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FORMULATION AND EVALUATION OF TASTE MASKED ORAL RECONSTITUTABLE SUSPENSION OF FLUROQUINOLONE ANTIBIOTICS

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Abstract. The purpose of this research was to mask the intensely bitter taste of fluroquinolone antibiotics and to formulate suspension powder (cachets) of the taste masked drug. Taste masking was done using beta-cyclodextrin. To characterize and formulate taste masked cachets of ciprofloxacin, the 1:25 M physical mixture was selected based on bitterness score. Phase solubility studies, fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRPD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Cachets were evaluated for angle of repose, sedimentation characterization and pH. In vitro drug release studies for physical mixture and kneaded system were performed at pH, 1.2 and 6.8. Bitterness score was evaluated using gustatory sensation test. Phase solubility studies showed weak interaction between CIPRO and CD. The FTIR, DSC and XRPD studies indicated inclusion complexation in physical mixture and kneaded system. In addition, kneaded system and physical mixture exhibited better drug release at pH 1.2 and negligible effect at pH 6.8. Cachets prepared using physical mixture, (DS24), showed complete bitter taste masking and easy redispersibility. Taste evaluation of cachets in human volunteers rated tasteless with a score of 0 to DS24 and 3 to DS25. Thus, results conclusively demonstrated successful taste masking and formulation of cachets with taste masked drug.

KEY-WORDS: Cachets; Cyclodextrin; Fluroquinolone Antibiotics; Taste Masking.

INTRODUCTION

Fluroquinolone antibiotics an antibacterial drug that has an extremely unpleasant bitter taste. It has been reported that they depolarize taste cells by closing K^+ channels and produce bitterness (2).

Palatable formulation development is one of the most difficult tasks, although various taste masking techniques such as the addition of sweeteners and flavors (3), coating with polymers (4), adsorption to ion-exchange resin (5,6), and chemical modifications such as the use of insoluble pro-drugs (7,8) have been reported. Each technique has its own disadvantages. Addition of sweeteners and flavors is not very successful for extremely bitter drugs. Ion-exchange resins are functional group specific (amino group) and sometimes cause delayed drug release while coating with polymer requires sophisticated instruments. Chemical modification may alter the therapeutic activity of drug substance.

Reduction of bad tastes by beta-cyclodextrin (CD) is a long known method (9, 10). The first such observation was already described in 1953 in the very first drug/CD patent by Freudenberg et al. The bad taste of bromoisovaleryl urea was masked by CD complexation (10). The CD itself cannot be considered as a tasteless or only slightly sweet substance, although its taste threshold value is lower than that of sucrose (detection, 0.03 and 0.27%; recognition, 0.11 and 0.52%, respectively). A 0.5% CD solution was as sweet as sucrose and a 2.5% solution as sweet as a 1.71% solution of sucrose (11). Sucrose and beta-CD showed an additive effect on sweetness. The cavity of CD is occupied by water molecules (about 13–14% w/w) both in crystalline state as well as in aqueous solution. Roughly half of this water is so-called ‘crystal water’ and the other half is ‘inclusion water’. The ‘crystal water’ is located and bound between the adjacent CD molecules, while ‘inclusion water’ is included into the hydrophobic cavity of CD. Hydrophobic drugs form complex by replacing ‘inclusion water’ while easily migrating (hydrophilic, well soluble) drugs form complex, assuming replacement of ‘crystal water’ (12). CD is the ‘host’ molecule and an important component of the ‘driving force’ for the inclusion complex formation is the substitution of high enthalpy water molecules by the ‘guest’ molecules. As the guest molecule is included into the CD molecule, which is enwrapped into a hydrate shell, the interaction of the guest molecule with cell membranes and receptors is considerably inhibited, resulting in reduced cytotoxicity or reduced taste (12).

There are two theoretical possibilities (a) the CD enwraps the bad tasting molecule (=inclusion complexation), impeding its interaction with the taste buds or (b) the CD interacts with the gate-keeper proteins of the taste buds, paralyzing them. All taste sensation (sweet, salt, sour, bitter) would be extinguished, as long as the adhered CDs are not removed from the taste buds.

The bitter taste of a substance disappears in the presence of CD, only when the drug molecule which causes the bitter taste is complexed by an appropriate CD molecule. These complex molecules are strongly hydrated on their outer surface; therefore, they don't get attached to the taste-bud receptors on the tongue in oral cavity (12).

The objective of the present work is to study the effect of cyclodextrin for its bitterness masking ability for hydrophilic drug, ciprofloxacin. ciprofloxacin was studied for the cyclodextrin complexation and evaluated for bitterness score. The complexed drug increased the bulk for preparing taste masked rapid disintegrating tablets (RDTs). To avoid this problem single dose of suspension powder (cachets) were prepared.

MATERIALS AND METHODS

Materials

Fluroquinolone antibiotics (CIPRO) and beta-cyclodextrin (CD) were kindly gifted by Ajanta Pharma Ltd., Mumbai. Methanol, hydrochloric acid, potassium chloride, potassium dihydrogen phosphate, sodium hydroxide of analytical grade was purchased from S.D. Fine Chem Ltd. All reagents and solvents used in the study were of analytical grade.

Preparation of Solid Binary Systems

The following binary systems of CIPRO and CD were prepared in 1:1, 1:5, 1:10, 1:15, 1:20 and 1:25 molar ratios.

Physical mixtures (PM)

The physical mixture of CIPRO and CD was obtained by mixing individual components geometrically, that had previously been sieved through sieve no. 44, together with a spatula.

Kneaded system (KS)

The physical mixture of CIPRO and CD was triturated in a mortar with a small volume of water-methanol (1:1% v/v) solution. The thick slurry was kneaded for 15 min and then dried until dryness. The dried mass was pulverized and sieved through sieve no. 44. Wetting agent (water: methanol, 1:1% v/v) was used mainly to achieve better interaction of CIPRO with CD during kneading process.

Solubility Determination

The solubility study was carried out according to the method of Higuchi and Conner (13). An excess of CIPRO was added to screw-capped vials containing CD solution (2 to 14 mM concentration range), in distilled water. Vials were shaken mechanically at 28±0.5°C for 24 h. At equilibrium after 2 days, aliquots were withdrawn, filtered (0.22 µm pore size) and UV spectrophotometrically (Shimadzu UV visible spectrophotometer 1601) assayed for drug content at 259 nm. The apparent stability constant (K1:1) was calculated from the phase-solubility diagram (14), using the following equation:

$$K_{1:1} = \frac{\text{Slope}}{S_0(1 - \text{Slope})} \qquad (1)$$

Where S0 is the intrinsic solubility of CIPRO in the absence of CD and the slope refers to the gradient of the plot of CIPRO solubility (mM) vs. CD concentration (mM).

Fourier Transform Infra-red Spectroscopy (FTIR)

FTIR transmission spectra were obtained using a Fourier Transform Infrared spectrophotometer (FTIR-8300, Shimadzu, Japan). Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 500 to 4,000 cm^{-1} and the resolution was 4 cm^{-1}. The characteristic peaks were recorded.

Differential Scanning Calorimeter (DSC)

Differential scanning calorimetry study was performed using Differential Scanning Calorimeter (Mettler Toledo, DSC 822). Samples were heated in an open aluminum pans at a rate of 5°C per min^{-1} under a nitrogen flow of 40 mL/min.

X-ray Powder Diffractometry (XRPD)

X-ray powder diffraction patterns were recorded on a X- ray diffractometer (Philips X'Pert MPD, Eindhoven, The Netherlands) using Ni-filtered, CuKα radiation, a voltage of 40 kV, and a

25-mA current. The scanning rate employed was 1° min^{-1} over the 10 to 30° diffraction angle (2θ) range.

In Vitro Drug Release

In vitro drug release study of physical mixture and kneaded system was performed by powder dispersion method at 37±0.5°C, using six-station USP XXII apparatus (TDT-50, Electrolab, Mumbai, India) with paddle rotating at 50 rpm. The drug release study was carried out in phosphate buffer, pH 6.8 because the pH of the saliva is in the range from 6.3 to 7.2. Further the drug release study was performed in hydrochloric acid buffer, pH 1.2 to demonstrate the availability of CIPRO in gastric pH. Complexes containing equivalent of 13.12 mg of CIPRO were suspended in 500 mL of the buffer solution, and 2 mL sample was withdrawn at 1, 5, 10, 15, 30 and 60 min and analyzed using UV spectrophotometer (Shimadzu UV visible spectrophotometer 1601). Each sample was replaced with fresh buffer solution having the same temperature.

Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time 't' (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (15).

Gustatory Sensation Test

Gustatory sensation test was carried out according to the method described by Mouying et al (16). Twenty healthy human volunteers, of either sex, in the age group of 23– 27 years were selected based on quinine taste sensitivity test. The non-taster and super tasters were rejected. Binary systems equivalent to 1 g of CIPRO was dispersed in 100 ml of water for 15 s. For comparison pure CIPRO was subjected to taste evaluation by the panel. Immediately after preparation, each volunteer held about 1 ml of the dispersion in the mouth for 30 s. After expectoration, bitterness level was recorded. A numerical scale was used with the following values: 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. This numerical scale was validated by testing samples randomly. The oral cavity was rinsed with distilled water three times to avoid bias. Wash out period between testing different samples was 15 min.

Preparation and Evaluation of the Dry Suspension

The physical mixture equivalent to 13.12 mg of CIPRO was very high to formulate a rapid disintegrating tablet (RDT). Hence dry suspension powder containing equivalent of 13.12 mg of CIPRO (equivalent to 7.5 mg primaquine base) was prepared from CIPRO and physical mixture. Sodium carboxy methyl cellulose (HVP) was used as suspending agents. Citric acid monohydrate was used as pH modifier.

The following procedure was applied to prepare a suspension powder. The smallest amount of physical mixture was mixed with the same amount of another excipient, following the principle of the geometric dilution.

To prepare the reconstituted suspension, an appropriate 10 mL of water was added to the suspension powder (cachet) and stirred with spoon until a homogeneous product was obtained.

Angle of Repose

For measurement of angle of repose of suspension powder, they were passed through a funnel on the horizontal surface. The height (h) of the heap formed was measured with a cathetometer and the radius (r) of the cone base was also determined. The angle of repose (Φ) was calculated from following equation:

$$\phi = \tan^{-1}\left(\frac{h}{r}\right) \qquad (2)$$

Sedimentation Characteristics

To study the sedimentation in suspension, the sedimentation volume was determined as a function of time.

The sedimentation volume, F is defined as the ratio of the final, equilibrium volume of the sediment, Vu to the total volume V_o before settling, as expressed in the following equation:

$$F = \left(\frac{\mathrm{Vu}}{\mathrm{Vo}}\right) \qquad (3)$$

In this study, the sedimentation volume was determined as a function of time. 10 mL suspension (height=12 cm) was decanted in a cylinder of 10 mL with a diameter of 1.5 cm. After 1 h, the sedimentation volume F was determined.

RESULTS AND DISCUSSION

Phase Solubility Studies

The phase solubility diagram of CIPRO in CD is constructed by plotting CIPRO solubility (mM) against the concentration of CD (mM). As it appears in Fig. 1, CD has increase in aqueous solubility of CIPRO, suggesting the formation of inclusion complexes of the AL− type following Higuchi and Conner's classification (13). The stability constant value calculated was 42 M^{-1}, which is within a range from 10 to 1,000 M^{-1}, considered as ideal. The smaller K1:1- value indicates weak interaction. In addition, this confirms that the hydrophilic drugs like CIPRO forms a complex, replacing 'crystal water', located and bound between the adjacent CD molecules (12). This may be the reason why more amount of CD required for complete complexation and thus for masking the bitter taste of CIPRO.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed to detect the possible molecular interaction between CIPRO and CD. The FTIR spectrum of CIPRO, CD, physical mixture and kneaded system in 1:25 M are shown in Fig. 2. The characteristic peaks of CIPRO at 2,968 and 2,878 cm^{-1} were assigned to C–H stretch- ing vibration in CH3, CH2. In addition, the absorption peak at 2,844 cm−1 was assigned to C–H stretching vibration in C–O– CH3. The peak at 1,119 cm−1 was assigned to C–O stretching vibration in C–O–C. The peak at 3,305 cm−1 was assigned to N–H stretching in primary amines. The FTIR spectrum of physical mixture and kneaded system corresponds to the CD, with no major peaks corresponding to CIPRO. This suggests formation of inclusion complexation between the CD and CIPRO in physical mixture and kneaded system.

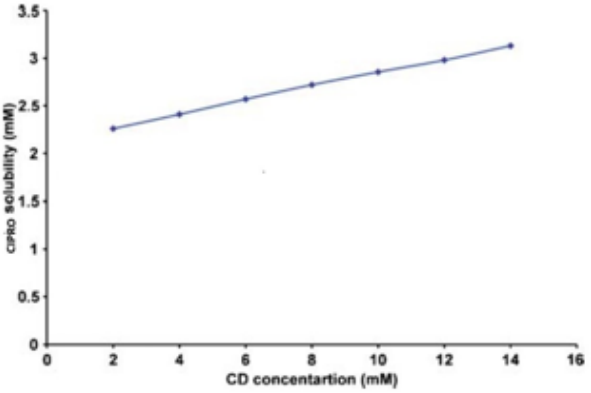

Fig. 1. Phase-solubility diagram for the CIPRO-CD system

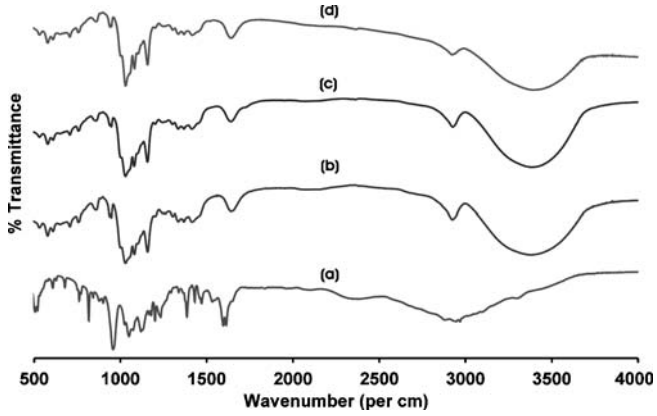

Fig. 2. FTIR spectra of a CIPRO, b CD, c physical mixture and d kneaded system

Differential Scanning Calorimetry (DSC)

Figure 3 shows the DSC curves of CIPRO, CD, physical mixture and kneaded system in 1:25 M. The pure CIPRO showed a sharp endothermic peak at 202.68°C. The curve of CD displayed a wide and strong endothermic effect in the 100–130°C interval (peak T_{max}=121.03°C), which may be ascribed to dehydration (17). Moreover, the melting peak of the CD was T_{max}=319.66°C.

The characteristic endothermic peak corresponding to melting peak of CIPRO in was broaden and shifted towards higher temperature, with reduced intensity in physical mixture (267.35°C) and kneaded system (276.77°C). It has been reported that the formation of inclusion complexes is indicated by the disappearance or shift of the endothermic peaks corresponding to the drug melting process (18). Hence this shifting of endothermic peak confirms formation of inclusion complex between the CD and CIPRO in physical mixture and kneaded system.

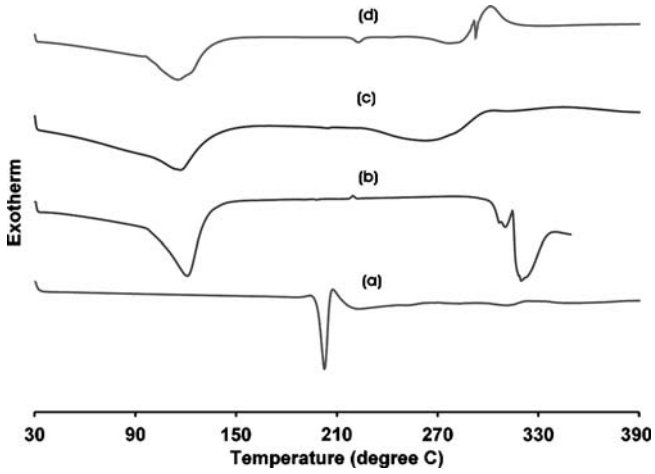

Fig. 3. DSC curve of a CIPRO, b CD, c physical mixture and d kneaded system

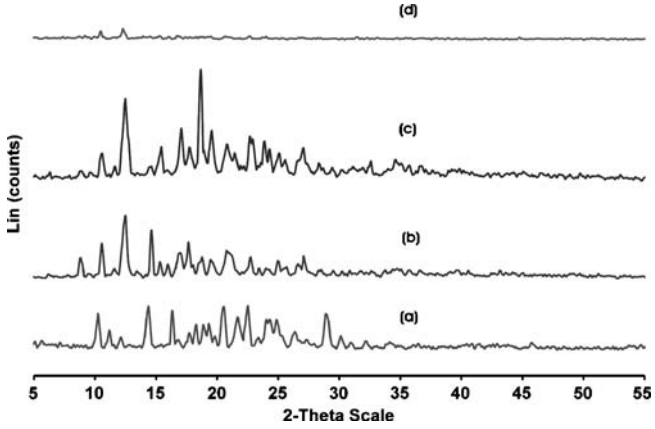

Fig. 4. XRPD pattern of a CIPRO, b CD, c physical mixture and d kneaded system

X-ray Powder Diffractometry (XRPD)

XRPD analysis was performed to confirm the results of DSC studies. XRPD patterns of CIPRO, CD, physical mixture and kneaded system in 1:25 M are shown in Fig. 4. In X-ray diffractogram of CIPRO, sharp peaks at a diffraction angle (2θ) of 10.26°, 11.26°, 12.13°, 14.35°, 16.34°,

17.74°, 18.26°, 18.83°,19.32°, 19.32°, 20.54°, 21.69°, 22.51°, 23.46°, 24.34°, 24.87°,26.37° 28.93°, 30.12° and 32.15° indicates the presence of crystalline drug. The diffractograms of CD showed peaks at a diffraction angle (2θ) of 10.58°, 12.39°, 14.61°, 15.33°, 15.98°,17.07°, 17.63°, 18.85°, 19.65°, 20.93° 22.76°, 24.16°, 25.07°,25.76°, 26.86°, 27.07°, 28.61° and 32.15°.

The diffractograms of kneaded system, differed from those of CIPRO and CD, where the characteristic peaks of CIPRO disappeared, indicating the formation of inclusion complex in these systems. Also, the diffractograms of physical system differed from those of CIPRO and CD where the peaks at 15.44° and 17.78° were appeared with reduced intensity while the peaks at 16.99°, 18.66° and 19.49° were appeared with increased intensity. In addition, the new peaks at a diffraction angle (2θ) of 9.06°, 9.77°, 23.87°, 29.49°, 30.38°,

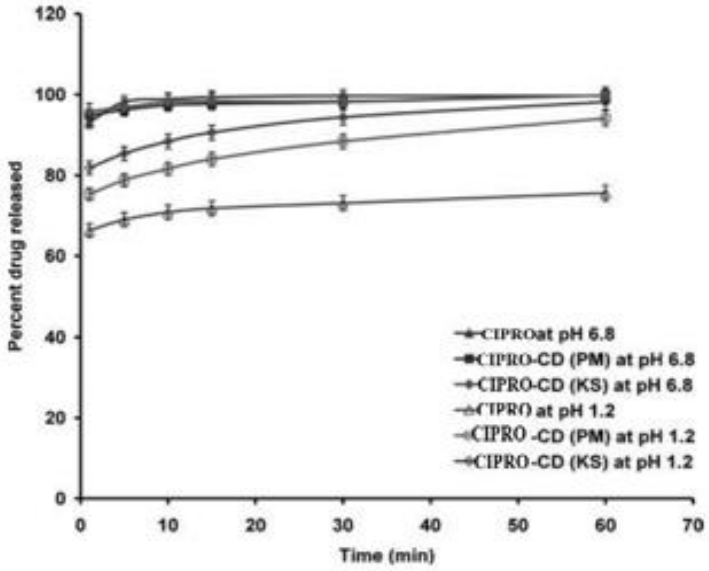

Fig. 5. Dissolution profile of CIPRO, physical mixture and kneaded system

Table I. Percent Dissolution and Dissolution Efficiency of CIPRO from Binary Systems in Comparison with Pure Drugs

	DP5 (%)		DE15 (%)		DE60 (%)	
Formulations	At pH 1.2	At pH 6.8	At pH 1.2	At pH 6.8	At pH 1.2	At pH 6.8
CIPRO	69.15	98.26	67.32	94.51	72.12	98.37
Physical mixture	78.82	96.28	77.39	93.43	86.52	97.35
Kneaded system	85.53	96.92	83.82	94.10	92.23	97.70

DP5 Percent drug dissolved at 5 min, DE15 and DE60 dissolution efficiency at 15 and 60 min 32.61°, 34.78° and 35.78° were observed in physical mixture. This suggests the presence of a new solid phase in physical mixture and solid dispersion. XRPD studies, thus, confirm the findings of DSC patterns indicating formation of a solid form with different properties or CIPRO-CD inclusion complex in physical mixture and kneaded system.

In Vitro Drug Release

When physical mixture or kneaded system was dispersed in a dissolution medium, a very rapid dissolution was observed. Dissolution studies were based on the observation in order to characterize the inclusion complexation between the CD and drug. Figure 5 shows the dissolution profiles of pure CIPRO, CD, physical mixture and kneaded system at pH,1.2 and 6.8. The results in terms of dissolution efficiency and percent of CIPRO dissolved at 5 min are reported in Table I.

Dissolution studies showed that the drug release was slightly decreased in kneaded system (about 96.92% of drug dis- solved in 5 min) and their respective physical mixtures compared (about 96.28% of drug dissolved in 5 min) to pure CIPRO (about 98.26% of drug dissolved in 5 min) at pH 6.8. However the drug release is significantly improved in kneaded system (about 85.53% of drug dissolved in 5 min) and their respective physical mixtures compared (about 78.82% of drug dissolved in 5 min) to pure CIPRO (about 69.15% of drug dissolved in 5 min) at pH 1.2. This indicates increased availability of CIPRO in stomach.

The significant improvement in dissolution characteristics of the complexes is justified through the concurrence of several factors: increased particle wettability, and reduction of crystallinity of the product (19–21). Improved dissolution may be attributed to the high energetic

amorphous state and reduction in crystallinity of the CIPRO following complexation in physical mixture and kneaded system, which was confirmed by XRPD and DSC studies.

Table II. Formulation of Suspension Powder

Drug/excipients	Per cachet				
	DS21	DS22	DS23	DS24	DS25
CIPRO (g)	–	–	–	–	0.013
Physical mixture eq. to 13.12 mg CIPRO (g)	0.817	0.817	0.817	0.817	–
Xanthan gum (g)	0.002	0.003	0.004	0.005	0.005
Microcrystalline cellulose (Avicel PH 302) (g)	0.071	0.070	0.069	0.068	0.871
Citric acid (g)	0.006	0.006	0.006	0.006	0.006
Methyl paraben (g)	0.002	0.002	0.002	0.002	0.002
Propyl paraben (g)	0.001	0.001	0.001	0.001	0.001
Sunset yellow FCF (g)	0.001	0.001	0.001	0.001	0.001
Total filled weight per cachet (g)	0.900	0.900	0.900	0.900	0.900

Table III. Physical Properties of Suspension Powder

Parameters	DS21	DS22	DS23	DS24	DS25
Angle of repose (°) ±SD[a]	37.32±0.53	38.14±0.44	37.78±0.48	37.56±0.32	37.68±0.43
F value (after reconstitution) ±SD[a]	0.34±0.08	0.68±0.09	0.83±0.07	0.94±0.04	0.96±0.02
pH (after reconstitution)	4.5–4.6	4.5–4.6	4.5–4.6	4.6–4.7	4.6–4.7

aValues represent the mean±SD of three experiments.

Table IV. Bitterness Score Evaluation by a Panel of Twenty Human Volunteers

Formulations	Number of volunteers rating the preparation as							
	0	0.5	1	1.5	2	2.5	3	3+
DS25						1	17	2
DS24	20	1						

Gustatory Sensation Test

Bitterness evaluation results made by the consents of trained persons are listed in Table II. No bitterness was imparted in physical mixture with reference to pure drug and kneaded system. It has been reported that CIPRO depolarize taste cells by closing K+ channel and produce bitterness (2). In addition, it has been reported that the CD enwraps bitter tasting drug, impeding

its interaction with the taste buds (12). This complexed CIPRO is strongly hydrated on the outer surface, therefore it didn't interact with K+ channel and thus reduces bitterness. Further the sweet taste of CD imparted additive effect. Surprisingly, kneaded system showed high bitterness score. This might be because of the reduced particle size of CIPRO, due to kneading, confirmed by XRPD studies. These small complexed drug particles might be retained on the tongue for longer period and attached to K+ channel, which results in bitterness.

Preparation and Evaluation of Dry Suspension

To formulate a dry suspension of CIPRO, the 1:25 M physical mixture was selected, based on its bitterness score.

The formula of different suspension powders prepared is summarized in Table II. The formula of optimized suspension powder (DS24) was further used to prepare suspension powder of pure CIPRO (DS25). The characteristics of suspension powder are summarized in Table III.

Gustatory Sensation Test for Suspension Powder

The cachets prepared using CIPRO and the physical mixture of the CD and CIPRO were subjected to taste evaluation by the same panel of twenty selected volunteers. For DS25, the 10% of panel rated it as very strongly bitter, 85% strongly bitter and 5% moderate to strong bitter while DS24 was rated as tasteless by 100% of volunteers of panel (Table IV).

CONCLUSION

The study conclusively demonstrated the complete masking of bitter taste of CIPRO with CD in physical mixture. The FTIR, DSC and XRPD studies indicated inclusion complexation in physical mixture and kneaded system. This may be of value for the pharmaceutical industries dealing with bitter drugs to improve patient compliance and thus effective pharmacotherapy.

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