerged in phosphate buffer (pH 6.8, 10 ml). Thereafter, wafer was removed from buffer solution, any excess solution wiped and reweighed. Increase in wafer weight was recorded at 0.5, 1, 2, 3, 4 and 5 hr time intervals. Experiment was continued until a constant weight was obtained. Following formula was used for calculation of swelling index:

Swelling index = $\{(W_t - W_o) / W_0\} X 100$

Where W_0 and W_t indicates wafer weight at time zero and t, respectively [34].

5.9. Adhesiveness analysis

Texture analyzer (TA-XT Plus, Stable Microsystems) was used for *in vitro* adhesion studies using bovine buccal mucosa, acquired from a slaughter house. Mucosal tissue was cleaned, washed and preserved at −20°C. At the time of the experiment, the buccal mucosa was hydrated in phosphate buffer (pH 6.8) for 1 h at room temperature. Wafer was attached to the removable probe by using a double-sided adhesive tape. The probe was lowered with a constant force 0.2 N and 0.1 mm/s speed on the surface of a bovine buccal mucosa. The probe was moved upward after 60 s contact time. Area under the curve (AUC) calculation was

performed by using force versus time curve data. Following equation was utilized for calculation of work of adhesion and the results are expressed in mJ/cm^2:
Work of adhesion = AUC /πr^2
Where, πr^2= membrane surface area in contact with formulation [35, 36].

5.10. FT-IR analysis

Compatibility of ingredients was evaluated by using FT-IR spectroscopy (Alpha II Platinum ATR, Bruker, USA). Spectral analysis of MN, MN physical mixture with excipients and MN loaded wafer formulation (W8) was performed over 400– 4000 cm^{-1} range using FT-IR spectrophotometer.

5.11. DSC analysis

Nearly 5 mg quantity of MN, physical mixture of MN with excipients and MN loaded wafer formulation (W8) samples were kept in the aluminium pan. Scanning of samples was performed at 10°C per min in nitrogen gas environment (flow rate of 20 ml/min) and 35°C-245°C temperature (Perkin Elmer, USA). Alpha alumina discs empty cell of high purity were used as a reference in calorimetric measurements. Highly pure indium metal was used as a standard for calibration of the instrument. Obtained thermogram was observed and interpreted.

5.12. XRD analysis

XRD (Rigaku-Ultima IV, Japan) was used to assess the crystallinity of MN, physical mixture of MN with excipients and formulation W8. Copper radiation source was utilized as anode material. 45 kV voltage and 30 mA current was applied in the range of $0° < 2\theta < 100°$ to obtain diffraction pattern by using step scan model.

5.13. *In vitro* drug release studies

USP type II dissolution apparatus (paddle type) (TDT-08L, Electrolab, India) was employed for drug release profiling. To prevent floating and imitate *in vivo* adhesion, wafer formulations were fixed on a glass slide and positioned at the bottom of the dissolution vessel. 250 ml of phosphate buffer (pH 6.8) was employed as a dissolution medium (37°C±0.5°C). Speed of paddle rotation speed was maintained at 50 RPM. Periodically, samples of dissolution fluid were withdrawn and dissolution vessel was replenished with a fresh medium to maintain sink condition. Filtered samples were analyzed by using UV spectrophotometer (UV 1800 Shimadzu, Japan) at 272 nm wavelength to determine the amount of drug released. Cumulative % of drug released vs. time profiles were constructed to study drug release pattern [37, 38].

5.14. Drug release kinetics

Drug release from buccoadhesive wafer formulations was studied by utilizing zero-order, first-order, Higuchi and Kosrsmeyer-Peppas models. Zero-order model (equation 1) describe concentration-independent drug release, while first-order model (equation 2) express concentration-dependent drug release. Higuchi model (equation 3) depict Fickian drug release from a matrix proportional to square root value of time. Fickian and non-Fickian pattern of drug diffusion can be identified by using Korsmeyer-Peppas model (equation 4). Regression analysis was performed to calculate the coefficient of determination (R^2).

$Q_t = K_0 t + Q_0$ (Equation 1)

$\log Q_t = K_1 t / 2.303 + \log Q_0$ (Equation 2)

$Q_t = K_H t^{1/2}$ (Equation 3)

$\log Q_t = n \log t + \log K_{KP}$ (Equation 4)

Where, K_0 = zero-order release constant, , K_1 = release constant of first order, K_H = Higuchi drug release constant, K_{KP} = Korsmeyer-Peppas drug release constant, n = 0.5 for Fickian diffusion in diffusion-controlled drug delivery systems, n = 1 indicates zero-order release mechanism (case II transport) in swelling controlled drug delivery system, $0.5<n<1$ specifies anomalous transport, $n>1$ defines super case-II transport, Q_0 = initial amount of drug in solution, Q_t = cumulative % of drug released at t time [39].

5.15. Statistical evaluation

Results are expressed as mean (n = 3) ± standard deviation. One-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test ($p<0.05$) was employed for statistical evaluation of results.

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REFERENCES

[1] Singh A, Verma R, Murari A, Agrawal A. Oral candidiasis: An overview. J Oral Maxillofac Pathol. 2014;18(S1):S81–S85. https://doi.org/10.4103/0973-029X.141325

[2] Zhang L-W, Fu J-Y, Hua H, Yan Z-M. Efficacy and safety of miconazole for oral candidiasis: a systematic review and meta-analysis. Oral Dis. 2016;22(3):185–195. https://doi.org/10.1111/odi.12380

[3] Rizzetto L, De Filippo C, Cavalieri D. Richness and diversity of mammalian fungal communities shape innate and adaptive immunity in health and disease. Eur J Immunol. 2014;44(11):3166–3181. https://doi.org/10.1002/eji.201344403

[4] Mady OY, Donia AM, Al-Madboly LA. Miconazole-urea in a buccal film as a new trend for treatment of resistant mouth fungal white patches. Front Microbiol. 2018; 9: 837. https://doi.org/10.3389/fmicb.2018.00837

[5] Collins CD, Cookinham S, Smith J. Management of oropharyngeal candidiasis with localized oral miconazole therapy: efficacy, safety, and patient acceptability. Patient Prefer Adherence. 2011; 5: 369–374. https://doi.org/10.2147/PPA.S14047

[6] Vazquez JA, Sobel JD. Miconazole mucoadhesive tablets: a novel delivery system. Clin Infect Dis. 2012;54(10):1480–1484. https://doi.org/10.1093/cid/cis205

[7] Isham N, Ghannoum MA. Antifungal activity of miconazole against recent Candida strains. Mycoses. 2010; 53 :434–437. https://doi.org/10.1111/j.1439-0507.2009.01728.x

[8] Fothergill AW. Miconazole: A historical perspective. Expert Rev Anti Infect Ther. 2006;4(2):171–175. https://doi.org/10.1586/14787210.4.2.171

[9] Cevher E, Taha MM, Orlu M, Araman A. Evaluation of mechanical and mucoadhesive properties of clomiphene citrate gel formulations containing carbomers and their thiolated derivatives. Drug Deliv. 2008;15(1):57–67. https://doi.org/10.1080/10717540701829234

[10] Yehia SA, El-Gazayerly ON, Basalious EB. Design and in vitro/in vivo evaluation of novel mucoadhesive buccal discs of an antifungal drug: relationship between swelling, erosion, and drug release. AAPS PharmSciTech. 2008;9(4):1207–1217. https://doi.org/10.1208/s12249-008-9166-1

[11] Mazzarino L, Borsali R, Lemos-Senna E. Mucoadhesive films containing chitosan-coated nanoparticles: A new strategy for buccal curcumin release. J Pharm Sci. 2014;103(11):3764–3771. https://doi.org/10.1002/jps.24142

[12] Anlar S, Capan Y, Hincal AA. Physico-chemical and bioadhesive properties of polyacrylic acid polymers. Pharm. 1993;48(4):285–287

[13] Park H, Robinson JR. Physico-chemical properties of water insoluble polymers important to mucin/epithelial adhesion. J Control Release. 1985;2:47–57. https://doi.org/10.1016/0168-3659(85)90032-X

[14] Shojaei AH, Zhuo SL, Li X. Transbuccal delivery of acyclovir (II): feasibility, system design, and in vitro permeation studies. J Pharm Pharm Sci. 1998;1(2):66–73.

[15] Chen X, Yan J, Yu S, Wang P. Formulation and ın vitro release kinetics of mucoadhesive blend gels containing matrine for buccal administration. AAPS PharmSciTech. 2018;19(1):470–480. https://doi.org/10.1208/s12249-017-0853-7

[16] Boateng JS, Matthews KH, Auffret AD, Humphrey MJ, Stevens HN, Eccleston GM. In vitro drug release studies of polymeric freeze-dried wafers and solvent-cast films using paracetamol as a model soluble drug. Int J Pharm. 2009;378(1-2):66–72. https://doi.org/10.1016/j.ijpharm.2009.05.038

[17] Eouani C, Piccerelle P, Prinderre P, Bourret E, Joachim J. In-vitro comparative study of buccal mucoadhesive performance of different polymeric films. Eur J Pharm Biopharm. 2001;52(1):45–55. https://doi.org/10.1016/s0939-6411(01)00146-1

[18] Patel VM, Prajapati BG, Patel MM. Effect of hydrophilic polymers on buccoadhesive eudragit patches of propranolol hydrochloride using factorial design. AAPS PharmSciTech. 2007;8(2):E119–E126. https://doi.org/10.1208/pt0802045

[19] Lalla RV, Bensadoun R-J. Miconazole mucoadhesive tablet for oropharyngeal candidiasis. Expert Rev Anti Infect Ther. 2011;9(1):13–17. https://doi.org/10.1586/eri.10.152

[20] Puratchikody A, Prasanth VV, Mathew ST, Kumar BA. Development and characterization of mucoadhesive patches of salbutamol sulfate for unidirectional buccal drug delivery. Acta Pharm Zagreb Croat. 2011;61(2):157–170. https://doi.org/10.2478/v10007-011-0011-9

[21] Ko SY, Sand A, Shin NJ, Kwark Y-J. Synthesis and characterization of superabsorbent polymer based on carboxymethyl cellulose-graft-itaconic acid. Fibers Polym. 2018;19:255–262. https://doi.org/10.1007/s12221-018-7837-9

[22] Dong Y, Sang D, He C, Sheng X, Lei L. Mxene/alginate composites for lead and copper ion removal from aqueous solutions. RSC Adv. 2019;9:29015–29022. https://doi.org/10.1039/C9RA05251H

[23] Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. Eur J Pharm Biopharm. 2011;77(2):187–199. https://doi.org/10.1016/j.ejpb.2010.11.023
[24] Tejada G, Barrera MG, Piccirilli GN, Sortino M, Frattini M, Salomón CJ, Lamas MC, Leonardi D. Development and evaluation of buccal films based on chitosan for the potential treatment of oral candidiasis. AAPS PharmSciTech. 2017;18(4):936–946. https://doi.org/10.1208/s12249-017-0720-6
[25] Hassan N, Ali M, Ali J. Novel buccal adhesive system for anti-hypertensive agent nimodipine. Pharm Dev Technol. 2010;15(2):124–130. https://doi.org/10.3109/10837450903055494
[26] Chakraborty P, Dey S, Parcha V, Bhattacharya SS, Gosh A. Design expert supported mathematical optimization and predictability study of buccoadhesive pharmaceutical wafers of loratadine. BioMed Res Int. 2013;2013:197398. https://doi.org/10.1155/2013/197398
[27] ElMeshad AN, El Hagrasy AS. Characterization and optimization of orodispersible mosapride film formulations. AAPS PharmSciTech. 2011;12(4):1384–1392. https://doi.org/10.1208/s12249-011-9713-z
[28] Abruzzo A, Bigucci F, Cerchiara T, Cruciani F, Vitali B, Luppi B. Mucoadhesive chitosan/gelatin films for buccal delivery of propranolol hydrochloride. Carbohydr Polym. 2012;87(1):581–588. https://doi.org/10.1016/j.carbpol.2011.08.024
[29] Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2011;13(2):123–133. https://doi.org/10.1016/S0928-0987(01)00095-1
[30] Rai VK, Dwivedi H, Yadav NP, Chanotiya CS, Saraf SA. Solubility enhancement of miconazole nitrate: binary and ternary mixture approach. Drug Dev Ind Pharm. 2014;40(8):1021–1029. https://doi.org/10.3109/03639045.2013.801487
[31] Bhalekar MR, Pokharkar V, Madgulkar A, Patil N, Patil N. Preparation and evaluation of miconazole nitrate-loaded solid lipid nanoparticles for topical delivery. AAPS PharmSciTech. 2009;10(1):289–296. https://doi.org/10.1208/s12249-009-9199-0
[32] Nair AB, Kumria R, Harsha S, Attimarad M, Al-Dhubiab BE, Alhaider IA. In vitro techniques to evaluate buccal films. J Control Release. 2013;166(1):10–21. https://doi.org/10.1016/j.jconrel.2012.11.019
[33] Karki S, Kim H, Na S-J, Shin D, Jo K, Lee J. Thin films as an emerging platform for drug delivery. Asian J Pharm Sci. 2016;11(5):559–574. https://doi.org/10.1016/j.ajps.2016.05.004
[34] Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing. Int J Pharm. 2003;264(1-2):1–14. https://doi.org/10.1016/S0378-5173(03)00371-5
[35] M. Ways TM, Lau WM, Khutoryanskiy VV. Chitosan and Its derivatives for application in mucoadhesive drug delivery systems. Polymers. 2018;10(3):267. https://doi.org/10.3390/polym10030267
[36] Bhatia MS, Deshmukh R, Choudhari P, Bhatia NM. Chemical modification of pectins, characterization and evaluation for drug delivery. Sci Pharm. 2008;76(4):775–784. https://doi.org/10.3797/scipharm.0805-23
[37] Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J Control Release. 1985;2:257–275. https://doi.org/10.1016/0168-3659(85)90050-1
[38] Hu Y, Hu S, Zhang S, Dong S, Hu J, Kang L, Yang X. A double-layer hydrogel based on alginate-carboxymethyl cellulose and synthetic polymer as sustained drug delivery system. Sci Rep. 2021;11:9142. https://doi.org/10.1038/s41598-021-88503-1
[39] Jadach B, Świetlik W, Froelich A. Sodium alginate as a pharmaceutical excipient: Novel applications of a well-known polymer. J Pharm Sci. 2022;111(5):1250-1261. https://doi.org/10.1016/j.xphs.2021.12.024