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Formulation and Characterization of Furosemide Syrup for Paediatric Use

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ABSTRACT:

Background- A popular loop diuretic used to treat hypertension and edema is furosemide. It can be difficult to find an appropriate pediatric formulation, though. Developing and testing a stable and pleasant furosemide syrup for use in children is the goal. The formulation of furosemide syrup involved the use of sorbitol, glycerin, and flavoring. The syrup was assessed for flavor, viscosity, pH, and chemical and physical stability.

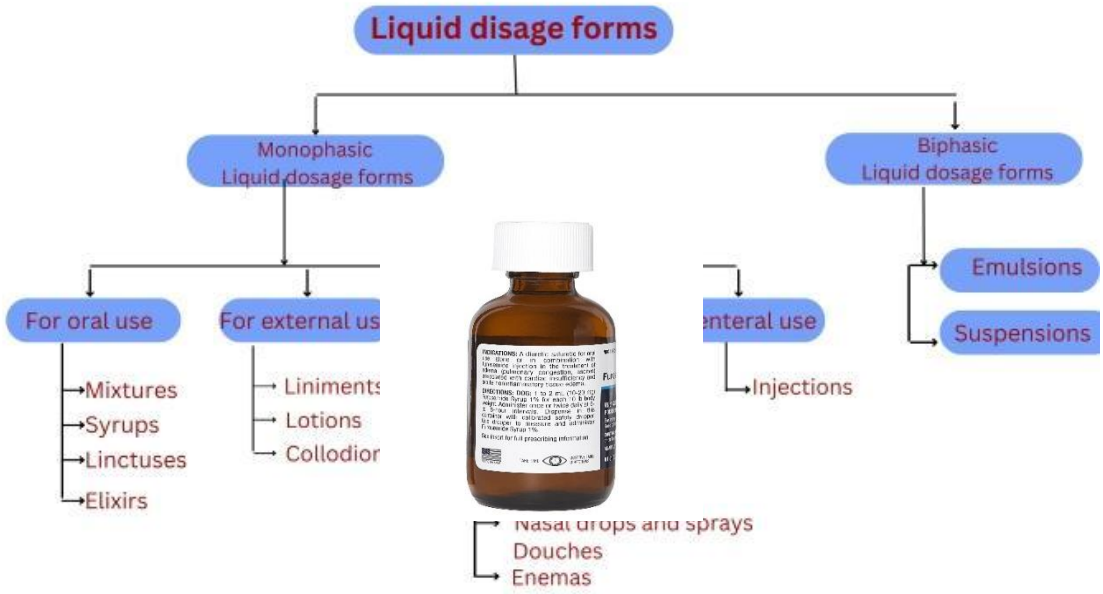
Keywords: Furosemide, syrup, oral liquid, citric acid, viscosity.

Introduction: Oral liquids:

Pharmaceutical preparations known as liquid dosage forms include mixing an active ingredient with non-active ingredients like additives and solvents to produce a liquid medicine(1,2). Although liquid oral dosage forms include benefits like dose flexibility and kid-friendly swallowing, they may also call for components that are not suitable for young patients. Due to safety concerns or possible negative effects, several substances or excipients that are often used in liquid formulations—such as alcohol, artificial sweeteners, or specific preservatives—may not be appropriate for young children(1,3).There are several dose forms within each of the two main categories of monophasic and biphasic formulations, which are frequently used to categorize them. Monophasic liquids, such as syrups, elixirs, linctuses, etc., only include one phase. Conversely, biphasic liquids are distinguished by the formulation's existence of two separate parts.(for instance, emulsion or suspension)(1,4).

Classification of oral liquid:

Syrup :



Syrups are concentrated aqueous formulations that include medicinal medicines, either with or without flavoring agents, and 85% sugar or sugar substitute. Medicinal nomenclature defines medicinal syrups as almost saturated solutions of 85% sugar in water for the dissolution of medicines. Numerous therapeutic syrups are available, including calcium syrups, iron syrups, cough syrups, and anti-allergy syrups(5,6). **Fig.1: Marketed syrup**

There are two kinds of syrups: therapeutic syrups and aromatic or adjuvant syrups. The main purpose of aromatic syrups is to improve the flavor of salty, bitter mixtures(5,6).Medicinal syrups has therapeutic qualities. They come in two varieties. This product is made from extractive drugs. The fluid extract of the various medications is mixed with the syrup. This product is made with chemicals and medications: either a straightforward solution or one that results from a chemical process. This technique significantly changes the flavor of the medicinal ingredients. Apart from distilled water and some medicinal substances, the majority of syrup comprises the following components: Many types of syrups, especially those produced commercially, contain thickeners, stabilizers, flavoring, colorants, antimicrobial preservatives, solubilizing agents, specific solvents, and sweetening chemicals that provide a combination sweetness and viscosity.(5,7)

These are the main ingredients of syrups Clean water Sugar (sucrose) or artificial sweeteners, which are sugar replacements. Traditionally, pure water and sugar (often 60–80%) make up syrups. These systems are naturally sweet and have a somewhat high viscosity, thus additional sweeteners and viscosity-modifying agents are not needed. Preservatives may need to be added as the concentration of sucrose is lowered below the upper limit (for example, via dilution). Other non-sucrose bases could be used in place of conventional syrup in specific formulations. Although there are additional options based on combinations of sorbitol and glycerin, one of the most often used is Sorbitol Solution, which contains 64% w/w sorbitol. You can combine these non-sucrose bases with conventional syrups if necessary, when creating oral syrups with a lower sugar content than conventional syrups. Because sucrose has glycogenetic and cariogenic qualities, numerous products have been developed as therapeutic sugar-free syrups in recent years. All medications intended for use by children and diabetes patients must be sugar-free for the reasons listed above. Therefore, syrup alternatives need to have the same level of sweetness, viscosity, and preservation as the original syrups. These qualities are attained by adding non-glycogenetic viscosity modifiers (like methylcellulose and hydroxyethylcellulose), artificial sweeteners (mostly aspartame and sodium saccharin), and preservatives (such sodium benzoate, benzoic acid, and parahydroxybenzoate esters). High-intensity sweeteners are a significant class of sugar alternatives. These substances frequently have the same sweetness as sucrose, a popular table sugar. As a result, a lot less sweetener is needed, and the energy input is frequently minimal. These substances are frequently employed In complicated mixes to provide the most natural sweet experience because their "sweetness profile"—the feeling of sweetness they produce—can occasionally differ noticeably from sucrose(8,9).

Syrup types

1. Simple syrups: These non-medicated liquid preparations are mostly employed as a vehicle or medium for other liquid treatments. They add taste and sweetness to improve palatability and make drug administration easier.
2. Medicated syrups: Medicated syrups are frequently used orally and can include a variety of drugs, such as expectorants, analgesics, antitussives, and antihistamines.
3. Flavoured syrups: In the culinary arts, flavoured syrups are frequently used to improve the flavour of drinks, baked products, desserts, and other foods. They are available in a variety of tastes, including well-liked choices like strawberry, mint, chocolate, caramel, vanilla, and more. Coffee, tea, and cocktails can all benefit from the addition of these syrups, or they can be used as toppings for ice cream, pancakes, waffles, and other treats.(1,4)

Benefits

1. Ease of swallowing: Children and elderly people who may have trouble swallowing are better suited for liquid medicines since they are often simpler to swallow than solid pills or capsules.
2. Quicker absorption: Since liquid dose forms are already dissolved or distributed, the medicine can enter the circulation more quickly than with solid dosage forms. This may lead to more fast therapeutic benefits and a speedier commencement of action.
3. Uniform dosage: Because liquid formulations are homogeneous, the medication is dispersed uniformly throughout the mixture. Unlike suspensions or emulsions, which may need to be shaken to disperse the medication before administration, this guarantees that each dosage has a constant quantity of the active component.
4. Simplified formulation: Compared to solid dosage forms, developing liquid dosage forms might be quicker and easier. A appropriate liquid vehicle can be used to dissolve or disseminate the medication, and it is simple to add more flavorings or excipients to improve taste, stability, or other properties.
5. Multiple administration routes: Liquid formulations provide a range of administration ways. They can be applied as otic preparations (ear drops), nasal sprays, or ophthalmic (eye) preparations, orally (by mouth), intravenously (parenterally), or as enemas for rectal usage. This makes it possible to choose the best course of action depending on the patient's particular requirements or the type of ailment being treated(1,10,11).

Drawbacks :

1. Bulky and challenging to carry and store: This describes liquid dose forms, including syrups or suspensions, which may need extra care when being transported and stored and can occupy more space.
2. Water is frequently employed as a solvent or carrier in liquid pharmaceuticals, which makes it susceptible to microbial development. Antibiotics are frequently added to water because it creates an ideal habitat for bacteria to develop and prevent microbial diseases.
3. Susceptibility to hydrolysis in direct sunshine: When exposed to direct sunlight, certain drugs, especially liquid ones, may hydrolyze. A chemical reaction known as hydrolysis might occur when water breaks down a molecule. To keep stability, it is best to keep liquid medications out of direct sunlight by keeping them in cold, dark locations.

4. Shorter expiration dates than solid dosage forms: Because liquid medications are more vulnerable to oxidation and hydrolysis, they may have shorter expiration dates than solid dosage forms (like tablets or capsules), which are less likely to experience these degradation reactions.
5. Indications of unstable drugs: A number of signs, such as color changes, precipitation (the production of solid particles or crystals), and microbiological growth, might point to medication instability. These symptoms emphasize the need of appropriate handling and storage as they might point to a loss of potency or other safety hazards(1,10,11).

Introduction to Furosemide:

Furosemide is a typical high-ceiling (loop) diuretic drug. Furosemide is used to treat edematous symptoms associated with liver cirrhosis, congestive heart failure, and chronic renal failure in addition to hypertension. Due to its mild acidity (acid dissociation constant, pKa = 3.93), furosemide is mostly absorbed in the stomach and upper small intestine. Furosemide has a short half-life (t1/2=1.3±0.8 hours, mean±SD) and a rapid onset. Furosemide's reduced bioavailability is expected to be primarily caused by its poor solubility. Furosemide's low bioavailability (49%±17%, mean±SD) is also a result of its small absorption window brought on by poor solubility(12).

The medicine's low oral bioavailability and solubility have led to its categorization as a class IV drug under the biopharmaceutical classification system (BCS); its solubility is one of the main factors contributing to its low oral bioavailability(13,14,15).. A drug's solubility and/or rate of dissolution determine its oral bioavailability, and the rate at which therapeutic activity begins may be determined by dissolution. As a result, attempts to improve medication solubility are frequently required. Salt production, micronization, and the addition of solvent or surface active chemicals are among techniques that can be used to enhance dissolving. One of these techniques is solid dispersion (SD), which entails dispersing one or more active components in a solid state within an inner carrier or matrix that has been created by melting, dissolving in a solvent, or using a melting-solvent technique.(13,16).

Furosemide is a weekly acidic, non-steroidal anti-inflammatory medication that has a high permeability through the stomach but is unable to enter the systemic circulation due to its solubility limitation. The gastric emptying time ranges from 30 to 2 hours, after which the medication enters the small intestine, where it dissolves but is unable to pass through its membrane. It is difficult and logical to improve the drug's solubility. to create a tasty, stable, and efficient furosemide syrup formulation for the management of hypertension and edema. Create a stable syrup of furosemide. Create a syrup recipe that guarantees furosemide's stability and effectiveness. Boost patient adherence Make a syrup that tastes good and is simple to administer. Boost the bioavailability Optimize the formulation to guarantee that furosemide has sufficient bioavailability. Assess stability in terms of both physical and chemical aspects. Examine the furosemide syrup's stability in a range of scenarios. Particular Objectives Find the best formulation. Determine the best mix of components and production method. Evaluate performance both in vitro and in vivo. Analyze furosemide's release profile and bioavailability. Verify patient acceptability Assess the syrup's flavor, aroma, and general acceptability. By creating floating granules, the current study enhances the solubility of furosemide. Furosemide is a weekly acidic loop diuretic medication that is prescribed to treat edema and hypertension with high stomach permeability because it remains 99.8% soluble in the stomach (pKa of 3.9, pH of gastric fluid -1.2).Numerous studies have been published on the use of solid dispersion to increase the pace at which poorly water-soluble drugs dissolve(17).

Mechanism of action of furosemide by blocking the sodium-chloride cotransport system, furosemide prevents the proximal and distal tubules and the thick ascending loop of Henle from reabsorbing sodium and chloride. This causes an increased excretion of water together with sodium, chloride, magnesium, and calcium(18).

Side effects of furosemide is The Digestive System Hepatic encephalopathy in cirrhosis patients Intrahepatic cholestatic jaundice, or pancreatitis jaundice Elevated liver enzymes anorexia gastric and oral irritation. The act of cramping having diarrhea constipation feeling queasy(19).

Material and methods:

1. **Pre- formulation test:**
   - FTIR Analysis
   - Angle of repose
   - Bulk density
   - Tapped density
   - Hausners ratio
   - Compressibility

I. FTIR Analysis – Furosemide Fourier transform infrared (FTIR) spectrum These ingredients were recorded using the KBr mixing method on an FTIR instrument (FTIR-Perkin Elmer-Spectrum Version 10.03.06), which is available at a sophisticated analytical instrument facility(20).

II. **Angle of Repose:**The angle of repose is the greatest angle that can be established between the powder pile's surface and a horizontal surface. The angle-of-repose values for the majority of medicinal powders fall between 25 and 45°; lower values denote superior flow properties. Tan $\theta = h / r$, where r is the radius of the pile's base and h is the pile's height(21).

III. **Bulk density** is calculated by calculating the amount of powder with a known mass that made it past the screen.

IV. **Tapped density:** The measuring cylinder holding powder is mechanically tapped to acquire this value.

V. **Compressibility index:** A powder's "compressibility" is its capacity to reduce volume when compressed, and its "compactability" is its capacity to compress into a tablet with a given tensile strength. On the basis of density measurement, it may be utilized to forecast the flow characteristics.(21,22,23).

$$carr's\ index = \frac{tapped\ density - \ pored\ density}{pored\ density} \times 100$$

Method of Preparation

Formulation table:

Sr.no.	Ingredients	S1	S2	S3	Role
1	Furosemide	60 mg	60 mg	60 mg	Active Ingredient
2	Propylene glycol	6 ml	8 ml	10 ml	Humectant, stabilizer
3	Sodium benzoate	0.06 gm	0.06 gm	0.06 gm	Antimicrobial, Preservative
4	Citric acid	0.06 gm	0.06 gm	0.06 gm	pH adjuster
5	Distilled water	Qs to 30 ml	Qs to 30 ml	Qs to 30 ml	Vehicle

Process :

Step 1: Weighing and Getting the Ingredients :Weigh the following ingredients in accordance with the formulation: propylene glycol, citric acid, sodium benzoate, and furosemide

Step 2: Dissolving furosemide in two steps use a suitable solvent, such as pure water or a water-glycerin combination, to dissolve furosemide stir until all of the furosemide has dissolved.

Step 3: Getting the Syrup Base Ready in Step Three In this syrup propylene glycol and water is syrup base.

Step 4: Adding buffering agents and preservatives in step four Mix the syrup base with sodium benzoate Incorporate citric acid into the syrup base.

Step 5: Mixing the Syrup Base with Furosemide Solution: combine the syrup base and the furosemide solution. Stir until the mixture is homogeneous.

Step 6: Filling and Filtration use an appropriate filter to filter the syrup transfer the syrup into sterile, clean bottles.

2. Evaluation of syrup:

Physical-chemical characteristics: Numerous physicochemical characteristics, including pH and physical appearance (color, taste, and odor), were assessed for the syrup.

- **A color analysis** : Five ml of the resulting syrup were transferred into watch glasses and set up under a white tube light with a white background. Its hue was detected with the unaided eye.
- **Analysis of odor** : Each of the two ml of finished syrup was sniffed. To counteract the impact of prior smelling, a 2-minute gap was maintained between two sniffs.
- **Evaluation of taste:** To test the final syrup's flavor on the tongue's taste buds, a pinch was taken.
- **Calculating pH:** 10 ml of the finished syrup, precisely measured, were added to a 100 ml volumetric flask, and the remaining volume was filled with distilled water to reach 100 ml. For around ten minutes, the solution was sonicated. Using a digital pH meter, the pH was measured

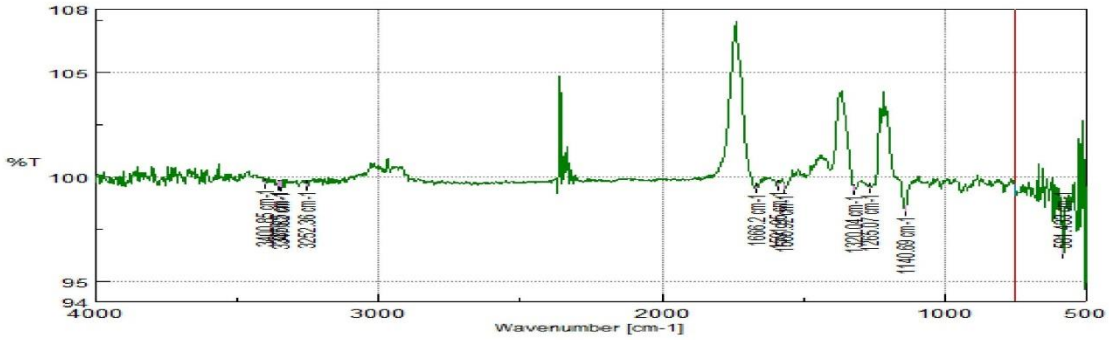
Result and Discussion : Pre formulation test :

Table 2: Pre-formulation test of Furosemide Drug

Sr. No.	Test	Result
1	Color	White
2	Odour	Odourless
3	Taste	Bitter
4	Angle of Repose	32.00°
5	Bulk density	0.41 gm/ml
6	Tapped density	0.48 gm /ml
7	Carrs index	14.5%

FTIR Analysis :

Fig 2 : FTIR analysis of pure furosemide drug



Post Formulation Evaluation test :

Table 3 : Evaluation test of furosemide drug

Sr. No.	Test	S1	S2	S3
1	Color	White	White	White
2	Odour	Odourless	Odourless	Odourless
3	Clarity	Clear	Clear	Clear
4	Taste	Slightly bitter	Slightly bitter	Slightly bitter
5	pH	6.9	7.2	8

Conclusion:

Furosemide syrup's formulated formulation demonstrated effectiveness, stability, and acceptance. The syrup complies with all standards after evaluations of its physical and chemical stability. Increased patient compliance The syrup formulation is a user-friendly and straightforward alternative to traditional pills or injections. Effective medical care With furosemide syrup, edema and hypertension can be efficiently controlled. Maintaining consistency and compatibility: The formulation demonstrated stability and compatibility with additional constituents. Possible Routes: Additional study may be needed to evaluate the furosemide syrup's long-term stability and efficacy. In conclusion, the new formulation of furosemide syrup offers a stable, effective, and comfortable approach to treating patients with edema and hypertension.

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