ROQUETTE
Offering the best of nature™

Evaluation of a Novel Modified Starch Polymer as a Ready to Use Excipient in Oral Disintegrating Film (ODF) for Benzocaine Delivery

Carmen POPESCU[1], Michael MOORE[1], Alain FRANCOIS[2], Bo ZHOU[3], María Elisa LUQUE[3], Pierre KOCH[3], Delphine DAMOUR[2], Liuming ZHOU[1], Qi FANG[4], Philippe LEFEVRE[2] and Rodolfo PINAL[3]

[1] **Roquette America Inc.**, Geneva, IL - [2] **Roquette Frères**, Lestrem, France - [3] **Purdue University**, West Lafayette, IN - [4] **Banner Pharmacaps Inc**, High Point, NC

INTRODUCTION

- In recent years ODF became a very popular drug delivery system due to the fact that it can deliver the drug directly to the systemic circulation (avoiding the first pass metabolism).
- It enhances drug efficacy by lowering the dose and improving the onset of action and consequently patient compliance.
- To get the required rheological properties several hydrosoluble polymers and plasticizers are generally selected. Using only one polymer, a non-GMO pregelatinized hydroxypropyl pea starch, LYCOAT® RS720 we obtained the desired mechanical, rheological, and functional properties.
- Using the film casting technique (at room temperature) we obtained an ODF construct having good drug uniformity and dissolution performance.

MATERIALS & METHODS

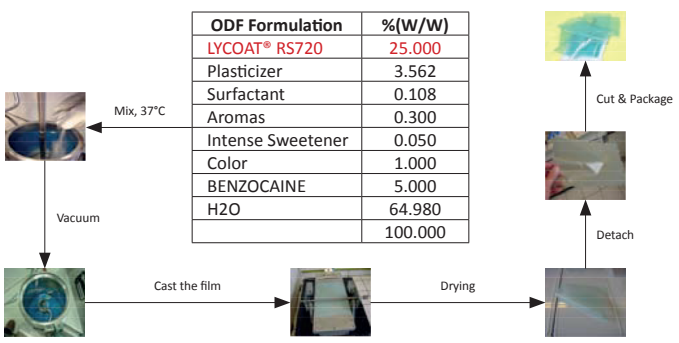
ODF PREPARATION METHOD: The film solution was prepared at room temperature by incorporating the polymer in the aqueous plasticizer solution under continuous mixing. The Benzocaine powder was incorporated after adding the surfactant and the emulsifier, followed at the end by the color and flavor. The film formulation was casted using a BYK- Gardner, mechanical drive Resource I equipment. The film was dried at room temperature. Final weight of dry cut strips (30X20 mm) is shown (Results section).

ODF EVALUATION METHODS:

- **Drug content uniformity:** ODF strips were dissolved in 100ml HCl solution pH 1.5 with sonication until completely dissolved and then filtered through a 0.2µm syringe filter. The drug concentration was evaluated by UV absorption at 226nm, in triplicate, using a UV-Vis spectrometer Lambda 20 ,Perkin Elmer.
- **Dissolution:** Simulated saliva solution consisted of a phosphate buffer saline solution (2.38 g Na2HPO4 and 0. 19 g KH 2PO4 and 8.00 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6 .75). Dissolution profile of Benzocaine ODF was obtained using a DISTEK (Rainbow Dynamic Dissolution Monitor System coupled with Indigo data process software) in 500 ml of simulated salivary fluid dissolution medium (pH 6.8) at 37 ± 0.5 °C with stirring at 100 rpm. Benzocaine ODF was coupled with a pin and the dissolution process was progressed at the bottom site of vessel Absorbance was determined by DISTEK, Rainbow Dynamic dissolution Monitor system, data process software: Indigo. The drug concentration was evaluated by UV absorbance at 282nm, in triplicate, using a UV-Vis spectrometer Lambda 20, Perkin Elmer.
- **Rheological properties evaluation:** Young modulus, Tensile strength and Elongation at break were evaluated using a Universal Testing Machine (INSTRON 4502), equipped with 2 pneumatic grips. The ODF was placed between the two grips and tensile stress was applied at 50 mm/minute until rupture.
- **PXRD:** Powder X-ray diffraction (PXRD) data were collected using an X'Pert Pro MPD system (PANalytical, B.V.,Almelo,Netherlands) equipped with a copper anode (Kα = 1.5406 Å), programmable divergence slit and X'CeleratorTM RTMS detector. The operational voltage and amperage were set to 45 kV and 40 mA, respectively. Diffraction data were collected over a 2-60o 2θ angular range at a step size of 0.0170° and an irradiation time of 31.75 s/step. Analyses were performed using Bragg–Brentano reflectance geometry (equipped with a horizontal spinning sample stage rotating at 16 rpm). The benzocaine powder sample (LOT 0560608) was back-filled into a stainless steel sample holder, while the Benzocaine ODF was placed into a zero-background stainless steel sample holder.
- **Dynamic Vapor Sorption:** ODF hygroscopicity was evaluated using a DVS1(automated analysis of water sorption properties of material system). The sample was equilibrated at 50% RH followed by desorption down to 10% RH. Moisture sorption up to 90% RH was then assessed.
- **Environmental Scanning Electron Microscopy (ESEM):** ODF loaded with benzocaine and placebo were analyzed using an Environmental Scanning Electron Microscope manufactured by FEI, model Quanta 200 FEG (Field Emission Gun) using a 20kV voltage with backscatter detector under low vacuum (30Pa).
- **Optical Microscopy:** Film images were taken using an Olympus BH2 RFCA.

RESULTS & DISCUSSION

Figure 1. Benzocaine ODF Formulation Process.



ODF Formulation	%(W/W)
LYCOAT® RS720	25.000
Plasticizer	3.562
Surfactant	0.108
Aromas	0.300
Intense Sweetener	0.050
Color	1.000
BENZOCAINE	5.000
H2O	64.980
	100.000

Table 1. Benzocaine ODF Content Uniformity.

Sample ID	Benzocaine ODF weight/strip	Benzocaine weight/strip	Benzocaine concentration
	(mg)	(mg)	(w/w) %
1	74.4	9.3	12.5
2	74.8	9.5	12.7
3	93.2	12.6	13.5

Figure 2. Benzocaine ODF Dissolution.

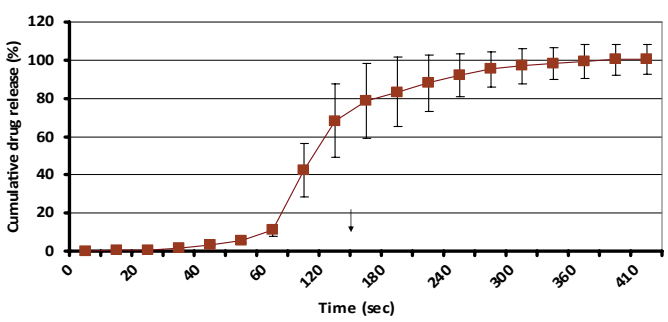


Table 2. Benzocaine ODF Mechanical Properties.

	Thickness (mm)	Tensile strength (at break) (MPa)	Elongation at break (%)	Young modulus (MPa)
ODF placebo	0.098	12.8	2	575 +/-35
Benzocaine ODF	0.102	6.5	2	195 +/- 60

Figure 3a. Benzocaine PXRD.

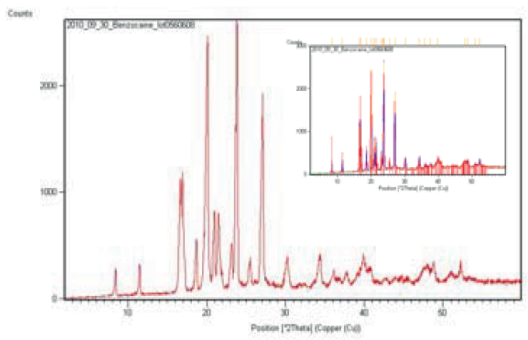


Figure 3b. Benzocaine ODF PXRD.

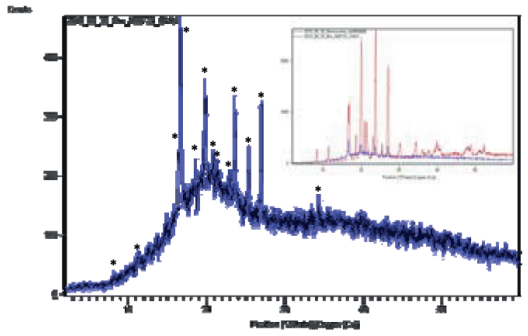


Figure 4. Benzocaine ODF Dynamic Vapor Sorption.

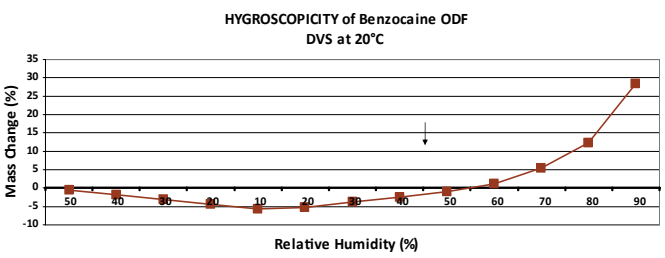


Figure 5. Benzocaine ODF Environmental Scanning Electron Microscopy.

Placebo ODF | Benzocaine ODF

Figure 6. Benzocaine ODF Optical Microscopy.

DISCUSSION:

A. ODF preparation with LYCOAT® RS720 (**Figure 1**):
- LYCOAT® RS720 disperses easily in cold water without formation of lumps within minutes,
- LYCOAT® RS720 is neutral from taste and color point of view,
- LYCOAT® RS720 is able to form films without using organic solvents,
- Very simple method for ODF preparation and freedom from patent restriction,
- API can be loaded in crystalline form or solubilized in an organic solvent.

B. Good content uniformity and dissolution profile (**Table 1** & **Figure 2**).

C. Mechanical properties were evaluated for this system (**Table 2**) and exhibit appropriate behavior.

D. PXRD data for benzocaine powder sample: sharp diffraction peaks confirm crystallinity. Inset: precise alignment of diffraction peaks across 2θ range corresponds exactly with known crystal structure for benzocaine, indicating phase purity of sample (**Figure 3a**).

E. PXRD data for Benzocaine ODF confirm the presence of crystalline API (**Figure 3b**). Significant diffuse scattering over 2θ range is representative of polymer film matrix (**Figure 3b**), however, the presence of Bragg diffraction peaks confirm crystallinity. Inset: superimposition of benzocaine PXRD pattern (red) with film pattern (blue). Asterisks indicate benzocaine diffraction peaks in film pattern.

F. Due to plasticizing effect of water moisture uptake and dryness can have an impact on ODF stickiness or brittleness but it is not decisive in packaging selection. The LYCOAT® RS720 based ODF formulation exhibits low sensitivity to RH% changes (**Figure 4**).

G. ESEM (**Figure 5**) further shows the crystallinity of Benzocaine dispersed in the LYCOAT® film.

H. Optical microscopy (**Figure 6**) images were analyzed using Image J software showing a uniform distribution of particles (18µm ± 9 µm) within the film matrix.

CONCLUSION

LYCOAT® RS720 has unique film forming properties capable of producing an ODF using a sole polymer. It allows incorporation of hydrophilic, hydrophobic and temperature sensitive APIs. This film offers dose homogeneity with fast dissolution.