Hot-melt Ram extrusion 3D printing: a smart method for compounding orodispersible films in hospital pharmacies

Umberto M. Musazzi, Francesca Selmin, Garba Khalid Mohammed, Silvia Franzé, Paola Minghetti, Francesco Cilurzo

Department of Pharmaceutical Sciences, Università degli Studi di Milano, via G. Colombo, 71 – 20133 Milan, Italy; Email: umberto.musazzi@unimi.it

UNIVERSITÀ DEGLI STUDI DI MILANO

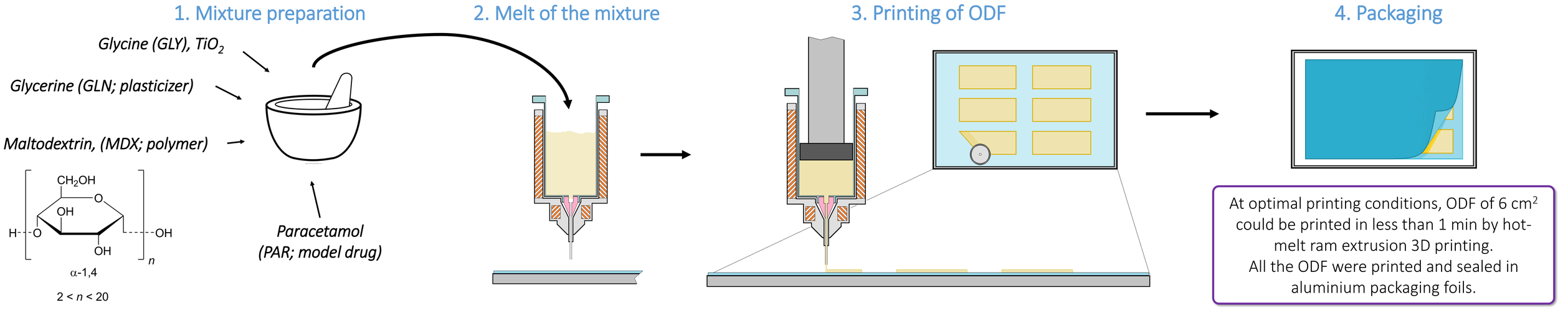
Orodispersible films (ODF) have gained growing interest as an alternative to immediate oral dosage forms to improve patient compliance and, therefore, adherence [1]. Unlike conventional tablets and capsules, they dissolve rapidly in the mouth and can be used in patients with swallowing problems or fear of chocking. Moreover, they assure accurate dosing by the patient and do not require the assumption of water.

Recently, ODF have been proposed for the personalization of the therapies in special patient populations [2], such as dysphagic patients, children and elderly people. Although the ODF have been compounded in a pharmacy setting by casting and printing technologies, many issues are far to be solved.

OBJECTIVE OF THE PRESENT WORK

To demonstrate the feasibility of the extemporaneous preparation of ODF by hot-melt ram extrusion 3D printing [3]

Preparation method and *critical attributes*



At optimal printing conditions, ODF of 6 cm^2 could be printed in less than 1 min by hot-melt ram extrusion 3D printing.
All the ODF were printed and sealed in aluminium packaging foils.

Polymer/plasticizer ratio, other, excipients, drug loading

Heating temperature

Extrusion pressure, plate speed, matrix thickness, filled angles

Placebo ODF

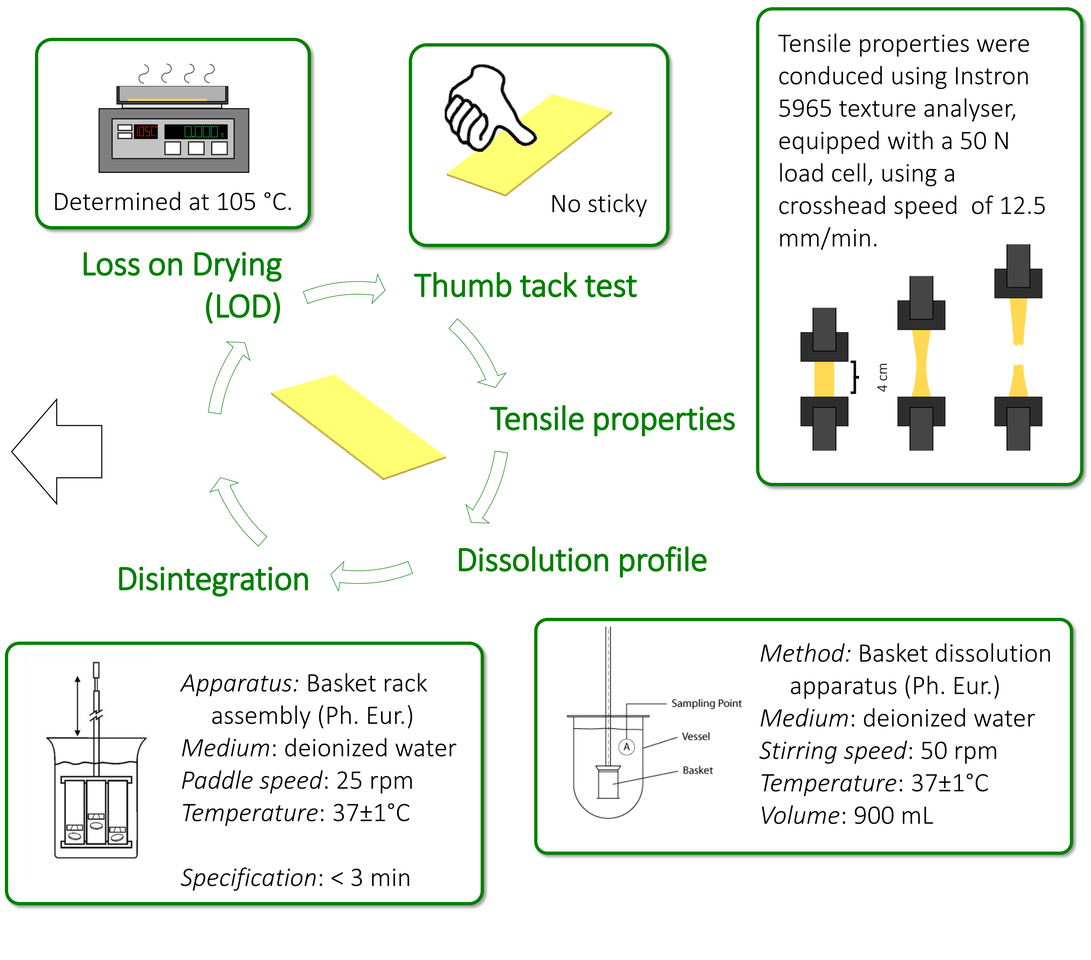
Unlike formulations containing 20 % w/w of GLN, those with 16% w/w were not consistently printable unless GLY was also added at the concentration of 2.5 %, w/w. The printed ODF (6 cm^2; thickness 150-250 µm) disintegrated in less than 2 min. The water contents in ODF (LOD: 5-10% w/w) resulted lower than other ODF made by solvent casting technique [4].

Form.	Composition (%)				Thumb tack test	σ_{max} (MPa)	Y (MPa)	ε (%)
	MDX	GLN	GLY	TiO_2				
1	84.00	16.00	-	-	-	-	-	-
2	82.75	16.00	1.25	-	-	-	-	-
3	81.50	16.00	2.50	-	No sticky	0.09±0.05	2.44±0.87	>1000
4	81.40	16.00	2.50	0.10	No sticky	0.06±0.01	0.82±0.30	992±83
5	80.00	20.00	-	-	No sticky	0.19±0.05	2.76±1.69	431±155
6	79.90	20.00	-	0.10	No sticky	0.05±0.03	0.81±0.47	312±146
7	78.75	20.00	1.25	-	Sticky	0.09±0.01	1.37±0.68	423±60
8	77.50	20.00	2.50	-	Very sticky	0.01±0.01	0.13±0.01	414±76

σ_{max}: tensile strength; Y: Young's Modulus; ε: elongation at break

The printed ODF showed acceptable tensile properties for product handling by patients. For 20% w/w of GLN, GLY impacted negatively on the film toughness. The higher GLY concentration, the lower σ_{max} and Y values. The stickiness of film also increased for high GLY concentrations. No significant change of the ε-values was observed, signifying a negligible impact of GLY on the film ductility. The addition of TiO_2 decreased the Y-values suggesting that peeling of the film from the packaging foil should be facilitated.

ODF characterization

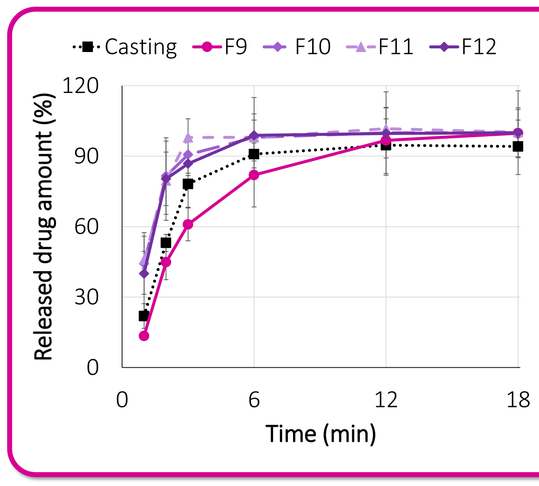


Drug-loaded ODF

PAR was loaded in printed ODF up to 35% w/w. Regardless of the drug content, the CV% of PAR assay remained lower than 5%, suggesting that hot-melt ram extrusion 3D printing permitted to maintain the uniformity of prepared films within the limits of Ph. Eur. monograph (L_1= ±15%).

Form.	Composition (%)				Drug content (%)	σ_{max} (MPa)	Y (MPa)	ε (%)
	MDX	GLN	GLY	PAR				
9	61.60	11.60	1.80	25.00	23.49±0.23	0.75±0.12	23.13±1.72	71±15
10	70.00	17.50	-	12.50	11.83±0.36	0.53±0.15	10.91±6.36	142±34
11	60.00	15.00	-	25.00	25.10±1.31	0.43±0.04	8.83±2.06	160±55
12	50.00	12.50	-	37.50	35.76±0.29	0.43±0.10	8.68±4.07	86±24

All PAR-loaded ODF maintained acceptable **tensile properties.** The PAR increased ODF toughness and decrease its ductility with respect to placebo ODF (i.e., Form. 4 and 5).



The complete disaggregation of PAR-ODF occurred within 1 min.
The PAR **dissolution** profile of 20% w/w containing ODF (t_{80} ≤ 2 min) was faster than 16% w/w ones (t_{80} < 6 min).
The dissolution profiles overlapped that obtained by ODF prepared by solvent casting technique.

Conclusions

The overall results suggested that hot-melt ram extrusion 3D printing can be used to prepare well-accepted orodispersible dosage forms and to personalize the drug strength according to the patient needs. Considering the simple preparation method and the good uniformity of dosage forms, such technology appears promising to extemporaneously prepare tailored solid dosage forms in pharmacy settings.
Moreover, the possibility to print the dosage forms directly on the packaging material also permit to reduce their handling by pharmacist.

Bibliography

[1] Cilurzo et al., Drug Discov Today, 2018, 23, 251.
[2] Visser et al., Int J Pharm, 2015, 478, 155
[3] Musazzi et al., Int J Pharm, 2018, 551, 52.
[4] Musazzi et al. ,Eur J Pharm Sci, 2018, 115, 37.

http://www.eahp.eu/24-3PC-060