Developing and assessing herbal effervescent floating granules utilizing liquorice extract and essential oil.

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Abstract:

The anti-inflammatory and antioxidant properties of liquorice root extract were utilized to create carbonated granules that enhance drug release and stomach retention. Effervescent granules offer advantages for drug delivery such as improved drug release, enhanced stomach retention and patient friendly dosage form. Three varieties (F1, F2, and F3) were created, with F2 being the best. Comparing F2 to F1 and F3, F2 performed better in terms of size, buoyancy, pH, and stability. According to this study, these carbonated granules containing peppermint oil and liquorice may be useful for administering medication to the stomach. We ought to investigate their functionality and stability in further detail. The anti-inflammatory and antioxidant properties of liquorice root extract were utilized to create carbonated granules that enhance drug release and stomach retention. Three varieties (F1, F2, and F3) were created, with F2 being the best. Comparing F2 to F1 and F3, F2 performed better in terms of size, buoyancy, pH, and stability. According to this study, these carbonated granules containing peppermint oil and liquorice may be useful for administering medication to the stomach. We ought to investigate their functionality and stability in further detail.

Keywords: Liquorice, effervescent granules, peppermint oil, Antioxidant, gastric retention.

INTRODUCTON

In the past ten years, a great deal of research has been done on medication dosage forms with sustained release with the goal of prolonging gastric emptying time (GET). In fed individuals, the GET has been shown to vary between 2 and 6 hours.

Drug delivery systems that remain in the stomach extend the duration of the gastrointestinal transit, improving the drug's bioavailability. Studies using scintigraphy to measure the rates of stomach emptying have shown that controlled-release pills taken orally are susceptible to Floating drug delivery systems (FDDS) have been developed using two quite different approaches, namely effervescent and non-effervescent systems, depending on the buoyancy mechanism. Effervescent medication delivery systems make use of matrices made of effervescent substances such sodium bicarbonate and citric or tartaric acid, as well as swell able polymers like methocel or polysaccharides. Floating drug delivery systems have several benefits, including decreased intra- and inter-subject variability in plasma drug levels due to their reduced susceptibility to gastric emptying, effective delivery of medications with limited absorption windows, decreased dosage and improved patient compliance, decreased Cmax and extended drug levels above the minimum effective concentration, and enhanced safety profile for medications with high Cmax-related side effects.[1,2]

Floating systems first described by Davis (1986), are low-density systems that have sufficient buoyancy to float over the gastric content and remain in stomach for a prolonged period while the system floats over the gastric content, the drug is released slowly at the desired rate which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration. Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system.

Liquorice root extract, derived from the Glycyrrhiza glabra plant, has garnered attention for its potential role in the treatment of gastroesophageal reflux disease (GERD), primarily attributed to its antioxidant and anti-inflammatory properties. One of the key active components in liquorice root are glycyrrhizin, which has been studied for its various therapeutic effects. GERD is characterized by the chronic regurgitation of stomach acid into the esophagus, leading to symptoms like heartburn and irritation. Liquorice root extract may provide relief by forming a protective layer on the esophageal lining, helping to alleviate discomfort associated with acid reflux. The antioxidant properties of liquorice root extract are crucial in the context of GERD. Antioxidants help combat oxidative stress, which is an imbalance between free radicals and the body's ability to counteract their harmful effects. By neutralizing free radicals, liquorice root extract may contribute to reducing inflammation in the esophagus, a key factor in GERD symptoms. Its therapeutic properties are attributed to a diverse range of compounds, with glycyrrhizin being a key player. [13]

Glycyrrhizin Content:

Anti-Inflammatory Action:- Glycyrrhizin is renowned for its anti-inflammatory effects. It inhibits the activity of enzymes involved in inflammation, potentially reducing redness and swelling in various tissues, including the gastrointestinal tract.

Antioxidant Properties: - Neutralizing Free Radicals: Liquorice root extract is recognized for its potent antioxidant properties. It contains flavonoids, isoflavones, and other polyphenol compounds that help neutralize free radicals in the body. By doing so, it may mitigate oxidative stress, a factor implicated in various health issues.

Gastro protective Effects: - Mucosal Protection: Liquorice root extract has mucosal protective effects, forming a soothing layer on the mucous membranes. This property is particularly valuable in gastrointestinal health, where it may aid in protecting the stomach and esophageal lining from irritation.

Expectorant Properties: - Traditionally, liquorice root has been used as an expectorant, helping to relieve respiratory issues by loosening mucus and facilitating its expulsion. This property can be beneficial in addressing conditions like coughs and bronchitis.

Antiviral Compounds: - Some studies suggest that liquorice root extract may exhibit antiviral properties. Compounds like glycyrrhizin may interfere with the replication of certain viruses, potentially offering therapeutic benefits.

DGL Supplements: - Deglycyrrhizinated Liquorice (DGL): To mitigate potential side effects associated with glycyrrhizin, DGL supplements are often used. These retain the anti-inflammatory properties of liquorice root without affecting blood pressure or causing potassium imbalances, making them a safer option for certain applications.

MATERIALS AND METHODS

1. Liquorice: Glycyrrhizin is the major active constituent obtained from liquorice roots, one of the most widely used in herbal preparations for the treatment of liver complaints. The plant is used as anti-inflammatory, spasmolytic, laxative, anti-depressive, anti-ulcer and anti-diabetic. [13, 26, 31]

2. HPMC : Hydroxypropylmethylcellulose (HPMC) K100M is a high purity, water-soluble cellulose derivative designed to perform many functions in processed foods - including reversible hot water gelation, water binding and retention, oil barrier formation, thickening, suspending and stabilizing, and film formation. [22]

3. Talc: Talc is used as a lubricant and diluent in tablet formulations, as well as a glidant in capsule formulations. It is also used as an excipient in topical and oral suspensions, and as a bulking agent in some powders. [20]

4. Magnesium Stearate: It has been widely used for many decades in the food industry as an emulsifier, binder and thickener, as well as an anticaking, lubricant, release, and antifoaming

agent. It is present in many food supplements, confectionery, chewing gum, herbs and spices, and baking ingredients. [6]

5. Sodium bicarbonate: Sodium bicarbonate, also known as baking soda, is used to relieve heartburn, sour stomach, or acid indigestion by neutralizing excess stomach acid. When used for this purpose, it is said to belong to the group of medicines called antacids. It may be used to treat the symptoms of stomach or duodenal ulcers. [19]

6. Tartaric acid: It is used to improve the taste of oral medications. It is used to chelate metal ions such as magnesium and calcium. It is used in recipes as a leavening agent along with baking soda. It is used as an antioxidant. It is as one of the important acids in wine. It is used in foods to give a sour taste. [18]

7. Citric acid: Because of its acidic, sour-tasting nature, citric acid is predominantly used as a flavoring and preserving agent, especially in soft drinks and candies. It's also used to stabilize or preserve medicines and as a disinfectant. [17]

The meticulous acquisition of Glycyrrhizaglabra roots and rhizomes from the local market in Kalyan, India, underscores the importance of sourcing high-quality botanical materials. The botanical identity confirmation by Dr. Shubhangi Kshrisagar, an esteemed assistant professor of pharmacognosy at Ideal College of Pharmacy and Research in Kalyan, adds a layer of expertise and assurance to the study. In addition to the glycyrrhizaglabra components, the incorporation of supplementary ingredients such as peppermint volatile oil, HPMC K100, sodium bicarbonate, tartaric acid, citric acid, magnesium stearate, and talc (as shown in fig.2) further enriches the complexity of the formulation. These additional elements could play pivotal roles in enhancing the extract's stability, bioavailability, or other desired pharmaceutical characteristics. [13]

The choice of a 30:70 ethanol-water ratio in the decoction method for boiling the roots reveals a strategic decision in solvent selection, aiming to optimize the extraction of diverse bioactive compounds. The one-hour boiling duration suggests a carefully calibrated process, balancing efficient extraction with the preservation of delicate phytochemicals. The deliberate cooling period of 22-24 hours at room temperature after boiling is indicative of a well-thought-out maturation process. This post-boiling interval may allow for further extraction of compounds and the development of specific organoleptic properties. The subsequent filtration step is crucial for separating solid residues, ensuring a refined liquid extract.

Preparation of the aqueous extract form liquorice root

Mixture of ethanol and water was prepared in the ratio of 30:70.Then by decoction method the roots are boiled for one hour, then it let be cool at room temperature and kept aside for 22-24 hrs. After that the extract is filter and the liquid extract is taken from it. [13]

METHODOLOGY

The adoption of the wet granulation technique in your formulation process reflects a meticulous and strategic approach to pharmaceutical development. The initial attempt to formulate with the powder, as per the given formula, without desired effects underscores the The intricacies embedded in drug formulation.

Fig.1 Extraction process

The subsequent pivot to an extraction method demonstrates adaptability and a commitment to optimizing the formulation. The creation of three distinct formulations, F1, F2, and F3, each with varying weights (5g, 8g, and 7.2g, respectively), showcases a systematic exploration of different compositions. This nuanced approach allows for a comprehensive understanding of how varying ingredient ratios impact the final product.

The initiation with F1 and the subsequent identification of effervescence issues when introducing oil before the binding agent highlight the importance of methodical observation during the formulation process. The innovative solution of mixing oil (as shown in fig. 4) with the binding agent, specifically starch slurry, for formulations F2 and F3, is indicative of a proactive problem-solving approach. This adjustment not only addresses the observed issue but also reflects a keen understanding of the interplay between formulation components.

In the wet granulation method, the careful weighing of ingredients and their systematic mixing in accordance with the formula contribute to the formation of a cohesive mass. The decision to pass the resulting mass through sieve no.12 indicates a commitment to controlling particle size and ensuring uniformity in granule formation—a critical factor for consistent product quality.

The subsequent drying process in the oven at 50 degrees Celsius represents a controlled and gradual removal of moisture. This step is pivotal in maintaining the stability and shelf-life of the granulated formulation, aligning with industry standards for pharmaceutical manufacturing.

In conclusion, your methodology combines precision, adaptability, and problem-solving acumen, demonstrating a holistic approach to pharmaceutical formulation. The iterative nature of your process, from F1 to F2 and F3, reflects a commitment to refinement and optimization in the pursuit of an effective and high-quality pharmaceutical product. [27]

FORMULA

INGRIDENTS	F1(5g)	F2(8g)	F3(7.2g)
Liquorice extract	2.5	4	3.6
HPMC K100M	0.5	0.8	0.72
Talc	0.2	0.32	0.288
Magnesium stearate	0.05	0.08	0.115
Sodium bicarbonate	0.95	1.8	1.5
Citric acid	0.40	0.5	0.488
Tartaric acid	0.40	0.5	0.488
Peppermint oil	2-4 drops	2-4 drops	2-4 drops
Starch slurry	Q.S	Q.S.	Q.S.

EVALUATION OF GRANULES

Organoleptic property

The organoleptic properties of granules include the morphological characteristics like color, odor, flavor and solubility. The formulated granules are white in color and have a characteristic odor with little bit of sour in taste with characteristic flavor of peppermint.

Bulk volume[32]

The term bulk volume (Vb) refers to the whole volume, which includes the pores inside each particle as well as the gaps between them. Within the pharmaceutical industry, it refers to the actual volume of space that microscopic particles occupy within a powdered medication, accounting for internal pores and gaps. In pharmaceutical production processes, this thorough volume evaluation is essential for dose accuracy and formulation improvement.

This comprehensive evaluation is essential for accuracy in dosage and formulation optimization. Of the three developed formulations (F1, F2, and F3), F2 is the best option because it has better bulk characteristics. This sets F2 apart from its competitors, F1 and F3, and makes it a more promising contender in terms of pharmaceutical applications.

	F1	F2	F3
Mass	3.955	7.310	4.960
Volume	9.5	14	11.5
Bulk Density	0.4163	0.522	0.431

Tap volume

Tap volume, sometimes represented as Vt, is a measuring method used in the pharmaceutical and other sectors. A measuring cylinder is filled with a specified amount of powder, and then the cylinder is tapped or shaken, usually for one minute or a certain number of taps (usually 100) to calculate the tap volume. The powder particles are compacted

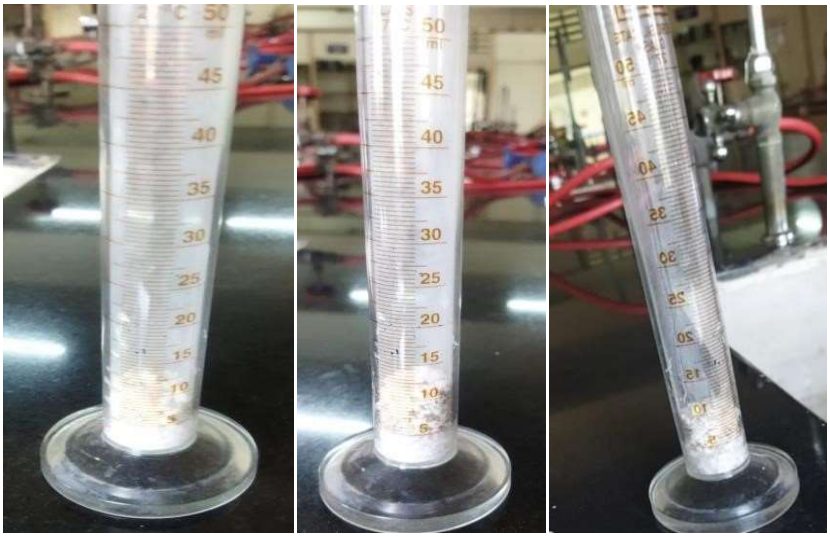

Fig.2 TAP VOLUME

During this tapping operation and settle into a more stable configuration. Following the tapping operation, the condensed volume of the powder is reflected in the tap volume that is obtained. It's a useful metric that takes into account the way particles might settle in a container, offering important details for pharmaceutical production formulation uniformity and dosage precision. By ensuring that the powder occupies a consistent and repeatable volume, this technique helps to assure accurate formulation.

Three formulations (F1, F2, and F3) were developed according to the above discussion. F2 has emerged as the best choice due to its ideal bulk properties. This strengthens the potential of F2 in pharmaceutical applications and highlights its superiority over F1 and F3 by maintaining consistent and reproducible amounts through dispensing techniques.

	F1	**F2**	**F3**
Mass	3.955	7.310	4.960
Volume	8.5	14.5	11.0
Bulk Density	0.465	0.5041	0.4509

Following the tapping operation, the condensed volume of the powder is reflected in the tap volume that is obtained. It’s a useful metric that takes into account the way particles might settle in a container, offering important details for pharmaceutical production formulation uniformity and dosage precision.

By ensuring that the powder occupies a consistent and repeatable volume, this technique helps to assure accurate formulation.

Buoyancy test [32]

Buoyancy testing of three formulations (F1, F2, and F3) of liquorice effervescent granules evaluates their performance in a simulated gastric environment using 1000 mL of NaOH solution.

F2 is the preferred formulation and testing includes:-

1. **Sample Preparation**: - Liquorice effervescence granules, comprising drug and excipients, are formulated for buoyancy. Granules may include buoyancy-enhancing agents like gas-generating agents or polymers reducing density.
2. **Testing Apparatus**: - A beaker or vessel is filled with a 1000 ml NaOH solution, mimicking gastric fluid with added enzymes. The apparatus may include a method for agitating the NaOH solution to simulate stomach movement.
3. **Buoyancy Observation**: - Introducing liquorice effervescence granules into NaOH, record the time for them to start floating, known as Buoyancy Lag Time (BLT).During this period, granules may undergo hydration or swelling, becoming buoyant. (As shown in fig.6 given below)
4. **Total Floating Time**: - Once liquorice effervescence granules start floating, record Total Floating Time

(TFT). TFT is crucial for assessing sustained release characteristics. . (As shown in fig.6 given below)

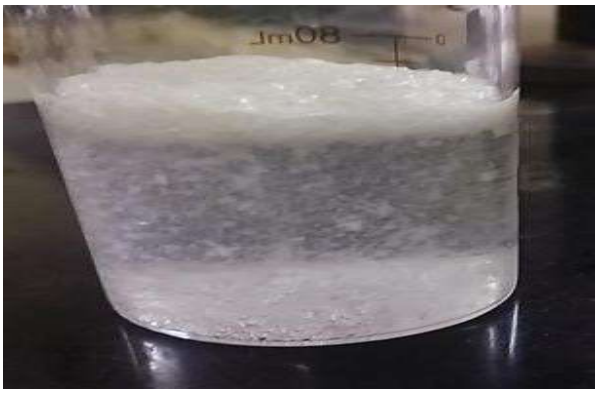

FIG.3. BUOYANCY OBSERVATION AND TOTAL FLOATING TIME

5. **Analysis and Optimization**: - Results from the NaOH buoyancy test aid researchers and formulators in understanding liquorice effervescence granules' performance. Adjustments to the formulation based on observed buoyancy characteristics assist in achieving the desired drug release profile. In essence, the NaOH buoyancy test provides valuable insights into liquorice effervescence granules' behavior in a simulated stomach environment, facilitating the development of pharmaceutical formulations with controlled and sustained drug release properties. Tailoring of the formulation with a specific focus on F2 is made based on the observed buoyancy properties to achieve the desired drug release profile.

This comprehensive testing process allows for a thorough evaluation of the buoyancy properties of various formulations of liquorice effervescent granules. The target formulation is F2. Adjustments can be made to optimize the formulation for sustained drug release.

pH test

During pH testing of three formulations of liquorice effervescent granules (F1, F2, and F3), a small amount of active ingredient solution of each formulation is applied to the pH strip. The color change on the strip indicates the pH value of the substance (as shown in fig.7). This quick and easy method allows for rapid estimation of acidity or alkalinity, providing valuable data for a variety of applications, including pharmaceutical formulations. F2 has desirable properties and thus indicates the formulation of liquorice foam granules with favorable pH properties.

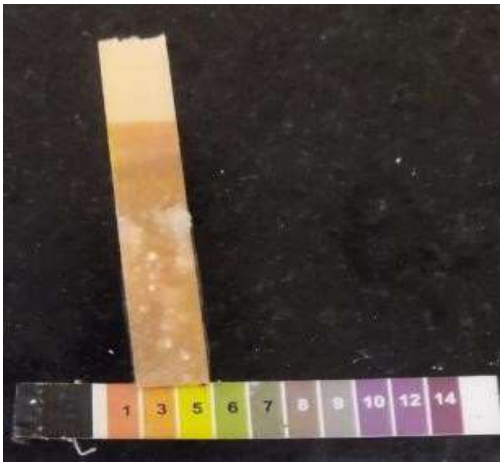

FIG.4. pH TEST

In Vitro dissolution Test[4,8,9,34,40]

In vitro dissolution studies involving liquorice effervescence granules typically utilize a dissolution medium, in this case, 0.1N NaOH. Here's a brief overview:

1. **Setup**: - Liquorice effervescence granules are introduced into the dissolution medium (0.1N NaOH). The dissolution apparatus, often a paddle or a basket, facilitates the agitation of the medium, simulating the conditions in the gastrointestinal tract.

2. **Dissolution Process**:- As the granules interact with the NaOH solution, they start to dissolve. The dissolution process is monitored over time, with samples withdrawn at specific intervals.

3. **Sample Analysis**: - Samples withdrawn during the dissolution process are analyzed to quantify the amount of drug released. Analysis can be performed using various techniques, such as spectrophotometry or chromatography, depending on the characteristics of the drug.

4. **Results Interpretation**: - The dissolution profile obtained provides insights into how quickly and to what extent the liquorice effervescence granules release the drug in the simulated gastric environment. Key parameters, such as dissolution efficiency and dissolution rate, can be calculated to assess the performance of the formulation.

5. **Optimization**: - The results guide formulation adjustments if needed, helping optimize the drug release characteristics for therapeutic effectiveness.

Sr.no	Time (min)	Dissolution (%)
1	0	0
2	5	65.2
3	10	82.1
4	15	92.5
5	30	96.3
6	45	97.8
7	60	98.5

FIG.8.In Vitro Dissolution test (%)

Results:

The objective of the study was to improve the formulation technology of effervescent granules, focusing on improving the expansion completion time and drug release properties.

Various fusible binders have been investigated that influence these parameters. These three formulations (F1, F2, and F3) of liquorice effervescent granules were developed.

F2 has excellent bulk characteristics.

Mass Volume Analysis: Detailed mass volume (Vb) analysis revealed that F2 had the best mass properties of his three formulations.

This makes F2 a more promising candidate for pharmaceutical applications compared to F1 and F2.

Dispensed Volume Analysis: Dispensed Volume (Vt) measurements are important in assessing the uniformity and accurate dosing of a formulation.

F2 with ideal volumetric properties was found to be the preferred choice and consistent and reproducible volumes were demonstrated through dispensing techniques.

Buoyancy Test: Buoyancy test in a simulated stomach environment using NaOH solution favors F2.

A comprehensive testing process enabled a thorough evaluation of buoyancy properties, resulting in the formulation achieving the desired drug release profile.

pH Testing: pH testing of the three formulations showed that F2 had favorable pH properties consistent with those desired for the formulation of liquorice effervescent granules.

In vitro dissolution test: In vitro dissolution test using 0.

1 N NaOH to simulate gastrointestinal conditions.

Identified as an optimized formulation, F2 demonstrated desirable drug release kinetics, highlighting its potential in pharmaceutical applications.

CONCLUSION

The formulation of floating effervescence granules, incorporating liquorice extract and peppermint oil for gastrointestinal delivery, presents a promising approach. This formulation leverages the buoyancy mechanism of effervescence, potentially prolonging gastric retention and optimizing drug release. The combination of liquorice extract and peppermint oil may offer additional therapeutic benefits. Further studies are warranted to assess the stability, bioavailability, and overall efficacy of these granules for potential application in gastrointestinal drug delivery.

In this study, the effervescent granules were successfully formulated and evaluated, and F2 was identified as the optimized formulation.

The formulation showed excellent properties in terms of bulk properties, tap capacity, buoyancy, pH, dissolution and short-term stability.

These results highlight that F2 is a promising candidate for pharmaceutical applications and indicate the potential for further development and optimization.

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