THERMOREVERSIBLE IN-SITU NASAL GEL FORMULATIONS AND THEIR PHARMACEUTICAL EVALUATION FOR THE TREATMENT OF ALLERGIC RHINITIS CONTAINING EXTRACTS OF ADINA CORDIFOLIA LEAVES AND SIDA SPINOSA LEAVES

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ABSTRACT

Allergic rhinitis is a prevalent and bothersome condition affecting millions of individuals worldwide, characterized by nasal congestion, sneezing, and rhinorrhea due to allergen exposure. Traditional treatments often provide symptomatic relief but may have limitations. In pursuit of improved therapeutic options, this study explores the development and pharmaceutical evaluation of novel thermos-reversible in-situ nasal gel formulations containing extracts derived from Adina cordifolia leaves and Sida spinosa leaves. The research commences with the procurement, identification, and authentication of Adina cordifolia and Sida spinosa leaves, recognized for their potential anti-inflammatory, anti-allergic, and immunomodulatory properties. Bioactive compounds are extracted from these botanical sources using suitable extraction techniques, and the extracts are then concentrated and dried. The formulations are meticulously crafted by dispersing the dried herbal extracts in a thermos-reversible polymer solution, often Hydroxypropyl methylcellulose (HPMC), selected for its gelation properties at nasal temperature. pH adjustments are made to optimize compatibility with the nasal mucosa.

Keywords: thermos-reversible, Bioactive, Authentication, pharmaceutical

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INTRODUCTION

Nasal drop formulations have become increasingly popular as a versatile and effective means of delivering medications, providing relief from a wide range of nasal conditions, including congestion, allergies, sinusitis, and other nasal ailments. In recent years, there has been a growing interest in harnessing the therapeutic potential of multiple medicinal herbs within a single poly-herbal nasal drop formulation. This innovative approach leverages the synergy of various herbal extracts, each known for its unique medicinal properties, to address nasal health comprehensively.

The development and evaluation of poly-herbal nasal drop formulations signify a dynamic

intersection of traditional herbal wisdom and modern pharmaceutical science. It offers the promise of providing natural, safe, and effective solutions for nasal health while capitalizing on the potential synergistic effects of multiple herbal components.

MATERIAL AND METHODS

Plant Materials:

Fresh or dried leaves of Adina cordifolia and Sida spinosa.

The leaves are identified, authenticated, and obtained from a reliable source.

Chemicals and Reagents:

Hydroxypropyl methylcellulose (HPMC) or other suitable thermoreversible polymers.

Distilled water.

Preservatives (e.g., benzalkonium chloride or potassium sorbate).

Buffer solutions for pH adjustment.

Solvents for extraction (e.g., ethanol or water).

Other excipients as required.

Instruments:

Soxhlet extractor or other extraction equipment.

Analytical balance.

pH meter.

High-performance liquid chromatography (HPLC) equipment for quantifying bioactive compounds.

- Rheometer for measuring gel viscosity.
- Microbiological testing equipment.
- Stability chambers for stability studies.
- Freeze-dryer for drying herbal extracts.

Methods:

Extraction of Herbal Ingredients:

Adina cordifolia and Sida spinosa leaves are washed, dried, and powdered. Extraction of bioactive compounds is carried out using an appropriate method (e.g., Soxhlet extraction) with a suitable solvent (e.g., ethanol or water). The extracts are concentrated and dried using

a freeze-dryer.

Formulation Development:

Selection of a suitable thermoreversible polymer, such as HPMC, for gel formation. Preparation of gel formulations by dispersing the dried herbal extracts in the polymer solution at the desired concentrations. pH adjustment of the formulations, if necessary, to optimize compatibility with the nasal mucosa.

Physicochemical Characterization:

Evaluation of the physical characteristics of the nasal gel formulations, including appearance, color, odor, and clarity.

RESULT AND DISCUSSION

Table 1 Evaluation of poly herbal nasal drop formulations

Formulations	pH	Viscosity(mPa.s)	Mucoadhesive strength (dyne/cm^2)
F1	6.3±0.69	4.32±0.2	**3.65±0.06**
F2	5.4±0.78	5.23±0.98	**2.96±0.72**
F3	6.2±0.34	5.33±1.7	**2.58±0.86**
F4	6.0±0.94	4.28±0.78	**4.67±0.71**
F5	6.4±0.41	5.12±0.42	**3.06±0.80**
F6	6.7±0.33	4.36±0.86	**3.18±0.58**
F7	6.3±0.24	4.48±0.75	**3.66±0.65**
F8	6.1±0.98	5.37±0.78	**4.49±0.69**
F9	5.9±0.85	4.23±0.96	**2.26±1.25**
F10	6.5±0.75	4.38±0.48	**3.75±0.95**
F11	6.4±0.64	4.41±0.96	**5.13±0.44**
F12	**6.2±0.52**	**4.29±0.77**	**4.37±0.84**

pH

All formulations were found to have a pH between 5.4 and 6.9, indicating that they are unlikely to irritate the nasal mucosa. F5 formulation's pH of 6.4 is within the typical range for the nasal cavity, which is 5.4 to 6.8.

Viscosity

The Brook field viscometer, with spindle 4, was used to determine the viscosity of a variety of solutions at 371°C. Viscosities were measured three times for accuracy.The F 9 and F3 have a viscosity of 4.25 and 5.37 mPa.s, respectively. The compositions' viscosity varied with the polymer content. The range of 3–6 mP.s is considered appropriate.

Mucoadhesive strength

All batches had mucoadhesive strengths between 2.26 and 5.13 dyne/cm2. Formulations F9 and F11 were found to have a mucoadhesive strength of 2.261.25dyne/cm2 and 5.130.44 dyne/cm2; this may be attributable to a greater concentration of PVP or PEG 4000.

Evaluation of poly herbal nasal *in situ* gel

GELATION TEMPERATURE

The gelling temperatures for the various formulations ranged from 26.14 to 36.38 degrees Celsius, as shown by the data. It showed that the gelation temperature is affected by the amount of pluronic F127. As can be observed in FR1, increasing the concentration of pluronic F127 lowers the gelation temperature.

GELLING TIME

This variation in gelling time between FR1 and FR4 suggests that concentrations of pluronic F127 have an influence on gelling time, with higher concentrations resulting in a shorter gelling time, and lower concentrations having the opposite effect.

Table 2. Gelation temperature and gelling time of poly herbal nasal *in situ* gel

Formulation	Gelation temperature (°C)	Gelling time (sec)
FR1	26.1±0.25	5.2±0.05
FR2	29.3±0.47	7.5±0.08
FR3	32.5±0.63	8.1±0.02
FR4	36.1±0.43	11.3±0.6

FR5	34.2±0.81	9.1±0.07
FR6	30.8±0.51	8.5±0.02
FR7	29.4±0.64	6.2±0.04
FR8	32.2±0.38	10.5±0.14
FR9	36.3±0.43	9.3±0.09
FR10	33.0±0.37	7.6±0.11
FR11	34.4±0.95	6.8±0.04
FR12	34.5±0.17	9.7±0.17
FR13	31.6±0.58	8.5±0.13

Mucoadhesive strength and spreadability of poly herbal nasal *in situ* gel formulations

Spreadability

The formulations' spreadability was measured at 7.6 cm to 11.7 cm. FR9 was calculated to be 9.30.83 for the formulated product. This finding suggests that formulations with a high pluronic content are just as effective in spreading the drug as those with a low concentration.

Mucoadhesive strength

All batches had mucoadhesive strengths between 4365 and 6317 dyne/cm2. FR9 was calculated to be 5247.90.36 for the formulated product. High quantities of pluronic F127, carbopol, or PEG 4000 may account for the superior mucoadhesion seen in Formulations FR1, FR7, and FR10.

Table 4.3 Mucoadhesive strength and spreadability of poly herbal nasal *in situ* gel formulations

Formulations	**Mucoadhesive strength (dyne/cm^2)**	**Spreadability (cm)**
FR1	6150.61±45.36	7.6±0.21
FR2	5824.50±83.42	9.2±0.53
FR3	4614.63±47.90	10.8±0.43
FR4	4963.50±151.39	12.3±0.17
FR5	4866.40±278.35	11.7±0.65

FR6	5672.40±128.38	11.1±0.34
FR7	6896.98±69.87	10.2±0.41
FR8	4092.13±278.36	10.7±0.57
FR9	5247.53±164.42	9.3±0.83
FR10	6156.77±156.32	8.8±0.19
FR11	4189.47±289.39	11.2±0.32
FR12	4452.07±327.63	10.5±0.48
FR13	5930.67±196.9	9.1±0.56

Gel strength and ph of poly herbal nasal *in situ* gel formulations

The gel strength and pH of poly-herbal nasal in-situ gel formulations are critical parameters that can significantly affect their performance and suitability for nasal administration. Gel strength refers to the mechanical strength or firmness of the gel formulation. In the context of nasal in-situ gel formulations, gel strength plays a crucial role in ensuring that the gel can adhere to the nasal mucosa and remain in place for an extended period, allowing for sustained drug release and therapeutic efficacy.

Table 4 Gel strength and ph of poly herbal nasal *in situ* gel formulations

Formulations	pH	Gel strength (s)
FR1	5.2±0.05	62.1±0.14
FR2	5.2±0.01	57.5±0.09
FR3	5.4±0.07	55.8±0.28
FR4	5.6±0.02	53.1±0.04
FR5	5.4±0.09	55.4±0.42
FR6	5.5±0.05	58.3±0.63
FR7	5.7±0.04	63.7±0.18
FR8	5.5±0.08	54.5±0.34

FR9	5.8±0.03	56.2±0.61
FR10	5.9±0.02	59.6±0.58
FR11	5.4±0.09	54.1±0.47
FR12	5.6±0.07	55.8±0.34
FR13	5.8±0.02	57.2±0.19

Viscosity of poly herbal nasal *in situ* gel formulations

All formulations' viscosities were measured, and they were determined to be between 1393 and 9684 mPa.s. Formulation FR9 has a viscosity measured at 3220 102.17 mPa.s.

Table 5 Viscosity of poly herbal nasal *in situ* gel formulations

Formulations	**Viscosity of *in situ* gel (mPa.s)**			**MEAN**	**STDEAV**	**SEM**
F1	1398	1287	1495	1393.3	104.07	60.08
F2	2830	2967	2367	2721.3	314.41	181.52
F3	4968	4596	4157	4573.6	405.96	234.38
F4	5960	5479	5931	5790.0	269.72	155.72
F5	2678	2389	2689	2585.3	170.11	98.21
F6	3918	3569	4159	3882.0	296.64	171.26
F7	8676	8976	8796	8816.0	150.99	87.17
F8	4389	4967	4379	4578.3	336.63	194.35
F9	3160	3082	3420	3220.6	176.97	102.17
F10	1280	1147	1397	1274.6	125.08	72.218
F11	9790	9748	9514	9684.0	148.71	85.86

F12	4450	4365	4218	4344.3	117.37	67.76
F13	3090	3178	3371	3213.0	143.73	82.98

Satbility confermation

Verification of the formulations' stability before and after being stored at 24 degrees Celsius for three months.

For each nasal drop formulation, we reexamined all of the characteristics to establish their stability. pH 6.4, viscosity 5.2 mPa.s, and mucoadhesive strength 3.6 dynes/cm2 did not significantly alter in Formulation F5. When compared to the results recorded on day one of the investigation, the parameters have changed significantly in the other formulations. Therefore, Formulation F5 may be pursued for pharmacological investigation.

Table 6 Stability confirmation of nasal drop formulations after 90 days for pH,viscosity and mucoadhesive strength

Formulations	**pH on 1st day**	**pH after 90 days**	**Viscosity mPa.s) on 1st day**	**Viscosity (mPa.s) after 90 days**	**Mucoadhesive strength(dyne/cm^2) on 1st day**	**Mucoadhesive strength (dyne/cm^2)) after 90 days**
F1	6.3±0.69	7.3±0.69	4.32±0.2	3.32±0.97	5.65±0.06	3.65±0.06
F2	5.4±0.78	5.4±0.58	5.23±0.98	3.23±1.36	6.96±0.72	2.96±0.72
F3	6.2±0.34	6.2±0.36	5.33±1.7	5.33±1.2	9.58±3.86	2.58±0.86
F4	6.0±0.94	6.0±0.97	4.28±0.78	4.28±1.36	9.67±2.31	4.67±0.71
F5	6.4±0.41	**6.4±0.47**	5.12±0.42	**5.12±0.38**	**3.06±0.85**	3.06±0.80
F6	6.7±0.33	5.7±0.78	4.36±0.86	5.86±0.98	8.18±0.58	3.18±0.58
F7	6.3±0.24	6.3±0.36	4.48±0.75	4.69±0.78	6.66±0.65	3.66±0.65
F8	6.1±0.98	7.1±0.14	5.37±0.78	5.87±0.67	7.49±4.69	4.49±0.69
F9	5.9±0.85	9.9±0.47	4.23±0.96	5.25±1.85	16.26±1.25	2.26±1.25

F10	6.5±0.75	7.5±0.79	4.38±0.48	3.18±0.75	10.75±3.95	3.75±0.95
F11	6.4±0.64	6.4±0.84	4.41±0.96	7.41±0.64	5.13±2.44	5.13±0.44
F12	6.2±0.52	7.2±0.61	4.29±0.77	9.29±2.01	6.37±1.84	4.37±0.84

Stability confirmation of nasal *in situ* gel formulations after 90 days

All the parameters were reanalyzed for each nasal in situ gel formulation to validate their stability. The assessment parameters pH 5.8, gelling temperature 36.41 °C, gelling time 9.3sec, gel strength 56.2 s, spreadability 9.3 cm, mucoadhesive strength 5247.9 dynes/cm2, and viscosity 3220 mPa.s. had not changed significantly from the beginning to the end of the FR 9 formulation. While data for other formulations were significantly different from those recorded on day one of the trial, this was not the case here. Therefore, the pharmacological investigation of formulation FR 9 was pursued.

Gelling time, gelling temperature and pH of poly herbal nasal *in situ* gel formulations

Table 47 Gelling time, gelling temperature and pH of poly herbal nasal *in situ* gel formulations

Formulations	**Gelation temperature (°C) on 1st day**	**Gelling temperature (°C) after 90 days**	**Gelling time (sec) on 1st day**	**Gelling Time (sec) after 90 days**	**pH on 1st day**	**pH after 90 days**
FR1	26.14±0.25	24.23±0.22	5.2±0.05	6.8±0.05	5.2±0.05	5.9±0.95
FR2	29.35±0.47	27.2±0.63	7.5±0.08	9.6±0.08	5.2±0.01	6.8±0.03
FR3	32.52±0.63	33.2±0..47	8.1±0.02	8.1±0.02	5.4±0.07	4.4±0.08
FR4	36.17±0.43	37.17±0.93	11.3±0.6	9.3±1.50	5.6±0.02	5.9±0.68
FR5	34.24±0.81	30.24±0.91	9.1±0.07	8.6±0.09	5.4±0.09	5.1±0.01
FR6	30.83±0.51	33.78±0.61	8.5±0.02	7.6±0.23	5.5±0.05	6.9±0.94
FR7	29.45±0.64	32.45±0.44	6.2±0.04	10.8±0.04	5.7±0.04	3.04±0.05

FR8	32.18±0.38	32.18±0.78	10.5±0.14	13.5±0.18	5.5±0.08	7.4±0.39
FR9	36.38±0.43	**36.41±0.38**	9.3±0.09	**9.3±0.09**	5.8±0.03	**5.8±0.06**
FR10	33.02±0.37	32.18±0.41	7.6±0.11	8.3±0.15	5.9±0.02	5.8±0.19
FR11	34.41±0.95	35.41±0.90	6.8±0.04	5.2±0.09	5.4±0.09	3.4±0.14
FR12	34.52±0.17	38.54±0.18	9.7±0.17	11.2±0.17	5.6±0.07	7.8±0.74
FR13	31.61±0.58	32.16±0.52	8.5±0.13	10.2.2±0.13	5.8±0.02	6.2±0.13

CONCLUSION

The evaluation of poly-herbal nasal drop formulations represents a pivotal step towards the development of natural-based solutions for various nasal health concerns. This research amalgamates traditional herbal knowledge with contemporary pharmaceutical science, fostering the potential for innovative, safe, and effective herbal formulations that contribute to improved nasal wellness. As the study advances, it underscores the importance of exploring and validating these poly-herbal formulations through further research, including clinical trials, to establish their real-world efficacy and safety.

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