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Formulation characterization and evaluation of *In-Situ* nasal gels of amitriptyline

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Abstract

The main aim of the present work is to formulate and evaluate Amitriptyline In-Situ Nasal gels. To achieve more constant blood levels with lower dosage of drugs by continuous drug input and by passing hepatic first pass metabolism and consequent degradation. In FTIR & DSC spectra there is no incompatibility between pure drug, polymers & lipids. The Formulation of Amitriptyline hydrochloride In-Situ Nasal gels, The evaluation of Amitriptyline hydrochloride In-Situ Nasal gels. Carbopol containing gels were found to be sparkling and transparent Poloxamer, Hydroxy Propyl Methyl cellulose gels were found to be translucent and white viscous. The PH value of all developed formulations of gels (F1-F8) was in the range of 6.8 to 6.9. Spread ability of gels was in the range 23.99 - 26.37 g.cm/sec. Viscosity of various formulated gels was found in range of 942 to 938 centipoises. The percentage drug content of all prepared gel formulations were found to be in the range of 98.93 to 84.47 %. The percentage drug content of formulations was found satisfactory. The gel strength of all prepared formulations of gels was found to be in the range of 64 to 95%. The In-vitro release of Amitriptyline hydrochloride was prolonged release of drug ranges from 95 % of released within 7 hours. Among the eight formulations the best formulation is F1 formulation follows both Zero order and Korsemeyer-Peppas models, It indicates diffusion release mechanism followed by non-fickian transport.

Keywords: In-Situ; Nasal gels; Amitriptyline HCL; *In vitro* diffusion; Carbopol

1. Introduction

A gel can be looked upon as being composed of two interpenetrating phase (the gelling agent and a fluid component). Gels are semisolid, being either suspensions of small inorganic particle or large organic molecule interpenetrated with liquid. Thus gels exhibit characteristics intermediate to those of liquid and solids. Oral administration is the most common route of administration used for systemic effect. For some drugs the systemic effect is not in desirable condition due to oral bioavailability and promoted for the search of more effective route for systemic delivery. Usually the nasal cavity is used for the treatment of local diseases such as rhinitis, migraine, cold, pain and nasal congestion [1].

In recent years it has been proved that many drugs achieved better systemic bioavailability through the nasal route. The various formulations used by nasal route are nasal gels, sprays, powders, etc. Tran mucosal route of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular, oral cavity) in nasal mucosa is the major route of administration to achieve faster and higher level of drug absorption. This is due to the anatomy and physiology of nasal passage that is porous endothelial membrane, large surface area, high total blood flow, the avoidance of first pass metabolism and readily accessibility [2].

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Nasal drug delivery also provides a way to the brain that circumvents the blood-brain barrier because the olfactory receptor cells are in contact with central nervous system directly. The nasal route is an attractive not only for delivery of vaccines due to large surface area and low proteolytic activity but it also improves the patient compliance and decrease the production cost compared to parenteral production. Due to their high permeability the nasal route show only small molecular weight drugs the absorption will be more. For large molecular weight drugs or hydrophilic drugs show low bioavailability or no absorption due to the less permeable to the protease drugs in the nasal membrane, so that the drugs are cleared rapidly before reaching the blood stream that is the drug does not pass through the mucosal barrier [3].

2. Material and methods

Amitriptyline hydrochloride is a gift sample from Aurovindo Pharma LTD, Hyderabad, and other polymer mixtures such as Hydroxy Propyl Methyl Cellulose, Carbopol, Methylparaben, Poloxamer 188, Ethanol and Phenyl mercuric nitrate.

2.1. Pre-Formulation Study

2.1.1. Compatability Study

FT-IR studiesfor drug andexcipientscompatibilities: Prior to the development of the dosage forms the preformulation study was carried out. IR spectral studies lies more in the qualitative identification of substances either in pure form or in combination with polymers and excipients and acts as a tool in establishment of chemical interaction. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structur ef molecular compounds. Inorder to establish his point, comparisons were made between the spectrums of the substances and the pure compound [4].

2.1.2. Differential Scanning Calorimetric

Differential Scanning Calorimetric of pure drugs and polymers used were studied to investigate any changes in melting points of the drug after combining it with the excipients. Differential Scanning Calorimeter curves were obtained by a differential scanning calorimeter at a heating rate of 10°C/min from 25°-250°C in nitrogen atmosphere (20 mL/min) with a sample weight of 3mg [5].

2.2. Formulation of Amitriptyline hydrochloride Nasal Gels

Methodof Formulation: Amitriptyline hydrochloride Nasal Gels was prepared by Dispersion method. In this method weighed quantities of polymers such as HPMC K100, Carbopol 934 was dissolved in known quantity of distilled water (Solution-A).After complete dispersion the polymer solution was kept it aside for 24hrs for complete the swelling. Accurately weighed amount of Amitriptyline hydrochloride, Poloxamer188wasdissolvedinaspecified quantity to this solution; specified quantity of Phenyl mercuric nitrate was added and dissolved (Solution-B). Solution A and B were mixed thoroughly with the help of high speed magnetic stirrer (500rpm) taking precautions that air did not entrap. Finally distilled water was added to obtain a homogenous dispersion of gel [6]. The pH of the formed gel was adjusted to pH 6.8.

Table 1 Formulation data of Amitriptyline hydrochloride Nasal gels

Formulations Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Amitriptyline Hcl	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Carbopo (gms)	2	2.0	3	3.0	3.0	3	2.0	2
HPMC(gms)	3.0	3	2.0	2	2	2.0	3	3.0
Poloxamer (gms)	1.0	2	2.0	3	1.0	2	2.0	3
Methyl Paraben (%)	2	2	2	2	2	2	2	2
Distilled water (ml)	100	100	100	100	100	100	100	100

2.2.1. Evaluationof Nasal Gels Gel

Formulated gel was evaluated for their physico- chemical properties,in-vitro release studies and drug content.

2.2.2. Clarity

The clarity of various formulations was determined by visual inspection under black and white background and it was graded as follows; turbid: +, clear: ++, very clear (glassy): +++.

2.2.3. Measurement of Ph

The pH of Amitriptyline hydrochloride gel formulation was determined by using digtal pH meter 1gram of gel was dissolved in 100ml of distilled water [7]. The pH of all formulation was determined by using digital pH meter (Systronics Digital pH meter).

2.2.4. Spreadability

Spreadability was determined by glass plate apparatus which was suitably modified in the laboratory and used for the study [8]. Spreadability was measured on the basis of 'slip' and drag characteristics of gel. The spredability was measured by using the following formula

$$S = M/T$$

2.2.5. Viscosity

The viscosity of all gels was measured using a brook field viscometer (DV II +). First, the spindle was dipped into the gel till the notch on the spindle touched the gel surface.100 gm each of formulation gels was used in the study [9].The spindle no. 61 was selected based on the viscosity of the gel, this spindle was rotated at 50 rpm, and dial reading was recorded until 2 consecutive similar readings were obtained.

2.2.6. Drug content

Drug content of gel was determined by dissolving accurately weighed 1 gm gel in 6.8 pH Phosphate buffer. After suitable dilution absorbance was recorded using UV visible spectrometer at 250 nm. Drug content was determined using slope of standard curve [10]. The drug content was determined by using following equation

$$\text{Drug content} = (\text{concentration} \times \text{volume taken}) \times \text{conversion factor}$$

2.2.7. Gelling strength

In 100 ml measuring cylinder containing 50 gm of gel at thermostat at 37oC, it allows to penetrate intothe Carbopol & HPMC gel. At physiological temperature while applying pressure on the device sink at 5cm down, to measure the time in seconds [11].

2.2.8. In vitro diffusion studies

The in vitro diffusion study of prepared gel was carried out in Franz diffusion cell using through an egg membrane. 20 ml of phosphate buffer was taken in as receptor compartment, then5gmAmitriptyline hydrochloridegelwasspreaded uniformly on the membrane. The donor compartment was keptincontactwitha receptor compartment and the temperature was maintained at 37±0.50C. The solution on the receptorpipette out 5 ml of solution from the receptor compartment at specified time intervals like 1,2, 3, 4, 5, 6 & 7hrs and immediately replaced with the fresh 2 ml phosphate buffer [12]. The results of in-vitro release profile obtained for all formulations were plotted in Release order kinetics as follows:

Kinetic study the Release Order kinetics Mechanism [13-15]

The results of in-vitro release profile obtained for all formulations were plotted in modes of data treatment as follows:

- Cumulative percent drug release V/s. Time (Zero-order).
- Cumulative percent drug release V/s. Square root of Time (Higuchi Matrix Model).
- Log Cumulative percent drug retained V/s. Time (First-order).
- Log Cumulative percent drug release in V/s. log Time (Krosmeyer-Peppas Model).

2.2.9. Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation.

$$Qt = Qo + Ko\ t$$

2.2.10. First order kinetics

To study the first order release kinetics the release rate data

$$Log\ Qt = log\ Qo + K\ t\ /\ 2.303$$

2.2.11. Higuchimodel

Higuchi developed sever all theoretical models to study the release of water-soluble and low soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media, the equation is

$$Q\ t = KH.\ t1/2$$

2.2.12. Korsemeyer and Peppas Release model

To study this model the release rate data are fitted to the following equation

$$F = Mt\ /\ M = K.tn$$

3. Results and discussion

3.1. Preformulation Studies

3.1.1. Compatibility studies

Table 2 FTIR spectrum of drug and polymer mixtures

Functional Groups	Amitriptyline hydrochloride	Carbopol	Poloxamer	HPMC	Mixture
C=C (Alkynes)	2360.95	1608.69	2438.10	3174.94	3244.38
NO_2 (Nitro Compounds)	1452.45	1552.75	1514.86	2692.72	2249.07
CH (Alkane)	1155.40	3084.28	3138.29	2852.81	2171.92
CO (Alcohols)	1116.82	1639.55	1542.56	1629.90	1643.62

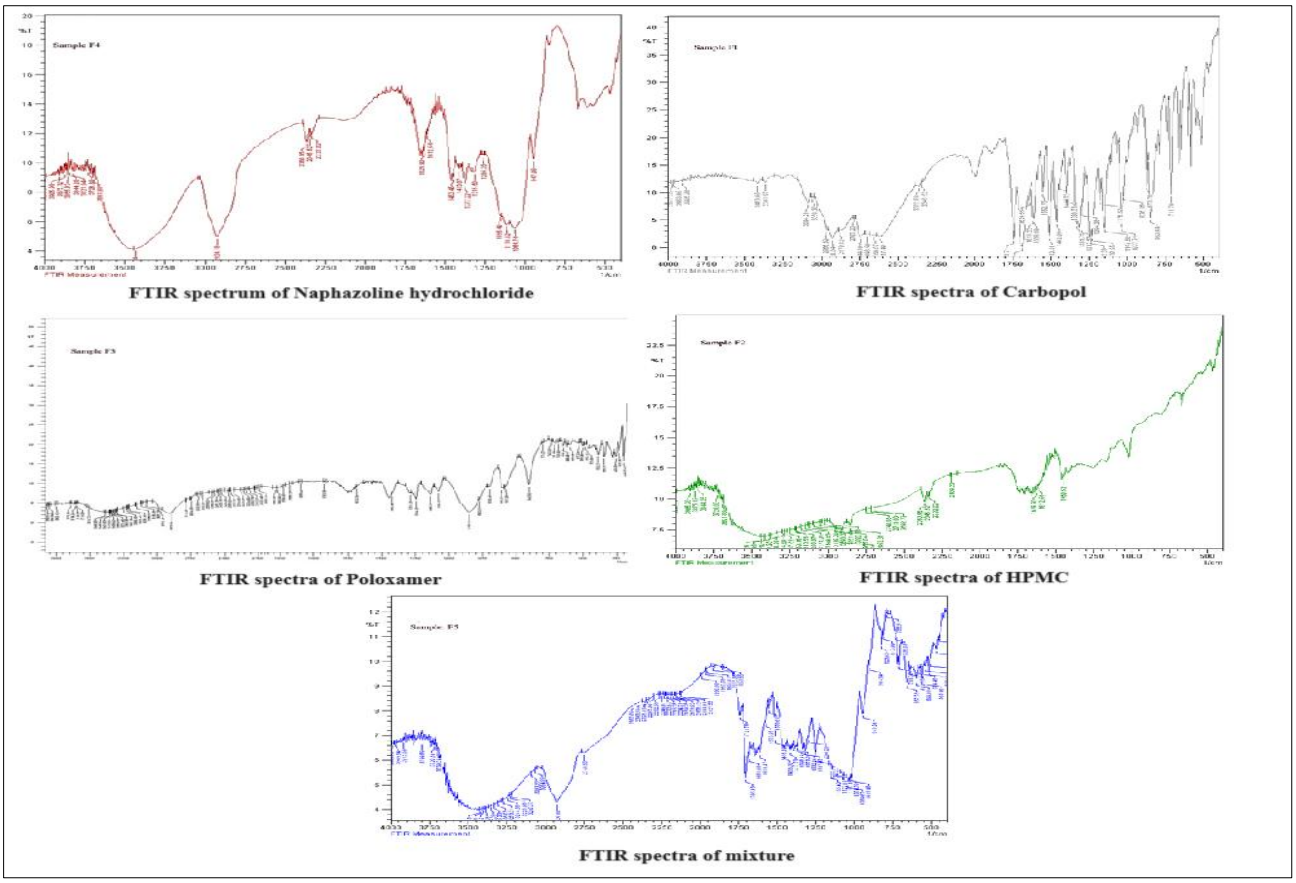

Figure 1 FTIR spectrums of drug and Polymer mixtures

The drug and polymers were characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the Amitriptyline hydrochloride were found to be unaltered in the spectra of the drug-polymer mixture.

3.2. Differential Scanning Calorimetry

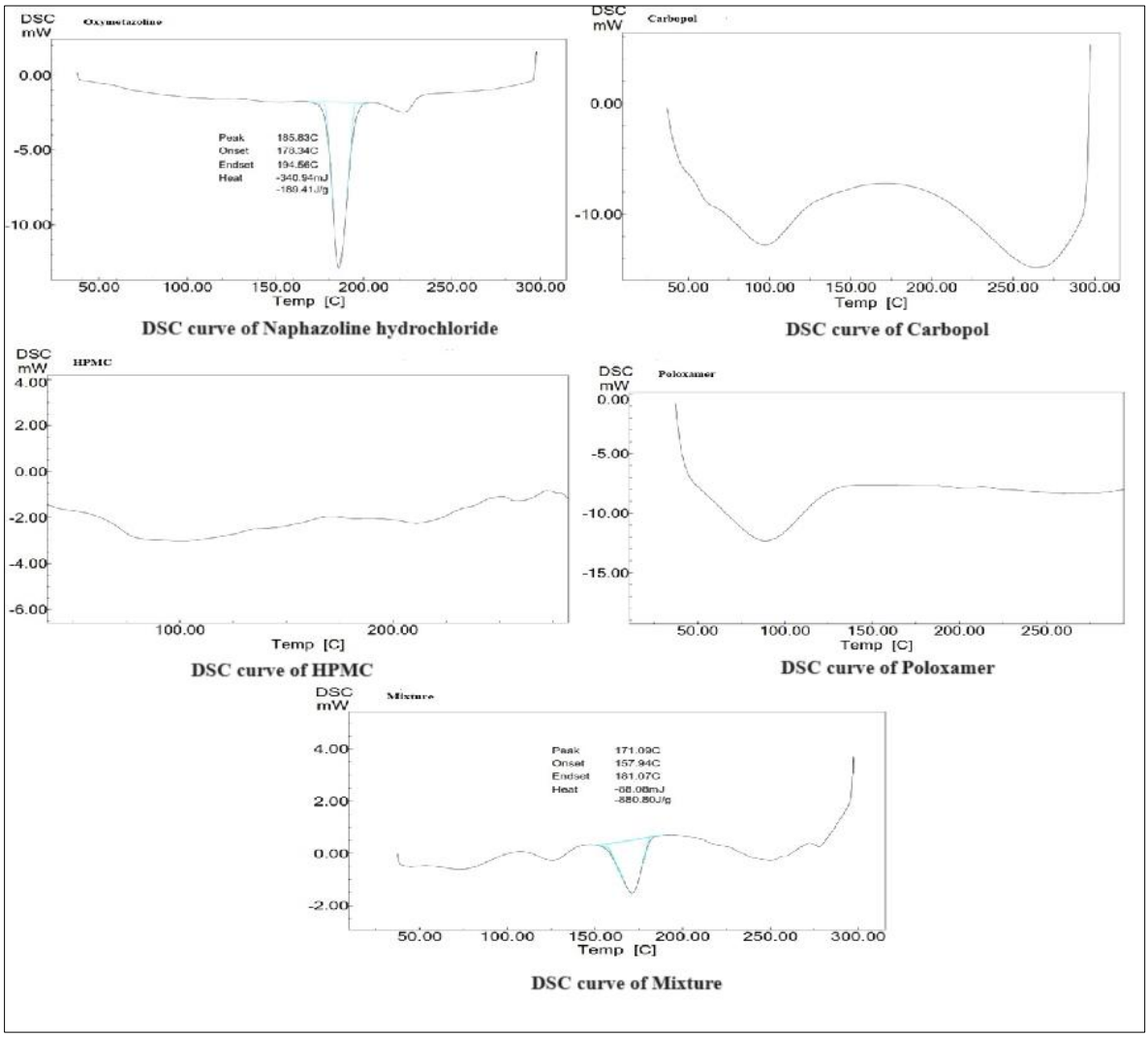

Figure 2 DSC curve of drug and polymer Mixtures

The Amitriptyline hydrochloride of endothermic peak was found to be 194.56°C. The Carbopol of endothermic peak was found to be 250°C. The HPMC the endothermic peak was found to be 99°C. The Poloxamer of endothermic peak was found to be 95°C. The Mixture of endothermic peak was found to be 95°C. There is no interaction between pure drug, polymer & lipids. As shown in figure 6.

3.3. Evaluation of Amitriptyline hydrochloride NasalGels

- Clarity: Carbopol containing gels were found to be sparkling and transparent Poloxamer, Hydroxy Propyl Methyl cellulose gels were found to be translucent and white viscous. All gels were free from presence of particles as shown in table 3.
- pH: The pH value of all developed formulations ofgels (F1-F8) were in the range of 6.8 to 6.9 as shown in Table 3 & figure 3.

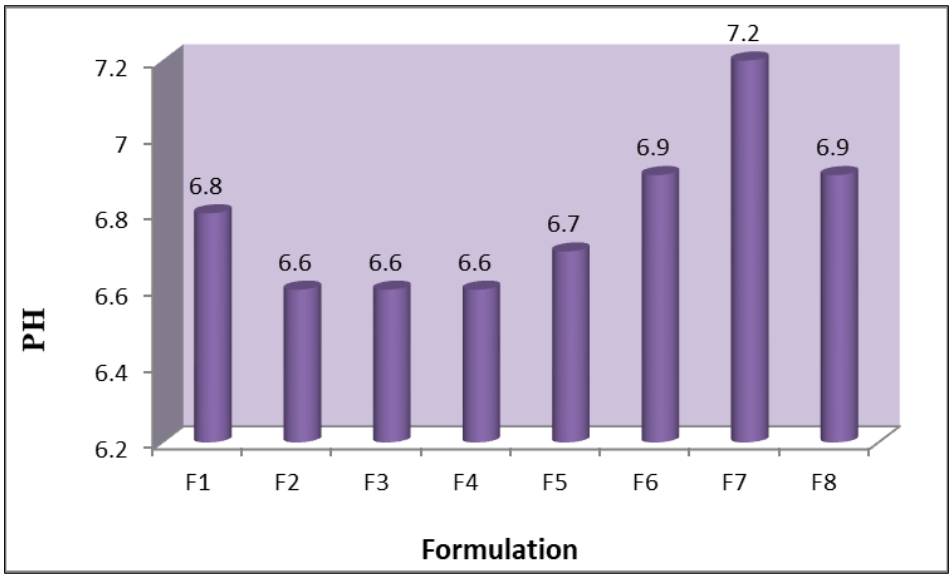

Figure 3 pH of Amitriptyline hydrochloride In-Situ Nasal Gels

Spreadability: The value of spreadability indicates that the gel is easily spreadable by small amount of shear. Spreadability of gels was in the range 23.99 - 26.37 g.cm/sec, as shown in Table 3 & figure 5.

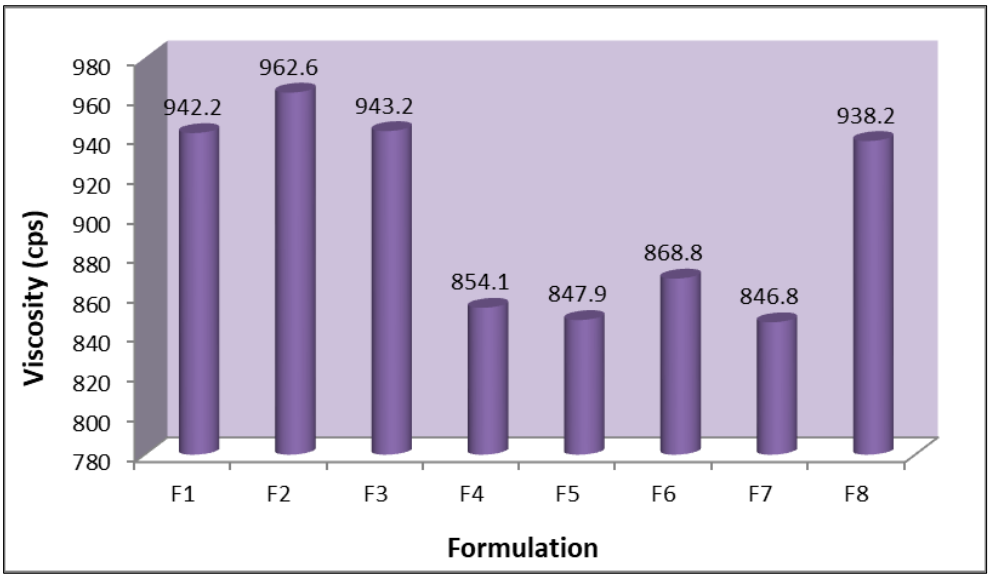

Figure 4 Viscosity of Amitriptyline hydrochloride In-Situ Nasal Gels

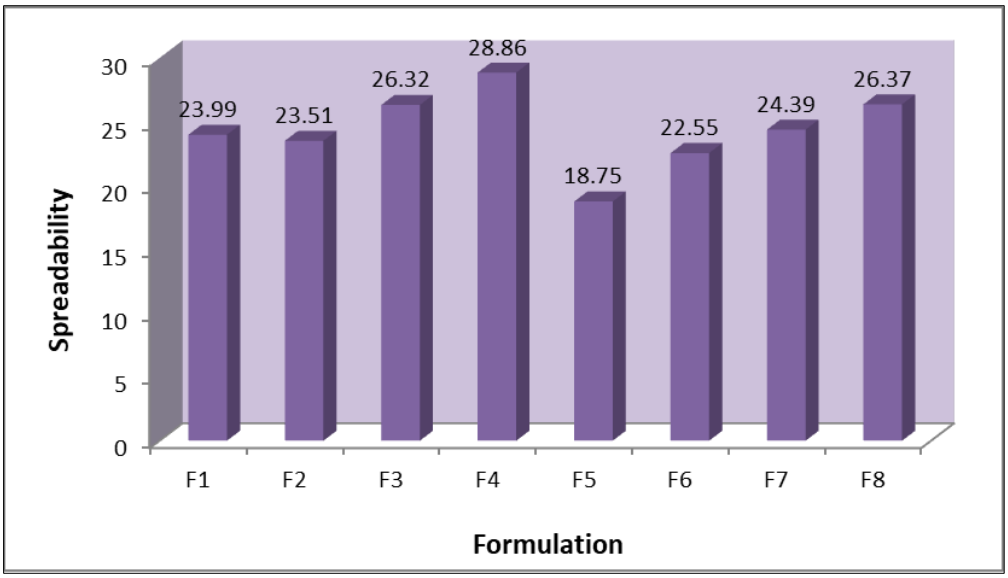

Figure 5 Spreadability of Amitriptyline hydrochloride In-Situ Nasal Gels

- Viscosity measurement: The viscosity of various formulated Amitriptyline hydrochloridegels was measured using a Brookfield viscometer. The rheological behavior of all formulated gels systems was studied. In gel system, consistency depends on the ratio of solid fraction, which produces the structure to liquid fraction. Viscosity of various formulated gels was found in range of 942 to 938 centipoises as shown in Table 3 & figure 4.

Drug content: The percentage drug content of all prepared gel formulations were found to be in the range of 98.93 to 84.47 %. The percentage drug content of formulations was found satisfactory. Hence methods adopted for gels formulations were found suitable. As shown in Table 3 & figure 6.

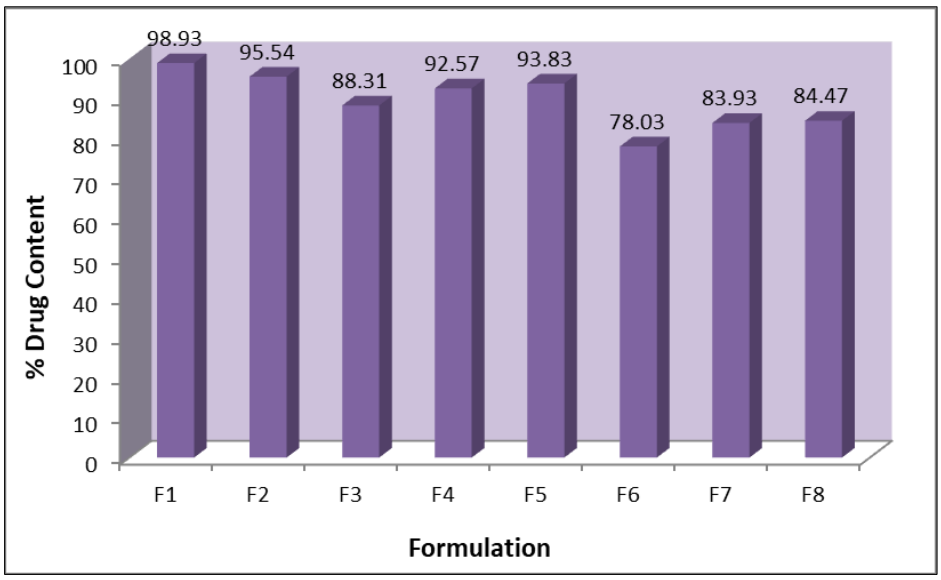

Figure 6 Drug Content of Amitriptyline hydrochloride In-Situ Nasal Gels

Gel strength: The gel strength of all prepared formulations of gels was found to be in the range of 64 to 95 %. The percentage drug content of formulations was found satisfactory. Hence methods adopted for gels formulations were found suitable.As shown in Table 3 & figure 7.

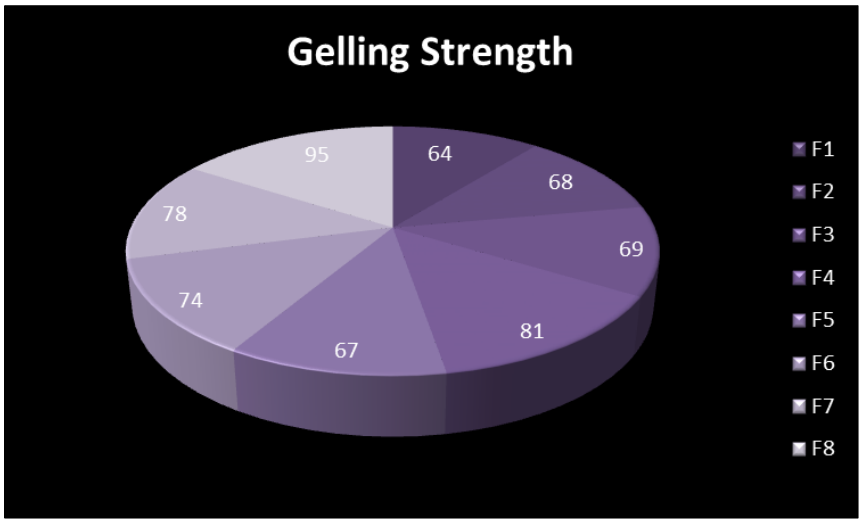

Figure 7 Gel strength of Amitriptyline hydrochloride In-Situ Nasal Gels

Table 3 Evaluation parameters of Amitriptyline hydrochloride nasal gel

Formulation code	Clarity	pH	Spreadability(g.cm/sec)	Viscosity(cps)	%Drug Content	Gellingstrength
F1	+++	6.8	23.99	942.2	98.93	64±2
F2	+	6.6	23.51	962.6	95.54	68±5
F3	++	6.6	26.32	943.2	88.31	69±4
F4	+	6.6	28.86	854.1	92.57	81±6
F5	++	6.7	18.75	847.9	93.83	67±3
F6	+	6.9	22.55	868.8	78.03	74±4
F7	+	7.2	24.39	846.8	83.93	78±4
F8	+	6.9	26.37	938.2	84.47	95±4

In vitro drug diffusion studies: *In vitro* drug release studies were carried out on diffusion test apparatus Franz diffusion cell figure 8, 9. these release studies revealed that, the order of release was found as shown in table 4.

Figure 8 *In vitro* Franz's diffusion cell

Table 4 In-vitro diffusion drug release of Amitriptyline hydrochloride of In-Situ Nasal Gels

Time(Hrs)	Percentage amount of drug release							
	F1(%)	F2 (%)	F3(%)	F4(%)	F5(%)	F6(%)	F7(%)	F8 (%)
1	42 ± 0.1	48 ± 0.3	40 ± 0.6	32 ±0.4	20 ±0.2	21 ±0.4	22±0.2	19 ±0.1
2	43 ± 0.4	44 ± 0.6	44 ±0.4	48 ±0.7	34 ± 0.5	37 ±0.6	36 ±0.4	28 ±0.4
3	47 ± 0.6	52 ± 0.4	58 ±0.2	62 ±0.1	46 ± 0.7	54 ±0.7	48 ±0.5	38 ±0.6
4	56 ± 0.3	62 ± 0.1	69 ±0.6	64 ±0.2	56 ± 0.6	64 ±0.8	54 ±0.7	46 ±0.5
5	78 ± 0.2	72 ± 0.6	78 ±0.2	75 ±0.6	72 ±0.1	76 ±0.9	62 ±0.3	58±0.3
6	79 ± 0.6	83 ± 0.7	87 ±0.7	83 ± 0.3	76 ± 0.2	82±0.3	65 ±0.6	71 ±0.7
7	95 ± 0.7	93 ± 0.8	94 ±0.3	94 ± 0.1	82 ±0.4	89±0.1	77 ±0.4	84± 0.8

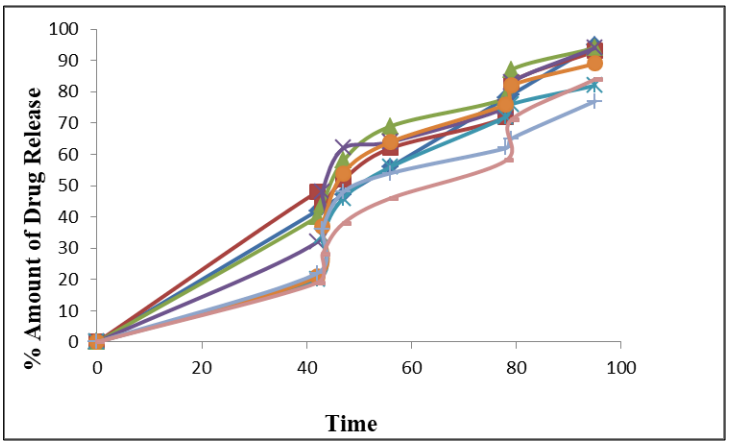

Figure 9 *In-vitro* drug release Profiles of Formulations F1-F8

Kinetic Models Data Analysis: The results of diffusion data fitted to various drug release kinetic equations like Zero order, First order, Higuchi model and Korsemeyer-Peppas. The kinetic values obtained for all formulations F1, F2, F3, F4, F5, F6, F7 & F8were tabulated respectively, Graphs are Plotted for Zero order, First order, Higuchi model and Korsemeyer-Peppas against cumulative % drug release Vs Time (Hrs), Log cumulative % drug remaining Vs Time (Hrs), cumulative % drug release Vs Square root of Time, Log cumulative % drug release Vs Log Time as shown in Table 5.

Table 5 Drug Release Kinetics of Amitriptyline hydrochloride Nasal Gels

Order Of Process	Zero order		First Order		Higuchi		Korse Meyer Pep pass		Mechanism
	R^2	slope	R^2	slope	R^2	slope	R^2	N	
F1	0.9056	11.476	0.8278	0.151	0.875	29.806	0.8969	0.823	Non-Fickian
F2	0.9025	1.1449	0.4821	0.0664	0.7269	39.64	0.6042	0.943	Zeroorder
F3	0.9262	1.272	0.893	0.0838	0.9215	41.404	0.8592	0.852	Non-Fickian
F4	0.939	1.386	0.6231	0.0779	0.7635	41.716	0.8095	0.756	Non-Fickian
F5	0.9648	0.1224	0.971	0.0963	0.9409	47.483	0.9721	0.865	Non-Fickian
F6	0.9659	0.1607	0.9804	0.1131	0.454	34.502	0.9706	0.831	Non-Fickian
F7	0.9319	0.201	0.0158	0.0173	0.0103	5.7846	0.3191	0.975	Zeroorder
F8	0.9029	0.2005	0.1054	0.0235	0.0129	4.2484	0.2692	0.853	Non-Fickian

F1, F2, F3, F4, F5, F6, F7 &F8 formulations were followed Korsemeyer-Peppas with correlation coefficient R^2=0.8969, 0.6042, 0.8592, 0.8095, 0.9721, 0.9706, 0.3191& 0.2692 respectively. F1 formulation follows both Zero order and Korsmeyer-Peppas models, It indicates diffusion release mechanism followed by non-fickian transport.

4. Conclusion

The percentage drug content of formulations was found satisfactory. The gel strength of all prepared formulations of gels was found to be in the range of 64 to 95%. The *In-vitro* release of Amitriptyline hydrochloride was prolonged release of drug ranges from 95% of released within 7 hour. Among the eight formulations the best formulation is F 1 formulation follows both Zero order and Korsemeyer-Peppas models, It indicates diffusion release mechanism followed by non-fickian transport.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest, financial or otherwise.

Author Contribution

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

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