



A REVIEW ON SUGAR-FREE RECONSTITUTED DRY SYRUP USING NATURAL SUSPENDING AGENT

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ABSTRACT

Reconstitutable oral dry syrups are vital pharmaceutical dosage forms designed for medications that exhibit instability in aqueous environments, most notably antibiotics such as amoxicillin, cephalexin and ciprofloxacin. These formulations consist of dry mixtures of finely divided insoluble particles, typically ranging from 0.5 to 5 in diameter, intended to be suspended in a vehicle at the time of dispensing. This review evaluates the development of sugar-free systems to accommodate pediatric, geriatric and diabetic populations while utilizing natural suspending agents like fenugreek seed mucilage (*Trigonella foenum-graecum*), acacia and xanthan gum. Natural agents are prioritized due to their biodegradability, non-toxicity and superior thixotropic properties compared to synthetic alternatives. The article details comprehensive preformulation, formulation and post-formulation methods. Key evaluation parameters, containing micromeritic flow properties (Angle of Repose, bulk/tapped density), sedimentation volume (F) and in-vitro dissolution kinetics, are discussed. Findings indicate that natural polymers grant excellent physical stability and dose regularity, ensuring a long shelf life of at least two years in dry form.

KEYWORDS: Dry syrup, Natural suspending agent, Sugar-free formulation.

INTRODUCTION

Oral route of administration is the most widely favored direction due to patient convenience, safety and ease of administration. However, conventional solid dosage forms such as tablets and capsules are often unsuitable for pediatric and geriatric patients due to difficulty in swallowing.^[1] Liquid dosage forms overcome swallowing difficulties but frequently suffer from poor stability, microbial growth and shorter shelf life.^[2] To overcome these problems, dry syrups were developed in which the drug is supplied in dry form and reconstituted with water immediately before use.^[3] Antibiotics represent the largest group of drugs formulated as dry syrups because many antibiotics undergo hydrolytic degradation in aqueous media during storage.^[4]

Reconstitution dry syrups offer improved chemical stability, reduced microbial contamination, ease of

transport and extended shelf life compared to liquid syrups. Azithromycin dihydrate is a semi-synthetic azalide antibiotic derived from erythromycin and belongs to the macrolide class.^[5] It exerts its antibacterial action by inhibiting bacterial protein synthesis through binding to the 50S ribosomal subunit.^[6] Azithromycin is widely used in the treatment of respiratory tract infections, skin infections and sexually transmitted diseases. Despite its therapeutic efficacy, azithromycin dihydrate exhibits poor aqueous solubility, bitter taste and instability in liquid formulations.^[7] These drawbacks necessitate formulation of azithromycin as a dry syrup to improve stability, palatability and patient acceptance, especially in pediatric therapy.^[8]

Suspending agents play a vital role in reconstituted suspensions by maintaining uniform dispersion of drug particles throughout the dosing period.^[9] Synthetic

suspending agents such as sodium CMC and xanthan gum are commonly used but may cause gastrointestinal irritation and are less eco-friendly.^[10] Therefore, natural suspending agents obtained from plant sources are increasingly explored due to their safety and biodegradability. Fenugreek (*Trigonella foenum-graecum*) seeds contain a high amount of mucilage composed mainly of galactomannan polysaccharides.^[11] Fenugreek mucilage exhibits excellent swelling, viscosity-enhancing and suspending properties, making it suitable for pharmaceutical use. It is biodegradable,

biocompatible, non-toxic and economical, which makes it a promising substitute to synthetic polymers.^[12] The increasing prevalence of diabetes has increased the demand for sugar-free pharmaceutical formulations. Sugar-free dry syrups are particularly beneficial for diabetic patients as well as pediatric patients who require long-term antibiotic therapy.^[13] Hence, the present study focuses on the formulation and evaluation of a sugar-free reconstitution dry syrup of azithromycin dihydrate using fenugreek mucilage as a natural suspending agent.^[14]

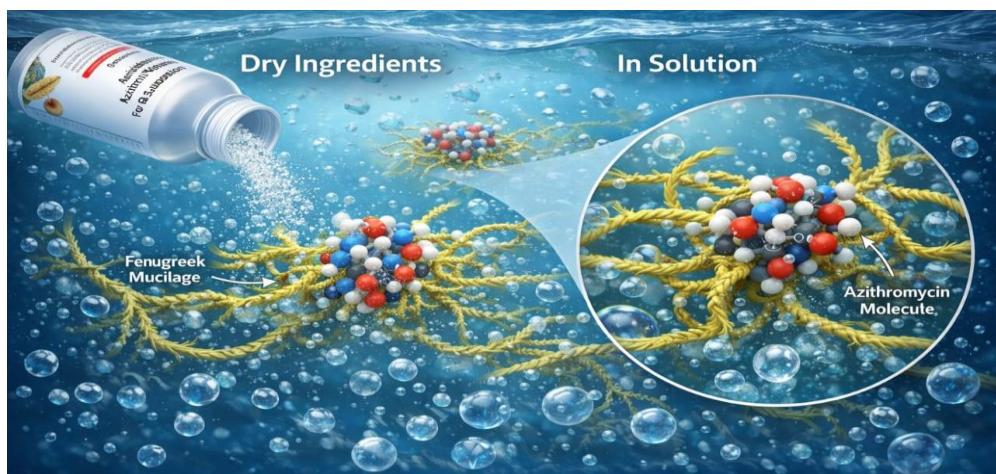


Figure 1: Schematic representation of dispersion and stabilization of Azithromycin dihydrate in aqueous medium using Fenugreek mucilage as a natural suspending agent.

ADVANTAGES

1. Sugar-free formulation is appropriate for diabetic patients as it avoids sucrose-induced hyperglycemia.^[15]
2. Use of fenugreek mucilage increases formulation safety due to its natural, non-toxic and biocompatible nature.^[16]
3. Dry syrup formulation improves chemical stability and shelf life of azithromycin dihydrate by preventing hydrolytic degradation.^[17]
4. Natural excipients are biodegradable, eco-friendly and cost-effective compared to synthetic suspending agents.^[18]

MATERIALS AND METHODS

MATERIALS

S.NO	MATERIALS ^[24]	CHARACTERS
1.	Active pharmaceutical agent (API)	Therapeutic effect.
2.	Natural Suspending agent	Increases viscosity, Retards settling.
3.	Sweeteners (Zero calories)	Masking bitterness (Zero calories).
4.	Bulking agent	Provide volume, improve flowability.
5.	Buffering agent	Maintains optimal pH stability.
6.	Preservatives	Prevent microbial growth and extend the shelf life of formulations.
7.	Stabilizer	Maintain the physical, chemical and therapeutic stability of the drug.
8.	Flavoring agent	Patient acceptability and elegance.
9.	Anticaking agent	Prevents moisture agglomeration.
10.	Wetting agent	Aids dispersion of hydrophobic drug.
11	Lubricant	Reduce friction'

5. Improved patient compliance is achieved due to better palatability and ease of administration.^[19]

DISADVANTAGES

1. Natural mucilage may show batch-to-batch variation depending on plant source and extraction conditions.^[20]
2. Higher concentration of mucilage may lead to increased viscosity, affecting pourability.^[21]
3. Improper reconstitution by patients may result in dosing errors.^[22]
4. The reconstituted suspension has limited stability and must be used within a specified period.^[23]

PREFORMULATION METHODS

IDENTIFICATION

MELTING POINT (CAPILLARY METHOD)

This method is used to determine the temperature at which a solid drug substance transitions into a liquid state, serving as a primary indicator of purity and identity. The procedure involves filling a small capillary tube (with one end closed) with a specific quantity of the drug. The tube is placed in a thermoelectric melting point apparatus, and the temperature is recorded at the moment the medication melts. A substance is considered pure if its melting point meets established pharmacopoeia standards for instance, pure cephalexin monohydrate is typically identified at a melting point of 190°C.^[25]

UV ABSORPTION SPECTROSCOPY

UV Absorption Spectroscopy: This analytical technique identifies a drug by its unique light absorption pattern, specifically its absorption maximum. To determine the maximum the standard stock solution is prepared (e.g., 1 mg/ml in methanol or a buffer) and significantly diluted to a concentration range suitable for measurement, such as 2–12 µg/ml. The solution is scanned using a double-beam UV/VIS spectrophotometer across the 200–400 nm wavelength range. The resulting spectrum shows the peak absorbance wavelength, such as 271 nm for quinethazone or 232 nm for cefpodoxime proxetil, which is used for further quantitative evaluation and drug content determination.^[26]

COMPATIBILITY STUDIES

FTIR SPECTROSCOPY

Fourier Transform Infrared (FTIR) Spectroscopy: FTIR is a powerful tool for chemical recognition and examining the interface between a drug and its carriers to ensure no deleterious interactions occur. Samples are typically prepared using the potassium bromide (KBr) pellet method, where approximately 5 mg of the sample is mixed with 50–100 mg of IR-grade KBr powder and compacted under vacuum/high pressure to form a transparent disc. The resultant disc is scanned in the infrared range of 500 to 4000 cm⁻¹. Compatibility is confirmed by comparing the spectra of the pure drug with its physical mixtures; the preservation of characteristic peaks (such as O-H or C=O stretching) and the absence of new peaks indicate that the drug and excipients are compatible.^[27]

DIFFERENTIAL CALORIMETRY(DSC)

DSC is an extensively used thermal analysis technique that measures the heat loss or gain resulting from physical or chemical changes in a sample as a function of temperature. A precisely weighed sample (e.g., 3–10 mg) is placed in a hermetically sealed aluminum pan and heated at a constant rate, such as 10°C or 20°C per minute, over a range from 50°C to 450°C. The test is conducted under a continuous stream of inert nitrogen gas to prevent oxidation. DSC thermograms provide insights into the crystalline or amorphous nature of the

SCANNING

drug; a sharp endothermic peak corresponds to the drug's melting point, while a broad peak or the disappearance of the sharp peak may suggest a transition to an amorphous state or the formation of a complex.^[28]

MICROMERITICS CHARACTERIZATION

Micromeritics predicts the flowability and fill uniformity of dry powder blends, which is essential for accurate dosing and high-speed manufacturing.

BULK DENSITY

The predetermined or pre weighed mass of the powder blend volume was measured for determination of bulk density

$$\text{Bulk Density (Db)} = (\text{M}) / (\text{Vo})$$

Where,

M = Weight of the powder blend

Vo = Apparent volume of the powder blend.^[29]

TAPPED DENSITY

The measuring cylinder which contains a powder sample was mechanically tapped. The initial volume was observed before tapping, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed.

$$\text{Tapped density (Dt)} = (\text{M}) / (\text{Vf})$$

Where,

M = weight of the powder blend.

Vf = Final volume of the powder blend.^[29]

CARR'S INDEX OR COMPRESSIBILITY INDEX

The Carr's Index or Compressibility Index was calculated by the formula

$$I = Dt - Db / Dt \times 100\%$$

Where,

Db = Bulk density,

Dt = Tapped density.^[29]

ANGLE OF REPOSE(θ)

The angle of repose of powder blend was determined by using employing fixed funnel method

$$\text{Tan } \theta = h/r$$

Where,

h = height of the heap.

r = radius of the heap.^[29]

SOLUBILITY STUDIES

Saturation solubility is determined by adding an excess amount of drug to various pH buffers (ranging from 1.2 to 6.8) and agitating the mixture for a specific period, such as 48 hours at 37°C. This study determines the drug's absorption window and its classification under the Biopharmaceutics Classification System (BCS) based on the dose solubility ratio.^[30]

THRESHOLD BITTERNESS EVALUATION

This evaluation uses a panel of healthy human volunteers (typically 6–10 people) to find the minimum concentration at which a drug's bitterness is perceived. Volunteers hold varying concentrations of drug solutions

in their mouths for 20–60 seconds to establish a bitterness provocativeness threshold, which guides the extent of taste-masking required in the final formulation.^[31]

SWELLING INDEX

The swelling index assesses the hydration capacity of natural gums, such as fenugreek mucilage, which serve as viscosifying agents. A precisely weighed amount (e.g., 1g) is placed in water and allowed to swell for 1 to 24 hours; a high index (e.g., 150%) indicates superior potential for retarding sedimentation via high viscosity.

Formula.

$$SI\% = [(w_2 - w_1) / w_1] \times 100$$

Where,

w₁ = initial weight

w₂ = hydrated weight.^[32]

LOSS ON DRYING(LOD)

LOD measures the moisture content in dry mixtures by heating samples (often at 105°C) until a constant weight is achieved. Maintaining low LOD values is critical to prevent caking and powder agglomeration during long-term storage.^[33]

PARTICLE SIZE ANALYSIS

Using optical microscopy, the average diameter of particles is examined (typically across at least 100–200 particles) to ensure they are within the ideal range of 0.5–5 μm . This range is vital for ensuring rapid dissolution, high homogeneity, and preventing a gritty mouthfeel upon administration.^[34]

ZETA POTENTIAL

Zeta potential measures the electrokinetic nature of particles to predict the physical stability of the reconstituted suspension. A potential of more than +30 mV or more negative than -30 mV indicates a stable system, as high surface charges prevent particle aggregation and hard caking.^[35]

FORMULATION METHODS

DIRECT MIXING

Direct mixing, or powder blending, is the simplest and most economical method. It involves the geometric dilution of sieved powders where excipients present in small quantities are first mixed with a portion of a major excipient to ensure even distribution.

Equipment: V-blenders, double cone mixers, and ribbon blenders.^[36]

WET GRANULATION

Wet granulation is the most common process for preparing granulated dry syrups. The ingredients are mixed with a granulating fluid (usually water, isopropyl alcohol, or an aqueous binder solution) to form a wet mass. Equipment: Planetary mixers for massing and fluid bed dryers or tray ovens for drying.^[37]

DRY GRANULATION(SLUGGING)

Dry granulation involves the mechanical compression of dry powder mixtures into large compacts (slugs) without the use of liquid or heat.^[37]

SOLID DISPERSION

Solid dispersion is used to improve the dissolution rate and bioavailability of BCS Class II drugs (e.g., Simvastatin) by dispersing the drug in a hydrophilic carrier.

Sub-Methods

Solvent Evaporation: Dissolving drug and carrier in a common solvent followed by evaporation.

Fusion (Melting) Method: Melting the carrier and drug together, then cooling to form a solid mass.^[38]

SPRAY DRYING

Spray drying is a rapid, one-step process that converts a liquid feedstock (solution or suspension) into precise dry particles.^[39]

ION-EXCHANGE COMPLEXATION

This technique is primarily used for taste masking bitter drugs (e.g., Ciprofloxacin, Azithromycin). High molecular weight polyelectrolytes (resins) exchange their mobile ions with drug molecules to form a Drug-Resin Complex (DRC).^[40]

HOT MELT TECHNIQUE

Hot Melt Technique Also known as melt granulation, this method involves embedding or coating drug particles with lipid carriers, waxes, or fats that are in a molten state.^[41]

LYOPHILIZATION

Lyophilization is a process used to produce dry powders that are highly stable, porous, and rapidly reconstitutable.^[42]

NANOPRECIPITATION

Nanoprecipitation is used to produce particles of less than 50 nm (nanosuspensions) to improve the bioavailability of potent but insoluble drugs.^[43]



Figure 2: Fenugreek seeds, coarse powder and dried mucilage powder used for preparation.

EVALUATION PARAMETERS

FLOW PROPERTIES

The flow properties such as bulk density, tap density, angle of repose and porosity of the powder mixture, granulation and combination product should be carried out.

BULK DENSITY

The predetermined or pre weighed mass of the powder blend volume was measured for determination of bulk density

$$\text{Bulk Density (Db)} = (M) / (V_o)$$

Where,

M = Weight of the powder blend

V_o = Apparent volume of the powder blend

TAPPED DENSITY

The measuring cylinder which contains a powder sample was mechanically tapped. The initial volume was observed before tapping, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed.

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$$\tan \theta = h/r,$$

Where,

h = height of the heap.

r = radius of the heap.

RHEOLOGICAL BEHAVIOUR

Using Brookfield viscometer, the rheological behaviour of the oral reconstituted suspensions is determined.^[44]

SEDIMENTATION BEHAVIOUR

a) REDISPERSIBILITY

It is determined by studying the number of strokes required to redisperse the formed at the end of seven days of storage. Redispersibility should be at most 100 strokes.

b) SEDIMENTATION VOLUME RATIO(SVR)

It is expressed by the ratio of the equilibrium volume of the sediment (V_u) to the total volume (V_o) of the suspension.

$$F = V_u / V_o$$

F values lie between 0 to 1 for any pharmaceutical suspension.^[45]

PH VALUES

The PH of the suspensions is measured with the help of PH meter.^[46]

DISSOLUTION STUDIES

The dissolution studies were performed using a US Pharmacopeia XXIV type II dissolution test apparatus. The samples equivalent to 100 mg Azithromycin Dihydrate were placed in a dissolution vessel containing 900 mL of phosphate buffer (pH 6.0) maintained at 37.0 \pm 0.5°C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration, concentration of Azithromycin Dihydrate was determined spectrophotometrically at 215 nm.^[47]

CONCLUSION

The development of sugar-free reconstitutable dry syrups using natural suspending agents like fenugreek mucilage is a robust strategy for delivering drugs susceptible to hydrolysis. Natural polymers provide superior thixotropic and suspending properties while remaining non-toxic and cost-effective. Future research scope includes the formulation of sustained-release dry syrups to reduce dosing frequency for chronic infections in pediatric care.

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