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NOVEL EXPANDABLE PLATFORM FOR RETENTIVE DRUG DELIVERY SYSTEMS

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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, esoph-agus, 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. Based on these needs, the present study addressed the design and evaluation of novel expandable delivery systems. The new Organ-Retentive Osmotically-Driven Systems (ORODS) are based on the use of originally fluid-free compartments that are connected with one or more prolonged-release units. The expandable compartments are made from an insoluble but permeable polymeric membrane and contain an osmotic agent that promotes the influx of aqueous fluids, thus increasing in volume and leading to an overall enlargement of the ORODS. Once the concentration of the osmotic agent decreases, the expandable compartment returns to a collapsed shape, allowing the physiological expulsion of the device from the organ without any invasive intervention. Drug-containing units made of soluble and/or biodegradable polymers can be obtained by tableting, injection molding, hot-melt extrusion or 3D printing. They have through or blind openings, into which the osmotic units are inserted and firmly fixed. In the case of gastro-retentive systems, the devices assembled in the initial configuration would be conveniently administered in conventional hard gelatin capsules. The bulky configuration should be larger than the gaping pylorus by at least 2 dimensions. After operation, the drug-containing units dissolve and/or erode, while the semipermeable tubes detach and shrink, thus allowing passage through the pylorus. Devices intended for retention within the urinary bladder must be inserted into the organ using a catheter. Therefore, the system in its original configuration should be smaller than the inner diamater of commonly employed catheters, whereas there are no particular constraints in terms of length. Once depleted, the drug-containing units would undergo dissolution and erosion, and the reduced osmotic unit would be emptied through the urethra. In this preliminary study, feasibility and proof of principle of the ORODS platform were assessed. Particularly, prototypes having H-shape design were conceived, manufactured and evaluated for behavior in deionized water. 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) containing 50% paracetamol, 40% hypromellose and 10% microcrystalline 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. The increase in volume of the osmotic unit immersed in deionized water was fast, reaching about 80% of the maximum within the first 30 min of testing and maintaining a plateau for about 6 h. Afterwards, the volume slowly decreased to approximately 20% of the maximum at 24 h. While expanding, the osmotic unit acquired stiffness as assessed by three-point bend method adapted from ASTM D790 standard. H-shaped ORODS conveyed in hard-gelatin capsules were evaluated for release, which was shown to be prolonged for more than 24 h. 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.

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