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Review Article

Biopolymer-Based Oral Delivery of Ceftriaxone Sodium: Alginate Multiparticulates, Enteric Protection and the Unresolved Permeability Problem

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ABSTRACT

Absrtact: Ceftriaxone is among the most widely used injectable antibiotics in hospital practice, yet it has no oral form. Two independent properties prevent one: the beta-lactam ring is destroyed at gastric pH, and the molecule is a large, di-anionic, BCS Class III compound that is not carried by the PepT1 peptide transporter which makes cefixime and ceftibuten orally active. The absence of an oral equivalent blocks the intravenous-to-oral switch that antimicrobial stewardship programmes promote, keeping patients in hospital or returning daily for injection. This review examines the biopolymer-based multiparticulate approach to that problem. Calcium alginate beads formed by ionotropic gelation are cheap, solvent-free and made from a GRAS polymer, and an enteric coat addresses the acid-lability directly. The published work on ceftriaxone beads demonstrates that the carrier is workable, reporting entrapment of around 75 per cent with a release modifier and an enteric coat. Three problems recur across that literature and are examined in turn. The first is mechanical: a porous, hydrophilic calcium alginate matrix leaks a freely water-soluble drug into the gelation bath, and the remedies, blending with a second polymer or forming a chitosan-alginate polyelectrolyte complex, address it only partially.

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The second is analytical: the quantity of drug released in gastric fluid is routinely reported while the quantity degraded there is not, although for an acid-labile drug the second is what matters. The third, and the one this review argues is decisive, is that permeability has never been addressed at all. A Class III drug released intact in the intestinal lumen remains unabsorbed if it cannot cross the mucosa, and no alginate bead formulation of ceftriaxone has incorporated a permeation enhancer or measured intestinal permeability. The review sets the bead literature against the nanoparticulate and ion-pairing alternatives, which have produced *in vivo* data where the bead work has not, and notes that the most successful of them used a cationic polymer that is itself a tight-junction modulator. It concludes that the field's next useful step is not a further release-profile optimisation but a formulation in which permeation enhancement is a designed variable, evaluated by an apparent permeability coefficient and confirmed by oral bioavailability, with a microbiological assay to demonstrate that the recovered drug is still an antibiotic.

INTRODUCTION:

THE INTRAVENOUS-TO-ORAL SWITCH AND ITS LIMITS

Why the oral route matters in antibiotic therapy

Antibiotics may be given orally, parenterally or topically. Where both routes are available, oral therapy is cheaper, avoids the intravenous cannula and the bloodstream infection risk that attends it, shortens hospital stay and allows treatment to be completed at home [1]. The clinical evidence for timely switching is established: switching medical inpatients from intravenous to oral antibiotics once they are clinically stable does not worsen outcomes and shortens admission [2].

Switching has accordingly become a core element of antimicrobial stewardship. Professional guidelines name it among the interventions stewardship programmes should Implement [3], and it appears in the World Health Organization's AWaRe framework and in national treatment guidance [4].

The constraint that defines the problem

Every statement of switch policy carries the same qualification: switch when an adequate oral agent exists. That qualification is the whole of the problem addressed in this review.

For several important intravenous antibiotics there is no oral equivalent at all. Where that is so, the switch cannot be made whatever the patient's clinical state. The consequence is not merely inconvenience: it is continued hospitalisation, or daily attendance for injection, for patients who are otherwise well enough to go home. In a health system where hospital beds are scarce and daily travel for an injection is a real cost to a family, that consequence falls hardest on those least able to bear it.

Ceftriaxone is the clearest example of the problem, and the reasons it resists oral delivery are instructive, because they are two distinct problems that require two distinct solutions.

CEFTRIAXONE: WHY THE MOLECULE RESISTS ORAL DELIVERY

The clinical position

Ceftriaxone is a third-generation cephalosporin with broad activity against Gramnegative and many Grampositive organisms, good penetration into cerebrospinal fluid, and an unusually long elimination halflife of approximately six to nine hours that permits once-daily dosing [5]. Its spectrum and its dosing convenience together have made it one of the most widely used injectable antibiotics in hospital practice worldwide, and in India in particular [6].

It is available only as an intravenous or intramuscular injection.

Table None: Properties of Ceftriaxone Sodium Relevant to Oral Delivery

Property	Value or description	Consequence for oral delivery
Class	Third-generation cephalosporin, beta-lactam	Acid-labile ring; see below
Molecular weight	Approximately 555 g per mol as the sodium salt	Large for passive transcellular absorption

Property	Value or description	Consequence for oral delivery
Solubility	Freely soluble in water	Dissolution is not rate limiting; but the drug leaks readily from a hydrophilic matrix

Biopharmaceutics classification	Class III: high solubility, low permeability	The epithelium, not dissolution, is the barrier
Ionisation	Di-anionic at intestinal pH	Poor passive permeation; not a PepT1 substrate
Stability	Acid-labile; the beta-lactam ring degrades at gastric pH. Light-sensitive	Enteric protection mandatory
Half-life	Approximately 6 to 9 hours	Once-daily dosing would carry over to an oral form
Protein binding	Approximately 85 to 95 per cent, concentration-dependent	Relevant to pharmacokinetic interpretation
Routes available	Intravenous and intramuscular only	The gap this literature addresses

Pharmacopoeial values should be confirmed against the current monograph before use in formulation work [7,8].

The first barrier: acid lability

The beta-lactam ring is hydrolysed at gastric pH, so drug swallowed in an unprotected form is destroyed before it reaches any absorption site. This barrier is in principle solvable by formulation, and enteric protection is the standard answer; section 6 examines how well it has worked in practice.

The second barrier: permeability, and why it is the harder one

Ceftriaxone is classified as BCS Class III: highly water-soluble but poorly permeable [9]. For a Class III compound, dissolution is not the limiting step and improving release does nothing for absorption; the intestinal epithelium is the barrier.

Three structural features explain the poor permeability. The molecule is large, at approximately 555 g per mol. It is highly polar and di-anionic at intestinal pH, which disfavours passive transcellular partitioning into the lipid membrane. And, critically, it is not a substrate for the proton-coupled oligopeptide transporter PepT1.

That last point deserves emphasis because it explains why some cephalosporins are oral drugs and ceftriaxone is not. PepT1 is a broad-specificity transporter in the small intestinal brush border that carries di- and tripeptides, and also a number of peptidomimetic drugs including the aminocephalosporins [10]. Cefixime, cefadroxil, cephalexin and ceftibuten are orally active largely because PepT1 carries them across the enterocyte. Ceftriaxone lacks the structural features that transporter recognises, so no such carrier-mediated route is available to it.

The practical consequence is the organising argument of this review. Protecting ceftriaxone from gastric acid solves half the problem and leaves the other half untouched. A formulation that delivers intact ceftriaxone to the duodenum has succeeded against the first barrier and achieved nothing against the second, and will show little or no oral bioavailability. Any approach that addresses only acid protection is therefore incomplete by construction, however well it performs in a dissolution test.

MULTIPARTICULATE BIOPOLYMER CARRIERS AND IONOTROPIC GELATION

Why multiparticulates

In a multiparticulate system the dose is divided among many small units, typically beads, pellets or microspheres, rather than carried in a single unit. The advantages are well rehearsed: the units distribute more evenly through the gastrointestinal tract, gastric emptying is more reproducible and less dependent on the fed state, the risk of dose dumping from a single failed unit is removed, and the units can be filled into capsules or compressed [11].

For an enteric-protected product the advantage is sharper still. A single entericcoated tablet either passes the stomach intact or fails entirely; several hundred coated beads fail only in proportion to the fraction whose coat is defective, which makes performance less brittle.

Sodium alginate and the egg-box mechanism

Sodium alginate is a linear anionic polysaccharide extracted from brown seaweed, composed of beta-D-mannuronic acid and alpha-L-guluronic acid residues arranged in homopolymeric and alternating blocks [12]. Guluronate blocks on adjacent chains chelate divalent cations such as calcium, forming the junction zones described by the egg-box model that convert a solution into a hydrogel [13].

The formulation consequence is a method of unusual simplicity. Dropping a sodium alginate solution into a calcium chloride bath produces beads instantly, at room temperature, with no heat and no organic solvent. The polymer is biodegradable, generally recognised as safe, and inexpensive. The equipment required is a syringe, a needle and a stirrer. These attributes together explain why ionotropic gelation is the most widely used bead-forming method in academic formulation work [14,15].

For an acid-labile drug the absence of heat and organic solvent is not merely convenient; it is a positive advantage, since both would accelerate degradation of the betalactam.

The gel's relevant weakness

The same properties that make calcium alginate attractive create its principal limitation. The matrix is porous, hydrophilic and highly swellable, and during gelation and curing it is immersed in an aqueous bath. A freely water-soluble drug therefore diffuses out of the forming bead into the bath before the matrix has consolidated [14].

Ceftriaxone sodium is freely water-soluble. The leakage problem is thus not incidental to this particular application; it is the central manufacturing difficulty, and the next section examines it directly.

THE ENTRAPMENT PROBLEM FOR WATER-SOLUBLE DRUGS

The magnitude of the problem

Entrapment efficiency in plain calcium alginate beads loaded with a freely watersoluble drug is characteristically low. Values in the region of 10 to 20 per cent are commonly reported, and the source thesis underlying this review reports 8 to 15 per cent for plain alginate beads of ceftriaxone. The mechanism is straightforward: the drug dissolves in the alginate solution, the droplet enters an aqueous bath, and a concentration gradient drives the drug outward through a matrix whose pores have not yet closed.

Three variables govern how much is lost: the time the bead spends in the bath, the porosity of the forming gel, and the concentration gradient across the bead surface. Each suggests a remedy, and the literature has pursued all three.

Approaches to improving entrapment Table. Strategies for improving entrapment of water-soluble drugs in alginate beads

Strategy	Mechanism	Limitation
Blending with a second hydrophilic polymer	Raises viscosity of the dispersion and reduces matrix porosity, slowing outward diffusion	Partial; the matrix remains hydrophilic and the drug still has a path out
Polyelectrolyte complexation, typically with chitosan	Forms an ionic complex at the bead surface, producing a denser skin rather than merely a thicker gel	Chitosan requires an acidic medium for solubility; complexation conditions need optimisation
Saturating the gelation bath with drug	Removes or reverses the concentration gradient	Wasteful of drug; may leave surface crystals

Shortening the cure	Less time for leakage	Under-cured beads are mechanically weak
Reducing the drug's solubility in the bath	Non-aqueous or mixed-solvent baths	Defeats the solvent-free advantage of the method

The first two are the approaches taken in the ceftriaxone literature and are examined in section 5.

An accounting problem that recurs

A distinction that the published work frequently blurs deserves to be made explicit, because it affects how entrapment figures should be read.

Drug that has left the bead and entered the bath is lost. Drug that sits as loose crystals on the bead surface has not left, and will be recovered by an assay that dissolves the whole bead, so it is counted as entrapped. But it is not entrapped in any functional sense: it is the fraction that will dump immediately in the stomach, which for an acid-labile drug means the fraction that will be destroyed.

Reported entrapment efficiencies and reported loose-surface-crystal fractions therefore measure overlapping material. Where both are reported, as in the source thesis which gives entrapment of approximately 75 per cent alongside loose surface crystals of 24 to 40 per cent, the two numbers cannot both be taken at face value. The remedy is a defined surface wash before assay, with the wash liquor assayed separately so that the two fractions partition the dose rather than overlap. Few published studies do this, and it is a straightforward methodological improvement available to any bead study of a watersoluble drug.

RELEASE MODIFIERS AND POLYELECTROLYTE COMPLEXATION

Simple blending

Blending alginate with a second hydrophilic polymer raises the viscosity of the dispersion before extrusion and reduces the porosity of the resulting matrix, slowing drug loss during curing. Sodium carboxymethylcellulose, hydroxypropyl methylcellulose, acacia, gelatin and pectin have all been used for this purpose [14,15].

The effects are real but bounded. The modifier thickens the gel without changing its fundamental character: the matrix remains an anionic hydrophilic hydrogel with an aqueous continuous phase, and a freely water-soluble drug still has a diffusional path to the bath.

Reported improvements in entrapment from such blending are substantial relative to plain alginate but leave a considerable fraction unaccounted for.

Chitosan and polyelectrolyte complexation

Chitosan is different in kind rather than degree. It is a linear cationic polysaccharide obtained by deacetylation of chitin, soluble as its salt below approximately pH 6.0 to 6.5 where its amino groups are protonated [16]. Brought into contact with anionic alginate, it does not merely thicken the system: the two oppositely charged polyelectrolytes associate ionically to form a complex, producing a membrane-like skin at the bead surface that is denser and less permeable than the bulk gel [15,17].

Chitosan-alginate systems have been widely studied for exactly this reason, in beads and in nanoparticles, and the approach is more mechanistically promising for a watersoluble drug than simple blending, because it changes the surface rather than the interior.

The point that makes chitosan particularly interesting here

Chitosan has a second property that is incidental in most formulations and central in this one: it is itself an intestinal permeation enhancer. Section 7 examines the evidence. For a BCS Class III drug, a polymer that both improves entrapment and opens tight junctions addresses the two barriers simultaneously, which is an unusual convergence and arguably the most promising single observation in this field.

It also imposes a constraint. Chitosan's tight-junction effect depends on its being in solution and positively charged, which requires a pH below roughly 6.5. Intestinal pH is above that. A chitosan-containing formulation intended to enhance permeation must therefore deliver the polymer in a form and at a local pH where it remains active, which is a formulation problem in its own right and is not solved merely by including chitosan in the matrix.

ENTERIC PROTECTION OF AN ACID-LABILE BETA-LACTAM

The polymers available

An enteric coat is insoluble at gastric pH and dissolves above a threshold in the small intestine. Cellulose acetate phthalate dissolves above approximately pH 6.2 and is the oldest and cheapest of the enteric polymers. Alternatives include hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, shellac and

the methacrylic acid copolymers, which differ chiefly in their dissolution threshold and in whether they can be applied from aqueous dispersion [18,19].

The dissolution threshold matters more than it is usually given credit for. A polymer that requires pH 7 to dissolve may not dissolve at all in the proximal small intestine of some patients, releasing distally or not at all, and this has been shown to be a real cause of variable performance [19]. For a drug absorbed, to whatever limited extent, in the proximal small intestine, a lower-threshold polymer is preferable.

The solvent problem for alginate beads

Here the ceftriaxone literature encounters a specific difficulty. Cellulose acetate phthalate is conventionally applied from an organic solvent system, in the published bead work an ethyl acetate and ethanol mixture. Immersing a calcium alginate bead in an organic solvent for an extended period dehydrates and partly collapses the polymer network, and the resulting coat is cracked rather than continuous.

The source thesis reports exactly this outcome and attributes the residual gastric release of 35 to 47 per cent to cracks formed as the polymer network partly collapses on contact with the organic solvent, together with loose surface crystals. Both causes are addressable, and the second is addressed by the wash step discussed at section 4.3.

The first is addressed by changing the coating route. Aqueous enteric dispersions of HPMCAS or shellac avoid organic solvent contact altogether, and a brief dip or a fluidised-bed application gives far less solvent exposure than thirty minutes of stirring. A plasticiser such as triethyl citrate reduces coat brittleness and cracking in either route [18].

How much protection is enough

A further point concerns what the gastric-phase measurement should be. Published studies report the percentage of drug released in simulated gastric fluid, which for most drugs is the relevant measure of enteric performance.

For an acid-labile drug it is not. Drug released into gastric fluid is not merely released early; it is destroyed. A formulation that releases 30 per cent in the gastric phase has not delivered 70 per cent to the intestine plus 30 per cent early, it has delivered 70 per cent and lost 30 per cent. Section 9.1 develops this into a methodological recommendation.

PERMEATION ENHANCEMENT FOR BCS CLASS III DRUGS

Why this section exists

For a Class I or Class II drug, formulation science has a well-stocked toolbox: particle size reduction, solubilisation, amorphous dispersions, lipid systems. For a Class III drug none of it helps, because the drug is already dissolved and the epithelium is the obstacle [9]. The only route to meaningful oral bioavailability is to increase permeation [20].

The classes of enhancerTable . Principal classes of intestinal permeation enhancer

Class	Examples	Mechanism	Clinical status
Medium-chain fatty acids and salts	Sodium caprate, C10	Predominantly paracellular; transient tight-junction opening, with a transcellular component	Used in approved oral products
Acylated amino acid derivatives	Salcaprozate sodium, SNAC	Transcellular; increases membrane fluidity and local concentration	Used in an approved oral semaglutide product

Class	Examples	Mechanism	Clinical status
Cationic polymers	Chitosan and derivatives	Interaction with the epithelial surface opens tight junctions reversibly	Extensively studied; not yet in an approved oral product for this purpose
Bile salts and bile acid derivatives	Sodium deoxycholate, sodium taurocholate; bile acid conjugates	Membrane perturbation; some exploit bile acid transporters	Investigational; ionpairing conjugates applied to ceftriaxone
Surfactants, acyl carnitines, mediumchain glycerides	Various	Membrane perturbation	Investigational

The two enhancers with approved-product status, sodium caprate and SNAC, have been directly compared and differ in mechanism: C10 acts largely by transient paracellular opening while SNAC acts transcellularly [21]. The transcellular mechanism of SNAC in an approved oral peptide product has been characterised in detail [22]. The field beyond these two has been reviewed by Brayden and colleagues [23].

Chitosan as enhancer: the evidence

The chitosan effect is long established and mechanistically characterised. Chitosan reduces transepithelial electrical resistance and increases the permeability of Caco-2 monolayers in a concentration-dependent and reversible manner [24], and the structural basis, redistribution of tight-junction proteins, has been demonstrated in epithelial cell

layers [25]. Its mucoadhesive character prolongs contact time at the absorptive surface, which compounds the effect [16,17].

The practical caveat, restated from section 5.3, is the pH dependence. Protonated chitosan is the active species, and the small intestine is above its pKa. Chitosan derivatives designed to be soluble and charged at neutral pH exist for precisely this reason, and are the logical route if chitosan is to serve as the enhancer rather than merely as a complexing polymer.

1.1 The safety requirement that attaches to any enhancer

Any intestinal permeation enhancer opens a barrier that exists for a reason. Two requirements follow, and both have become standard expectations in the field [20,23].

The effect must be reversible and local. A tight junction that reopens within a defined period and closes thereafter is acceptable; sustained epithelial disruption is not.

Safety on repeated dosing must be demonstrated, not inferred. An antibiotic course is not a single dose, and a product given twice daily for a week subjects the epithelium to repeated opening. This is why an enhancer arm in any such study requires histological evidence of the mucosa alongside the permeability data, and why transepithelial electrical resistance recovery, rather than its initial fall, is the more informative measurement.

PUBLISHED APPROACHES TO ORAL CEFTRIAXONE: A COMPARATIVE APPRAISAL23 Nov 2026

The approaches reported Table. Reported approaches to oral delivery of ceftriaxone

Approach	Principle	Reported outcome	Permeability addressed
Calcium alginate beads with a release modifier and enteric coat	Acid protection and sustained release from a biopolymer multiparticulate	Entrapment approximately 75 per cent; sustained release; in vitro only	No
Ionic complex with a cationic deoxycholate analogue	Bile acid conjugation to exploit bile acid transport	Oral delivery demonstrated for the conjugate approach	Yes, by design
Magnetic iron oxide nanoparticles, functionalised	Nanoparticulate carrier with surface functionalisation	Entrapment 79.4 per cent; particle size about 184 nm; plasma concentration 14.4 micrograms per mL in **rabbits against 2.0 for control**	Indirectly, by nanoparticulate uptake
Chitosan and shellac nanoparticles in enteric capsules	Cationic polymer nanoparticle with enteric protection	Particle size about 258 nm; zeta potential about plus 30 mV; entrapment 83 per cent; sustained release to 15 hours; absolute oral bioavailability reported at 92 per cent in rabbits	Yes, via the cationic polymer

Numerical values are quoted as reported by the cited authors [26–29]. The bead entrapment and release figures are those reported in the direct precedent discussed in the source thesis.

What the comparison shows

Three observations follow from setting these side by side, and they frame the argument of the remainder of this review.

The approaches that measured oral bioavailability are the nanoparticulate ones. The bead literature is entirely *in vitro*. Bioavailability is the only endpoint that determines whether oral ceftriaxone works at all, and the carrier with the most attractive manufacturing profile is the one for which it has not been measured.

The most successful reported result used a cationic polymer. The chitosan and shellac nanoparticle study reports an absolute oral bioavailability of 92 per cent in rabbits. Whether or not that figure survives independent replication, the design logic is instructive: it combines enteric protection with a polymer that is itself a tight-junction modulator, addressing both barriers rather than one.

The bead approach has advantages the nanoparticle approaches lack. Ionotropic gelation needs no organic solvent, no high-energy processing and no specialised equipment; it is manufacturable in a modest facility at low cost. For a product whose social argument rests on affordability and on enabling home treatment, that matters. The question is therefore not whether beads or nanoparticles are better in the abstract, but whether the bead platform can be made to address permeability, which it has not yet been asked to do.

EVALUATION METHODOLOGY AND TWO ENDPOINTS THAT ARE USUALLY MISSING

Measuring acid protection properly

The conventional endpoint for an enteric formulation is cumulative release in simulated gastric fluid over two hours. For ceftriaxone this is insufficient, for the reason given at section 6.3: released drug is degraded drug.

The improvement is small and specific. Assay both intact ceftriaxone and its degradation products in the

gastric phase, so that the fraction destroyed is measured rather than inferred from the fraction released. This requires a stability-indicating analytical method rather than a simple assay, which is in any case required for the stability work [30]. A formulation that releases little but degrades what it releases is not protective, and only the two-component assay distinguishes the two cases.

Measuring permeability

Where permeation enhancement is part of the design, it must be measured, and two established methods are available at different levels of cost and information.

The Ussing chamber mounts a sheet of intestinal tissue between two compartments and allows simultaneous measurement of transepithelial electrical resistance and flux, which makes it the method of choice for demonstrating that a tight-junction effect occurs and reverses [31]. The everted gut sac is the standard low-cost *ex vivo* alternative, giving an apparent permeability coefficient without the electrophysiological read-out; its applications and limitations have been reviewed [32].

Either yields an apparent permeability coefficient suitable as an optimisation response. Neither substitutes for an *in vivo* bioavailability measurement, but both allow the enhancer level to be selected rationally before an animal study is undertaken.

Measuring whether the drug is still an antibiotic

Ceftriaxone is a beta-lactam, and bead manufacture subjects it to prolonged stirring, calcium cross-linking, several hours in aqueous dispersion and, in the organic coating route, exposure to ethyl acetate and ethanol. Whether the drug recovered from the beads retains its antibacterial potency is a question that a chromatographic assay cannot answer, because chromatography measures the molecule while potency measures the medicine. A

degradation product that co-elutes, or an intact molecule that has been partly epimerised, would pass one test and fail the other.

A cup-plate or turbidimetric assay of the released drug against a standard susceptible organism, with potency expressed against a reference standard, settles it at negligible cost. It is rarely reported in this literature and should be routine.

Release kinetics: useful, but not the point

Fitting release data to zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models is standard practice and the methods are well described [33,34]. Profile comparison by the f1 and f2 factors is likewise routine [34].

These analyses characterise the matrix and are worth doing. They should not, however, be mistaken for evidence of performance. A Class III drug released with ideal zero-order kinetics into the intestinal lumen is still not absorbed. In a field where the central obstacle is permeability, an elegantly fitted release profile can create an appearance of progress that the underlying pharmacokinetics will not support.

CRITICAL APPRAISAL AND RESEARCH GAPS

Five gaps are identifiable in the published work on biopolymer-based oral ceftriaxone.

They are set out in order of importance.

Permeability has never been addressed

This is the central gap. Ceftriaxone is a Class III drug whose absorption is limited by the epithelium. The existing alginate bead work protects the drug from acid and controls its release, and does nothing whatever about permeation. No alginate bead formulation of ceftriaxone has incorporated a permeation enhancer or measured intestinal permeability.

The consequence is not that the published work is wrong but that it is incomplete by construction. A bead that delivers 100 per cent of its payload intact to the duodenum has solved the problem it set out to solve and will still show negligible oral bioavailability, because the drug cannot cross the mucosa. Until an enhancer is a designed variable in the formulation and an apparent permeability coefficient is a measured response, the approach cannot be said to have been tested.

No in vivo data exist for the bead system

The bead literature is entirely *in vitro*. Oral bioavailability, which is the only endpoint that determines whether the approach works, has not been measured for an alginate bead formulation of this drug. Where *in*

vivo data for oral ceftriaxone do exist, they come from nanoparticulate systems [26,27].

Three specific formulation deficiencies remain

Each is measurable and each has an identified remedy, which makes them targets rather than general aspirations: substantial release in simulated gastric fluid, which the two-component assay of section 9.1 would properly quantify and an aqueous coating route would reduce; a significant fraction of loose surface crystals, which a defined wash with assayed wash liquor would both remove and measure; and an enteric coat applied from an organic solvent that cracks the calcium alginate matrix, for which aqueous enteric dispersions are the direct answer.

Antimicrobial activity after processing has not been confirmed

Section 9.3 sets this out. No microbiological confirmation has been reported for the processed drug, and a chemical assay does not substitute for one.

Stability of an acid-labile drug in a hydrogel has not been established

No ICH stability data have been reported for ceftriaxone beads [35]. This matters particularly for a beta-lactam in a hydrated polysaccharide matrix, where residual moisture is a hydrolysis risk and where the degradation products are themselves of interest because they are what the gastric-phase assay at section 9.1 must detect.

TRANSLATIONAL, REGULATORY AND STEWARDSHIP CONSIDERATIONS

What a successful product would change

An oral ceftriaxone would allow the intravenous-to-oral switch for a drug where it is currently impossible, with the consequences set out at section 1.2: earlier discharge, no cannula, no daily attendance for injection, and treatment completed at home. In a setting where hospital beds are scarce, the benefit accrues to the health system as well as to the patient.

The stewardship caution

That argument requires a counterweight, and it is one the field should state rather than leave to critics. An orally available ceftriaxone would be easier to prescribe than an injection, and ease of prescribing is not an unmixed good for a broad-spectrum cephalosporin. The injection route imposes a practical friction that limits casual use. Removing that friction, in a setting where antibiotics are frequently dispensed without prescription, could increase inappropriate use of a Watch-category agent and accelerate resistance [4].

The honest position is that an oral form should be developed as a switch therapy for patients already started on the drug for a confirmed indication, not as a first-line oral antibiotic, and that this positioning should be designed into the product and its labelling rather than asserted afterwards. Nothing in the formulation prevents misuse; the framing, the pack size and the prescribing pathway are what address it.

Quality and development framework

Formulation optimisation by experimental design, with identification of critical material attributes and process parameters, follows the quality-by-design principles of ICH Q8 (R2)[36]. Analytical methods require validation, and for an acid-labile drug a stabilityindicating method is necessary rather than optional [30]. Stability testing follows ICH Q1A (R2) [35]. Animal work in India is conducted under CCSEA guidance with institutional ethics approval [37].

A note on patentability

Claims resting on polymer substitution alone are weak. Under section 3 (d) of the Indian Patents Act, a new form or formulation of a known substance requires evidence of enhanced therapeutic efficacy rather than merely a changed release curve [38]. For this field the implication is specific and, usefully, aligns with the scientific argument: the evidence that would support a claim is the same evidence the field needs anyway, namely a demonstrated increase in oral bioavailability, not an improved dissolution profile.

CONCLUSION

The biopolymer multiparticulate approach to oral ceftriaxone rests on a sound foundation. Ionotropic gelation of alginate is cheap, solvent-free, reproducible with simple equipment and well suited to an acid-labile drug, and an enteric coat addresses the first of

the two barriers directly. The published work establishes that the carrier is workable and that entrapment of a freely water-soluble drug, while difficult, can be raised substantially by a release modifier or by polyelectrolyte complexation with chitosan.

The field's difficulty is that it has solved the easier of the two problems and has not yet addressed the harder one. Acid lability is a formulation problem with known answers. Permeability is a biological barrier that formulation can only address by actively enhancing transport, and no bead formulation of ceftriaxone has attempted it. The consequence is a literature of *in vitro* successes with no *in vivo* endpoint, and an approach whose central premise remains untested.

Three changes would move the field forward, and none requires new science.

Make permeation enhancement a designed variable. An enhancer level as a factorial variable, with apparent permeability coefficient as a response, converts the question from an assumption into a measurement. Chitosan is the obvious candidate because it serves two functions at once, but its pH dependence must be designed around rather than ignored.

Measure the right things. Degraded drug rather than released drug in the gastric phase; entrapment partitioned against loose surface crystals rather than overlapping with them; microbiological potency alongside chemical assay; and an apparent permeability coefficient alongside the release profile.

Carry the work into an animal model. Oral bioavailability against an intravenous reference is the endpoint that decides whether the approach works, and it is also the evidence that a patent claim would require.

If those three changes are made and the result is a low bioavailability, that is a definite and publishable answer which saves the next group the same work. If the result is a usable bioavailability from a bead made at room temperature without organic solvent, the clinical and economic consequences would be considerable.

NOTE ON SOURCES:

This review synthesises the published literature on biopolymer-based oral delivery of ceftriaxone sodium and on the component technologies the approach draws upon: multiparticulate design, alginate ionotropic gelation, polyelectrolyte complexation, enteric coating and intestinal permeation enhancement.

Numerical values for the reported ceftriaxone formulations, including entrapment efficiencies, particle sizes, plasma concentrations and bioavailability figures, are quoted as given by the cited authors and have not been independently verified. Two references are flagged in the reference list itself where the citation available to this review is a review or a methodological precedent rather than the primary report of the ceftriaxone work described; those should be traced to the primary source before being cited in a thesis or a filing.

Pharmacopoeial and regulatory statements should be confirmed against the current editions of the monographs and guidelines cited, which are revised periodically.

The critical appraisal at section 10 and the recommendations at section 12 are the view of this review, drawn from the published record, and are offered as a reading of where the field stands rather than as findings.

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