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Formulation Development and Evaluation of Cinnarizine Nasal Spray

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ABSTRACT

The objective of the present study was to formulate and evaluate nasal delivery system contains cinnarizine 12 mg/ml. Cinnarizine loaded colloidal dispersions 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 bioadhesive strength. Therefore a nasal delivery system of Cinnarizine which was developed and formulated in this study is ideal for nasal administration for the treatment of antiemetic.

Keywords: Cinnarizine, Polymers, Nasal spray.

1. INTRODUCTION

Cinnarizine is a 1-(Diphenylmethyl)-4-(3-phenylprop-2-eny)l-piperazine [1]. Cinnarizine is a short acting drug for management of nausea and vomiting. Cinnarizine exerts its effects by inhibiting the calcium channel blocking activity for arterial smooth muscle. It acts as alabyrinthine sedative. It also improves microcirculation by reducing ischaemia induced blood viscosity. It have short biological half life of 3.1h. [2, 3].

The most commonly reported adverse events with cinnarizine are headache, constipation and diarrhea, which are mild to moderate in severity and rarely necessitate treatment withdrawal. Various polymers are

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used to improve bioavailability of the drug administered by nasal route. Improving nasal residential time, 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 states 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 possibility for peptide and proteinous endogenous compounds for therapeutic use [9, 10]. The greater permeability of nasal mucosa and low metabolic activity has potential to overcome limitation of oral route and duplicate the benefits of intravenous infusion [10, 11]. 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 [12]. However short nasal residential time and low permeability (drugs having molecular weight more than 1000 Daltons) of the drug retards the bioavailability of nasally administered drug [13].

Nasal delivery has been paying attention as an alternative dosage form. The advantages of administering drugs nasally 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 [14].

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 [15].

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

2. MATERIALS AND METHODS

Cinnarizine USP was obtained as a gift sample from Medopharm, Pvt. Ltd Chennai. β-CD and hydroxyl propyl β-cyclodextrin(HPβ-CD) were purchased from Signet chemicals, Mumbai. Other materials and excipients used in the preparation of colloidal dispersions were I.P grade. Acetonitrile, water and methanol used were of HPLC grade. All other ingredients used throughout the study were of analytical grade.

2.1 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 cinnarizine and spray dried (lyophilized) formulations were used to verify the chemical compatibility of cinnarizine with the excipients used in the formulation development. IR Spectrum was taken for identification which was 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 4000-400cm$^{-1.}$.

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

2.2 Preparation of colloidal dispersions

All the twelve batches, of the prepared formulations contained 12 mg of cinnarizine per ml. β-CD, HPβ-CD, microcrystaline cellouse (MCC) 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. 1.2g of the Cinnarizine, and 20 mg of EDTA were dissolved in the proposed ratio of solubilizer and sonicated for the period of 30 min with polyvinyl pyrolidine, 20min with polyethylene glycol in 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 with disodium hydrogen phosphate, phosphate buffer of pH 6.0 was prepared. 70 ml of drug solution was incorporated in a drop wise manner in 30 ml of polymeric dispersion and stirred gently using a magnetic stirrer. Throughout the formulation the temperature was maintained at 50^{0}C ± 0.5^{0}C. A clear transparent colloidal dispersion 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.

2.3 Evaluation of colloidal dispersions:

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

Table 1: Composition of colloidal dispersions

Ingredients(g)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cinnarizine	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Sodium chloride	-	-	-	0.9	0.9	-	0.9	-	0.9	-	0.9	0.9
β- CD	-	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
HPβ-CD	-	-	-	-	-	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

2.3.1 pH

The pH [16,17] of the nasal formulation is very important mainly to avoid irritation of the nasal mucosa, to prevent the growth of pathogenic micro organism and to sustain normal physiological ciliary movement. Lysozyme which is present in nasal secretion, that is responsible for destroying certain pathogenic micro organisms at acidic pH. Under alkaline pH, Lysozyme is deactivated and the nasal tissue is susceptible to microbial infection. It is therefore pH of the formulation was adjusted between 4.5-6.5 and pH of

the all prepared formulations was measured for pH using by digital pH meter.

2.3.2 Viscosity

Viscosity measurement of different polymeric dispersions (only for HPβ-CD, in phosphate buffer, pH 6.0 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.

2.3.3 Clarity test

The test was performed to find out whether the colloidal dispersion is free from the particulate matter or not. The dispersion 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 may increase with time, temperature and stress.

2.3.4 Sterility

The test for sterility was designed to reveal the presence of microorganisms in the colloidal dispersions. 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^{o}C for 24h, and another portion used for the detection of fungi at 23^{o}C for seven days.

2.3.5 Drug content

Content uniformity study is used to determine the drug content in the different formulations [18.] One ml of the colloidal dispersion (12mg) 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 HPLC mobile phase. Drug content estimation of cinnarizine was carried out by HPLC method and the chromatographic conditions are column-Lichrosphere, CN , 250×4.6mm, 5 µm, wavelength at 273 nm, flow rate at 1ml/min, injection volume is 20µl, run time 15 min, UV-detector and the mobile phase composition is HPLC grade water and acetonitrile in the proportion of 50:50 v/v. Comparing the content from the calibration curve prepared with standard cinnarizine in the same medium. The concentration of the drug present in the formulation was computed from the calibration curve.

2.3.6 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.

2.3.7 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 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 colloidal dispersion was placed on mucosal surface in the diffusion cell. At

predetermined intervals samples of 1.0 ml was withdrawn through the recipient chamber tube and replaced with buffer solution. The samples were diluted appropriately and the drug content was analyzed at 270 nm using HPLC [1]. The actual content in the different samples was read from the calibration curve prepared with standard cinnarizine.

2.3.8 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 the 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.

3. RESULTS AND DISCUSSION

3.1 Preformulation:

The active component cinnarizine 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 cinnarizine 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 used as a preservative and disodium EDTA used as antioxidant in all formulations.

Table 2: Characterizations of the colloidal dispersions

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
pH	6.0	5.9	6.1	5.9	6.0	6.0	6.2	6.1	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 (%)	94.0± 0.5	94.9± 0.2	97.0± 0.5	95.2± 0.1	98.2± 0.4	94.6± 0.2	93.0± 0.3	95.2± 0.1	94.3± 0.1	94.6± 0.2	93.2± 0.4	96.1± 0.6
BAS (g)	3.04± 0.06	3.17± 0.72	3.28± 0.86	3.07± 0.71	4.26± 0.80	3.03± 0.58	3.06± 0.65	3.89± 0.69	3.56± 1.25	3.45± 0.95	3.05± 0.44	3.37± 0.84

T:Transparent; S:Sterile; n=3; Vis: Viscosity(cps); BAS: *In vitro* bioadhesive strength.

3.2 pH:

To stabilize the Cinnarizine 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.

3.3 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 as an indication of the drug product integrity in all batches which was presented in table 2.

3.4 Sterility:

Sterility may have an influence on contamination, but as far as concerning cinnarizine, pKa value is 7.4 which is greater than pH of the formulation. All the formulations were found to be sterile from both detection of bacteria and fungi.

3.5 Drug content and viscosity:

Drug content was found to be uniform among all the different batches of the formulations are ranged from

95 ± 0.1% to 104.5 ± 0.2% (Table 2). The viscosity of the formulation is low hence the spraying from container have good spreadability of a solution within the nose. All the formulations were lies within the acceptable limitations (3-6 cps) which was presented in table 2.

3.6 Pump delivery and stability:

Weighed the content in 10 actuations was performed for F5, which is the optimized formulation found to be 0.914 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 spary

Formulation / Time(min)	Drug Release (%)			
	5	10	15	20
F1	25.0	25.5	78.0	99.0
F2	25.0	32.5	70.9	100.9
F3	30.61	56.0	66.5	92.0
F4	21.2	21.0	54.5	75.2
F5	26.0	45.5	78.2	99.2
F6	18.2	21.5	52.5	75.0
F7	44.9	67.3	69.8	73.0
F8	38.0	44.5	80.4	85.2
F9	40.8	59.6	79.0	90.3
F10	42.0	47.7	70.5	81.6
F11	40.8	88.9	76.0	92.2
F12	20.4	76.0	79.5	80.1

3.7 In vitro bioadhesive strength

The order of bioadhesieve force of the formulation was obtained as β-CD >HPβ-CD >MCC. Even though β-CD 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-CD was found to be an ideal mucoadhesive polymer for nasal drug delivery.

3.8 In vitro drug release:

The results of the *in vitro* drug release study for the formulations F1to F12 are shown in figure1&2 respectively. 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 20-30 min. F5 with the sodium chloride release was found to be fast release 10-15 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 cinnarizine 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 of F5 gave release within 15 min which is faster than other formulations. Drug polymer ratio 1:4 shows best results for formulation F5 evidently proved.

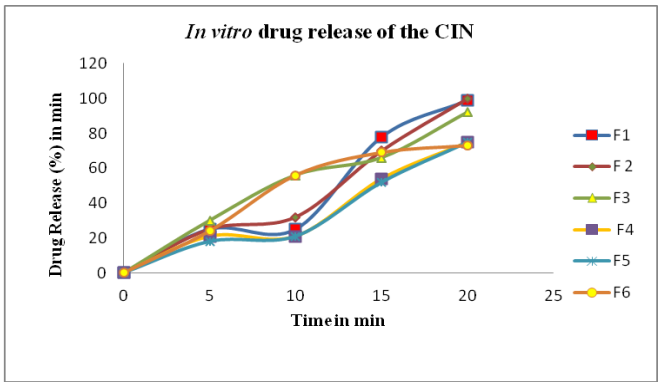

Fig. 1: *In vitro* drug release of F1-F6 formulated batches

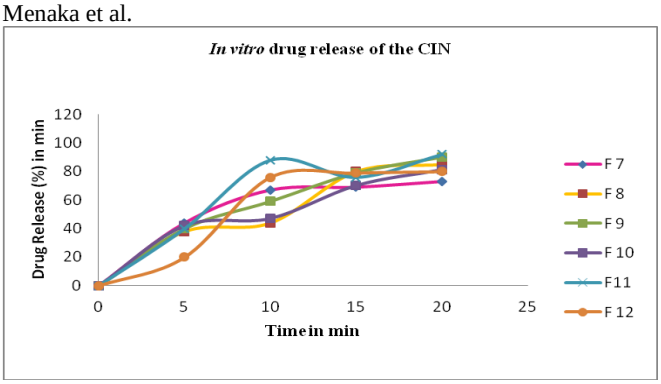

Fig. 2: *In vitro* drug release of F7-F12 formulated batches

4. CONCLUSION

Transnasal drug delivery system acclaims a novel approach to modulate both the rate and extent of drug input into systemic circulation. Cinnarizine was selected as a drug candidate for the present study; which was aimed to develop new nasal mucoadhesive colloidal dispersion using various mucoadhesive polymers and solubilizer. Both β-CD and HPβ-CD contained formulations showed a good release profile, in the ratio of 1:4. Hence β-CD was found to be ideal mucoadhesive polymer for cinnarizine. 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 colloidal dispersion 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 cinnarizine nasal sprays.

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