Research Article

Formulation and Evaluation of Mucoadhesive Microspheres Loaded Intra-Nasal Gel of an Anti-Psychotic Drug

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Received: 08-07-2024; **Revised:** 30-09-2024; **Accepted:** 09-10-2024; **Published on:** 15-10-2024.

ABSTRACT

Aim: The objective of the present study is to design and evaluate mucoadhesive microspheres loaded Intra nasal gel for brain targeting.

Materials and methods: Clozapine microspheres containing different concentration of mucoadhesive polymers i.e. Hydroxy propyl cellulose (HPC), Xanthan gum, Carboxy methyl cellulose (CMC) were prepared using ion gelation method. The optimized microspheres were selected for the preparation of Nasal gel using different concentrations of Carbopol 934 and underwent various evaluation parameters.

Results: The prepared optimized microsphere formulation was spherical. The % entrapment efficiency was 92.2% for formulation 6 and showed excellent mucoadhesive property. The drug release of formulation 8 was slow and extended over 12hrs of duration.

The prepared optimized gel formulation showed good gel strength with 87.8% of drug content and the drug release was found to be extended over 12hrs of duration and fitted to different kinetics models following first order.

Conclusion: The prepared microspheres loaded nasal gel are thus suitable for nasal administration and helps in avoiding first pass metabolism giving drug release for extended period of time.

Keywords: Mucoadhesive microspheres, Clozapine, Mucoadhesive polymers, metabolism, gel formulation.

INTRODUCTION

The combination of mental health symptoms that cause a person to lose touch with reality is called psychosis. Many psychiatric, neuropsychiatric, neurologic, neurodevelopmental, and medical disorders share psychosis as a common behaviour. Medical practitioners now address psychosis as their main therapeutic goal since it can cause patients and their loved ones great anguish. Substance abuse, fundamental psychiatric disorders, and other neurological or medical conditions can all lead to psychosis. First-episode psychotic illnesses have been linked to anomalies in the brain, such as decreased prefrontal, superior, and medial temporal grey matter.[1]

In the Indian medical system of Ayurveda, intranasal therapy has long been recognized as a valid therapeutic modality. Many medications have demonstrated recently to have superior systemic bioavailability when administered via the nasal route compared to the oral route. Research and review papers covering different aspects of nasal medication administration are becoming more and more common. This interest originates from the various potential benefits that the nasal cavity may offer, including: a highly vascularized epithelium, a large surface area that can be used for drug absorption, a lower level of enzymatic activity than the gastrointestinal tract and liver, and the direct transport of drugs into the systemic circulation, which prevents hepatic first-pass metabolism and gastrointestinal membrane irritation. As a substitute administration approach, the nasal route has drawn a lot of interest. The nasal route delivers drugs directly to the brain via the olfactory neurons, providing more opportunity for the drugs to enter the central nervous system (CNS).[2,3]

Microspheres are tiny, spherical particles with dimensions between one and a thousand of an inch or Micrometres. They can be created from various materials, including glass, polymer, and ceramic. The densities of these microspheres vary, making them useful for various applications. Microspheres can be used to regulate medication delivery, making it easier to administer strong medications, lower drug concentrations, and protect labile compounds. Combining medication with a carrier particle can change the drug's *in vivo* behaviour, potentially improving treatment outcomes.[4,5] Mucoadhesive microspheres combine muco-adhesion properties with microspheres for efficient drug absorption and enhanced bioavailability. These microspheres have a high surface to volume ratio, intimate contact with mucus layers, and specific targeting of drugs. Microspheres have potential for targeted and controlled drug delivery in the pharmaceutical industry, offering higher efficacy, reduced toxicity, lower dosage, and longer-lasting stability compared to traditional formulations.[6,7]

The nasal route offers promising opportunities for drug delivery to the brain, with successful cases including sulphonamides, insulin, and hyaluronidase. Intranasally administered drugs are used for various diseases like Alzheimer's, epilepsy, pain, and sleep disorders. The route

is non-invasive, easy to administer, and offers rapid absorption, self-medication, and patient compliance. Molecules can enter the nasal epithelium through paracellular transport. The cribriform plate and nerve bundle traverse the cribriform plate before reaching the olfactory bulb. The drug molecules then reach the olfactory bulb and cerebrospinal fluid (CSF) through olfactory neurons. The olfactory neural route enters the brain through two pathways: the extra-neuronal pathway and the intra-neuronal pathway. The deeper brain regions are the cortex, cerebrum, and cerebellum.[8,9,10]

Here the work is done to know and understand the effect of various mucoadhesive polymers in nasal formulation and also to reduce the dosing frequency with less side effects and toxicity.

MATERIALS AND METHODS

Materials:

Clozapine (CLZ), Sodium alginate, Calcium chloride (3.5%w/v), Hydroxy propyl cellulose, Xanthan gum, Carboxy methyl cellulose, Carbopol 934, Methyl paraben.

Method:

1. Standard calibration curve of clozapine:

100 mg Standard Clozapine (CLZ) was accurately weighed and transferred to 100 ml volumetric flask and was dissolved properly using ethanol and diluted up to the mark with buffer to produce a stock solution of 1000 µg/ml. Then 10 ml of this solution was diluted to 100 ml using buffer to obtain100 µg/ml of primary solution (1^0 solution). Again 10ml of primary solution (1^0 solution) is taken into 100 ml volumetric flask and make up to the mark to obtain 10 µg/ml of secondary solution (2^0 solution). Appropriate amounts of this 2^0 solution were diluted with the same buffer, yielding concentrations of 2 µg/ml, 4 µg/ml, 6 µg/ml 8 µg/ml and 10 µg/ml and absorbance were measure at 245 nm under UV spectrophotometer and the values were noted down as shown in Table 1, hence construction of standard curve (as shown in Figure 1).

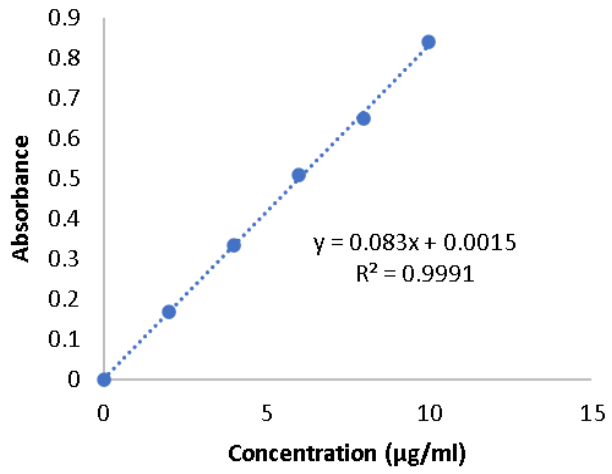


Figure 1: Standard curve of clozapine in pH 6.8 Phosphate buffer

Table 1: Standard curve data for clozapine (CLZ)

S. No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.168
3.	4	0.335
4.	6	0.509
5.	8	0.649
6.	10	0.839

1. Preparation of microspheres:

Clozapine loaded microspheres were prepared by ionotropic gelation method employing sodium alginate in combination with various mucoadhesive polymers such as Hydroxy propyl cellulose, Xanthan gum and Carboxy methyl cellulose in different concentrations as given in Table 2. Sodium alginate along with polymers of different concentrations were dissolved in purified water (100ml) and placed on a magnetic stirrer for proper mixing. After the viscous solution is ready, clozapine drug dissolved using ethanol was poured with mild stirring and kept under mechanical stirrer till the solution colour changes to yellow. The prepared solution was taken into syringe with a needle size no. 26 and poured drop by drop into calcium chloride solution (3.5 %w/v). The added droplets were retained in the calcium chloride solution for 30 minutes to complete curing time. The microspheres were filtered using Whatman filter paper and washed repeatedly with distilled water and dried using hot air oven at 60^0C.[11,12]

Evaluation of microspheres:

1. Particle size and percentage yield:

Particle size of the microspheres was evaluated using optical microscopy method. Approximately more than 300 microspheres were counted for particle size determination using a calibrated stage and eye piece micrometer.[13,14]

Percentage yield of microspheres was determined by weighing the obtained microspheres for each formulation and calculated using the given formula and the values were given in Table 4.[15]

% yield = total weight of microspheres / combined weight of drug and polymer ×100.

2. Entrapment efficiency:

Weighed amount of microspheres (100 mg) was placed in 60 ml of 6.8 pH phosphate buffer and kept it for 24 hrs. The solution is filtered after 24 hrs of soaking and sonicated for 10 min. and observed under UV spectrophotometer, the absorbance was noted down and entrapment efficiency was calculated by using the given formula in Table 4.[16]

% EE = Total drug concentration – free drug concentration/ total drug concentration ×100

Table 2: Formulation composition of Clozapine loaded microspheres

Ingredients	Batch-1			Batch-2			Batch-3			Batch-4		
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Clozapine (mg)	50	50	50	50	50	50	50	50	50	50	50	50
Sodium alginate (%w/v)	1.5	2.5	3.5	1.5	2.5	3.5	1.5	2.5	3.5	1.5	2.5	3.5
Hydroxy propyl cellulose (mg)	-	-	-	100	200	300	-	-	-	-	-	-
Xanthan gum (mg)	-	-	-	-	-	-	100	200	300	-	-	-
Carboxy methyl cellulose (mg)	-	-	-	-	-	-	-	-	-	100	200	300
Calcium chloride (%w/v)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Ethanol (ml)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

3. Swelling index:

Accurately weighed amount of microspheres(100 mg) were allowed to swell in phosphate buffer for 24 hrs then filtered and dried for 10 min. The swelling index was determined by the given formula and values were noted in Table 4.[14]

$$\text{Swelling index} = W_2 - W_1 / W_1$$

W_1 – weight of microspheres before swelling ; W_2 – weight of the microspheres after swelling

4. *In-vitro* wash off test:

In-vitro wash off test is done to determine mucoadhesive property of microspheres, weighed amount of microspheres (100 mg) was placed on the sheep nasal mucosa of size 1×1 cm and was placed on the glass slide and this slide was hung to the disintegrating apparatus giving up and down movements in a beaker containing 6.8pH phosphate buffer. The percentage muco-adhesion was calculated after 1hr and calculated using the given formula and the data is given in Table 4.[17]

$$\% \text{ Muco-adhesion} = W_0 - W_1 / W_0 \times 100.$$

Amount of adhered microspheres(W_1); Amount of applied microspheres(W_0)

5. *In-vitro* drug release studies:

The drug release studies of clozapine loaded microspheres was performed with 6.8 pH phosphate buffer by using dissolution apparatus USP I basket type. Accurately weighed amount of microspheres (100 mg) and was inserted in the basket wrapped with muslin cloth. The basket was filled with phosphate buffer (900 ml) and the apparatus was adjusted at 100 rpm. The samples were taken for every 1hr till 8 hrs. To maintain the sink condition, the volume of samples withdrawn were replaced with an equal volume of buffer at particular time intervals. The absorbance of collected samples were observed by using UV spectrophotometer and percentage cumulative drug release (% CDR) was determined by the following formula.[14-17]

6. Calculating theoretical release profile:

$D_t = \text{Dose}\ (1 + 0.693 \times t / t_{1/2})$

Where D_t = Total dose of drug (i.e. 50mg)

Dose = Dose of immediate release part

t = time during which sustained release is desired (i.e. 12 hours)

$t_{1/2}$ = half-life of drug (i.e. 3 hours)

$$50 = \text{Dose}\ (1 + 0.693 \times 12 / 3)$$

Dose = 50 / 3.772 = 13.25 mg in the 1st hour (initial release)

D_t – initial dose = 50 – 13.25 = 36.75 / 11

= 3.34 mg / hr

7. Morphology studies:

The shape and surface properties of optimized formulated microspheres were performed by scanning electron microscopy (SEM) and showed results with nearly smooth surface. After gold sputtering, the samples were placed on double-sided tapes that had been previously attached to aluminium stubs. An argon environment was used for analysis at an acceleration voltage of 20 kV.

2.3.8. Similarity factor (f_2) analysis:

The similarity factor is calculated by the given formula with the compared values of In-vitro drug release and theoretical drug release.

$$f_2 = 50 \log \{[1 + (1/N) \sum (R_i - T_i)^2]^{-0.5} \times 100\}$$

where, N = number of time points,

$R_i - T_i$ = Dissolution of reference and test product at time i.

If f_2 is greater than 50, it is considered that two products share similar drug release behaviours.

Formulation of mucoadhesive microspheres loaded intra nasal gel:

Nasal gel was prepared with varied concentrations of Carbopol 934, different concentrations of Carbopol was mixed in purified water(100ml). This prepared solution was left overnight to ensure complete hydration to this accurate amount of clozapine microspheres were mixed with continuous stirring. Finally preservative is added and pH is adjusted to 5.5 – 6.5.[18] The composition of all the gel formulations (GF) is given in Table 3.

Table 3: Formulation composition of microspheres loaded nasal gel

Ingredients	Gel formulation 1 (GF1)	Gel formulation 2 (GF2)	Gel formulation 3 (GF3)
CLZ loaded microspheres (%w/w)	0.5	0.5	0.5
Carbopol 934 (%w/v)	0.1	0.2	0.3
Methyl paraben (%w/v)	0.02	0.02	0.02
Distilled water (ml)	q.s.	q.s.	q.s.

Evaluation of prepared nasal gel:

1. pH and viscosity measurement:

The pH was determined using Systronic digital pH meter. The pH meter was calibrated before use by using 6.8pH buffer solution. The viscosity of the formulated gel is determined by DV-E Brookfield viscometer using spindle no. 64. The gel formulations that had been made were transferred into the beaker. The temperature was maintained at 37°C while the spindle was lowered perpendicularly into the gel at a speed of l00 rpm and viscosity was measured.[18]

2. Gel strength determination:

A 50 g sample was put in a 100 ml graduated measuring cylinder and gelled by adding simulated nasal fluid in a thermostatically controlled water bath at 32–34 ^{0}C. The disk, which had a diameter of 2.3 cm, a thickness of 0.5 cm, and a clearance of 0.4 cm from the cylinder's side wall, was then loaded with 35 g of weight and placed on top of the gel. The amount of time (in seconds) needed to move the piston 5 cm through the gel was used to determine the gel strength. The degree of cross-linking, molecular weight, and other factors affect gel strength. If the apparatus took longer than five minutes to sink into the gel, extra weights were added to the top of the equipment, and the gel's strength was reported by the minimal weights that pushed the apparatus 5 cm down through the gel.[19,20]

3. Drug content:

In a 50 mL volumetric flask, 0.5 g of the formulation was collected and diluted with 25 mL of pH 6.8 buffer. The formulations were dissolved in pH 6.8 buffer by shaking the mixture for 10 minutes in an incubator. After filtering and diluting the solution sufficiently, the drug concentration was measured spectrophotometrically using a calibration curve plotted at 245 nm.[21]

4. *In-vitro* diffusion studies:

The *in-vitro* studies of formulated gel were evaluated using Franz diffusion cell with a semi - permeable egg membrane. The diffusion cell included an upper cylindrical compartment that was open from above, a diffusion membrane at its base, and a diameter of 1.5 cm with a capacity of 20 ml. The donor part contained 1g of drug-loaded gel, whereas the receptor section had 20 ml of 6.8 pH phosphate buffer. During the experiment, the temperature was kept at 37°C ± 0.5 °C, and a magnetic stirrer was used to agitate the buffer at 100 rpm. After then, for a maximum of 12 hours, 5 ml samples were taken out of the receiving chamber every hour and replaced with a fresh buffer solution of the same volume. The extracted samples were observed for absorbance using UV spectrophotometer at 245 nm.[22]

RESULTS AND DISCUSSION

FTIR study of drug and excipients:

Compatibility studies were performed by using FT-IR spectrophotometer. The IR Spectrum of pure Clozapine (CLZ) drug was compared with the IR spectrum of physical mixture of Clozapine with Hydroxy propyl cellulose, Xanthan gum, carboxy methyl cellulose and other excipients. The results showed that there were no chemical incompatibility of drugs and excipients.

Evaluation of prepared microspheres:

1. Particle size and percentage yield determination:

The particle size of each formulation was evaluated with more than 30 microspheres from each formulation observed under microscope. The particle size of microspheres was found within the range (i.e. 20 – 80 µm) and was seen dependent on the concentration of microspheres. The values were given in Table 4.

Percentage yield was calculated for each formulation and the increase in yield was seen directly proportional to the concentration of sodium alginate used. All the values are noted and shown in Table 4.

2. Entrapment efficiency and swelling index:

The values of entrapment efficiency stated that the concentration of sodium alginate is directly proportional to

the obtained values. Out of all the formulations F6 gave the highest entrapped value. All the values of entrapment efficiency are given in Table 4.

The swelling index was calculated for 24 hrs and it was mostly dependent on the concentration of sodium alginate. Out of all the formulations F3 & F12 shows the highest swelling index value. All the values of swelling index was calculated and noted down in Table 4.

3. Moisture content and In-vitro wash off test:

Moisture content values were independent of the sodium alginate i.e. concentration and all the values were noted down in Table 4.

In-vitro wash off test was evaluated for muco-adhesion property and it was carried for 8 hrs which was directly proportional to the concentration of polymer. It was evaluated by the number of microspheres applied to the number of microspheres washed out and the values of all the formulations were given in Table 4. Formulation 6 gave the highest value from all other formulations.

4. *In-vitro* drug release studies:

In vitro release profile of clozapine loaded microspheres in 6.8 pH phosphate buffer was performed for 12 hrs and the samples were withdrawn for every consecutive hours as stated and the absorbance was measured at 245 nm using UV spectrophotometer and the cumulative drug release (% CDR) was determined. The release of drug was indirectly proportional to the concentration of polymer and sodium alginate. All the values were noted down in Table 5 and the graphs were shown in Figure 2.

6. Similarity factor (f_2) analysis:

The similarity factor values of each formulation was calculated and based on similarity factor analysis of prepared formulations, F8 was considered as optimized formulation based on its highest similarity factor (f_2) value with theoretical drug release values when compared to other formulations.

Evaluations of prepared nasal gel formulations:

1. Determination of pH:

The pH of all the prepared nasal gel formulations GF1, GF2 & GF3 was found to be 5.62, 5.78 & 5.86 respectively. The variation in pH was observed based on the concentration of Carbopol 934.

2. Viscosity measurement:

The viscosity of GF1, GF2 and GF3 was found to be 1043cps, 1176cps and 1241cps. The viscosity of the formulation is directly dependent on the concentration of Carbopol used in the formulation. The viscosity range for nasal administration should be in between 56.8 – 4618.04cps. Hence all the prepared formulation was suitable for nasal administration.

3. Gel strength determination:

The gel strength was determined by the time (sec.) taken by the apparatus to sink 5cm down through the prepared gel. The values of gel strength between 25 and 50 are considered to be sufficient for nasal administration because the formulation with less than 25 may not preserve its integrity whereas more than 50 will be rigid and difficult to administer nasally. The time taken for GF1, GF2, GF3 was found to be 14.23, 24.8, 45.36 seconds.

4. Drug content:

The samples were observed under the UV spectrophotometer and absorbance was noted down and hence drug content was calculated. The values obtained for GF1, GF2, GF3 consecutively found to be 91.5, 92.1, 94.8. Gel Formulation 3 (GF3) shows highest drug content when compared with other formulations.

Table 4: Evaluation of Clozapine loaded mucoadhesive microspheres

Formulation code	Particle Size	Percentage yield	Entrapment Efficiency	Swelling Index	Moisture content	*In-vitro* Wash off test
F1	49.86 ± 1.25	83.8	88.1 ± 0.17	17.3	8.3 ±0.254	50 ± 1.55
F2	62.8 ±1.34	86.2	89.8 ± 1.22	20	4.7 ±0.275	60 ± 1.24
F3	77.6 ±2.12	87.3	91.6 ± 0.53	32	3.3 ±0.251	75 ± 0.23
F4	48.7 ±1.27	90.9	88.04 ± 0.76	12.6	7.1 ±0.365	45.4 ±1.86
F5	56.07 ±1.36	72.7	89.3 ± 0.62	10	8.1 ±0.451	54.5 ±0.36
F6	70 ± 2.1	83.1	92.2 ± 0.55	22.6	1.5 ±0.54	88.8 ±0.84
F7	54.8 ± 1.8	96.9	89.04 ± 0.24	16.6	10.3 ±0.127	53.8 ±1.45
F8	64.1 ± 2.08	80	92.1 ± 0.46	24	10 ±0.213	75 ± 1.62
F9	71.6 ± 2.09	85.7	91.3 ± 0.19	21.3	5.7 ±0.325	62.5 ±1.27
F10	57.69 ±1.54	98.1	89 ± 1.43	25.3	5.19 ±0.365	55 ± 1.56
F11	71.4 ± 1.97	80	91.78 ± 0.61	31.3	1.8 ±0.246	78 ± 0.49
F12	74.6 ± 2.05	90.9	90.9 ± 0.36	32	9.3 ±0.542	71.4 ±1.65

The values are expressed as mean ± SD, (n=3).

Table 5: Cumulative drug release profile of prepared formulations (F1-F12)

Time Intervals (hrs)	Cumulative drug release (%) ± S.D											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	18.92 ± 0.12	17.62 ± 0.82	13.7 ± 1.54	16.86 ± 0.62	17.28 ± 0.54	9.58 ±1.23	16.42 ± 0.69	23.58 ± 0.45	15.76 ± 0.25	21.4 ± 0.64	22.82 ± 1.52	18.7 ± 0.29
2	33.66 ± 0.45	32.36 ± 0.65	30.3 ± 0.94	31.16 ± 0.65	29.98 ± 0.67	18.8 ±0.29	29 ± 1.24	37.34 ± 0.78	25.96 ± 0.58	36.8 ± 0.59	36.04 ± 0.39	27.36 ± 0.46
3	51 ± 0.48	48.84 ± 0.87	40.06 ± 0.36	48.74 ± 1.27	46.56 ± 0.23	29.76 ±0.58	40.16 ± 0.36	47.76 ± 0.56	33.44 ± 0.36	48.52 ± 0.47	46.56 ± 0.47	33.56 ± 0.61
4	59.04 ± 0.13	57.74 ± 1.21	44.5 ± 0.74	58.06 ± 0.59	55.34 ± 0.35	37.46 ±0.46	52.52 ± 0.96	58.28 ± 0.32	38.98 ± 0.26	56.98 ± 0.75	58.82 ± 0.28	41.68 ± 0.58
6	75.74 ± 0.16	75.74 ± 0.63	61.42 ± 0.58	72.7 ± 0.84	75.08 ± 0.45	55.56 ±0.73	72.36 ± 0.45	76.82 ± 0.44	61.64 ± 0.59	75.74 ± 1.58	76.82 ± 0.37	55.34 ± 0.43
8	88.86 ± 0.49	87.66 ±0.58	71.4 ± 0.69	87.98 ± 0.58	86.58 ± 1.29	70.42 ±0.45	88.3 ± 0.28	87.88 ± 1.32	71.94 ± 1.45	88.1 ± 0.49	87.68 ± 0.62	71.28 ± 1.45
10	93.3 ± 0.56	91.6 ± 0.45	75.74 ± 1.55	93.4 ± 0.47	90.48 ± 1.69	75.62 ±1.47	92.1 ± 0.35	92.42 ± 1.54	75.08 ± 1.26	88.74 ± 0.68	92.1 ± 1.28	76.82 ± 1.38
12	98.5 ± 0.36	97.42 ± 0.35	81.8 ± 1.64	96.98 ± 0.22	96 ± 0.75	80.94 ±1.22	97.2 ± 0.49	95.9 ± 0.98	81.92 ± 0.65	96.66 ± 0.93	96 ± 1.34	81.7 ± 0.22

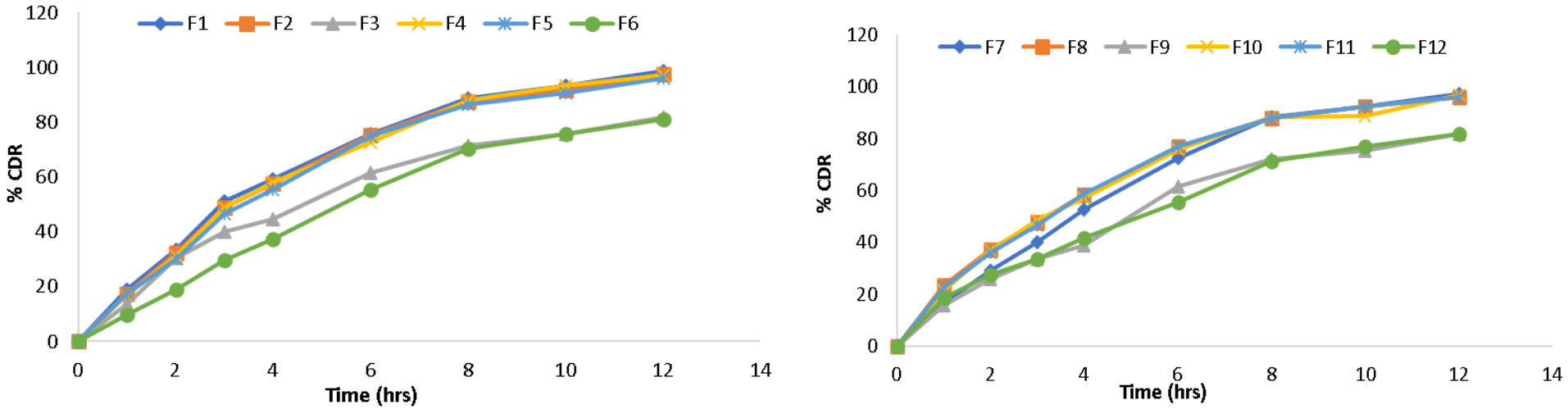


Figure 2: *In – vitro* dissolution profiles of formulation (A) F1 – F6; (B) F7 – F12

5. *In-vitro* dissolution studies of nasal gel:

The *In-vitro* dissolution studies of nasal gel was performed by using Franz diffusion cell for 12 hrs and the absorbance was noted for the calculation of % CDR (as given in Table 6) and graphical representation of data was shown in Figure 3.

Table 6: Cumulative drug release values of gel formulations

Time Intervals (hrs)	Cumulative drug release (%) ± S.D		
	GF1	GF2	GF3
1	20.76 ± 0.52	21.52 ± 0.23	24.36 ± 0.42
2	29.38 ± 0.24	30.56 ± 0.39	35.97 ± 0.39
3	38.72 ± 0.19	40.68 ± 0.48	47.2 ± 0.67
4	49.8 ± 0.65	51.43 ± 0.36	58.89 ± 0.25
6	67.83 ± 0.58	69.91 ± 0.45	75.76 ± 0.62
8	75.21 ± 1.22	79.23 ± 1.37	88.71 ± 1.38
10	83.13 ± 0.57	86.4 ± 1.42	93.1 ± 0.22
12	91.41 ± 0.85	91.52 ± 0.78	96.14 ± 1.45

The value are expressed as mean ± SD, (n=3)

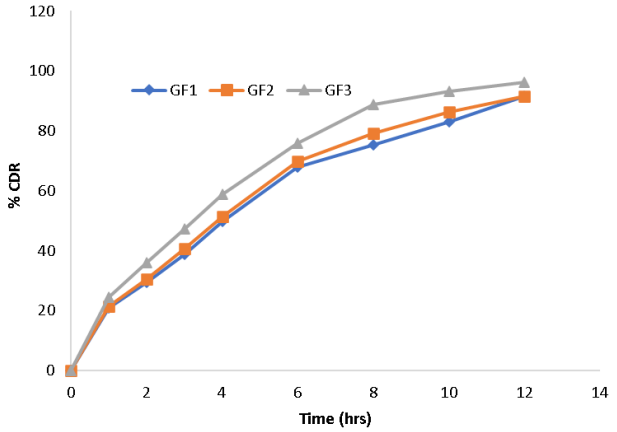
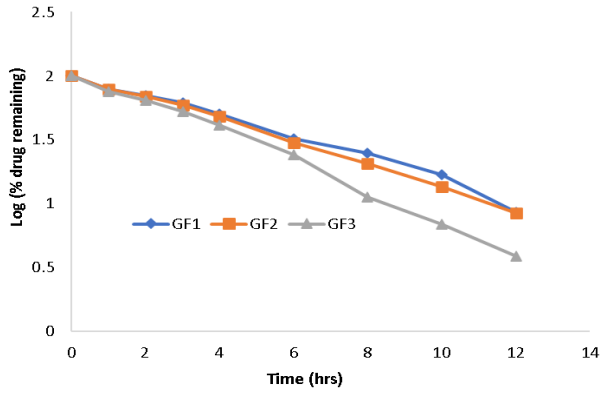


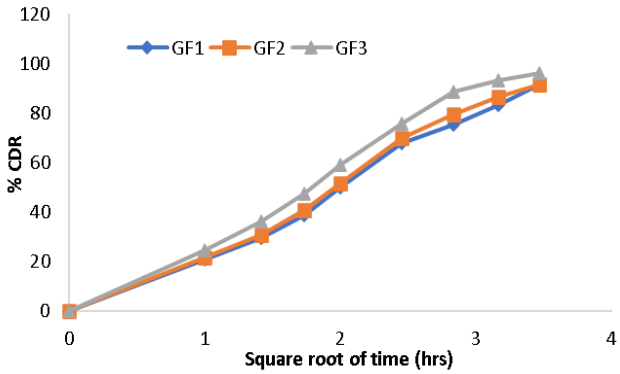
Figure 3: *In-Vitro* dissolution studies of gel formulations (GF)

6. Drug release kinetics for In-vitro dissolution studies:

The kinetic models such as First order, Higuchi model and Korsmeyer & Peppas model were fitted in different gel formulations (as shown in Figure 4).



(A)



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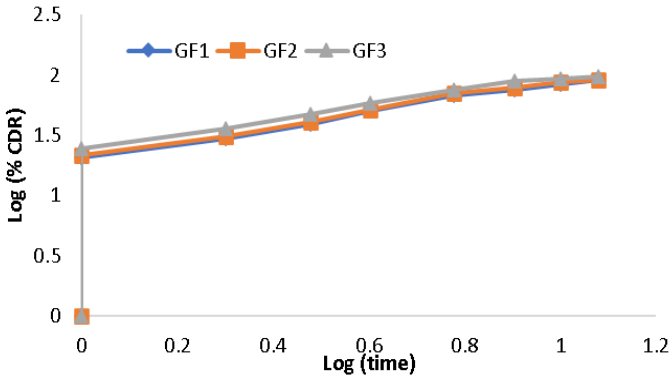

(C)

Figure 4: Drug release kinetics of prepared gel formulations **(A)** First Order; **(B)** Higuchi model; **(C)** Korsmeyer & Peppas model.

7. Similarity factor (f_2) analysis:

The similarity factor of gel formulations were calculated and the values for GF1, GF2, GF3 were known to be 36.5, 46.55, 55.1. Based on the values obtained GF3 found to be with the highest value.

CONCLUSION

From the present study, it can be concluded that the mucoadhesive microspheres of clozapine drug can be prepared by using external ion-gelation method employing various mucoadhesive polymers i.e. Hydroxy propyl cellulose (HPC), Xanthan gum, Carboxy methyl cellulose (CMC) of different concentrations. Prepared microspheres of formulation 8 was found to be optimized based on the similarity factor (f_2) analysis. The microspheres loaded intra nasal gel was formulated using different concentrations of Carbopol 934 and weighed amount of optimized formulation (F8) microspheres. The evaluation parameters i.e. pH, gel strength, drug content, viscosity and In-vitro diffusion studies were performed for all gel formulations. Gel formulation 3 was selected as optimized formulation based on the highest similarity factor value and was observed to follow first order kinetics after fitting into various kinetic models.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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