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Short communication

An investigation into applicability of sodium carboxymethylcellulose and sodium alginate as film-forming agents for semi-solid 3D printing

Erna Turković[1], Elena Velkoska[2], Ana Marija Nančeva[2], Ivana Vasiljević[1], Katerina Goračinova[2], Jelena Parojčić[1]

[1]*Department of Pharmaceutical Technology and Cosmetology, University of Belgrade-Faculty of Pharmacy, Vojvode Stepe 450, 1100 Belgrade, Serbia*
[2]*Institute of Pharmaceutical Technology, SS Cyril and Methodius University in Skopje, Faculty of Pharmacy, Mother Tereza 47, 1000 Skopje, North Macedonia*

Introduction

Semi-solid 3D printing technology has gained increased interest in the pharmaceutical field as it enables on-demand fabrication of personalized dosage forms. Orodispersible films (ODFs) are good candidates for 3D printing because of their relatively simple formulation, flexible dosing, and suitability for administration in different populations. The aim of this work was to investigate the applicability of sodium carboxymethyl cellulose and sodium alginate as film-forming agents for 3D printed ODFs incorporating amlodipine or warfarin as selected model active pharmaceutical ingredients (API).

Materials and methods

Sample preparation: ODFs were prepared by dispersing the polymer carboxymethylcellulose sodium salt (CMC-Na, Fluka Chemie AG, Switzerland) or sodium alginate (SA - Fisher Scientific, USA) in the previously prepared water and glycerol mixture with or without API (amlodipine or warfarin) on the magnetic stirrer. Prepared dispersions were printed in one, three or six layers using the semi-solid 3D printer Ultimaker 2+ and printing objects were designed in Ultimaker Cura 4.3. software (Ultimaker, Netherlands). As a reference, ODFs were also prepared by solvent casting using the same dispersions. Composition of the prepared dispersions is shown in Table 1.

Table 1. Composition of dispersions used for ODF preparation

Constituents (%, w/w)	Samples					
	S1	S2	S3	S4	S5	S6
Glycerol	1	1	1	1	1	1
CMC-Na	7	7	7	-	-	-
SA	-	-	-	7	7	7
Amlodipine	-	2	-	-	2	-
Warfarin	-	-	2	-	-	2
Water (up to)	100	100	100	100	100	100

Sample characterization: The prepared dispersions were characterized in terms of adhesion and pH value and printed/casted samples were evaluated with respect to weight and thickness uniformity, disintegration time (DT) and mechanical properties.

Adhesion measurements and film mechanical properties were performed on the Precision universal tester (Shimadzu EX, Shimadzu Corporation, Japan). For the adhesion measurements the cylindrical probe was lowered into the dispersion and retracted at the controlled rate, while measuring the force and producing the force displacement curve. T-test was used to compare obtained results.

Results and discussion

Dispersions pH value changed noticeably with the addition of warfarin, while in the case of amlodipine it was

*erna.turkovic@pharmacy.bg.ac.rs

not affected. Adhesion increased with the addition of API, which is advantageous for 3D printing as it will not tend to lift off the printing plate when the nozzle moves over it (Table 2).

Table 2. Dispersions characteristics

Sample	pH value	Adhesion (N)
S1	6.54	0.0113
S2	6.19	0.0333
S3	8.63	0.0393
S4	5.56	0.0037
S5	5.56	0.0202
S6	8.57	0.0376

The results obtained indicate that the number of printed layers had a prominent effect on the ODF weight, while the effect of polymer selection or API addition was not apparent. The sample thickness was, also, mainly affected by the number of printed layers. Since the APIs were homogeneously distributed throughout the samples, ODF thickness was uniform. Film-forming agents primarily affected the ODF tensile strength (Table 3). The method of preparation and the number of printed layers had no noticeable effect on the sample strength. When comparing samples printed with different polymer layers, it is evident that slightly lower values were presented for samples S13D6 and S43D6. There is a significant difference in strength and brittleness between different polymer samples ($p < 0.05$). SA-based films exhibited higher tensile strength values than CMC-based films. The addition of amlodipine drastically lowered the strength of the specimen, while warfarin did not have as much effect. There were no significant differences at flexibility of the samples ($p > 0.05$) and the overall elongation at break values were not as high. Samples printed with six layers were generally the most flexible. The API addition affected CMC samples by making them more brittle.

Table 3. Properties of the prepared ODF samples

Sample	Tensile strength (MPa)	Elongation at break (%)	Young`s modulus (MPa)	DT (s)
$S1_C$	32.2	1.9	2365.2	38
$S1_{3D1}$	30.5	3.1	1856.0	19
$S1_{3D3}$	27.6	2.4	1684.7	91
$S1_{3D6}$	20.1	4.5	794.2	682
S2	7.5	0.8	1580.8	145
S3	20.9	0.7	3174.4	116
$S4_C$	62.4	2.4	4120.1	47
$S4_{3D1}$	62.4	3.6	2564.7	12
$S4_{3D3}$	55.3	3.2	2449.0	90
$S4_{3D6}$	41.2	6.1	1112.9	618
S5	2.3	4.9	206.1	133
S6	41.9	4.8	2424.5	100

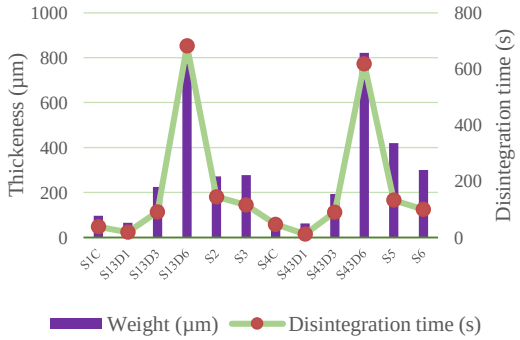

Fig. 1. Sample thickness and disintegration time

Film DT (Table 3) was mainly influenced by the sample thickness (Figure 1). API addition resulted in the increased film DT, which was particularly noticeable in the case of amlodipine. For samples printed with six polymer layers, the disintegration time increased up to 682 s, which is not acceptable for ODF. ODFs should disintegrate in less than 60 s (Turković et al, 2022) which was achieved for casted films and samples printed with one polymer layer. Such findings indicate that optimization of the number of printed layers and/or disintegration enhancer addition should be considered.

Conclusion

The results obtained indicate that CMC-Na and SA can be used as film-forming agents to fabricate uniform films with good mechanical properties by semi-solid 3D printing. The obtained printed samples were comparable to casted films. Addition of APIs had an impact on the films mechanical and disintegration properties. This indicates that the selection of the optimal polymer must include detailed analysis of the interactions between chosen API and polymers, in order to obtain final dosage form with targeted characteristics.

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