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Formulation Development and Evaluation of Cost-Effective Sucralfate Oral Suspension: A Comprehensive Review

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Abstract- ***Sucralfate, a basic aluminium salt of sucrose octasulfate, remains one of the most widely prescribed locally acting cytoprotective agents for peptic ulcer disease, gastro-oesophageal reflux, and radiation- or chemotherapy-induced oral and gastrointestinal mucositis. Because the drug is practically insoluble in water and is required in gram-scale doses, an oral suspension is the pharmaceutical form of choice for patients who cannot swallow tablets, including paediatric, geriatric, post-surgical, and enterally fed patients. This review synthesises current literature on the chemistry, mechanism of action, and clinical indications of sucralfate; the formulation science underlying suspension dosage forms, including the selection of suspending agents, sweeteners, preservatives and buffers; the application of Quality-by-Design (QbD) methodology to rationally engineer a robust suspension; and, most importantly, the strategies available to formulation scientists for developing a sucralfate suspension that is cost-effective without compromising quality, safety, or efficacy. Evaluation parameters recommended for such a suspension, spanning physical, chemical, microbiological, and stability testing consistent with ICH and pharmacopoeial expectations, are discussed and summarised in tabular form. The review concludes that a deliberately planned, low-cost excipient strategy, anchored in QbD principles and rigorous evaluation, can deliver an affordable, stable, and patient-acceptable sucralfate suspension suitable for resource-constrained healthcare settings.***

Keywords: Sucralfate; oral suspension; cost-effective formulation; suspending agents; Quality by Design; peptic ulcer; oral mucositis; stability evaluation

I. INTRODUCTION

Peptic ulcer disease and its related acid-peptic disorders continue to represent one of the most common gastrointestinal complaints encountered in both primary care and hospital practice, and the search for agents that protect rather than merely neutralise or suppress acid has shaped an important branch of gastroenterological pharmacotherapy. Sucralfate was developed as a locally acting, cytoprotective alternative to systemic antisecretory agents, and unlike histamine H2-receptor antagonists or proton pump inhibitors, it exerts its therapeutic effect predominantly through adherence to the ulcer bed rather than through suppression of gastric acid secretion. [1,2,3]

Because sucralfate is administered in comparatively large unit doses of up to one gram, and because a proportion of patients, particularly children, elderly individuals, post-operative patients, and those with dysphagia or nasogastric or percutaneous feeding tubes, are unable to swallow the conventional 1 g tablet, a palatable and easily measurable oral suspension has long been recognised as an essential complementary dosage form. Suspension dosage forms in general offer the advantage of flexible, titratable dosing, ease of swallowing, and the ability to mask the unpleasant taste or texture of an insoluble active pharmaceutical ingredient (API), which makes them particularly suited to a bulky, poorly soluble drug such as sucralfate. [4,5]

A recurring challenge in health systems of low- and middle-income countries, including India, is that patients frequently discontinue or under-dose chronic and semi-chronic therapies because of cost, and antiulcer suspensions compounded with imported specialty excipients or manufactured through capital-intensive processes can be priced beyond the reach of

many patients. The present review was therefore undertaken with the specific objective of consolidating the scientific literature on sucralfate suspension formulation and evaluation while placing particular emphasis on rational, evidence-based strategies for cost containment during formulation development, so that the resulting product remains both pharmaceutically sound and economically accessible. [6,7,8]

This review is organised to first summarise the chemistry, mechanism of action, pharmacokinetics, and clinical uses of sucralfate; to then examine the pharmaceutical rationale for the suspension dosage form and the excipient categories required to build one; to describe how Quality-by-Design and related process-optimisation tools can be harnessed specifically to reduce development and manufacturing cost; and finally to compile, in tabular and narrative form, the physical, chemical, microbiological, and stability evaluation parameters that such a suspension must satisfy before it can be considered fit for patient use. [9,10]

II. CHEMISTRY, MECHANISM OF ACTION, AND PHARMACOKINETICS OF SUCRALFATE

2.1 Chemical Structure and Physicochemical Properties

Sucralfate is chemically described as a basic aluminium salt in which each of the eight hydroxyl groups of the disaccharide sucrose has been esterified with a sulfate group to yield sucrose octasulfate, with each sulfate anion in turn forming a salt bridge with an aluminium hydroxide moiety; hydrogen bonding between adjacent hydroxyl groups and water molecules further links these units into a high molecular weight polymeric aggregate with an average molecular mass in the region of 2000 daltons. The compound is obtained as a white, amorphous powder that is practically insoluble in water and in alcohol but dissolves in strongly acidic or strongly alkaline media, a property that is central to both its mechanism of action and to the technical challenges encountered when it is formulated as an aqueous suspension. [11,12,13]

Because the free drug is essentially insoluble across the physiological pH range encountered in an aqueous vehicle, sucralfate behaves, from a pharmaceutics perspective, as a coarse, dense, inorganic-organic hybrid solid that must be uniformly and stably dispersed, rather than dissolved, within the suspension vehicle. Its high true density and tendency to agglomerate on standing make particle size control and suspending agent selection especially important, a point elaborated further in Section 4. Table 1 summarises the key physicochemical attributes of sucralfate relevant to suspension formulation. [13,14]

Table 1. Key Physicochemical Properties of Sucralfate Relevant to Suspension Formulation

Property	Characteristic	Formulation Relevance
Chemical nature	Basic aluminium salt of sucrose octasulfate (sucrose polysulfate-aluminium complex)	High molecular weight polymeric aggregate influences particle behaviour in suspension
Average molecular weight	~2086 daltons	Contributes to high density and settling tendency of dispersed particles
Appearance	White, amorphous powder	Requires colourant/opacifier consideration for uniform product appearance
Aqueous solubility	Practically insoluble in water and alcohol	Formulated as a true suspension, not a solution; particle size control critical
Solubility in extremes of pH	Soluble in strong acids and strong alkalis	Underlies acid-triggered gel formation at the ulcer site; vehicle pH can be optimised independent of API solubility
Typical dose	0.5-1 g per administration (1 g/10 mL or 500 mg/5 mL)	High drug loading demands efficient, low-viscosity-at-high-shear suspending system

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Property	Characteristic	Formulation Relevance
Systemic absorption	Minimal; acts locally in the GI lumen	Removes need for conventional bioavailability-driven formulation constraints
Mechanism trigger	Acid-catalysed dissociation and polymerisation in the stomach	Vehicle need not replicate gastric acidity; buffering chosen for stability, not activation

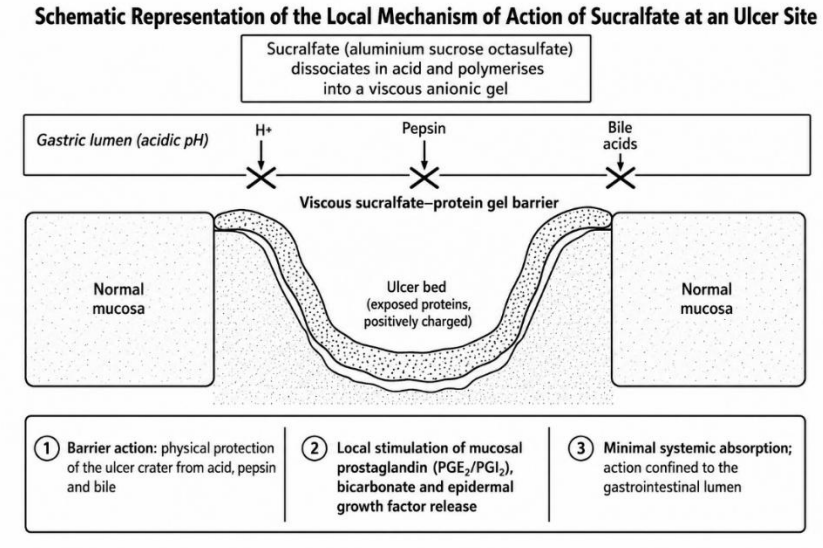
2.2 Mechanism of Action

The originally proposed mechanism of action centred on two complementary properties: an ability to antagonise pepsin activity and a capacity to adhere selectively and preferentially to damaged, rather than intact, gastric or duodenal mucosa. On exposure to the acidic gastric environment, sucralfate dissociates into aluminium hydroxide and sucrose octasulfate; the latter spontaneously polymerises into a highly viscous, negatively charged gel that forms polyvalent electrostatic bridges with the positively charged proteins exposed at the base of an ulcer or erosion, thereby generating a discrete, ulcer-adherent barrier that can persist at the lesion site for several hours. [2,3,15]

This adherent barrier is now understood to protect the mucosa through several complementary actions rather than through simple mechanical occlusion alone: it limits back-diffusion of hydrogen ions, inactivates luminal pepsin, adsorbs bile acids that would otherwise be injurious to the gastric mucosa, and, importantly, stimulates local production of prostaglandins E2 and I2, bicarbonate secretion, and epidermal growth factor release, all of which favour mucosal repair and regeneration. Imaging mass spectrometry studies of the related molecule sucrose octasulfate have visualised a thin, homogeneous protective film on the oesophageal mucosal surface, lending mechanistic support to its efficacy in reflux oesophagitis as well as peptic ulcer disease. [15,16,17]

A further consequence of this mechanism is that sucralfate exerts negligible systemic pharmacological activity: because its action depends upon direct contact with the mucosal surface, the majority of an administered dose remains within the gastrointestinal lumen and is eliminated in the faeces, with only trace amounts of the sulfated disaccharide absorbed and subsequently excreted in the urine. Figure 1 depicts this local barrier-forming mechanism schematically. [13,18]

Figure 1. Schematic representation of the local mechanism of action of sucralfate at an ulcer site.



2.3 Pharmacokinetic Considerations

Because of its minimal systemic absorption, sucralfate has essentially no conventional pharmacokinetic profile in the sense of a measurable plasma concentration-time curve; nonetheless, its local pharmacokinetics within the gastrointestinal lumen, namely the rate at which it forms the viscous gel on contact with acid, its residence time at the ulcer surface, and its subsequent transit and elimination, are pharmaceutically important because they are directly influenced by the physical form (tablet versus suspension), particle size, and rheological behaviour of the dosage form administered. Suspension formulations, by presenting the drug as finely divided particles already dispersed in an aqueous vehicle, can achieve more rapid and uniform contact with the gastric mucosa than a disintegrating tablet, which must first undergo wetting and break-up before the same gel-forming process can begin. [13,19]

Clinically, this has translated into recommendations that, when used for topical applications such as an oral rinse in mucositis, sucralfate should be retained in the mouth for a period before swallowing or expectoration to maximise local contact time, while for its systemic gastrointestinal indications the suspension is typically dosed on an empty stomach, separated in time from other orally administered medicines because its aluminium content and adsorptive properties can reduce the bioavailability of co-administered drugs such as fluoroquinolones, tetracyclines, phenytoin, digoxin, and warfarin. [13,20]

III. CLINICAL APPLICATIONS OF SUCRALFATE SUSPENSION

3.1 Peptic Ulcer Disease and Gastro-Oesophageal Disorders

Sucralfate suspension has been demonstrated in multicentre, double-blind, placebo-controlled trials to be superior to placebo for short-term healing of active duodenal ulcer at a dosage regimen of one gram administered four times daily, and healing rates with sucralfate have historically been reported in the range of sixty to ninety percent at four to six weeks for duodenal ulcer and up to ninety percent at twelve weeks for gastric ulcer, broadly comparable to those achieved with H2-receptor antagonists such as cimetidine and ranitidine. Maintenance therapy with sucralfate has also been associated with comparably low relapse rates relative to H2-receptor antagonists, although the labelled indication for the suspension itself has generally been restricted to short-term, up to eight-week, treatment of active duodenal ulcer, with formal bioequivalence between the suspension and tablet formulations not established in regulatory submissions. [21,22,23]

Beyond frank ulceration, sucralfate suspension and its parent compound sucrose octasulfate have been studied for their protective action against reflux oesophagitis, where the same viscous, mucosa-adherent gel is believed to form a thin protective film over the inflamed oesophageal epithelium, reducing further acid-mediated injury even though sucralfate does not itself alter gastric acid secretion or pH. [16,17]

3.2 Oral and Gastrointestinal Mucositis in Oncology Patients

A substantial body of clinical research has evaluated sucralfate suspension, most often used as an oral rinse that is swished and either expectorated or swallowed, for the prevention and treatment of oral mucositis induced by head and neck radiotherapy or by cytotoxic chemotherapy. Early randomised trials produced mixed findings: some placebo-controlled studies found no statistically significant reduction in the incidence or severity of mucositis with prophylactic sucralfate rinsing, although a reduction in early treatment-related oral pain was noted in several of these trials, whereas other studies reported clinically meaningful improvements in pain scores and reduced colonisation with pathogenic organisms among children receiving chemotherapy for acute leukaemia. [24,25,26]

Subsequent work explored whether reducing sucralfate particle size to a micronised form (below approximately twenty-five micrometres) could improve the uniformity of mucosal coating achieved by the mouthwash and thereby its clinical benefit, while randomised comparisons against composite regimens such as diphenhydramine-dexamethasone-nystatin “magic mouthwash” combined with sucralfate, benzydamine hydrochloride, and normal

saline rinses have continued to refine the evidence base, with meta-analyses of the mucositis prevention literature generally concluding that the benefit of sucralfate in this setting is inconsistent across trials and populations. [27,28,29]

More recent randomised evaluation of sucralfate suspension as a post-surgical oral rinse for secondary-healing intraoral surgical wounds reported a statistically significant reduction in postoperative pain scores relative to normal saline rinsing, together with an acceptable safety profile, reinforcing a continuing clinical role for the suspension formulation as a topical, locally acting agent independent of its systemic antiulcer indication. Sucralfate suspension has additionally been evaluated as a rectal preparation for the prevention of acute radiation proctitis and has been compared with chlorhexidine mouthwash in recurrent aphthous stomatitis, underscoring the versatility that a well-formulated, low-viscosity oral suspension confers across several distinct anatomical and clinical applications. [30,31,32]

Table 2 summarises representative clinical studies of sucralfate suspension across these indications, illustrating the diversity of dosing regimens, patient populations, and outcome measures reported in the literature and reinforcing the pharmaceutical requirement for a suspension that is stable, accurately dosable, and palatable across a broad range of clinical settings, from paediatric oncology wards to adult surgical recovery units. [24,30,31]

Table 2. Representative Clinical Studies of Sucralfate Oral Suspension Across Therapeutic Indications

Indication / Setting	Study Design (Representative)	Dosage Regimen	Key Reported Outcome
Active duodenal ulcer	Multicentre, double-blind, placebo-controlled trial	1 g (10 mL) four times daily, up to 8 weeks	Suspension superior to placebo in ulcer healing
Radiation-induced oral mucositis (head & neck cancer)	Double-blind, placebo-controlled randomised trial	Sucralfate mouth rinse, multiple times daily during radiotherapy	No statistically significant reduction in mucositis incidence; reduced early oral pain reported
Radiation-induced oral mucositis	Randomised trial, micronised vs standard suspension mouthwash	Micronised (<25 micron) sucralfate mouthwash vs salt & soda rinse	Investigated whether micronisation improves mucosal coating and clinical benefit
Chemotherapy-induced mucositis (paediatric leukaemia)	Double-blind randomised trial	Sucralfate suspension every 6 hours during induction chemotherapy	Reduced colonisation with potentially pathogenic microorganisms vs placebo
Recurrent aphthous stomatitis	Randomised comparative trial	Sucralfate suspension oral rinse vs chlorhexidine	Comparable efficacy in pain relief and healing time between groups
Post-surgical intraoral wounds	Randomised controlled trial	Sucralfate suspension (1 g/5 mL) oral rinse every 6 hours for 14 days	Significant reduction in postoperative pain vs normal saline rinse
Acute radiation proctitis	Phase III double-blind randomised trial	Rectal sucralfate suspension	Evaluated for prevention of acute radiation-induced proctitis

IV. RATIONALE FOR THE ORAL SUSPENSION DOSAGE FORM

4.1 Advantages of Suspensions for a Poorly Soluble, High-Dose Drug

Pharmaceutical suspensions are classified as heterogeneous, thermodynamically unstable, two-phase dispersed systems in which finely divided solid drug particles, typically greater than approximately one micrometre in diameter, are distributed throughout a liquid or semisolid continuous phase with the assistance of a suspending agent; they are the dosage form of choice whenever the API is poorly soluble in an acceptable vehicle, is required in a dose too large to be conveniently delivered as a solution, or must be

presented to patients unable to swallow solid dosage forms. For sucralfate specifically, which is both practically insoluble in water and dosed at up to one gram per administration, the suspension format allows the entire dose to be delivered in a measured, swallowable volume without requiring the drug to first dissolve, a particular advantage given that dissolution of sucralfate itself is neither expected nor pharmacologically necessary for its local mechanism of action. [4,33,34]

Suspensions additionally allow the unpleasant chalky texture and mildly astringent taste characteristic of aluminium-containing compounds to be masked with sweeteners and flavourants, provide resistance to the chemical degradation that can affect a drug in true solution, and, because doses can be adjusted by simply varying the administered volume, are particularly well suited to paediatric and geriatric patients and to those requiring administration through enteral feeding tubes. [5,35]

4.2 Patient Populations Particularly Reliant on the Suspension Form

Children represent perhaps the most formulation-sensitive population for any oral liquid, since palatability is repeatedly identified in the paediatric formulation literature as the single greatest barrier to treatment completion, with a majority of prescribing paediatricians reporting that unpleasant taste undermines adherence more than any other formulation attribute; the same considerations of swallowability and taste acceptance extend to elderly patients with dysphagia, to post-operative patients recovering from oral or gastrointestinal surgery, and to critically ill patients receiving medication through nasogastric or gastrostomy tubes, for whom a well-flocculated, easily resuspended, low-viscosity suspension that will not obstruct a feeding tube is essential. [36,37,38]

The clinical mucositis literature reviewed in Section 3.2 further illustrates that sucralfate suspension is frequently used topically as a mouth rinse rather than swallowed, a mode of administration that places additional demands on organoleptic acceptability, since the product must remain in contact with an already painful oral mucosa for a clinically meaningful period, reinforcing the pharmaceutical importance of taste-masking and mouthfeel optimisation discussed in Section 5.3. [24,39]

V. FORMULATION DEVELOPMENT CONSIDERATIONS

5.1 Preformulation Studies and Drug-Excipient Compatibility

Systematic formulation development begins with preformulation characterisation of the API, encompassing organoleptic evaluation, particle size and morphology assessment, solubility profiling across the physiological pH range, and determination of any polymorphic or hydration variability, followed by compatibility screening between the drug and each candidate excipient, typically performed using Fourier-transform infrared spectroscopy and differential scanning calorimetry to detect unexpected shifts in characteristic absorption bands or thermal transitions that would indicate a chemical interaction. Because sucralfate is a highly charged, aluminium-containing polyanion, particular attention must be paid to potential interactions with cationic or multivalent excipients, and with cellulose ether-type suspending agents that have in other systems shown incompatibility with certain drugs, since such interactions could compromise either the physical stability of the suspension or the local bioadhesive mechanism upon which the drug depends. [40,41,42]

A recently published Quality-by-Design study using sucralfate explicitly as the model drug for an anti-ulcer, gastroprotective oral suspension performed thermal and infrared spectroscopic compatibility testing between the API and each excipient during the preformulation phase, and used the resulting data, together with an Ishikawa fishbone risk assessment and a full factorial design of experiments, to identify the critical material attributes and critical process parameters that most strongly influenced the suspension's viscosity, resuspendability, pH, and density; the robustness of the resulting formulation was confirmed by physicochemical testing after one month under super-accelerated stress conditions. This work provides one of the most directly relevant templates in the published literature for the type of systematic, risk-based development programme recommended in the present review. [43]

5.2 Selection of Suspending Agents and Rheology Modifiers

The suspending agent is arguably the single most influential excipient class in determining both the physical stability and the manufacturing cost of an oral suspension, since it must impart sufficient viscosity and yield value at rest to retard sedimentation of the dispersed drug particles while remaining sufficiently shear-thinning, that is, pseudoplastic, to pour easily from the bottle and to be swallowed comfortably. Commonly used suspending agents documented across the pharmaceutical suspension literature include semisynthetic cellulose derivatives such as methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and microcrystalline cellulose, natural gums and mucilages such as xanthan gum, acacia, tragacanth, guar gum, and pectin, and inorganic clays such as bentonite and magnesium aluminium silicate, each offering a distinct combination of viscosity-building efficiency, flow behaviour, compatibility, and, critically for the purposes of this review, unit cost. [34,44,45]

Several comparative studies of suspending agents provide a useful evidence base for excipient selection on cost as well as performance grounds: xanthan gum has repeatedly been shown to impart higher apparent viscosity and superior sedimentation volume relative to comparator gums such as sodium carboxymethylcellulose across a range of model suspensions, while a variety of inexpensive, locally available plant mucilages, including Aloe elegans mucilage and Grewia ferruginea mucilage, have been evaluated as lower-cost natural alternatives to xanthan gum and shown to achieve acceptable, if somewhat lower, sedimentation volume, viscosity, and redispersibility performance at equivalent concentrations. Such natural gum substitution represents one of the most direct and well-documented cost-reduction levers available to a formulator working in resource-limited settings, provided that batch-to-batch variability in the natural material can be adequately controlled through appropriate incoming-material specifications. [46,47,48,49]

Because pharmaceutical suspensions are, by definition, thermodynamically unstable, formulators must additionally decide whether to design a controlled flocculated system, in which particles are permitted to associate loosely into porous, rapidly and completely resuspendable flocs at the cost of a higher, but still acceptable, sediment volume, or a deflocculated system, in which individual particles settle more slowly but ultimately form a denser, harder-to-redisperse cake; the majority of modern pharmaceutical suspensions, including antiulcer suspensions such as sucralfate, are deliberately formulated as flocculated systems using a combination of an appropriately charged suspending agent and, where required, a flocculating electrolyte, precisely to avoid the caking that would otherwise compromise dose uniformity on redispersion. [34,50]

5.3 Sweeteners, Flavourants, and Taste-Masking Strategy

Given the astringent, chalky organoleptic character of aluminium-containing suspensions and the reliance of sucralfate suspension on paediatric, geriatric, and oral-mucositis patient populations for whom palatability is a primary determinant of adherence, taste-masking strategy is a central rather than incidental element of formulation design. Approaches documented in the pediatric and general oral-liquid formulation literature range from the straightforward addition of intense sweeteners such as sucralose, aspartame, or sodium saccharin, often in combination with a small quantity of sodium chloride to blunt residual bitterness, through to more elaborate techniques including cyclodextrin inclusion complexation, ion-exchange resin adsorption, polymer coating of drug particles, and lipid-based spray congealing, the more complex of which add cost and manufacturing complexity that must be weighed against the marginal palatability benefit achieved. [51,52,53,54]

For a cost-sensitive suspension such as sucralfate, a pragmatic taste-masking strategy generally favours the simplest effective combination, most often a blend of an inexpensive bulk sweetener such as sorbitol or sucrose together with a small proportion of an intense sweetener and a compatible flavouring agent, since sucralfate itself does not require complex particle-coating taste-masking technology given that its bitterness arises chiefly from the aluminium salt rather than from a strongly bitter parent molecule. Regulatory and paediatric-safety literature also cautions that excipients selected purely for

palatability, including certain parabens and high concentrations of sugar alcohols, must be assessed for age-appropriate safety, since methylparaben has been associated with hypersensitivity reactions and excessive sugar content raises concerns regarding dental caries in long-term paediatric use. [52,55,56]

5.4 Preservatives, Buffering Agents, and Antimicrobial Protection

Because an aqueous suspension provides a hospitable environment for microbial proliferation over its intended shelf life and in-use period, an effective antimicrobial preservative system is essential; commonly employed preservatives for oral suspensions include methylparaben and propylparaben, often used in combination to broaden the antimicrobial spectrum, sodium benzoate, and benzyl alcohol, with the specific choice governed by compatibility with the suspending agent, by the target patient population, given the paediatric safety concerns noted above, and by unit cost, since parabens remain among the least expensive pharmacopoeial-grade preservatives available. [45,56,57]

Buffering agents, typically selected from citrate, acetate, or phosphate systems, are incorporated as required to maintain the suspension within a target pH range that optimises both the physical stability of the suspending agent, since many cellulose ethers and gums exhibit pH-dependent viscosity, and the chemical stability of the API, while also influencing the palatability and the local irritancy of the formulation; because sucralfate itself does not depend upon a specific vehicle pH for its ultimate mechanism of action, which is triggered by gastric acid after administration, the formulator retains considerable latitude to select a vehicle pH that favours suspending-agent performance and cost over any requirement dictated by the API. [45,58]

5.5 Quality-by-Design Approach to Suspension Development

The Quality-by-Design paradigm, first articulated in the ICH Q8, Q9, and Q10 quality guidelines, reframes pharmaceutical development away from empirical trial-and-error and quality-by-testing toward a systematic, risk-based process that begins with an explicitly defined Quality Target Product Profile and proceeds through identification of Critical Quality Attributes, risk assessment linking Critical Material Attributes and Critical Process Parameters to those attributes, structured Design of Experiments, and a documented control strategy; this approach has been applied across diverse dosage forms, including tablets, dispersible tablets, mucoadhesive systems, and nanoparticulate delivery systems, and, as noted in Section 5.1, has been directly demonstrated for an anti-ulcer oral suspension using sucralfate as the model drug. [43,59,60,61]

From a cost-effectiveness standpoint, the principal value of QbD lies in its capacity to identify, early and systematically, which material attributes and process parameters genuinely drive product quality, allowing the formulator to standardise on the least expensive excipient grade, source, or process condition that still satisfies the defined Critical Quality Attributes, rather than defaulting to premium specialty excipients or unnecessarily tight process controls out of caution. Design of Experiments methodology in particular allows several candidate low-cost suspending agents, preservative levels, or buffer systems to be screened simultaneously in a structured factorial or response-surface design, reducing both the number of experimental batches required and the risk of costly late-stage reformulation. Figure 2 illustrates a recommended QbD workflow adapted specifically for the development of a cost-effective sucralfate suspension. [43,62]

Complementary risk-assessment tools such as the Ishikawa, or fishbone, diagram and Failure Mode and Effects Analysis are typically used at the risk-assessment stage to visually map the many potential causes, spanning raw material variability, equipment, environment, and process steps, that could give rise to an out-of-specification suspension, allowing development effort and analytical resource to be concentrated where the probability and severity of failure are greatest rather than spread evenly, and therefore expensively, across every conceivable variable. [43,63]

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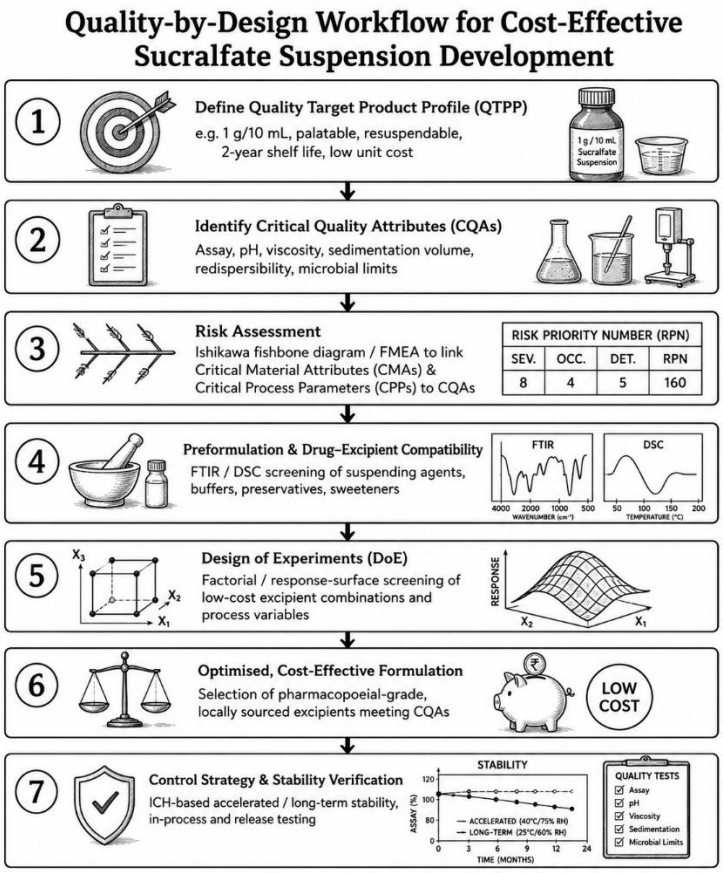
Figure 2. Recommended Quality-by-Design workflow for cost-effective sucralfate suspension development.



VI. STRATEGIES FOR COST-EFFECTIVE FORMULATION DEVELOPMENT

6.1 Excipient Sourcing and Substitution

Because the active pharmaceutical ingredient typically accounts for roughly half of total manufacturing cost in a small-molecule oral dosage form, with excipients and formulation materials contributing a further meaningful share, formulation-level cost control is most effectively achieved by favouring pharmacopoeial-grade, commodity excipients that are readily available from multiple qualified suppliers over patented, single-source specialty materials, since switching from a proprietary excipient to a functionally equivalent pharmacopoeial-grade alternative has been estimated to reduce per-unit material cost meaningfully at production scale. For a sucralfate suspension, this principle favours, where technically justified, the substitution of premium synthetic suspending agents with well-characterised, lower-cost natural gums or mucilages of the type evaluated in the comparative suspending-agent literature discussed in Section 5.2, provided that appropriate specifications and batch-release testing are established to manage the inherent variability of plant-derived materials. [46,47,64,65]

Excipient selection strategy should also anticipate downstream manufacturing efficiency, since an excipient that improves powder flow, wetting, or ease of dispersion can reduce processing time and equipment downtime, thereby lowering the labour and overhead component of unit cost even when the excipient itself carries no price premium; conversely, an inappropriately selected suspending agent that requires prolonged high-shear mixing to achieve adequate dispersion, or that is prone to lump formation, will increase manufacturing cost regardless of its raw material price. [65,66]

6.2 Process and Formulation Optimisation for Cost Reduction

Beyond excipient choice, process-level decisions such as order of addition, mixing speed and duration, and the use of simple, widely available manufacturing equipment rather than specialised homogenisers or micronisation equipment can materially affect cost of goods; where micronisation of sucralfate particles is not clinically required, as appears to be the case for its systemic antiulcer indication in contrast to its use as a topical mucositis rinse where finer particles have been associated with improved mucosal coating, avoiding an unnecessary particle-size-reduction step represents a straightforward cost saving without loss of therapeutic performance for the intended indication. [27,67]

A further cost-effective strategy is to design the formulation and manufacturing process to be compatible with standard batch equipment already available within a manufacturing facility, thereby avoiding capital expenditure on specialised process technology, and to select a preservative and buffer system that is compatible with ambient-temperature, rather than cold-chain, storage and distribution, since a suspension requiring refrigerated transport and storage would incur substantially higher logistics costs that are particularly burdensome in tropical, resource-limited settings such as much of India. [65,68]

Generic product development literature more broadly emphasises that bioequivalence testing, where required, represents one of the highest-cost and highest-risk steps in bringing a generic formulation to market, and that the most reliable strategy for a generic product intended to match an existing reference formulation is comprehensive characterisation of the innovator product, including identification of its critical, performance-defining excipients, so that development effort and analytical resource are directed toward matching those specific attributes rather than unnecessarily replicating the entire innovator formulation in full, which would raise both development cost and, potentially, intellectual property risk. [64,69]

6.3 A Consolidated Cost-Effective Formulation Strategy for Sucralfate Suspension

Drawing together the excipient- and process-level considerations discussed above, a consolidated, evidence-based strategy for developing a cost-effective sucralfate suspension can be framed around four pillars: first, selection of pharmacopoeial-grade suspending agents, preservatives, and sweeteners sourced from multiple qualified local or regional suppliers in preference to single-source specialty materials; second, judicious use of QbD and Design of Experiments tools during development to minimise the number of costly experimental batches and to avoid over-specification of non-critical attributes; third, a manufacturing process built around standard, widely available batch equipment and ambient-temperature-stable formulation components; and fourth, rigorous but appropriately scoped evaluation and stability testing, calibrated to the actual risk profile of the formulation rather than defaulting to the most exhaustive possible testing regimen. Table 3 summarises these strategies together with the corresponding formulation or process decision points at which they are applied. [43,64,65,69]

Table 3. Consolidated Strategies for Cost-Effective Sucralfate Suspension Development

Formulation/Process Decision Point	Cost-Effective Strategy	Anticipated Benefit
Suspending agent selection	Prefer pharmacopoeial-grade cellulose ethers or well-characterised natural gums/mucilages over patented specialty polymers	Lower raw-material cost; multiple qualified supplier sources
Preservative system	Use compendial parabens or benzoate systems compatible with the vehicle, at the minimum effective concentration confirmed by preservative efficacy testing	Reduced excipient cost while maintaining microbiological quality

Formulation/Process Decision Point	Cost-Effective Strategy	Anticipated Benefit
Sweetener/flavour system	Simple bulk + intense sweetener combination rather than complex taste-masking technology (coating, cyclodextrin complexation)	Avoids added process complexity and cost not clinically required for sucralfate's mild bitterness
Particle size control	Avoid micronisation unless specifically required (e.g., topical mucositis rinse use)	Eliminates an energy- and equipment-intensive processing step where not clinically justified
Development methodology	Apply Quality-by-Design with risk assessment (Ishikawa/FMEA) and Design of Experiments to screen candidate low-cost excipients efficiently	Fewer experimental batches; early elimination of non-critical, cost-adding attributes
Manufacturing process	Design for standard batch mixing equipment; avoid specialised homogenisation where not essential	Avoids capital expenditure on specialised equipment
Storage/distribution	Formulate for ambient-temperature stability rather than cold-chain requirements	Reduces logistics and distribution cost, particularly relevant in tropical regions
Stability programme	Apply ICH-endorsed bracketing/matrixing designs where multiple strengths or pack sizes exist	Reduces number of stability samples and analytical tests required without compromising shelf-life reliability
Regulatory strategy	Focus generic development on comprehensive characterisation of reference product's critical excipient attributes rather than full replication	Directs development resource efficiently; reduces risk of costly late-stage reformulation

VII. EVALUATION AND QUALITY CONTROL PARAMETERS

7.1 Physical Evaluation

Physical evaluation of a pharmaceutical suspension begins with organoleptic assessment of colour, odour, and taste, followed by determination of sedimentation volume, defined as the ratio of the final, equilibrium height of sediment to the original height of the total suspension, which provides a simple, widely used index of physical stability, with an ideal or well-flocculated suspension approaching a sedimentation volume ratio of one, indicating minimal net settling, and lower ratios indicating progressively greater compaction and reduced redispersibility on storage. The related degree of flocculation, calculated as the ratio of the sedimentation volume of the flocculated system to that of an equivalent deflocculated system, provides a complementary, more discriminating measure of the extent to which particles have associated into loose, easily redispersed flocs rather than settling as discrete, close-packed particles. [34,50,70]

Redispersibility, assessed qualitatively by the number of gentle inversions or shakes required to restore a homogeneous suspension after a defined storage period, is regarded in the literature as the single most important practical determinant of whether a suspension will deliver a uniform dose to the patient, since even a suspension with an acceptable sedimentation volume is of limited clinical value if the sediment cannot be readily and completely redispersed by an ordinary patient shaking the bottle by hand. [34,70]

Rheological evaluation, typically performed using a rotational or cone-and-plate viscometer such as a Brookfield-type instrument, characterises the suspension's flow behaviour across a range of shear rates, with a well-designed pharmaceutical suspension expected to display pseudoplastic, shear-thinning behaviour, that is, comparatively high viscosity at the low shear rates experienced during storage, which retards settling, and lower viscosity at the higher shear rates experienced during pouring, shaking, and swallowing, which preserves ease of administration; plots of shear stress against shear rate, or of apparent

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viscosity against suspending agent concentration, are commonly used to compare candidate suspending agents during formulation development. [47,49,71]

Particle size analysis and, where feasible, zeta potential measurement complete the physical evaluation package, since changes in mean particle size or particle size distribution over the course of storage can signal crystal growth, aggregation, or Ostwald ripening long before these changes become visually apparent, while zeta potential provides an indirect electrokinetic indicator of the degree and stability of flocculation achieved. Figure 3 summarises these physical evaluation parameters together with the chemical, microbiological, and stability categories discussed in the following sections. [33,72]

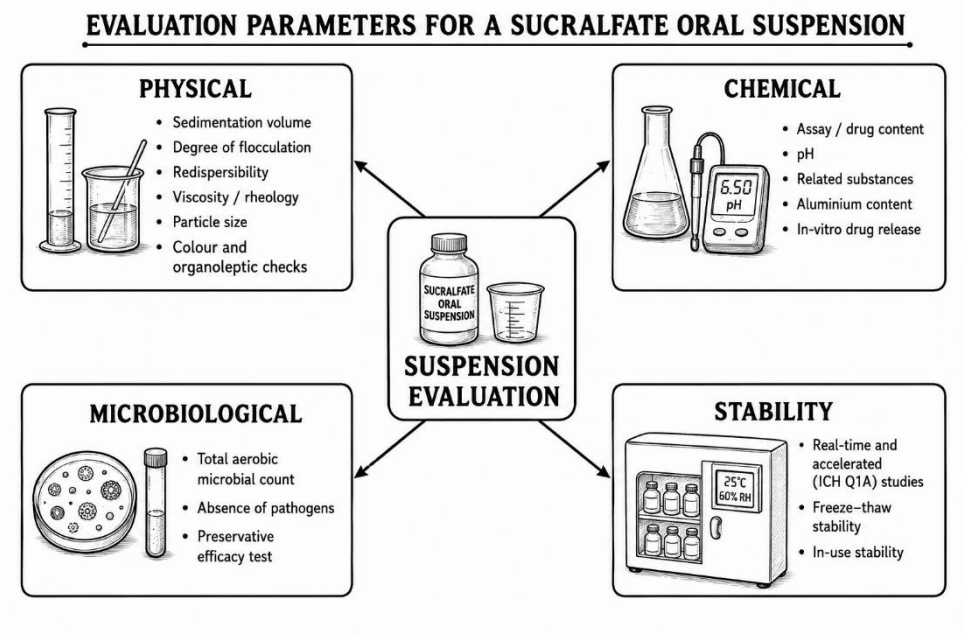

Figure 3. Overview of physical, chemical, microbiological, and stability evaluation parameters for a sucralfate oral suspension.

7.2 Chemical Evaluation

Chemical evaluation of a sucralfate suspension centres on assay of drug content, typically performed by a validated, stability-indicating analytical method, to confirm that the labelled strength is delivered uniformly across the container and that content remains within pharmacopoeial limits throughout the shelf life, together with determination of pH, which, as noted in Section 5.4, influences both suspending-agent performance and overall product stability and must therefore be verified at release and at each stability time point. Related substances or degradation product testing, together with quantification of aluminium content given the aluminium-based nature of the molecule, provide further assurance of chemical integrity, while in-vitro drug release or dissolution testing, although less central for sucralfate than for a systemically absorbed drug given its local, non-absorptive mechanism of action, can nonetheless serve as a useful, discriminating quality-control tool for detecting batch-to-batch or formulation-related changes in the availability of the suspended particles for local action. [33,73,74]

7.3 Microbiological Evaluation

Given that oral suspensions are aqueous, multidose products that may be stored at ambient temperature for extended in-use periods after first opening, microbiological quality control encompasses testing for total aerobic microbial count and absence of specified objectionable organisms in accordance with pharmacopoeial limits for oral liquid preparations, together with a preservative efficacy test in which the finished product is deliberately challenged with a

defined panel of bacterial and fungal test organisms to confirm that the incorporated preservative system, discussed in Section 5.4, provides an adequate margin of antimicrobial protection across the intended in-use period. [45,56]

7.4 Stability Testing

Stability evaluation of the finished suspension should be conducted in accordance with the internationally harmonised ICH Q1 framework, which specifies long-term storage testing, typically at twenty-five degrees Celsius and sixty percent relative humidity, or at thirty degrees Celsius and sixty-five percent relative humidity for products intended for warmer climatic zones, together with accelerated testing at forty degrees Celsius and seventy-five percent relative humidity to enable more rapid, predictive assessment of shelf life, with testing performed at defined intervals, commonly zero, three, six, nine, twelve, eighteen, and twenty-four months for long-term studies and zero, three, and six months for accelerated studies, across at least three representative batches. [75,76,77,78]

At each time point, the suspension should be evaluated for the full panel of physical, chemical, and microbiological attributes described above, together with any suspension-specific stress conditions such as freeze-thaw cycling and simulated in-use conditions that mimic repeated opening, dosing, and resealing by the patient over the labelled in-use period, since these represent realistic conditions under which physical instability such as caking, crystal growth, or loss of redispersibility is most likely to manifest. Bracketing and matrixing designs, whereby stability testing is reduced to a representative subset of strength or packaging combinations rather than every possible permutation, provide a further, ICH-endorsed opportunity to reduce the cost of the stability programme without compromising the reliability of the resulting shelf-life claim, an approach of direct relevance to the cost-effectiveness objective of this review. [76,79]

7.5 In-Vitro Drug Release

Although sucralfate acts locally rather than through systemic absorption, an in-vitro release or dissolution test, generally performed using a paddle or basket apparatus in an appropriate acidic medium, remains a valuable quality-control and formulation-development tool, since the rate and extent to which suspended sucralfate particles interact with the dissolution medium under standardised hydrodynamic conditions can serve as a sensitive surrogate for changes in particle size, crystallinity, or suspending-agent interaction that might otherwise go undetected by physical evaluation alone, and can support comparability assessments between different suspending-agent systems or between a generic and reference suspension formulation. [33,49]

VIII. REGULATORY AND PHARMACOPOEIAL CONSIDERATIONS

Development of a sucralfate suspension intended for the Indian market must be conducted with reference to the monograph requirements and general chapters of the Indian Pharmacopoeia, alongside relevant chapters of the United States Pharmacopeia-National Formulary and, where applicable, the European Pharmacopoeia, for tests including uniformity of dosage units, microbial limits, and preservative effectiveness, while stability protocols should conform to ICH Q1 requirements as harmonised for the applicable climatic zone. For a generic sucralfate suspension seeking regulatory approval against an existing reference product, demonstration of pharmaceutical equivalence, encompassing identical active ingredient, strength, and dosage form, is typically required, together with, depending on the regulatory pathway, evidence that the qualitative and quantitative excipient profile does not introduce clinically meaningful differences in local availability of the drug at the intended site of action. [64,69,80]

Because sucralfate acts locally and is not systemically absorbed to a pharmacologically relevant extent, conventional systemic bioequivalence testing based on plasma pharmacokinetics is not applicable in the same manner as for an orally absorbed drug, and regulatory expectations for such locally acting gastrointestinal suspensions instead tend to emphasise pharmaceutical equivalence, comparative in-vitro performance testing, and, where available, comparative clinical or pharmacodynamic endpoints, an important consideration that should inform the design of the

generic development and evaluation programme for a cost-effective sucralfate suspension. [13,80]

IX. CHALLENGES AND FUTURE PERSPECTIVES

Despite the extensive formulation science available for pharmaceutical suspensions in general, several challenges remain specific to sucralfate. The drug's high dose, poor solubility, and dense, aluminium-rich particulate character make achieving both an acceptably low viscosity for comfortable oral administration and an acceptably slow sedimentation rate for physical stability a genuinely competing set of design objectives, particularly when formulators are simultaneously constrained by cost considerations that limit the use of premium, highly efficient suspending agents. Batch-to-batch variability in natural gums and mucilages proposed as lower-cost suspending-agent alternatives represents a further practical challenge that must be managed through robust incoming-material specifications and, where feasible, standardisation against a reference viscosity or rheological profile. [46,48,65]

Looking forward, continued application of Quality-by-Design and Design of Experiments methodologies, of the type already demonstrated for a sucralfate anti-ulcer suspension, together with growing interest in locally sourced, pharmacopoeial-grade natural suspending agents as documented in the comparative mucilage literature, offer a credible pathway toward suspensions that are simultaneously robust, patient-acceptable, and genuinely affordable for health systems in India and other resource-constrained settings. Continued clinical research clarifying the specific circumstances, such as micronised particle size for topical mucositis use, under which formulation modifications translate into meaningful clinical benefit will further help formulators avoid unnecessary complexity and cost where it does not improve patient outcomes. [27,43,46]

X. CONCLUSION

Sucralfate remains a clinically valuable, locally acting cytoprotective agent across a range of gastrointestinal and oral mucosal indications, and the oral suspension dosage form continues to play an essential role in ensuring that patients unable to take conventional tablets, including children, the elderly, post-surgical patients, and those receiving enteral nutrition, retain access to this therapy. This review has drawn together the pharmaceutical rationale for the suspension dosage form, the specific formulation and evaluation considerations relevant to an insoluble, high-dose, aluminium-containing drug, and the practical, evidence-based strategies, spanning excipient selection, Quality-by-Design methodology, and appropriately scoped evaluation and stability testing, through which a sucralfate suspension can be developed to be both pharmaceutically robust and cost-effective. [43,64,65]

Future formulation work would benefit from head-to-head comparative studies of low-cost natural suspending agents against established synthetic alternatives specifically in sucralfate systems, from continued application of systematic QbD frameworks to further reduce development cost and risk, and from health-economic evaluation of the real-world impact of improved affordability on patient adherence and clinical outcomes in peptic ulcer disease and oral mucositis management. [46,64]

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