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FORMULATION DEVELOPMENT AND EVALUATION OF INTRANASAL NANOGEL OF BROMOCRIPTINE MESYLATE

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ABSTRACT
The aim of this study was to investigate the potential use of solid lipid nanoparticles as a delivery system to enhance the brain targeting efficiency of Bromocriptine mesylate following intranasal administration for Parkinson's disease. The drug loaded solid lipid nanoparticles were prepared by high speed homogenization. These nanoparticles had the highest entrapment efficiency of 72.45%, a mean particle size (167.52nm) and zeta potential (-22.8mV). The Intranasal nanogel was prepared by using 3^2 factorial design. The prepared formulations were evaluated for clarity, pH, viscosity, mucoadhesive strength, gel strength, drug content, *in-vitro* drug release, permeation study and stability studies. Formulation batch F9 was selected as optimized on the basis of evaluations. The results of stability studies show that the formulation was stable at accelerated temperature condition (40°C± 2°C, 75% RH ± 5%).

KEYWORDS
Solid lipid nanoparticles, Nasal, Nanaogel, Bromocriptine mesylate and Parkinson's disease.

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INTRODUCTON
Bromocriptine mesylate classified as a BCS class II drug (high permeability and poor solubility) is a dopamine receptor agonist used predominantly in the therapy of Parkinson's disease. Parkinson's disease (PD) is one of the most prevalent progressive neurodegenerative disorder characterized by massive depletion of striatal dopamine as a result of degeneration of dopaminergic neurons in the substantia nigra. It is a chronic condition affecting 1-2% of the population over the age of 65, causing difficulties in the control

of movements. The main symptoms of PD are akinesia, bradykinesia, resting tremor, rigidity and disturbance of posture and gait. There is no cure for PD, since currently available therapies can neither arrest nor reverse the progression of the disease. However, the symptoms can be managed with several different drugs. Bromocriptine mesylate is rapidly absorbed, after oral administration; the bioavailability of the drug is 28%. It is highly distributed in the liver, stomach, and intestine and extensively metabolized in the liver with terminal half-life of 15 hrs[1-3].

Any drug that needs to reach central nervous system (CNS) requires crossing BBB. Delivery of drugs to the brain has been filled with many issues like low bioavailability due to the impervious nature of the Blood-Brain-Barrier. The development of therapies to treat brain diseases has long been frustrated by the failure of systemically administered drugs to permeate the brain. The delivery mechanism through the BBB and the physicochemical properties of the molecule of the drug are factors that must be considered when designing drug delivery systems for brain targeting[4]. In the past few years, intranasal delivery has come to the forefront as an alternative to invasive delivery methods to bypass the CNS barriers and target drugs directly to the brain. This is due to its ability to bypass the BBB and directly propel the drugs through the olfactory lobe to the brain which enhances their bioavailability. Drugs meant for direct nose-to-brain delivery should have a protective embodiment that can entrap/encapsulate the therapeutic substances whilst in the nasal cavity. There is therefore a need for the drugs to be protected in the nasal cavity and be delivered into the brain in a controlled manner[5,6].

Novel developments emerging in the field of polymer science, lipid formulations and nanotechnology provide an option by which the obstacles of limited brain entry can be overcome. Solid lipid nanoparticles (SLNs) have gained an increasing interest as drug delivery system in neurodegenerative disorders because of their small size, biocompatibility, and ability to incorporate lipophilic as well as hydrophilic drugs and controlled release properties, storage stability and to prevent the incorporated drug from degradation. They are colloidal dispersions or particulates in the size range of 50-1000 nm composed of biocompatible lipid matrix. The drug is usually dispersed or dissolved in the lipid and core is coated by surfactants. However, the low viscosity of SLN dispersion is disadvantageous for nasal administration. They must be converted into gel to ease of application and to prolong residence time in nose[7,8].

The present studies, therefore, have been undertaken to develop SLN loaded gel with controlled release properties for the effective intranasal delivery of Bromocriptine mesylate by using various polymers. The developed nanogel was characterized by using various evaluation parameters.

MATERIAL AND METHODS

Materials

Bromocriptine mesylate was received as a kind gift sample from Teva Czech Industries, Czech Republic. Poloxamer 407 was obtained from Signet Chemicals, Mumbai. Carbopol 934 and HPMC K4M were purchased from Research Lab Fine Chem, Mumbai.

Methods

Development of Nanogel

Formulation of Nanogel[9,10]

Preparation of Solid lipid Nanoparticles

Preparation of Aqueous Phase 'A'

Accurately weighed quantity of surfactant i.e., Poloxamer 407 was added in distilled water (60ºC).

Preparation of Lipid Phase 'B'

Weighed quantity of lipid i.e., stearic acid was melted and simultaneously accurately weighed quantity of Bromocriptine Mesylate was added in to it.

Incorporation of solution 'B' in dispersion 'A'

The drug loaded lipidic phase was dispersed in a hot aqueous surfactant solution under continuous stirring to form a coarse o/w emulsion. It was then homogenized at the temperature above the melting point of the lipid using high speed homogenizer for 30 min at 25000rpm. Then it was cooled to room

temperature for formation of Solid lipid nanoparticles.

Preparation of Nanogel

The weighed quantity of carbopol 934 and HPMC K4M was mixed properly in distilled water (40°c) with continuous stirring. The benzalkonium chloride and triethanolamine was added to the above polymeric solution. The uniformity in the stirring was maintained and then incorporation of drug loaded solid lipid nanoparticles into the polymeric solution to form intranasal nanogel. Further keep it in the refrigerator for 24 hrs.

Evaluations of Intranasal Nanogel of Bromocriptine Mesylate

Evaluations of Solid Lipid Nanoparticles

Entrapment efficiency (EE)

The SLN suspension was centrifuged at 15000 rpm for 40 min at 4ºC. The supernatant collected after each centrifugation step during the preparation was combined to estimate the EE. Amount of unentrapped drug was quantified by UV spectrophotometry using methanol as blank. The amount of drug in the nanogel systems was calculated using the formula given below (values were taken in triplicates, n = 3).

$$EE\ (\%) = \frac{\text{Amount of drug in nanogel}}{\text{Amount of drug taken initially}} \times 100$$

Particle size and polydispersity index

Particle size analysis of optimized batch was determined by the (nanozs, Malvern, Worcestershire, UK) instrument at 25ºC, which is based on the Brownian motion. Samples were diluted in the free purified water to scattering intensity approximately 150300keps. The mean z-average diameter and polydispersity indices were obtain by cumulative analysis using MALVERN software.

Zeta potential

Zeta potential is key indicator of the stability of formulation. The magnitude of zeta potential indicates the degree of electronic repulsion between adjusts, similarly charge particle in dispersion. Zeta potential of the optimized batch was measured by folded capillary cells using the zetasizer. 1ml sample was taken from formulated nanosuspension and dispersed with 10ml double distilled water. The samples were ultrasonicated for 5min prior size determination measure the primary particle size. Then the sample was taken in disposable cuvette and placed in the instrument for size and zeta potential measurement[11,12].

Evaluation of Intranasal Nanogel

Clarity

The formulation was visually checked for the clarity.

pH

The pH of each formulation was determined using digital pH meter (Sistronic Digital pH meter 335) previously calibrated by pH 4 and pH 7. The pH values were recorded immediately after preparation.

Viscosity

The viscosity of different nanogel formulation was determined at room temperature using a Brookfield viscometer type DV-II + PRO at 5, 10, 15, 20, 25, 30 rpm using spindle (LPV) No. 64. The viscosity of the formulation batches was determined in triplicate and the average mean was then taken to obtain the viscosity of formulations. The viscosity results were also plotted against speed to obtain rheological behavior of formulations[13].

Measurement of Gel Strength

A sample of 25ml of gel was put in a 50ml graduated cylinder. A weight of 14.33g was placed on the gel surface. The gel strength, which is an indication for the nasal gel at physiological temperature, was determined by time in seconds required by the weight to penetrate 5cm into the gel. All measurements were performed in triplicate (n=3). The apparatus used for measuring the gel strength at room temperature is shown in Figure below.

Mucoadhesive Strength

"Detachment Stress is the force required to detach the two surfaces of mucosa when a formulation/gel is placed in between them". The detachment stress was measured by using a modified analytical balance.

Fabrication of equipment

The equipment was fabricated by us in the laboratory as shown in Figure No.3. A double beam physical balance was taken, both the pans were

removed. The left pan was replaced with a brass wire, to which was hanged a Teflon disc (A), also locally fabricated. The dimensions are 2cm height and include an expanded cap of diameter 3.8cm and thickness 2cm. Another teflon disc of 2cm height and 1.5cm diameter was placed right below the suspended disc upon the base of the balance. The right pan (C) was replaced with a lighter pan so that, the left pan weighs 5.25gm more than the right pan. The lower polypropylene block was intended to hold the mucosal tissue (D) of goat nasal mucosa and to be placed in a beaker containing simulated nasal solution pH 6.7 (E).

Measurement of adhesion force

The following procedure was used for all the test formulations using the above equipment. The nasal mucosa was removed from refrigerator and allowed to attain equilibrium with ambient conditions in the laboratory. The goat nasal mucosa was carefully excised, without removing connective and adipose tissue and washed with simulated nasal solution. The tissue was stored in fresh simulated nasal solution. Immediately afterwards the membrane was placed over the surface of lower teflon cylinder (B) and secured. This assembly was placed into beaker containing simulated nasal solution pH 6.7 at 37 ± 2°C. From each batch, some quantity of gel was taken and applied on the lower surface of the upper teflon cylinder. The beaker containing mucosal tissue secured upon lower cylinder (B), was manipulated over the base of the balance so that, the mucosal tissue is exactly below the upper cylinder (A). The exposed part of the gel was wetted with a drop of simulated nasal solution, and then a weight of 10gms was placed above the expanded cap, left for 10 minutes. After which the gel binds with mucin. The weight was removed. Then slowly and gradually weights were added on the right side pan till the gel separates from the mucosal surface/ membrane.

The weight required for complete detachment is noted (W1) (W1-5.25G) gives force required for detachment expressed in weight in grams. Procedure was repeated for two more times. Average was computed and recorded[14].

Calibration of test equipment

Initially, a gel from the same batch was taken ten times and individual force required for complete detachment was noted and S.D. was calculated.

Force of adhesion (N) = (bioadhesive strength/1000) × 9.81

Bond strength (N/m^2) = force of adhesion (N)/surface area of disk (m^2).

Drug content

1ml of formulation was taken containing 10ml volumetric flask and 10ml of methanol was added to dissolve the formulation completely. Aliquote 1ml from this solution was diluted up to 10ml methanol to get final concentration. The absorbance of prepared solution was measured at 237λ_{max} by using UV visible spectrophotometer and % drug content was calculated in the range of 95-105%.

***In-vitro* Drug Release Study (Diffusion study)**

In-vitro release study of the formulated nanogel was carried out by using diffusion cell through egg membrane as a biological membrane. Diffusion cell with inner diameter 1.4cm was used for the study. The formulation 1ml were placed in donor compartment and Freshly prepared 100ml simulated nasal electrolyte solution (sodium chloride 0.745gm, potassium chloride 0.129gm, calcium chloride dehydrated 0.005gm, distilled water q.s. 100ml) in receptor compartment. Egg membranes were mounted in between donor and receptor compartment. The position of the donor compartment was adjusted so that egg membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 2ml of sample is withdrawn from receiver compartment after 30 min, 1, 2, 3, 4, 5, 6, 7 and 8 hrs and same volume of fresh medium is replaced. The withdrawn samples was diluted to 10ml in a volumetric flask with Methanol and analyzed by UV spectrophotometer at 237nm[15].

***In-vitro* permeation study**

Natural membranes are utilized to determine in vitro permeation study to mimic the in vivo permeation patterns. In this experiment goat nasal mucosa was utilized because the respiratory area of

goat is large and it is easy to get. Fresh mucosal tissue was removed from the nasal cavity of goat. The tissue was placed on the diffusion cell with permeation area 0.786cm^2. The acceptor chamber of the diffusion cell (laboratory designed) with a volume capacity 100ml was filled with simulated nasal fluid (SNF) contained accurately 7.45mg/ml NaCl, 1.29mg/ml KCl and 0.32mg/ml $CaCl_2 \cdot 2H_2O$. 0.5 (10mg equivalent) ml of formulation was placed in donor compartment. At predetermined time intervals of 30 min, 1, 2, 3, 4, 5, 6, 7 and 8 hrs 1ml of sample was withdrawn from the acceptor compartment replacing the sample removed with simulated nasal fluid after each sampling for period of 8 hrs. Then samples were specifically diluted and absorbance was noted at 237nm. Permeability coefficient (p) was calculated by the following formula,

$$P = (dQ/dt) / (C_0 \times A)$$

Where, dQ/dt is the flux or permeability rate (mg/h), C_0 is the initial concentration in the donor compartment, and A is the effective surface area of nasal mucosa[16].

Accelerated Stability Studies

For the stability study the formulation was taken for 3 months. The test conditions for stability studies were Temperature condition at room temperature (40^{o}C±2^{o}C), relative humidity was 75± 5%. The formulations were evaluated mainly for their physical characteristics at the predetermined intervals of 30 days like appearance/clarity, pH, viscosity and drug content[17].

RESULTS AND DISCUSSION

Particle size and polydispersity index

The particle size of the optimize batch (F9) is given in Table No.2.

The particle size of the Solid lipid nanoparticles of optimized batch was found to be 167.25nm.

Zeta potential

Zeta potential of optimized batch (F9) is given in Table No.3.

Zeta potential shows the stability of the (colloidal dispersion) solid lipid nanoparticle under the stress testing condition according to ICH guidelines of stability studies of various pharmaceutical formulations. Zeta potential is affected by particle size, lowest particle size in nanosize i.e. 167.25, shows -22.8mV zeta potential which indicates the thermodynamic instability of the dispersion.

Physical parameters

Clarity

On careful visual inspection against dark and white background, all the prepared nasal gel formulations were found to be free from any suspended particulate matter. All the formulations were found to be clear. The prepared formulations are as shown in Figure No.6.

Physical appearance

The physical appearance of the nanogel formulation was found to be translucent, homogeneous and consistent.

pH

The pH value of the formulation is given in the Table No.5.

pH of various batches of intra-nasal nanogel are shown in the Table No.5 which was found to be in range of 6.25-6.34 pH values indicates the suitability of nanogel for nasal application.

Viscosity

The viscosity is resistance to flow which is important physical property for nasal preparation because it influences drug release as well as jellification the rheological behavior of the intra-nasal nanogel indicates that the systems were shear thinning in nature showing decrease in viscosity at increasing shear rate. This viscosity result reflects that the decrease in proportion of stearic acid and increase in shear rate results in decrease in viscosity which indicate that gel has the pseudo plastic flow.

Measurement of the Gel Strength

The gel strength was found to be affected by concentrations of gelling agent, mucoadhesive polymers and also by the temperature. Optimal mucoadhesive gel must have suitable gel strength so as to be administered easily and can be retained at Nasal region without leakage after administration. Gel strength of all formulations showed comparable results as that of viscosity.

Mucoadhesive strength

The mucoadhesion force increased significantly as the concentration of mucoadhesive polymers increased.

Results of this test indicate that the variable Poloxamer-407 and HPMC K4M both are having effect on mucoadhesive strength. It shows that mucoadhesive force was increased with the increasing concentration of the Poloxamer-407 and HPMC K4M.

Drug content

The drug content of formulations is shown in the Table No.8.

The drug content was carried out to ascertain the concentration of drug in each formulation was uniform. The percentage drug content of all prepared nanogel formulations was found to be in the range 94-99%. Therefore uniformity of content was maintained in all formulations.

***In-vitro* drug release study**

In order to study the effect of concentration of stearic acid on drug release, it was found that decrease in concentration level of stearic acid in the formulation drug release rate was increased and increase in speed of homogenizer results in increase in the drug release. Out of nine formulations maximum release after 8 hrs was found for F9 formulation. This indicates release of 97.67% drug availability. Nasal gel containing SLN can show better residence and contact with nasal membrane which is requirement for any formulation to show its efficacy. The obtain results of F1 to F9 formulation have shown significant prolongation of drug release across biological membrane but considering 8 hours release pattern.

***In-vitro* permeation Study**

Drug release profile was obtained by plotting percent drug release against time (Figure No.8).

The *In-vitro* permeation study was performed for the optimized batch F9 using nasal goat mucosa. The percent drug permeated after 8hr was found to be 90.79% from intra-nasal nanogel formulation.

Accelerated Stability study

Stability study of optimized F9 formulation was performed at room temperature. The results of stability studies show that the formulation was stable at accelerated temperature condition (40^{o}C ± 2^{o}C, 75% RH ± 5%). Results have been given in Table No.9. A slight increase in pH and viscosity and a slight decreased in drug content were observed however, these were not significant so as to affect the quality and safety of the formulation after storage.

Table No.1: Composition of formulation batches as per 3^2 Full Factorial Design

S.No	Formulation code (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredient										
1	Bromocriptibe Mesylate (w/v)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2	Stearic Acid(w/v)	10	10	10	7.5	7.5	7.5	5	5	5
3	Poloxamer 407 (w/v)	18	18	18	18	18	18	18	18	18
4	HPMC K4M (w/v)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
5	Carbopol 934	1	1	1	1	1	1	1	1	1
6	Benzalkonium chloride (w/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
7	Triethanolami-ne	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
8	Purified water(v/v)	100	100	100	100	100	100	100	100	100

Table No.2: Size distribution and PDI

S.No	Formulation code	Particle size Z average (nm)	Particle size (d.nm)	PDI
1	Optimized batch(F9)	167.25	Peak 1: 214.68	0.169

Table No.3: Zeta potential

S.No	Formulation	Zeta potential (mV)	Zeta deviation
1	Optimized batch (F9)	-22.8	6.34

Table No.4: Physical appearance of formulations

S.No	Parameters	Inference
1	Colour	Translucent gel
2	Homogeneity	Homogeneous
3	Consistency	Consistent

Table No.5: pH value of formulations

S.No	Formulation code	Observed pH(±SD)
1	F1	6.25±0.005
2	F2	6.28±0.005
3	F3	6.35±0.005
4	F4	6.33±0.005
5	F5	6.26±0.005
6	F6	6.28±0.005
7	F7	6.32±0.005
8	F8	6.30±0.005
9	F9	6.34±0.005

Table No.6: Gel strength of formulations at room temperature

S.No	Formulation code	Gel strength (sec) (±S.D)
1	F1	0.58±0.005
2	F2	0.63 ± 0.011
3	F3	0.84 ±0.01
4	F4	0.79 ± 0.005
5	F5	0.74 ± 0.011
6	F6	0.96 ± 0.007
7	F7	0.75 ± 0.005
8	F8	1.29 ± 0.086
9	F9	2.04 ± 0.005

Table No.7: Mucoadhesive strength of formulations

S.No	Formulation code	Detachment stress/Mucoadhesive strength (gm) (±S.D.)	Detachment Force/ Bond strength (N) (±S.D)
1	F1	0.045 ± 0.002	0.0025 ± 0.0001
2	F2	0.049 ± 0.001	0.0027±0.0001
3	F3	0.053 ± 0.002	0.0029 ±0.0001
4	F4	0.058 ± 0.002	0.0032 ± 0.0001
5	F5	0.062 ± 0.002	0.0035 ± 0.0001
6	F6	0.067 ± 0.001	0.0040 ± 0.0001
7	F7	0.072 ± 0.001	0.0039 ± 0.0001
8	F8	0.076 ± 0.001	0.0043 ± 0.0001
9	F9	0.078 ± 0.002	0.0042± 0.0001

Table No.8: Drug content of formulations

S.No	Formulation code	Drug content (%) (±S.D)
1	F1	94.70±0.25
2	F2	96.96±0.37
3	F3	95.39±0.50
4	F4	97.60±0.05
5	F5	98.50±0.50
6	F6	97.30±0.25
7	F7	96.90±0.05
8	F8	95.80±0.25
9	F9	99.20±0.05

Table No.9: Stability Study data for F9 formulation at Accelerated temperature condition (40^{o}C± 2^{o}C, 75% RH ± 5% RH)

S.No	Observations		Before Stability Testing	During study (3rd month)
1	Clarity		Clear	Clear
2	Visual appearance		Transparent	Transparent
3	pH		6.31±0.005	6.33±0.008
4	Drug content		97.24 %	96.98 %
5	Viscosity	05	532.7	539.9
		10	493.2	504.1
		15	477.8	486.3
		20	465.9	472.5
		25	452.8	467.9
		30	424.2	431.8

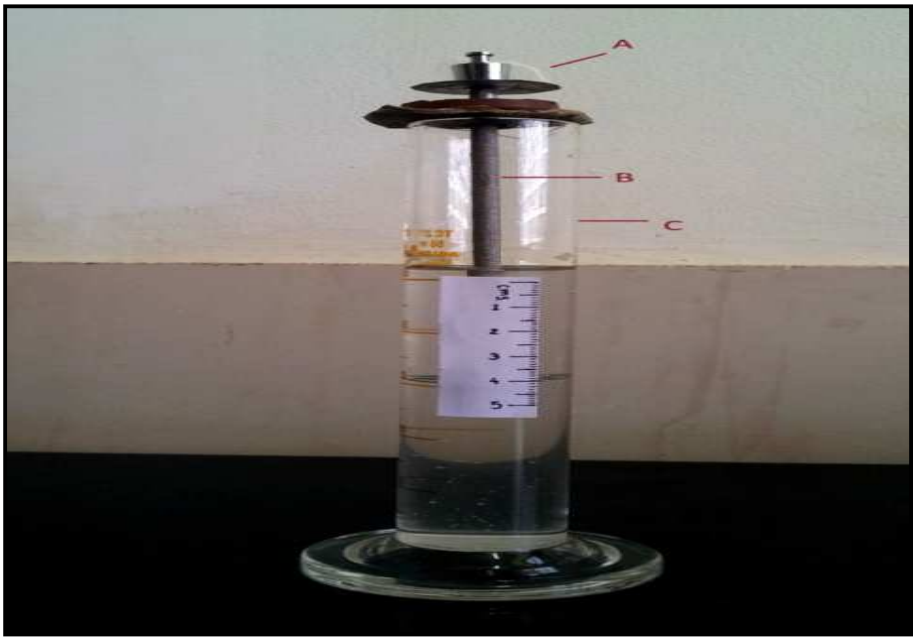

Figure No.1: Gel Strength measuring device
(A) Weights (B) Device (C) Graduated cylinder (D) gel

Figure No.2: Modified balance for mucoadhesive study
A: Modified balance, B: Weighing pan, C: Weight D: Gel, E: Nasal mucosa F: polypropylene cylinder

Figure No.3: Laboratory designed diffusion cell
A: Test tube containing formulation, B: Egg membrane, C: Beaker containing simulated nasal solution, D: Magnetic stirrer

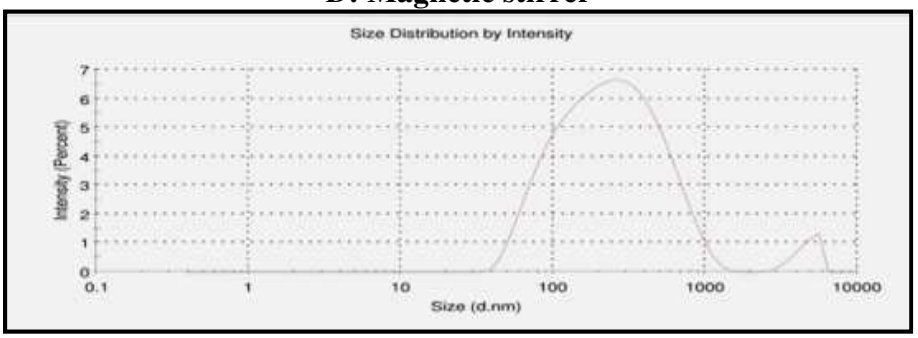

Figure No.4: Graph of Particle size

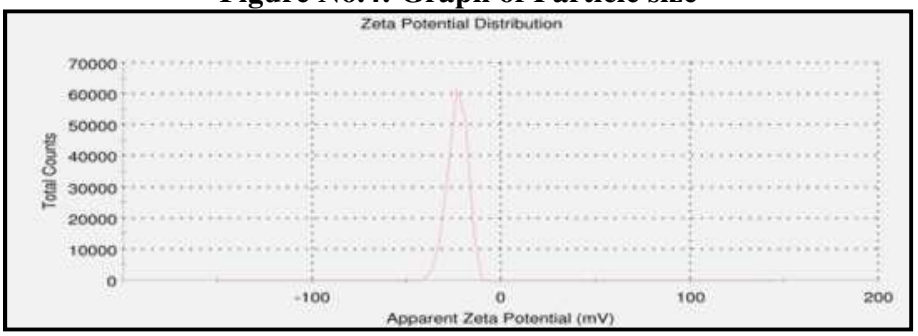

Figure No.5: Graph of Zeta potential

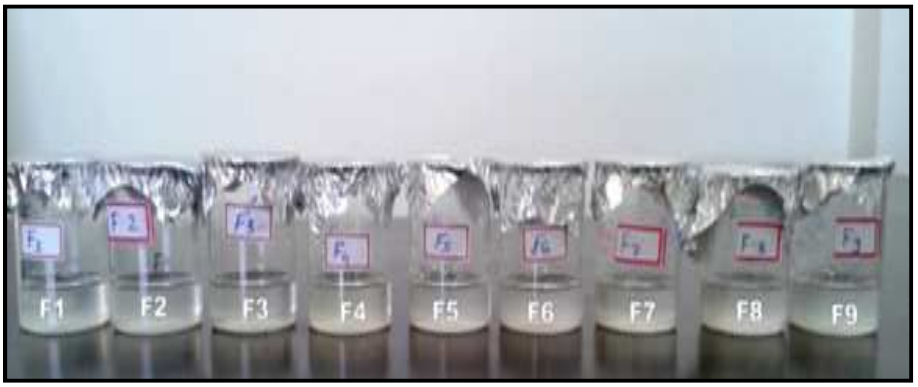

Figure No.6: Formulation Batches F1-F9

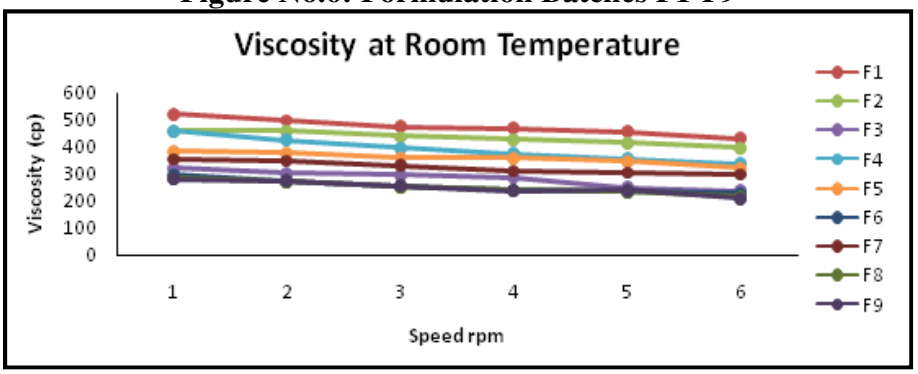

Figure No.7: Viscosity of formulations

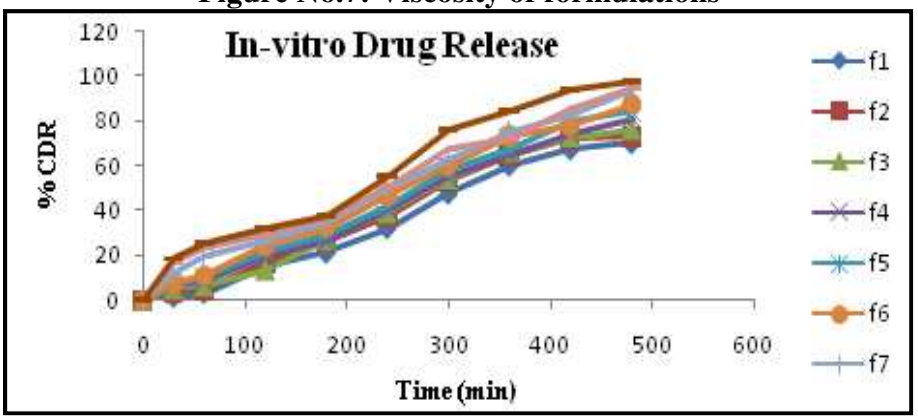

Figure No.8: *In-vitro* Drug release profile of optimized formulation (F1-F9)

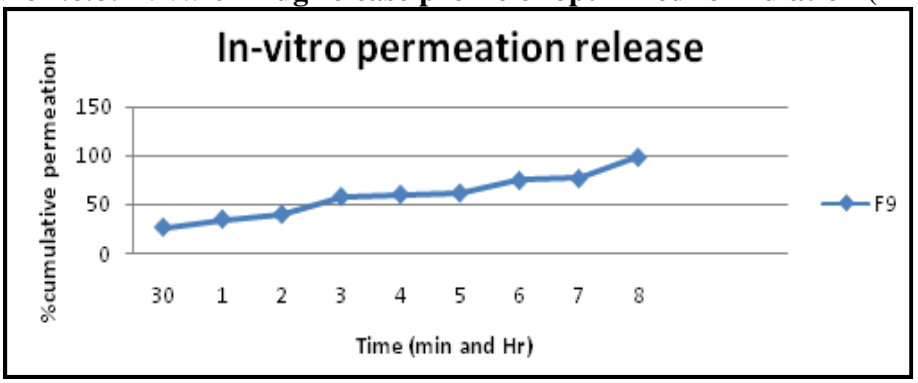

Figure No.9: *In-vitro* drug permeation profile of optimised formulation batch F9

CONCLUSION

The study involved Formulation and Development and Evaluation of Solid Lipid Nanoparticle loaded Intra-nasal gel of Bromocriptine Mesylate. The main aim of the study was to deliver drugs in its nanosize to the brain which is an effective and targeted therapy for neurodegenerative disorder (Parkinson's disease). There has been an increased interest during recent years in the use of nanotechnology systems that could modify drug delivery and bioavailability at targeted site of action. Therefore it is desirable to develop a nanogel and administer it by nasal route is more reliable method for drug delivery to the brain than the systemic administration. Finally it can summarize and concluded that this formulation of Intra-nasal gel of Bromocriptine Mesylate fulfills all necessary parameters required for nasal mucosal use. This optimized formulation containing SLN's of Bromocriptine Mesylate proved to be a better mucoadhesive property and improved bioavailability of drug at targeted site by nasal administration for effective and longer treatment of Parkinson's disease.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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