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PREPARATION AND EVALUATION OF TASTE MASKING COMPLEX OF CIPROFLOXACIN HYDROCHLORIDE BY USING INCLUSION COMPLEXATION APPROACH

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ABSTRACT

Administration of an oral drug delivery system having bitter taste and acceptable level of palatability has always been challenge in developing a formulation for pediatric and geriatric purpose. The present study evaluates the possibility of inclusion Complexation of Ciprofloxacin HCl with β-Cyclodextrin as an approach for taste masking. Improvement in taste masking capability of β-cyclodextrin towards Ciprofloxacin HCl was evaluated by formulating a complex. Complex was prepared using kneading method and was further characterized by DSC and FT-IR study. *In-vitro* dissolution study was carried out to investigate the effect of inclusion complexation on drug release. Taste perception study was carried out on human volunteers to evaluate the taste masking ability of inclusion complexation. Kneading complex showed effective taste masking and at the same time showed no limiting effect on the drug release. The effective taste masking was attributed to the enhanced complexation of ciprofloxacin HCl in kneading complex and the same was confirmed from the characterization studies. In conclusion, the study succeeded in inclusion complexation's utilization as an alternative approach for effective taste masking.

KEY WORDS- β-cyclodextrin, Inclusion Complexation, Ciprofloxacin HCl, Taste Masking.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms.

Administration of an oral drug delivery system having bitter taste and acceptable level of palatability has always been challenge in developing a formulation for pediatric and geriatric purpose. The bitterness of drug or drug product is minimized or eliminated by various physical, chemical and physiological means such as use of flavors, sweeteners, amino acids and by using various techniques such as lipophilic vehicles, coating, inclusion complexation, ion exchange, effervescent agents, rheological modification, solid dispersion system, group alteration and prodrug approach, freeze drying process, wet spherical agglomeration technique and continuous multipurpose melt technology (1).

Taste is the ability to respond to dissolved molecules and ions "gatekeeper to the body". Human detects taste with taste receptor cells that are clustered in to onion-shaped organs called taste buds. Each taste bud has a pore that opens out to surface of the tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside (2). Human have around 10,000 taste buds which appear in fetus at about three months. A single taste bud contains 50-100 taste cells. Each taste cells receptors on its apical surface. These are transmembrane proteins which bind to the molecules and ions that give rise to the four primary taste sensations namely: salty, sour, sweet and bitter. Recently, a fifth basic taste umami has been discovered. The umami is the taste of certain amino acids (e.g. monosodium glutamate). There is often correlation between the chemical structure of a compound and its taste. Low molecular weight salts tend to taste salty where as high molecular weight salts tend toward bitterness. Nitrogen containing compounds, such as alkaloids, tend to be quite bitter. Organic compounds containing hydroxyl groups tend to become increasingly sweet as number of OH group increase (3). Accordingly, it is important to mask the unpalatable taste of a drug in order to improve the product quality. This will also increase the value of the finished product as well as patient compliance, especially where infants, children and elderly are concerned (4).

Recently, a number of novel techniques for bitterness inhibition in pediatric and geriatric formulations have been attempted. Addition of flavouring and sweetening agents is the foremost and the simplest approach for taste masking, especially in the case of pediatric

formulations, chewable tablets, and liquid formulations (5,6). Microencapsulation as a process has been defined by Bakan(7) as a means of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion.

Ion exchange resins are water insoluble, cross-linked polymers containing salt forming groups in repeating position on the polymer chain. The exchange of counter ions from resin is competitive. Most of the bitter drugs have amine as a functional group, which is the cause of their obnoxious taste. If the functional groups are blocked by complex formation the bitterness of the drug reduces drastically (8-10). Granulation is a common processing step in the production of tablet dosage form. This step can be exploited as a mean for taste masking of slightly bitter tasting drug (11,12). Adsorbate of bitter tasting drug can be considered as the less saliva soluble versions of these drugs. Adsorption involves preparing a solution of the drug and mixing it with an insoluble powder that will absorb the drug, removing the solvent, drying the resultant powder, and then using these dried adsorbates in the preparation of the final dosage form. A prodrug is chemically modified inert drug precursor which upon biotransformation liberates the pharmaceutically active parent compound (13,14). The development of a specific universal inhibitor for bitter taste has been widely required in the fields of taste physiology and pharmaceutical sciences, but no such inhibitors has been available. Sodium salts such as sodium chloride, sodium acetate, sodium gluconate have been shown to be potent inhibitors of some bitter compounds (15,16). A novel technique for taste masking of drugs employing multiple emulsions has been prepared by dissolving drug in the inner aqueous phase of w/o/w emulsion under conditions of good shelf stability (17). Water insoluble gelation on the surface of tablet containing bitter drug can be used for taste masking (18). Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agents for dosage forms that are not dissolved in water prior to administration (19,20). Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds (21,22). The bitter taste of a substance disappears in the presence of β-Cyclodextrin only, when the drug molecule which causes the bitter taste is complexed by an appropriate β-Cyclodextrin molecule (23). Beside this not only the drugs are ‘‘masked’’ from the receptors by inclusion in the CD cavity, but also increased hydrophilicity enables the easier removal of the bitter substance from the receptor surface as well (24). The Objective of present study was to mask the bitter taste of ciprofloxacin HCl by using β-Cyclodextrin.

MATERIAL AND METHODS

Ciprofloxacin HCl (Ranbaxy labs. Gurgaon, India), β-Cyclodextrin (S.A. Pharmachem. Mumbai, India) were received as gift samples.

Methods

Determination of Threshold Bitterness of Ciprofloxacin HCl (25-26)

A panel of six healthy human volunteers (age 20–25) was selected. A series of solutions of Ciprofloxacin HCl in distilled water of concentrations 10, 20, 30, 40, and 50, 60 µg/ml was prepared. The volunteers were asked to hold 10 ml of each solution in oral cavity for 30 s and rate the taste on a scale from 0 to 3+. A numerical scale was used shown in Table No. 1.

Random sampling was carried out for the validation of above scale. The oral cavity was rinsed with distilled water twice to avoid bias. Time interval between testing different samples was 10 min.Based on the opinion of the volunteers, threshold bitterness concentration of Ciprofloxacin HCl was studied.

Preparation of Ciprofloxacin HCl and β-Cyclodextrin Inclusion Complexes

Inclusion complexes were prepared by physical mixture method and by kneading complex method in the sequential w/w ratios of 1:0.5, 1:1, 1:1.5, 1:2, 1:2.5, 1:3. Kneading Complex was prepared by using the physical mixture of Ciprofloxacin HCl and β-Cyclodextrin and it was then triturated in a mortar with a small volume of distilled water. The thick slurry was kneaded until mild dryness (~40 minutes). The dried mass was then pulverized and sieved through # 44.

Characterization of Prepared Complexes

***In-vitro* taste evaluation**

Inclusion complexes containing about 100 mg Ciprofloxacin HCl were put into a test tube containing 10 ml distilled water. The mixture was immediately vibrated for 15 seconds and then filtered. The clear solution was analyzed in a spectrophotometer (Systronics UV Visible spectrophotometer 2201) at 272 nm to determine the concentration of drug in water after the appropriate dilutions, which was then compared with the threshold value. The calibration curve between absorbance (A) and concentration (C) was, $A = 0.109C - 0.0068$ ($r^2 = 0.9996$, $n = 5$) which was used for the determination of concentration drug.

In-vivo taste evaluation

In-vivo taste evaluation was carried out by panel of human volunteers. Six healthy human volunteers, of either sex, in the age group of 20–25 years were selected for study. Inclusion complexes equivalent to 100 mg of Ciprofloxacin HCl was dispersed in 10 ml of water for 15 seconds. Immediately after preparation, each volunteer held about 1 ml of the dispersion in the mouth for 30 seconds. After expectoration, bitterness level was recorded. A numerical scale was used with the values mentioned in Table 1. Random sampling was carried for the validation of above scale. The oral cavity was rinsed with distilled water twice to avoid bias. Time interval between testing different samples was 10 min.

Characterization of complexes

Fourier Transformed Infra-red Spectroscopy (FT-IR)

FT-IR transmission spectra were obtained using Shimadzu 8400, Japan. Fourier transform infrared spectrophotometer. The IR spectrum of pure drug with β-Cyclodextrin and its kneading complex were recorded in the stretching frequency range 500-4500 cm^{-1}. The samples were prepared by KBr press pellet technique.

Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure drug, β-Cyclodextrin and its kneading complex were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C per minute over a temperature range of 60°C to 300°C.

In-vitro Dissolution Study

A quantity of physical mixture and kneaded complex equivalent to 100 mg Ciprofloxacin HCl was subjected to dissolution studies at 37±5°C using USP type II apparatus at 100 rpm speed. The drug release study was carried out in hydrochloric pH 1.2 and pH 6.8. Complexes containing equivalent to 100 mg of Ciprofloxacin HCl were suspended in 900 ml of the buffer solution and 10 ml sample was withdrawn at 10, 20, 30, 45, 50 and 60 min and analyzed using UV spectrophotometer (Systronics UV visible spectrophotometer 2201). Each sample was replaced with fresh buffer solution.

RESULT AND DISCUSSION

Determination of Threshold Bitterness

Most of the volunteers reported as 60 µg/ml as the threshold bitterness concentration for Ciprofloxacin HCl

Table No. 1: Numerical Scale for Determination of Threshold Bitterness

Rating	Description
0	Tasteless
0.5	Very slightly bitter
1	Slightly bitter
1.5	Slight to moderate bitter
2	Moderately bitter
2.5	Moderate to strong bitter
3	Strongly bitter
3+	Very strong

Table No. 2: *In-vitro* Taste Evaluation

Formulation	Drug Release after 50 Min. (%)	
	pH 1.2	pH 6.8
Pure drug	96.23	95.58
Physical Mixture	86.22	87.89
Kneading Complex	81.54	82.45

Table No. 3. *In-vivo* taste evaluation

Sr. No.	Drug: β-CD Ratio	Drug Concentration (µg/ml)	
		Physical Mixture	Kneading Complex
1	1:0.5	43.55 ± 0.074	41.67 ± 0.074
2	1:1	42.93 ± 0.070	46.62 ± 0.043
3	1:1.5	41.13 ± 0.076	47.00 ± 0.025
4	1:2	35.91 ± 0.072	42.80 ± 0.036
5	1:2.5	40.79 ± 0.072	45.48 ± 0.056
6	1:3	41.38 ± 0.073	35.97 ± 0.069

Table No. 4: In-vitro Drug Release from Inclusion Complexes

Numerical scale	Pure Drug	Kneading Complex					
		1:0.5	1:1	1:1.5	1:2	1:2.5	1:3
0	-	-	-	-	-	-	5
0.5	-	-	-	-	1	4	1
1	-	-	2	3	4	2	-
1.5	-	2	4	3	1	-	-
2	-	3	-	-	1	-	-
2.5	-	1	-	-	-	-	-
3	1	-	-	-	-	-	-
3+	5	-	-	-	-	-	-

Table No. 5: Thermal Transition and Enthalpy Values of Ciprofloxacin HCl, β-Cyclodextrin and its Kneading Mixtures

Sr. No.	Chemical	DSC Thermal Transition (°C)	Enthalpy (J/g)
1.	Ciprofloxacin HCl		
2.	β-Cyclodextrin	120	(-)148.22
3.	Kneading Complex		

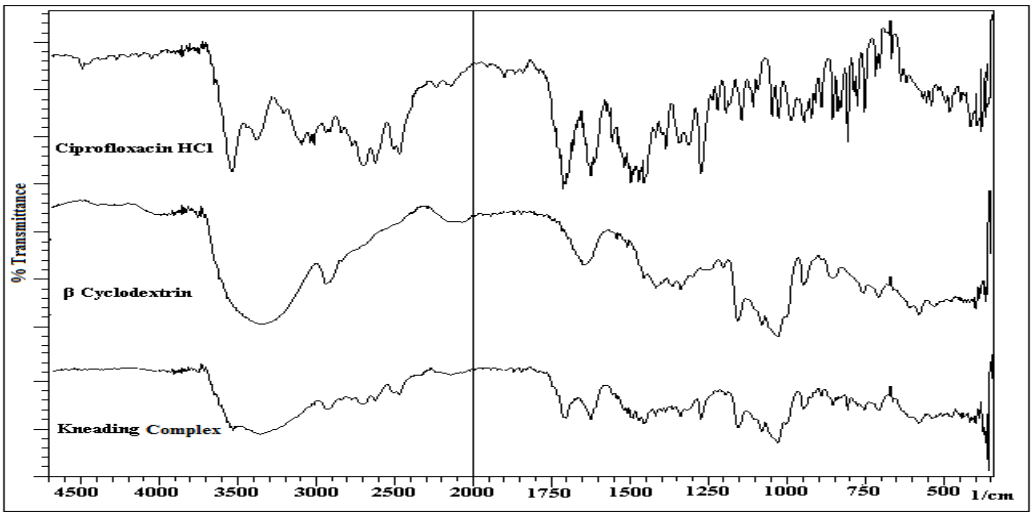

Figure No. 1: Fourier Transform Infrared (FT-IR) Studies

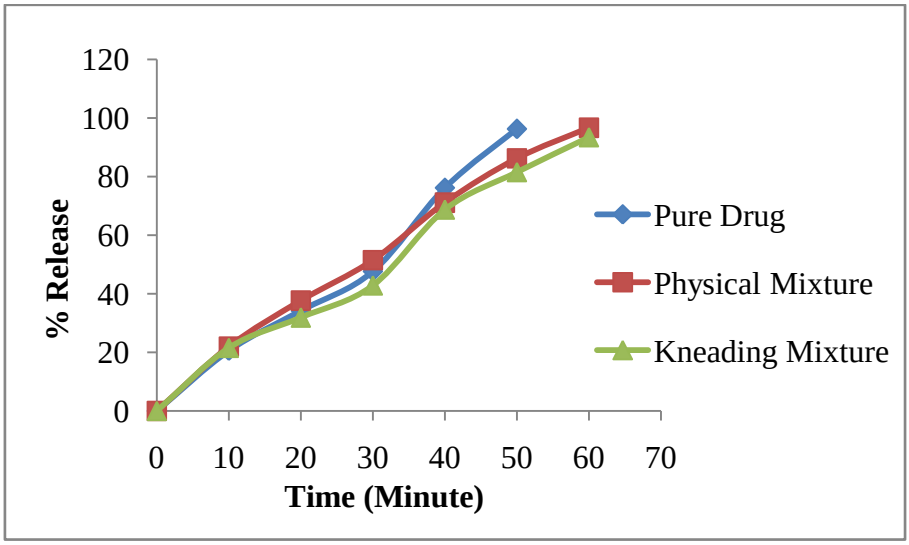

Figure No. 2. In-vitro Dissolution Studies in pH 1.2

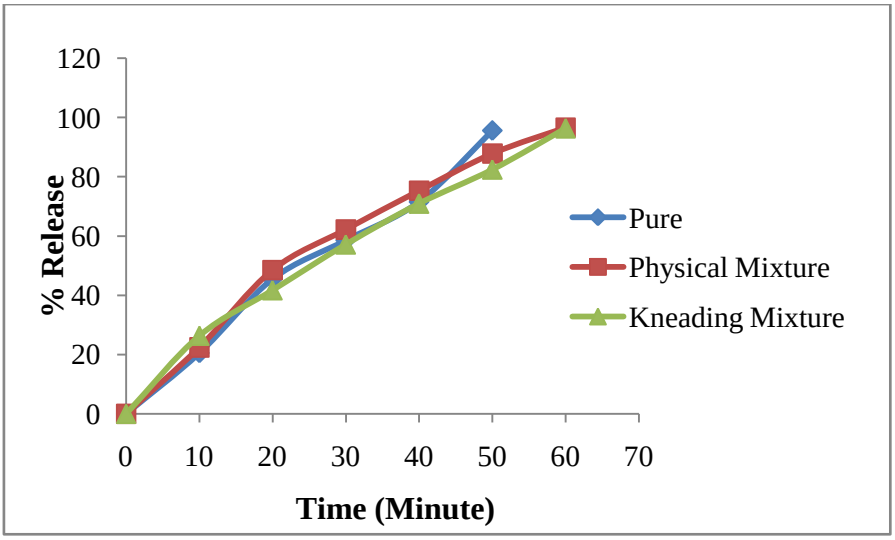

Figure No. 3: In-vitro Dissolution Studies in pH 6.8

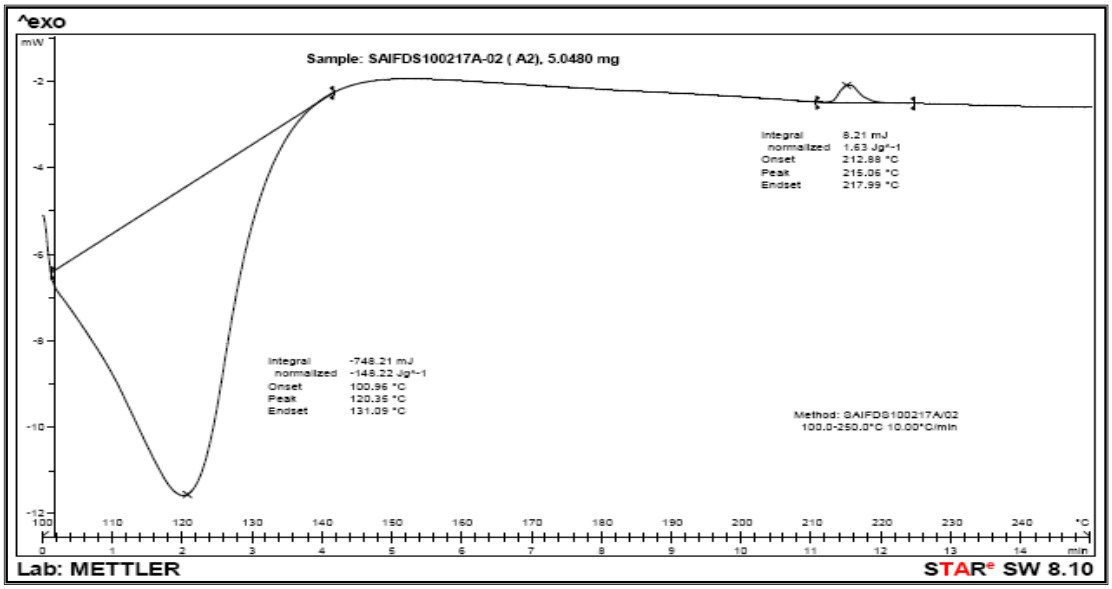

Figure No. 5: DSC Thermogram of Kneading Mixture β-Cyclodextrin

Characterization of Prepared Complexes

In-vitro taste evaluation

Drug concentrations of physical mixture and kneading complex were determined spectrophotometrically and were compared with the threshold bitterness and it was found to be below the threshold value of bitterness as shown in Table No. 2.

In-vivo taste evaluation

From the results shown in Table No. 3., kneading complex of Ciprofloxacin HCl and β-Cyclodextrin in the ratio 1:3 was reported as tasteless on numerical scale as compared to other ratio.

Fourier Transform Infrared (FT-IR) Studies

IR spectroscopy can be used as a useful tool to characterize complex formation. FT-IR spectra of the samples are illustrated in Figure No. 1. As seen from the spectra of Ciprofloxacin HCl, C-F stretching occur at 1143.79 cm^{-1}, δO-H bending occur at 1273.02 cm^{-1}, characteristic N-H bending occur at 1614.42 cm^{-1}, C=O stretching occur at 1712.79 cm^{-1}, O-H stretching occur at 2910.58 cm^{-1} and O-H stretching (Intermolecular H Bonded) occur at 3525.88 cm^{-1}. In IR spectra of β-Cyclodextrin, C-O-C stretching occurs at 1155.36 cm^{-1}, C-H stretching occurs at 2912.51 cm^{-1} and O-H stretching occur at 3288.63. The ratio of physical mixture and kneading complex of Ciprofloxacin HCl, β-Cyclodextrin were used for IR spectra and from the graph of IR spectra some peaks of β-Cyclodextrin overlap the peaks of Ciprofloxacin HCl.

Differential Scanning Calorimetry (DSC)

The DSC thermo grams of Ciprofloxacin HCl, β-Cyclodextrin and kneading complex are shown in Figure No. 4-6. Thermal transition and enthalpy values of Ciprofloxacin HCl, β-Cyclodextrin and kneading complex was shown in Table No. 5.

In-vitro Dissolution Study

Results of in-vitro drug release were as shown in Table No. 4. and graph showing drug release were shown in Figure No. 2 and 3.

CONCLUSION

Inclusion complex prepared by using kneading complex method showed effective taste masking and at the same time showed no limiting effect on the drug release. The effective taste masking of Ciprofloxacin HCl in kneading complex was confirmed from the characterization studies. The study succeeded in inclusion complexation's utilization as an alternative approach for effective taste masking.

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