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Formulation And Evaluation Of Caffine Nasal Drop For The Treatment Of Alzheimer Disease

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ABSTRACT

Caffeine is a widely consumed psychoactive substance known for its stimulating effects on the central nervous system, including enhanced alertness, attention, and cognitive function. While caffeine is traditionally ingested orally, recent research has explored alternative administration routes, such as nasal delivery, to potentially enhance its bioavailability and cognitive effects. This review investigates the feasibility and efficacy of caffeine nasal drops as a novel approach for cognitive enhancement. A comprehensive literature search was conducted to identify relevant studies investigating the pharmacokinetics, pharmacodynamics, and cognitive effects of caffeine nasal drops. The review discusses the nasal mucosa's permeability to caffeine and the potential advantages of nasal delivery in achieving rapid absorption and bypassing first-pass metabolism.

For local, systemic, and central nervous system medication delivery, intranasal delivery is the preferred route of drug administration. Nasal drop is an increasingly popular dosage form for nasal drugs because to its benefits, including being affordable, convenient to use and carry, and highly patient compliant delivery. It makes intuitive sense to assume that this review will id in understanding nasal formulation and its in-vitro properties.

Overall, preliminary findings suggest that caffeine nasal drops have the potential to offer rapid and effective cognitive enhancement with fewer gastro-intestinal side effects compared to oral administration. However, further research is warranted to optimize dosing regimens, assess long-term safety, and explore the potential applications of caffeine nasal drops in various cognitive tasks and populations.

Nasal compositions useful for the delivery of the caffeine alone or with other therapeutic agents.

Keywords: Nasal drop, Nasal drug delivery system, formulation and in-vitro properties

INTRODUCTION

The disorders of the central nervous system (CNS) desire a targeted delivery or therapeutic agent to the brain for their treatment. But the impervious nature of the blood brain barrier (BBB) restricts the entry of drugs into the brain compartment. This physiological barrier has been a prime hurdle for the delivery of therapeutic agents especially the ones that are hydrophilic in its nature as well as the ones that have a high molecular weight.

Nasal administration is a route of administration in which the drugs are insufflated through the nose for either local or systemic effect. Nasal route is an alternative to invasive administration and provides a direct access to the systemic circulation. . For instance, localized nasal drug delivery is usually used to treat conditions related to the nasal cavity, such as congestion, rhinitis, sinusitis and related allergic conditions.

Intranasal route: nose-to-brain drug delivery:

Delivery of the drug via IN route is a suitable route for potent drugs with low or almost no oral bioavailability .It is a safe, non-invasive , and suitable form and strategy to be considered as a brilliant substitute approach to several conventional dosage forms. They are having the advantages of providing a direct transport route to the target CNS via nasal route, overcoming the limitations of BBB. The major aim of these drug delivery pathways is to deliver the desired drug concentrations to the site of action. Additionally, the degradation of drugs through metabolism can be diminished, and physical clearance can also be minimized . Highly permeable nasal epithelium allows rapid drug absorption to the brain due to a high total blood flow, porous endothelial membrane, large surface area, and avoidance of first-pass metabolism. The intranasal method can deliver a wide variety of therapeutic agents (small molecules and macromolecules) to the CNS. Further, nasal drug delivery neither requires any modification of the therapeutic agent nor requires the drug to be coupled to any carrier. Nasal drug delivery consisting of various pathways has always been a key development area for both pharmaceutical and medical device companies, presenting compelling advantages over other drug delivery methods

- **Advantages of Nasal Drug Delivery System :**

1. Intranasal administration offers several practical advantages from the viewpoint of patients (non-invasiveness, essentially painless, ease drug delivery and favourable tolerability profile)
2. Rapid drug absorption.
3. Quick onset of action.
4. Hepatic first – pass metabolism is absent.
5. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
6. Better nasal bioavailability for smaller drug molecules.

• **Limitations:**

Dose is limited because of relatively small area available for the absorption of drug.

1. Time available for drug absorption is limited.
2. Diseased condition of nose impairs drug absorption.
3. The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.
4. Absorption surface area is less when compared to GIT.

Certain surfactants used as chemical enhancers may disrupt and even dissolve Membrane in high concentration

MATERIAL AND MATHOD

All the ingredients which is used in formulation of caffeine nasal drop like methylparaben, propylparaben, sodium chloride,xanthan gum, acetic acid, sodium acetate, propylene glycol, caffeine, codeine

Sr.No	Ingredients	Use
1.	Methylparaben	Preservative
2.	Propylparaben	Preservative
3.	Sodium chloride	Isotonicity enhancer
4.	Xanthan Gum	Thickening agent
5.	Acetic acid	Antimicrobial Agent
6.	Sodium acetate	Buffer
7.	Propylene glycol	Humectant
8.	Caffeine	Active ingredient

9.	Codeine	Narcotic analgesic
10.	Purified Water	Vehicle

Drug and excipients profile:[6,7]

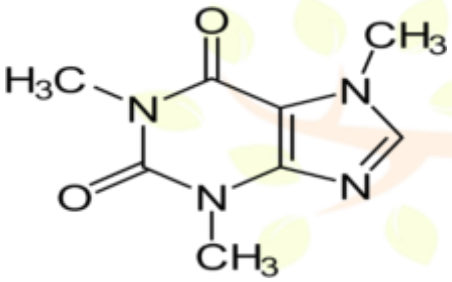
1)Caffeine :

Caffeine is odourless and has a characteristics bitter taste .It is colourless powder , moderately soluble in water.

Chemical Name: 1, 3, 7-Trimethylpurine-2,6-dione

Molecular Formula:$C_8H_{10}N_4O_2$

Molecular weight:194.19 g/mol



❖Pharmacodynamics:

Caffeine stimulates the central nervous system (CNS), heightening alertness, and sometimes causing restlessness and agitation. It relaxes smooth muscle, stimulates the contraction of cardiac muscle, and enhances athletic performance. Caffeine promotes gastric acid secretion and increases gastrointestinal motility. It is often combined in products with analgesics and ergot alkaloids, relieving the symptoms of migraine and other types of headaches. Finally, caffeine acts as a mild diuretic.

❖ Pharmacokinetics:

- Absorption

Caffeine is rapidly absorbed after nasal administration, reaching peak plasma concentration within 30 minutes to 2 hours after administration .After nasal administration, onset of action takes place within 45 to 1 hour.The peak plasma level for caffeine ranges from 6-10mg/L. Distribution

Caffeine has the ability to rapidly cross the blood-brain barrier. It is water and fat soluble and distributes throughout the body .Caffeine concentrations in the cerebrospinal fluid of preterm newborns are similar to the concentrations found in the plasma. The mean volume of distribution of caffeine in infants is 0.8-0.9 L/kg in the adult population.

- **Metabolism**

Caffeine metabolism occurs mainly in the liver via the cytochrome CYP1A2 enzyme.The products of caffeine metabolism include paraxanthine, theobromine, and theophylline. The first step of caffeine metabolism is demethylation, yielding paraxanthine (a major metabolite), followed by theobromine, and theophylline, which are both minor metabolites.

They are then excreted in urine as urates after additional metabolism.

- **Mechanism of action:**

Caffeine exerts several actions on cells, but the clinical relevance is poorly understood. One probable mechanism is the inhibition of nucleotide phosphodiesterase enzymes, adenosine receptors, regulation of calcium handling in cells, and participates in adenosine receptor antagonism.
Caffeine demonstrates antagonism of all 4 adenosine receptor subtypes (A_1, A_2a, A_2b, A_3) in the central nervous system. Caffeine's effects on alertness and combatting drowsiness are specifically related to the antagonism of the A_2a receptor.

- **Clearance**

The clearance of caffeine varies, but on average, is about 0.078 L/kg/h (1.3 mL/min/kg).

- **Toxicity:**

In the case of caffeine overdose, seizures may occur, as caffeine is a central nervous system stimulant. It should be used with extreme caution in those with epilepsy or other seizure disorders. Symptoms of overdose may include nausea, vomiting, diarrhea, and gastrointestinal upset.

METHOD OF PREPARATION:

For the preparation of nasal drops:

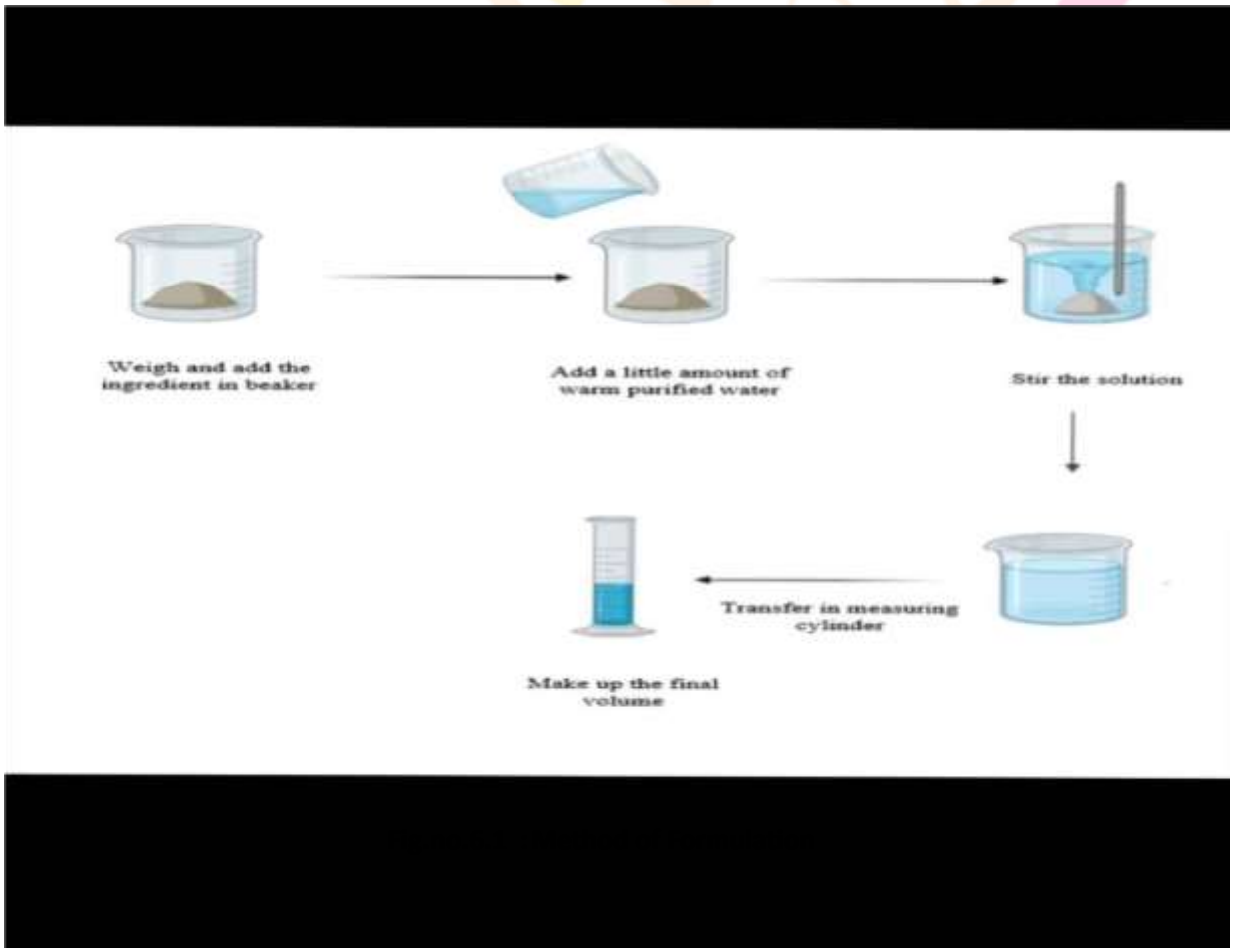
1.Calculate the required quantity of ingredients

2. Weigh it according to the calculated quantity and add it to the beaker.

3. Now heat 40 ml of purified water up to 70^{o}C and add it to the ingredients with stirring.

4. After this, allow the mixture to cool at room temperature, followed by adding the remaining ingredients to it with constant stirring so it will be uniformly distributed.

5. Add the sufficient amount of the purified water to it, for making final volume of the nasal drop.



EVALUATION TEST

1.Physical appearance :

The formulated nasal drop was visually evaluated for colour, odour and it's appearance. The colour of the nasal drop is colourless and it's odour is pungent.

2.pH test:

The overall range of pH of the anterior part of the nose was 5.17 to 8.13 while that of the posterior part was 5.20 to 8.00, indicating that an average baseline human nasal pH is approximately 6.3. Thus the stability can achieve by proper selection of pH of formulation. The lysozyme is present in nasal secretions and plays a role in destroying some microorganisms at acidic pH. Nasal tissues are susceptible to microbial infection under the alkaline conditions due to inactivation of lysozyme. However, the pH of formulation should be near on human nasal mucosa (5.0-6.5) to prevent the sneezing.

Procedure:

- The pH meter was first calibrated using phosphate buffer.
- The 40ml sample was taken in 50 ml beaker.
- The electrode placed in the beaker.
- Then pH meter was used to determine pH.[22,23]

3.Sterility test :

It is a process that destroys or eliminates all type of microbial life and micro-organisms like viruses , fungi , bacteria and spore forms . Because of the high temperatures and pressure being used within the autoclave system, it's an effective way to sterilize pharmaceutical product.

Procedure:

- Place the sample to be sterilized in the autoclave . the door is locked.
- A vacuum pump sucks the air from the chamber.
- The temperature reaches to 121^0c for 30 minutes.
- Steam kills bacteria and microbes.
- Steam is released, the door was opened and sterility of sample was checked.[22,23]

4.Viscosity test :

The absorption of the drug mainly depends upon the residence time of the molecule in contact with the mucosal membrane. For formulations containing an agent contributing to the viscosity, this parameter should be tested and controlled at release and on stability. The contact time between the drug and the nasal mucosa is increased by higher viscosity of formulation thereby increasing the time for permeation. Also high viscosity of formulations interferes with normal ciliary beating and/or MCC and, thus, increases the permeability of drugs.

Procedure :

- Firstly wash and dry viscometer.
- Take empty gravity bottle and weigh it.
- Fill the gravity bottle with water and sample.
- Weigh the filled gravity bottle and calculate the densities of water and sample.
- Take 20ml water and put it in viscometer , suck water up to the upper mark and then note time (t_w) taken by water to reach the lower mark of the viscometer.
- Take 20ml of sample in viscometer and note the time (t_s) taken as for water. Calculate viscosity of sample using formula.[22,23]

5.Skin irritability test:

These test is performed to analyse human skin response to the drug . Any allergic reactions or skin rashes and other symptoms can occurred was checked by using this test.

Procedure:

- The formulated gel in the quantity of 0.5 g was applied to the normal skin at an area of 6 cm.
- Then covered with a semi-occlusive bandage for the duration of 1 hr.
- After the application time, the bandage was removed, the applied gel was scrapped off completely,
- The area was visually inspected for any rashes or similar symptoms. The test was done for a period of 7 days.[22,23]

6.Clarity test:

The nasal preparation comes under the sterile preparation it should be clear and free from particulate matter.

Clarity test is performed to check the presence of particulate matter in sample.

Particles of size 30-40 micrometre and large size can be easily seen with eyes.

Procedure :

- Sample is poured in clean and clear glass beaker.
- Light is placed over the sample.
- The dark coloured particles can be detected against white background and light reflective particles appear against black background.
- Clarity test is also performed under microscope for more accuracy.[22,23]

RESULTS

1.Physical appearance:

Colour : Colourless

Odour : Pungent

2.pH test :

Sample	pH value
F1	5.48
F2	5.50
F3	5.51
F4	5.52
F5	5.50

The mean pH value of the sample was found to be **5.51** .

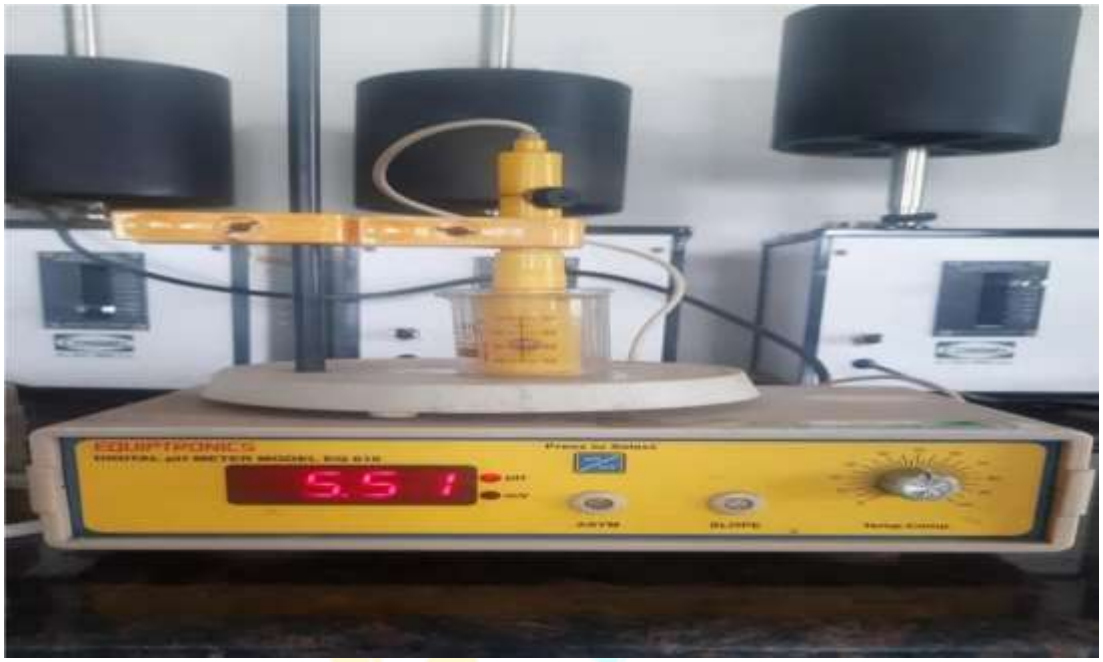


Fig.:Ph test

3.Sterility test :

There would be no microbial growth occurred in the media culture after incubation period of 14 days. Hence the sample passed the test.

Fig.:Sterility test

4.Viscosity test :

Mass of empty gravity bottle (m_1) = 18.56gm

Mass of filled gravity bottle with water = 28.48gm

Mass of filled gravity bottle with sample = 27.68gm

Density of water (d_w) = 0.99gm/ml

Density of sample (d_s) = 0.91gm/ml Time

taken by water (t_1) = 80 sec.

Time taken by sample (t_2) = 145sec.

Viscosity of water (n_w) = 1.003

Formula :

$$n_s = \frac{d_s t_s}{d_w t_w} n_w$$

$$ns = \frac{0.91 \times 145}{0.99 \times 80} \times 1.003$$

ns = 1.671 N.s/m2

The viscosity of the sample was found to be **1.671N.s/m².**

5.Skin irritability:

No irritation found on skin after application of sample on skin. No allergic reactions, no rashes occurred on skin after application of sample on skin for continuous 7 days.

6.Clarity test:

No any particulate matter had been seen in the sample solution. Sample solution of nasal drop was found to be clean and clear and free from any particulate matter.

CONCLUSION

- All the sample drugs and their excipients used were as per the standards.
- The prepared formulation was evaluated.
- The physical evaluation parameters like colour, odour, pH test, irritability test, clarity, viscosity were found to be satisfactory.
- Hence , formulation passed the irritability test it is compatible for skin.

- So it can be concluded that the formulation had better pH, and viscosity value.
- The bioavailability of formulation was high due no hepatic first pass metabolism.
- It was more stable and efficient than the other formulations.
- The formulation was found to be stable at room temperature.

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