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Research Article

Formulation and Evaluation of Taste Masked Oral Reconstitutable Suspension of Primaquine Phosphate

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Abstract. The purpose of this research was to mask the intensely bitter taste of primaquine phosphate (PRM) 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 PRM, 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 PRM 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; primaquine phosphate; taste masking.

INTRODUCTION

Primaquine phosphate (PRM), an antimalarial drug that was active against exo-erythrocyte forms of Plasmodium that is *P. vivax*, *P. ovale* and the early preerythrocytic form of *Plasmodium falciparum*, was used to induce "radical cures" of relapsing malarias (1). PRM has an extremely unpleasant bitter taste. It has been reported that PRM 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 prodrugs (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 can not 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).

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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, PRM. PRM 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

Primaquine phosphate 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 were purchased from S.D. Fine Chem Ltd, Boisar. The diluents used were microcrystalline cellulose (Avicel PH 302, FMC Biopolymer, Ireland), and spray-dried lactose (Lactopress, Friesland, The Netherlands). The superdisintegrants were crospovidone (Kollidon CL, BASF, Germany), croscarmellose sodium (Ac-Di-Sol, FMC Biopolymer, Ireland). Talc and magnesium stearate were purchased from ACS chemicals (Ahmedabad, India) and Suvidhinath laboratories (Baroda, India), respectively. All reagents and solvents used in the study were of analytical grade.

Preparation of Solid Binary Systems

The following binary systems of PRM 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 PRM 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 PRM 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 PRM 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 PRM 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 ($K_{1:1}$) was calculated from the phase-solubility diagram (14), using the following equation:

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

Where S_0 is the intrinsic solubility of PRM in the absence of CD and the slope refers to the gradient of the plot of PRM 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 PRM in gastric pH. Complexes containing equivalent of 13.12 mg of PRM 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 Mou-ying *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 PRM was dispersed in 100 ml of water for 15 s. For comparison pure PRM 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 PRM was very high to formulate a rapid disintegrating tablet (RDT). Hence dry suspension powder containing equivalent of 13.12 mg of PRM (equivalent to 7.5 mg primaquine base) was prepared from PRM 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:

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

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 Vo before settling, as expressed in the following equation:

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

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 PRM in CD is constructed by plotting PRM solubility (mM) against the concentration of CD (mM). As it appears in Fig. 1, CD has increase in aqueous solubility of PRM, suggesting the formation of inclusion complexes of the A_L- 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 $K_{1:1}$-value indicates weak interaction. In addition, this confirms that the hydrophilic drugs like PRM 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 PRM.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed to detect the possible molecular interaction between PRM and CD. The FTIR spectrum of PRM, CD, physical mixture and kneaded system in 1:25 M are shown in Fig. 2. The characteristic peaks of PRM at 2,968 and 2,878 cm^{-1} were assigned to C–H stretching vibration in CH_3, CH_2. In addition, the absorption peak at 2,844 cm^{-1} was assigned to C–H stretching vibration in C–O–CH_3. 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 spectra of

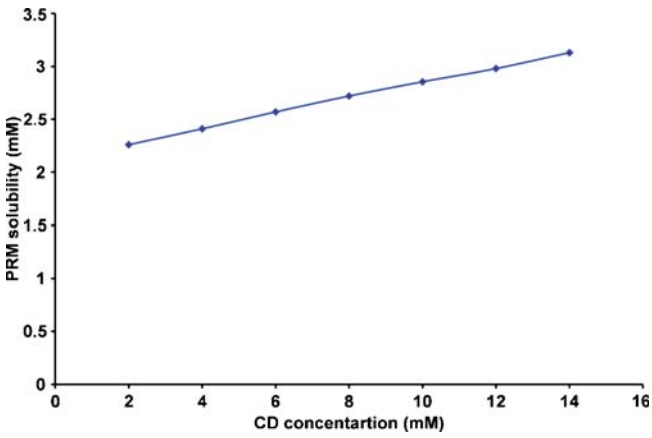

Fig. 1. Phase-solubility diagram for the PRM-CD system

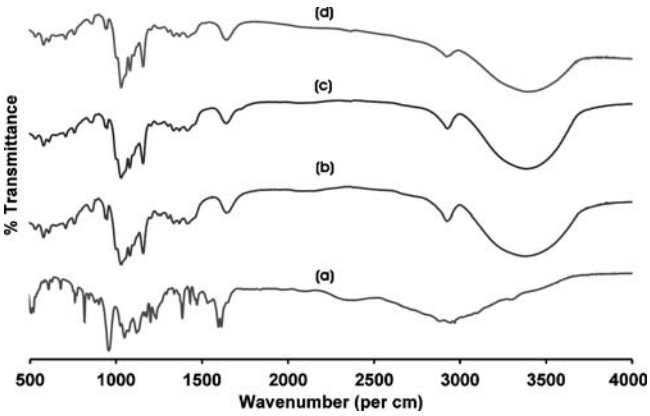

Fig. 2. FTIR spectra of **a** PRM, **b** CD, **c** physical mixture and **d** kneaded system

physical mixture and kneaded system corresponds to the CD, with no major peaks corresponding to PRM. This suggests formation of inclusion complexation between the CD and PRM in physical mixture and kneaded system.

Differential Scanning Calorimetry (DSC)

Figure 3 shows the DSC curves of PRM, CD, physical mixture and kneaded system in 1:25 M. The pure PRM 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 Tmax=121.03°C), which may be ascribed to dehydration (17). Moreover, the melting peak of the CD was Tmax=319.66°C.

The characteristic endothermic peak corresponding to melting peak of PRM 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 PRM in physical mixture and kneaded system.

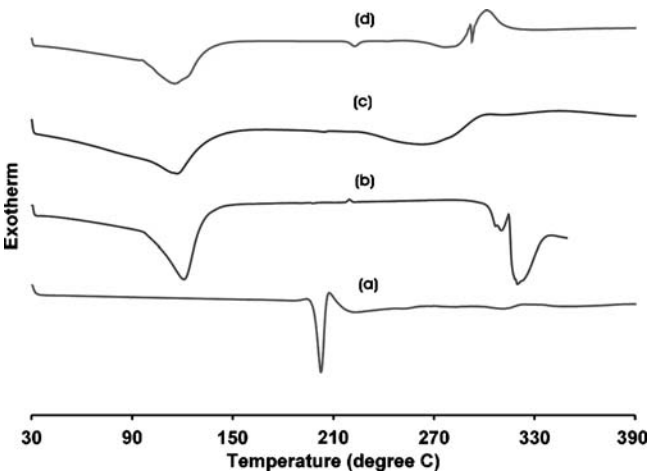

Fig. 3. DSC curve of **a** PRM, **b** CD, **c** physical mixture and **d** kneaded system

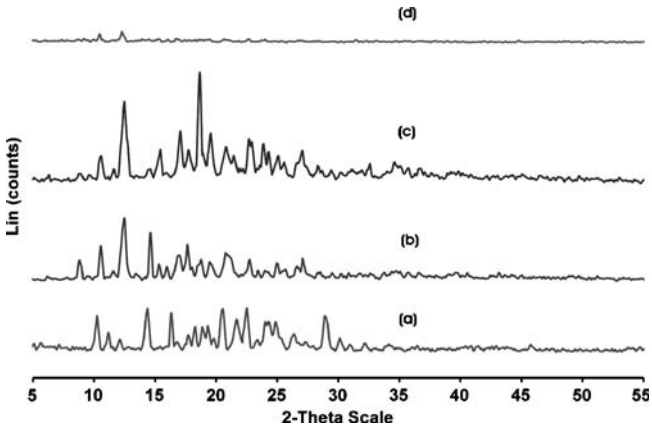

Fig. 4. XRPD pattern of **a** PRM, **b** CD, **c** physical mixture and **d** kneaded system

X-ray Powder Diffractometry (XRPD)

XRPD analysis was performed to confirm the results of DSC studies. XRPD patterns of PRM, CD, physical mixture and kneaded system in 1:25 M are shown in Fig. 4. In X-ray diffractogram of PRM, 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 PRM and CD, where the characteristic peaks of PRM disappeared, indicating the formation of inclusion complex in these systems. Also, the diffractograms of physical system differed from those of PRM 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°,

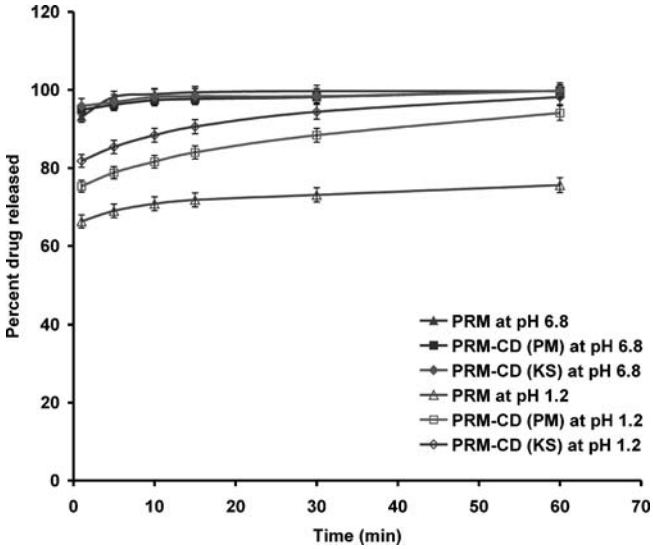

Fig. 5. Dissolution profile of PRM, physical mixture and kneaded system

Table I. Percent Dissolution and Dissolution Efficiency of PRM from Binary Systems in Comparison with Pure Drug

	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
PRM	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

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

	Number of volunteers rating the preparation as							
Formulations	0	0.5	1	1.5	2	2.5	3	3+
Pure PRM							19	1
Physical mixture	20							
Kneaded systems							18	2

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 PRM-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 PRM, CD, physical mixture and kneaded system at pH, 1.2 and 6.8. The results in terms of dissolution efficiency and percent of PRM 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 dissolved in 5 min) and their respective physical mixtures compared (about 96.28% of drug dissolved in 5 min) to pure PRM (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 PRM (about 69.15% of drug dissolved in 5 min) at pH 1.2. This indicates increased availability of PRM 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 PRM following complexation in physical mixture and kneaded system, which was confirmed by XRPD and DSC studies.

Table III. Formulation of Suspension Powder

	Per cachet				
Drug/excipients	DS21	DS22	DS23	DS24	DS25
PRM (g)	–	–	–	–	0.013
Physical mixture eq. to 13.12 mg PRM (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 IV. 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

[a] Values represent the mean±SD of three experiments.

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

	Number of volunteers rating the preparation as							
Formulations	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 PRM 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 PRM 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 PRM, 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 PRM, the 1:25 M physical mixture was selected, based on its bitterness score.

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

Gustatory Sensation Test for Suspension Powder

The cachets prepared using PRM and the physical mixture of the CD and PRM 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 V).

CONCLUSION

The study conclusively demonstrated the complete masking of bitter taste of PRM 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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