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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF METOCLOPRAMIDE HYDROCHLORIDE NASAL SPRAY

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ABSTRACT

The objective of the present study was to formulate and evaluate nasal delivery system contains Metoclopramide hydrochloride 4 mg/ml. Metoclopramide hydrochloride loaded nasal solutions were prepared for nasal drug delivery using various polymers like β-cyclodextrin, hydroxyl propyl β-cyclodextrin at different concentrations. The optimized formulation contains 0.02% benzalkonium chloride as a preservative, 0.02% of disodium EDTA as an antioxidant, 1.36% of potassium dihydrogen phosphate and 3.58% of disodium hydrogen phosphate mixture was used as a buffer to maintain the pH of the formulation. The finished formulation was characterized for its clarity, pH, viscosity, drug content, pka, pump delivery, net content, weight loss on storage, *in vitro* diffusion and *in vitro* bioadhesive strength. Therefore a nasal delivery system of Metoclopramide hydrochloride which was developed and formulated in this study is ideal for nasal administration for the treatment of antiemetic.

Keywords: Metoclopramide, Polymers, Nasal spray.

INTRODUCTION

Metoclopramide hydrochloride is a Benzamide,4- amino -5 chloro-N-(-2diethyl amnioethyl)-2-methoxy monochloride –monohydrate. [1]. Metoclopramide hydrochloride is a short acting drug for the management of nausea and vomiting. Chemotherapeutic agents and radiotherapy cause release of 5HT in the small intestine initiating the vomiting reflux by activating vagal afferents via $5HT_3$ receptor. It blocks the initiation of these reflexes [2,3]. It has a short biological half life of 5.1h and a distribution half –time of 0.03h.

The most commonly reported adverse events with Metoclopramide hydrochloride are restlessness, drowsiness, dizziness, diarrhea or constipation, trismus, a bulbar type of speech and breast engorgement, which are mild to moderate in severity and rarely necessitate treatment withdrawal. Various polymers are used to improve bioavailability of the drug administered by nasal route. Improving nasal residential time, the enhancement of nasal absorption (by penetration enhancer) and without altering its pharmacological activity [4]. Studies concerning the safety of cyclodextrin [5] in nasal drug formulations demonstrate the non-toxicity of the cyclodextrin and also clinical data shows no adverse effects [6]. Some cyclodextrin reports state that it is effective and safe excipients in nasal drug delivery [7, 8].

Delivery of drugs through nasal route for systemic activity which provides a lot of possibilities for peptide and protein endogenous compounds for therapeutic use [9-12]. The greater the permeability of nasal mucosa and low metabolic activity has potential to overcome limitation of oral route and duplicate the benefits of intravenous infusion [13]. Possibility of bypassing the blood brain barrier by delivery of drugs through the nose to the brain along with neural pathway to target the brain [14]. However short nasal residential time and low permeability (drugs having molecular weight more than more than 1000 Daltons) of the drug retards the bioavailability of nasally administered drug [15].

Nasal delivery has paid attention as an alternative dosage form. The advantages of administering drugs nasally [11] are rapid absorption, higher bioavailability, lower doses, fast onset of action; bypass that of the GIT, reduced risk of overdose, self medication, ease of convenience, improved patient compliance feasibility of beneficial adjunct product to an existing product and reduced risk of infectious disease transmission [16].

The nasal release drug delivery is to ensure safety and to improve efficacy of the drug as well as patient compliance. The dosage release properties of spray may be dependent upon the solubility of the drug in the polymer dispersion [17].

The objective of the present study was to formulate and evaluate nasal solution release using different β-cyclodextrin derivatives. Based on the *in vitro* results, the most suitable formulation was constructed. Elucidated the release pattern of the drug solution and compared with the effects of vehicles and absorption enhancers on the permeation of Metoclopramide hydrochloride across the excised goat nasal mucosa were examined.

MATERIALS AND METHODS

Metoclopramide hydrochloride IP was obtained as a gift sample from MMC healthcare Chennai, Pvt. Ltd. β-cyclodextrin and hydroxyl propyl β-cyclodextrin were purchased from Signet chemicals, Mumbai. Other materials and excipients used in the preparation of nasal solutions were I.P Grade. Acetonitrile, water and methanol used were of HPLC grade. All other ingredients used throughout the study were of analytical grade.

Preformulation studies

Preformulation studies were carried out in order to find out of the drug excipient interactions and solubility. UV absorption spectrum and TLC were used to find out the interaction between the drug and excipients. Viscosity measurements of 0.05% polymeric dispersion were measured in order to find out the effect of viscosity of vehicles on drug release using Brookfield Viscometer DV. pKa was determined by half neutralization of pH. The specific identification tests were carried out in order to find out the drug excipients interactions. Infrared spectrum obtained for pure Metoclopramide hydrochloride and spray dried (lyophilized) formulation was used to verify the chemical compatibility of Metoclopramide with the excipients used in the formulation development. IR Spectrum which was taken for identification which, prepared by pellet technique with 2-3 mg of sample and potassium bromide using a FTIR spectrometer (Jasco model, Tokyo, Japan) and the sample was scanned from 4000-400$cm^{-1.}$.

An excess amount of Metoclopramide hydrochloride was added to various vehicles and shaken in a water bath set at $37^0C \pm 0.5^0C$ for more than 48h.The solutions were centrifuged at 3000 rpm for 5 min, and the supernatant was assayed by HPLC after appropriate dilution.

Preparation of nasal solutions

All the twelve batches, of the prepared formulations contained 4 mg of drug per ml. β-cyclodextrin, hydroxyl propyl β-cyclodextrin were used as mucoadhesive polymers in the concentration range of 1-5%. Polyvinyl pyrolidine (PVP), polyethylene glycol (PEG) were used as solubilizer and lubricants respectively. Disodium EDTA, benzalkonium chloride was used as an antioxidant and preservative respectively. Sodium chloride was used to maintain the tonicity. Potassium dihydrogen phosphate, disodium hydrogen phosphate

was used as a buffer to maintain the pH of the formulation. The different compositions of all the formulations were given in Table 1. Total quantity of 100 ml of formulation was prepared for each batch. 400 mg of the drug, and 20 mg of EDTA were dissolved in the proposed ratio of solubilizer and sonicated for the period of 30 min with polyvinyl pyrolidine, 20 min and polyethylene glycol with different proportion of cyclodextrins and the volume was made up to 70 ml. Simultaneously 1% polymeric dispersions contained 0.02% of benzalkonium chloride (pH 6 was adjusted with 0.1M sodium hydroxide). Potassium di hydrogen phosphate in disodium hydrogen phosphate buffer solution was prepared. 70 ml of drug solution was incorporated in a drop wise manner in 30 ml of polymeric solution and stirred gently using a magnetic stirrer. Throughout the formulation the temperature was maintained at $50^0C \pm 0.5^0C$.A clear transparent solution was formed, cooled at room temperature and subjected to further evaluations. All the operations were carried out in a sterile aseptic condition in the laminar flow chamber.

Evaluation of nasal solutions:

The prepared nasal solution were evaluated for their pH, viscosity, clarity, sterility, drug content uniformity, pump delivery, stability, *in vitro* diffusion studies and *in vitro* bioadhesion strength.

Table 1: Composition of nasal solutions

Ingredients (g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Metoclopramide hydrochloride	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Nacl	-	-	-	0.9	0.9	-	0.9	-	0.9	-	0.9	0.9
β-cyclodextrin	-	1.0	2.0	2.0	1.0	-	-	--	-	-	-	-
Benzalkonium Chloride	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Disodium EDTA	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Caffeine	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Hydroxyl propyl β-cyclodextrin	-	-	-	-	-	5.0	5.0	-	-	-	-	-
PVP	-	-	-	-	-	-	-	2.9	2.9	-	-	-
PEG	-	-	-	-	-	-	-	-	-	4.8	4.8	-
MCC	2	-	-	-	-	-	-	-	-	-	-	2
PDP	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36	1.36
DHP	3.58	3.58	3.58	3.58	3.58	3.58	3.58	3.58	3.58	3.58	3.58	3.58
Purified water(Q.S)	100 ml	100 Ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

pH

The pH [18,19] of the nasal formulation is very important mainly to avoid irritation of the nasal mucosa, to prevent the growth of pathogenic micro organism, to sustain normal physiological ciliary movement. Lysozyme which is present in nasal secretion, that is responsible for destroying certain micro organisms at acidic pH, under alkaline pH, Lysozyme is deactivated and the nasal tissue is susceptible to microbial infection [20]. It is therefore pH of the formulation was adjusted between 4.5 - 6.5 [21] and pH of the all prepared formulations was measured for pH using by digital pH meter.

Viscosity

Viscosity measurement of different polymeric soultions (only for HPβCD, in phosphate buffer, pH 6.3 which was adjusted with phosphoric acid) was measured in order to find out the effect of viscosity of vehicles on drug release using Brokefield Viscometer DV [22].

Clarity test

The test was performed to find out whether the nasal solution is free from the particulate matter or not. The solution in the test tube was observed against black and white background under light using clarity testing apparatus. Particulate matter may originate during manufacturing, from formulation component, container and closure component. Level of particulate matter in the drug product was increased with time, temperature and stress [23].

Sterility

The test for sterility was designed to reveal the presence of microorganisms in the nasal solutions. Soya bean casein digested media was used in this study in order to find out both bacteria and fungi. One portion of intended media was used for detection of bacteria at 37^oC for 24h, and another portion used for the detection of fungi at 23^oC for seven days.

Drug content

Content uniformity study [24] is used to determine the drug content in the different formulations [19]. One ml of the nasal solution (4mg) was pipetted, transferred into 100 ml volumetric flask and made up to 100 ml with distilled water. 1ml of the above solution was transferred into 50 ml volumetric flask and made up to 50 ml with a mobile phase of HPLC. Drug content estimation of Metoclopramide hydrochloride was carried out by HPLC method and the chromatographic conditions are column-Lichrosphere, silica gel , 250×4.6mm,5 µm, wavelength at 273 nm, flow rate at 1.5ml/min, injection volume is 20µl, run time 30min, UV-detector and the mobile phase composition in phosphate buffer and acetonitrile 50:50 v/v. Comparing the content from the calibration curve prepared with standard Metoclopramide hydrochloride in the same medium. The concentration of the drug present in the formulation was computed from the calibration curve.

Pump delivery

The formulation has been filled into a container having a single nozzle (0.2 mm diameter) was actuated for 10 times in a pre-weighed weighing bottle. After actuation the weight of the weighing bottle was reweighed and the difference was calculated.

Stability

The formulated drug product was filled in single nozzle (0.2 mm diameter), stored in upright and inverted and horizontal position was evaluated for weight loss due to the leakage, clarity, pH, viscosity and drug content.

***In vitro* drug release studies**

In vitro drug release study [25] was carried out by the nasal diffusion cell which was fabricated in glass chamber (20ml capacity). The water jacketed recipient chamber has the total capacity of 60 ml. The lid comprises of 3 openings, one for sampling, second for placing thermometer and the other for donor tube chamber which was a 10 cm long tube with the internal diameter of 1 cm. The nasal mucosa of the goat was separated from sub bony layer tissues and stored in distilled water containing 0.5 ml of gentamycin sulfate (400 mg) injection. After complete removal of blood from the surface of the mucous sub bony layer tissues was attached to the donor chamber tube, which just touches the buffer (Phosphate buffer pH 7.4) medium in which continuous magnetic stirring at 100 rpm was performed. 0.5 ml of the nasal solution was placed on

mucosal surface in the diffusion cell. At predetermined intervals samples of 1.0 ml were withdrawn through the recipient chamber tube and replaced with a buffer solution. The samples were diluted appropriately and drug content was analyzed at 273 nm using HPLC. Throughout the experimental study the temperature was maintained at 37° C ± 5°C. The actual content in the different samples was read from the calibration curve prepared with standard Metoclopramide hydrochloride.

***In vitro* Bioadhesive strength**

In vitro bioadhesion study was carried out using nasal mucosa assembled with modified chemical balance. The two-rod surface was covered with fresh nasal mucosa of goat. The balance beam was calibrated with 7.0 g on the right pan and then the weight of the right pan was removed. 1 ml of he formulation was placed in between two nasal mucosal surfaces in the modified balance, allowed to attach for the period of 3 min. The weights were kept in another pan of the modified balance and weight required to detach the nasal mucosal surface was measured. Total weight was subtracted with the weight of 7.0 g which was counted as bio adhesive force.

RESULTS AND DISCUSSION

Preformulation

The active component Metoclopramide hydrochloride with cyclodextrin derivatives were individually and physical mixtures were taken for FTIR and found no interactions were observed. A trial was made by alteration in the excipients. The buffer has been used to maintain the pH and stability of the formulation. Sodium chloride has been used to maintain the tonicity and increase the absorption through the nasal mucosa in the formulation. PVP and PEG were used to increase the solubility in the formulation. Among the PEG and PVP which were used for the solubilizer PEG was considered as a good candidate of the vehicle for the formulation of the Metoclopramide nasal delivery system due to the viscosity, which could prevent nasal dryness as well as it has a relatively high solubility. It has been performed in F6 and F7 and observed in the data, which was presented in Table 2. PVP was also evaluated as a candidate vehicle because of its property of moisturizing the nasal mucosal surface. Benzalkonium chloride [26] used as a preservative and disodium EDTA used as antioxidant in all formulations.

Table 2: Characterizations of the nasal solutions.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
pH	6.1	5.8	6.3	5.9	6.0	6.1	6.2	6.3	6.0	6.1	6.3	5.9
Viscosity(cps)	4.42	4.43	4.43	4.40	4.46	4.42	4.43	4.33	4.42	4.46	4.43	4.38
Clarity	T	T	T	T	T	T	T	T	T	T	T	T
Sterility	S	S	S	S	S	S	S	S	S	S	S	S
Drug content (%)	92.0± 0.5	92.9±0. 2	91.0±0. 5	97.2±0. 1	98.2±0. 4	92.6±0. 2	93.0±0. 3	95.2±0. 1	94.3±0. 1	94.6±0. 2	93.2±0. 4	94.1±0. 6
In vitro bioadhesive strength(g)	2.04± 0.06	3.17±0. 72	3.58±0. 86	3.67±0. 71	4.06±0. 80	3.13±0. 58	3.06±0. 65	3.49±0. 69	3.26±1. 25	3.95±0. 95	3.15±0. 44	3.37±0. 84

T=Transparent;S=Sterile; n=3

pH

To stabilize the drug Metoclopramide hydrochloride nasal delivery system, it was preferably adjusted to a weak acidity of pH 4.5 - 6.5, so as to increase the chemical stability of the active ingredient and aid to prevent the growth of microorganism. 0.02 g of EDTA was added to phosphate buffer (pH 6.0). All the twelve formulations were maintained pH 5.5 -6.5.

Clarity

The appearance of the content of the container and closure system was analyzed for the twelve formulations. There is no change in color, size, shape, texture and clarity of the formulation [27] as an indication of the drug product integrity in all batches which was presented in Table 2.

Sterility

Sterility may have an influence on contamination, but as far as concerning Metoclopramide, pKa value of Metoclopramide is 8.1 which is greater than pH of the formulation. All the formulations were found to be sterile in both detection of bacteria and fungi.

Drug content and viscosity

Drug content was found to be uniform among all different batches of the formulations are ranged from 92 ± 0.1% to 104.5 ± 0.2% (Table 2). The viscosity of the formulation is low hence the spraying from container have good spread ability of a solution within the nose. All the formulations were lying within the acceptable limitations (3-6 cps) which was presented in Table 2.

Pump delivery and stability

Weighed the content in 10 actuations was performed for F5, which is the optimized formulation found to be 0.904 g and average delivery of the formulations was found to be 0.091g. Individual spray delivery was within 15% of the target weight and their mean weight was within 10% of the target weight in 10 actuations (Table 2). Total net content from 10 containers was found to be not less than 90% of labeled amount (Table 2). There was no loss of weight in the product stored in an upright, inverted and horizontal position. (Table 3). Stability study of F5 indicates that there was no change in pH, viscosity, drug content, appearance, particulate matter and weight loss (leakage & evaporation).

Table 3: *In vitro* drug release of the developed nasal spray.

Formulation code	Drug Release (%)			
Time (min)	10	20	30	40
F1	15.0	25.5	75.0	95.0
F2	14.0	24.5	73.9	94.9
F3	7.61	26.0	76.5	95.0
F4	13.2	21.0	74.5	95.2
F5	25.0	35.5	75.2	95.2
F6	17.2	21.5	72.5	75.0
F7	45.9	67.3	72.8	93.0
F8	39.0	64.5	78.4	95.2
F9	43.8	69.6	79.0	94.3
F10	42.0	67.7	70.5	94.6
F11	43.8	68.9	69.0	93.2
F12	46.4	66.0	78.5	94.1

***In vitro* bioadhesive strength**

The order of bioadhesieve force of the formulation was obtained as β-cyclodextrin>hydroxyl propyl β-cyclodextrin >microcrystalline cellulose. Even though β-cyclodextrin showed better bioadhesive property than other polymer, the problems associated with alkali (leads to inactivation of lysozyme) and retarded release. So finally in the formulation setup which contains 1:4 ratio of drug and β-cyclodextrin was found to be an ideal mucoadhesive polymer for nasal drug delivery.

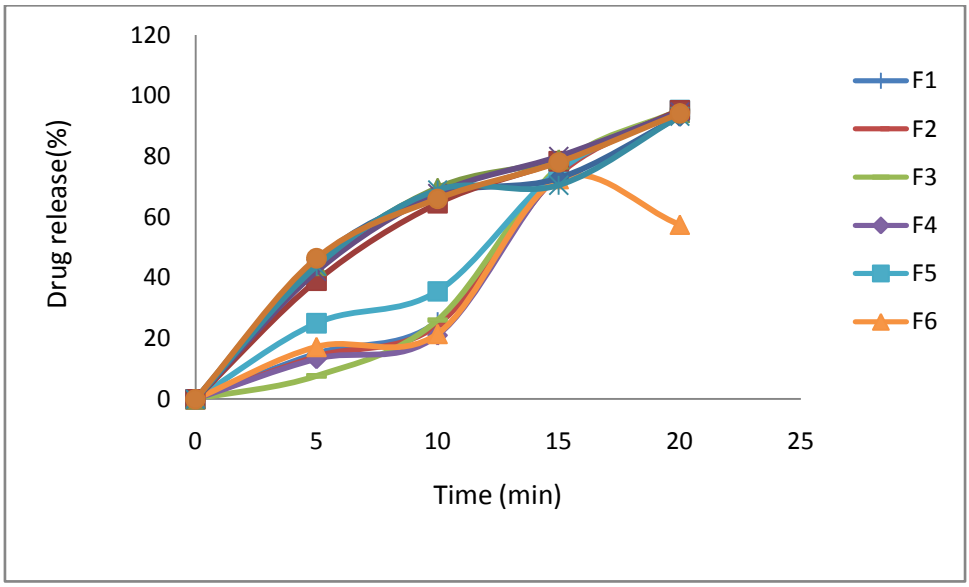

Fig. 1: *In vitro* drug release of F1-F6 formulated batches

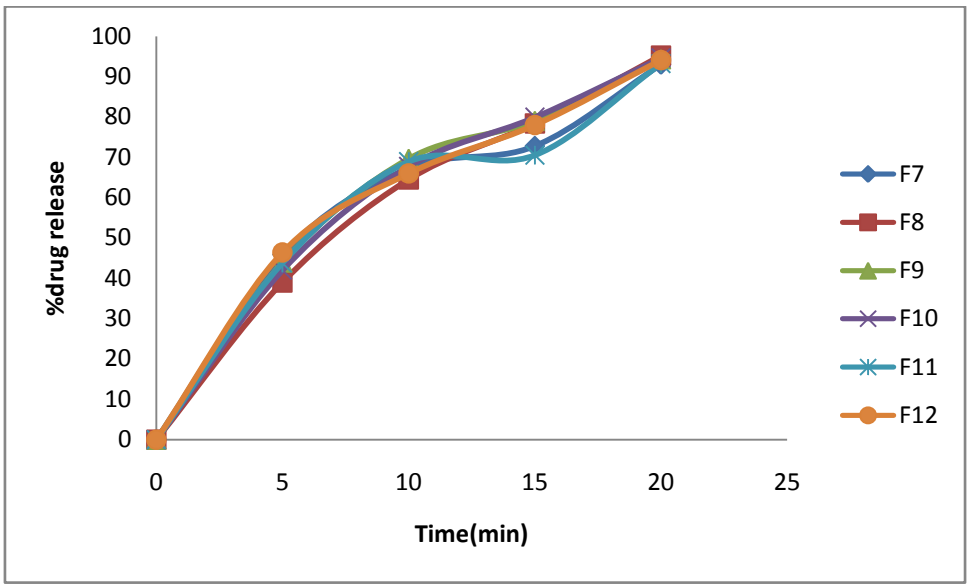

Fig. 2: *In vitro* drug release of F7-F12 formulated batches

***In vitro* drug release**

The results of the *in vitro* drug release study for the formulations F1-to F12 are shown in fig1&2. Drug release from the recipient medium was found to be decreased with an increase in the drug polymer ratio. Formulation F6 (without sodium chloride) and F7 (with sodium chloride) which was compared with a polymer ratio of 1:5, that was failed due to delayed release. Formulation F2, F3 and F4 shows slow release ranges from 40- 60 min. F5 with the sodium chloride release was found to be fast release 30 -45 min, which was satisfactory. The release of drug depends not only on the nature of spray but also upon the drug polymer ratio. Sodium chloride used as washing agent and isotonicity purpose. Buffered solution used as bioavailability enhancer polymer, which enhances the absorption of the drug in nasal mucosa. All the essential features of the formulation containing Metoclopramide hydrochloride as nasal spray make it good delivery in the nasal cavity. Formulation F5 was most satisfactory in all respects as compared to all other formulations. Drug release pattern F5 gave release in (30 min) faster than other formulations. Drug polymer ratio 1:4 best results for formulation F5 evidently proved.

CONCLUSION

Transnasal drug delivery system acclaims a novel approach to modulate both the rate and extent of drug input into systemic circulation. Metoclopramide hydrochloride was selected as a drug candidate for the present study; which was aimed to develop new

nasal mucoadhesive nasal solution using various mucoadhesive polymers and solubilizer. Both β-cyclodextrin and hydroxyl propyl β-cyclodextrin contained formulations showed a good release profile, in the ratio of 1:4. Hence β-cyclodextrin was found to be ideal mucoadhesive polymer for Metoclopramide hydrochloride. An important innovation in this research is the percentage of polymer in sodium chloride was found to be a transnasal permeation enhancer. PEG 800 and PVP are used as co-solubilizer which increased the solubility and reduced the solubility time. From the present study, it can be concluded that the nasal solution was found to be a good candidate for nasal administration. Intranasal drug delivery definitely reduces the dose size by minimizing first pass effect, thereby reduction in dose related side effects and sodium chloride was to be a good permeation enhancer for Metoclopramide hydrochloride nasal sprays.

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