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Rolled-up gastroretentive oral dosages for controlled release of riboflavin and propranolol.

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Abstract:

We present a simple approach to make gelatin gastroretentive oral dosages for controlled release of riboflavin and propranolol. The approach is based on rolling-up of thin self-adhesive gelatin films, on which the reservoirs of the drugs are formed by casting. The radial position of the reservoir and, hence, the lag time and the rate of the drugs release are determined by the lateral position of the reservoir on the film before rolling. Gelatin is stabilized against dissolving in the gastric environment by enzymatic cross-linking mediated by transglutaminase (Tgase). The dosages, which have the form of tight scrolls, are stabilized against unrolling by the crosslinking of the consecutive layers. The scrolls swell in the release media, Fasted State Simulated Gastric Fluid (FaSSGF), to the dimensions which make difficult their passage by the human pyloric sphincter, but remain mechanically robust to resist the stomach peristaltic contractions during at least 24 hours, sufficient for the drug release. Eventually the scrolls are degraded by the release media and can be evacuated from the stomach.

Keywords: Controlled release; riboflavin; propranolol; rolled-up oral dosage

I- Introduction

Low stability, pH-dependent solubility, narrow absorption window in the proximal small intestine, and short half-life are the major problems that limit bioavailability of drugs administered by the oral route [1]. Riboflavin, known as vitamin B2, is particularly affected by the low availability issues. This vitamin used by the body to metabolize fats, proteins and carbohydrates into glucose for energy is mainly absorbed by the jejunum and much less by the large intestine by a process which rapidly saturates the RFVT3 transporter protein [2,3]. To increase the bioavailability, it is recommended to uptake the vitamin in divided doses several times per day [4]. For adult females, the recommended dietary allowance of riboflavin on average is 1.1 mg per day, with variations depending on age and reproductive status including pregnancy and lactation. In fact, during pregnancy, it is 1.4 mg and during breastfeeding is 1.6 mg. For men aged 19 years and over, it is 1.3 mg daily [5]. On another side, it was found that the maximal amount that can be absorbed from a single dose appears to be 27 mg [6]. Riboflavin turnover appears to be related to energy expenditure, and periods of increased physical activity are associated with a modest increase in requirements [7]. Hence, to obtain

the best therapeutic effect, the release of B2 must be individualized and administered slowly by sustained release.

Propranolol, a drug belonging to the beta-blockers class, is another important example of a drug with a limited bioavailability. It has low solubility in intestinal fluids, and its adsorption through P-glycoprotein (P-gp) efflux transporter is low [8], so that only about 25% reaches the systemic circulation [9]. Its C_{max} occurs about 1 to 4 h after an oral dose administration and its elimination half-life is 3 to 4 h [10]. To ensure an optimal effect, propranolol in the form of conventional tablets should be administered several times a day. Indeed, with once-daily dosing of conventional formulations, therapeutic plasma propranolol concentrations can't be maintained and large swings in plasma drug concentrations may occur.

Multiple research efforts have been devoted to the development of new gastroretentive drug delivery technologies [11-13], to achieve effective delivery of drugs with low bioavailability or narrow absorption windows. Floating [14-17], mucoadhesive [18], swellable [14,19], expandable [20-25], magnetic [26], and high-density [27] systems, as well as systems that contain retarding agents with biocompatible polymeric materials [28,29] have been investigated extensively to prolong gastric residence time. Ion-exchange resins forming complexes with drugs have been explored as physiological supports smart gastroretentive drug delivery systems [30]. These technologies have emerged to improve the effectiveness of drugs or to promote local activity in the stomach and duodenum showing different mechanisms for retaining the drug in GI region for longer duration with increased bioavailability.

There have been designed many devices for sustained release of riboflavin. These include PLLA microcapsules [31], PDLA and PDLAGA capsules [32], as well as intelligent pH-sensitive carriers based on chitosan hydrogels [33]. Thanks to their appropriate structural architecture, swelling behavior and mechanical resistance, hydrogels represent a very interesting material for the controlled release. Drug release systems flowing in the gastric fluids is another approach to the sustained release in the upper part of the gastro-intestinal tract (GIT). Superporous floating hydrogels prepared by copolymerization [34], microparticles [35], floating matrix delivery systems, monolayer and bilayer tablets prepared by direct compression [36], microballoons prepared by the diffusion method of emulsion solvent [37] have also shown their effectiveness in ensuring better absorption as well as better bioavailability of riboflavin following prolonged release in the upper gastro-intestinal tract (GIT). In the same vein, a new controlled-release gastroretentive dosage form known as Accordion Pill™ [38], terpolymer devices [39] as well as unfolding multilayer polymeric films [40] have shown their potential to maintain and control the release the riboflavin longer in the stomach.

Sustained release formulations of propranolol have been also designed. The density of P-gp is higher at the distal part of the GIT, therefore floating tablets made from various polymers such as xanthan gum or sodium alginate [9] have been proposed. Gastroretentive floating tablets were prepared by using a polyethylene oxide as release retarding polymers and calcium carbonate as gas generating agent [41]. Polyvinyl alcohol and polylactic acid filaments were used to design gastroretentive floating tablets for the sustained release of the drug [42].

In our previous studies [43,44], we have introduced a new approach to the design of the oral dosage formulation for personalized sustained drug release. The idea of the approach consists in rolling up a biopolymer film, on which one or several drug reservoirs are formed by printing or casting. The radial position of the reservoir and, hence, the lag time and the rate of the drugs release are determined by the lateral position of the reservoir on the film before rolling. Complex kinetics can be obtained by superposition of the release from two or more reservoirs. A biphasic release is demonstrated in computer simulation [43] and in the real experiment [44]. In the real experiment, a model drug from the quick release reservoir, placed at the walls of the cavity of the roll, is released immediately upon the scroll's contact with the phosphate buffer solution (PBS) and the drug from the sustained release reservoir, embedded between the roll's layers, diffuses steadily, with the lag time defined by the radial position of the reservoir [44].

In the present study, we explore *in vitro* the application of the rolling-up approach to the design of gastro-retentive drug delivery systems (GRDDS). A centimeter long, a few millimeters thick cylindrical scrolls are produced by rolling-up of plasticized gelatin films. Riboflavin or propranolol reservoirs were formed on the films by casting prior to rolling. In a set of preliminary experiments, we studied also the release of fluorescein disodium, explored as a model drug. The scrolls are stabilized against unrolling and dissolution at 37°C by transglutaminase-mediated crosslinking. In fact, different enzymes have been used to crosslink gelatin films, such as tyrosinase, laccase, horseradish peroxidase (HRP) and transglutaminase. These enzymes are capable of creating covalent cross-links in proteinaceous substrates by participating in the reaction that catalyzes the formation of the isopeptide bonds between the glutamine residue of γ -carboxamide and the primary ϵ -amine groups of gelatin [45,46]. Transglutaminase is a natural enzyme commonly found in animal tissues and intercellular fluid. It's listed as GRAS (Generally Recognized As Safe) [45]. Transglutaminase is also used for cell culture preparation, tissue engineering, tissue regeneration and in several biomedical applications [47,48].

The scrolls swell in the Fasted State Simulated Gastric Fluid (FaSSGF) to the dimensions exceeding the average adult pyloric sphincter. Nevertheless, the scrolls retain certain rigidity sufficient to resist the peristaltic contractions of a stomach. A drug is released then slowly according to a kinetics programmed by the radial position of the drug reservoir in the scroll. After 48 hours, erosion of the scrolls by FaSSGF make them soft enough to be crashed and evacuated from the stomach to the lower sections of the GIT.

II- Methods

Gelatin film preparation

Crosslinked gelatin films were formulated according to the protocol of the Ref.48 modified by the use of sorbitol explored as a plasticizer. The film ingredients included gelatine from porcine skin (Suitable for microbiology, ultrahigh gel strength) supplied by Sigma Aldrich, transglutaminase (Tgase) (Ajinomoto meat glue, Tokyo, Japan), and sorbitol (Sigma-S1876-500G). First, 5.0 grams of gelatin powder was dissolved in 100 ml of DPBS heated to 70°C and stirred at 200 rpm for 30 minutes. 18 μ L of chloroform were introduced into the mixture

to sterilize it [48] and then evaporated for 30 minutes. A solution of Tgase prepared by dissolving 0.5g of Tgase in 10ml of distilled water, was added to the gelatin solution and then 5g of sorbitol was slowly added to the mixture until obtaining a homogeneous solution. 20 ml of this mixture were taken and gently poured into a plastic mold to prevent the aggregation before drying. The dried film was then peeled from the mold and cut into 10.0 x 2.0 (cm x cm) strips for storage and use as a drug matrix.

Drugs loading and scrolls formation.

The scrolls were fabricated according to the scheme depicted by the Figure 1. Prior to rolling, a drug reservoir was formed by casting the drug solution over rectangular area using a micropipette. Right before rolling, the borders of the stripe were gently wetted, in order to activate Tgase, avoiding the drug reservoir position. The average diameter of the scroll is $d \approx 5.6\text{mm}$, and the number of the turns is between 8 and 9. The cross-section of the scroll is approximated by the Archimedean spiral, $r(\theta) = r_0 + \frac{h}{2\pi}\theta$, where $r_0 \approx 0.45\text{mm}$ is the initial curvature radius, $h \approx 0.33\text{mm}$ is the effective film thickness, and θ is the spiral rotation angle. The effective thickness is somewhat larger than the measured thickness of the films before rolling, because imperfections on the films surface do not allow for the perfectly tight rolling.

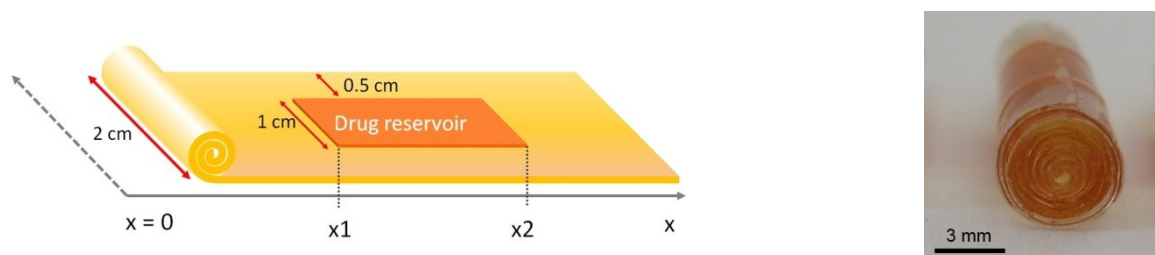


Figure 1. (a) The scheme of the scroll formation by rolling-up of a gelatin stripe with a drug reservoir. (b) side view of a typical scroll.

A reservoir of fluorescein disodium (FD) (Alfa Aesar™, Ward Hill, MA, USA), containing 500 μg of the drug, were formed by casting 20 μL of solution at the FD concentration 25 $\mu\text{g}/\mu\text{L}$. The coordinates of the boundaries of the FD reservoirs (denoted as F-reservoirs) on the stripe with respect to the end of the gelatin strip, from which the rolling started, are given in the Table 1. The radial positions of the reservoirs, estimated numerically (see Supplementary Material) are given in the same table.

Reservoir	x_1 [mm]	x_2 [mm]	r [mm]
F ₁ (R ₁)	20	30	1.2
F ₂ (R ₂)	35	47	1.7
F ₃ (R ₃)	60	74	2.2

Table 1 Lateral limits (x_1 , x_2) on the gelatin stripe before rolling, and average radial position (r) of the reservoirs after rolling, for fluorescein disodium (F) and riboflavin (R).

Riboflavin reservoirs (denoted as R-reservoirs) were formed by casting two 150 µl doses of 50 mg/ml water onto the predetermined reservoir positions given in the Table 1. After each dose casting, the film was dried, in order to prevent solution spreading beyond the reservoir. The total amount of the deposited drug per reservoir was 15 mg.

Propranolol reservoirs (denoted as P-reservoirs) were formed by the same method, but the positions of the reservoirs were slightly different (see Table 2). 20 mg of propranolol was deposited in the reservoirs using the same method described previously, by repetitive casting and drying.

Reservoir	x ₁ [mm]	x ₂ [mm]	r[mm]
P ₁	44	56	1.9
P ₂	70	85	2.4
P ₃	85	100	2.7

Table 2 Lateral limits (x₁, x₂) on the gelatin stripe before rolling, and average radial position (r) of the reservoirs after rolling, for propranolol.

The surfaces of the gelatin stripes not covered with drugs were slightly moistened. Then the stripes placed on the clean glass surface and rolled up. The scrolls were placed for a day at a temperature of 100 ° C to obtain a completely dried scroll then stored away from light. The dimensions of the scrolls correspond approximately to the of size of standard 000-capsules for oral administration [49].

Swelling capacity and dimensions change

The swelling tests were conducted according to the beaker test method. A scroll was weighed and placed inside a beaker. Then, 200 ml of the FaSSGF [50] was poured into the beaker at 37°C. The surface of the swollen scroll were wiped using a filter paper. The swelling degree was determined by the formula:

$$\%SC = \frac{W_t - W_0}{W_0} \times 100\%$$

where W₀ is the weight of the scroll before immersion in the solution and W_t is the weight of the sample at time t. The swelling measurements were performed every 30 minutes for 8 hours. The diameter (d) and length (l) of the withdrawn samples were measured using a ruler to determine the dimension changing every one hour before brought back to the medium. All experiment was conducted in triplicate for each time point.

Mass Loss Study

In the same condition as for the swelling test, the swollen scrolls were withdrawn from the FaSSGFat each time point (1, 2, 4, 8, 12, 18 and 24 hours) and placed in the hood fume for

seven days, 25⁰C to reach the constant weight (final dry weight W_{dry}). The percentage of scrolls mass remaining after erosion in FaSSGF was calculated using the following equation:

$$MassLoss = \frac{W_{dry}}{W_0} \times 100\%$$

Characterization of mechanical strength

The mechanical strength tests were conducted in order to characterize the changing in mechanical properties of the swollen scrolls versus the time passed by the scrolls in FaSSGF. Before measurement, the scroll was kept swelling in the FaSSGF medium at 37⁰C, then was taken after predetermined times 1, 4, 8, 12, 18, 24, and 36 hours. Residue water from the scroll surface was gently removed by a tissue paper. A MTS-Lhomargy Dynamometer with a 1KN load cell was used for the measurement. A stainless steel disk elevated at a constant rate of 5mm/minute compressed the swollen scroll against the sensor. The force measured at the displacement 4mm was recorded in triplicate for each experiment.

Drug release tests.

The release experiments were performed using the United States Pharmacopeia (USP) dissolution apparatus 2 (Agilent 708-DS, Agilent Technologies, Santa Clara, CA, USA) with a 50 rpm as a rotation speed at 37⁰C. All the experiments were performed in triplicate.

The preliminary study, in which FD is chosen as a model drug, PBS (pH=7.4) was used as a dissolution medium. The Fasted Simulated Gastric Fluid FaSSGF (pH=1.2) was used as the dissolution medium for riboflavin and propranolol to simulate in vivo conditions. An aliquot of 200 ul was withdrawn every 30 minutes for 8h from each vessel and then immediately refilled with an equal fresh volume of FaSSGF. The amount of the released riboflavin from the scrolls was determined by fluorimetry at the riboflavin's emission peak at 455 nm (Thermo Scientific™ Varioscan™ LUX multimode microplate reader) using predetermined calibration curves for riboflavin in FaSSGF. All results presented are average ± SE of at least 3 independent experiments. The dissolution test with propranolol scrolls was conducted in the same conditions described above, except that 1ml of the sample was taken every one hour, and the concentration was determined using UV-Vis spectrophotometer Jasco at 290nm. All the formulations were tested six times, and an average value was taken.

III- Results

Scrolls swelling and erosion in the release media.

Prior to the drug release tests, we have explored the effects of the scrolls exposure to FaSSGF. The scrolls at different degrees of swelling and degradation are shown on the Figure 2a.

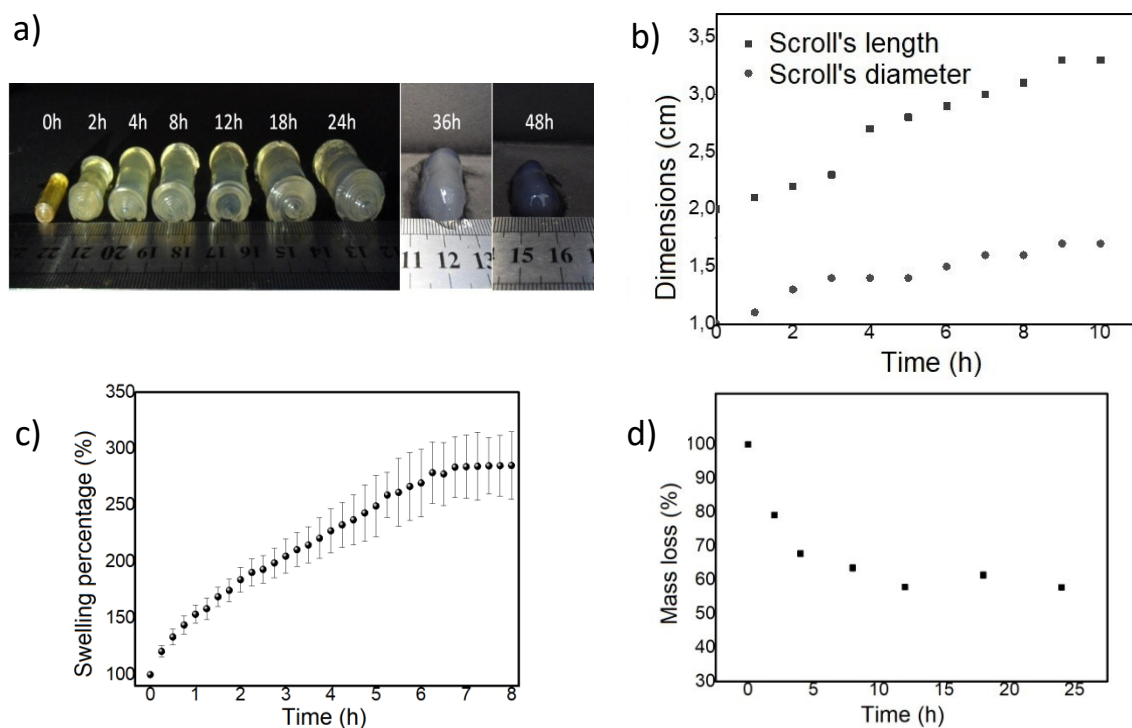


Figure 2. Swelling and erosion of the scrolls in the gastric medium (FaSSGF). (a) Optical photography of the scrolls immersed for different times in the release media. (b) Dimensions change of a scroll. (c) The relative mass uptake of the scrolls. (d) Mass loss (dry residue) of the scrolls after different time in FaSSGF.

After approximately 6 hours, the diameter of a scroll reaches 16 mm (Figure 2b). The maximal mass of the scrolls after swelling in FaSSGF is approximately 270% of their initial mass (Figure 2c). Swelling in FaSSGF is accompanied by the mass loss of the polymer in the scrolls (dry residue), presumably due to the enzymatic degradation of the polymer. After 24 hours, the scrolls lost approximately 60% of their initial mass (Figure 2d). Gelatin is soluble over the whole pH range and its digestion is not complicated. Acids hydrolyze gelatin and weakens its gelling capacity in water due to protonation of amine groups which increases the electrostatic repulsion between the polymer chains. Hence, gelatin swelling is high in acidic media [51] such as FaSSGF. Additionally, gelatin is readily and extensively digested by pepsin which is released at the stomach level upon ingestion and serves to break down proteins [52].

Importantly, during the whole duration of the experiment, the scrolls remain rolled-up and show excellent resistance to unrolling. This minimizes the risk of the burst release of a drug from the scroll. Yet, gelatin erosion results in softening the scrolls after 48h in the media to the state when their mechanical stiffness does not suffice to retain their own weight (see the last images on the Figure 2a). This guarantees that the scrolls can be evacuated after a certain time from the stomach by the peristaltic activity of the GIT, and not accumulate in it.

The mechanical properties of the scrolls.

As noted above, extended exposure of the scrolls to FaSSGF is accompanied by the strong change of their mechanical characteristics, presumably due to polymer hydrolysis and enzymatic degradation. In order to explore this point, important for the evacuation of the scrolls from the stomach, we have undertaken the study of the scroll's resistance to compression in function of the exposure to the release media (Figure 3a). The mechanical resistance of the scrolls upon their compression by 4mm gradually decreases over time and drops from 12N to

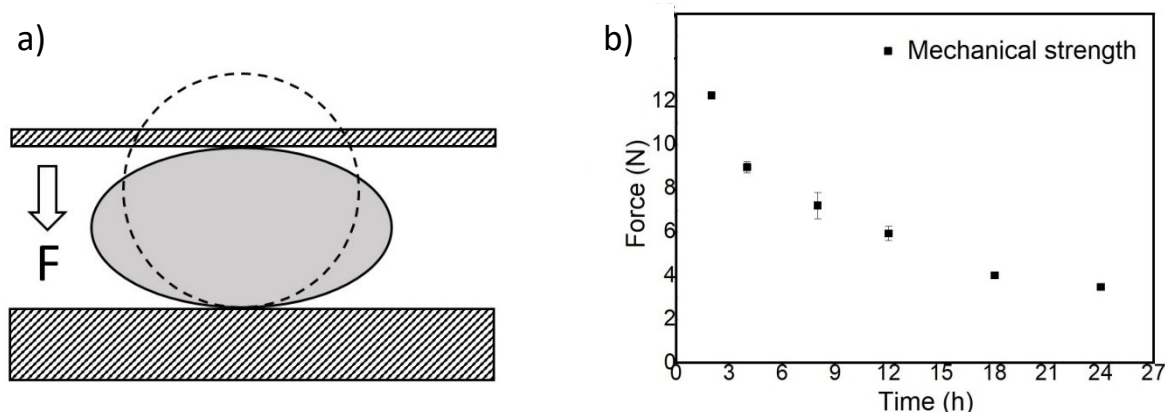


Figure 3. The compression resistance characterization of the scrolls. (a) The scheme of the experiment. (b) The compression resistance force, as the function of time in FaSSGF.

approximately 4 N after 24 hours of immersion in FaSSGF (Figure 3b). Nevertheless, the scroll retains its cylindrical shape at the end of the study. Indeed, this ultimate compression force is greater than the compression force of the stomach (estimated to ~ 1.9 N) [53] cannot break the scroll. The scroll can therefore overcome the compression of the stomach without breaking after 24 hours. Beyond this term, the mechanical properties of the scrolls cannot be characterized reliably with the available equipment. But, since the scrolls cannot hold their own weight after 48 hours in FaSSGF (see Figure 2a), it is safe to suppose, that the compression resistance of the scrolls became well below the critical value of 1.9N.

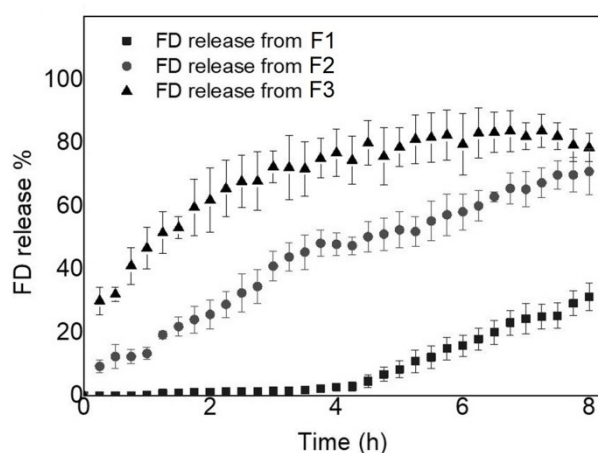


Figure 4 FD release from 3 positions in PBS.

Release tests.

Prior to the study of the release of the real drugs in the media simulating the in vivo conditions, we have explored the release of a popular model drug, Fluorescein Disodium (FD) in the phosphate buffer solution (PBS), in order to obtain the proof-of-concept release kinetics and to estimate the characteristic release times from the scrolls.

FD is a harmless fluorophore with a steric hindrance similar to many small drugs, such as for example steroids and other

neuroprotecting agents [54]. In the preliminary study, it served as a fluorescent tracer to assess the diffusion (release) within the layers. It's known for its high sensitivity to fluorescence so can be easily detected in very small amounts. In our previous experiments carried out on the same designed system [44], it was possible to start simple, traditional, and inexpensive release experiments using FD.

In our system, drug release is simultaneously swelling-controlled, diffusion-controlled, and erosion-controlled. Dissolution of the drug in the reservoir and its diffusion starts after the swelling of the outer layers, separating the drug reservoir from the surface of the scroll. Thus, the lag time of the drug release is the convolution of the characteristic time of swelling of the outer shells, and the characteristic diffusion time. Since swelling continues also after the penetration of the solvent to the reservoir, the two mechanisms are inseparable from each other. Moreover, the gelatin matrix undergoes simultaneously enzymatic degradation. All these factors make the mathematical description of the release kinetics notoriously difficult. In the present study, we limit ourselves to the experimental study. The swelling degree, the swelling kinetics and the diffusion rate of a drug depend on the crosslinking degree of a polymer excipient [55,56]. In our work, the amount of Tgase, added to the gelatin solution, was optimized in a series of experiments, which aimed to find the compromise between the ability of the gelatin stripes to self-sticking (the property promoted by the relatively low content of Tgase) and the mechanical stability of the scrolls (at too low content of Tgase, inhomogeneous swelling of the outer and inner shells leads to the rupture of the scrolls and the burst-like release of the drug).

Although the rolling-up technique allows the design of the scrolls containing several reservoirs at different radial positions, in the present study we constrain ourselves to the case of the single-reservoir scrolls, for the sake of clarity. The release kinetics of FD in the PBS dissolution medium are shown on the Figure 4. After 8 h of dissolution, less than 30 % of the FD is released from reservoir F₁ with a delay of 4 h, in comparison to 70% from R₂ and 80 % from R₃. The release from the reservoir F₃, which is close to the outer surface of the scroll, starts almost immediately after the scroll immersion in the dissolution medium. Nevertheless, after 8 h of dissolution, 20% of the model drug remains retained in the matrix. The release from F₂ was slower than the release from F₃ and reached the 70% level after 8 h. After the 4 hours long lag time, the release rate from F₁ is almost linear and equals to 38μg/hour.

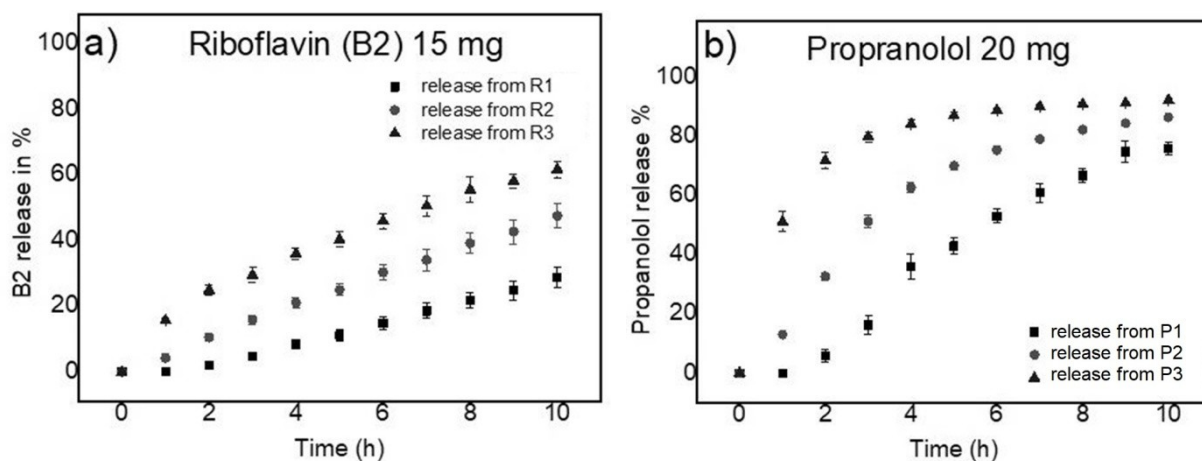


Figure 5. Release kinetics of riboflavin (a) and propranolol (b) in the FaSSGF.

The riboflavin release kinetics in FaSSGF are presented on the Figure 5a . After 10 h in the media, less than 20% of riboflavin is released from the reservoir R₃, against about 40% from R₁ and 58% from R₀ with a delay of about 3 h. Release from the reservoir which is the closest to the outer surface of the scroll is the fastest. The curves representing the release kinetics have quasi-linear zero order release after 2 hours of the experiment, and vary from ≈ 0.42 mg/hour, for the deepest reservoir R₁, to ≈ 0.75 mg/hour, for the peripheral reservoir R₃. The dissolution results show an immediate and rapid release of propranolol from the reservoir located on the outer layer of the scroll (reservoir P₁) (Figure 5b). After 10 h of dissolution, almost all of the riboflavin incorporated into P₁ is released. The release kinetics from P₂ is also immediate but has a slower kinetic and reaches 80% after 10 h of dissolution. Regarding P₃, the release is delayed by about an hour and the percentage of propranolol released after 10 h is about 70%.

IV. Discussion

The rolling-up approach to the fabrication of the scrolls with the programmable release kinetics may be considered as a simple alternative to 3D printing of the controlled-release tablets [57]. An “ideal” material for the rolled-up scrolls would be a water-permeable biocompatible polymer stripe, which has 3 important properties: 1) The stripes should be stable above the temperature of human body and in the human stomach; 2) The stripes should be flexible, to enable easy rolling up, and 3) The stripes should be self-sticky, and should not unroll at the physiological conditions.

The present paper introduces a system whose properties approach these requirements. Tgase catalyzes a chemical reaction of lysine crosslinking with glutamine residues. This reduces solubility of the gelatin scrolls while improving their mechanical properties. A recent study showed the increased resistance of gelatin films, crosslinked via the transglutaminase-catalysed reaction, to biodegradation compared to the control films [58]. The addition of the enzyme promotes the cross-linking of the polymer matrix, maintaining the integrity of the films for a longer time. Combining plasticizers with cross-linking agents results in flexible films that are easy to roll up so that scrolls can be formed without a central cavity. Finally, our gelatin films are self-sticky due to transglutaminase-mediated crosslinking of the consecutive layers of the rolls.

The scrolls swell sufficiently fast to the size which might prevent their evacuation via the pyloric sphincter prior to the stomach emptying. It is generally believed, that a size-increasing drug delivery system should be larger than roughly 13mm in size to be retained in the stomach [59]. The scrolls reach these dimensions after approximately 2 hours in FaSSGF (Figure 2b). This period is essentially larger than the average time which is needed for the evacuation of solid particles of the diameter $d > 5-7$ mm from the stomach, which is estimated to more than 4 hours [60]. It should be noted also that the gastric emptying time depends on many factors such as food's nature, it's caloric content, simultaneous administration of drugs, biological factors (gender, posture, age, disease state, physical activity) and the action of digestive hormones [59,61]. Moreover, gastric emptying for solid food is the subject of strong circadian variations, with the increase for evening meal time up to 53% [62]. Taking into account these factors, one can develop recommendations for prologation of the retention of

the gelatin scrolls in the stomach. In particular, it may be recommended to administer them during the evening meal. Standard stomach emptying studies with the use of radioisotope counting would clarify the real retention times of the rolled-up oral dosages.

The scrolls remain sufficiently rigid to sustain the peristaltic motion of the stomach during approximately 24 hour, that is sufficient for the release of the major part of the drug. After this period, enzymatic degradation of gelatin leads to softening of the scrolls to the degree enabling their evacuation in the lower sections of the GIT.

Although we constrained ourselves in the present study to the single-reservoir scrolls, the rolling-up technique allows easy fabrication of the scrolls containing two or more reservoirs, for a mono-drug or multi-drugs release with the programmed kinetics. In particular, for the mono-drug, one can program complex kinetics as the superposition of the release kinetics from the reservoirs formed at different radial positions.

To demonstrate potential clinical applications of the rolled-up gelatin scrolls, we used real drugs relevant to the gastroretentive release, riboflavin and propranolol. The dissolution tests demonstrate clear correlation of the release rate with the radial position of the reservoirs. From a pharmacological point of view, the outer position of the drug reservoir is ideal for treating an acute deficiency, and the inner position is more suitable for a daily dosing. In both cases, the rolled-up system has successfully shown its ability to be gastro-retentive.

The major obstacle of the proposed system to its commercialization is the low degree of automatization of the rolls fabrication and reservoirs formation. Nevertheless, these problems do not seem to be unsurmountable. We have shown already that the polymer stripes can be tailored by infrared laser cutting, while the drug reservoirs can be printed on the stripes with the use of an ink-jet printer [43]. The remaining engineering challenge consists in automatization of the rolling-up procedure. We see the future of this approach in fabrication of personalized dosages, produced in small batches, on the base of the information of the individual absorption, distribution, metabolism and elimination (ADME) characteristics of the patients.

Conclusion

Oral dosage (scrolls) for programmable drug release are produced by the rolling-up approach. The release rate of the drugs was programmed by the radial position of the drug reservoir inside the scroll. The radial position of the reservoir is determined by the lateral position of the drug reservoir on the polymer stripe prior to rolling. In the present study, we have introduced the formation of the scrolls by rolling up of the self-sticky stripes of plasticized and enzymatically cross-linked gelatin. Gastroretention is provided by swelling of the scrolls. Controlled release has been successfully demonstrated in for a model drug (fluorescein disodium), and real drugs (riboflavin and propranolol), with the use of PBS and FaSSGF.

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