NOVEL EXPANDABLE PLATFORM FOR RETENTIVE DRUG DELIVERY SYSTEMS

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INTRODUCTION

Maintaining effective drug concentrations for prolonged period of time for the local treatment of pathologies affecting hollow organs has always been an important goal in the technological field. Over time, various approaches have been proposed to obtain the retention of prolonged-release systems in organs such as the stomach, esophagus, urinary bladder, vagina, including bioadhesion, flotation and enlargement the devices. In the case of gastro-retentive delivery systems, in particular, there is also a strong interest in the possibility of improving the bioavailability of drugs that have an absorption window in the upper gastrointestinal tract or a lower solubility or stability in the intestinal environment.

Fig.2 Photographs of H-shape prototype having a space-saving configuration and after the assumption of the bulkier configuration

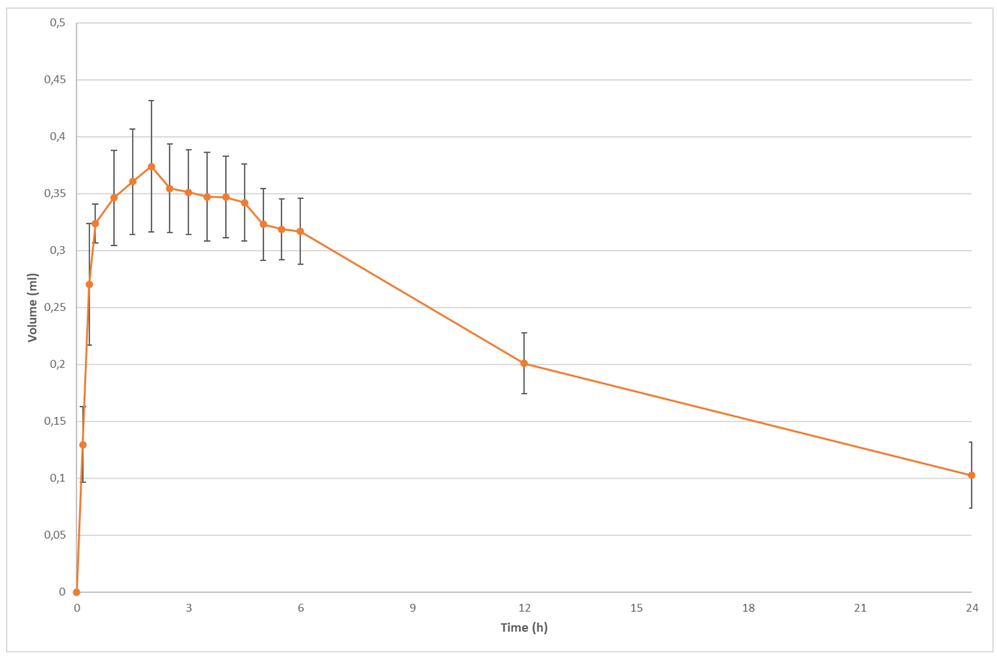

Fig.3 Mean volume vs. time profile for isolated osmotic units of H-shaped ORODS immersed in deionized water (n=3, bars represent standard deviation).

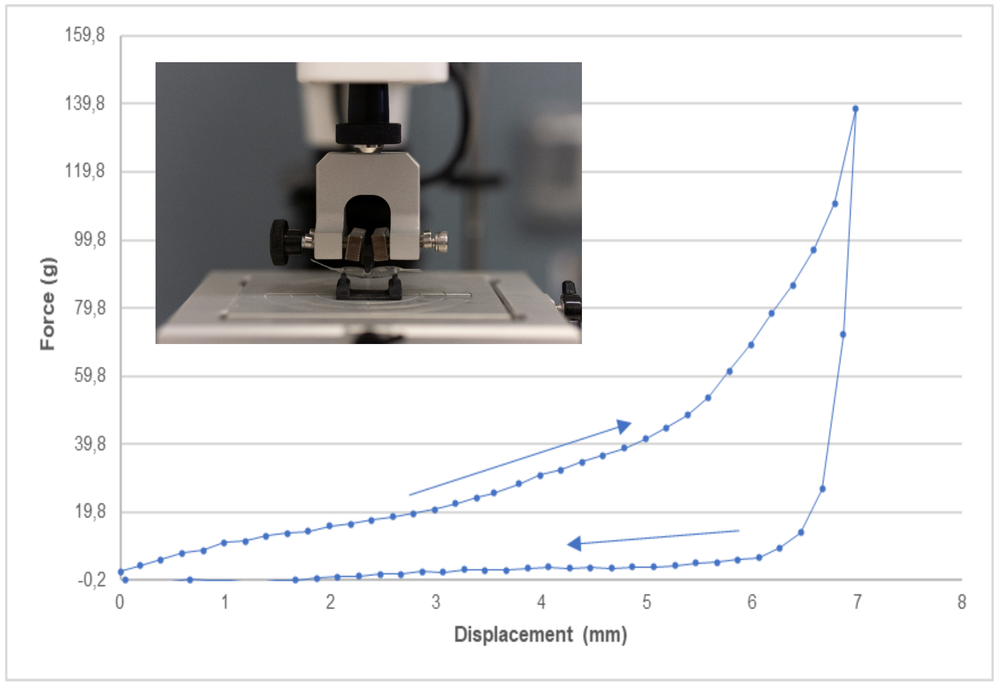

Fig. 4 Force/displacement profile obtained from an isolated osmotic unit at their maximum volume (2 h immersion in deionized water) and three-point bend fixture.

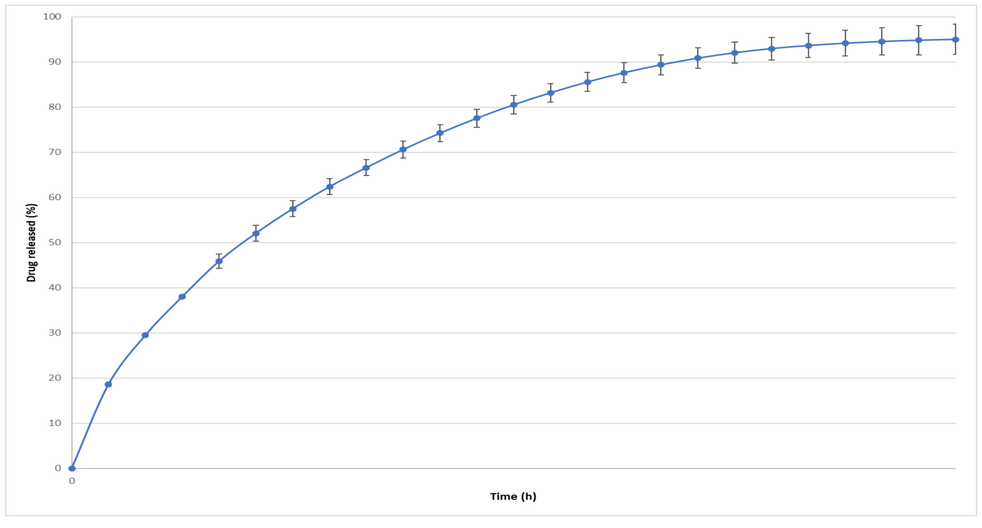

Fig. 5 Paracetamol release profiles from ORODS having H-shape configuration (n=3, bars represent standard deviation).

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AIM

Based on the current need for more effective and tolerable drug therapies, the present study dealt with the design and evaluation of novel expandable delivery systems called Organ-Retentive Osmotically-Driven Systems (ORODS). Such systems are based on the use of originally fluid-free limp compartments which are connected with one or more prolonged-release units, *e.g.*, hydrophilic matrices (Fig. 1).

These compartments are delimited by an insoluble though **permeable polymeric membrane and contain an osmotic substance that promotes inflow of aqueous fluids, expand and cause an overall enlargement (encumbrance) of the ORODS**. The liquid-fillable compartment, once the osmotic agent decreases its concentration, returns to a collapsed form, allowing for physiological expulsion of the device from the organ without any invasive intervention.

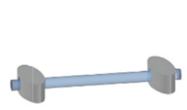
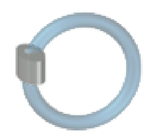
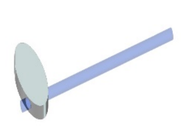
	Gastro-retentive system		*Urinary bladder retentive system*
	H-shape	*Ring-shape*	*T-shape*
drug-containing unit *osmotic compartment*			

Fig.1 Drawings of ORODS prototype having different configurations

RESULTS AND DISCUSSION

The system had a temporary space-saving configuration fit for size 00 hard-gelatin capsules, as intended for oral administration. Moreover, they were expected to take on a bulkier configuration when in contact with aqueous fluids due to osmotic water inflow (Fig. 2).

Fig. 3 shows the increase in volume of the osmotic unit immersed in deionized water. The volume reached about 80% of the maximum within the first 30 min of testing and maintained a plateau for about 6 h. Afterwards, the volume slowly decreased to approximately 20% of the maximum at 24 h.

In Fig. 4 mechanical behavior of the H-shape prototype is reported. The osmotic unit exhibited a rigid texture which would hamper gastric emptying.

A prolonged release performance for over 24 h was obtained from H-shaped ORODS (Fig. 5). Exhausted HPMC matrices would undergo dissolution and erosion, while the shrunk compartment would spontaneously be emptied.

MATERIALS AND METHODS

- Dialysis membrane made of regenerated cellulose having a cutoff of 12-14000 Dalton (Spectrum™ Spectra/Por™ 2);
- NaCl (VWR international S.r.l., water solubility 360 mg/ml at 37°C);
- Paracetamol (Compap™, Mallinckrodt, IE);
- Microcrystalline cellulose (MCC, Avicel® PH 200, FMC, BE);
- Hypromellose (Methocel® K4M, Colorcon, UK);
- Gelatin capsule (Capsugel® ConiSnap® Size 00, Lonza, BE).

Fabrication of ORODS:

The prototypes were assembled by manually inserting a tube made of regenerated cellulose (osmotic unit) into the holes of 2 tableted hydrophilic matrices (tablet press FA/8, Officine Ronchi, IT, 20x8 mm concave punches, compaction force 10 kN), having a weight of 500 or 1000 mg, containing 50% paracetamol, 40% hypromellose and 10% microcrystal-line cellulose. The matrices (4 mm in thickness) were perforated by a precision driller. The osmotic unit (average diameter and flat width of 3.7 mm and 4.8 mm, respectively) was obtained by folding and gluing a plain regenerated cellulose, and 50 mg of sodium chloride was loaded inside. (Proxxon, DE).

Release test:

ORODS were evaluated for drug release in a USP 40 paddle dissolution apparatus (At7 Smart, Sotax, CH, 100 rpm, 800 mL water, 37±0.5°C), and paracetamol was quantified spettrophotometrically (Lambda 35, Perkin Elmer, US, 248 nm, 1 mm cuvette).

Evaluation of increase in volume of the osmotic unit:

Samples were placed in 800 ml of deionized water at 37±0.5°C and the relevant diameter was measured in different positions (n=5) using a digital caliper (Absolute Digimatic CD-15CP, Mitutoyo, UK) at pre-established time points.
The compartment volume was finally calculated based on the original length.

Mechanical testing of isolated osmotic units:

Performed adapting the standard test method ASTM D790. The test was carried out using TA-XT2 analyzer (Texture Technologies, Hamilton, USA) equipped with a three-point bend fixture (support span of 22 mm, support rods and nose of 2 mm in diameter, 50 N load cell) and software for analyzing displacement and load (Fig. 2). 7 mm was the maximum displacement, and 2 mm/min was the rate of displacement. Profiles were acquired after immersion of the isolated osmotic units for 120 min in 800 mL distilled water at 37 °C (n=3).

CONCLUSIONS

The results obtained in terms of changes in volume and stiffness undergone by the isolated osmotic compartment turned out potentially suitable for the pursued in vivo performance. Moreover, the expected slow release of a tracer drug was obtained from the assembled device.