IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 13, Issue 3 Series. I (March 2023), PP.22-30
www.iosrphr.org

Influence of type and quantity of three hydrophilic cellulose derivatives on orodispersible films' characteristics

Ognjenka Rahić[1], Nejira Vehabović[1], Amina Tucak-Smajić[1], Jasmina Hadžiabdić[1], Merima Šahinović[1], Lamija Hindija[1], Edina Vranić[1]

[1]*Department of Pharmaceutical Technology, University of Sarajevo – Faculty of Pharmacy, Bosnia and Herzegovina.*

Corresponding Author:Ognjenka Rahić; email: ognjenka.rahic@ffsa.unsa.ba

Received 17 March 2023; Accepted 31 March 2023

Abstract: Orodispersible films are a relatively new intraoral dosage form. In addition to facilitating oral administration of drugs in dysphagia patients, they can be used in the context of personalized therapy in geriatric and pediatric populations. In this study, a total of nine formulations were made using the solvent casting method, containing different concentrations of three hydrophilic polymers (hydroxypropyl methylcellulose, hydroxypropyl cellulose, and sodium carboxymethyl cellulose), glycerol as a plasticizer, and raspberry and blueberry flavor. The characterization of orodispersible films included the thickness and weight uniformity, disintegration time, pH, folding endurance, transparency, moisture uptake, moisture loss, and FTIR spectroscopy. Thickness and weight of films were dependent on type of polymer as well as its concentration. Hydroxypropyl cellulose films had the highest thickness and weight. Formulations with hydroxypropyl cellulose had the longest disintegration time as well as the highest folding endurance. Formulations with hydroxypropyl methylcellulose proved to be less hygroscopic than formulations with sodium carboxymethyl cellulose. All orodispersible films were transparent and had a pH value similar to salivary pH. FTIR spectroscopy revealed compatibility of substances used in each formulation.

Keywords: orodispersible films, characterization, hydrophilic cellulose derivatives, formulation

I. INTRODUCTOION

The oral route is the most commonly used drug delivery pathway due to its ease of administration, non-invasiveness, adaptability, and high degree of patient adherence[1]. Tablets and capsules make up the majority of oral dosage forms available today[2]. However, conventional dosage forms continue to have considerable drawbacks, particularly for pediatric and geriatric populations, as well as people with dysphagia, due to various medical conditions[3]. For these patients, the main difficulty is swallowing, which involves the synchronized action of several nerves and muscles[4]. Patient's adherence and the effectiveness of orally administered drugs might be jeopardized due to inadequate tactics for adjusting these forms, such as breaking and crushing tablets, opening capsules, or dissolving dosage forms in liquids[5]. In addition, many drugs administered by the oral route have poor bioavailability due to the low pH of the stomach, the presence of enzymes, and the extensive presystemic metabolism in the liver. Drugs with low bioavailability are traditionally administered via the parenteral route, resulting in a lower level of patient adherence[6].

The design of intraoral dosage forms has become significant in the pharmaceutical industry to achieve better adherence and a more comfortable way of administering drugs[7]. Intraoral drug administration provides quicker onset of action and the avoidance of the metabolism of the first pass and potential degradation in lower parts of the gastrointestinal tract. This refers to substances that are absorbed through the oral mucosa. Some of the drawbacks of intraoral dosage forms include washing away with saliva, the possibility of swallowing, the need for a pleasant flavor of the formulation, and the potential of dislodging[8].

Orodispersible films are relatively new dosage forms, developed as an alternative to conventional oral dosage forms[3]. In the monograph "Oromucosal preparations" of the current European pharmacopeia, two types of oromucosal films are defined: mucoadhesive buccal films and orodispersible films. They are described as single or multi-layered sheets made of suitable material[9]. The name orodispersible films (ODFs) has been accepted by EMA, while FDA uses the term "soluble films"[10,11].

ODFs are innovative dosage forms that disintegrate or dissolve after coming into contact with saliva.

No additional liquid or chewing is necessary for the film to disintegrate (dissolve)[12–14].

ODFs are most often placed on the tongue, and the released drug is largely swallowed with saliva. However, one part of the drug is absorbed through the oral cavity, which can single-hand the effect of presystemic metabolism in the liver[15]. Unlike mucoadhesive buccal films that can be used to treat systemic and local diseases, ODFs are predominantly used to achieve a systemic effect[15].

The very important component of ODFs are polymer matrices that can be effectively used as drug carriers. These matrices can be composed of several polymers, but usually, they contain hydrophilic polymers[16]. Hydrophilic cellulose derivatives are very suitable to be used in ODFs because of their compatibility with the majority of other excipients, their pharmacologically inert nature, and their indigestibility by human gastrointestinal enzymes[17]. Another desirable feature is their compatibility with flavors and sweeteners[18] as it is recommended that ODFs contain some taste masking agent in order to be more acceptable to patients.

Having the above in mind, our work was focused on examining the influence of the type and quantity of film-forming hydrophilic polymers, namely three cellulose derivatives, on ODFs characteristics. Based on those findings, we would be able to determine the type and concentration of polymers, as well as the concentration of plasticizer, that would be best suited to form films with desirable properties.

II. MATERIALS AND METHODS

2.1 Materials

Hydroxypropyl methylcellulose (HPMC, Pharmacoat 606, Mw 35 600 g/mol), hydroxypropyl cellulose (HPC, Mw 100 000 g/mol) (Shin-Etsu Chemical Co., Ltd., Tokyo), and sodium carboxymethylcellulose (Na-CMC, Mw 90 000 g/mol) (TCI-Tokyo Chemical Industry Co., Ltd., Japan) were kindly provided by HARKE Pharma GmbH (Germany). Glycerin, blueberry flavor, and raspberry flavor were ordered from Centrohem (Serbia), Eterika (Serbia), and Aromar, Kloštar Ivanić (Croatia), respectively.

2.2 Preparation of ODFs

ODFs were prepared by the solvent casting method (Fig. 1).

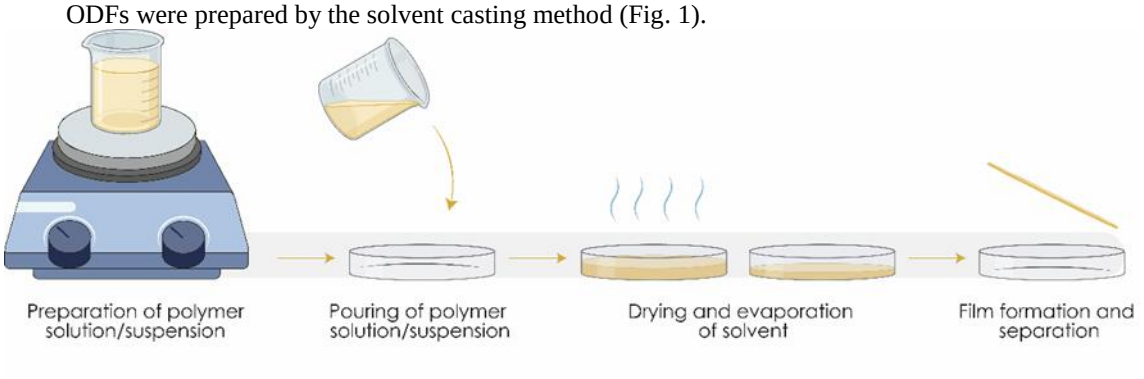

Figure 1: Preparation of ODFs. The image was created with Adobe Illustrator CC (Version 23.0.1.; Adobe Inc., San Jose, CA, USA, 2019)

A total of nine formulations had a composition presented in Table 1.

Table 1: Composition of ODFs' formulations

Substance	*F1 (%)*	*F2 (%)*	*F3 (%)*	*F4 (%)*	*F5 (%)*	*F6 (%)*	*F7 (%)*	*F8 (%)*	*F9 (%)*
HPMC	2	1.75	2.25	/	/	/	/	/	/
HPC	/	/	/	4	5	6	/	/	/
Na-CMC	/	/	/	/	/	/	2	1.5	2.5
Glycerin	20	17.5	22.5	0.4	0.5	0.6	1	0.75	1.25
Distilled water	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g	q.s. to 100 g
Raspberry flavor	0.5	2	4	/	/	5	/	/	/
Blueberry flavor	/	/	/	3	3	/	2	3	4

Formulations F1–F3 were prepared by dissolving HPMC in glycerin in a laboratory glass by stirring with a glass stick, and then distilled water was added up to 100 g. After that, the glass with the mixture was transferred to the WiseStir MSH-20D magnetic stirrer (Daihan Scientific Co., Ltd., South Korea) and stirred at a speed of 200–300 rpm until the polymer was completely dissolved. Then aroma was added, and the solution was

additionally stirred for 1 minute. The prepared solutions were poured into Petri dishes (diameter 90 mm) and dried for four days at room temperature. The dried films were then cut to the desired size (2 × 2 cm) and removed from the Petri dish.

When it comes to formulations F4–F9, hydrophilic polymers were first mixed with a part of water in a laboratory glass, and glycerin was mixed with other part of the water in another glass. Those mixtures were conjoined in one glass and stirred on a magnetic stirrer at 300–500 rpm until the polymer was completely dissolved. Afterwards, aroma was added, and the solution was additionally stirred for 1 minute. The prepared solutions were poured into Petri dishes (diameter 90 mm) and dried for four days at room temperature. The dried films were then cut to the desired size (2 × 2 cm) and removed from the Petri dish.

2.3 Characterization of ODFs

2.3.1 Thickness of Films

The thickness of the films was investigated from 3 randomly selected points of all films (n = 3) with a screw micrometer (Mitutoyo Co. Ltd., Kawasaki, Japan), and the sensibility was 0.001 mm.

2.3.2 Weight uniformity of Films

The weight uniformity of the films was determined by weighing 3 randomly selected films (n = 3) for each formulation with a scale OHAUS Scout® Pro (Mettler Toledo, Columbus, USA).

2.3.3 Disintegration time

Three 2 × 2 cm ODFs were placed in a Petri dishes, followed by the addition of 2 ml of distilled water. The Petri dishes were shaken constantly to allow water to rinse over the film. The time at which the film totally disintegrated was noted[19]. The time was measured by a stop clock, and the total disintegration was visible since the films contained aromas that gave them color as well.

2.3.4 pH of ODFs

Three samples of 2 × 2 cm films of each formulation were placed in a Petri dish and moistened with 0.5 ml of water and left to equilibrate for 30 seconds. The pH of the ODF surface is determined by placing the pH strip on the surface[20]. After dissolving three samples of 2 × 2 cm films of each formulation in 2 ml of distilled water, the pH was measured again[21].

2.3.5 Folding endurance

Folding endurance was measured manually by one operator for all formulations' 2 × 2 cm ODFs. A strip of film was cut evenly and repeatedly folded at the same place till it broke. The folding endurance value was determined by the number of times the film could be folded at the same location without breaking. The measurement was performed in triplicate for each formulation[21].

2.3.6 Transparency of ODFs

The transparency of three 2 × 2 cm ODFs of each formulation was determined using a UV-VIS spectrophotometer Shimadzu UV-1601 (Shimadzu Corporation, Kyoto, Japan). ODFs were positioned on the inner wall of the cuvette and then transmittance and absorbance at a wavelength of 600 nm were measured[1,22]. Since the films were adhesive, they adhered to the inner wall of the cuvette, which ensured that they stayed in the same position throughout the test.

2.3.7 Moisture uptake and moisture loss

Moisture loss was determined by placing three 2 × 2 cm samples of ODFs of all formulations in an exicator above silica gel for three days. Moisture loss was calculated using Eq. 1:

$$\text{Moisture loss} = \frac{\text{initial weight - weight after drying}}{\text{inital weight}} \times 100 \quad (1)$$

The moisture uptake was determined by placing three 2 cm x 2 cm ODFs of each formulation in an exicator above the water for 24 hours. The samples were placed on a perforated holder and kept at a constant, controlled room temperatre. Moisture uptake was calculated using Eq. 2:

$$\text{Moisture uptake} = \frac{\text{weight after 24 hours - initial weight}}{\text{initial weight}} \times 100 \quad (2)$$

2.3.8 FTIR spectroscopy

Spectra of raw materials and formulations were recorded using Cary 630 (Agilent Technologies, Inc., Santa Clara, CA, USA). The samples (pure substances and films) were placed on the diamond crystal, and the sample pressure press was rotated downward until adequate pressure was placed on the sample to observe a spectrum in the MicroLab FTIR software. Attenuated Total Reflectance (ATR) method was used and the applied spectral range was 600–4000 cm^{-1}. The spectra were collected from 32 scans, at 4 cm^{-1} resolution.

2.3.9 Statistical analysis

The collected data were analyzed with one-way analysis of variance (ANOVA) followed by Tukey's difference test as post-hoc test and presented as mean values ± standard deviations (SD).

III. RESULTS AND DISCUSSION

The characteristics of the formulations are shown in Table 2.

Table 2: Characteristics of ODFs (mean ± SD; n = 3)

Sample	*Thickness (µm)*	*Weight (g)*	*Disintegration time (sec)*	*Surface pH*	*pH of dissolved ODF*	*Number of folds*	*Transmittance (λ=600nm) (%)*	*Moisture uptake (%)*	*Moisture loss (%)*
F1	163.3 ± 3.54	0.1677 ± 0.0025	31.00 ± 0.63	6.0 ± 0.0	6.0 ± 0.0	10 ± 3.00	87.34 ± 0.05	5.39 ± 0.10	17.0 ± 2.13
F2	155.3 ± 0.74	0.1630 ± 0.0026	26.43 ± 1.24	6.0 ± 0.0	6.0 ± 0.0	8 ± 1.73	92.00 ± 0.46	6.76 ± 0.10	16.10 ± 2.44
F3	167.9 ± 1.46	0.1777 ± 0.0021	32.86 ± 0.96	6.0 ± 0.0	6.0 ± 0.0	11 ± 0.57	81.91 ± 0.11	6.76 ± 0.10	18.72 ± 0.20
F4	229.4 ± 0.87	0.2383 ±0.0015	38.71 ± 4.62	6.0 ± 0.0	6.0 ± 0.0	20 ± 2.52	90.06 ± 0.03	-	24.12 ± 9.00
F5	255.3 ± 3.68	0.2597 ±0.015	41.00 ± 2.66	6.0 ± 0.0	6.0 ± 0.0	18 ± 2.52	93.27 ±0.03	-	26.80 ± 1.84
F6	260.7 ± 4.50	0.2693 ±0.0038	51.71 ± 2.26	6.0 ± 0.0	6.0 ± 0.0	22 ±3.22	91.25 ± 0.05	-	23.23 ± 0.64
F7	127.9 ± 1.98	0.1360 ±0.0010	32.57 ± 1.62	6.0 ± 0.0	7.0 ± 0.0	16 ± 1.53	97.29 ± 0.04	14.85 ± 2.32	21.86 ± 0.62
F8	122.0 ± 2.15	0.1287 ±0.0012	32.03 ± 2.62	6.0 ± 0.0	7.0 ± 0.0	14 ± 2.08	94.10 ± 0.05	17.70 ± 2.89	19.80 ± 0.67
F9	130.3 ± 0.85	0.1363 ±0.0012	35.29 ± 2.50	6.0 ± 0.0	7.0 ± 0.0	17 ± 1.53	87.32 ± 0.03	19.53 ± 1.02	22.52 ± 0.34

Upon visual inspection, the appearance of all ODFs was uniform and smooth. All formulations were not sticky and separated easily from the bottom of the Petri dishes. In comparison to ODFs with HPMC, the HPC and Na-CMC formulations were firmer and even easier to remove from the Petri dishes. It can be assumed that a higher concentration of glycerin in F1–F3 played a key role in this, since high concentration of glycerin causes stickiness in films[23].

As demonstrated in Table 2, the thickness and weight of various film compositions rise with increasing polymer and glycerin concentrations. In comparison to ODFs with a lower polymer concentration, those with the highest polymer content (F3, F6, and F9) are thicker and heavier. This is in accordance with published data that the increase in polymer concentration can increase the thickness and weight of the films[16]. The thickness and weight are affected by the type of polymer as there are statistically significant differences ($p<0.05$) between all three polymers. Since glycerin has a water retention effect, it can increase the distance of bonding; therefore, the thickness of the films can be increased[24], which was the case with HPMC films that were significantly thicker ($p<0.05$), than Na-CMC films. On the other hand, although HPC films had the lowest glycerin concentration (10% w/w of polymer), their thickness and weight were the highest ($p<0.05$), which could probably relate to the amount of polymer (4–6%, as opposed to 1.75–2.25% of HPMC and 1.5–2.5% of Na-CMC).

The influence of the type and quantity of hydrophilic polymer on the disintegration time of ODFs has been evaluated in all formulations. Based on the results presented in Table 2, it can be noted that the concentration of HPMC, which has a molar mass of 35 600 g/mol, had no significant effect ($p>0.05$) on the disintegration time. The formulation with the lowest polymer concentration (F2) had the shortest disintegration time, which is consistent with the literature findings[25].

Formulations that contain HPC have significantly ($p<0.05$) longer disintegration time compared to formulations with HPMC, as well as F5 and F6 compared to Na-CMC formulations ($p<0.05$). Formulations with 4% and 5% polymer (HPC) have a similar disintegration time ($p>0.05$), which in turn could indicate that the

concentration of a polymer does not have to necessarily significantly affect the time of disintegration..

The properties of polymers depend on their molar mass. Generally, low molar mass polymers dissolve faster than polymers with a high molar mass. Films formulated with HPC, a polymer of high molar mass (100 000 g/mol), showed the longest disintegration time, and the molar mass of the polymer may have played a key role in slowing down the disintegration. On the other hand, HPMC has the lowest molar mass compared to other polymers used, which supports the fact that the formulations F1–F3 with HPMC had the shortest disintegration time and is in accordance with literature data[26].

According to literature data, increasing the concentration of glycerin reduces the disintegration time[27]. When HPMC (F1–F3) formulations with a highest amount of glycerin are compared to other formulations, the HPMC formulations had significantly ($p<0.05$) shorter disintegration time than HPC (F4–F6), while F1 and F2 had shorter ($p>0.05$) disintegration time than F7–F9. Analogously, formulations with HPC (F4–F6) contain lowest concentrations of glycerin and have longest disintegration time.

Requirements for the disintegration of orodispersible tablets may also apply to ODFs, as no specific requirements for ODFs are available. Therefore, the disintegration time of ODF should be up to 3 minutes[28]. From Table 2 it can be concluded that all formulations have a satisfactory disintegration time (since disintegration time of all our formulations was below 60 seconds).

Table 2 shows the surface pH values, as well as the pH values of ODFs dissolved in distilled water. It can be noted that all formulations have the same surface pH. All films have identical surface pH and pH after dissolution, except for formulations with Na-CMC (F7–F9), where the surface pH is 6, and after dissolving the film, the pH value is increased to 7. This could be because Na-CMC water dispersions have higher pH (pH 6.5–8.5) than the water dispersions of HPMC or HPC (pH 5–8)[29]. It is noticeable that the pH value of all formulations is in a range close to the pH of saliva, which indicates that films with HPMC, Na-CMC, and HPC are suitable and should not cause any irritation or inflammation to the oral cavity mucosa. In this way, the degree of patient adherence can also be increased, which is in line with existing data[2,30].

Based on the results presented in Table 2, it can be observed that the folding endurance of ODFs increases with an increase in polymer concentration (F2 < F1 < F3; F8 < F7 < F9), but not significantly ($p>0.05$). This is in line with available literature data[31]. The deviation from this observation can be noted with formulations containing HPC, where the formulation with the lowest level of HPC (F4) has medium folding endurance, but still, the formulation with the highest amount of polymer (F6) has the highest folding endurance.

But according to the literature, by increasing the concentration of plasticizers, in this case, glycerin, films become more flexible[32,33]. It could be assumed that ODFs with HPMC will have the highest folding endurance since they have the highest concentration of glycerin in their composition. This cannot be applied to F1–F3 formulations. This could be due to a higher concentration of glycerin compared to the polymer since glycerin increases the flexibility of films when the hydrophilic polymer is used at a concentration greater than glycerin[32,33]. Since the polymer concentration in these formulations were much lower than that of glycerin, those formulations had lower ($p<0.05$) folding endurance compared to formulations with HPC ($p<0.05$) and with Na-CMC ($p>0.05$). Unlike F1–F3; F4–F6 and F7–F9 acted differently. The folding endurance of F7–F9 was lower ($p>0.05$) compared to that of F4–F6. This could probably be due to polymer/plasticizer ratio, which proved to be optimal for HPC formulations.

The obtained results show that ODFs with HPC have the greatest folding endurance of all formulations, which is in accordance with the literature data, that states that ODF with better mechanical properties are produced from polymers with a higher molar mass[26]. In addition, formulations with Na-CMC should have lower folding endurance than formulations F1, F2, and F3[26,34], which is not the case here. As mentioned above, the reason for this may be the glycerin-HPMC ratio in the formulations F1, F2, and F3.

The transparency testing of ODFs in visible region (600 nm) revealed that Na-CMC films were most transparent. They were significantly ($p<0.05$) more transparent than the HPC ODFs, and HPMC ODFs. Statistical analysis also revealed that not only the type of polymer but also the concentration of polymer has influence ($p<0.05$) on film transparency.

As can be seen from Table 2, ODFs with Na-CMC absorbed significantly ($p<0.05$) more moisture than formulations with HPMC. According to the literature, Na-CMC is more hygroscopic than HPMC[35], so these results are expected. These results could relate to the disintegration time since HPMC films had lower moisture uptake and therefore probably disintegrated slower than Na-CMC films. On the other hand, HPC films had the highest disintegration time, but the samples absorbed so much water that they became liquid and consequently could not be weighted. This could be because HPC is the least swellable and absorbs water much slower than the other two polymers, but the absorption is more complete[36]. Moreover, having in mind the results of the moisture uptake, it would be very important that the films be packed in a moisture-proof packaging material and kept in a cool and dry place.

In general, moisture loss increased slightly ($p>0.05$) with increased polymer concentration. Moisture loss of films containing polymer with a higher molar mass (HPC ODFs) was higher, but not statistically

different ($p>0.05$) than moisture loss of films containing polymer of lower molar mass (HPMC and Na-CMC ODFs), probably due to longer polymeric chains of polymer molecules with a higher content of hydrophilic groups, which at the start could lead to a higher water binding capacity[37].

3.1 FTIR spectroscopy

The spectra of individual substances in the formulations are shown in Fig. 2 and Fig 3.

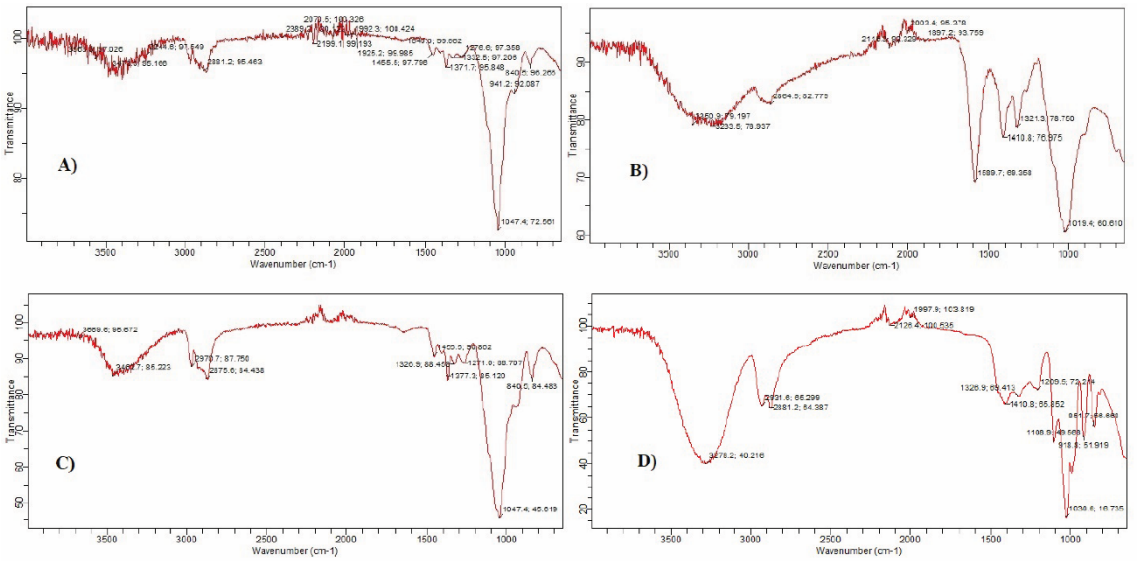

Figure 2: FTIR spectra of (A) HPMC, (B) Na-CMC, (C) HPC and (D) glycerin

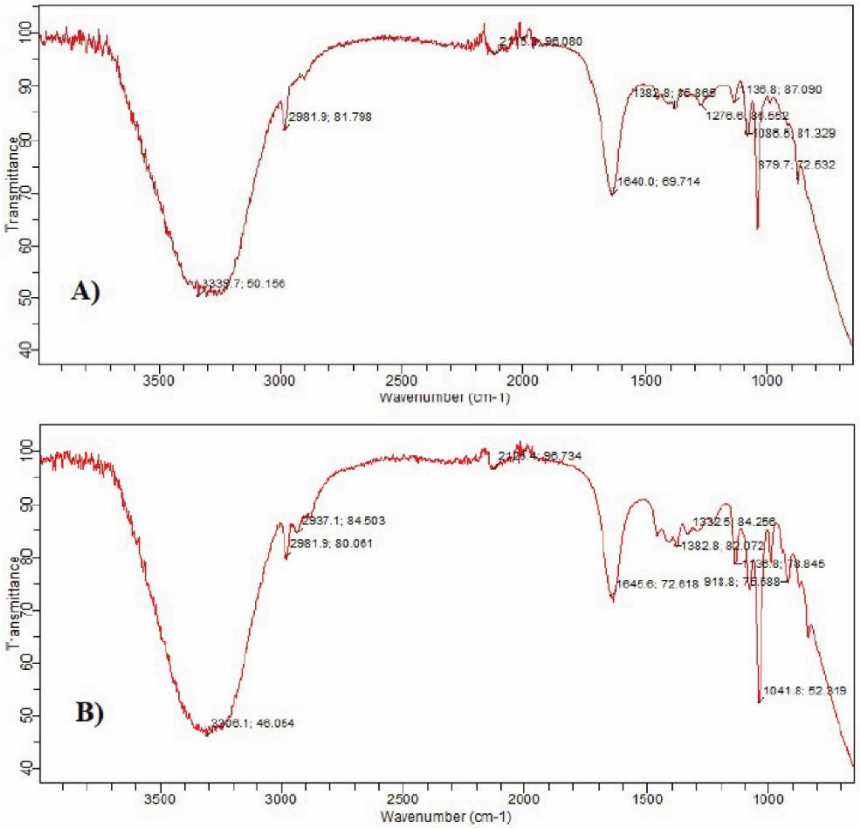

Figure 3: FTIR spectra of (A) raspberry flavor and (B) blueberry flavor

Fig. 4 show representative FTIR spectra of formulations with HPMC, HPC and Na-CMC.

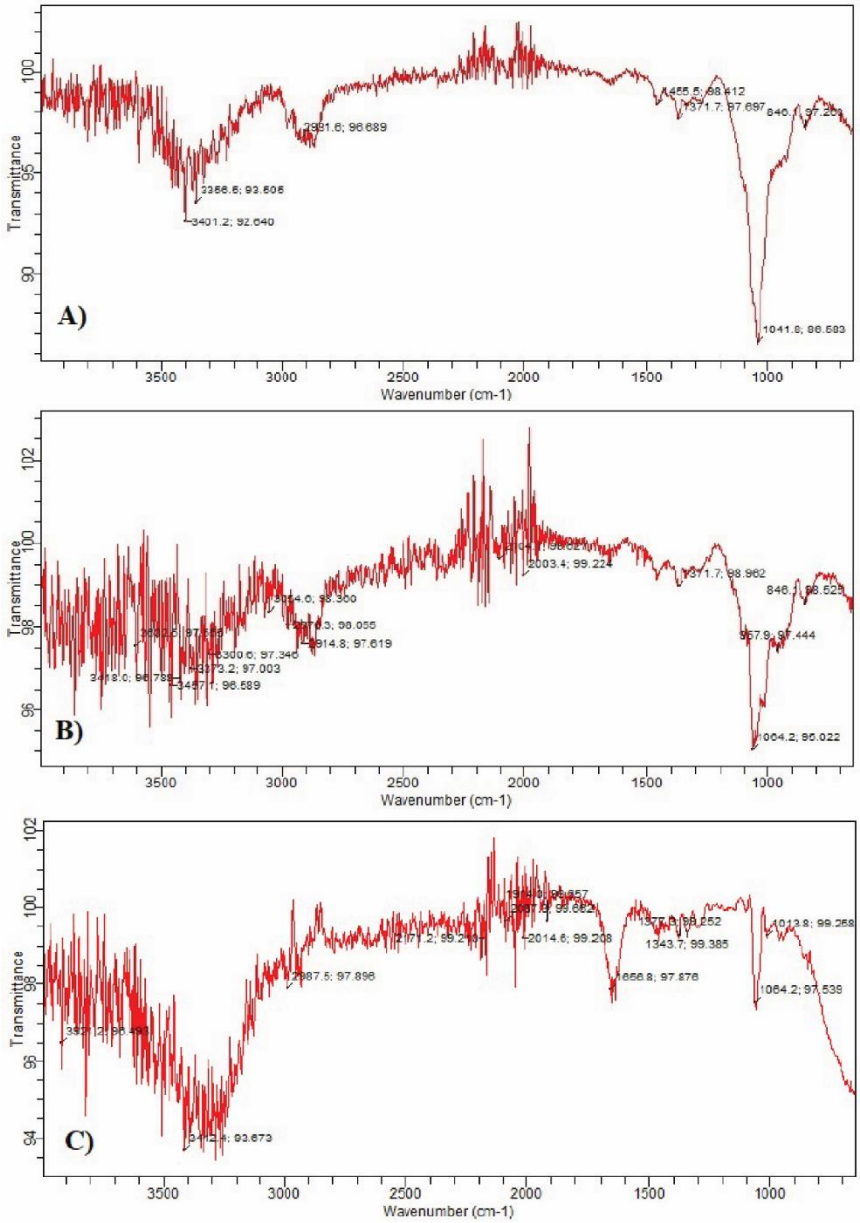

Figure 4: Representative FTIR spectra of formulations with: (A) HPMC, (B) HPC and (C) Na-CMC

FTIR spectra of all ODFs exhibit signals at 3500–3200 cm^{-1}, characteristic for the O-H group. These signals can also be seen in the spectra of all individual, pure substances (Fig. 2 A–D), but the signals are of more intensity. Nevertheless, molecular interactions occur as long as there is a shift in the characteristic absorption peak[24]. Signals at 1100–1000 cm^{-1} indicate the stretching vibration of the C-O-C group, and they have been shifted in FTIR spectra of all ODFs compared to the spectra of pure polymers with which they were made. The assumption is that these findings are indication of plasticization with glycerin, which was expected.

Given that most signals from the FTIR spectra of individual substances can also be seen in the spectra of ODFs, it can be assumed that the substances used are compatible in the mixture and that no interactions occurred when forming the film.

IV. CONCLUSION

The type of polymer had little effect on the thickness and weight of the films, but its concentration showed a greater effect on mentioned parameters. HPC-based films had the highest thickness and weight since they contained the highest polymer concentration. HPMC and Na-CMC-based films contained similar polymer concentrations, but HPMC films were thicker and heavier, since they contained more glycerin. Small variations

in polymer concentrations do not significantly affect the disintegration time of ODFs, unlike the type of polymer and glycerin concentration. The formulations of ODFs with HPMC and the highest glycerin concentration have the shortest disintegration time. ODFs with HPMC, Na-CMC, and HPC have a pH like saliva, therefore they are suitable and not expected to cause any irritation or inflammation in the oral cavity, which can increase patient adherence. Contrary to the type of polymer, the concentration of polymers has no impact on the pH level of ODFs. By increasing the concentration of HPMC, HPC, and Na-CMC in the formulation, ODFs become more resistant to folding. Formulations containing HPMC absorb less moisture than ODFs containing Na-CMC or HPC. FTIR spectroscopy has shown that all components in all formulations are compatible.

Abbreviations

ODFs: Orodispersible Films; EMA: European Medicines Agency; FDA: Food and Drug Administration; HPMC: Hydroxypropyl Methylcellulose; HPC: Hydroxypropyl Cellulose; Na-CMC: Sodium Carboxymethylcellulose; FTIR: Fourier-Transform Infrared Spectroscopy; ATR: Attenuated Total Reflectance; ANOVA: Analysis of Variance; SD: Standard Deviation.

REFERENCES

[1]. Irfan M, Rabel S, Bukhtar Q, et al. Orally disintegrating films: A modern expansion in drug delivery system. Saudi Pharm J. 2016;24(5):537–546.

[2]. Dahiya M, Saha S, Shahiwala A. A review on mouth dissolving films. Curr Drug Deliv. 2009;6(5):469–476.

[3]. Lee Y, Kim K, Kim M, et al. Orally disintegrating films focusing on formulation, manufacturing process, and characterization. J Pharm Investig. 2017;47(3):183–201.

[4]. Borges AF, Silva C, Coelho JFJ, et al. Oral films: Current status and future perspectives: I - Galenical development and quality attributes. J Control Release. 2015;206:1–19.

[5]. Messerli M, Aschwanden R, Buslau M, et al. Swallowing difficulties with medication intake assessed with a novel self-report questionnaire in patients with systemic sclerosis – a cross-sectional population study. Patient Prefer Adherence. 2017;11:1687.

[6]. Danckwerts MP. Intraoral drug delivery. Am J Drug Deliv. 2012;1(3):171–186.

[7]. Hannan PA, Khan JA, Khan A, et al Oral Dispersible System: A New Approach in Drug Delivery System. Indian J Pharm Sci. 2016;78(1):2.

[8]. Hearnden V, Sankar V, Hull K, et al. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Adv Drug Deliv Rev. 2012;64(1):16–28.

[9]. European Pharmacopoeia Convention. European Pharmacopoeia 9th edition (9.0): European Directorate for the Quality of Medicines and HealthCare, Council of Europe, 2016.

[10]. European Medicines Agency. Guideline on the investigation of bioequivalence. London; 2010. Available: http://www.ema.europa.eu [Accessed 13 Mar 2023].

[11]. Dosage Forms | FDA. Available: https://www.fda.gov/industry/structured-product-labeling-resources/dosage-forms [Accessed 13 Mar 2023].

[12]. Yadav A, Tripathi S, Sharma V, et al. Formulation, optimised and evaluation of mouth dissolving film of amoxapine. Asian J Pharm Res Dev. 2021;9(1):67–70.

[13]. Chidi E, Nwobodo N, Offiah RO. Development and Evaluation of Fast Dissolving Thin Films of Aripiprazole. Univers J Pharm Res. 2017;2(5):23–27.

[14]. Cilurzo F, Cupone IE, Minghetti P, et al. Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm. 2008;70(3):895–900.

[15]. Tian Y, Orlu M, Woerdenbag HJ, et al. Oromucosal films: from patient centricity to production by printing techniques. Expert Opin Drug Deliv. 2019;16(9):981–993.

[16]. Pamlényi K, Kristó K, Jójárt-Laczkovich O, et al. Formulation and optimization of sodium alginate polymer film as a buccal mucoadhesive drug delivery system containing cetirizine dihydrochloride. Pharmaceutics. 2021;13(5).

[17]. Marques-Marinho FD, Vianna-Soares CD, Marques-Marinho FD, et al. Cellulose and Its Derivatives Use in the Pharmaceutical Compounding Practice. In: Cellulose - Medical, Pharmaceutical and Electronic Applications. IntechOpen; 2013. p. 141–162.

[18]. Kashyap K, Yadav K, Yadav D. Encapsulation of Flavoring Compounds in Functional Foods and Dairy Nutraceuticals. In: Selvamuthukumaran M, Pathak YV, eds. Flavor Development for Functional Foods and Nutraceuticals. Boca Raton: CRC Press 2019:99–110.

[19]. Preis M, Woertz C, Schneider K, et al. Design and evaluation of bilayered buccal film preparations for local administration of lidocaine hydrochloride. Eur J Pharm Biopharm. 2014;86(3):552–561.

[20]. Prabhu P, Malli R, Koland M, Vijaynarayana K, D'Souza U, Harish N, et al. Formulation and evaluation of fast dissolving films of levocitirizine di hydrochloride. Int J Pharm Investig. 2011;1(2):99–104.
[21]. Jadhav SD, Kalambe RN, Jadhav CM, et al. Formulation and evaluation of fast dissolving oral film of levocetrizine dihydrochlorid. Int J Pharm Pharm Sci. 2012;4(Suppl 1):337–341.
[22]. Rotta J, Ozório RÁ, Kehrwald AM, et al. Parameters of color, transparency, water solubility, wettability and surface free energy of chitosan/hydroxypropylmethylcellulose (HPMC) films plasticized with sorbitol. Mater Sci Eng C. 2009;29(2):619–623.
[23]. Khan Q, Siddique MI, Rasool F, et al. Development and characterization of orodispersible film containing cefixime trihydrate. Drug Dev Ind Pharm. 2020;46(12):2070–2080.
[24]. Gao W, Liu P, Li X, et al. The co-plasticization effects of glycerol and small molecular sugars on starch-based nanocomposite films prepared by extrusion blowing. Int J Biol Macromol. 2019;133:1175–1181.
[25]. Liew KB, Tan YTF, Peh KK. Effect of polymer, plasticizer and filler on orally disintegrating film. Drug Dev Ind Pharm. 2014;40(1):110–119.
[26]. Hoffmann EM, Breitenbach A, Breitkreutz J. Advances in orodispersible films for drug delivery. Expert Opin Drug Deliv. 2011;8(3):299–316.
[27]. Pandey GS, Kumar R, Sharma R, et al. Effects of Maltodextrin and Glycerin on Mechanical Properties of Oral Fast Dissolving Film of Salbutamol Sulphate. Int J Adv Pharm Biol Chem. 2014;3(1):199–209.
[28]. Saab M, Mehanna MM. Disintegration time of orally dissolving films: various methodologies and in-vitro/in-vivo correlation. Pharmazie. 2019;74(4):227–230.
[29]. Shaskey PJ, Cook WG, Cable CG. Handbook of Pharmaceutical Excipients. London: Pharmaceutical Press 2017:401–405.
[30]. Hamza MY. Development and Evaluation of Orodispersible Films of Lamotrigine:Hydroxypropyl B Cyclodextrin Inclusion Complex. Az J Phar Sci. 2017;56:31–46.
[31]. Patel P, Rikisha L, Mayur C, et al. Development and Optimization of Fast Dissolving Orodispersible Film of Baclofen Using 3^2 Central Composite Design. Int J Pharm Sci Res. 2014;5(12):5539–5547.
[32]. Takeuchi Y, Ikeda N, Tahara K, et al. Mechanical characteristics of orally disintegrating films: Comparison of folding endurance and tensile properties. Int J Pharm. 2020;589.
[33]. Sakhare AV. Effect of Glycerin as Plasticizer in Orodissloving Films of Losartan Potassium. Int J Sci Res. 2014;3(8):772–778.
[34]. Rani KC, Parfati N, Aryani NLD, et al. Development, Evaluation, and Molecular Docking of Oral Dissolving Film of Atenolol. Pharmaceutics. 2021;13(10).
[35]. Callahan JC, Cleary GW, Elefant M, et al. Equilibrium Moisture Content of Pharmaceutical Excipients. Drug Dev Ind Pharm. 1982;8(3):355–369.
[36]. Kimbell G, Azad MA. 3D printing: Bioinspired materials for drug delivery. Bioinspired Biomim Mater Drug Deliv. 2021;295–318.

Ognjenka Rahić, et. al. "Influence of type and quantity of three hydrophilic cellulose derivatives on orodispersible films' characteristics." *IOSR Journal of Pharmacy (IOSRPHR)*, 13(03), 2023, pp. 22-30.