JPP Journal of Pharmacy and Pharmacology

JPP 2008, 60: 1279–1285

Received December 12, 2007
Accepted June 17, 2008
DOI 10.1211/jpp/60.10.0003
ISSN 0022-3573

Formulation and evaluation of primaquine phosphate taste-masked rapidly disintegrating tablet

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Abstract

This work investigates the complete bitter-taste-masking of primaquine phosphate (PRM) using a solid dispersion with mono ammonium glycyrrhyzinate pentahydrate (GLY). This work also describes the preparation of rapidly disintegrating tablets (RDTs) of PRM by a direct compression method using superdisintegrant, croscarmellose sodium. A solid dispersion was prepared by the solvent evaporation method. Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. In-vitro drug release studies were performed for RDTs at both pH 1.2 and 6.8. Bitterness score was evaluated using a human gustatory sensation test. FTIR spectroscopy and DSC showed no interaction of PRM in GLY solid dispersion. RDTs prepared from solid dispersion showed complete bitter-taste-masking of PRM. RDTs containing solid dispersion exhibited a better dissolution profile, at both pH 1.2 and 6.8, than pure PRM. Thus, the solid dispersion technique can be successfully used for complete bitter taste masking of PRM.

Introduction

Primaquine phosphate (PRM), an antimalarial drug that is active against exo-erythrocyte forms of *Plasmodium* (*P. vivax*, *P. ovale*) and the early pre-erythrocytic form of *P. falciparum*, was used to induce radical cures of relapsing malarias (Bhadra et al 2005). PRM has an extremely unpleasant bitter taste. It has been reported that PRM depolarizes taste cells by closing K^+ channels and produces bitterness (Yamamoto et al 1998).

The complete bitter-taste-masking of PRM is an extremely important factor in the formulation of rapidly disintegrating tablets (RDTs). The palatability of RDTs is a critical factor in ensuring patient compliance (Fu et al 2004; Khan et al 2007). RDTs are useful in patients such as paediatrics and geriatrics who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup (Shu et al 2002; Chue et al 2004; Gohel et al 2004; Kaushik et al 2004). In addition, it is a major challenge to develop taste-masked RDTs with improved drug release.

Much research has been carried out and many techniques have been employed in the art of effectively masking the taste of bitter pharmaceuticals. The use of sweeteners, amino acids, flavours and adsorbents have been often unsuccessful in masking the bitter taste of water-soluble drugs like PRM. One method involves the enteric coating of bitter-tasting drugs with various copolymers (Chopra et al 2002). The coating of fine particles is usually unsuccessful and coating of granular particles is readily ruptured by chewing and compression. Coating with polymers requires sophisticated instruments. In addition, most coatings do not have an acceptable in-vivo drug releasing mechanism. Ion-exchange resins have been used to adsorb amine drugs for taste masking (Jaskari et al 2001; Vuorio et al 2003). However, this causes delayed drug release. Chemical modifications such as the use of insoluble prodrugs have been reported (Borodkin & Yunker 1970; Vyas et al 1973). However, this may alter the physiological availability of the drug substance.

Glycyrrhizin, which is also known as glycyrrhizinic acid, is an oleanane-type triterpene glycoside whose use as a sweetener has been reviewed. This compound is extracted from the rhizomes and roots of liquorice (*Glycyrrhiza glabra* L., Fabaceae) and other species of the genus *Glycyrrhiza* (Anonymous 1998; Kinghom & Compadre 2001). In the USA, ammoniated glycyrrhizin is included in the generally recognized as safe (GRAS) list

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Acknowledgements and funding: The authors are thankful to Ajanta Pharma Ltd, Mumbai and Sami Labs, Bangalore, for providing the gift sample of artemether and mono ammonium glycyrrhyzinate pentahydrate, respectively. Further, the support from STIC, Cochin is greatly acknowledged.

of approved natural flavouring agents (Smith et al 1996). Ammoniated glycyrrhizin has been rated as having approximately 50 times the sweetness of sucrose (Hanrahan 2001; Kinghom & Compadre 2001). Monosodium glycyrrhyzinate, together with flavours, has been used to mask the bitter taste of guaifenesin (Fawzy et al 1998) and an extract containing pogostemi herba (Okudaira & Kakuta 1997).

In this study an attempt has been made to formulate taste-masked RDTs of PRM with improved dissolution, so as to prepare a patient-friendly dosage form, using mono ammonium glycyrrhyzinate pentahydrate (GLY) as the hydrophilic carrier. Furthermore, the study undertakes to investigate solid-state characterization and attempts to determine the possible mechanism of taste masking and improved dissolution rate.

Materials and Methods

Materials

Primaquine phosphate (PRM) was a gift from Ajanta Pharma Ltd, (Mumbai, India). Mono ammonium glycyrrhyzinate pentahydrate (GLY; molecular weight 839.97) was received as a gift from Sami Labs (Bangalore, India). Methanol was purchased from Qualigens Fine Chemicals (Mumbai, India) and was used as received. Sodium hydroxide, hydrochloric acid, potassium chloride and potassium dihydrogen phosphate were purchased from S. D. Fine-Chem Ltd (Mumbai, India) and were used as received. The diluents used were microcrystalline cellulose (Avicel PH 302p; FMC Biopolymer, Ireland), and dibasic calcium phosphate directly compressible (SBF Pharma, Ahmadabad, India). The superdisintegrants were crospovidone (Kollidon CL; BASF, Germany) and croscarmellose sodium (Ac-Di-Sol; FMC Biopolymer, Ireland). Talc and magnesium stearate were purchased from ACS chemicals (Ahmadabad, India) and Suvidhinath laboratories (Baroda, India), respectively. All reagents and solvents used in the study were of analytical grade.

Preparation of PRM–GLY solid dispersion

The solid dispersion of PRM and GLY in 1:0.5 and 1:1 molar ratio was carried out using the solvent evaporation method. An accurately weighed quantity of PRM (750 mg in 7 mL) was dissolved in water. Previously dissolved GLY (207.4 mg in 7 mL) in water was added with constant stirring on a magnetic stirrer. The solid mass was dried to a constant weight in a hot-air oven at 100°C. The dried powder was passed through sieve No. 44 (ASTM 45, 355 μm) and stored in a desiccator (Tarsons Products Pvt. Ltd, Baroda, India) until further evaluation.

The physical mixtures of PRM and GLY were prepared by mixing individual components geometrically, which had previously been sieved through sieve No. 44 (ASTM 45, 355 μm), together with a spatula.

Characterization of solid dispersions

Fourier transform infra-red spectroscopy (FTIR)

FTIR transmission spectra were obtained using a Fourier transform infrared spectrophotometer (Avatar 360 E.S.P. FTIR spectrophotometer; Thermo Nicolet Corp., Madison, WI, USA). A total of 2% (w/w) of sample, with respect to the potassium bromide (KBr; S. D. Fine Chem Ltd., Mumbai, India) disc, was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar before compressing into a disc under a hydraulic press at 10 000 psi. Each KBr disc was scanned 16 times at 4 mm s^{-1} at a resolution of 2 cm^{-1} over a wave number region of 500–4000 cm^{-1}. The characteristic peaks were recorded.

Differential scanning calorimetery (DSC)

Differential scanning calorimetry study was performed using differential scanning calorimeter (DSC 822; Mettler Toledo, Columbus, OH, USA). All the samples were accurately weighed (4–6 mg), sealed in an aluminium pan and heated at a scanning rate of 5°C min^{-1}. Nitrogen was used as the purge gas with the flow rate set at 40 mL min^{-1}. Aluminium pans and lid were used for all samples. An empty aluminium pan was used as reference.

Tablet formulation and characterization

Rapidly disintegrating tablets (RDTs) containing the equivalent of 13.16 mg of PRM (7.5 mg primaquine base) were compressed on an 8-station single rotary tabletting press (GMC, Mumbai, India) using a 6-mm round shaped flat punch with break line by the direct compression technique (Fu et al 2004).

Prepared RDTs were evaluated for hardness (Hardness tester 5Y; Electrolab, Mumbai, India), friability (Friabilator EF2; Electrolab, Mumbai, India), disintegration time (Disintegrating apparatus ED 2; Electrolab, Mumbai, India) and weight variation. The bitterness score was evaluated using a human gustatory sensation test.

In-vitro drug release

An in-vitro drug release study was performed at 37 ± 0.5°C, using a 6-station USP XXII apparatus (TDT-50; Electrolab, Mumbai, India) with the paddle rotating at 50 rev min^{-1}. The study was carried out in phosphate buffer at pH 6.8 because the pH of the saliva is in the range 6.3–7.2 (Shah & Mashru 2008). Further, the in-vitro drug release study was performed in hydrochloric acid pH 1.2 to demonstrate the availability of PRM at gastric pH. RDTs containing the equivalent of 13.16 mg of PRM were suspended in 500 mL of the buffer solution, and a 3-mL sample was withdrawn at 1, 5, 10, 15, 30 and 60 min and analysed using a UV spectrophotometer (Shimadzu UV visible spectrophotometer 1601) at 259 nm. GLY didn't interfere with the PRM estimation. Each sample was replaced with fresh buffer solution having the same temperature.

Statistical analysis

Dissolution data was statistically analysed using Kruskal–Wallis test (non-parametric). Individual differences between the variables was then examined using Tukey's post-hoc test.

The Kruskal–Wallis test is a nonparametric test that compares three or more unpaired groups. To perform this test, all the values are first ranked from low to high, paying no attention to which group each value belongs. The smallest

number is ranked as 1. The largest number is ranked as N, where N is the total number of values in all the groups. The discrepancies among the rank sums are combined to create a single value called the Kruskal–Wallis statistic (some books refer to this value as H). A large Kruskal–Wallis statistic corresponds to a large discrepancy among rank sums.

Tukey's test is a statistical test generally used to find which means are significantly different from one another. It compares all possible pairs of means, and is based on a Studentized range distribution, q (this distribution is similar to the distribution of *t* from the *t*-test). The test compares the means of every treatment to the means of every other treatment, and identifies where the difference between two means is greater than the standard error would be expected to allow.

Gustatory sensation test

A gustatory sensation test was carried out according to the method described by Mou-ying et al (1991); this study was approved by Institutional Human Ethical Committee (IHEC). Twenty healthy subjects (age 23–27 years) were selected based on a quinine taste sensitivity test. The non-taster and super tasters were rejected. The taste threshold for all subjects was determined by making a range of dilutions of PRM (0.5–3.5 mg mL^{-1}). The threshold concentration of bitter taste of PRM was 2.5 mg mL^{-1}; the evaluation was based on a numerical scale (Table 1). Hence, the solid dispersion and physical mixture containing 250 mg of PRM was dispersed in 100 mL of water for 15 s. For comparison, pure GLY was subjected to taste evaluation by the panel. Immediately after preparation, each subject held about 1 mL of the dispersion in the mouth for 30 s. After expectoration, the bitterness level was recorded. A numerical scale was used with the following values: 0 = tasteless, 1 = slightly bitter, 2 = moderately bitter, 3 = strongly bitter, 3+ = very strongly bitter. This numerical scale was validated by testing samples randomly. The oral cavity was rinsed with distilled water 3 times to avoid bias. The washout period between testing different samples was 15 min.

Table 1 Determination of threshold concentration of primaquine phosphate giving bitter taste

Concentration (mg mL^{-1})	Number of subjects rating the preparation as:				
	0	1	2	3	3+
0.5		20			
1		19	1		
1.5			14	6	
2			12	8	
2.5[a]			2	18	
3				18	2
3.5				14	6

[a]Threshold concentration of PRM = 2.5 mg mL^{-1}. Rating: 0 = tasteless, 1 = slightly bitter, 2 = moderately bitter, 3 = strongly bitter, 3+ = very strongly bitter.

RDTs were allowed to disintegrate in the mouth for 30 s and evaluated for bitterness using the numerical scale. RDTs of pure PRM (RDT65) were also subjected to taste evaluation by the panel and the results were compared. The bitterness of each sample was determined as the mode score (the score assigned by the greatest number of subjects).

Results and Discussion

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectra of PRM, GLY, physical mixture (PM) and solid dispersion (SD) in 1:1 molar ratio are presented in Figure 1. The characteristic peaks of PRM at 2968 and

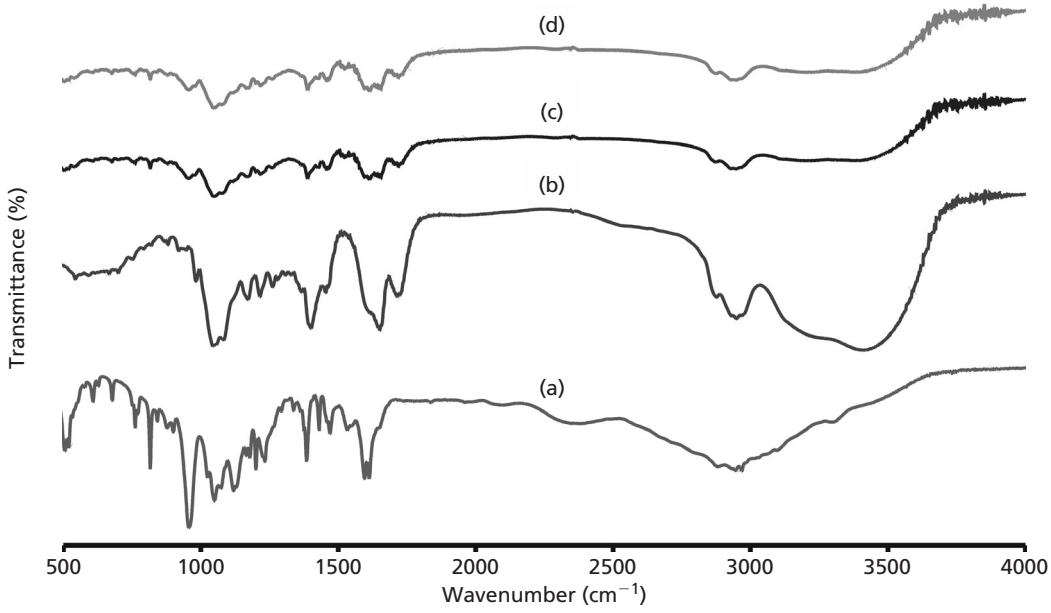

Figure 1 FT-IR spectra of PRM (a), GLY (b), physical mixture (c) and solid dispersion (d).

2878 cm^{-1} are assigned to the C-H stretching vibration in CH_3, CH_2. In addition, the absorption peak at 2844 cm^{-1} can be assigned to the C-H stretching vibration in C-O-CH_3. The peak at 1119 cm^{-1} can be assigned to the C-O stretching vibration in C-O-C. The peak at 3305 cm^{-1} can be assigned to the N-H stretching in primary amines. The characteristic peaks of GLY at 1740–1690 cm^{-1} and 1092 cm^{-1} can be assigned to the -COOH and C-O stretching vibration in C-O-C, respectively. All the above characteristic peaks appear in the spectra of all binary systems at the same wavenumber, indicating no modification or interaction between the drug and carrier.

Differential scanning calorimetry (DSC)

The thermal behaviour of PRM, GLY, physical mixture (PM) and solid dispersion (SD) in 1:1 molar ratio is depicted in Figure 2. Pure PRM shows a sharp endothermic peak at 202.68°C. The characteristic endothermic peak corresponding to the melting peak of PRM was broadened and shifted towards a lower temperature with reduced intensity in both physical mixtures as well as the solid dispersions. This could be attributed to the higher GLY concentration and uniform distribution of PRM in the crust of GLY, resulting in complete miscibility of molten PRM in GLY.

Tablet preparation and characterization

To formulate RDTs of PRM, the 1:1 molar ratio of binary mixture was selected, based on its bitterness score.

The use of superdisintegrants for preparation of RDTs is highly effective as well as commercially feasible. These superdisintegrants accelerate disintegration of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in the breaking of the tablets and therefore faster disintegration. This disintegration is reported to have an effect on dissolution characteristics as well.

Two different superdisintegrants, croscarmellose sodium and crospovidone, were tried to achieve rapid disintegration of tablets. Granular microcrystalline cellulose and dibasic calcium phosphate were tried to achieve the hardness. The formula of the different tablets prepared is summarized in Table 2. Tablets containing croscarmellose sodium and granular microcrystalline cellulose (RDT63) showed the

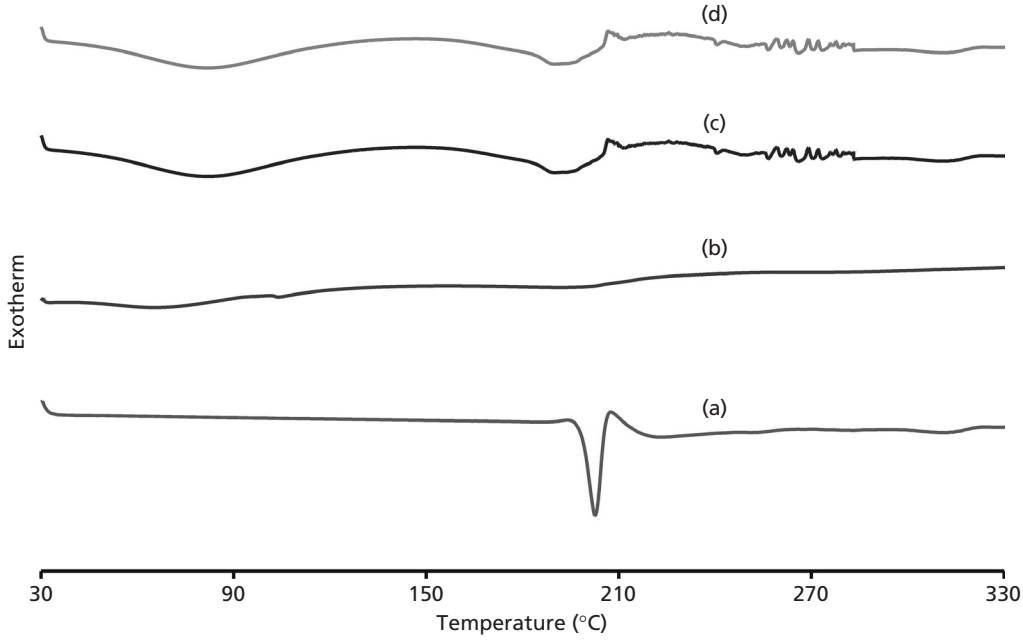

Figure 2 DSC curve of PRM (a), GLY (b), physical mixture (c) and solid dispersion (d).

Table 2 Formulation of RDTs

Drug/excipients	RDT61	RDT62	RDT63	RDT64	RDT65	RDT66
PRM (mg)	—	—	—	—	13.16	13.16
GLY (mg)	—	—	—	—	—	24.26
Solid dispersion equiv. to 13.16 mg PRM	37.42	37.42	37.42	37.42	—	—
Microcrystalline cellulose (Avicel PH 302) (mg)	29.88	—	29.88	—	54.14	29.88
Dibasic calcium phosphate (directly compressible) (mg)	—	29.88	—	29.88	—	—
Croscarmellose sodium (mg)	—	—	2.4	2.4	2.4	2.4
Crospovidone (mg)	2.4	2.4	—	—	—	—
Magnesium stearate (mg)	0.3	0.3	0.3	0.3	0.3	0.3

fastest disintegration (34–40 s) with improved hardness and friability. The formula of optimized RDT was used to prepare RDTs of pure PRM (RDT65) and a physical mixture of PRM and GLY (RDT66). Tablet characteristics of RDTs are summarized in Table 3.

In-vitro drug release studies

Drug release profiles of RDTs prepared from PRM, physical mixture (PM) and solid dispersion (SD) are presented in Figure 3. It is evident that the solid dispersion technique improved the dissolution rate of PRM to a great extent. Table 4 summarizes the results of the Kruskal–Wallis test and Tukey's post-hoc test. The smaller *P* value and larger Kruskal–Wallis statistics value for dissolution at pH 1.2 rejects the idea that the difference was due to random sampling. In addition, it could be concluded that the populations have different distributions. The large *P* value and small Kruskal–Wallis statistics value for dissolution at pH 6.8 did not give any reason to conclude that the distributions differ. This is not the same as saying that the distributions are the same. Tukey's test suggested that the dissolution of RDT63 and RDT66 showed significant improvement compared with RDT65 at pH 1.2, while there was no significant difference in dissolution at pH 6.8. Thus Tukey's test confirms the result obtained by the Kruskal–Wallis test.

This enhancement of dissolution of PRM from drug-carrier systems can be ascribed to several factors. It has been reported that GLY has structural similarity to triterpenes and shows a surfactant like action (Polyakov et al 2005; Motlekar et al 2006). Increased wettability and dispersibility are the main reasons for improvement of dissolution of PRM (Ford 1986).

Dry mixing of PRM with GLY resulted in greater wetting and increased surface available for dissolution by reducing the interfacial tension between the hydrophobic drug and dissolution media. Furthermore, solid dispersion results in uniform distribution of PRM in the GLY crust in a highly dispersed state. Thus, when such a system comes into contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increase the dissolution surface available (Modi & Tayade 2006). This result is in agreement with that obtained from DSC studies.

Gustatory sensation test

Bitterness evaluation results, made by the consent of trained persons, are listed in Table 5. No bitterness was imparted in

Table 3 Physical properties of RDTs

Parameter	RDT61	RDT62	RDT63	RDT64	RDT65	RDT66
Weight (mg) ± s.d.[a]	70.21 ± 1.28	69.89 ± 1.19	70.35 ± 0.87	69.75 ± 1.32	70.43 ± 0.69	70.28 ± 0.76
Disintegrating time (s)	43–49	47–52	34–40	44–51	36–41	36–42
Hardness (kg)	4.1–4.2	4.1–4.2	4.4–4.5	4.2–4.3	4.3–4.4	4.3–4.4
Friability (%) ± s.d.[a]	0.27 ± 0.09	0.29 ± 0.12	0.19 ± 0.10	0.31 ± 0.13	0.21 ± 0.09	0.21 ± 0.11

[a]Values represent the mean ± s.d. of 3 experiments.

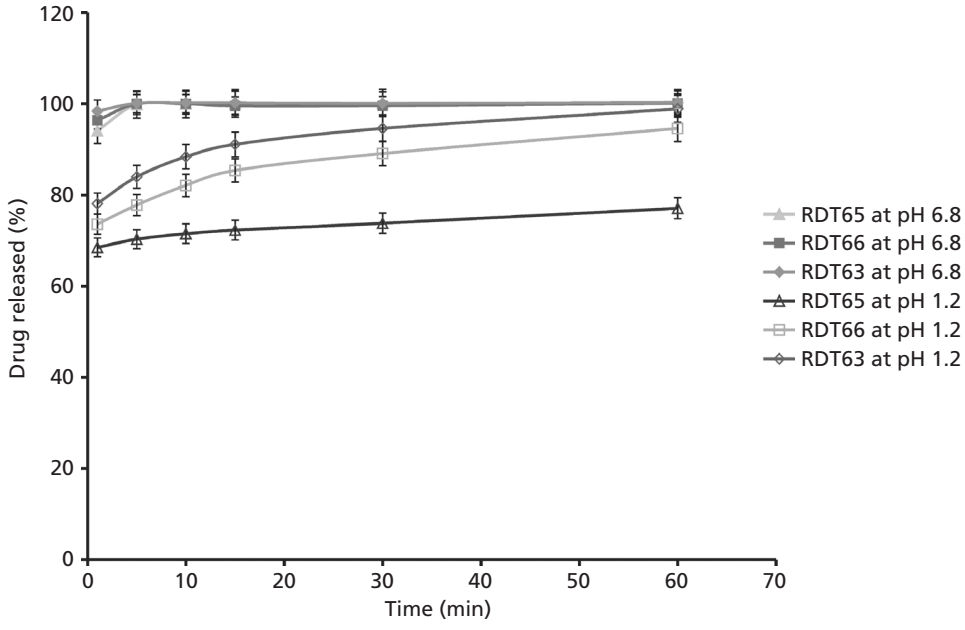

Figure 3 Dissolution profile of RDTs prepared from PRM (RDT65), physical mixture (RDT66) and solid dispersion (RDT63).

Table 4 Results of Kruskal–Wallis test and Tukey's post-hoc test

Drug release at pH 1.2 ***P* value 0.041** **Kruskal–Wallis statistic 11**			
Tukey's Multiple Comparison Test	Mean difference	q	Significance
RDT63 vs RDT65	16.93	6.492	Yes
RDT63 vs RDT66	5.417	2.077	No
RDT65 vs RDT66	–11.52	4.415	Yes
Drug release at pH 6.8 ***P* value 0.1139** **Kruskal–Wallis statistic 4.346**			
Tukey's Multiple Comparison Test	Mean difference	q	Significance
RDT63 vs RDT65	0.85	1.235	No
RDT63 vs RDT66	0.6183	0.8984	No
RDT65 vs RDT66	–0.2317	0.3366	No

q is the Studentized range distribution.

Table 5 Bitterness score evaluation by a panel of twenty subjects

Formulations	**Number of subjects rating the preparation as:**				
	0	1	2	3	3+
Pure PRM				2	18
Pure GLY	18	2			
Physical mixture (PM)		5	15		
Solid dispersion (SD)	20				
RDT65				3	17
RDT66		4	16		
RDT63	20				

Bitterness rating: 0 = tasteless, 1 = slightly bitter, 2 = moderately bitter, 3 = strongly bitter, 3+ = very strongly bitter.

solid dispersion with reference to pure drug. It has been reported that PRM depolarizes taste cells by closing K^+ channels and produces bitterness (Yamamoto et al 1998). It has also been reported that GLY has structural similarity to triterpenes and shows a surfactant-like action (Polyakov et al 2005; Motlekar et al 2006). This prevents retention of PRM on the tongue surface and avoids contact of PRM with K^+ channels. GLY is astringent and might interact with G-proteins and paralyze them, resulting in reduced taste transduction and thus reduced bitterness score. Further, the sweet taste of GLY imparts an additive effect.

PRM was uniformly distributed in the crust of GLY solid dispersion, which avoids contact of PRM with K^+ channels. Further, the sweet taste of GLY imparted an additive effect (Kinghom & Compadre 2001). This results in complete taste masking of PRM in GLY solid dispersion. Though the physical mixing of PRM with GLY brings the drug into close contact with the carrier, PRM was not as uniformly distributed in GLY as in the solid dispersion. This might be the reason for incomplete masking of the bitter taste of PRM in GLY physical mixture.

The RDTs prepared using PRM, physical mixture and solid dispersion were subjected to taste evaluation by the same panel of twenty selected subjects. For RDT65, 85% of the panel rated it as very strongly bitter and 15% strongly bitter. RDT63 was rated as tasteless by 100% of subjects on the panel.

Conclusion

This study conclusively demonstrated complete masking of the bitter taste of PRM with improved dissolution by the solid dispersion technique. This method is simple and easy to scale up in industry. The FTIR and DSC studies indicated no interaction of PRM, at the molecular level, in GLY solid dispersion. PRM-GLY solid dispersion, along with use of superdisintegrant, could be considered for formulation of RDTs of PRM. This may be of value for the pharmaceutical industries dealing with bitter drugs to improve patient compliance and thus effective pharmacotherapy.

References

Anonymous. (1998) Glycyrrhyza glabra. In: *Indian herbal pharmacopoeia*. Vol. 1, a joint publication of Regional Research Laboratory, Jammu and Indian Drug Manufacturer's Association, Mumbai, pp 89–98

Bhadra, D., Yadav, A. K., Bhadra, S., Jain, N. K. (2005) Glycodendrimeric nanopartiulate carriers of primaquine phosphate for liver targeting. *Int. J. Pharm.* **295**: 221–233

Borodkin, S., Yunker, M. H. (1970) Interaction of amine drugs with a polycarboxylic acid ion-exchange resin. *J. Pharm. Sci.* **59**: 481–485

Chopra, R., Alderborn, G., Newton, J. M., Podezeck, F. (2002) The influence of film coating on pellet properties. *Pharm. Dev. Tech.* **7**: 59–68

Chue, P., Welch, R., Binder, C. (2004) Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizoaffective disorders. *Can. J. Psychiatry* **49**: 701–703

Fawzy, A. A., Clemente, E., Anaebonam, A. O. (1998) Pleasant tasting aqueous liquid composition of a bitter-tasting drug. *PCT Int. Appl.* WO9805312

Ford, J. L. (1986) The current status of solid dispersions. *Pharm. Acta Helv.* **61**: 69–88

Fu, Y., Yang, S., Jeong, S. H., Kimura, S., Park, K. (2004) Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. *Crit. Rev. Ther. Drug Carrier Syst.* **21**: 433–476

Gohel, M., Patel, M., Amin, A., Agrawal, R., Dave, R., Bariya, N. (2004) Formulation, design and optimisation of mouth dissolve tablets of nimesulide using vacuum drying technique. *AAPS PharmSciTech* **5**: article 36

Hanrahan, C. (2001) Licorice. In: *Gale encyclopedia of alternative medicine*. Thomson Gale, Farmington Hills, MI, USA

Jaskari, T., Vuorio, M., Kontturi, K., Manzanares, J. A., Hirvonen, J. (2001) Ion- exchange fibers and drugs: an equilibrium study. *J. Control. Release* **70**: 219–229

Kaushik, D., Dureja, H., Saini, T. R. (2004) Mouth dissolving tablets: a review. *Indian Drugs* **41**: 187–193

Khan, S., Kataria, P., Nakhat, P., Yeole, P. (2007) Taste masking of ondansetron hydrochloride by polymer carrier system and formulation of rapidly disintegrating tablets. *AAPS PharmSciTech* **8**: article 46

Kinghom, A. D., Compadre, C. M. (2001) Less common sweetners. In: Nabory, L. O. B. (ed.) *Alternative sweetners.* CRS Press, London, pp 209–223

Modi, A., Tayade, P. (2006) Enhancement of dissolution profile by solid dispersion (kneading) technique. *AAPS PharmSciTech* **7**: article 68

Motlekar, N. A., Srivenugopal, K. S., Wachtel, M. S., Youan, B. C. (2006) Evaluation of the oral bioavailability of low molecular weight heparin formulated with glycyrrhetinic acid as permeation enhancer. *Drug Dev. Res.* **67**: 166–174

Mou-ying, F. L., Saul, B., Linda, W., Ping, L., Diesner, C., Hernandez, L., Vadnere, M. (1991) A polymeric carrier system for taste masking of macrolide antibiotics. *Pharm. Res.* **8**: 706–712

Okudaira, I., Kakuta, K. (1997) Liquids containing kakko-shoki-san extract with improve taste. JP 09309836

Polyakov, N. E., Khan, V. K., Taraban, M. B., Leshina, T. V., Salakhutdinov, N. F., Tolstikov, G. A. (2005) Complexation of lappaconitine with glycyrrhizic acid: stability and reactivity studies. *J. Phys. Chem. B* **109**: 24526–24530

Shah, P. P., Mashru, R. C. (2008) Development and evaluation of artemether taste masked rapid disintegrating tablets with improved dissolution using solid dispersion technique. *AAPS PharmSciTech* In press

Shu, T., Suzuki, H., Hironaka, K., Ito, K. (2002) Studies of rapidly disintegrating tablets in oral cavity using coground mixture of mannitol with crospovidone. *Chem. Pharm. Bull.* **50**: 193–198

Smith, R. L., Newburne, P., Adams, T. B., Ford, R. A., Hallogan, J. B., Panel, F. E. (1996) GRAS flavoring substances. *Food Tech.* **50**: 72–81

Vuorio, M., Manzanares, J. A., Murtomaki, L., Hirvonen, J., Kankkunen, T., and Kontturi, K. (2003) Ion exchange fibers and drugs: a transient study. *J Controlled Release* **91**: 439–448

Vyas, A. H., Bhat, C. V., Kamath, B. R., Bafna, S. L. (1973) Cinchona alkaloids on ion-exchange resins V: ammonium form of resins. *J. Pharm. Sci.* **62**: 1386–1387

Yamamoto, T., Nagai, T., Shimura, T., Yasoshima, Y. (1998) Roles of chemical mediators in taste system. *Jpn J. Pharmacol.* **76**: 325–348