International Journal of Medicine and Pharmaceutical Research
Journal Home Page: www.pharmaresearchlibrary.com/ijmpr
CODEN (USA): IJCPNH | ISSN: 2321-2624 | Publisher: Pharma Research Library
DOI: https://doi.org/10.30904/j.ijmpr.2024.4719
Int. J. Med. Pharm. Res., 2024, 12(1): 82-86

Formulation and evaluation of donepezil Loaded nasal in-situ gel

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A B S T R A C T

The nasal route has been explored as a route of administration, due to the benefits it offers. The formulation in the form of in situ gel has been utilized for the local and systemic effect. This type of formulation first exists in sol form, but once they are administered, it undergoes gelation to form gel, and this approach can be used for successful drug delivery system. Thus, in the present study, formulation of in situ gel for nasal administration for donepezil hydrochloride (HCL), to improve its nasal bioavailability. It was developed by increasing its nasal retention time and arrive at an optimized formulation. The formulation was developed by the use of cold method, by incorporation of thermoreversible polymer poloxamer 188 and mucoadhesive agent carbopol 974P. The in situ gel was later evaluated for different parameters such as pH, gel strength, drug content, viscosity, in vitro drug diffusion, and stability. Based on results obtained, F3 formulation was found to be optimum. The concentration of 18% w/w Poloxamer 188 with carbopol 974P shown promising nasal drug delivery system for donepezil HCl, with enhanced residence time due to increase in viscosity and mucoadhesion characteristics. The use of in situ gel formulation thus can effectively and safely improve the nasal residence time and absorption of donepezil HCl.

Keywords: Nosal in situ gel, Poloxamer 188, Carbopol 974P, Donepezil HCl

A R T I C L E I N F O

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Article History:
Received : 11 April 2024
Revised : 27 May 2024
Accepted : 11 July 2024
Published : 09 Aug 2024

Citation: *V. Vanivineelakshmi, et al. Formulation and evaluation of donepezil Loadednasal in-situ gel. Int. J. Med. Pharm. Res., 2024, 12(1): 82-86.*

Contents

1. Introduction

Alzheimer's disease (AD) is one of the types of central nervous brain disease that is featured by different symptoms that cannot be ignored. The symptoms include defeat of cognitive functions (such as memory, thinking ability, and learning), obstruction in conduct of daily activities, alter intellectual functions, and it's predicted that this disease may double by the year 2040.[1-3]

The major cause of dementia is the AD. It is characterized by degeneration of cholinergic neurons and synaptic loss that result in deficiency of cholinergic transmission and acetylcholine levels. Hence, cholinesterase inhibitors catalyze breakdown of acetylcholine in synaptic cleft that helps in enhancement of acetylcholine for the treatment of AD.[4] Thus, to deliver drugs to the central nervous system (CNS), nasal route can be one of the non-invasive routes that overcome the blood–brain barrier (BBB). Hanson and Frey have proposed intranasal delivery as an important novel route to bypass the BBB to deliver therapeutic agent to brain.[3] Number of studies has focused on the nasal route for CNS delivery of drug.[5] This non -invasive nasal to brain delivery of drugs provides advantages over other routes of administration, with good patient compliance. In general, in market, the acetyl-cholinesterase inhibitors are

available in oral dosage forms. The oral dose of these cholinesterase inhibitors in the market is once a daily tablet or capsule (5 mg or 10 mg/day) but these cholinesterase inhibitors suffer from different gastrointestinal side effects such as nausea and diarrhoea muscle convulsions. There are number of cholinesterase inhibitors that have been used to improve the levels of acetylcholine in brain. One of them is donepezil hydrochloride (DPZ), is reversible acetylcholine inhibitor, and helps to produce neuroprotective effect. With that, it possesses few side effects than other inhibitors, so it can be considered as first line of treatment of AD. Hence, there is a need to develop a formulation that will deliver cholinesterase inhibitors for the management of AD (5).[6]

2. Materials and Methods

Donepezil HCL was obtained gift sample from Cipla Pharmaceutical and Research Center, Patalganga, Navi Mumbai. Poloxamer 188 was purchased from Evonik Catalysts India Private Ltd., Mumbai. Carbopol 974P procured fromLoba Chemie Pvt. Ltd., Mumbai, other agents were purchased from Research Fine Lab, Mumbai.

Methods

Preparation of nasal in situ gel

Firstly, Carbopol 934 was added in some amount of cold distilled water with continuous stirring or trituration on an ice-cold water until clear solution was formed.Then 18% w/w poloxamer 188 added and triturate well until clear solution was formed and kept aside for 3 hours. This was considered as first solution. The ethanol, methylparaben and donepezil HCl was added in cold distilled water and triturate on an ice cold water until clear solution was formed. This is the second solution. Then second solution was poured in a first solution and triturate. Then second solution was poured in a first solution and triturate. This final obtained solution poured in a buffer pH 6.8 to form gel. This is called SOL-GEL formation. Continue the same procedure using another gelling agent.

Evaluation of in situ nasal gels

Clarity

The clarity of various formulations was determined by visual inspection under black and white background by using clarity test apparatus and it was graded as follows;

Turbid +, Clear ++, Very clear (glassy):+++

Appearance

The appearance of gel was examined for clarity. The clarity of various formulations was determined by visual inspection against black and white background.7

Determination of pH

The pH of gels was determined using calibrated pH meter. The determinations were done in triplicate and average of these determinations was taken as the pH of the gel.8

Drug content determination

One gram of gel was taken in 10 ml volumetric flask and diluted up to 10 ml with distilled water. One milliliter from this above solution was taken and again diluted to 10 ml with distilled water. After that, the absorbance of prepared solution was measured at particular wavelength using ultraviolet (UV)–visible spectrophotometer. The tests were carried out in triplicate.9

Gel Strength Determination

Gel strength is related to the viscosity of the gel. A 50 gm sample was placed in 100 ml graduated measuring cylinder and placed into water bath at 37℃. Then marking at upper meniscus level was done as a starting point and measured 5 cm distance from that point and marked as an end point. Stopwatch was kept ready. Then piston was placed onto the gel which having weight 35 g and measured the time in seconds which required for moving the piston 5 cm down through the gel was noted.10-13

Spreadability study:

Spreadability defines the extent of the gel spread onto the skin when applied. The method includes the use of two glass plates (20cmx20cm). Specific amount of prepared gel (1g) was placed in one of the glass slide and then second glass was placed above it. Then a weight (125g) was placed over the plates for proper spreading. Spreadability is the time in seconds for two slides to slip off from in situ gel which was placed in between the slides. The slides are under the influence of certain load. The spreadability is expressed in g cm sec-1 (gram centimetre/seconds).14-17

Viscosity

The viscosity measurements were carried out by using Nunes viscometer. The spindle no. 4 was used and rotated at 0.2 rpm. The temperature of sample was maintained with the help of temperature control unit. The measurement was taken at 37℃.18,19

In vitro diffusion studies:

In vitro diffusion study was conducted to determine the release of drug from the formulation. In this technique a two sided open cylindrical tube was used. One side of the cylindrical tube was mounted with egg membrane of suitable molecular weight and coated with 3.2ml of donepezil hydrochloride from one side. The egg membrane used as a semi permeable membrane. The setup was made in a way that the end of cylindrical tube containing gel gets in contact with the diffusion medium i.e. phosphate buffer pH 6.8 (25ml). The assembly was then placed on a magnetic stirrer and the content was stirred at 700 rpm. At specific time interval of 1 hour, 3 ml samples were withdrawn from the receptor compartment and replaced with the same volume of fresh phosphate buffer pH 6.8 after each sampling, for a period of 8hrs. The samples withdrawn were filtered and used for analysis. These samples were analyzed by spectrophotometrically at 313nm by using Shimadzu-1800 UV- Visible spectrophotometer. Dissolution studies for each formulation were performed in triplicates.20,21

Release Kinetics

To analyze the in vitro release data various kinetic models were use to describe the release kinetics. The zero order rate Eq. (2) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (3) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:

Zero - order kinetic model – Cumulative % drug released versus time.

First – order kinetic model – Log cumulative percent drug remaining versus time.

Higuchi's model – Cumulative percent drug released versus square root of time.

Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus logtime.

3. Results and Discussion

Melting Point Determination

The melting point of Donepezil hydrochloride was found to be 2230C. The melting point values reported for Donepezil hydrochloride in the range of 2230C to 2270C.

Solubility study: Donepezil is easily soluble in ethanol, pH 6.8 phosphate buffer and water.

Calibration curve

The wavelength of maximum absorbance (λ max) selected was 313 nm for Phosphate buffer having pH 6.8 for Donepzil hydrochloride. The graph which was plotted was found to be linear in the concentration range of 0 to 5µg/ml and obeys the Beer-Lambert's law in the same ranges.

Determination of pH

The pH of all formulations was found to be in the range of 5.27-6.2. All were within the range specified for nasal formulation. Because, the lysozyme was present in the nasal secretions, which was responsible for destroying certain microbes at acidic pH. Under alkaline pH lysozyme is inactive and nasal tissue is susceptible to microbial infection. Hence, it was advisable to keep the formulation's pH in the range of 4.5-6.5.

Drug Content

The percentage drug content of all prepared nasal formulations were checked and found to be in the range of 83.23 – 98.97% .

Viscosity

The single apparent viscosity values, measured by using Nunes viscometer with spindle no.4 at 0.2 rpm for formulation F1 to F9. The viscosity was directly dependent on the polymeric content of the formulations. It is to be noted that the addition of increasing concentrations of polymer from 5% to15% increases the viscosity of formulations. From viscosity studies it was found that viscosity increase with concentration of mucodhesive polymer.

Gel strength

The gel strength value between 25 to 50 seconds is considered sufficient. The formulation with gel strength less than 25 second may not preserve its integrity and may erode rapidly. In case of formulations with gel strength more than 50 second is too stiff and may cause discomfort. It was observed from data, only F1, F2, F3, F4, F5 and F7 were found to be in this range. In situ gel must have suitable gel strength so as to be administered easily and can be retained at nasal mucosa without leakage after administration. It is very important that the nasal gel formulation must have suitable gel strength. Table 16 & figure 14 showed the data of gel strength measurement.

Spreadability

Spreadability of a gel is an important characteristic parameter. The spreadability of the prepared donepezil HCl loaded in situ gel was ranges from as 14.53±0.51 to 33.28±4.23 which indicate easy spreadability of gel on application of small amount of shear. The figure 1 shown graphical representation of viscosity, gel strength and spreadability of F1-F9 formulations and table 1 shown different parameters results.

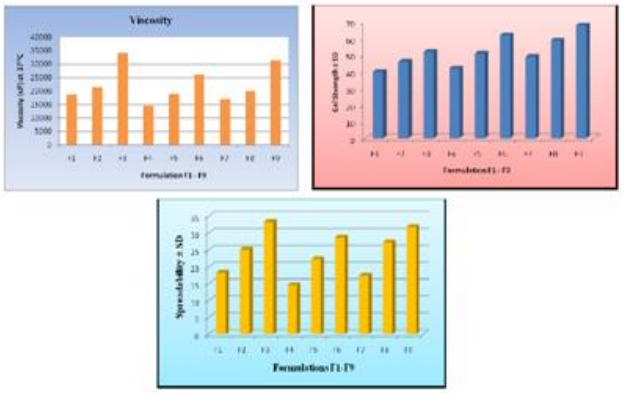

Figure:1 Graphical representation of Viscosity, Gel strength and Spreadability of F1-F9 Formulations

In vitro diffusion study:

The more percent of drug was diffused if the concentration of Carbopol 974P increased in the formulation. In presence of carbopol 974P (Fig 2) very rapid dissolution and release of highly soluble drug of Donepezil hydrochloride due to rapid swelling and dissolution of carbopol at pH 6.8. The addition of 5% and 15% carbopol 974Penhanced the diffusion of drug from gel significantly. This result could be attributed to increase in concentration of ionized carboxyl group to a level required to cause conformational changes in the polymer chain. Electrostatic repulsion of the ionized carboxyl group results in decoiling of the polymer chain, resulting in the relaxation of the polymer network. At this stage, drug is rapidly dissolved and released from the gels as a result of very high swelling or fast dissolution of the ionized carbopol974P.

Kinetics of In-vitro drug diffusion:

The kinetics of in-vitro drug permeation was determined by applying the drug release datato various kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas. The obtained results were shown in table 2.

Table:1Results of different parameters for formulations **(F1-F9)**

Formulation Code	pH ± SD	% Drug content±SD	Viscosity (cP)at37°C	Gel Strength (sec)± SD	Spreadability (gm.cm/sec) ±SD
F1	5.92±0.14	96.56±0.26	18600	40±1.2	18.22±0.61
F2	5.27±0.12	97.11±0.27	21400	46±1.4	25.15±1.22
F3	6.15±0.06	98.97±0.16	34200	52±1.3	33.28±1.05

F4	5.82±0.19	84.23±0.52	14500	42±1.0	14.53±0.51
F5	6.26±0.07	87.64±0.43	18800	51±1.5	22.25±1.42
F6	5.40±0.02	83.23±0.27	26100	62±2.0	28.73±1.63
F7	6.21±0.02	92.42±0.99	16900	49±2.5	17.43±1.52
F8	5.78±0.24	88.52±0.33	20100	59±1.5	27.23±1.02
F9	6.15±0.06	90.92±0.21	31500	68±2.0	31.82±1.42

All the values are expressed as mean±S.D., n=3

Table: 2 Regression coefficients values of all the Kinetic model graphs

Formulation	**Zero order kinetics**	**Firstorder kinetics**	**Huguchi kinetics**	**Korsmeyer- Peppas**
F3	0.988	0.675	0.955	0.675

Discussion

The present study was aimed to develop a mucoadhesive nasal in situ gel delivery system for the treatment of alzimer's disease. Nine batches of mucoadhesive nasal in situ gels (F1- F9) were prepared by using carbopol 974P, xanthum gum and sodiumalginate with drug by Cold method. Preformulation study was carried out for crude drug. The initial part of work was started from the identification of drug. Identification of drug was determined by melting point and solubility. The compatibility studies by FTIR and DSC analysis of in situ gels suggest that the drug donepezil with polymers do not interact to form any additional chemical entity but remain as a mixture. Therefore, it could indicate that there was no incompatibility between drug and polymers. The similarity in peaks indicates there is no incompatibility between drug and the polymers. pH of the all formulations were found to be within 5.27-6.26 that is between physiological range of pH of nasal mucosa. The percentage drug content of all the prepared in situ gel formulations were checked and found to be in the range of 83.23-98.97%. The viscosity was directly dependent on the polymeric content of the formulations. It is to be noted that the addition of increasing concentrations of polymer from 5% to15% increases the viscosity of formulations. From viscosity studies it was found that viscosity increase with concentration of mucodhesive polymer. From in-vitro permeation studies it was concluded that formulation F3 found to be best formulation among other formulations, which showing the most desired drug permeation. It will be considered as best formulation.

4. Conclusion

Out of the nine formulations, it appears that Formulation F3 has the maximum potential in providing *In situ gel* nasal delivery system. This formulation was considered as best formulation for nasal *in situ gelling* system for the treatment of Alzimer's with respect to its evaluation parameters like clarity, pH, drug content, Gel strength, Spreadability and *in-vitro* drug release and this formulation may give patient friendly and needle free dosage form.

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