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FORMULATION AND EVALUATION OF NASAL INSITU GEL OF FLUOXETINE HYDROCHLORIDE

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Abstract:
Purpose of this study was to formulate and evaluate in-situ gel of Fluoxetine Hydrochloride for nasal delivery using polymers possessing in-situ gelling properties.Formulations containing carbopol and sodium alginate were prepared using poloxomer as copolymer.Formulations were liquid before administration and underwent rapid gelation upon oral administration.FT-IR studies of drug, polymer and their physical mixture were carried out. The result of these studies revealed that there are no definite changes obtained in the bands of drug with respect to pure drug. Hence it was confirmed that formulations do not have any drug polymer interactions.In order to evaluate rheological behavior, viscosity of the formulations was evaluated using Brookfield viscometer. It showed that viscosity was found to be decreased at increasing rpm exhibiting shear thinning behaviour and increase in viscosity was observed with increase in concentration of polymer indicating that it obeys Newtonian system.Invitro release of fluoxetine from formulations was carried out which will indicate the effects of the variables on the mechanism and kinetics of drug release from dosage form. For the present work, in-vitro diffusion studies were carried out in simulated nasal fluid.
Release kinetic studies showed that insitu gels followed zero order drug release mechanism. Korsmeyer-peppas 'n' value 0.96 indicated that the formulation followed non-fickian diffusion controlled release mechanism.
Keywords: insitu gel systems,Nasal drug delivery,Fluoxetine Hydrochloride.

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INTRODUCTION:

Gels are an intermediate state of matter containing both solid and liquid components. The solid component comprises a three dimensional network of inter connected molecule or aggregates which immobilizes the liquid continuous phase[1,2].

Gels may also be classified based on the nature of the bonds involved in the three-dimensional solid network. Chemical gels arise when strong covalent bonds hold the network together and physical gels when hydrogen bonds and electrostatic and vander waals interaction maintain the gel network.

Importance Of In Situ Gelling System [3]

- In-situ forming polymeric delivery system such as ease of administration
- Reduced frequency of administration.
- Improved patient compliance & comfort.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.
- Extended nasal retention time.

Ideal Characteristics of Polymers

- It should be capable of adherence to mucus.
- It should have pseudo plastic behaviour.
- It should be good tolerance & optical activity.
- It should influence the tear behaviour.
- The polymer should be capable of decrease the viscosity with increasing shear rate there by offering lowered viscosity during blinking & stability of the tear
- Film during fixation.

Polymers Used In In-Situ Gelling Systems

Materials that exhibit sol to gel transition in aqueous solution at temperatures between ambient and body temperature is of interest in the development of sustained release vehicles with in situ gelation properties. Polymers capable of in-situ gelation include Poloxamer, Pluronics, various copolymers such as PEO-PLLA and PEG-PLGA-PEG, cellulose acetophalate latex,Pectin, Gelrite, Gellan gum, Alginate, Carbopol, chitin and Matrigel. The gel formation is induced by temperature change (Poloxamer, Pluronics, PEO-PLLA diblock copolymer, PEG-PLGA-PEG triblock copolymer, and Matrigel), pH change (cellulose acetophalate latex and Carbopol), or reaction with mono- or di-valent cations (Gelrite)[4-8].

Nasal Anatomy and Physiology

In recent decades, the nasal mucosa has become an established administration site for systemic drug delivery and a desirable alternative to parenteral medication since it is amenable to self-medication, has potential for direct-to-central nervous system delivery, no first-pass metabolism, non-invasiveness and virtually painless. From a pharmacokinetic standpoint, intranasal administration circumvents first-pass elimination and drug absorption is rapid due to the existence of a rich vasculature and a highly permeable structure within the nasal membranes[9,10].

The nasal cavity may also be exploited as a route of entry into the systemic circulation mainly for those compounds which cannot be given orally because they get destroyed in the gastrointestinal fluids, metabolized in the wall of gastrointestinal tract or undergo extensive first-pass metabolism by the liver during their first passage around the circulation. Currently, many nasal drug products on the market are indicated for the treatment of local disease such as allergic rhinitis, pain and for centrally acting drugs where the direct pathway from the nose to brain might offer a quicker and further specific therapeutic effect. Many low-molecular-weight, non-polar drugs (<300Da) in solution form are able to infiltrate the nasal epithelium with effortlessness. The proposed mechanism of absorption is suggested via aqueous channels. Molecules higher than 300 Da, experience difficulty in absorption similar to Gastrointestinal tract. The nasal epithelium adds one more hurdle in absorption, which is mucociliary clearance. Absorption enhancers are being used to enhance absorption across the nasal membrane, which may work by solubilize and stabilize the drug or by altering properties of the mucus layer by opening tight junctions between the cells or by increasing membrane fluidity. Currently, there are several various nasal drug delivery systems available in various phases of development to deliver high molecular weight compounds. A system for the nasal drug delivery is highly unlikely given the types of materials being considered, the different physical and chemical characteristics of drugs and the different target areas of the drug within the body. The effectiveness of a particular delivery system is also affected by its formulation as a liquid, powder, gel, microsphere, liposome or nanoparticle. This review focuses on the current state of art in the field of drug delivery through nasal route[11-15].

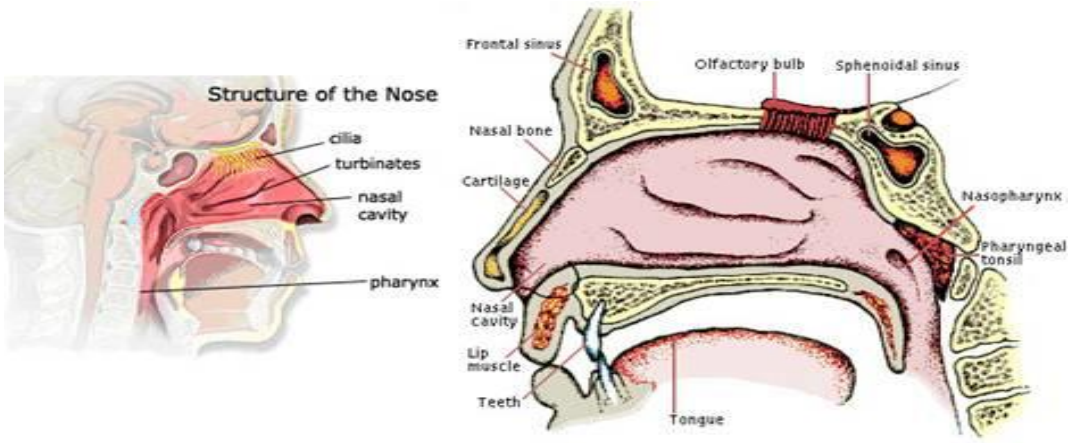

Fig 1: Structure of Nasal Cavity

Advantages of Nasal Route

- Higher bioavailability allowing lower doses
- Fast onset of therapeutic action
- Avoidance of liver or gastrointestinal metabolism.
- Avoidance of gastric irritation.
- Ease of selfmedication,
- Improved patient compliance
- Reduced risk of infectious disease transmission.
- Unlike the skin, nasal mucosa is not constructed from the keratinized stratum corneum. The subepithelial layer of the nasal mucosa with numerous microvilli is highly vascularized, with large and fenestrated capillaries facilitating rapid absorption.
- The rate and extent of absorption as well as plasma concentration *vs* time profiles are comparable with I.V. administration.
- Various nasal drug delivery systems are available for user-friendly noninvasive painless application.

Limitation of Nasal Drug Delivery System

There is risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the drug substances and from the constituents added to the dosage forms.

- Certain compounds when used as absorption enhancers may disrupt and even dissolve the nasal membrane in high concentration.
- Nasal atrophic rhinitis and severe vasomotor rhinitis can reduce the capacity of nasal absorption, e.g., Caerulein.
- There could be mechanical loss of the dosage form into the other parts of the respiratory tract like lungs.

METHODOLOGY:

Pre Formulation studies

Pre formulation testing is the first step in the rationale development of dosage forms of drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre - formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms, which can be mass produced.

Identification of Fluoxetine Hcl

Identification of Fluoxetine Hcl is carried out by FT-IR Spectrophotometer.

Determination of wavelength (λ max) A Solution of drug containing concentration of 100 µg/ml was prepared in distilled water. Later solution was scanned in the range of 200-400 nm using UV Spectrophotometer.

Fourier transform Infra-red spectroscopy

During gelation process, the nature of interacting forces can be evaluated using this technique by employing potassium bromide pellet method.

Preparation of Calibration curve of Fluoxetine Hcl

Dissolve 10mg of drug in distilled water and then further diluted with distilled water in 100 ml volumetric flask to get Ist stock solution. From this solution aliquots were prepared and diluted up to the mark to produce 2, 4,6,8,10,12 mcg/ml solutions. The absorbance was measured at 226 nm using a UV spectrophotometer

Preparation of Formulations

Solutions of sodium alginate and carbopol , were made in deionized water. The solution was heated to 60°C with constant stirring on a magnetic stirrer. The solution was allowed to cool to 40°C, then the drug and polaxomer 407 were dissolved and dispersed, respectively, in the resulting solution and finally stored in amber color bottles until further use.

Table 1: Formulation of Nasal Insitu Gels

Formulation Code	Drug (mg)	Sodium Alginate (mg)	Carbopol (mg)	poloxamer 407 (mg)	Deionised water (ml)
F1	500	500	-	1000	100
F2	500	500	-	_	100
F3	500	500	500	1000	100
F4	500	500	500	_	100
F5	500	1000	_	1000	100
F6	500	1000	_	_	100
F7	500	1000	500	1000	100
F8	500	1000	500	-	100
F9	500	500	1000	1000	100
F10	500	500	1000	_	100

Evaluation and Characterization of in- situ Gel Systems:

In situ gels may be evaluated and characterized for the following parameters: **Physical appearance:**

All the prepared in situ solutions were checked for their clarity and the time required for gel formation.

Determination of $P^{H:}$

The pH was measured of in situ solutions using a calibrated digital pH meter at 25°C.

In-vitro gelation:

Gelling capacity of formulations was evaluated in order to identify the formulations suitable as in-situ gelling systems. Gelling capacity was determined by mixing the formulation with simulated nasal fluid.

The composition of pH (6) simulated nasal fluid was sodium chloride (0.65%), KH_2PO_4 (0.04%), K_2HPO_4 (0.09%) & benzalkonium chloride (0.02%).

Measurement of Rheological properties

This is an important parameter for the in situ gels, to be evaluated. Viscosity and rheological properties of in situ forming drug delivery systems may be assessed using Brookfield rheometer or some other type of viscometers such as Ostwald's viscometer. The viscosities of the prepared solutions were determined by brookfield viscometer (Brookfield viscometer, model DV-II pro viscometer). The samples (10 ml) were sheared at a rate of 100 r/min using S63 spindle at room temperature. The viscosity of these formulations should be such that no difficulties are envisaged during their administration by the patient.

Determination of drug content

Accurately, 1 ml of in-situ gel was measured and transferred to 10 ml volumetric flask and 10ml simulated nasal fluid was added, followed by vigorous shaking until the formed gel got

Completely dispersed to give a clear solution. From this solution, 1 ml of sample was withdrawn and diluted to 10ml with simulated nasal fluid. Contents of Fluoxetine were determined spectrophotometrically at 226 nm using double beam UV-Visible spectrophotometer.

Invitro drug release studies:

In vitro release study of the formulated in situ gel was carried out in franz diffusion cell, 20ml of simulated nasal fluid pH 6 was added to the acceptor chamber. Gel containing drug equivalent to 5mg was placed in donor compartment. At predetermined time points (1 hr), Samples (1 ml) were withdrawn from the acceptormcompartment, replacing the sampled volume with SNF after each sampling for a period of 8 hrs. The samples were suitably diluted and measured spectrophotometrically at 226nm.

RESULTS AND DISCUSSION:

Determination of wavelength (λ max):

λ max of Fluoxetine Hydrochloride was found to be 226nm in distilled water.

Table 2: Standard Graph of Fluoxetine Hcl

S.NO	Concentration	Absorbance
1.	2	0.082
2.	4	0.170
3.	6	0.248
4.	8	0.335
5.	10	0.417
6.	12	0.528

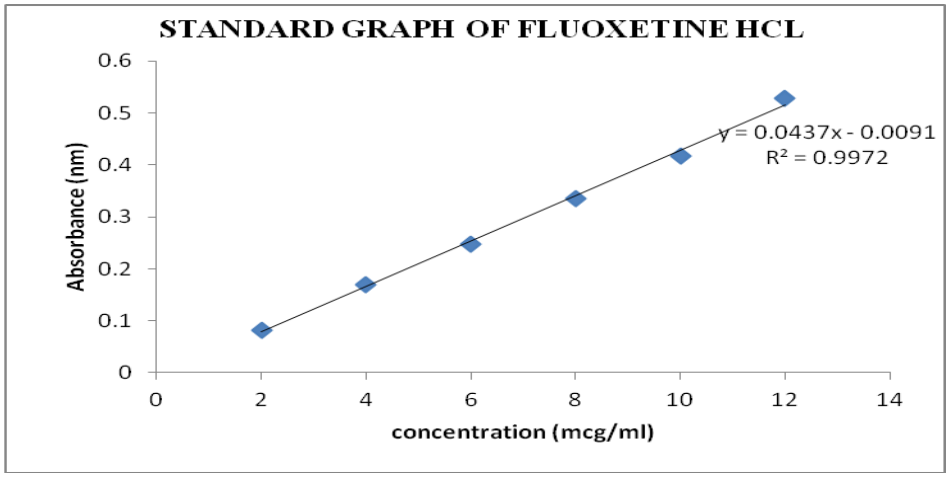

Fig 2: Standard graph of Fluoxetine Hcl

Compatibility studies:

All the characteristic peaks of Fluoxetine were observed in IR spectra of drug-excipient mixtures also. These characteristic IR absorption bands of Fluoxetine were all retained in the presence of the selected excipients indicates that there is no interaction between the Fluoxetine and excipients

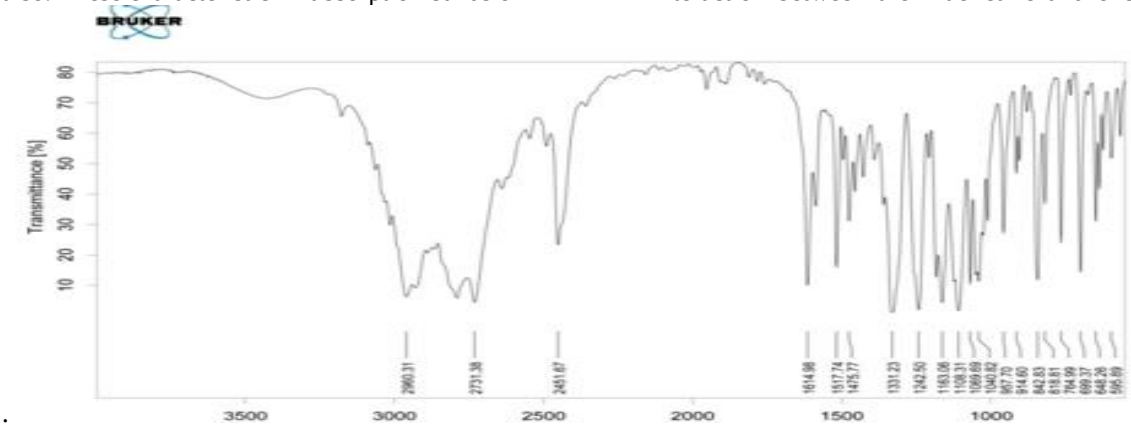

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Fig 3: FT-IR of Fluoxetine

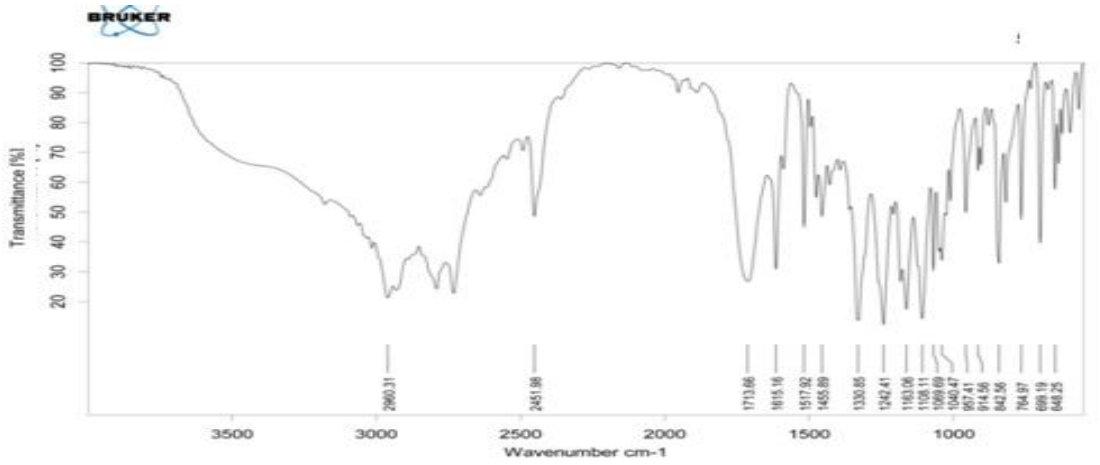


Fig 4: FT-IR of Fluoxetine+Mix

Determination of PH:

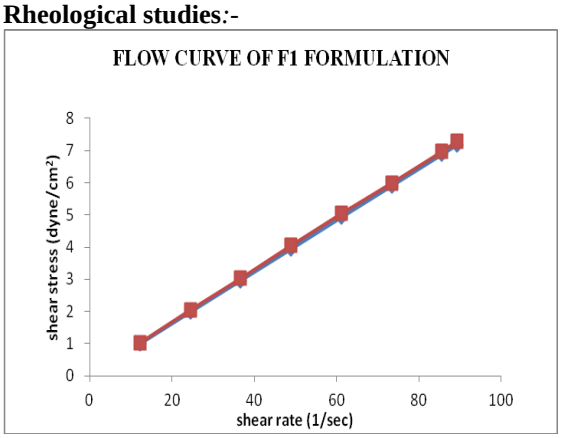
Table 3: Determination of PH

Formulation	PH(±SD)
F1	5.1±0.21
F2	4.8±0.27
F3	5.2±0.1
F4	5.1±1.0
F5	5.3±0.58
F6	6.4±0.75
F7	5.5±0.3
F8	4.9±1.12
F9	5.3±0.16
F10	6.1±0.23

In-Vitro Gelation:-

Prepared in-situ gelling systems were evaluated for the in-vitro gelation. All the formulations gave satisfactory results.

Rheological studies:-



Blue line represents increase in rpm

Red line represents decrease in rpm.

Fig 5: Flow Behavior Studies of F1 Formulation

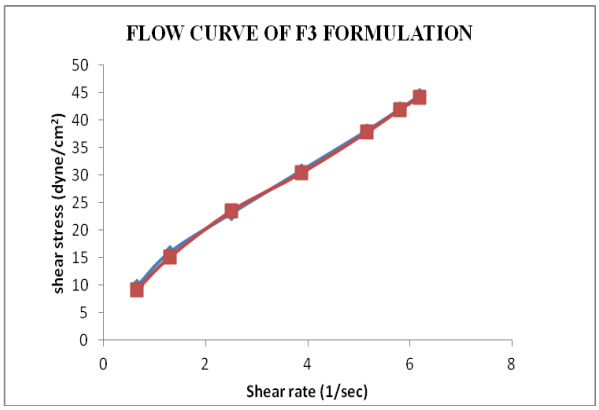


Fig 7: Flow Behavior Studies of F3 Formulation

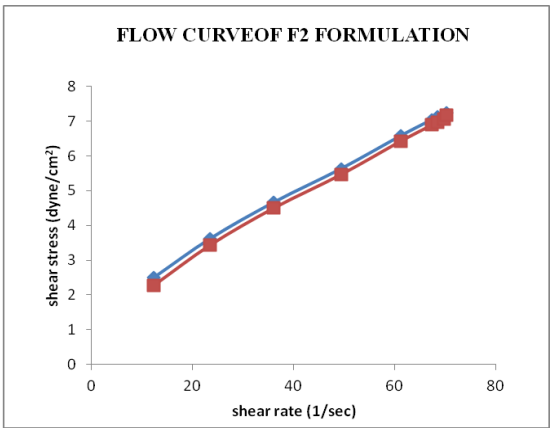


Fig 6: Flow Behavior Studies of F2 Formulation

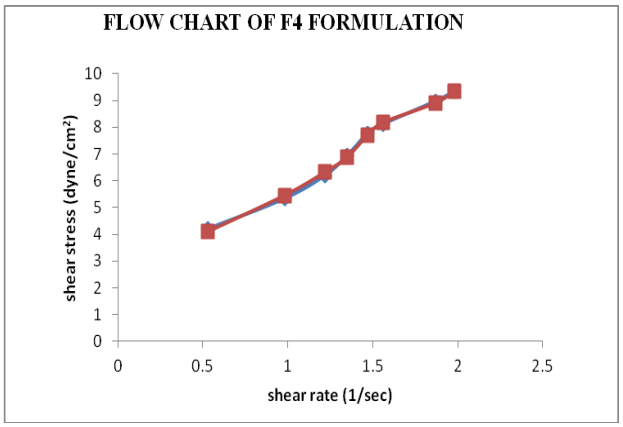


Fig 8: Flow Behavior Studies of F4 Formulation

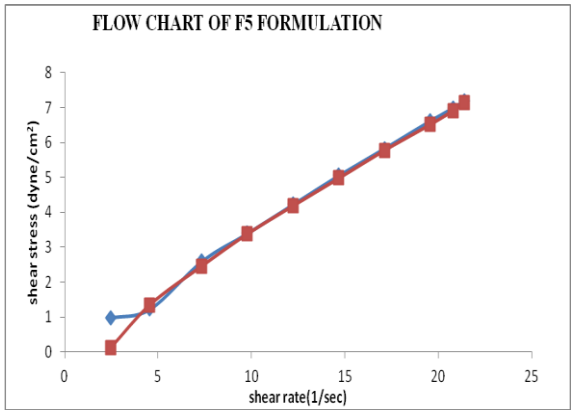


Fig 9: Flow Behavior Studies of F5 Formulation

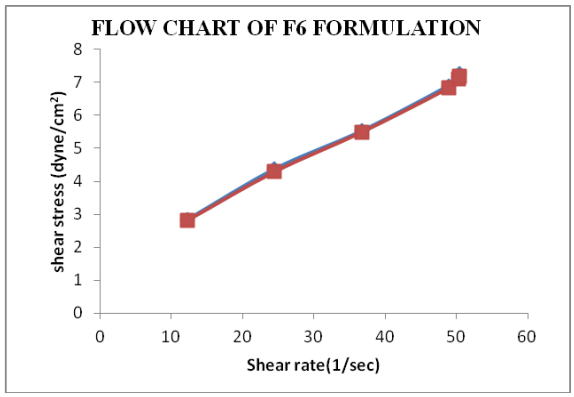


Fig 10: Flow Behavior Studies of F6 Formulation

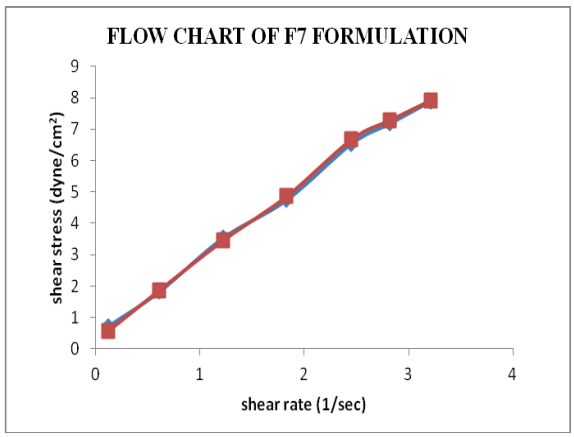


Fig 11: Flow Behavior Studies of F7 Formulation

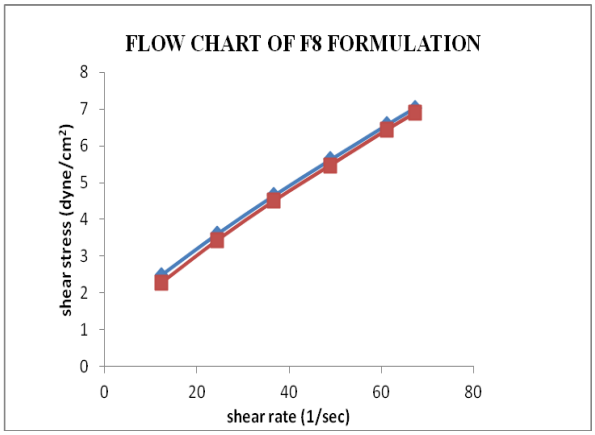


Fig 12: Flow Behavior Studies of F8 Formulation

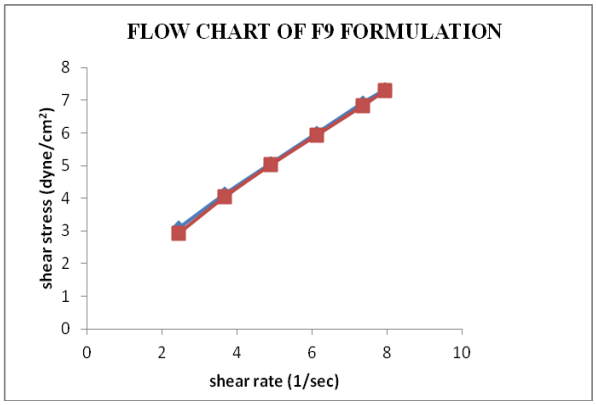


Fig 13: Flow Behavior Studies of F9 Formulation

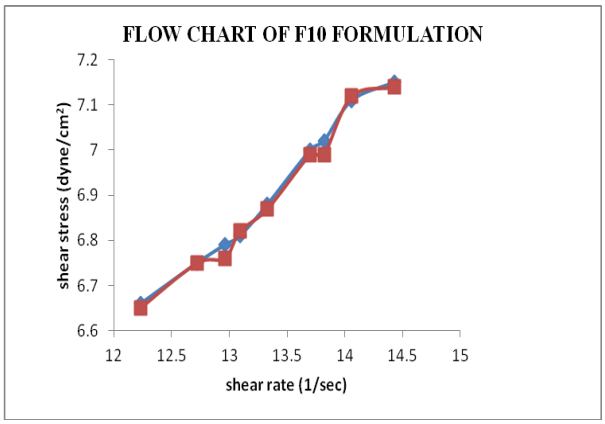


Fig 14: Flow Behavior Studies of F10 Formulation

Determination of drug content:-

It is an important requirement for any kind of dosage form. The amount of drug present in the formulation should not deviate from certained specified limits from labelled amount. All the formulations were found to having drug content in the range of 97-100%.

***In-Vitro* Release Studies:-**

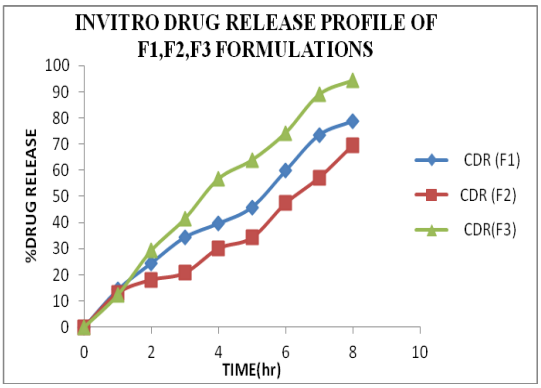


Fig 15: *In vitro* Drug Release Profile of F1, F2, F3 Formulation

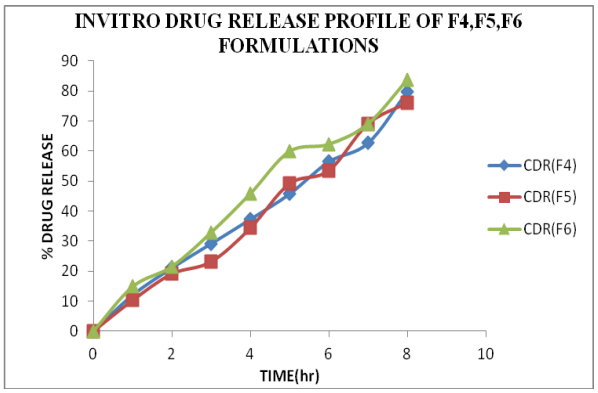


Fig 16: *In Vitro* Drug Release Profile of F4, F5, F6 Formulations

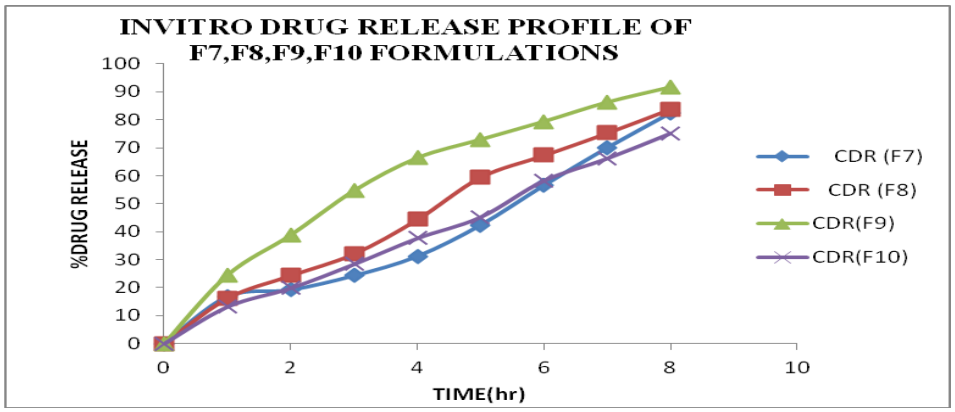


Fig 17: *In Vitro* Drug Release Profile of F7, F8, F9, F10 Formulations

Table 4: Drug Release Kinetics of Optimized (F3) formulation

Zero order		First order		Higuchi		Peppas	
R^2	*K*	R^2	*K*	R^2	*K*	R^2	*n*
0.990	11.99	0.859	0.112	0.941	35.67	0.988	0.964

CONCLUSION:

In this study "Formulation and evaluation of in-situ gel of Fluoxetine Hydrochloride for nasal delivery" Insitu gels were prepared using poloxamer as cross linking agent. It was found that increase in concentration of polymer decreased the drug release. Formulations were liquid before administration and underwent rapid gelation upon administration. Formulations having good insitu gelling capacity, having drug content 98-99%, release kinetic studies showed that in-situ gels followed zero order drug release and followed non-fickian diffusion controlled release mechanism.Hence from above results we can conclude that it is possible to formulate insitu gels of fluoxetine hydrochloride for nasal delivery using carbopol, sodium alginate and poloxamer.

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