Original Article

STUDIES ON THE TASTE MASKING EXTRACT OF NEEM (*Azadirachta indica*) AS A DRY SUSPENSION

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Abstract

The creation of oral dosage forms depends heavily on taste and odour. The primary goal of this research is to identify methods for disguising the unpleasant taste and odour of neem leaves (*Azadirachta indica*). Organoleptic characteristics, LOD, particle size and shape, and other preformulation investigations were carried out. Neem leaf was extracted using the percolation technique with ethanol as a solvent (menstrum). Human participants underwent the Pleasant Taste Perception Test (PTP), which involved masking unpleasant tastes and odours using solvent evaporation and solid dispersion techniques. According to the monograph, dry suspension was created using sodium starch glycolate (SSG) as a disintegrant and was then characratized. The outcomes demonstrated the effectiveness of various flavour masking technologies in enhancing the features of the dose form and enhancing patient compliance.

Keywords: *Azadirachta indica*, Taste masking, Dry suspension, Patient compliance, Drug product.

Introduction

The majority of medications are taken orally. The taste of disagreeable medications makes it difficult to administer them, especially to children and the elderly (Mennella et al., 2013). The taste of unpleasant pharmaceuticals can be covered up using a variety of techniques, including coating, inclusion complexes, microencapsulation, granulation, adsorption, and the prodrug approach, the addition of flavours and sweeteners, and ion exchange resins. Any strategy, nonetheless, is not appropriate for covering up all the unpleasant medications' tastes. The technique to be utilised for masking the taste of bitter pharmaceuticals depends on a number of factors, including the degree of bitterness, dose, administration form, and kind of patient (Coupland et al., 2014). In addition to oral medication administration, taste-masked drug delivery research is becoming more significant for enhancing the calibre of paediatric and geriatric therapy. One of the most effective recognised blood cleaners, detoxifiers, and immune system boosters is neem (Alzohairy 2016). Functionally, there are two different kinds of taste receptor cells. A trans membrane protein known as an ion channel type receptor is one that permits the ions that cause the salty and sour sensations. These ionic interactions lead to electrical changes in taste cells, which in turn drive neurons to transmit chemical messages to the brain.

In their natural condition, these cells have a net negative charge. Taste change this condition by employing a variety of techniques to raise the concentration of positive ions inside the taste cell.

The cell releases neurotransmitters as a result of this depolarization, which then transmits the electrical signals to the brain (Roper et al., 2017). The other is a surface protein receptor that permits the attachment of tastants, or taste-giving molecules, which provide the sensations of sweetness, bitterness, and umami. When a stimulus is

bitter, it binds to G-Protein coupled receptors and has an effect. Leads to more G-Protein subunit splitting, activation of a neighbouring enzyme, and ultimately, the release of secondary messengers.

The taste cell endoplasmic reticulum releases Ca^{2+} ions during the initiation of the secondary messengers (Ahmad et al., 2020). The cell depolarizes and releases neurotransmitters as a result of the elevated calcium ion concentration. Sensory neurons transmit this data to the brain, which interprets it as "bitter" taste. In order to increase patient adherence and achieve the required therapeutic efficacy, the medicine must be made more pleasant. The fluoroquinolone antibiotics, penicillins, macrolide antibiotics, and non-teroidal anti-inflammatory medicines are potential for taste masking going forward because of their extremely bitter flavour (Sohi et al., 2004).

Nearly all of the components of the neem tree are used for a variety of purposes, making it one of the most extensively studied tropical trees. Traditional medicine uses neem as a source for several medicinal substances. When used as a medical plant, neem extracts may be helpful in preventing the growth of the cancer-causing bacteria *S. sobrinus* (Kumar et al., 2013). Alkaloids, glycosides, flavanoids, and saponins are plant compounds that have antibacterial properties.

The formulation of oral dosage forms takes into account aspects including flavour, aroma, and texture. The quality of the product and patient compliance are now both influenced by taste. An old saying that has completely altered is, "The worse the taste of the medicine, the greater the cure". Given that the majority of unpleasant medications are taken orally, taste masking has become more significant. This motivation is an effort to enhance the properties of the dose form and increase patient compliance through the development of various taste-masking technologies.

Experimental

Collection of neem leaf

Azadirachta indica (Neem leaf) was procured from a tropical zone of a farm in Unaizah, Saudi Arabia, and authenticated (Ref. No: R1401157 - V.R. College, Dept. of Botany, India). The leaf was chosen for study because it was healthy and rich in cartilage. Neem leaf was collected and dried for a week in the shade and at room temperature (25–27 ºC) (April-May 2022). The dried leaves were ground in a blender to lower the particle size, and the average particle size was 827 µm after sieving through sieve no. 20.

Extraction by Percolation method

In most cases, a percolator—a thin, conical vessel open at both ends—was employed. Azadirachta indica was soaked with the right quantity of the required 90% ethanol (menstruum) and let to stand for around 4 hours in a tightly covered container before the mass was packed and the percolator's top was secured. The combination was given 24 hours to macerate in the closed percolator after additional menstruum was added to create a thin layer above the bulk. The percolator's outlet was then opened, allowing the liquid within to trickle gradually (Mohamed et al., 2022). Menstruum was added as needed until the percolate was roughly three-quarters of the end product's necessary volume. The liquid from the squeezed marc was then added to the percolate. Menstrual fluid was added in sufficient amounts to provide 50 mL, and the resulting mixture was purified using filtration or by standing followed by decanting.

Neem leaf powder was combined with percolator, then with cotton, sand, and filter paper while being extracted with ethanol from menstrual fluid. According to the literature, ethanol works well for extracting neem leaves. The aforementioned arrangement was left undisturbed for 48 hours, at which time 20 mL was collected and discarded (Mohamed et al., 2021). The remaining extract was collected without pressing the mark, and after it had been evaporating in a water bath, the concentrate was dried in a tray dryer at 40 ºC. After collecting the extract paste, a concentrated form of neem extract was predicted theoretically and practically. By performing a calorimetric experiment at 450 nm, the extract was verified.

Taste Masking Technique

The combination of identical compositions created with the existing techniques. The techniques adopted from dry granulation methods. The amount of extract utilised in each formulation was 100mg. In this investigation, drug extract to polymer ratios of 1:0.5, 1:1, 1:1.5, and 1: 2 were utilised. The neem leaf has an extremely bitter character; its bitterness was calculated using spectrophotometry.

Solvent evaporation method

As polymers, povidone, HPMC, urea, mannitol, and ethyl cellulose were employed. Drug (extract) polimer ratios of 1:1, 1:1.5, and 1:2 was utilised, while ethanol was used as the solvent (Moideen et al., 2020). Extract was dissolved in ethanol, then polymer was distributed and agitated with a magnetic stirrer at 40 ± 1 °C (REMI-2MLH). The same solution was transferred to a petri dish, and a hot plate was used to evaporate it at 50 ± 0.5 °C in order to eliminate the solvent. The finished product was dried for 24 h at 40 °C. IT CAN BE IN TABLE

Solid dispersion (SD) method

The SD was made by adding 100 mg of extract to the molten polymer at 60 °C while swirling continuously for 15 minutes at a speed of 700 rpm to achieve a homogenous dispersion. The end result was allowed to harden before being cooled to room temperature (28 °C), ground, sieved, and stored in a desiccator at 25 °C (Mohamed et al., 2021).

Preparation of dry suspension

Pass through filter #60 dry extract, xanthan gum, aspartame, and citric. Separately pour sodium starch glycolate (**SSG**), sodium benzoate, sodium laurayl sulphate (SLS), and citric acid into filter #100. Check the mixing process as you combine all the materials in a polybag (Table 1). Mix and shake the dry suspension with 100 mL of warm water. There are 5 mg of drug in each 5 mL (Srividya et al., 2022).

Table 1. Various formulation of dry suspension preparation

Formulation code	**Drug (%)**	**Xanthin Gum (%)**	**Aspertase (%)**	**Citric acid (%)**	**Sodium benzoate (%)**	**SLS (%)**	**SSG (%)**
S1	10	10	14	1.6	0.8	4	4
S2	10	11	18	1.6	0.8	3	6
S3	10	12	16	1.6	0.8	3.2	8

Evaluation of dry suspension

Loss on drying and pH

The dry suspension should be placed in a clean Petridis hot air oven and baked for one hour at

105 ^{o}C before being weighed. The starting and final weights were subtracted to get the percentage of loss on drying **(**LOD). The electrode of the handheld digital pH metre (LJ-131; India) was submerged in the suspension for five minutes while reading the pH of the mixture.

Sedimentation volume

The sedimentation volume was measured at predetermined intervals during storage without agitation for a period of 10 days in order to study the sedimentation in reconstituted suspension. The sedimentation volume was recorded in terms of the ratio of the ultimate settled height (Hu) to the original height (Ho), as expressed in the following equation F=Hu/Ho (Senthilvel et al., 2022).

Determination of redispersibility

Following the completion of the sedimentation trials, the cylinder is manually shaken as part of the test. The formulation was assessed based on the time and work needed to turn the silt into a homogenous suspension. One inversion was regarded as 100% redispersible. The percent ease of redispersibility dropped by 5% for each subsequent inversion.

Rheological studies

Utilizing the Ostwald's viscometer, the rheological profile of each formulation's reconstitution in terms of viscosity was identified. All measurements were done at a constant temperature of 25 ^{o}C plus or minus 1 ^{o}C. Using a pycnometer metre, the suspensions densities were measured.

Pleasant taste perception test (PPT)

In order to reduce the considerable changeability of drug concentration in the mouth due to different salivation states among participants, a pleasant taste precipitation test was conducted on the suspension for assessment. Six young human volunteers participated in the PPT test to ascertain the threshold for bitterness perception. Seven standard solutions of pure neem extract in distilled water were created at various concentration levels (0, 0.01, 0.025, 0.05, 0.1, 0.2, and 0.4% w/v). The volunteers were then instructed to sample 5L of the aforementioned solution in order to determine whether their tastes differed (Matsuo 2000).

Spectrophotometric method

10 mL of distilled water and 1 mL of the taste-mapping formulation (dry suspension) were combined in a 10 mL syringe by turning it five times from end to end over the course of 30 minutes.

After passing the test medium through a membrane filter, the concentration of the drug in the filtrate was determined spectrophotometrically. It was determined that bitter taste would be disguised *in vivo* if the concentration was lower than the normal concentration.

Fourier transform infra-red spectrophotometry (FT-IR) analysis

To determine if the functional group, the FT-IR spectra of the *Azadirachta indica* extract and suspension formulation were examined. According to our earlier study, the infrared spectra in the 4000-400 cm^{-1} region were acquired using a JAS-CO/FTIR-6300, Japan FTIR Spectrometer (Senthilvel t al., 2022).

***In vitro* dissolution studies**

Under the following circumstances, an in vitro dissolution test for neem extract release was performed: 100 mg of neem extract in each sample, in 500 ml of phosphate buffer with a pH of 6.8, at a medium temperature of 37±1 ^{o}C. Samples were collected at 5 to 180 min, and samples were examined using UV spectrophotometry at 276 nm. Experiments were carried out in triplicate.

The artificial semipermeable membrane, which was sealed at both ends with 100 mg of drug solution, was used (Mohamed et al., 2022). The arrangement used a 1000 mL beaker with 500 mL of phosphate buffer pH 6.8 and a magnetic stirrer. The situation would sink when the magnetic bead was changed to revolve at 50 rpm. A semipermeable membrane containing a suspension was briefly submerged in the aforementioned solution, and a 5 mL aliquot was taken out of the bulk to replace the old buffer. After making a sufficient amount of dilution, the sample was then read spectrophotometrically.

Results and Discussion

The neem leaves that were harvested had a distinctive aroma, were dark green in colour, and were shaded for about two weeks before turning a greenish brown and becoming brittle. After achieving a satisfactory decreased size (since coarse powder was needed for extraction), size reduction by blending was carried out. It would then be placed inside a sealed container for later use and 5.4% of the LOD studied for preformulation had a spherical shape (Mohamed et al., 2020). It would be concluded that it would satisfy all extraction conditions. About 80 mL of menstrual fluid (ethanol) was introduced to a percolator filled with powdered neem leaf, and the percolator extracted roughly 640 mL of extract, or about 80% of the total amount. The yield would be 54% when it was concentrated using stream distillation and the extract was dried at 40 ^{o}C in a tray dryer until it resembled paste. By calorimetrically confirming the extract's active components at 450 nm. According to a melting point instrument, the extract's melting point is 92 ^{o}C.

Taste Masking

Table 2 shown that the absorbance less than that of standard absorbance (0.207) it indicates that the 1:0.5 ratio of drug polymer complex is better that that of other formulation also formulation of dry suspension would be effective.

Table 2. Various concentration of drug: polymer ratio with absorption

Solid dispersion		Solvent evaporation		
Drug: polymer ratio	Absorbance	Drug: polymer ratio	Absorbance	Standard absorbance (Extract) 0.207
1;0.5	0.181	1;0.5	0.063	
1:1	0.165	1:1	0.155	
1:1.5	0.182	1:1.5	0.123	
1:2	0.110	1:2	0.129	

Preformulation studies

The extract, aspartame, and citric acid particles that were coarse in size during the dry granulation process had difficulties passing through the sieve and were decreased by pulverisation thereafter. In another hand, the LOD of the extract was determined to be 0.12% and 3.8% of LOD was discovered in dry suspension after 1 hour at 105 ^{o}C. The created suspensions pH ranged from 4.32 to 4.87. Among the three formulations, S1 shows a lower release profile than S2 and poorer performance in terms of LOD, pH, density, viscosity, redispersibility, drug content, and *in vitro* dissolution profile (Muthu etal., 2020). It was determined that the formulation S2 was almost closer to having the right profile than the formulation S1 (S1< S2).

Sedimentation volume

The sedimentation volume was measured at predetermined intervals throughout storage without agitation for a period of 10 days in order to study the sedimentation in reconstituted suspension. The volume was recorded in terms of the ratio of the final settled height (Hu) to the original height (Ho), as shown in the example below, which would indicate that the suspension was deflocculated.

The viscosity values of the S3 formulation, which contains 16% aspartame, are sufficient for suspension dispersibility, according to a sedimentation volume and redispersibility result. One inversion was rated as being 100% re-dispersible. The percent ease of re-dispersibility fell by 5% for each subsequent inversion.

Rheological studies

Utilizing the Ostwald's viscometer, the rheological profile of each formulation's reconstitution in terms of viscosity was identified. All measurements were done at a constant temperature of 25 ºC plus or minus 1 ºC. The suspensions density was measured using a picnometer, and the findings were 2.4 g/cc. The prepared dry suspension's viscosity was measured between 45.52 - 61.34 mPa.s.

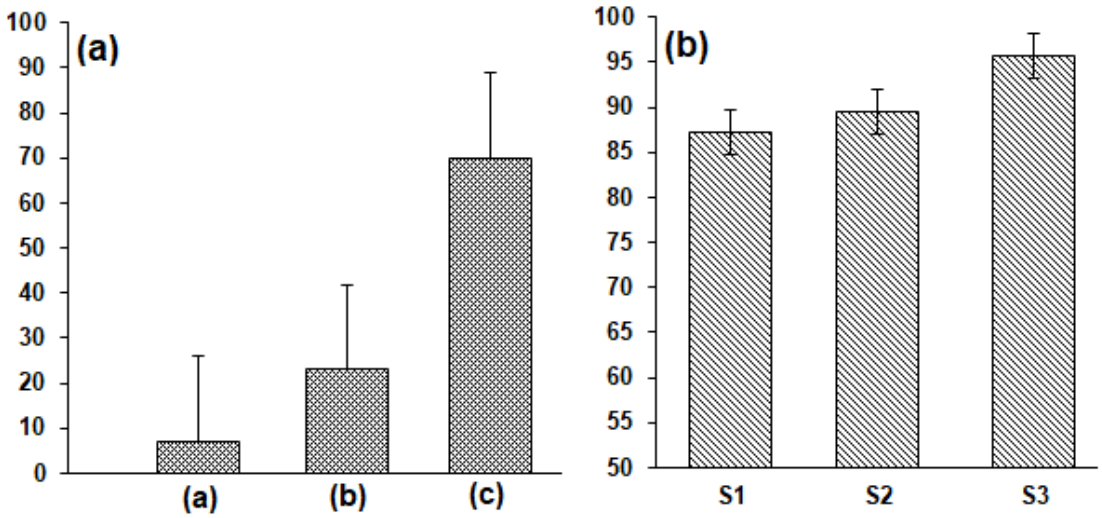
Pleasant taste perception test

The volunteers were then instructed to sample 5 mL of the aforementioned solutions based on their individual tastes. (a) I have a bitter taste, and (c) there is no change in how I feel between 0% and 0.05%. (c) I sense something, but I can't place the flavour (Figure 1a). Volunteers were invited to taste 0.1% solution if they said they did not notice any difference between 0% and 0.05% solutions, whereas those who said they tasted bitterness were asked to sample 0.025% solution. The perceptual threshold therefore lies between 0.25 and 0.5%w/v, or at a level of 0.5%w/v. As this came to the conclusion, there are certain solutions for taste that use different concentrations of neem extract to achieve a uniform bitterness intensity among the human volunteers.

Assay for drug content

S1 and S2 of the three formulations both exhibit a sizable quantity of drug in the dry suspension, however the test result mentioned above reveals that S3 has the highest amount of drug content and is the best formulation overall. To optimise the optimal formulation was the objective (Figure 1b).

Figure 1. (a) PPT of three different evaluations, and (b) drug content result of dry suspension from S1 to S3



UV-spectroscopy

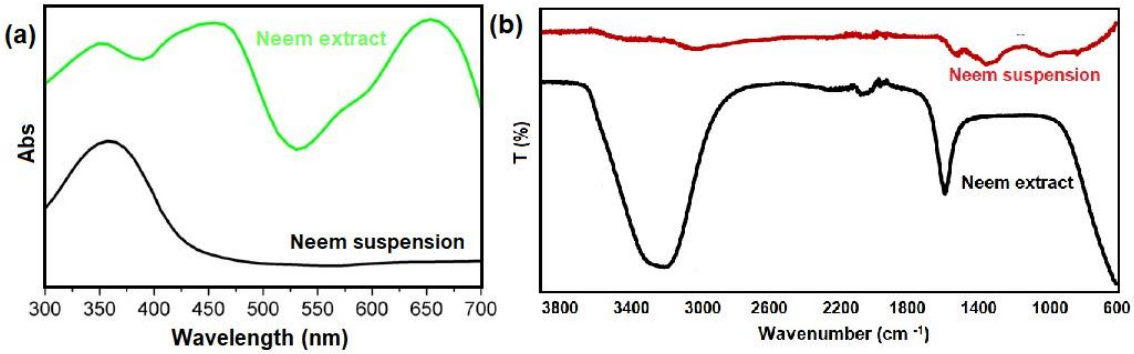
A single UV absorption peak with a centre of 425 nm, as shown in Figure 2a, was used to monitor and validate the formation of neem suspension. The neem extract suspension colour changed from off-white to yellowish after the addition of neem leaf extract, providing visible evidence that taste masking had been confirmed. Figure 2a displays a typical peak of neem extract that was measured at 378 nm.

FT-IR study

The FTIR spectra of pure neem leaf extract and suspension is shown in Figure 2b. The overlapping of the N-H bending vibration of the amine group and the OH stretching vibration of the phenolic group in the neem leaf extract is the cause of the strong stretching band that is seen at 3241 cm^{-1}. Neem suspension have been shown to be reduced by the OH groups in phenols. The peak at 3442 cm^{-1} lost intensity after the neem leaf extract, suggesting that the phenolic groups in neem are involved in the reduction process of suspension. Similar findings were observed when neem extract was formulated with suspension; there was a shift and a significant drop in the

OH group's intensity. The FTIR spectra in Figure 2b also exhibit a peak at 1644 cm^{-1}, which is connected to the -COOH group C=O stretching.

Figure 2. (a) UV-absorbance and (b) FT-IR spectra of neem extract and neem suspension

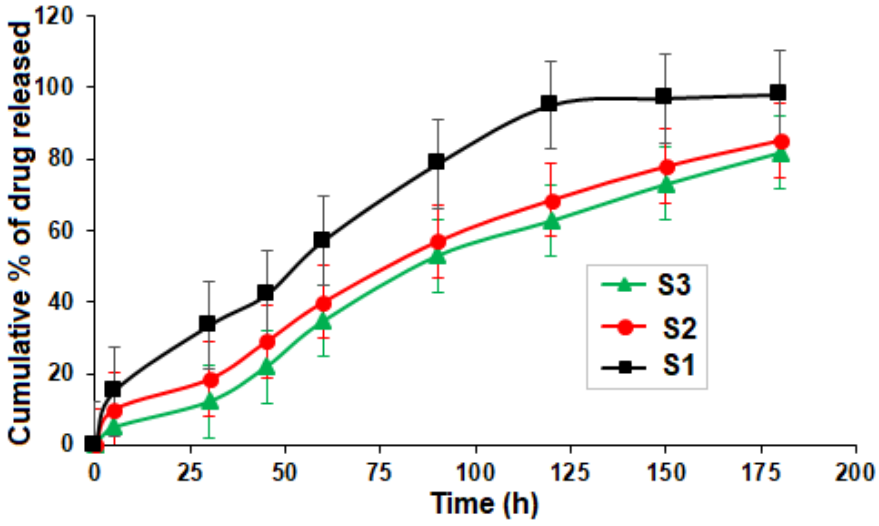


***In vitro* dissolution studies**

Under the following circumstances, an in vitro dissolution test for neem extract release was performed: Each sample contains 100 mg equivalent of suspension in 500 mL of phosphate buffer with a pH of 6.8 and a medium temperature of 37± 1 ºC. Samples were collected at intervals of 0.5, 1, 1.5, 2, and 3 hours, and samples were examined using UV spectrophotometry at 276 nm. Experiments were carried out in triplicate. The fabricated semipermeable membrane was secured at both ends with 100 mg of drug solution. The setup used a 1000 cc beaker with a magnetic stirrer and 500 ml of phosphate buffer pH 6.8. The situation would sink when the magnetic bead was changed to revolve at 50 rpm. A semipermeable membrane containing a suspension was briefly submerged in the aforementioned solution, and a 5 ml aliquot was then taken out of the bulk to replace the old buffer. After making a sufficient amount of dilution, the sample was then read spectrophotometrically.

The aforementioned findings demonstrate that the formulation S1 released instantly because of its high concentration of SSG and xanthan gum (about 4 and 10 respectively). However, S2 had a little better formulation than S1 because SSG and xanthan gum concentrations rose steadily. This clearly demonstrates that SSG increases the rate of dissolution (Elhasan 2022). Without a doubt, formulation S3 was superior to other formulations in terms of optimization (Figure 2). A loading dosage of around 1/4 of the medication is delivered in the first 30 minutes; the maintenance dose is thought of as the time between loading doses.

Figure 2. Cumulative % of drug released from dry suspension



The S3 formulation has been improved, and it exhibits a considerable, consistent release profile in all areas, including drug content of 96 ± 3.45% and second-hour release profile of 97 ± 3.77 %. The preformulation investigations and first assessment of formulation S3 yield improved results, leading to the conclusion that S3 is the optimal formulation.

Conclusion

This study suggests that masking the bitter taste of medication that is also taken orally as a dry solution. These would be laborious but necessary activities in the pharmaceutical industry. Neem materials were collected according to research standards, dried at room temperature to prevent active components from volatilizing, and then appropriately processed by size reduction and powder material evaluation. The active ingredient in the product is not soluble in water or any other neutral solvents, hence percolation technology was chosen as the extraction technique. The study came to the conclusion that ethanol should be used as a menstrual fluid since it has a high practical yield compared to other solvents. Neem extract was taste-masked, compounded, and refined to produce a dry solution in accordance with research ethics. This formulation is innovative and will be crucial for the general public health. Neem trees are typically utilised as medicinal plants, and the oral administration of a dry solution is one of the most difficult trends in the pharmaceutical industry.

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