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Formulation and Evaluationation of Anti-Alzheimer Drug MEM HCL Nanogel

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The object of present study was to formulate and evaluate MEM HCl loaded thermo sensitive in situ nanogel for 08 nasal delivery formulations. In present project a novel drug delivery system i.e. in situ polymeric gel was designed in the manner that the gel load MEM HCl in better concentration and it also incorporates penetration enhancer as a way to enhance the absorption of release drug from gel to the systemic circulation. In this research work Different Nanoparticles were (NP) prepared, using ionotropic gelation method with slight medication in which chitosan (0.4% w/v) was dissolved in aqueous acetic acid solutions (1 % v/v) (pH 6.1), while TPP (0.1% w/v) was dissolved in deionized water. Dried nanoparticles are incorporated with in situ gel. In situ gel was prepared by cold method using the solutions of Poloxamer-188 and Carbopol-934. From this study, it is concluded that, among all formulations prepared, NG8 was the best optimized formulation. Prepared gel can be used as promising nasal drug delivery system for the anti-Alzheimer drug MEM HCl, which enhance nasal residence time owing to increased viscosity and mucoadhesive characteristics; furthermore, it also exhibited a permeation enhancing effect.

Keywords: Ionotropic gelation method; chitosan based nasal drug delivery system; in situ gel system evaluation; in-situ polymeric gel formulation.

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1. INTRODUCTION

Alzheimer's disease (AD) is the most frequent cause of dementia among the elderly [1]. This disease is charac- terized by an insidious decline in cognitive and non-cognitive functions and is devastating for patients, their family and society. Many types of neurotrans-mitters are affected in this chronic and progressive neurode- generative disorder, and the relative importance of each in relation to clinical findings has not been fully elucidated. Today, no curative treatment exists [2]. The intranasal delivery enhances targeting and reduced systemic side effects [3]. The direct nose-to-brain transport can reduce drug distribution to non-targeted sites, minimizing adverse effects. Scientists started to look for different approaches for brain delivery of drugs, and nasal administration has recently gained special interest. There are various approaches to facilitate nose- to-brain drug delivery, and among them, one finds the use of getting formulation that inhibits the mucociliary clearance, and that of drug delivery nanosystems [4]. Memantine HCl is a reversible cholinesterase inhibitor used in the treatment of Alzheimer's disease. This does not cross the blood brain barrier (BBB) owing to its hydrophilic nature. Further, a particle size below 200 nm is a very important prerequisite for crossing BBB [5]. So, it was chosen as the drug candidate in present work which was designed to overcome the problems of conventional dosage forms and can be used for brain targeting. The object of present study was to formulate and evaluate Mamentine loaded thermo sensitive *in situ* nanogel for nasal delivery. In present project a novel drug delivery system *i.e. in situ* polymeric gel is designed in a manner that the gel loads Mamentine HCl in better concentration and also incorporate penetration enhancer as a way to enhance the absorption of release drug from gel to the systemic circulation. The prepared formula- tion will remain in liquid form before administration but on administering nasal path then it turns into gel due to its interaction with lachrymal fluid environments like pH, temperature, and ions. Its gel form will retain for maximum period of time and work as reservoir for mamentine. The *in situ* gel will release the drug in very sustained and controlled manner as well as it also increases the retention and contact time thus increase the bioavailability of entrapped mamentine by creating it bioavailable by raise contact time for longer period of time.

- **Drug Information**

Memantine hydrochloride is a low-moderate affinity, uncompetitive n-methyl-d-aspartate (NMDA) receptor antagonist with strong voltage dependency and rapid blocking/unblocking kinetics. These pharmacological features appear to allow memantine to block the sustained activation of the receptor by glutamate that may occur under pathological conditions, and to rapidly leave the NMDA receptor channel during normal physiological activation [1]. The preliminary study showed that acyclovir is White fine crystalline powder powder. It is freely soluble in 0.1 N HCL, soluble in Acetone, methanol, ethanol and phosphate buffer pH 7.2. The ƛmax of drug was found to be 254nm which confirm purity of MamentineHCl. From the FT-IR data of the physical mixture it is clear that functionalities of drug have remained unchanged including intensities of the peak. Preformulation studies reported that the formulation of nanoparticles gel of MamentineHCl can be prepared with appropriate methods [6].

2. MATERIALS AND METHODS

2.1 Material

Mamentine HCl was obtained as a gift sample from Aurobindo Pharmaceutical Pvt. Ltd. Goa. Chitosan was obtained from Himedia Laboratories Pvt. Ltd. Poloxamer-188 was obtained from Sigma Aldrich, Mumbai. Hydroxypropyl methylcellulose (HPMC) and Carbopol from Central Drug House, Mumbai, India. All other chemicals and solvents were of analytical grade and used as received. Distilled water was prepared in laboratory using all glass distillation apparatus.

2.2 Preparation of Chitosan Nanoparticle of Mamentine HCl

Nanoparticles (NP) were be prepared as indicated by Calvoet al., [7], utilizing ionotropic gelation method with slight modification in which chitosan (0.4% w/v) was dispersed in aqueous acetic acid solutions (1% v/v) (pH 6.1), while TPP (0.1% w/v) was dispersed in deionized water. Mamentine HCl solution was premixed with chitosan arrangement before the expansion of the TPP arrangement drop shrewd into the chitosan solution under magnetic stirring (600 rpm) at surrounding temperature for 2-4 hr. The acquired nanoparticles preparation was

lyophilized and store in 4- 8ºC until further utilization.

2.3 Optimization of Process Variable

The effect of formulation process variables such as stirring time, stirring speed, surfactant concentration on the particle size was studied. From the results obtained, optimum level of those variables was selected and kept constant in the subsequent evaluations.

2.4 Effect of Chitosan Quantity

The effect of chitosan quantity on the particle size was studied by varying one chitosan. Chitosan nanoparticles were prepared corresponding to varying concentrations of chitosan such as 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 and 0.9% keeping the amount of Acetic acid (1% v/v), stirring time (4 hours) and stirring speed (600 rpm) constant (Table 1).

2.5 Characterization of Nanoparticles

i. Determination of Particle Size

Particle size analyses were performed by Zetasizer 3000. The measurements were carried out at a fixed angle of 90°. The freeze dried powdered samples were suspended in Milli- Q water (1mg/ml) at room tem- perature (25˚C) and sonicated for 30 sec in an ice bath before measurement to prevent clumping. The mean particle diameter and size distribution of the suspension were assessed. Analysis was carried out thrice for each batch of sample under identical conditions and mean values were reported. The same suspension was used for measuring the Zeta potential of drug loaded nanoparticles, by using the same equipment [8].

ii. Determination of percentage yield and loding efficiency

The percentage yield of the nanoparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of the nanoparticles obtained [9].

The drug loading efficiency (%) and Drug entrapment efficiency (%) of the nanoparticles can be calculated according to the following equation:

$$EE\ (\%w/w) = \frac{Weight\ of\ the\ drug\ in\ nanoparticles}{Weight\ of\ the\ drug\ added} \times 100$$

$$DL\ (\%w/w) = \frac{Weight\ of\ the\ drug\ in\ nanoparticle}{Weight\ of\ the\ polymer\ and\ drug\ added} \times 100$$

Table 1. Composition of SLN by varying quantity of Chitosan

Components	Formulation code							
	NP1	NP2	NP3	NP4	NP5	NP6	NP7	NP8
Mamentine HCl	10	10	10	10	10	10	10	10
Chitosan	0.1%	0.2%	0.3%	0.4%	0.5%	0.6%	0.7%	0.8%
Acetic acid	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Stirring speed (rpm)	600	600	600	600	600	600	600	600
Stirring time (hrs)	4	4	4	4	4	4	4	4

Table 2. Formulation development of *in Situ* nanogel (NG1-NG8)

Formulation	NG1	NG2	NG3	NG4	NG5	NG6	NG7	NG8
Nanoparticles	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Poloxamer-188	14	16	20	14	16	20	14	16
Carbopol	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.3
HPMC	0.1	0.2	0.3	0.2	0.3	0.4	0.4	0.1
Propylene Glycol	1	1	1	1	1	1	1	1
Benzalkonium Chloride (% w/v)	1	1	1	1	1	1	1	1
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water (ml)	100	100	100	100	100	100	100	100

iii. Preparation of in situ nanogell

Precisely weighted amount of the nanoparticle was dissolved in distilled water. The solution of Poloxamer-188 and Carbopol-934 were prepared utilizing cold preparation. A specific volume of distilled water was cooled off to 4°C. Poloxamer-188 and Carbopol 934 was sprinkled over deionised cold water independently and was permitted to hydrate for 12 hours to create a clear solution. At that point both the polymer arrangements were blend legitimately with ceaseless mixing. The Benzalkonium chloride was added to the above polymer scattering. At that point put away in the fridge. The scatterings were then put away in an icebox until clear arrangements were acquired and polymer dispersion was gradually added to the drug solution under aseptic condition Table 2 [10].

2.6 Characterization of Nanoparticulate gel

i. Determination of pH

Weighed amount of gel formulations were transferred in 10 ml of beaker and estimated by using the advanced pH meter [11].

ii. Measurement of viscosity

The viscosity of gels was determined by using a Brook Field viscometer DV-II model. T-Bar spindles in combination with a helipath stand were used to measure the viscosity and have accurate readings [12].

iii. Mucoadhesive strength

Detachment Stress is the power required to detach the two surfaces of mucosa when a definition/gel is set in the middle of them. The detachment stress was measured by using a modified analytical balance [13].

iv. *In-vitro* diffusion study

An *in-vitro* drug release study was performed utilizing altered Franz dissemination cell. Dialysis layer (Hi Media, Molecular weight 5000 Daltons) was put among receptor and donor compartments. *In-situ* gel proportional to 100 mg of memantine was set in the contributor compartment and the receptor compart- ment was loaded up with phosphate cushion, pH 5.5. The dispersion cells were kept up at 37 ± 0.5°C with blending at 50 rpm all through the investigation [14].

2.7 Mathematical Treatment of *In-vitro* Release Data

The quantitative determination of the qualities acquired in disintegration/dissolution tests is simpler when scientific equations that express the disintegration results as an element of a portion of the measurement shapes attributes are utilized. The pharmacokinetic model to be applied for different method, like zero order, first order, higuchi and pappas model to be applied.

3. RESULTS AND DISCUSSION

The particle size is an important parameter as it has a direct effect on the stability, cellular uptake, drug release and biodistribution. The mean particle sizes of the prepared nanoparticles as measured by the Malvern zetasizer were in size range of 330 to 651 nm and the distribution of particle sizes are found to be monodispersed as the polydispersity index lies below 0 to 1 (0.234 to 0.642) in all the formulations. There were no noticeable differences between the sizes of nanoparticles obtained with different drug polymer ratio. The particle morphology can be modulated by selecting the agitation speed as well as drug polymer ratio. In the present study, the decrease in size of the particles has been reported (Table 4). The Particle size, Zeta potential, Entrapment efficiency and Poly dispersity index of optimized formulation NP5-NP8 was found to be 364.2±3.37, -8.46, 79.9±0.2 and 0.283± 0.048 respectively (Table 3).

3.1 Evaluation of Nasal *In situ* gel

The pH of the formulations was found to be satisfactory and was in the range of 6.8±0.28 to 7.4±0.83, as shown in Table 4. The preparations were fluid at room temperature and at the pH formulated. Terminal sterilization via autoclaving had no impact on the pH. The Helipath T-Bar spindles were rotated up and down in the sample giving variable viscosities at a number of points programmed over the time. Five readings taken over a period of 60 seconds were averaged to obtain viscosity. The results show that the viscosity of the gels increased with an increase in polymer concentration. The increase in viscosity with the polymer concen- tration may be due to increase in bonds between the polymer molecules which lead to formation of a hard and dense compact mass. This may also be due to less amount of liquid in gels with high polymer concentration as compared to gels of low

polymer concentration or in other words it can be said the higher the polymer concentration more shear stress if required to produce a specified rate of shear. *In-vitro* diffusion study of optimized formulation *in situ* gel (MG8) was performed using modified Franz diffusion cell with dialysis membrane in phosphate buffer pH 6.5 for a period of 24 hours. The data obtained from diffusion studies are summarized in Table 4. The *in vitro* release study were fitted into various kinetic models viz zero order, first order, higuchi model and korsmeyer peppas equation. When the regression coefficient values of were compared, it was observed that 'r' values of Higuchi model was maximum *i.e.* 0.978 hence indicating drug release from formulations was found to follow Higuchi release kinetics (Table 6 and Figs. 1-4).

Table 3. Evaluations of nanoparticle formulations by OVAT

Formulation	Particle Size* (nm)	Entrapment efficiency* (%)	Drug content* (%)	Polydispersity index*
NP1	337.2±4.84	76.7±0.2	64.63±0.78	0.234 ± 0.006
NP2	358.6±5.38	62.2±0.6	69.73±0.83	0.345 ± 0.012
NP3	382.8±3.85	78.6±0.8	72.56±0.63	0.380 ± 0.074
NP4	448.7±6.78	83.1±0.3	63.52±0.45	0.342 ± 0.098
NP5	455.6±8.27	86.3±0.5	69.48±0.54	0.245 ± 0.009
NP6	372.6±4.73	82.2±0.7	63.53±0.32	0.454 ± 0.004
NP7	411.5±6.83	79.2±0.9	72.12±0.25	0.319 ± 0.010
NP8	342.3±4.89	77.5±0.7	67.58±0.42	0.254 ± 0.098

** The values are expressed as mean ± SD for n=3*

Table 4. Results of mamentine HCl nasal *in Situ* gel formulations

Code	pH	Spreadability (gm.cm/sec.)	Viscosity (cps)	Drug content (%)
MG1	7.1±0.85	12.53±2.73	7643.68±0.96	98.74 ±0.53
MG2	7.3±0.58	12.08±4.42	9874.03±1.73	98.85 ± 0.63
MG3	7.3±0.69	12.75±3.59	6539.06±1.74	97.51 ± 0.74
MG4	6.9±0.65	13.63±5.69	9743.37±1.26	97.85± 0.37
MG5	6.8±0.47	12.83±4.58	8864.86±2.74	98.58± 0.85
MG6	7.1±0.28	11.53±6.46	9763.11±1.92	98.84± 0.73
MG7	6.8±0.63	11.29±3.52	7963.49±0.74	97.39± 0.62
MG8	7.3±0.48	13.89±3.51	9045.37±0.84	98.85± 0.63

Table 5. Results of in vitro drug release study of optimized formulation NG8

Time (h)	Square Root of Time(h)1/2	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	19.8±1.30	1.296	80.2	1.904
2	1.414	0.301	25.3±1.39	1.403	74.7	1.873
3	1.732	0.477	28.4±0.98	1.453	71.6	1.854
4	2.000	0.602	35.3±3.84	1.547	64.7	1.810
6	2.449	0.778	41.5±1.73	1.617	58.5	1.767
8	2.828	0.903	47.5±1.48	1.676	52.5	1.720
12	3.464	1.079	52.6±0.62	1.720	47.4	1.675
24	3.742	1.146	67.5±0.73	1.829	32.5	1.511

Table 6. Release kinetics of optimized formulation MG8

Zero order	First Order	Higuchi	Korsmeyer-peppas
		r2	
0.738	0.818	0.993	0.980

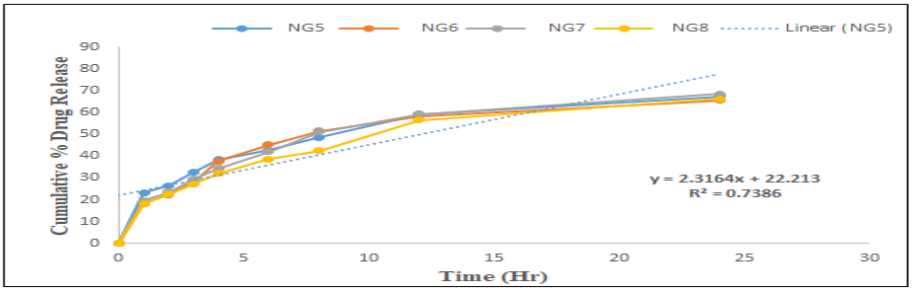

Fig. 1. Zero order release Kinetics of optimized formulation NG5-NG8

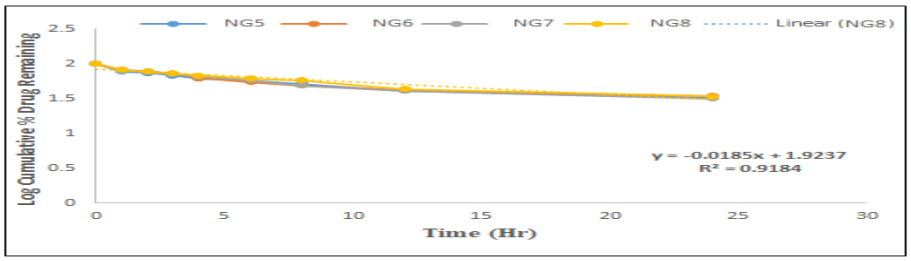

Fig. 2. First order release Kinetics of optimized formulation NG5-NG8

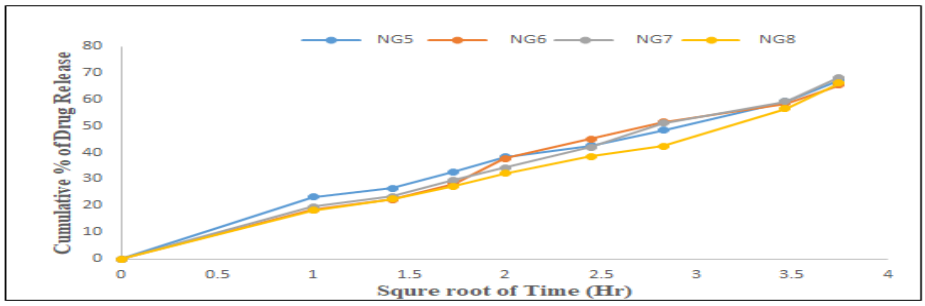

Fig. 3. Higuchi release Kinetics of optimized formulation NG5-NG8

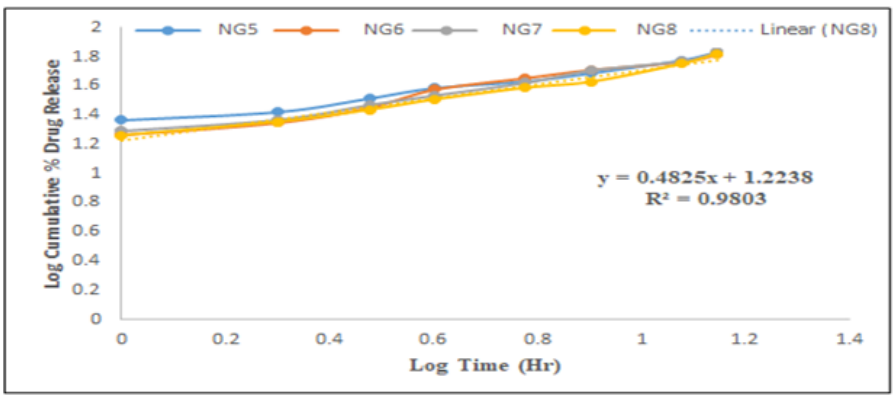

Fig. 4. Korsmeyer-peppas release Kinetics of optimized formulation NG5-NG8

4. CONCLUSION

The main objective of the study is to formulate hydrophilic drug loaded nanoparticles with the nanometer size and to increase the encapsulation efficiency of the drug. The nanoparticles were prepared by simple ionic gelation method using various concentrations of

chitosan and an optimum concentration of TPP and further taken to formulate 08 number of nasal gels with poloxamer and carbopol. The prepared formulations were evaluated for particle size, shape, encapsulation efficiency, in vitro drug release and in vitro cytotoxicity. results: The optimized drug loaded nanoparticles showed the size of 330 to 651nm (364.2±3.37), with PDI below 0 to 1 (0.234 to 0.642),zeta potential -8.46 mv encapsulation efficiency of 79.9±0.2, and the drug content of 72.56 ± 0.25% without an initial burst effect up to one hour followed by sustained release up to 24 hrs, Spreadability (gm.cm/sec.) 12.53±2.73to13.89±3.51 and pH ranging from 6.8±0.28 to 7.4±0.83. Further the optimized nanogel formulation was investigated as NG8 to conclude: these preliminary results demonstrates that the possibility of delivering hydrophilic drugs to brain with enhanced encapsulation efficiency. Prepared gel can be use as promising nasal drug delivery system for the anti-Alzheimer drug MEM HCL, which would enhance nasal residence time owing to increased viscosity and mucoadhesive characteristics; furthermore, it also exhibited a permeation enhancing effect.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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