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Research Article

RESEARCH ON FORMULATION AND EVALUATION OF INSITU MUCOADHESIVE NASAL GELS OF METOCLOPRAMIDE HYDROCHLORIDE

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ABSTRACT

The prolonged residence of drug formulation in the nasal cavity is of utmost importance for intranasal drug delivery. The objective of the present investigation was to develop a mucoadhesive in situ gel with reduced nasal mucocilliary clearance in order to improve the bioavailability of the antiemetic drug, Metoclopramide Hydrochloride. The in situ gelation upon contact with nasal mucosa was conferred via the use of the thermogelling Methyl cellulose whereas mucoadhesion and drug release enhancement were modulated via the use of sodium alginate and polyethylene glycol polymers respectively. The results revealed that the mucoadhesive polymer increased the gel viscosity but reduced its sol gel transition temperatures and the drug release. The inclusion of polyethylene glycol polymer counteracted the effect of mucoadhesive polymer where by it decreased the gel consistency and increased the sol gel transition as well as in vitro drug diffusion. The in vitro tests performed for mucoadhesive strength and drug diffusion showed that nasal in situ gelling formulations prepared are having good mucoadhesive strength with nearly100% drug diffusion within four hours. So this study points to the potential of mucoadhesive in situ nasal gel in terms of ease of administration, accuracy of dosing, prolonged nasal residence and improved nasal bioavailability.

Keywords: Nasal Gel, Metoclopramide Hydrochloride, Methyl Cellulose, Mucocilliary Clearance.

INTRODUCTION

Metoclopramide Hydrochloride (MET HCl) is a potent antiemetic, effective in the treatment of nausea and vomiting associated with cancer therapy, pregnancy, migraine, etc. Oral bioavailability of Metoclopramide Hydrochloride is highly variable, showing values between 32–98% due to extensive pre-systemic metabolism. [1] Oral forms of Metoclopramide Hydrochloride often get vomited out before systemic absorption. Parenteral or rectal administration results in low patient compliance. In this regard, the intranasal delivery seems to be an attractive alternative. The major disadvantage associated with nasal drug delivery is rapid mucocilliary clearance (MCC) that limits the time available for drug absorption from applied dosage form.[2] The half-life of clearance for both liquid and powder formulation that are not mucoadhesive is in the order of 15–20 min.[3] Therefore, a plausible strategy is to decrease MCC by the use of gel/mucoadhesive formulations to prolong the residence time at the nasal absorption site and thereby facilitate the uptake of drug. Ordinary gels are difficult to administer and an accurate drug dose cannot be measured. Mucoadhesive powders are not highly favoured products. They can cause irritation on the nasal mucosa and give a gritty feel to the tissue, besides the difficulty and the cost of manufacturing powders with specified morphology. A nasal mucoadhesive in situ gel appears very attractive since it is fluid like prior to nasal administration and thus can be easily be instilled as a drop, allowing accurate drug dosing.

Methyl Cellulose can markedly prolong the residence time of drugs in the nasal cavity due to their desirable mucoadhesive property. [4] Additionally, due to their high viscosity following hydration in the nasal cavity, methyl cellulose can sustain the release of drugs.

For these reasons, using methyl cellulose as absorption enhancer can lead to improved intranasal absorption and increased bioavailability. [5] The aim of the present study is to develop a Metoclopramide Hydrochloride, mucoadhesive nasal in situ gel using Methyl Cellulose polymer. The optimized nasal in situ gel with favourable gelation, rheological behaviour, release and mucosal permeation ability was selected for further bioavailability study.

MATERIALS AND METHOD

Materials

Metoclopramide Hydrochloride was a kind gift from Aldoc Pharmaceutical (Kota, India), Sodium alginate (Na alginate), and polyethylene glycol 6000 (PEG 6000) were collected from Kota College of Pharmacy, Kota.

Method

Preparation of mucoadhesive thermoreversible nasal gels:

Metoclopramide Hydrochloride along with mucoadhesive polymer, and /or PEG 6000 and methyl paraben was dissolved in double distilled water by agitation at room temperature. After cooling the solution to 4^0C, Methyl Cellulose was added slowly with agitation. The resulting dispersion was then kept overnight at 4^0C until clear and viscous transparent solution was formed. Finally volume was adjusted by using cold distilled water.

Evaluation of final formulations was done with respect to clarity, pH, content uniformity, gelation temperature, mucoadhesive force, diffusion through nasal mucosa and viscosity of formulation.

Table I: Composition of various thermoreversible mucoadhesive nasal gel formulations

Composition	F1	F2	F3	F4
Metoclopramide HCl	10	10	10	10
Methyl cellulose	18	18	18	18
Na-Alginate	...	0.2	0.2	...
PEG 6000	...	...	0.4	0.4
Methyl Parabens	0.33	0.33	0.33	0.33
Purified Water	q.s	q.s	q.s	q.s

*All concentrations in percentage; batch size 20ml

EVALUATION OF FORMULATION

Clarity

The clarity of various formulations was determined by visual inspection under black and white background and it was graded as follows; turbid: +, clear ++, very clear (glassy): +++.

pH of Formulation

1ml quantity of each formulation was transferred to the 10ml volumetric flask and diluted by using distilled water to make 10ml. pH of resulting solution was determined by using pH meter.

(Systronics ì pH System 362)

Content Uniformity

1ml of formulation was taken in 100ml volumetric flask, added 50ml of distilled water with gentle shaking and final volume was adjusted to 100ml. 1ml quantity from this solution was transferred into the 100ml volumetric flask and final volume was made to 100ml by using distilled water to get 10mg/ml. Finally the absorbance of prepared solution was measured at 212 nm by using UV visible spectrophotometer. (Shimadzu UV 1800, Japan)

Gelation Temperature

The gelation temperature of aqueous solution of Methyl Cellulose was measured by using procedures reported by Choi et al [6]. In brief, 10ml volume of solution was transferred to 20ml transparent vial containing a magnetic stirrer bar (1x5/16 inch octagonal). The vial was heated at an increasing rate of 10°C/min with constant stirring at 100 rpm. The temperature at which rotation of bar stopped was taken as the gelation temperature.

RESULT

Clarity, pH and Content Uniformity:

All the prepared sets of formulations were found to be clear. pH of all the formulations was found to be in the range of 4.9-6.3. The percentage drug content of all prepared nasal formulations were checked and found to be in the range of 70-103%. The percentage drug content of formulations from same batch was found to be uniform.

Table II: Clarity, pH and content uniformity of mucoadhesive nasal insitu gelling formulations

Formulation	Clarity	pH	Content Uniformity n = 3
F1	+++	6.3	103.88
F2	++	5.8	96.34
F3	+++	5.2	81.04
F4	+++	4.9	70.03

Gelation Temperature

Various excipients like mucoadhesive polymer as well as PEG 6000 had shown to have effect on the gelation temperature. Mucoadhesive polymer reduced the gelation temperature while PEG 6000 increased the $T_{sol\text{-}gel}$ of the corresponding mucoadhesive nasal insitu gelling formulations in a concentration dependent manner as described earlier.

Table III: Gelation temperature of mucoadhesive nasal insitu gelling formulations

Formulation	Gelation Temperature(^{0}C) Mean ± S.D. n=3
F1	28.88±0.13
F2	27.32±0.39
F3	30.03±0.19
F4	30.92±0.27

DISCUSSION

The physiological range of the nasal mucosal temperature lies between 32-34^0 C. [7] So the thermoreversible nasal gels were prepared with the phase transition temperature in the range of 27-30^{0}C. From viscosity studies all formulations are in a liquid state at room temperature for ease of administration and accurate measurement of dose and would be converted into gel with increased residence time at the lower limit of the nasal physiological temperature range. The loading of Metoclopramide Hydrochloride in the different formulations was kept at 10%w/v such that 100ìl gel (the optimum volume for nasal administration) would contain 10mg, which is the adult dose. [8]

Lysozyme is formed in the nasal secretions, which is responsible for destroying certain microbes at acidic pH. Under alkaline pH lysozyme is inactive and nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the pH of formulation in the range of 4.5-6.5. [9]

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