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Original Research Article

Sustained *In-Vitro* Release, Kinetic Modelling and Ex-Vivo Intestinal Permeation of Eluxadoline from Chitosan–Alginate Particles Intended for Local Action in Diarrhoea-Predominant Irritable Bowel Syndrome

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Abstract: Eluxadoline acts on the gut wall and is hardly absorbed, so a dosage form for it should deliver drug steadily at the intestinal surface. The drug is practically insoluble in water, however, and the pure powder dissolves poorly. We studied how eluxadoline leaves an optimised chitosan–sodium alginate particle system (mean size 300.4 nm, zeta potential +41.2 mV, entrapment efficiency 76.89%) and how it passes through excised goat small intestine. Release was followed for 24 h in phosphate buffer pH 6.8 by the dialysis bag method and compared with the unprocessed drug. The particles showed no burst effect: 4.97% of the drug was released at 2 h, 34.65% at 6 h, 63.76% at 12 h and about 80% at 16 and 24 h. The pure drug released only 39.45% in 24 h. The data were fitted to zero-order, first-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas models. First-order, Higuchi and Hixson–Crowell fits were almost equally good (R^2 0.9223, 0.9209 and 0.9126), so R^2 alone could not separate them, while the Korsmeyer–Peppas exponent for the first 60% of release was about 1.5, which points to a release controlled mainly by matrix swelling, relaxation or erosion rather than by simple diffusion. Permeation through goat intestine followed the release curve closely and reached 78.13% at 24 h. The particles therefore gave a slow, sustained supply of eluxadoline in the intestinal pH range. Behaviour in gastric and colonic media, mucoadhesion, safety and storage stability remain to be studied.

Keywords: Eluxadoline, Chitosan–Alginate Particles, Drug Release Kinetics, Korsmeyer–Peppas Model, Ex-Vivo Permeation, Irritable Bowel Syndrome with Diarrhea.

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1. INTRODUCTION

Irritable bowel syndrome with diarrhoea (IBS-D) takes a measurable toll on daily life. In one analysis of patients with IBS-D, health-related quality of life and work productivity were both reduced, with indirect costs from lost working time adding to the burden (Buono *et al*., 2017). Treatment has to be adapted to the dominant symptom, and the guidelines admit that the benefit of most drugs over placebo is small (Lacy *et al*., 2021; Ford *et al.,* 2020). Part of the problem may lie in how the drugs are delivered. Conventional tablets disperse in the upper gut, whereas the symptoms of IBS arise from the wall of the lower small intestine and colon.

Eluxadoline, one of the drugs approved for IBS-D, acts on opioid receptors in the enteric nervous system and is absorbed very poorly, which keeps its effect local. A locally acting drug of this kind is only as good as the amount that is in solution at the gut wall over time. Eluxadoline, though, is practically insoluble in water. We measured a solubility of 0.0023 mg/mL, and in the companion paper we showed that it can be taken up in chitosan–sodium alginate particles in a non-crystalline form (companion paper, in preparation). Whether such particles actually give a useful release profile is a separate question, and it is the one we address here.

Hydrogel particles release their cargo through several processes at once. Water enters, the polymer chains swell and relax, the drug dissolves and diffuses through the swollen network, and the matrix may erode or be broken down by enzymes (Bhattarai *et al.,* 2010; Hariyadi & Islam, 2020). Chitosan–alginate carriers have been shown to slow down the release of drugs of very different kinds compared with alginate alone (Mi *et al*.,

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2002; Anal & Stevens, 2005; Pasparakis & Bouropoulos, 2006; Xu *et al*., 2007; Lucinda-Silva *et al.,* 2010). Most of those studies used hydrophilic or macromolecular drugs, so we know less about a poorly soluble, zwitterionic molecule such as eluxadoline.

Mathematical models help to read the shape of a release curve. The zero-order and first-order equations describe constant-rate and concentration-dependent release, the Higuchi equation describes diffusion from a matrix, and the Hixson–Crowell equation takes account of a change in particle surface area. The Korsmeyer–Peppas power law is used to judge whether release is Fickian, anomalous or controlled by polymer relaxation (Higuchi, 1963; Hixson & Crowell, 1931; Korsmeyer *et al*., 1983; Ritger & Peppas, 1987; Costa & Sousa Lobo, 2001). Our aims were to follow the release of eluxadoline from the optimised particles over 24 h and compare it with the pure drug, to fit the release data to these models, and to measure the passage of the drug through excised small intestine.

2. MATERIALS AND METHODS

2.1 Particles

Eluxadoline-loaded particles were made from chitosan and sodium alginate by emulsification–solvent evaporation followed by polyelectrolyte complexation, as described in the companion paper. The optimised formulation used chitosan at 1.20 mg/mL, sodium alginate at 1.56 mg/mL and 15.4 mL of alginate solution, with Tween 80 (0.2% v/v) as stabiliser. The product was collected by centrifugation and freeze-dried. This batch had a mean size of 300.4 nm, a PDI of 0.305, a zeta potential of +41.2 mV and an entrapment efficiency of 76.89%. Eluxadoline was analysed throughout by UV spectrophotometry at 243 nm (Shimadzu UV-1800) against calibration curves prepared in the relevant medium.

2.2 *In-Vitro* Release

Release was studied by the dialysis bag method. A quantity of particles equivalent to a fixed dose of eluxadoline was placed in a dialysis bag, which was sealed at both ends and immersed in 200 mL of phosphate buffer pH 6.8 at 37 ± 2 °C and stirred at 75 rpm. Samples were taken at 0, 2, 4, 6, 8, 10, 12, 16 and 24 h, and each time the same volume of fresh medium was added so as to keep sink conditions (Gibaldi & Feldman, 1967). The samples were read at 243 nm. The unprocessed drug was tested in the same way for comparison. Dissolution in media that mimic the pH of the intestine is the standard first step in judging oral products (Dressman *et al*., 1998).

2.3 Kinetic Analysis

The cumulative percentage released (Q) was fitted to five models: zero order (Q against t), first order (log of the percentage remaining against t), Higuchi (Q against √t), Hixson–Crowell (cube root of the initial amount minus cube root of the amount remaining, against t) and Korsmeyer–Peppas (log Q against log t). Linear regression was used for each, and the coefficient of determination (R^2) was taken as the measure of fit. The Korsmeyer–Peppas equation was applied only to the first 60% of release, as the model requires, and its exponent *n* was read against the limits for spherical particles: *n* of about 0.43 or below suggests Fickian diffusion, values between 0.43 and 0.85 suggest anomalous transport, and values of 0.85 or above suggest release governed by polymer relaxation or erosion (Ritger & Peppas, 1987; Peppas & Sahlin, 1989).

2.4 *Ex-Vivo* Permeation

Permeation was studied with a segment of goat small intestine as the biological membrane, in a dialysis-type arrangement. Five millilitres of particle suspension was filled into the segment, both ends were tied with thread, and the segment was placed in a beaker containing 400 mL of phosphate buffer pH 6.8 at 37 ± 2 °C with stirring at 75 rpm. Samples were withdrawn at the same time points as above, replaced with fresh buffer, and analysed at 243 nm. [Source of the tissue and the ethical or institutional statement to be added by the authors.]

3. RESULTS AND DISCUSSION

3.1 Release from the Particles Compared with the Pure Drug

The release profile of the particles had three features (Table 1 and Figure 1). There was a slow start, with only 4.97% of the drug released after 2 h. This was followed by a fairly steady rise to 34.65% at 6 h and 63.76% at 12 h, and then a plateau at about 80% from 16 h to 24 h. By contrast, the pure drug released 2.34% at 2 h and only 39.45% after 24 h, so the particles delivered about twice as much drug into the medium over the same period.

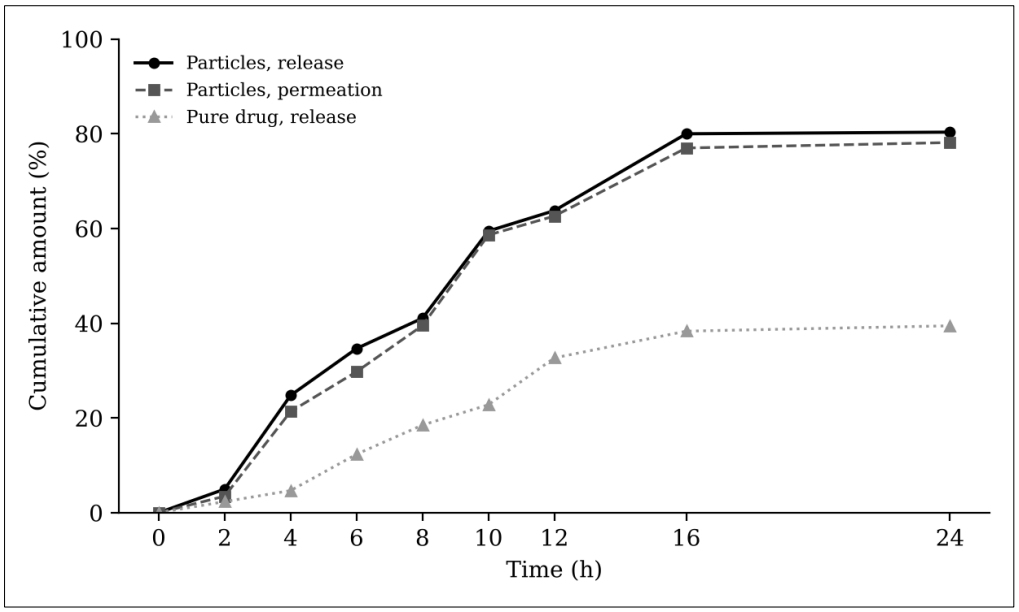


Figure 1: Cumulative in-vitro release of eluxadoline from the particles and from the pure drug (pH 6.8), and ex-vivo permeation through goat small intestine

Table 1: Cumulative release and ex-vivo permeation of eluxadoline (%)

Time (h)	Pure drug, release	Particles, release	Particles, permeation
0	0	0	0
2	2.34	4.97	3.47
4	4.67	24.76	21.34
6	12.34	34.65	29.76
8	18.50	41.06	39.50
10	22.78	59.45	58.61
12	32.67	63.76	62.61
16	38.32	79.98	76.98
24	39.45	80.33	78.13

Release: dialysis bag, 200 mL pH 6.8 phosphate buffer. Permeation: goat small intestine, 400 mL pH 6.8 phosphate buffer. 37 ± 2 °C, 75 rpm.

The absence of a burst is worth noting. Systems in which the drug sits close to the surface often lose a large fraction within the first hours, and for a locally acting drug that would mean the dose is spent before it reaches the target region. The low early release here is consistent with the drug being held inside the polymer network rather than on its surface, which fits the loss of the drug melting peak in DSC and of its sharp XRD reflections in the companion work. The lag is also what one expects while a dry, freeze-dried complex takes up water and begins to swell.

Several things probably act together to give the faster and more sustained release compared with the pure drug. Tween 80 and the hydrophilic polymers improve wetting of an otherwise hydrophobic powder, the drug is in a non-crystalline state, and the particles swell and erode gradually at the test pH. On that last point, the amino groups of chitosan have a pKa of about 6.2–6.5 (Rinaudo, 2006), so at pH 6.8 much of the chitosan is losing its positive charge. The electrostatic attraction that holds the complex together should weaken, and this would allow the network to relax and let the drug out. We offer this as a plausible reading and did not test it directly.

Two cautions apply. First, the profile is not perfectly smooth. Only 6.4 percentage points were released between 6 and 8 h, but 18.4 points between 8 and 10 h. Without replicate data and standard deviations we cannot say how much of this is real and how much is scatter. Second, about a fifth of the drug was not recovered, and the pure drug also levelled off, at about 39%. This suggests that part of the plateau may be set by the solubility of this very poorly soluble drug in the receptor medium and by transport across the dialysis membrane, not only by the carrier. We did not measure the solubility of eluxadoline in pH 6.8 buffer or check how much of the dose stayed inside the bag, so we cannot say whether sink conditions held for the full 24 h.

3.2 Release Kinetics

Table 2 gives the results of model fitting. The zero-order model fitted worst (R^2 0.866). First-order, Higuchi and Hixson–Crowell fits were close to one another (0.9223, 0.9209 and 0.9126), so a choice

between them on the basis of R^2 alone would not be convincing. With nine time points and no replicates, differences of this size in R^2 are well within what noise could produce.

Table 2: Fit of the release data to kinetic models

Model	Plot	R^2	Comment
Zero order	Q vs t	0.866	Poorest fit
First order	log (100 − Q) vs t	0.9223	Highest R^2 of the four simple models
Higuchi	Q vs √t	0.9209	Practically equal to first order
Hixson–Crowell	$\sqrt[3]{100} - \sqrt[3]{(100 - Q)}$ vs t	0.9126	Practically equal to first order
Korsmeyer–Peppas	log Q vs log t (Q ≤ 60%)	≈ 0.94	Exponent n ≈ 1.5

Values for the first four models were calculated on all nine time points including t = 0. The Korsmeyer–Peppas fit uses the first five points after t = 0 (up to 59.45% release); a recalculation gave n = 1.47 and R^2 = 0.939.

The Korsmeyer–Peppas result needs some explanation. Plotted as the log of the amount released against log time for the part of the curve up to about 60% release, the data give an exponent of about 1.5. For spherical particles an exponent above 0.85 is read as release governed mainly by swelling and relaxation of the polymer or by erosion of the matrix, rather than by diffusion alone (Ritger & Peppas, 1987). That agrees with the slow start followed by a steadier rise. The exponent rests on only five points, though, and a value as high as 1.5 should be read as a sign that release was strongly time-dependent, with the lag phase pulling the slope up, and not as an exact mechanistic constant. It is best taken together with the observation that several simple models fit about equally well (Siepmann & Siepmann, 2008).

3.3 Ex-Vivo Permeation through Goat Intestine

Drug appeared in the receptor compartment slowly at first (3.47% at 2 h) and then more quickly, with 21.34% at 4 h, 62.61% at 12 h and 78.13% at 24 h (Table 1). The permeation curve ran just below the release curve at every sampling time, by roughly 1 to 5 percentage points, and the two curves had the same general shape. The simplest reading is that the rate at which drug leaves the particles is what controls its passage, and that the intestinal segment adds only a modest extra barrier in this set-up. The two experiments used different media volumes (200 and 400 mL) and different arrangements, so the figures are not strictly comparable.

What the permeation figure means for a locally acting drug needs thought. Eluxadoline is poorly absorbed after oral dosing, and the aim of a delivery system is to put the drug at the gut wall, not to push as much as possible into the circulation. A dialysis-type experiment shows that the drug becomes available at the membrane in a controlled way, but it does not tell us how much stays in the tissue. Chitosan is known to loosen epithelial tight junctions and to raise the transport of poorly absorbed compounds (Schipper *et al*., 1996; Thanou *et al*., 2001), which could be an advantage or a drawback here. Tissue-content measurements and cell-based permeability work would be more informative than receptor-side concentration alone.

3.4 Relevance to the Intestinal Environment

A 24 h in-vitro profile should not be read as 24 h of release in the body. Transit through the small intestine takes a few hours and varies between people and with food (Davis *et al.,* 1986; Coupe *et al*., 1991; McConnell *et al.,* 2008), and colonic transit tends to be faster in diarrhoea-predominant disease (Ford *et al*., 2020). A particle that is carried through quickly will not experience the whole curve. Particles that stay in contact with the mucus layer for longer would have a better chance of delivering drug where it is needed (Johansson *et al*., 2013), and chitosan is attractive because of its mucoadhesive character, but we did not measure mucoadhesion. The same is true of release in gastric fluid and in colonic fluid with enzymes, where chitosan can be degraded (Pangburn *et al.*, 1982; Kean & Thanou, 2010). Our release test used one medium at one pH.

4. Limitations

This study has clear limits. Release and permeation were measured on one optimised batch in a single medium (pH 6.8), and no standard deviations or replicate profiles are reported, so the statistical strength of the comparisons is unknown. The kinetic models were fitted to nine points, and the Korsmeyer–Peppas exponent to five. The ex-vivo test used excised goat intestine in a simple dialysis arrangement that does not reproduce motility, luminal contents or the full mucus barrier. We did not check whether sink conditions held, and the stated dose was not related to the measured solubility. Mucoadhesion, cell safety, storage stability and release in gastric and colonic media were not examined, although they are part of the logic of a site-specific system.

5. CONCLUSION

Eluxadoline-loaded chitosan–sodium alginate particles released the drug slowly and without a burst effect, giving about 80% release over 24 h in pH 6.8 buffer against 39.45% for the pure drug. The release curve was described about equally well by first-order, Higuchi and Hixson–Crowell models, and the Korsmeyer–Peppas exponent of about 1.5 points to swelling, relaxation or erosion of the matrix as the main controlling process. Permeation through excised goat intestine followed the release curve, which suggests that release from the particles sets the pace. These findings

support the idea of using a chitosan–alginate carrier for a poorly soluble, locally acting IBS-D drug, but they come from one medium and one batch. Release in sequential gastric, intestinal and colonic media, mucoadhesion tests, cell-line safety work and stability studies are the logical next steps.

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