https://doi.org/10.15255/KUI.2023.037
KUI-16/2024
Original scientific paper
Received September 21, 2023
Accepted October 12, 2023

Correlation between Optical Characteristics of Orodispersible Films with Selected Process Parameters Supported by FTIR Analysis

O. Rahić,[a*] *A. Tucak-Smajić*,[a] *M. Šahinović*,[a] *B. Imamović*,[b] *L. Hindija*,[a] *J. Hadžiabdić*,[a] and *E. Vranić*[a]

[a] University of Sarajevo, Faculty of Pharmacy, Department of Pharmaceutical Technology, Zmaja od Bosne 8, 71 000 Sarajevo, Bosnia and Herzegovina
[b] University of Sarajevo, Faculty of Pharmacy, Department of Drug Analysis, Zmaja od Bosne 8, 71 000 Sarajevo, Bosnia and Herzegovina

Abstract

Paediatric and geriatric populations, as well as other special patient populations with swallowing problems, require patient-tailored dosage forms. One promising dosage form for these specific populations is orodispersible films.
When preparing orodispersible films using sodium carboxymethyl cellulose as the film-forming polymer and glycerine as the plasticizer, it is essential to determine the optimal mixing time and mixing speed of the casting solution to achieve the desired transparency/opacity of the orodispersible films. In this paper, the primary focus is on mixing time and mixing speed, and determining how these two parameters can influence optical characteristics. All tested parameters are supported by FTIR analysis. The obtained results show that either a mixing speed of 7000 rpm on a high-shear mixer for 15 min or a mixing speed of 9000 rpm for 5 min can produce films with optimal optical characteristics.

Keywords

Orodisperisble films, sodium carboxymethyl cellulose, glycerine, optical characteristics, FTIR

1 Introduction

Administering medicine to paediatric and geriatric populations can pose quite a challenge. One aspect of this challenge pertains to inadequate dosage forms for these sensitive populations, which is an issue attributed to the pharmaceutical industry. The second aspect involves the acceptability of produced doses.[1]

While the ideal dosage form for children should allow for less frequent dosing, adequate and reliable administration, minimal disruption to their daily routine, the use of non-toxic and well-tolerated excipients, and taste masking, these considerations can also be extrapolated to the geriatric population.[2] Both populations are characterised by altered drug bioavailability compared to the adult population due to different physiological and metabolic functioning. In addition, paediatric and geriatric populations have specific preferences regarding the taste and appearance of dosage forms.[2,3]

According to the European Pharmacopea, orodispersible films (ODFs) are defined as "single- or multilayer sheets of suitable materials, to be placed in the mouth where they disperse rapidly".[4] Furthermore, in the context of the mentioned populations, ODFs are highly acceptable and comfortable methods for drug administration. One of the main advantages of ODFs is their ability to quickly disintegrate or dissolve in the mouth, without the need for additional liquid intake.[5]

In addition, paediatric and geriatric patients often require tailored dosage forms prepared by community or hospital pharmacies. Considering the relative ease of ODF production, which enables their small-scale manufacturing in pharmacies, it is also possible to provide these vulnerable patients with extemporaneous ODFs.[6]

If ODFs are the chosen dosage form, challenges persist for the pharmaceutical industry. Several physical-chemical properties and production processes may impact the optimal characteristics of ODFs.[7]

The most commonly employed manufacturing method for ODFs is the solvent casting method, which utilises a wide range of film-forming polymers (most often hydrophilic cellulose derivatives) in which drug substances and other excipients (such as plasticizers, fillers, and taste-masking agents) are incorporated. Plasticizers are added to improve the mechanical properties of ODFs, with glycerine frequently chosen as the preferred plasticizer.[8]

One of the factors that can impact patient acceptability and adherence regarding ODFs is their optical characteristics, specifically transparency and opacity.[7] Therefore, our aim was to investigate whether process parameters, such as mixing speed and mixing time, could influence the transparency/opacity of ODFs. To support the obtained data, additional FTIR tests of prepared films were performed.

* Corresponding author: Assoc. Prof. Ognjenka Rahić, Ph.D.
Email: ognjenka.rahic@ffsa.unsa.ba

2 Experimental

2.1 Materials

Sodium carboxymethylcellulose (Na-CMC) (TCI-Tokyo Chemical Industry Co., Ltd., Japan) was kindly provided by HARKE Pharma GmbH (Germany). Glycerine was purchased from Centrohem (Serbia).

2.2 Preparation of ODFs

ODFs were prepared by solvent casting method. A Silverson L5M-A high shear mixer (Silverson Machines Ltd., England) was used to mix formulations comprising 2 % w/w Na-CMC and 1 % w/w glycerine in distilled water. All the formulations had the same composition, but differed in mixing speed and mixing time, as shown in Table 1.

Table 1 – Formulation mixing speed and time
Tablica 1 – Brzina i vrijeme miješanja formulacija

Formulation code	Mixing speed / rpm	Mixing time / min
F-1	5000	5
F-2	5000	15
F-3	5000	30
F-4	7000	5
F-5	7000	15
F-6	7000	30
F-7	9000	5
F-8	9000	15
F-9	9000	30

After mixing all the solutions, they were poured into Petri dishes (diameter 90 mm) and dried for two 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 Characterisation of ODFs

2.3.1 Thickness of ODFs

Using a 0.001 mm sensitive digital micrometre (Mitutoyo Co. Ltd., Japan), the thickness of the films was measured at three randomly chosen points on all the films ($n = 3$) and averaged to determine the mean thickness.

2.3.2 Optical properties of ODFs

With air as a blank, the ODFs were fixed to the inside of the cuvette, and the UV-VIS spectrophotometer Shimadzu UV-1601 (Shimadzu Corporation, Japan) was used to quantify absorbance and percent transmittance (%T). Eqs. (1) and (2) were used, respectively, to calculate the transparency and opacity of ODFs[9].

$$\text{transparency} = \left(\log \%T\right) / x \quad (1)$$

$$\text{opacity} = A_{600} / x \quad (2)$$

A_{600} is the absorbance at 600 nm, and x is ODF thickness. All measurements were made in triplicate.

2.3.3 FTIR of ODFs

Cary 630 (Agilent Technologies, Inc., Santa Clara, CA, USA) with MicroLab FTIR software was used to record the spectra of raw materials and ODFs. The samples were placed on the diamond crystal, and the sample press was rotated downward until sufficient pressure was applied to the sample. The applicable spectral range for the attenuated total reflectance (ATR) technique was 600–4000 cm^{-1}. The spectra were gathered from 32 scans with a resolution of 4 cm^{-1}.

2.3.4 Statistical analysis

The two-way analysis of variance (ANOVA) was used to analyse the obtained data, and Tukey's difference test was used as a *post-hoc* test. The results were provided as mean values ± standard deviations (SD).

3 Results and discussion

Formulations F1–F3 (prepared at 5000 rpm) were excluded from further evaluations as they had significantly higher absorbance/opacity ($p < 0.05$) and reduced transparency compared to other formulations.

On the other hand, formulations prepared at 7000 rpm and 9000 rpm with a mixing time of 30 min (designated as F-6 and F-9, respectively) were also disregarded from further analyses since they failed to significantly vary ($p > 0.05$) from formulations prepared at the same speed but with shorter mixing time. This is justified by the fact that longer mixing times use more resources without significantly enhancing formulation performance.

FTIR spectra of raw materials as well as those of ODFs are presented in Figs. 1 and 2, respectively.

Based on the signal of the individual spectra for the raw materials glycerine and Na-CMC (Figs. 1A and 1B, respectively), it can be concluded that the broad signal at 3261.4 cm^{-1} in the spectra of selected ODFs (Fig. 2), indicates the presence of a hydrogen bond between the OH groups of glycerine and Na-CMC. The signal at 2881.2 cm^{-1} is characteristic of the CH_2 group of glycerine.[10]

The characteristics of interest of selected formulations are presented in Table 2.

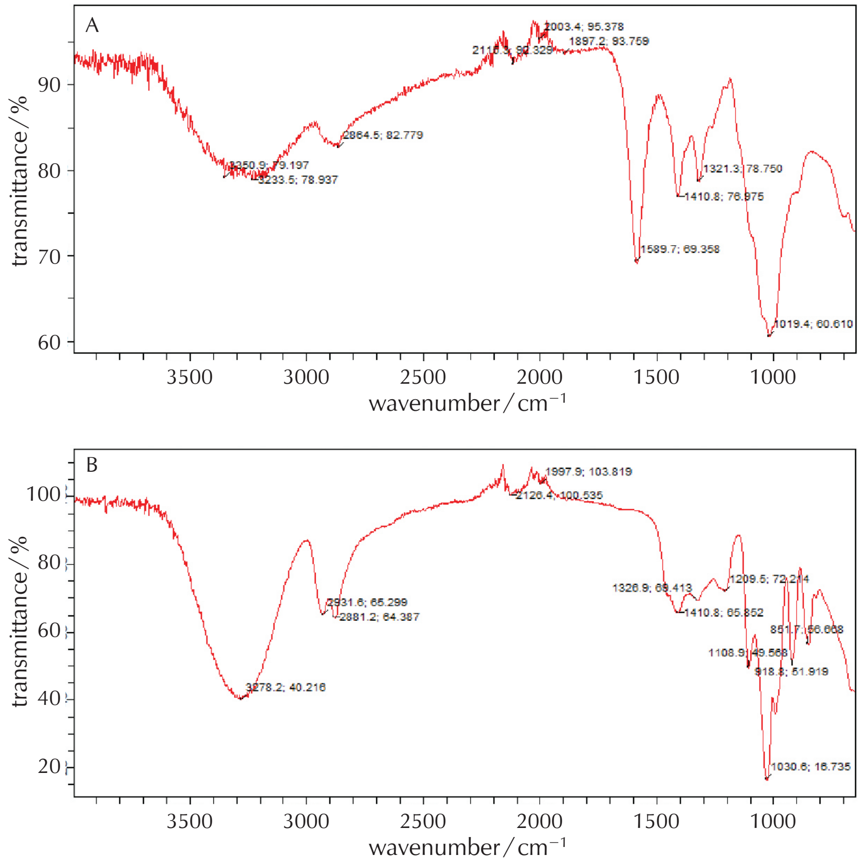

Fig. 1 – FTIR spectra: A. Na-CMC; B. glycerine
Slika 1 – FTIR spektri: A. Na-CMC; B. glicerol

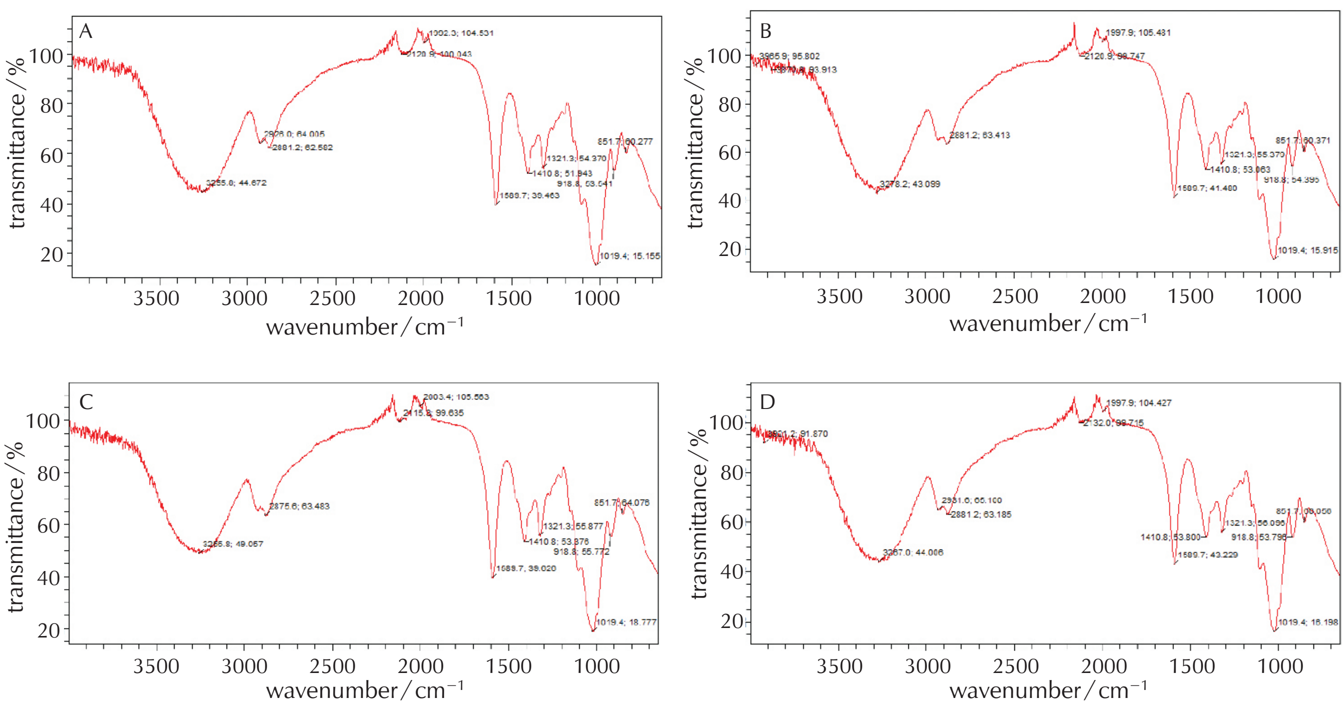

Fig. 2 – FTIR spectra: A. F-4; B. F-5; C. F-7; D. F-8
Slika 2 – FTIR spektri: A. F-4; B. F-5; C. F-7; D. F-8

Table 2 – Characteristics of ODFs (mean ± SD; $n = 3$)
Tablica 2 – Karakteristike ODF-a (srednja vrijednost ± SD; $n = 3$)

Formulation code	Thickness / mm	Transparency	Opacity / %
F-4	0.024 ± 0.002	78.93 ± 0.32	4.40 ± 0.34
F-5	0.027 ± 0.002	70.79 ± 0.06	3.27 ± 0.06
F-7	0.022 ± 0.003	86.61 ± 0.50	4.29 ± 0.50
F-8	0.020 ± 0.001	95.35 ± 0.30	4.64 ± 0.30

According to *Turković et al.*, thickness, as one of the QTPP (Quality Targeted Product Profile) elements for ODFs, is preferably less than 350 mm. In most studies, the thickness of ODFs ranged from 13 to 710 mm.[8] The film thickness obtained in our study falls well within those limits and is consistent with the results of several other studies, irrespective of the polymer used.[11–13] Since there are no variations in plasticizer content,[14] drying conditions,[14] or dimensions of Petri dishes that can affect film thickness, the only variation that can occur would be due to different mixing conditions. As all ODFs have similar thickness, it can be assumed that the selected process parameters had no influence on film thickness.

Optical experiments conducted by *Badri et al.* revealed that the optical transmittance of pure Na-CMC was above 80 %,[15] which conforms with the transparency and corresponding transmittance of F-7 and F-8.

As seen in Table 2, there is a statistically significant difference in transparency and opacity of F-4 and F-5 ($p < 0.05$), indicating that longer mixing speeds lead to a decrease in opacity and transparency. In the study by *Sharma et al.*[16], it was concluded that the opacity and compactness of polymer films decrease as the intermolecular forces between polymer and glycerine decrease.[16] This could possibly cause an increase in CMC matrix light scattering, as observed by *Bourbon et al.*[17] Given this, it can be assumed that prolonged mixing speeds, beyond a certain point, can lead to the formation of films with inferior characteristics. These assumptions find support in FTIR analysis.

In Fig. 2, the signal at 1589.7 cm^{-1} indicates the presence of a carbonyl group from Na-CMC to which sodium is bound. Because of this, the position of the carbonyl group signal is slightly shifted. The signal at 1410.8 cm^{-1} corresponds to the stretching of the C–H–O bond, at 1321.3 cm^{-1}, the signal represents the OH deformation vibration from glycerine; and the signal at 1019 cm^{-1} is associated with the primary OH group from Na-CMC, as observed by *Wahyuni et al.* and *Danish et al.*[18,19] All these signals are more intense in the spectra of ODFs than in the individual spectra of the raw materials glycerine and Na-CMC. This suggests that a strong connection has been established between these two substances in the process of film formation, as suggested by *Hebeish and Sharaf*.[20] Reduced transmittance in the spectrum of F-5 (Fig. 2B) compared to the spectrum of F-4 (Fig. 2A) is consistent with the analysis of opacity and transparency. Reduced transmittance, indicating a weaker connection between film-forming polymer and plasticizer, is also associated with reduced opacity. Therefore, it can be presumed that for a mixing speed of 7000 rpm, a 5-min mixing time (F-4) is more advisable than a 15-min mixing time (F-5).

Regarding F-7 and F-8, the results of transparency and opacity are vice versa. While there is a statistically significant difference ($p < 0.05$) between these two formulations, a longer mixing time leads to increased opacity. This further supports the fact that there exists an optimal value of mixing speed and mixing time for ODFs' performance, considering this combination of polymer and plasticizer. When using a speed of 9000 rpm, the opacity and transparency of ODFs exhibit different characteristics. While for formulations F-4 and F-5 (mixing speed 7000 rpm), an increase in mixing time leads to a decrease in opacity and transparency, for formulations F-7 and F-8 (mixing speed of 9000 rpm), an increase in mixing time leads to an increase in opacity, but not statistically different ($p > 0.05$). This observation is further supported by FTIR analysis, as the spectra of F-7 and F-8 exhibit no difference in transmittance. It cannot be excluded that at these lower, but not optimal mixing speeds and times, nanoparticles may form, leading to increased opacity.[3] However, due to limitations in the length of this manuscript, further investigations are needed.

4 Conclusion

The objective of this work was to determine the optimal mixing speed and mixing time on a high-shear mixer for a solvent casting solution comprising Na-CMC and glycerine. Our work demonstrates that there exists a specific combination of mixing time and mixing speed that yields the best optical characteristics of ODFs. When using Na-CMC as the film-forming polymer and glycerine as plasticizer, the best optical characteristics are achieved with a mixing speed of 7000 rpm for 15 min or a mixing speed of 9000 rpm for 5 min.

ACKNOWLEDGEMENTS

This work was supported by Erasmus+ project number: 618089-EPP-1-2020-BA-EPPKA2-CBHE-JP: "Innovating Quality Assessment Tools for Pharmacy Studies in Bosnia and Herzegovina/IQPharm".

List of abbreviations and symbols
Popis kratica i simbola

ODFs – orodispersible films
Na-CMC– sodium carboxymethylcellulose
FTIR – Fourier-transform infrared spectroscopy
ATR – attenuated total reflectance
%T – percent transmittance
QTPP – quality targeted product profile

References
Literatura

1. *B. Morath, S. Sauer, M. Zaradzki, A. H. Wagner*, Orodispersible films – Recent developments and new applications in drug delivery and therapy, Biochem. Pharmacol. **200** (2022) 115036, doi: https://doi.org/10.1016/j.bcp.2022.115036.
2. *K. Golhen, M. Buettcher, J. Kost, J. Huwyler, M. Pfister*, Meeting challenges of pediatric drug delivery: The potential of orally fast disintegrating tablets for infants and children, Pharmaceutics **15** (2023) 1033, doi: https://doi.org/10.3390/pharmaceutics15041033.
3. *Y. Perrie, R. K. Badhan, D. J. Kirby, D. Lowry, A. R. Mohammed, D. Ouyang*, The impact of ageing on the barriers to drug delivery, JCR **161** (2012) 389–398, doi: https://doi.org/10.1016/j.jconrel.2012.01.020.
4. Ph. Eur. 2018: European Pharmacopoeia, 9th Ed., Strasbourg (FR): Directorate for the Quality of Medicines and Health-Care of the Council of Europe (EDQM), 2018.
5. *E. M. Hoffmann, A. Breitenbach, J. Breitkreutz*, Advances in orodispersible films for drug delivery, Expert Opin. Drug Deliv. **8** (2011) 299–316, doi: https://doi.org/10.1517/17425247.2011.553217.
6. *W. C. Foo, Y. M. Khong, R. Gokhale, S. Y. Chan*, A novel unit-dose approach for the pharmaceutical compounding of an orodispersible film, Int. J. Pharm. **539** (2018) 165–174, doi: https://doi.org/10.1016/j.ijpharm.2018.01.047.
7. *M. Zamanian, H. Sadrnia, M. Khojastehpour, F. Hosseini, J. Thibault,* Effect of TiO_2 nanoparticles on barrier and mechanical properties of PVA films, J. Membr. Sci. Res. **7** (2021) 67–73, doi: https://doi.org/10.22079/JMSR.2020.112911.1283.
8. *E. Turković, I. Vasiljević, M. Drašković, J. Parojčić*, Orodispersible films – Pharmaceutical development for improved performance: A review, J. Drug Deliv. Sci. Tech. **75** (2022) 103708, doi: https://doi.org/10.1016/j.jddst.2022.103708.
9. *J. Zhao, Y. Wang, C. Liu,* Film transparency and opacity measurements, Food Anal. Methods **15** (2022) 2841–2846, doi: https://doi.org/10.1007/s12161-022-02343-x.
10. *F. Rouessac, A. Rouessac,* Chemical Analysis: Modern Instrumentation Methods and Techniques. 2nd Ed., John Wiley & Sons Ltd., Chichester, 2007, pp. 214.
11. *D. A. El-Setouhy, N. S. El-Malak*, Formulation of a novel tianeptine sodium orodispersible film, AAPS PharmSciTech. **11** (2010) 1018–1025, doi: https://doi.org/10.1208/s12249-010-9464-2.
12. *H. Kathpalia, B. Sule, A. Gupte*, Development and evaluation of orally disintegrating film of tramadol hydrochloride, Asian J. Biomed. Pharm. Sci. **3** (2013) 27–32, doi: https://doi.org/10.15272/AJBPS.V3I24.377.
13. *K. Mehta, N. Changoiwala, S. Modi, M. Gohel, R. Parikh*, Formulation, development and optimization of fast dispersible oral films of domperidone maleate, PharmaTutor. **1** (2013) 75–87.
14. *W. Gao, P. Liu, X. Li, L. Qiu, H. Hou, B. Cui*, The co-plasticization effects of glycerol and small molecular sugars on starch-based nanocomposite films prepared by extrusion blowing, Int. J. Biol. Macromol. **133** (2019) 1175–1181, doi: https://doi.org/10.1016/j.ijbiomac.2019.04.193.
15. *R. Badry, M. M. El-Nahass, N. Nada, H. Elhaes, M. A. Ibrahim*, Structural and UV-blocking properties of carboxymethyl cellulose sodium/CuO nanocomposite films, Sci. Rep. **13** (2023) 1123, doi: https://doi.org/10.1038/s41598-023-28032-1.
16. *V. Sharma, M. Kaur, K. S. Sandhu, S. K. Godara,* Effect of cross-linking on physico- chemical, thermal, pasting, in vitro digestibility and film forming properties of Faba bean (*Vicia faba* L.) starch, Int. J. Biol. Macromol. **159** (2022) 243–249, doi: https://doi.org/10.1016/j.ijbiomac.2020.05.014.5.
17. *A. I. Bourbon, M. J. Costa, L. C. Maciel, L. Pastrana, A. A. Vicente, M. A. Cerqueira*, Active carboxymethylcellulose-based edible films: influence of free and encapsulated curcumin on films' properties. Foods. **10** (2021) 1512, doi: https://doi.org/10.3390/foods10071512.
18. *H. S. Wahyuni, S. Yuliasmi, H. S. Aisyah, D. Riati,* Characterization of synthesized sodium carboxymethyl cellulose with variation of solvent mixture and alkali concentration, Open Access Maced. J. Med. Sci. **7** (2019) 3878–3881, doi: https://doi.org/10.3889/oamjms.2019.524.
19. *M. Danish, M. W. Mumtaz, M. Fakhar, U. Rashid*, Response surface methodology based optimized purification of the residual glycerol from biodiesel production process, Chiang Mai J. Sci. **43** (2016) 1570–1582.
20. *A. Hebeish, S. Sharaf*, Novel nanocomposite hydrogel for wound dressing and other medical applications, RSC Adv. **125** (2015) 103036–103046, doi: https://doi.org/10.1039/C5RA07076.

SAŽETAK

Korelacija između optičkih karakteristika orodisperzibilnih filmova s odabranim parametrima procesa potkrijepljena FTIR analizom

Ognjenka Rahić,[a*] *Amina Tucak-Smajić*,[a] *Merima Šahinović*,[a] *Belma Imamović*,[b]
Lamija Hindija,[a] *Jasmina Hadžiabdić*[a] i *Edina Vranić*[a]

Pedijatrijska i gerijatrijska populacija, kao i druge populacije pacijenata s problemima gutanja, zahtijevaju oblike doziranja prilagođene pacijentima. Jedan obećavajući oblik doziranja za te specifične populacije su orodisperzibilni filmovi.

Kod pripreme orodisperzibilnih filmova s natrijevom karboksimetil celulozom kao polimerom koji tvori film i glicerolom kao plastifikatorom, postoji potreba za uspostavljanjem odgovarajućeg vremena miješanja i brzine miješanja otopine za lijevanje da bi se postigla odgovarajuća prozirnost/neprozirnost orodisperzibilnih filmova. U ovom radu fokus je na vremenu miješanja i brzini miješanja te pokušaju da se utvrdi na koje načine ta dva parametra mogu utjecati na optičke karakteristike. Svi testirani parametri podržani su FTIR analizom. Dobiveni rezultati pokazuju da brzina miješanja od 7000 okretaja/min na miješalici s visokim smicanjem tijekom 15 min ili brzina miješanja od 9000 okretaja/min tijekom 5 min može proizvesti filmove s optimalnim optičkim karakteristikama.

Ključne riječi
Orodisperzibilni filmovi, natrij karboksimetil celuloza, glicerol, optičke karakteristike, FTIR

[a] *Univerzitet u Sarajevu, Farmaceutski fakultet, Katedra za farmaceutsku tehnologiju, Zmaja od Bosne 8, 71 000 Sarajevo, Bosna i Hercegovina*
[b] *Univerzitet u Sarajevu, Farmaceutski fakultet, Katedre za analitiku lijekova, Zmaja od Bosne 8, 71 000 Sarajevo, Bosna i Hercegovina*

Izvorni znanstveni rad
Prispjelo 21. rujna 2023.
Prihvaćeno 12. listopada 2023.