Summary and Conclusion

Today many antimalarial drugs that are used for some pediatric patients are not in appropriate dosage forms for use by children. In most cases, the solid formulations are coated with advice not to chew but to swallow the intact tablet. However, for small children the administration of the dose of a whole tablet is frequently not recommended and to administer tablets in general is not recommended. Only liquid formulations should be given or if these are not available, the tablet should be crushed to a suspension and administered by a spoon. The bitter taste in such cases is frequently a serious problem. Bitter taste of drug has always been a problem in patient and prescription compliance, especially in pediatrics. Taste masking of these drugs would help to improve the pharmacotherapy. This has led to continuous development of novel techniques for bitter taste masking.

Various methods have been reported for taste masking such as addition of sweeteners and flavors, coating with lipophilic and hydrophilic vehicles, inclusion complexation, adsorption to ion-exchange resin, chemical modifications such as the use of insoluble prodrugs, solid dispersions and freeze drying. Of these all the available techniques, some promising techniques were studied in the present work with different excipients to mask the bitter taste of antimalarials like artemether (ARM), mefloquine hydrochloride (MFL) and primaquine phosphate (PRM). The techniques studied are solid dispersion, inclusion complexation and microencapsulation using pH-dependent polymers. Further the literature revealed different methods available for evaluation of bitterness such as gustatory sensation test, paddle method, mini-column method, E-tongue, inversion and shaking method. Out of these reported methods for bitterness evaluation gustatory sensation test and *in vitro* drug release studies at pH 6.8 were performed. In addition, the reported mini-column method has been modified for evaluation of bitter taste in rapid disintegrating tablets. The reported mini-column method uses pneumatic pump to flow phosphate buffer through the column. However the developed mini-column method avoids use of pneumatic pump.

For the study purpose three antimalarial drugs namely, ARM, MFL and PRM were selected, based on their solubility characteristics. Similarly, five excipients namely, sodium saccharine, mono ammonium glycyrrhyzinate pentahydrate, beta-cyclodextrin (CD), Eudragit E (EE), and chitosan were

selected for the study. It was hypothesized that the grafting of Eudragit E with CD may give better results compared to EE and CD. Hence Eudragit E-Beta-Cyclodextrin (EE-CD) was also evaluated for its bitter taste masking property.

Analytical method development

Spectrophotometric methods were developed for all three drugs for routine analysis. ARM lacks ultraviolet (UV) chromophore and have famine fluorescent property. The problem of UV detection of ARM was tackled by acid treatment, inducing the production of a UV detectable product. MFL is soluble in methanol while PRM is soluble in water and showed UV maxima at 284 nm and 259 nm, respectively. Analytical methods for all drugs have been validated for stability, selectivity, precision and accuracy.

Solid dispersion using Sodium saccharin

Effect of sodium saccharin was studied on bitterness of all three drugs. Solid dispersion was prepared by solvent evaporation method. Physical mixtures and solid dispersions were characterized by FTIR, DSC and XRPD studies. The physical mixture and solid dispersion were evaluated for bitterness using human gustatory sensation test. These taste masked drugs were further incorporated in rapid disintegrating tablets (RDTs) using superdisintegrant. RDTs were further evaluated for *in vitro* drug release studies at pH, 1.2 and 6.8. Optimized RDTs were evaluated for bitterness using mini-column method and compared with human gustatory sensation test. Accelerated stability studies of optimized RDTs were carried out. FTIR spectrum indicated no interaction of ARM, in solid dispersion while DSC and XRPD studies suggests amorphization of ARM in solid dispersion. FTIR spectrum of MFL showed significant difference in characteristic peaks of MFL, revealing modification of drug environment. DSC and XRPD studies suggest reduced crystallinity of MFL in solid dispersion. FTIR spectrum of PRM indicated no modification or interaction of PRM while DSC studies revealed amorphization of PRM in solid dispersion. The bitterness score of solid dispersion of MFL and PRM was decreased to zero compared to 3 of pure drugs. However the bitter taste of ARM was not masked in solid dispersion. RDTs of taste masked drugs showed rapid disintegration with acceptable friability. In addition, RDTs showed

improvement in drug release at pH 6.8 while slight decrease in drug release at pH 1.2. In conclusion, sodium saccharin completely masked bitter taste of MFL and PRM with improved drug release at pH 6.8. Further sodium saccharin was not successful in masking the bitter taste of ARM. However it improved drug release at pH 6.8. Solid dispersion along with use of superdisintegrant could be considered for formulation of stable RDTs.

Solid dispersion using Mono amino glycyrrhyzinate pentahydrate

Effect of mono amino glycyrrhyzinate pentahydrate (GLY) was studied on bitterness of all three drugs. Solid dispersion was prepared by solvent evaporation method. Physical mixtures and solid dispersions were characterized by FTIR and DSC studies. The physical mixture and solid dispersion were evaluated for bitterness using human gustatory sensation test. These taste masked drugs were further incorporated in RDTs using superdisintegrant. RDTs were further evaluated for *in vitro* drug release studies at pH, 1.2 and 6.8. Optimized RDTs were evaluated for bitterness using mini-column method and compared with human gustatory sensation test. Accelerated stability studies of optimized RDTs were carried out. FTIR and DSC studies indicated no interaction of ARM, in GLY solid dispersion. FTIR spectrum of MFL showed no significant difference in characteristic peaks of MFL while DSC studies suggest uniform distribution of MFL in the crust of GLY, resulting in complete miscibility of molten drug in GLY. FTIR spectrum of PRM indicated no modification or interaction of PRM while DSC studies revealed reduced crystallinity of PRM in solid dispersion. The bitterness score of solid dispersion of all drugs was decreased to zero compared to 3 of pure drugs. RDTs of taste masked drugs showed rapid disintegration with acceptable friability. In addition, RDTs showed improvement in drug release at pH, 1.2 and 6.8. In conclusion, mono amino glycyrrhyzinate pentahydrate completely masked bitter taste of all drugs with improved drug release. Solid dispersion along with use of superdisintegrant could be considered for formulation of stable RDTs.

Inclusion complexation with Beta-cyclodextrin

Effect of beta-cyclodextrin (CD) was studied on bitterness of all three drugs. Inclusion complex was prepared by physical mixture and kneaded system.

Physical mixtures and kneaded systems were characterized by FTIR, DSC and XRPD studies. The physical mixture and kneaded system were evaluated for bitterness using human gustatory sensation test. These taste masked drugs were further incorporated in reconstitutable suspension using suitable suspending agent. Physical mixture and kneaded system were further evaluated for *in vitro* drug release studies at pH, 1.2 and 6.8. Optimized suspension was evaluated for bitterness using human gustatory sensation test. Accelerated stability studies of optimized suspension were carried out. FTIR, DSC and XRPD studies indicated formation of inclusion complex between all drugs and CD in physical mixture as well as kneaded system. In addition, inclusion complexes showed improvement in drug release at pH, 1.2 and 6.8. The bitterness score of physical mixture of all the drugs was decreased to zero compared to 3 of pure drugs. Suspension of taste masked drugs showed good flowability and ease of resuspendability. In conclusion, beta-cyclodextrin showed complete bitter taste masking of all drugs in physical mixture with improved drug release. Physical mixture along with use of suspending agent could be considered for formulation of stable dry suspension.

Microencapsulation using Eudragit E 100

Influence of Eudragit E 100 (EE) was studied on bitterness of all three drugs. Microparticles were prepared by coacervation technique. A 3^2 full factorial design was applied to investigate the effect of amount of drug and polymer on particle size, drug release at pH, 1.2 and 6.8 were selected as dependent variables along with bitterness score. Optimization was performed using desirability function. Optimized microparticles were characterized by FTIR and DSC studies. Optimized microparticles were further evaluated for *in vitro* drug release studies at pH, 1.2 and 6.8 and bitterness using human gustatory sensation test. These taste masked drugs were further incorporated in reconstitutable suspension using suitable suspending agent. Optimized suspension was evaluated for bitterness using human gustatory sensation test. Accelerated stability studies of optimized suspension were carried out. Present work suggests that both independent variables have its own significant complimentary role in enhancement of the process rather than having exclusive effect. Application of experimental design along with

desirability function can be proved as an ideal tool to optimize independent variables like amount of drug and polymer, which have significant effect on microparticle's desired properties. FTIR and DSC studies confirmed presence of ARM in microparticles. FTIR spectrum of MFL indicated no modification or interaction while DSC studies revealed phase transition of MFL in microparticles. FTIR spectrum of PRM indicated no modification or interaction while DSC studies indicated uniform dispersion of PRM in microparticles. In addition, *in vitro* drug release was improved at pH 1.2 while slightly decreased at pH 6.8. The bitterness score of optimized microparticles of all drugs was decreased to zero compared to 3 of pure drugs. Optimized suspension of taste masked drugs showed good flowability and ease of resuspendability. Microparticles along with use of suspending agent could be considered for formulation of stable dry suspension. In conclusion, Eudragit E100 showed complete bitter taste masking of all drugs in microparticles with improved drug release at pH 1.2.

Microencapsulation using Eudragit E-Beta-Cyclodextrin

Eudragit E-Beta-Cyclodextrin (EE-CD) grafting was performed using microwave and ultrasound. Influence of EE-CD was studied on bitterness of ARM. Microparticles were prepared by coacervation technique. Sodium hydroxide was used as precipitant. A 3^2 full factorial design was applied to investigate the effect of amount of drug and polymer on particle size, drug release at pH, 1.2 and 6.8 were selected as dependent variables along with bitterness score. Optimization was performed using desirability function. Optimized microparticles were characterized by FTIR and DSC studies. Optimized microparticles were further evaluated for *in vitro* drug release studies at pH, 1.2 and 6.8 and bitterness using human gustatory sensation test. These taste masked drugs were further incorporated in reconstitutable suspension using suitable suspending agent. Optimized suspension was evaluated for bitterness using human gustatory sensation test. Accelerated stability studies of optimized suspension were carried out. Present work suggests that both independent variables have its own significant complimentary role in enhancement of the process rather than having exclusive effect. Application of experimental design along with desirability function can be proved as an ideal tool to optimize independent variables like

amount of drug and polymer, which have significant effect on microparticle's desired properties. FTIR and DSC studies confirmed grafting of EE with CD and presence of drug in microparticles. In addition, *in vitro* drug release was improved at pH 1.2 while slightly decreased at pH 6.8. The bitterness score of optimized microparticles of all drugs was decreased to zero compared to 3 of pure drugs. Optimized suspension of taste masked drugs showed good flowability and ease of resuspendability. Microparticles along with use of suspending agent could be considered for formulation of stable dry suspension. In conclusion, EE-CD showed complete bitter taste masking of ARM in microparticles with improved drug release at pH 1.2. The results obtained from EE-CD did not show any significant difference in terms of incorporation efficiency and drug release at pH, 1.2 and 6.8, compared to EE. Further the grafting process is multi-step process and need sophisticated instruments. Hence further studies for MFL and PRM were not tried.

Microencapsulation using Chitosan

Influence of chitosan was studied on bitterness of all three drugs. Sodium hydroxide was used as crosslinking agent. Microparticles were prepared by phase separation coacervation technique. Central composite design was applied to investigate the effect of amount of drug and polymer on particle size, drug release at pH, 1.2 and 6.8 were selected as dependent variables along with bitterness score. Optimization was performed using desirability function. Optimized microparticles were characterized by FTIR and DSC studies. Optimized microparticles were further evaluated for *in vitro* drug release studies at pH, 1.2 and 6.8 and bitterness using human gustatory sensation test. These taste masked drugs were further incorporated in reconstitutable suspension using suitable suspending agent. Optimized suspension was evaluated for bitterness using human gustatory sensation test. Accelerated stability studies of optimized suspension were carried out. Present work suggests that all three independent variables have its own significant complimentary role in enhancement of the process rather than having exclusive effect. Application of experimental design along with desirability function can be proved as an ideal tool to optimize independent variables like amount of drug, chitosan and sodium hydroxide, which have significant effect on microparticle's desired properties. FTIR and DSC studies

confirmed presence of ARM in microparticles. FTIR spectrum of MFL indicated electrostatic interaction while DSC studies revealed phase transition of MFL in microparticles. FTIR spectrum of PRM indicated electrostatic interaction while DSC studies indicated uniform dispersion of PRM in microparticles. In addition, *in vitro* drug release was improved at pH 1.2 while slightly decreased at pH 6.8. The bitterness score of optimized microparticles of all drugs was decreased to zero compared to 3 of pure drugs. Optimized suspension of taste masked drugs showed good flowability and ease of resuspendability. Microparticles along with use of suspending agent could be considered for formulation of stable dry suspension. In conclusion, chitosan showed complete bitter taste masking of all drugs in microparticles with improved drug release at pH 1.2.

Table 1. Comparative formulation results

Drugs	Tablet (per unit)				Suspension powder (per cachet)	
	Sodium saccharin		Mono amino glycerrhyzinate pentahydrate		Beta-cyclodextrin	
	Amount required (mg)	Bitterness score	Amount required (mg)	Bitterness score	Amount required (mg)	Bitterness score
ARM	50+40.41=90.41	3 (not masked)	50+141=191	0	50+3800=3850	0
MFL	250+145=395	0	250+759.38=1009.38	0	100+2736=2836	0
PRM	13.16+16.94=20.12	0	13.16+24.26=37.42	0	13.16+817=830.16	0
Drugs	**Suspension powder (per cachet)**					
	Eudragit E100		**Eudragit E-Beta-Cyclodextrin**		**Chitosan**	
	Amount required (mg)	**Bitterness score**	**Amount required (mg)**	**Bitterness score**	**Amount required (mg)**	**Bitterness score**
ARM	50+236.40=286.40	0	50+232.32=282.32	0	50+88.80=138.80	0
MFL	100+350=450	0	-	-	100+186=286	0
PRM	13.16+88.17=101.33	0	-	-	13.16+331.84=345	0