Orally Disintegrating Films (ODF) as Vectors for Micro/Nanoparticle Delivery using Benzocaine as a Model Drug

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INTRODUCTION

ABSTRACT SUMMARY: Orally disintegrating film (ODF) was developed as a novel delivery system for micro/nanoparticle APIs. Using a single, non-GMO pregelatinized hydroxypropyl pea starch polymer (LYCOAT® RS720), ODFs were created by the film casting technique at room temperature. ODF constructs were loaded with benzocaine (a model drug): (1) microparticles; or (2) nanoparticles. Drug uniformity and dissolution were evaluated to compare their performance.

INTRODUCTION: Micronization and nanonization are methods used to increase the aqueous solubility of BCS class II and IV drugs. Traditionally, nanoparticles are delivered by iv route; however, the patient compliance is impaired. ODFs are patient friendly delivery systems due to the convenience of administration, dose uniformity, and portability.

The appeal of ODFs as a drug delivery system resides in the fact that it can deliver the drug directly to the systemic circulation (avoiding the first-pass metabolism). ODFs inherently provide for lower doses, thereby enhancing drug efficacy, improving the onset of action, and consequently patient compliance.

Micro/nanoparticle drug suspensions added to this specific polymer film formulation produce desirable dose uniformity and dissolution profile. Additionally, the polymeric platform prevents global coalescence of the micro/nanoparticles, thereby avoiding increases in particle size and subsequent loss of solubility enhancement.

MATERIALS & METHODS

BENZOCAINE NANOPARTICLES: A known amount of Benzocaine powder was mixed with a surfactant solution consisting of a combination of Pluronic P188, Tween 80 and VitE-TPGS in different concentration. After high speed homogenization the suspension was broken down by ultrasound (Vibra-Cell, Sonics) at different intensities of the probe and process time intervals as a function of chosen particle size. Particle size and distribution was analyzed by dynamic light scattering using Agilent 7030 Nicomp DLS/ZLS. The benzocaine nanoparticle size distribution is shown in **Figure 1**.

ODF PREPARATION METHOD: The film solutions were prepared at room temperature by adding the polymer to an aqueous plasticizer solution under continuous mixing. The benzocaine micro/nanoparticle suspensions were added to the polymer solution. The surfactant, emulsifier, color and flavor were then added to the previous mixture. The films were casted using a BYK-Gardner, mechanical drive Resource I equipment. The films were dried at room temperature and cut into 30X20 mm strips.

ODF EVALUATION METHODS:

Drug content uniformity: ODF strips were completely dissolved in 100ml HCl solution pH 1.5 under sonication 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 buffered saline solution (2.38g Na2HPO4 and 0.19g KH2PO4 and 8.00g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.75). Dissolution profiles of Benzocaine ODFs were obtained using a DISTEK(Rainbow Dynamic Dissolution Monitor System coupled with Indigo data process software) in 500 ml of simulated saliva fluid at 37 ± 0.5 °C with stirring at 100 rpm. Benzocaine ODFs were coupled with a pin and the dissolution process was progressed at the bottom site of vessel. 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's modulus, Tensile strength and Elongation at break were determined using a Universal Testing Machine (INSTRON 4502), equipped with 2 pneumatic grips. The ODFs were 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 Cu anode (Kα = 1.5406 Å), programmable divergence slit and X'CeleratorTM RTMS detector. The voltage and amperage were set to 45 kV and 40 mA, respectively. Diffraction data were collected over a 2-60° 2θ at a step size of 0.0170° and an irradiation time of 31.75 s/step. The benzocaine powder sample (LOT 0560608) was back-filled into a stainless steel spinning sample holder, while the Benzocaine ODF was placed into a zero-background stainless steel sample holder.

Optical Microscopy: Micronized benzocaine (purchased commercially) particle size (18µm ± 9 µm) was measured using an Olympus BH2 RFCA.

RESULTS & DISCUSSION

LYCOAT RS®720 dispersed easily in cold water within minutes without formation of lumps, is neutral in taste and color, is able to form films without using organic solvents, and permits loading of API in crystalline form as micro/nanoparticles.

Figure 1. Benzocaine nanoparticle size distribution.

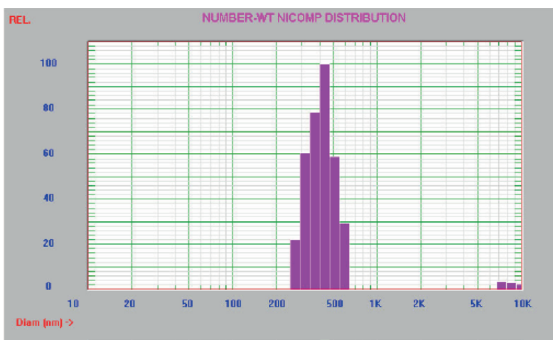


Table 1. Benzocaine ODF Content Uniformity.

Sample ID	Strip mass	Benzocaine mass / strip	Benzocaine concentration
	mg (SD)	mg (SD)	w / w% (SD)
Micro	80.8 (10.7)	10.4 (1.9)	12.9 (0.5)
Nano	53.2 (1.4)	4.0 (0.1)	7.5 (0.2)

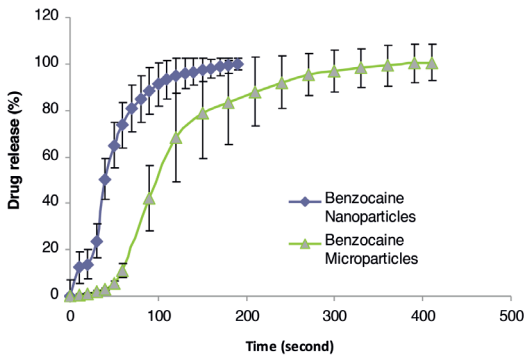
Both micro- and nanoparticle strips exhibited good content uniformity as evidenced in the concentration standard deviation (**Table 1**). The two different preparations illustrate a range of drug loading in this polymeric system, where the lower drug loading in the nanoparticles system remarkably exhibited excellent content uniformity.

Table 2. Benzocaine ODF Mechanical Properties.

	Thickness (mm)	Tensile strenght (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

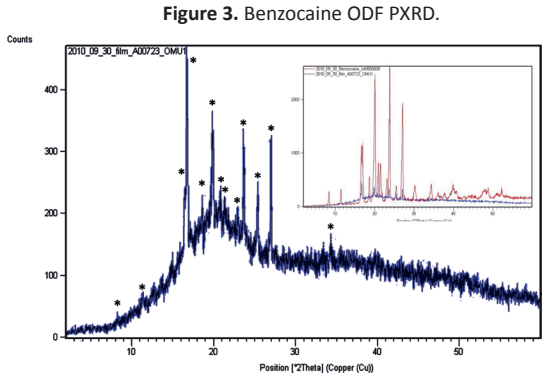
Mechanical properties were evaluated for this system (**Table 2**) and exhibit a good balance between tensile strength and elongation at break.

Figure 2. Benzocaine ODF Dissolution.



As expected, the dissolution profile of the nanoparticles ODF is more rapid than that of the microparticles ODF (**Figure 2**).

Figure 3. Benzocaine ODF PXRD.



PXRD data for Benzocaine ODF confirm the presence of crystalline API (**Figure 3**). Significant diffuse scattering over 2θ range is representative of polymer film matrix (**Figure 3**). The inset shows the superimposition of benzocaine PXRD pattern (red) with film pattern (blue) indicating benzocaine diffraction peaks in film pattern.

CONCLUSION

ODF technology is a classical dosage form which has been shown to be a novel vector for delivering BCS II and IV micro/nanoparticle drugs. This platform provides a non-invasive alternative to iv administration while producing excellent dose content uniformity and rapid dissolution performance. The ability to avoid first-pass metabolism makes ODF a very attractive delivery system, especially for the pediatric and geriatric populations.

ACKNOWLEDGEMENT

The authors would like to acknowledge Antonina Kuzmis and Hayat Onyuksel for assistance with the particle size analysis.