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FORMULATION AND EVALUATIONS OF NATURAL HERBS TULSI AND NUTMEG CONTAINING IN SITU NASAL GEL

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ABSTRACT

Tulsi and Nutmeg undergoes hepatic first pass, hence it shows very poor bioavailability. By creating a pH-induced in-situ gel, the formulation for this study aims to increase bioavailability. Mucoadhesive polymer in the gel reduces mucociliary clearance, increasing the gel's contact with the nasal mucosa and, ultimately, improving drug absorption. Carbopol 940, which has the ability to produce gelation due to pH, was utilized to accomplish in situ gelation, while HPMC E15 and HPMC 15cps were employed as the Mucoadhesive agents. Gels were made by Gelation research, Gel strength, Permeation studies,pH, Drug Content, drug polymer interaction, and Stability study are characteristics of the previously described cold technique.In an in-vitro drug release investigation, the drug content ranged from 91.30 to 97.13%, and the gel's pH ranged from 5 to 5.9.A rheological analysis of the gel formulation revealed that the viscosity increases with an increase in polymer concentration and that the gel strength ranged from 25 to 41.seconds. The results of the stability research show that the Tulsi and Nutmeg did not alter significantly. When administered via the nasal route, Tulsi and Nutmeg in a pH-induced, bioadhesive solution may be able to prevent the first pass impact that comes with taking it orally, improving the drug's bioavailability and providing a safe, long-lasting release nasal delivery method for depression management.From the above results it can be concluded that Tulsi and Nutmeg was successfully formulated as a pH induced in situ nasal gelling system using Carbapol 940, HPMC E15 and HPMC 15cps. The optimized formulation F1 provided sustain in vitro release of drug over an extended period of 8hrs.

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INTRODUCTION

Pharmaceutical scientists find that developing intranasal delivery to be one of the most fascinating and difficult projects. The traditional nasal medication delivery methods, which include ointments, suspensions, and solutions, have shortcomings such limited permeability, short nasal cavity residence times, and difficult administration. An intriguing polymeric system known as "in situ gel-forming systems" is one that, prior to injection, is a flowing aqueous solution that phases out to form a viscoelastic gel in a physiological setting. With suitable and sufficient pre-formulation investigations of the medicine, a stable, safe, and effective nasal product can be created. The nasal medication delivery method eliminates the risk of unpleasant side effects associated with injection-based drug delivery, allowing for excessively simple drug application and self-administration.[1, 2]In the last few years, an amazing number of in situ gel-forming systems driven by temperature, pH, and ions have been developed for use in nasal drug delivery, benefiting from the advantages of both a solution and a gel. Drug retention in the nasal cavity is improved by in situ gel-forming devices, some of which also exhibit permeation-enhancing properties.In underdeveloped nations, the nasal method is preferred for quick mass vaccination. Although the nasal administration form has several benefits, its bioavailability is limited. Carbopol 940often takes the form of cast solids or white, freely flowing prilled grains. They have virtually no flavor or smell. These are materials that exhibit stability, and their aqueous solutions also exhibit stability when exposed to metal ions, acids, and alkalis. On the other hand, mold grows well in watery solutions. The in situ gel-forming methods for nasal drug delivery are reviewed in this article along with their gelling mechanisms and other advantageous aspects of intranasal delivery. Additionally, it details the in situ gels' drug stability and release patterns, in vivo effects, and local the process of gel formation at the site of action following the application of the formulation is known as "in situ gelation". It is hygroscopic only when the relative humidity is more than 80% and has less than 0.5% w/w water content. Excipient are widely recognized as non-toxic and non-irritating substances and are utilized in a range of oral, parenteral, and topical medicinal formulations. The in situ gel phenomenon is a semi-solid mucoadhesive key depot that is derived from a liquid medication formulation. It allows for the medication to be supplied in a liquid or solution form. The intranasal route is taken into consideration for medications that are administered chronically, are ineffective when taken orally, and require small doses in order to achieve quick circulation entrance. Carbopol is a white powder with a small unique odor that is fluffy, acidic, and hygroscopic. Acrylic acid cross-linked polymers with a high molecular weight that meet USP/INF standards are known as carbomerrange. These polymers are soluble in water and are used to thicken materials to provide a variety of viscosities and flow characteristics. It is a suspended soluble component that will help to emulsify and stabilize the mixture. At 260 °C, carbopol 940 breaks down in about 30 minutes. It functions as a mucoadhesive, emulsifying, suspending, modulating release, tablet binder, and raising viscosity agent. [3]Medication absorption from the nasal mucosa most likely occurs through the membrane's aqueous channels. Consequently, the drug will be absorbed quickly through the membrane's aqueous pathway as long as it is in solution and has a small molecular size. Safety after nasal delivery is decreased by absorption from the nasal cavity. The medicine is released in a regulated and sustained manner from gels, which are formed in response to various stimuli including pH changes, ions, temperature changes, and ultraviolet light.Factors including ventilation perfusion mismatch and airflow obstruction may modify systemic absorption and drug deposition in individuals with moderate to severe asthma who require larger doses of inhaled corticosteroids.

Purpose/objectives:

The objective of the in-situ nasal drug delivery system are as follow
It improve retention time of the drug.
Reduced frequency of administration.
Extention of drug residence time.
Ease to application.
Protection of the frug from environmental condition.

MATERIAL & METHOD:

A) Material:

Tulsi and Nutmag was obtained from Botanical garden of P.S.G.V.P.M'sCollege of pharmacy Shahada and authentified by P.S.G.V.P.M's art, sci, college Shahada, India. Hydroxy propyl methyl cellulose E15 from Ozone International (INDIA). Carbapol from Ozone International (INDIA). Benzoalkonium chloride from LOBA CHEMIE PVT.LTD.Mumbai, India. Sodium Metabisulphide from Ozone International (INDIA).

B) Method :

Extraction procedure:

Maceration Process of Tulsi:

This is an extraction process wherein a container is filled with coarsely powdered drug material (leaves, stem bark, or root bark), and menstrum is poured on top of the drug material until it is fully coated. After that, the container is sealed and left for a minimum of three days. To guarantee full extraction, the material is frequently shaken and stirred if it is placed within a bottle. Filtration or decantation is used to separate the micelle from marc at the conclusion of extraction. Next, the micelle is evaporated in an oven or on top of a water bath to separate it from the menstrum.[4]

Maceration Processof Nutmeg:

The hydro distillation method had been used for the extraction of essential oils from nutmeg. Nutmeg which is the kernel of myristica fragrance were grounded into fine powder. The distillation flask of 500 ml contained water about 2/3 of its volume and 50 gm of the powder. The operation proceeded by heating the flask at 100˚C, heat was applied to the flask and the volatile oil was carried with the steam to a cold condenser, the lighter oil rises to the top of the separator. The essential oils collected was dried over an hydrous sodium sulphate, weighed and stored in a sealed vial dark colored at 4˚ C. [5]

Fig No. 1 Extraction of Tulsi and Nutmeg.

C) Formulation :

Formulation of in – situ gel:

The formulation as given in table no. 1 was prepared by cold technique method. The Carbopol 940 was dissolved completely in distilled water with continuously stirring with the help of magnetic stirrer and allow the solution to hydrate for overnight. For the preparation of the solution, firstly HPMC E15 was dissolved in distilled water and allow the solution to hydrate overnight. Then, carbopol was again added slowly and allow the solution to hydrate for overnight. After complete hydration of polymeric solution, a different solution of tulsi, nutmeg and sodium chloride was added to polymeric solution of carbopol. Now, Benzalkonium chloride and Sodium Metabisulphidewas mixed in the above solution. On next day both the solution were mixed together with continues stirring under cold condition. This resultanting formulation was kept overnight in a refrigerator until a clear solution was obtained.[6]

Fig. no. 2 Magnetic stirrer.

Table No. 1 Formulation of In-situ Gel.

Sr. No	Ingredients(mg)	F1	F2	F3
1	Tulsi	0.1	0.1	0.1
2	Nutmeg	0.1	0.1	0.1
3	Carbopol 940	0.7	0.7	0.6
4	HPMC E15	0.4	0.4	0.4
5	Sodium metabisulphate	0.1	0.1	0.1
6	Sodium chloride	0.9	0.9	0.9
7	Benzoalkonium chloride	0.02	0.02	0.02
8	Distilled water	q. s	q. s	q. s

F1 Formulation. **F2 Formulation.** **F3 Formulation.**

Evaluation parameter:

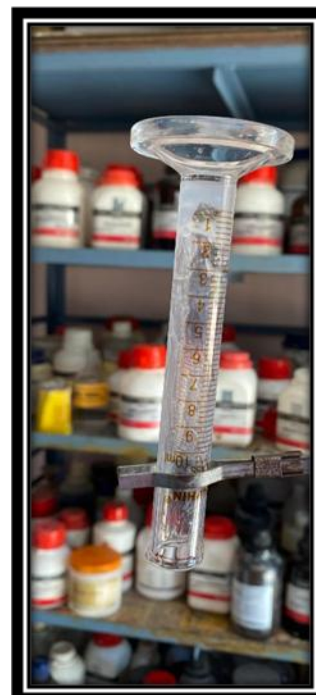
1. **Appearance and Efficiency:** The generated formulations were examined visually to assess their colour, clarity, and particle concentration in both the gel and sol states.[7]
2. **pH of Gel :**A pH meter was used to determine the pH of each mixture. The pH meter was initially adjusted using a pH 5 and 7 solution. At least three pH measurements were made, and the formulations' average pH values were computed.[8]

Fig.no 3 pH.

3. **el Strength:** A 3-5ml sample of formulation was placed in a 10ml graduated cylinder. A weight of 500mg was placed on the gel surface. The gel strength, which indicates the gel at physiological temperature, was calculated as the time in seconds required by the weight to penetrate 2 cm into the gel. All measurements were done in triplicate.[9]

F1 formulation.

F2 Formulation.



F3 Formulation.

4. **Viscosity:** A Brookfield viscometer was used to investigate the viscosity of in situ gels. For both the liquid formulation and the gel, viscosity was measured for 30 seconds at 10 rpm.
5. **Gel Capacity:** The gelling capability of the formulations was tested by adding one drop of the prepared formulation to a vial containing 2 ml of newly made SNF solution. Gelation was evaluated visually, with a focus on the time it took for the gel to develop and disintegrate. [10]
6. ***In-vitro*drug release study:** An in vitro release analysis of the created in-situ gel was conducted utilizing a diffusion cell via an egg membrane as the biological membrane. Prepared diffusion cell with an inner diameter of 1.4 cm was employed in the study. The formulation (1 ml) was deposited in the donor compartment, and a freshly made 100 ml simulated nasal electrolyte solution (sodium chloride 0.745 gm, potassium chloride 0.129 gm, calcium chloride dehydrated 0.005 gm, and distilled water q.s. 100 ml) was placed in the receptor compartment. Egg membranes were positioned between the donor and receptor compartments. The donor compartment's position was changed so that the eggmembrane only touched the diffusion medium. The entire apparatus was placed on the thermostatically controlled magnetic stirrer. The medium's temperature was kept at 37°C ±0.5°C. After 30 minutes, 1, 2, 3, 4, 5, 6, 7, and 8 hours, 2 ml of sample is removed from the receiver compartment and replaced with the same volume of new medium. The removed samples were diluted to 10 ml in a volumetric flask with Methanol and examined with a UV spectrophotometer at 239 nm.[11]

Fig.No.4 In-vitro drug release study.

7. **Drug content:** In a 10 ml volumetric flask, 1 ml of the formulation was added, followed by phosphate buffer pH 6.8 to make up the volume. Remove 1 ml of this solution and add methanol to form a volume of 10 ml. The formulation's absorbance was measured at a defined wavelength.[12]
8. **Mucoadhesive force:** The force required to remove the gel from the nasal mucosa tissue is used to calculate the mucoadhesive strength of in situ nasal gel. A slice of sheep nasal mucosa is glued to two glass slides using thread. On the first slide, 50 mg of gel is deposited, and this slide is then fixed below the height adjustable pan; on the other side of the pan, another slide with a mucosal region is placed inverted. Both slides are placed in touch with each other for two minutes to achieve intimate contact.Themucoadhesive force is determined from the minimal weight that detaches the mucosal tissue from surface of each formulation.[13-14]

RESULTS AND DISCUSSION:

Table No. 2 Various physical evaluation parameters such as appearance, pH, and drug content.

Sr. No.	Formulation code	Appearance	Fragnance efficience.	pH	Drug content
1	F1	Light white	Pleasant odour	6.99	95.94
2	F2	Light white	Pleasant odour	6.99	81.44
3	F3	Light white	Pleasant odour	6.99	89.9

Table No. 3 Gel strength, Gelling capacity, and mucoadhesive strength.

Sr. No.	Formulation code	Gelstrength (second)	Gelling capacity	Mucoadhesive strength (dyne/cm^{2})
1	F1	55.00	+	1267.45
2	F2	53.00	++	1340.77
3	F3	52.00	+	1970.40

Table No. 4 *In-Vitro* Drug release profile of prepared formulation.

Sr. No.	Time (hr.)	Cumulative percent drug release		
		F1	F2	F3
1	0	0	0	0
2	1	12.54	13.15	12.15
3	2	19.15	17.3	18.01
4	3	38.91	33.45	38.30
5	4	49.01	45.44	48.45
6	5	61.55	55.55	60.16
7	6	70.22	61.54	67.96
8	7	85.98	70.01	77.1
9	8	95.94	81.44	89.9

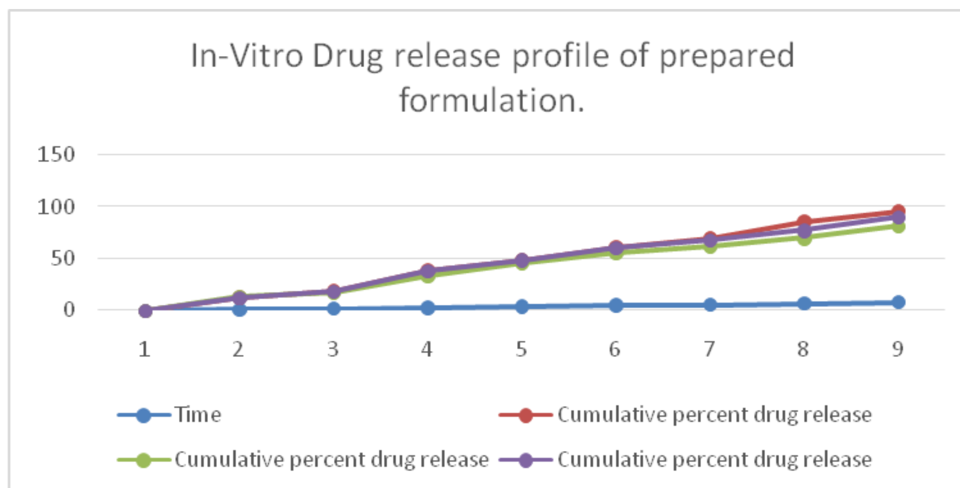


Fig. No. 5 In-Vitro drug release data of formulation F1-F3.

Table No. 5Stability evaluation of nasal gel (4°C ± 2ºC) Formulation F1.

Sr. No.	Parameter	Initial(0 days)	15 days	30 days	45 days
1	Colour	Colourless	Colourless	Colourless	Colourless
2	Drug Content	95.94	95.93	95.93	95.93
3	Microbialgrowth	No	No	No	No
4	pH	6.99	6.89	6.89	6.87

Table No. 6Stability evaluation of nasal gel (4°C ± 2ºC) Formulation F2.

Sr. No.	Parameter	Initial(0 days)	15 days	30 days	45 days
1	Colour	Colourless	Colourless	Colourless	Colourless
2	Drug Content	81.44	81.44	81.40	81.20
3	Microbial growth	No	No	No	No
4	pH	6.99	6.97	6.97	6.66

Table No. 7 Stability evaluation of nasal gel (4°C ± 2ºC) Formulation F3.

Sr. No.	Parameter	Initial(0days)	15 days	30 days	45 days
1	Colour	Colourless	Colourless	Colourless	Colourless
2	Drug Content	89.9	89.9	89.5	89.4
3	Microbial growth	No	No	No	No
4	pH	6.99	6.98	6.97	6.97

CONCLUSION:

From the above results it can be concluded that Tulsi and Nutmeg was successfully formulated as a pH induced in situ nasal gelling system using Carbapol 940, HPMC E15 and HPMC 15cps. The optimized formulation F1 provided sustain in vitro release of drug over an extended period of 8hrs. The optimized formulation can be a competent alternative to conventional nasal drops. As a consequence of its enhanced bioavailability and longer residence time, it avoids the first pass effect and reduces the dosing frequency as well. The future advantage of in-situ nasal drug delivery system is having less or no side effect within less time.

ABBREVIATION:

HPMC : Hydroxy propyl methyl cellulose.
pH : Power of hydrogen.
USP : United state pharmacopiea.
PVT : Private.
LTD : Limited.
Rpm : Revolution per meter.
SNF : Skilled nursing facility.

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