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TASTE MASKING OF AZITHROMYCIN USING ION-EXCHANGE RESINS FOR PAEDIATRIC SUSPENSIONS

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Abstract

Azithromycin is bitter, and that bitterness is a recognised obstacle to completing short antibiotic courses in young children. This review, which reports no new experimental data, examines how ion-exchange resins have been used to mask the taste of basic drugs and what that literature implies for azithromycin suspensions. It covers paediatric taste acceptability, the chemistry of weak and strong cation-exchange resins, the factors controlling drug loading and release, and the methods used to assess taste and stability. Resinates reliably reduce free drug in saliva and release it in gastric fluid, yet evidence specific to azithromycin is sparse, and taste assessment in children, bioavailability confirmation and long-term suspension stability remain the main gaps.

1. INTRODUCTION

Children do not swallow what tastes unpleasant. That simple observation has consequences for treatment, because short antibiotic courses depend on every dose being taken. Palatability is recognised as one of the main determinants of acceptance of a liquid medicine, alongside volume, viscosity and mouthfeel [1, 2]. Bitterness, which evolved as a warning against toxins, is especially strongly rejected by young children, and many active pharmaceutical ingredients trigger it [3, 4]. Formulators have long tried to deal with this by adding sweeteners and flavours, but these approaches often fall short when the drug is intensely bitter or is present at a high concentration in a small dose volume [5, 6]. Taste is therefore not a cosmetic matter, since a poorly accepted formulation can undermine the very therapy it

carries, and paediatric guidance reflects that by placing acceptability alongside safety and efficacy [7]. Sugar-heavy masking also sits uneasily with advice to limit sugar in children's medicines [6].

Azithromycin is a case in point. An azalide antibiotic related to the macrolides, it is given to children for respiratory, ear and some enteric infections, usually as a powder reconstituted into a suspension [8, 9]. Its long tissue half-life allows courses of three to five days or even a single dose, so adherence over a short period is the entire game [10, 11]. A child who spits out half of a single large dose does not receive an effective one. The bitterness of the drug therefore matters clinically, not only commercially, and has driven interest in physical taste-masking approaches that prevent drug dissolving in the mouth in the first place [12, 13]. Reconstituted azithromycin products are typically sweetened and flavoured, yet clinicians and carers still describe them as unpleasant, which suggests that conventional taste correction alone does not fully solve the problem [4].

Among physical approaches, ion-exchange resins have a long record. A basic drug can be bound to an insoluble polymeric acid so that it is held in a complex, called a resinate, until the complex meets the ion-rich environment of the stomach [14, 15]. This review draws on the published literature on taste masking with resins in general and on the limited work involving macrolides and azalides in particular, and it reports no experimental results of its own. The aim is to describe what is established, what is plausible but untested for azithromycin, and which questions an investigator would need to settle before relying on a resinate in a paediatric suspension [5, 16]. The discussion is organised around paediatric context, resin chemistry, loading and release, and assessment, followed by an honest account of what remains unknown.

A note on terminology helps. Taste masking and taste suppression are sometimes used interchangeably, but the first covers any approach that reduces perceived bitterness, including flavours and sweeteners, whereas the second suggests a physiological effect on taste receptors. Physical barrier methods, such as coating and complexation, work by limiting dissolved drug in saliva. Throughout, the term masking is used in the physical sense unless stated otherwise [12, 13]. Where a source uses a different convention, this review follows the original wording but explains the meaning in physical terms for clarity.

2. PAEDIATRIC TASTE AND AZITHROMYCIN

Children have strong taste preferences that differ from those of adults. Sweet tastes are accepted readily, while bitter and sour tastes are rejected more often, and genetic variation in bitter receptors adds individual differences to the picture [3, 4]. Studies of children's medicines show that flavour preference is only part of acceptability, and that the excipients chosen to address taste can themselves be a problem, for instance when a high sugar load, a strong preservative or a propylene glycol cosolvent is used [1, 6]. Regulatory guidance accordingly asks developers to demonstrate that a paediatric formulation is acceptable in the target age group, and expects justification of any excipients used for taste [7, 17]. These considerations carry over to a bitter antibiotic taken for only a few days, where reluctance on day one may be enough to derail a course [2, 4].

The physical chemistry of azithromycin explains much of its taste behaviour. It carries two basic amine functions, one in the desosamine sugar and one in the macrocyclic ring, so it exists mainly as a cation at the near-neutral pH of saliva [8, 18]. Solubility is therefore reasonably high in water at acidic and neutral pH, which means that a suspension of free drug releases enough dissolved molecules to taste bitter. The molecule is large, with a molecular weight a little under 750, and fairly lipophilic, which contributes to its extensive tissue penetration and long half-life but also affects how it diffuses within a resin matrix [8, 10]. In a suspension, a proportion of the dose is always in solution, so any masking approach has to cut the dissolved fraction substantially instead of merely hiding it behind sweetness [5, 6].

Absorption of azithromycin after oral dosing is incomplete, with bioavailability of the order of one third in adults, and food can alter the extent of absorption of some oral forms [10, 11]. This matters for taste masking because any technology that changes release in the stomach could, in principle, change how much of the dose is absorbed. Developmental changes in gastric pH, gastric emptying and transit time in infants add further variability [19, 20]. A resinate therefore has to be shown not only to mask taste but also to release the drug rapidly and completely in gastric conditions, and ideally to produce comparable exposure to the reference product [19, 21]. Transfers between formulations are therefore never trivial for a drug with a narrow absorption window in the gut, and the safest assumption is that exposure must be re-verified whenever the release mechanism changes [11].

Evidence on how bad azithromycin tastes comes mainly from clinical experience and from acceptability research on antibiotic suspensions as a class. Antibiotics are among the medicines children most often refuse, and the macrolides are commonly named as poor tasting [2, 4]. Reports of non-adherence because of taste are frequent in the general paediatric literature, but few studies attach numbers to a specific azithromycin product. A reviewer must therefore be cautious about quantifying the problem, even while accepting its direction [1, 4]. This lack of numerical data is itself a finding and points to an area where simple acceptability surveys could add value.

3. ION-EXCHANGE RESIN PRINCIPLES

Pharmaceutical ion-exchange resins are cross-linked polymers carrying fixed ionic groups, together with mobile counter-ions that can be exchanged for ions of the same charge in the surrounding solution [14, 15]. Cation-exchange resins have acidic groups and bind basic drugs. Two broad classes are used. Weak acid resins, typically a methacrylic acid and divinylbenzene copolymer with carboxylic groups, are ionised only at higher pH. Strong acid resins, usually sulfonated polystyrene cross-linked with divinylbenzene, are ionised across the whole physiological pH range [15, 22]. Commercial products in both classes are available in pharmaceutical grades, and they are generally regarded as safe because the polymer is not absorbed [15, 23]. The choice between the two classes shapes loading capacity, release rate and sensitivity to ions in the vehicle, which is why it is the first decision in any resinate project [14, 22].

The mechanism of taste masking follows from this chemistry. In the formulation, the basic drug is cationic and the resin is ionised, so the two associate strongly. In the mouth, saliva has a pH around 6 to 7 and only a modest ionic strength, so little drug is displaced before the suspension is swallowed [5, 14]. In the stomach, the acid concentration is large, and hydrogen ions together with sodium and potassium in gastric fluid displace the drug from the resin, which then dissolves and becomes available for absorption [15, 23]. Weak acid resins release more readily at gastric pH because the carboxylate groups are protonated, which removes the binding site [15, 22]. Because the exchange is driven by concentration, the same resinate behaves differently when diluted into a small volume of water than when swallowed with a large drink, a point that is easily missed [14, 23].

Selectivity of exchange is a further consideration. Resins bind competing cations with differing affinity, and divalent ions such as calcium and magnesium are held more tightly than monovalent ones. A drug with two cationic centres may in turn act as a divalent species at low pH and bind more strongly than a monobasic drug of similar size [14, 15]. This can improve masking, but it can also slow the release of the second charge in the stomach, where the competing ions are monovalent hydrogen, sodium and potassium. Whether azithromycin binds through one or both amine groups in practice has not been established in the sources reviewed, and it would be informative to know [8, 15, 22].

The idea of masking the taste of a macrolide with a polymer carrier is not new. Work from the 1970s showed that polycarboxylic acid resins adsorbed bitter drugs and gave taste coverage in chewable tablets [24]. Later, a polymer carrier system based on a carbomer

was described for macrolide antibiotics including erythromycin and clarithromycin, and reported substantial reduction in bitterness together with satisfactory release at gastric pH [16]. These studies are relevant to azithromycin because they involve large, basic, multi-functional molecules of similar type. They also illustrate that the principle works best when the carrier is matched to the drug's ionisation and size [16, 24]. The macrolide example is encouraging, though it concerned a different polymer type and different drugs, so it supports plausibility more than proof for azithromycin [16].

Published studies of resinates for other basic drugs add mechanistic detail. Higher cross-linking restricts swelling and slows diffusion in and out of the bead, which suits taste masking but may retard gastric release. Smaller particles shorten diffusion paths and speed exchange, though very fine particles can feel gritty in a suspension [22, 25]. Resin can also be combined with a coating or microencapsulation to modify release further, an approach used mostly for controlled-release rather than taste-masked products [26]. The balance between masking and release is the central design problem, and table 1 summarises how published approaches, including resin binding, address it, while fig. 1 shows the distribution of the approaches reviewed [5, 12, 16]. Even with careful design, residual bitterness can persist if a fraction of unbound drug remains on the surface of the particles, which is why washing the resinate after loading is a standard step [14, 23].

Resin is not the only way to hide bitterness, and comparisons with alternatives are instructive. Polymer coating with a pH-sensitive material, lipid-based coating, cyclodextrin inclusion and solid dispersion each reduce drug availability in saliva by a different route [5, 12, 13]. Resins have the advantage of simple, aqueous processing and no organic solvents, and they do not require heat. Their weakness is that the exchange is reversible, so any ionic excipient in the vehicle can displace some drug during storage [14, 23]. Which approach is best depends on the drug's properties, dose size and the intended dosage form [12, 13].

Table 1: Published taste-masking approaches relevant to bitter basic drugs and macrolide suspensions

Approach	Reported behaviour and comment	Ref.
Carboxylic acid resin weak cation exchanger	Binds basic drugs at near-neutral pH; releases readily at gastric pH as carboxyl groups protonate.	[15, 22]
Sulfonated polystyrene resin strong cation exchanger	Binds across the whole pH range; release depends on gastric ion concentration and cross-linking.	[14, 15]
Polycarboxylic acid adsorbate chewable tablets	Early demonstration that resin adsorbates reduce bitterness of basic drugs.	[5, 24]
Carbomer carrier system erythromycin, clarithromycin	Marked bitterness reduction for macrolides with satisfactory gastric release.	[12, 16]
pH-sensitive polymer coating enteric-type barrier	Limits drug dissolution in saliva; needs organic solvents or aqueous dispersions.	[5, 13]
Cyclodextrin inclusion complexation	Reduces free drug in solution; capacity limited for large molecules.	[12, 13]
Release in simulated saliva pH 6.8 medium	Screens for drug available in the mouth; compared with a bitterness threshold.	[21, 27]
Electronic tongue sensor array	Ranks formulations and correlates with panel bitterness data; blind to mouthfeel.	[28, 29]
Human sensory panel trained adults or children	Reference method; ethically and practically difficult for bitter antibiotics in children.	[4, 27]
Paediatric development guidance regulatory expectations	Requires acceptability and justified excipients in the target age group.	[7, 17]

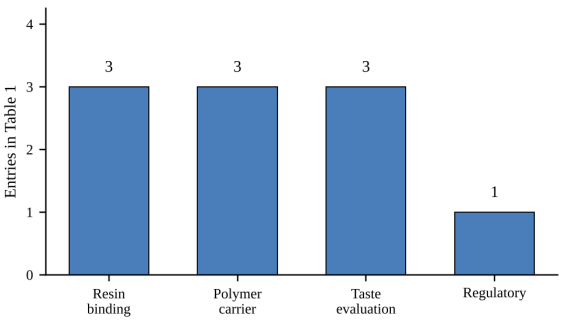


Fig. 1: Number of entries in table 1 by approach category

4. DRUG LOADING AND RELEASE

Drug loading is normally carried out by stirring the resin with a solution or suspension of the drug in water, sometimes with controlled pH, and then separating, washing and drying the complex. This is called the batch method. A column method, in which drug solution is passed through a bed of resin, is also described and can give higher loading but is less convenient to scale [14, 15]. The yield is expressed as drug loading efficiency, meaning the fraction of drug bound, and as the drug content of the dried resinate. The factors reported to influence loading include drug-to-resin ratio, pH, temperature, contact time, ionic strength and resin particle size [22, 23]. Washing removes unbound drug and counter-ions from the first stage, and the wash liquor should be assayed so that the mass balance can be closed and the true loading calculated [14, 23].

For azithromycin, the large size and two basic centres complicate matters. The loading pH must be low enough that the drug is protonated but high enough that the weak acid resin is ionised, which narrows the practical window. Diffusion of a molecule with a molecular weight near 750 into a cross-linked bead is slower than that of a small amine, so longer contact times are expected, and the final stoichiometry may be lower than the theoretical capacity of the resin [8, 22, 25]. Studies on other bulky bases suggest that resins with moderate cross-linking and small particle size give the best compromise between loading and exchange kinetics [25, 26]. Reports on other macrolides and large amines suggest that the loading pH should be explored systematically across a few units instead of fixed at an arbitrary value [23, 26].

Release is assessed in vitro by incubating the resinate in media that mimic saliva and the stomach. Simulated saliva at pH 6.8 should release as little drug as possible within the oral residence time, which is taken as roughly a minute or less, while 0.1 M hydrochloric acid should release most of the drug within the first 30 minutes [21, 27]. These conditions are a convenient screen, but they are not physiological: stomach contents are buffered by food and gastric emptying is variable, particularly in infants [19, 21]. Release tests are therefore best viewed as a way of ranking formulations and detecting problems, not as a predictor of absorption [20, 21]. Each measurement should be repeated on several batches, since resin lots vary in moisture content and in the number of functional groups per gram, and this variability can easily exceed the difference between two formulations [15, 21].

Once a resinate is placed in a liquid vehicle, equilibrium is reset. Drug can leach from the resin into the continuous phase over time, depending on the vehicle's pH and its content of ions such as sodium, potassium and calcium, and on the volume of liquid [14, 23]. For this reason, reconstituted suspensions of resinates are often formulated with non-ionic sweeteners and viscosity builders, kept at a pH that favours binding, and given a limited in-use shelf life. Powders for reconstitution have an advantage here, because the resinate stays dry until the pharmacist or carer adds water, which postpones the exchange [23, 30]. Stability of the suspension vehicle itself is influenced by preservatives, because some preservatives are cationic and would compete with the drug for resin sites [14, 30].

Excipient choice matters for another reason. Sweeteners, flavours and suspending agents can each interact with the resinate or influence perceived taste, and some of the best-known excipients in paediatric liquids carry safety restrictions in young children [6, 30]. A pragmatic strategy is to keep the excipient list short and to justify each addition. Resin loading reduces the sweetener demand, since less bitterness has to be hidden, and this is itself an advantage for products where sugar content is a concern [1, 6]. Short, well-justified excipient lists also ease regulatory review, since each ingredient needs a clear role.

5. TASTE ASSESSMENT AND STABILITY

Assessing taste is hard, and it is hardest in children. Human sensory panels remain the reference, but testing a bitter antibiotic on children raises ethical and practical difficulties, and adult panels may not predict child responses well [4, 27]. In practice, studies use trained adult panels, sometimes

with visual analogue or hedonic scales, or rely on in vitro surrogates [27, 28]. Free drug concentration in simulated saliva is the simplest surrogate, since it can be compared against the bitterness threshold of the drug. The lower the concentration of dissolved drug in the oral phase, the less bitter the product should be, provided the threshold has been properly established [5, 27]. Whichever tool is chosen, the same standard should apply to each formulation, including the reference product and a blank, so that results can be interpreted against something meaningful [4, 28].

Electronic tongue systems offer a second route. A sensor array responds to dissolved substances in a pattern that can be correlated with human bitterness ratings, which allows formulations to be ranked without human tasting [28, 29]. Published comparisons for bitter drugs, including taste-masked formulations, show good correlation with panel data when the system is calibrated against reference compounds [28, 29]. They cannot capture mouthfeel, grittiness or aftertaste, though, and calibration against a single bitter reference may not transfer to a different drug. Used alongside a small panel, they give a useful picture at modest cost [27, 28]. Practical advice from the e-tongue literature is to rank formulations rather than to assign absolute bitterness scores, and to confirm key findings with a small human panel [28, 29].

Physical stability of a resinate suspension depends on particle size, density and viscosity. Dense resin particles sediment quickly, which can cause dose variation unless the product is shaken well, and small particles may be needed for pourability and mouthfeel [22, 30]. Chemical stability of azithromycin in the bound state is less well documented than that of the free drug, and storage studies under defined long-term and accelerated conditions are needed to show that assay, degradation products and drug-resin binding stay within limits over shelf life [31]. In-use stability after reconstitution is a separate requirement and is especially relevant to resinates because of the leaching described above [23, 31]. Appearance after storage, redispersibility on shaking and the absence of caking are further indicators that should be recorded, since a product that cannot be dispensed uniformly is of no use however it tastes [30, 31].

A final point concerns equivalence. If a resinate replaces free drug in an existing product, regulators will usually expect comparative bioavailability data, since the change could in principle alter exposure [7, 19]. In vitro dissolution can support a waiver in some circumstances, but the discriminating power of the method has to be shown. For azithromycin, whose absorption is incomplete and food-sensitive, a conservative developer would expect to demonstrate similar release profiles and, where required, a bioequivalence study [11, 21]. A well-designed bridging study of this kind often costs far less than a failed product launch.

6. LIMITATIONS AND FUTURE DIRECTIONS

The evidence base has clear limits. Most resin taste-masking studies concern small, mono-basic drugs, and extrapolation to a dibasic macrocycle of nearly 750 daltons is a leap that has not been fully tested [8, 16]. Taste assessments are mainly in adults or in vitro, with few published comparisons in children. Long-term stability data on resinate suspensions are sparse, and the potential for ionic excipients to displace drug is often discussed but rarely quantified [14, 23]. Finally, much relevant work sits in patents and industrial reports that are not available for critical reading [13]. These limitations argue for modest claims and for transparent reporting of negative as well as positive results. Reproducibility across resin lots, a known source of variation, is similarly under-examined for this drug [15, 21].

Several research questions follow. Systematic comparison of weak and strong acid resins for azithromycin, with attention to loading, release at gastric pH and leaching on storage, would fill the most obvious gap [15, 22, 25]. Paired in vitro and child-acceptability studies would show how well surrogates predict real behaviour [4, 28]. Studies that report bioavailability against the established product would complete the picture [11, 19]. Meanwhile, the existing literature supports a

cautious view: resinates are a credible, simple route to a more palatable azithromycin suspension, but they are not yet proven for this particular drug [5, 12, 16]. Collaboration between formulation scientists, clinicians and taste researchers would speed progress considerably.

7. CONCLUSION

Ion-exchange resins offer a well-understood way of keeping a bitter basic drug out of solution in the mouth and handing it back in the stomach, and the published record shows this working for several drugs, including large macrolides carried on polycarboxylic polymers [15, 16, 24]. For azithromycin, the principle is chemically reasonable, but direct evidence in the literature is thin. That conclusion rests on analogy rather than direct azithromycin data, and should be stated as such wherever the approach is promoted.

Anyone developing a paediatric suspension on this basis would need to settle loading conditions for a dibasic molecule, confirm release at gastric pH, show stability on storage and after reconstitution, and test taste with methods that reflect how children actually respond [4, 27, 31]. Until such work is published, resinates should be seen as a promising option and not a settled solution to the bitterness of azithromycin, particularly for children who must take a short course reliably [2, 19]. Honest reporting of both successes and failures would help the field move faster.

8. ABBREVIATIONS

ICH-International Council for Harmonisation, EMA-European Medicines Agency, WHO-World Health Organization, USP-United States Pharmacopeia, pKa-Negative logarithm of the acid dissociation constant, HCl-Hydrochloric acid, API-Active pharmaceutical ingredient, pH-Negative logarithm of hydrogen ion activity

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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