ORODISPERSIBLE FILMS TO TREAT LACTOSE INTOLLERANCE: A PROOF OF CONCEPT

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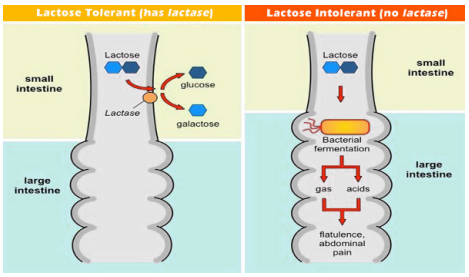
BACKGROUND

- Lactose is a disaccharide found in food, health products and has historically been used as an excipient in food supplements and oral solid medicinal products.
- More and more people today develop lactose intolerance.



- ODF combines advantages of liquid dosage forms (i.e., easy intake) and solid dosage forms (i.e., easy of handling, accurate and precise dosing, and stability of the drug). Moreover, they can be administered without water in uncooperative and dysphagics patients.
- ODF are also suitable in cases where personalised therapy is required, because they allow the dosage of drug to be easily adapted to the patient's therapeutic needs.
- ODF have so far been used for the delivery of small molecules.

AIM

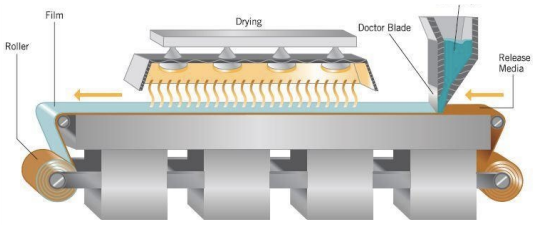
To design an ODF containing of β-galactosidase, derived from *Aspergillus Oryzae*, that can hydrolyze lactose contained in a glass of milk after its ingestion

PREPARATION OF ODF

ODF, made of maltodextrin (MDX) DE 6 plasticised by glycerol, were prepared by the solvent-casting technique. A surfactant (Capryol®90) was added to the composition to ensure a uniform spreadability of the slurry on the support and the maintenance of a homogeneous dispersion of the enzyme in the matrix during the casting and drying phases.

After a preliminary study, the following composition was selected as optimal to get a dry and well homogeneous ODF

Composition (% w/w)				
MDX (DE6)	***Glycerol***	***Capryol®90***	***H_2O***	***β-galactosidase***
52.0	***14.3***	***1.1***	***19.0***	***13.6***



The **drying process parameters** that influence enzymatic activity and ODF stickiness are **time** and **fan speed**

Run	Thickness (μm)	T (°C)	Time (min)	Fan speed (rpm)	ODF stickiness
1	300	70	40	1200	❌
2	300	70	30	1200	❌
3	300	70	20	1200	❌
4	300	70	25	1200	✅
5	300	70	20	1500	✅

β-GALACTOSIDASE CONTENT AND ENZYMATIC ACTIVITY

Bicinchoninic acid (BCA) assay

β-GAL content (%)
29.4 ± 0.5 ✅

ortho-Nitrophenyl-β-galactoside (ONPG) assay

Specific activity (U.I./mg of β-GAL)	***Enzymatic Activity/ 6 cm^2 film (U.I./cm^2)***
73.9±1.2	3910±75

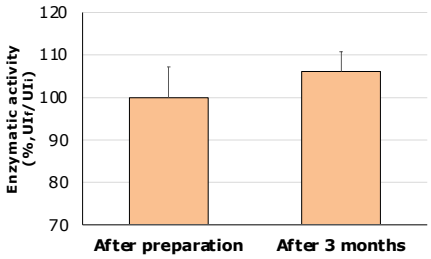
As reported, decreasing from 40 minutes to 20 minutes, it is possible to prepare ODF containing 30% of β-GAL equivalent to about 4000 U.I.

CHARACTERIZATION OF ODF

After identification of the optimal formulation and parameters, ODFs were characterised in terms of

Thickness	0.136 ± 0.022 mm
Weight	25.0 ± 0.5 mg/cm^2
Loss on drying	6-7% of the weight of the ODF
Disintegration time	< 30 s

Thought stability study, the enzymatic activity was evaluated after 3 months from the ODF's preparation



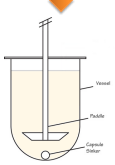
STABILITY STUDY

The results showed a good stability of the enzyme loaded in ODF at least for three months (t3) at 25°C (p-value= 0.61, Student's T Test)

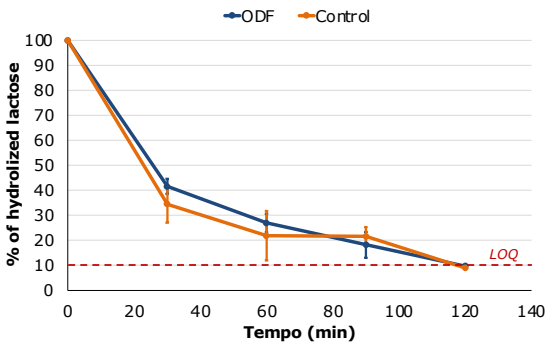
Once the ODF were characterised, the enzyme performance was compared to commercially-available products, in terms of the **kinetic of lactose hydrolysis.** Lacdigest Lactofree, a tablet containing 4500 UI and marketed as food supplement in Italy, was selected as control.

ODF and control were dissolved in middle fed-state simulated gastric fluid containing milk, using the paddle method (37±2 °C, 50 rpm). After defined periods of time (i.e., 30, 60, 90, 120 and 180 min), the remaining lactose was quantified by using HPLC-RID (calibration curve 1-25 mg/mL, R^2 = 0.9996). (Mean ± Dev.st., n = 3)

6.5 g of lactose in 150 mL



USP apparatus II



The ODF hydrolyzed more than 75% of milk lactose within 1 hour. After 2 hours, remaining lactose was below the quantification limit (LOQ = 1 mg/mL) hours in both ODF and the control, indicating that about 4000 U.I. are enough to hydrolyze the lactose content of a glass of milk.

CONCLUSIONS

- The in vitro hydrolysis studies provide promising evidence on the ODF use in preventing clinical symptoms in patients affected by lactose intolerance.
- Estimating the intake of lactose sourced from medicines in a polytherapy chronic patient would be around 1 g per day, proposed ODF can be a suitable solution for preventing discomforts. Indeed, ODF can be disintegrated directly in a glass of tap water together with medicines to have lactose digest before their ingestion.