Solid dispersion using Sodium saccharin

3.1. Introduction

Saccharin sodium (SS) is an intense sweetening agent widely used in beverages, food products, table-top sweeteners and pharmaceutical formulations such as tablets, powders, gel, suspensions, liquids and mouthwashes. Saccharin sodium is considerably more soluble in water and is more frequently used in pharmaceutical formulations.

There has been considerable controversy concerning the safety of saccharin sodium in recent years; however it is now generally regarded as safe (GRAS), sweetener (Rowe et al., 2003).

Though its sweetening power is approximately 300 times that of sucrose, it could not mask the bitter taste of all drugs. In addition many reported techniques mask the bitterness by controlling drug release at salivary pH (6.3-7.2). However it is a major challenge to develop palatable rapid disintegrating tablets (RDTs) without affecting drug release. Hence this was the objective of present study.

3.2. Artemether (ARM)

3.2.1. Experimental

3.2.1.1. Materials

Methanol was purchased from Qualigens Fine Chemicals (Mumbai, India) and was used as received. Sodium saccharin (SS), 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.

3.2.1.2. Preparation of ARM-SS solid dispersion

The solid dispersion of ARM and SS in 1:0.5, 1:1 and 1:2M was prepared using solvent evaporation method. Accurately weighed quantity of ARM (375 mg in 5 mL) was dissolved in methanol. Previously dissolved SS (601 mg in 4 mL) in water was added with constant stirring on magnetic stirrer. The solid obtained after evaporation, was further dried to a constant weight in hot air

oven 70^0C. Dried powder was passed through sieve no. 44 and stored in desiccator (Tarsons Products Pvt. Ltd, India) until further evaluation.

The physical mixtures of ARM and SS in 1:0.5, 1:1 and 1:2M were prepared by mixing individual components geometrically that had previously been sieved through sieve no. 44, together with a spatula.

3.2.1.3. Fourier transform infra-red spectroscopy (FTIR)

FTIR transmission spectra were obtained using a Fourier Transform Infrared spectrophotometer (FTIR-8300, Shimadzu, Japan). 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 KBr disc under a hydraulic press at 10,000 psi. Each KBr disc was scanned 16 times at 4 mms^{-1} at a resolution of 2 cm^{-1} over a wavenumber region of 500–4000 cm^{-1}. The characteristic peaks were recorded.

3.2.1.4. Differential scanning calorimeter (DSC)

Differential scanning calorimetry study was performed using Differential Scanning Calorimeter (DSC 822, Mettler Toledo). All the samples were accurately weighed (4-6 mg), sealed in aluminium pan and heated at a scanning rate of 10°C/min. Nitrogen was used as the purge gas with the flow rate set at 40 mL/min. Aluminum pans and lid were used for all samples. An empty aluminum pan was used as reference.

3.2.1.5. X-ray Powder Diffraction (XRPD)

Vacuum grease was applied over a glass slide to stick the sample. About 100 mg of sample was sprinkled over it to make a layer having a thickness of ~0.5 mm. All the experiments were performed on an X-ray diffractometer (Philips X'Pert MPD, Eindhoven, The Netherlands) having a sensitivity of 0.1 mg. The sample slide was placed vertically at an angle of zero degree in the sample chamber. An x-ray beam (Philips Cu target x-ray tube) of 2 kW was allowed to fall over the sample. As the slide moves at an angle of theta degree, a proportional detector detects diffracted x-rays at angle of 2-theta degrees. XRPD patterns were recorded using Philips JPCD software for powder diffractometry.

3.2.1.6. Tablet Formulation and Characterization

Rapid disintegrating tablets (RDTs) containing equivalent of 50 mg of ARM were compressed on an 8-station single rotary tabletting press (GMC, Mumbai, India) using an 8-mm flat punch with break line by direct compression technique (Mishra et al., 2006).

Two different superdisintegrants, croscarmellose sodium and crospovidone were tried to achieve RDTs. Granular microcrystalline cellulose and lactose were used as diluents. Prepared RDTs were evaluated for hardness (Monsanto hardness tester), disintegration time (Electrolab), friability (Roche Friabilator) and weight variation. The bitterness score was evaluated using mini-column, an *in vitro* model and further compared with gustatory sensation test.

3.2.1.7. *In vitro* drug release

In vitro drug release study was performed at 37 ± 0.5°C, using 6-station USP XXII apparatus (TDT-50, Electrolab, Mumbai, India) with paddle rotating at 50 rpm. The *in vitro* 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 *in vitro* drug release study was performed in hydrochloric acid buffer pH 1.2 to demonstrate the availability of ARM in gastric pH. RDTs containing equivalent of 50 mg of ARM were suspended in 900 mL of the buffer solution, and 3 mL sample was withdrawn at 1, 5, 10, 15, 30 and 60 min and analyzed using UV spectrophotometer (Shimadzu UV visible spectrophotometer 1700). 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 (Khan, 1975).

3.2.1.8. Gustatory sensation test

Gustatory sensation test was carried out according to the method described by Mou-ying et al.(Mou-ying et al., 1991) 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 ARM was dispersed in 100 ml of water for 15s. For comparison pure ARM 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, shown in Table 3.1 was used to evaluate bitterness score. This numerical scale was validated by testing samples randomly. The oral cavity was rinsed with distilled water 3 times to avoid bias. Wash out period between testing different samples was 15 min. The threshold of bitterness of RDTs was determined as point at which maximum number of the volunteers described the taste as bitter or slightly bitter.

RDTs were evaluated for taste masking by keeping in mouth till it disintegrated and evaluated for bitterness evaluation. For comparison, RDTs of pure ARM were also subjected to taste evaluation by the panel and the results were compared.

Table 3.1. Grading for gustatory sensory test

	Score
Tasteless	0
Very slightly bitter	0.5
Slightly bitter	1.0
Slight to moderate bitter	1.5
Moderately bitter	2.0
Moderate to strong bitter	2.5
Strongly bitter	3.0
Very strongly bitter	3.0 +

3.2.1.9. Mini-column Method

Yajima et al. reported a mini-column method for evaluation of bitterness using pneumatic pump (Yajima et al., 2002). This method has been modified for evaluation of bitterness in tablets without use of pneumatic pump. The

objective behind developing this method is to simulate the disintegration of tablet in oral cavity. The threshold of bitterness could be determined by comparing with gustatory sensation test. This finding shows relationship between the amount of drug released after disintegration of RDT in oral cavity and bitterness.

It is difficult to evaluate bitterness of varied shape and size of tablets and prepare different columns for different shape and size of tablets. This problem can avoided by crushing the RDT and tapping the powdered sample. Tapping forms a compact mass, similar to RDT, in lower column. High tapping frequency limits penetration of phosphate buffer in the compacted mass. Hence the tapping frequency was set at 3, 10 and 30 times. Similarly high flow rate results in less penetration of phosphate buffer in the compacted mass. Hence the flow rate of phosphate buffer was selected at 1, 1.3 and 1.5 mL/min.

Mini-column consists of 2 separate columns, upper and lower as shown in Figure 3.1. The inner side of nozzle (lower column) was closed with an accurately weighed piece of wet absorbent cotton. The weight of absorbent cotton piece was kept constant for all samples.

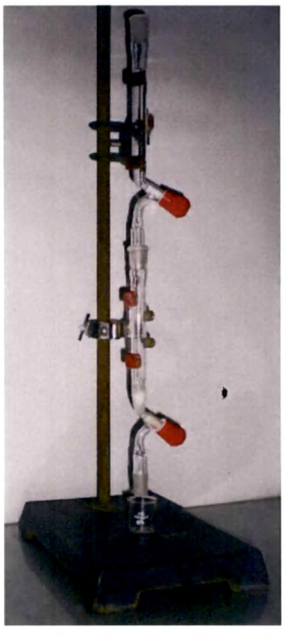

Figure 3.1. Mini-column apparatus for evaluation of bitterness

RDTs were crushed in mortar-pestle then the powdered sample was filled and packed in the column by tapping. After tapping the column 30, 10 or 3 times, accurately weighed absorbent cotton was packed on the sample bed to eliminate sample motion. The weight of absorbent cotton piece was kept constant for all samples. Upper column was filled with phosphate buffer pH 6.8 and attached to lower column. The phosphate buffer flowed through lower column at 1, 1.3, 1.5 mL/min. The residence time of the phosphate buffer was 3 min. The eluate was collected at 2 min intervals for 10 min. Each eluate was used as sample solution and further evaluated using UV spectrophotometer (Shimadzu UV visible spectrophotometer 1700) at 256 nm. The bitterness score of mini-column was compared with gustatory sensation test. The threshold of bitterness of RDTs was determined as point at which maximum number of the volunteers described the taste as bitter or slightly bitter.

3.2.1.10. Stability studies

The RDTs were packed in Aluminum foil with polyethylene inner linings (strips). The RDTs were subjected to stability testing according to the International Conference on Harmonization (ICH) guidelines for zone III and IV. The packed RDTs were kept for accelerated stability (40^0C/75%RH) in stability chamber (Remi Instruments Ltd, Mumbai) for upto 6 months. A visual inspection (for physical appearance), dissolution testing and drug content estimation were carried out each month for the entire period of the stability testing.

3.2.2. Result and Discussion

3.2.2.1. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of ARM, SS, physical mixture and solid dispersion in 1:1M are presented in Figure 3.2. The characteristic peak of ARM at 2873 cm^{-1} is assigned to C-H stretching vibration in CH_3, CH_2. In addition, the absorption peak at 2844 cm^{-1} can be assigned to C-H stretching vibration in C-O-CH_3. The peak at 1137 cm^{-1} can be assigned to C-O stretching vibration in C-O-C. The peaks at 2953 and 2916 cm^{-1} are assigned to C-H stretching in -CH_3. All the above characteristic peaks appear in the spectra of all binary systems at

same wavenumber indicating no modification or interaction between the drug and carrier.

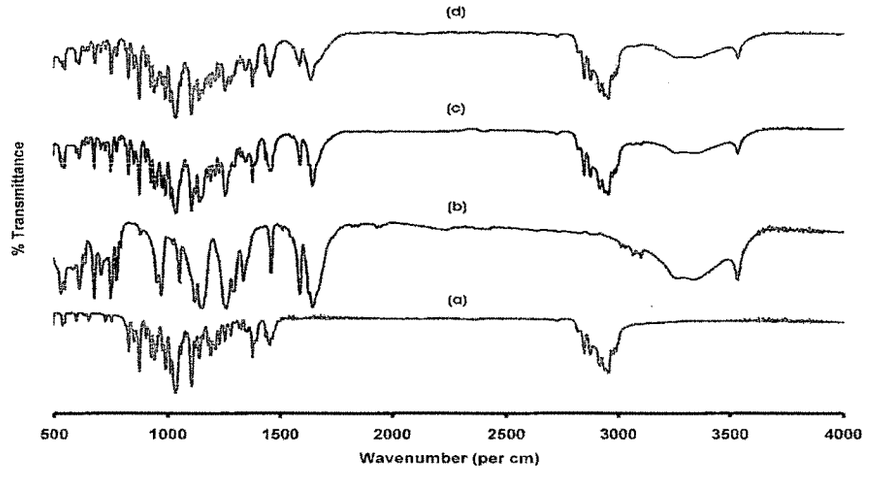

Figure 3.2. FT-IR spectra of (a) ARM, (b) SS, (c) physical mixture and (d) solid dispersion

3.2.2.2. Differential Scanning Calorimetry (DSC)

Thermal behavior of ARM, SS, physical mixture and solid dispersion 1:1M are depicted in Figure 3.3.

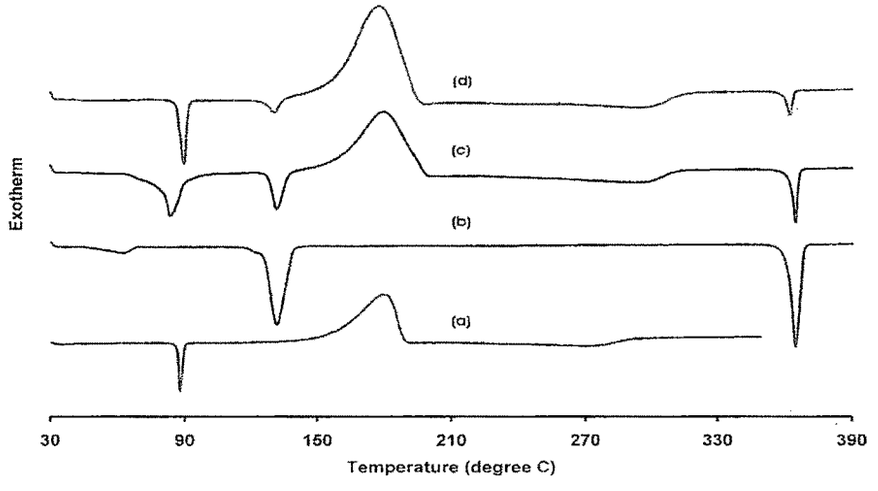

Figure 3.3. DSC curve of (a) ARM, (b) SS, (c) solid dispersion and (d) physical mixture

The pure ARM shows a sharp endothermic peak at 87.94^{0}C, followed by exothermic peak at 180.28^{0}C. The characteristic endothermic peak corresponding to melting peak of ARM was broaden and shifted towards lower temperature, with reduced intensity in both physical mixtures as well as solid dispersions. This might be due to the presence of the amorphous form of ARM in the solid dispersion.

3.2.2.3. X-ray Powder Diffraction (XRPD)

XRPD analysis was performed to confirm the results of DSC studies. XRPD patterns of ARM, SS, physical mixture and solid dispersion 1:1M are shown in Figure 3.4. In x-ray diffractogram of ARM, sharp peaks at a diffraction angle (2θ) of 9.39^0, 10.68^0, 11.16^0, 13.61^0, 17.54^0, 19.11^0, 20.10^0, 21.86^0, 22.69^0 indicates the presence of crystalline drug while solid dispersion showed sharp peaks at 6.04^0, 9.59^0, 10.12^0, 11.23^0, 17.38^0, 19.38^0, 22.84^0.

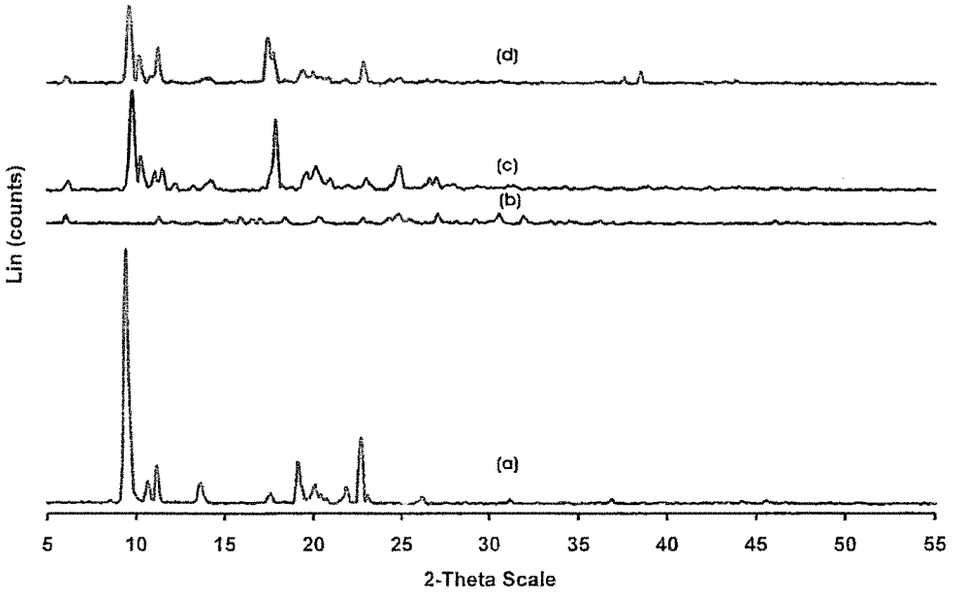

Figure 3.4. XRPD pattern of (a) ARM, (b) SS, (c) physical mixture and (d) solid dispersion

This data reveal that the typical drug crystalline peaks were still detected with reduced intensity in solid dispersion. The XRPD patterns of pure ARM, SS, and solid dispersion showed a total 11, 15, and 10 peaks, respectively. The XRPD

of solid dispersion exhibits 16 peaks less than the sum of the number of peaks of ARM and SS in their pure forms. This suggests that crystallinity of ARM is reduced in the solid dispersion.

3.2.2.4. Tablet Preparation and Characterization

SS is not successful in masking the bitter taste of ARM. Increased amount of SS showed increase in metallic bitter aftertaste rather than bitter taste masking. To formulate a RDT of ARM, the 1:1M binary mixture was selected.

The use of superdisintegrants for preparation of rapid disintegrating tablets 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 breaking of tablets and therefore faster disintegration. This disintegration is reported to have effect of dissolution characteristics as well. The formula of different tablets prepared is summarized in Table 3.2.

Table 3.2 Formulation of RDTs

Drug/Excipients	RDT1	RDT2	RDT3	RDT4	RDT5	RDT6
ARM (mg)	-	-	-	-	50	50
SS (mg)	-	-	-	-	-	40.41
Solid dispersion eq. to 50 mg ARM (mg)	90.41	90.41	90.41	90.41	-	-
Microcrystalline cellulose (Avicel PH 302) (mg)	90.85	-	90.85	-	131.26	90.85
Lactose (Lactopress) (mg)	-	90.85		90.85	-	-
Croscarmellose sodium (mg)	-	7.6	-	7.6	-	-
Crospovidone (mg)	7.6	-	7.6	-	7.6	7.6
Magnesium stearate (mg)	1.14	1.14	1.14	1.14	1.14	1.14

However, tablets containing crospovidone and granular microcrystalline cellulose (RDT3) showed the fastest disintegration (37-40 seconds) with improved hardness and friability. The formula of optimized RDT was used to

prepare RDT of pure ARM (RDT5) and physical mixture of ARM and SS (RDT6). Tablet characteristics of RDTs are summarized in Table 3.3.

Table 3.3. Physical properties of RDTs

Parameters	RDT1	RDT2	RDT3	RDT4	RDT5	RDT6
Weight (mg) ± SD*	190.56 ± 1.49	189.74 ± 1.63	191.38 ± 1.33	191.48 ± 1.28	189.39 ± 0.89	190.16 ± 1.37
Disintegrating Time (sec)	49-53	53-56	37-40	49-53	40-45	39-44
Hardness (kg)	3.8-3.9	3.7-3.8	3.9-4.0	3.8-3.9	3.8-3.9	3.9-4.0
Friability (%) ± SD*	0.39 ± 0.10	0.42 ± 0.13	0.37 ± 0.09	0.41 ± 0.15	0.39 ± 0.13	0.39 ± 0.15

**Values represent the mean ± SD of 3 experiments.*

3.2.2.5. *In vitro* drug release Studies

Drug release profiles of RDTs prepared from ARM, physical mixture and solid dispersion are presented in Figure 3.5. It is evident that the solid dispersion technique has improved the dissolution rate of ARM to a great extent. Table 3.4 summarizes % drug dissolved in 5 minutes (DP5), dissolution efficiency at 15 minutes (DE15), and dissolution efficiency at 60 minutes (DE60) for RDTs prepared from ARM and its binary systems with SS. RDT3 showed excellent dissolution efficiency (DE60 = 59.86%) and rapid dissolution (DP5 = 29.49%) at pH 6.8. However RDT3 showed slightly decreased dissolution efficiency (DE60 = 35.16%) and dissolution (DP5 = 5.28%) at pH 1.2. This attributes to the pH-dependent solubility of SS. It has been reported that the SS is more soluble in basic solution than acidic solution (Rowe et al., 2003).

The enhancement of dissolution of ARM from RDT3 at pH 6.8 can be ascribed to several factors. Lack of crystallinity, i.e., amorphization, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of a drug from the dispersion, dissolution of the

drug in the hydrophilic carrier, conversion of drug to amorphous state, and a combination of above are the main reasons for improvement of dissolution of ARM (Liu et al., 2004). RDT6 showed increase in drug release, which may be contributed to solubilization effect of hydrophilic carrier, conversion to amorphous state, and improved wettability of ARM. The results are in agreement with that obtained from DSC and XRPD studies.

Table 3.4. Percent dissolution and dissolution efficiency of ARM from binary systems in comparison with pure drug

Formulations	DP5 (%)		DE15 (%)		DE60 (%)	
	At pH 1.2	At pH 6.8	At pH 1.2	At pH 6.8	At pH 1.2	At pH 6.8
RDT5	7.78	20.00	13.18	25.96	37.79	49.96
RDT6	6.48	24.72	11.92	29.96	36.70	55.09
RDT3	5.28	29.49	10.76	34.40	35.16	59.86

DP5 – Percent drug dissolved at 5 min, DE15 and DE60 – dissolution efficiency at 15 and 60 min

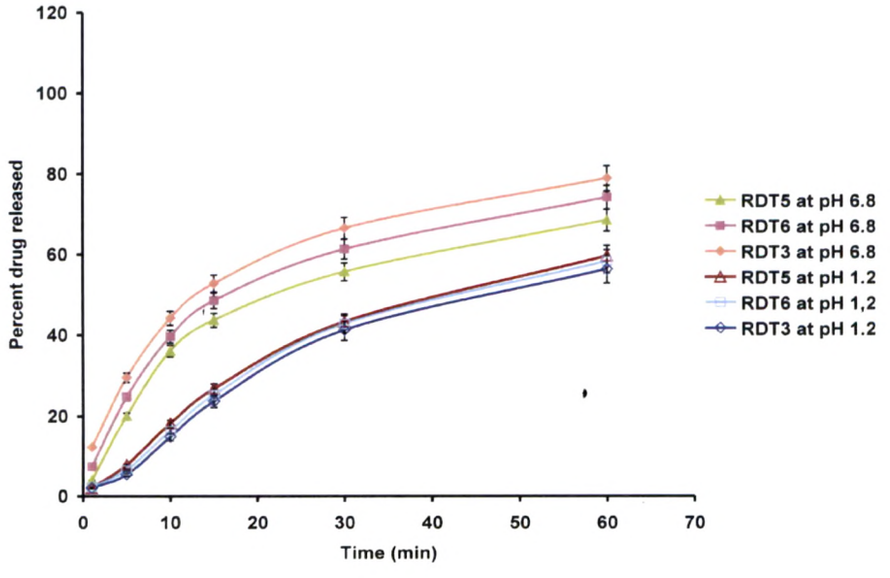

Figure 3.5. Dissolution profile of RDTs prepared from ARM, physical mixture and solid dispersion

3.2.2.6. Gustatory sensation test for RDTs

Bitterness evaluation results made by the consents of trained persons are listed in Table 3.5. Bitterness was imparted in solid dispersion with reference to pure drug. It has been reported that the bitter drug like ARM seem to bind G-protein coupled receptors, present on the apical taste cell membrane and produce bitterness (Yamamoto et al., 1998). However SS is sweet in taste and inhibits depolarization of taste cells through K^+ channels, thus producing sweet taste (Yamamoto et al., 1998). This finding suggests the action of SS on ionic channels rather at receptor level. This might be the possible reason for not masking the bitter taste of ARM using SS. RDT5 was rated as strongly bitter by 80% and very strongly bitter by 10% while RDT3 was rated as strongly bitter by 75% and very strongly biter by 15% of volunteers of panel.

Table 3.5. 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+
Pure ARM						2	17	1
Physical Mixture							18	2
Solid Dispersion							19	1
RDT5							18	2
RDT6							19	1
RDT3							17	3

3.2.2.7. Mini-column Method

The tapping frequency of column and flow rate of test solution were assumed to influence the mini-column method results. The tapping frequency was set at 30, 10 and 3 times. The effect of tapping frequency on the release rate is shown in Figure 3.6.

When the tapping frequency was 30 times, no release of ARM from compact powdered mass was observed. This might be because of the difficulty for the

test solution to penetrate the compact powdered mass. The release rate increased, when the tapping frequency was 3 times. However the release rate decreased, when the tapping frequency was 10 times. Thus the release rate decreased, as the tapping frequency increased.

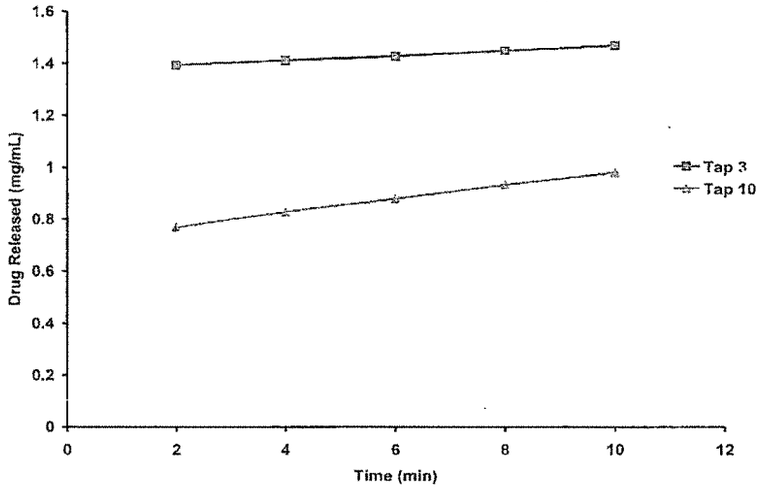

Figure 3.6. Effect of tapping frequency on the release of ARM from RDT3 with 1 mL/min flow rate

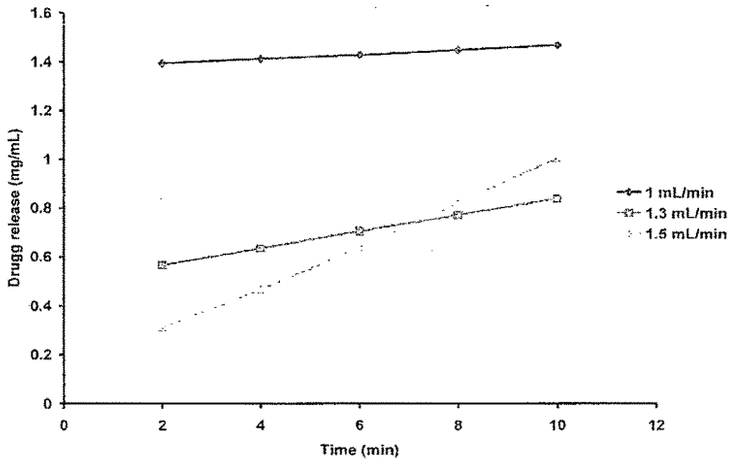

Figure 3.7. Effect of flow rate on the release of ARM from RDT3 with 3 times tapping frequency

Next, the tapping frequency was set at 3 times and flow rates at 1, 1.3 and 1.5 mL/min. The results are shown in Figure 3.7. When the flow rate

increased the release rate decreased. This was probably due to a delay in liquid penetration into the matrix, since the liquid flow rate on the matrix surface increased. The flow rate and tapping frequency were optimized, based on maximum drug release, at 1 mL/min and 3 times, respectively.

Table 3.6 shows the results of the sensory tests and amount of ARM released after 2 min interval with the mini-column method. RDT5 showed increased number of persons who sensed bitterness with increased amount of ARM released. RDT3 sensed very bitter with 1.39 mg/mL. The value (0.29 mg/mL) was about 4 times larger than that of pure ARM.

Table 3.6. Relationship between amount of release and results of sensory test of RDTs using mini-column method

Formulations	Time (min)				
	2	**4**	**6**	**8**	**10**
RDT5 (mg/mL) ± SD*	0.29 ± 0.05	0.30 ± 0.07	0.31 ± 0.05	0.32 ± 0.03	0.32 ± 0.04
Bitterness score	3	3	3	3	3
RDT6 (mg/mL) ± SD*	1.19 ± 0.06	1.20 ± 0.04	1.20 ± 0.07	1.21 ± 0.05	1.22 ± 0.03
Bitterness score	3	3	3	3	3
RDT3 (mg/mL) ± SD*	1.39 ± 0.05	1.41 ± 0.03	1.42 ± 0.07	1.44 ± 0.08	1.46 ± 0.06
Bitterness score	3	3	3	3	3

**Values represent the mean ± SD of 3 experiments.*

3.2.2.8. Stability studies

For the RDT3, the similarity factor (f2) was calculated by a comparison of the dissolution profiles in each storage condition with the control at the initial condition. The f2 values ranged from 85 to 93 with a 2%-4% average difference at pH, 1.2 and 6.8. Evaluation of the shelf life was carried out as per ICH Q1E, step 4 (Evaluation of stability data) guidelines for drug substances intended for room temperature storage. The accelerated stability data showed little change over time, and so a shelf life up to 1315.25 days

(43.84 months) can be proposed. The extrapolation to change with time is to determine the time at which 95% one-sided confidence limit for the mean curve intersects the acceptance criterion (not more than 5% change in assay from initial value).

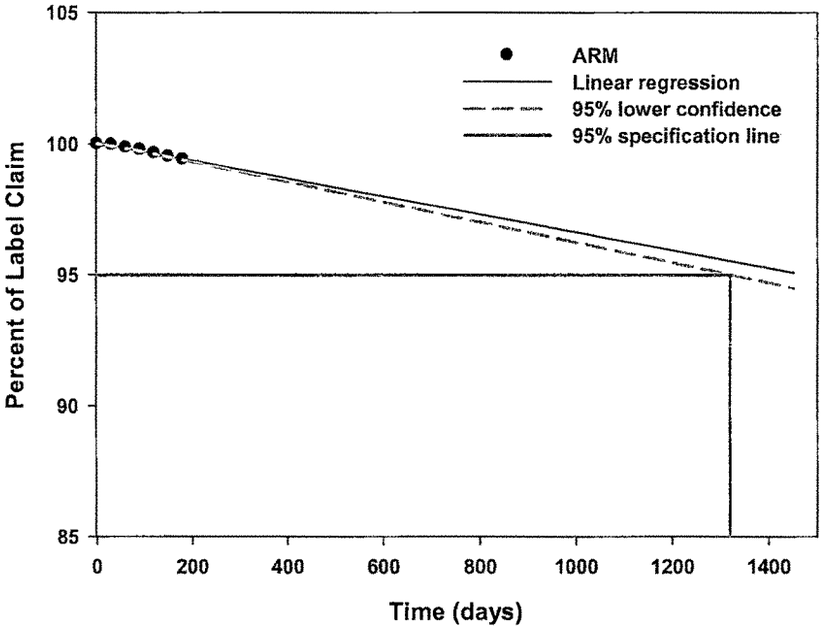

Figure 3.8. Extrapolation of accelerated stability data for shelf life calculation

The study conclusively demonstrated that SS is not efficient in masking the bitter taste of ARM by solid dispersion technique. However it improves ARM release at pH 6.8. The drug release at pH 1.2 decreased due to pH dependent solubility of SS. The FTIR and DSC studies indicated no interaction of ARM, at the molecular level, in SS solid dispersion. XRPD study showed amorphization of ARM. ARM-SS solid dispersion along with use of superdisintegrant could be considered for formulation of a stable RDTs of ARM. The use of mini-column method, an *in vitro* model, could be applicable to evaluate bitterness score, which simulates the disintegration of tablet in oral cavity.

3.3. Mefloquine Hydrochloride (MFL)

3.3.1. Experimental

3.3.1.1. Materials

Materials used were as mentioned in 3.2.1.1.

3.3.1.2. Preparation of MFL-SS solid dispersion

The solid dispersion of MFL and SS in 1:0.5 and 1:1M was prepared using solvent evaporation method. Accurately weighed quantity of MFL (500 mg in 5 mL) was dissolved in methanol. Previously dissolved SS (290 mg in 3 mL) in water was added with constant stirring on magnetic stirrer. The solid obtained after evaporation, was further dried to a constant weight in hot air oven at 100^0C. Dried powder was passed through sieve no. 44 and stored in desiccator (Tarsons Products Pvt. Ltd, India) until further evaluation.

The physical mixtures of MFL and SS in 1:0.5 and 1:1M were prepared by mixing individual components geometrically that had previously been sieved through sieve no. 44, together with a spatula.

3.3.1.3. Fourier transform infra-red spectroscopy (FTIR)

FT-IR study was carried out as mentioned in 3.2.1.3.

3.3.1.4. Differential scanning calorimeter (DSC)

DSC study was carried out as mentioned in 3.2.1.4.

3.3.1.5. X-ray Powder Diffraction (XRPD)

XRPD study was carried out as mentioned in 3.2.1.5.

3.3.1.6. Tablet Formulation and Characterization

Rapid disintegrating tablets (RDTs) containing equivalent of 250 mg of MFL were compressed on an 8-station single rotary tabletting press (GMC,

Mumbai, India) using a 9-mm round shaped flat punch with break line by direct compression technique.

Two different superdisintegrants, croscarmellose sodium and crospovidone were tried to achieve rapid disintegration of tablets. Granular microcrystalline cellulose and lactose were tried along with povidone (PVPK-30) to achieve the hardness. Prepared RDTs were evaluated as mentioned in 3.2.1.6.

3.3.1.7. *In vitro* drug release

In vitro drug release study was carried out as mentioned in 3.2.1.7.

3.3.1.8. Gustatory sensation test

Gustatory sensation test was carried out as mentioned in 3.2.1.8.

3.3.1.9. Mini-column Method

Mini-column method was studied as mentioned in 3.2.1.9.

3.3.1.10. Stability studies

Stability studies were carried out as mentioned in 3.2.1.10.

3.3.2. Results and discussion

3.3.2.1. Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectrum of the physical mixture of MFL and SS in 1:1M showed no significant shift or reduction in intensity of peaks of MFL. However the FTIR spectrum of solid dispersion was found to exhibit some significant difference in the characteristic peaks of MFL, revealing modification of the drug environment. As shown in Figure 3.9, a broad band of bonded N-H stretching vibration of MFL was observed at 3226 cm^{-1} while SS showed a sharp peak of intrahydrogen bonding at 3534 cm^{-1}. The solid dispersion showed shifting of intrahydrogen bonding of SS to 3448 cm^{-1} and disappearance of the N-H peak of MFL. This suggest the formation of hydrogen bond, $N^{(+)}$-H$\cdots N^{(+)}$, between $N^{(+)}$-H of MFL and $N^{(-)}$ of SS. This interaction of MFL and SS is favorable for masking the bitterness of MFL.

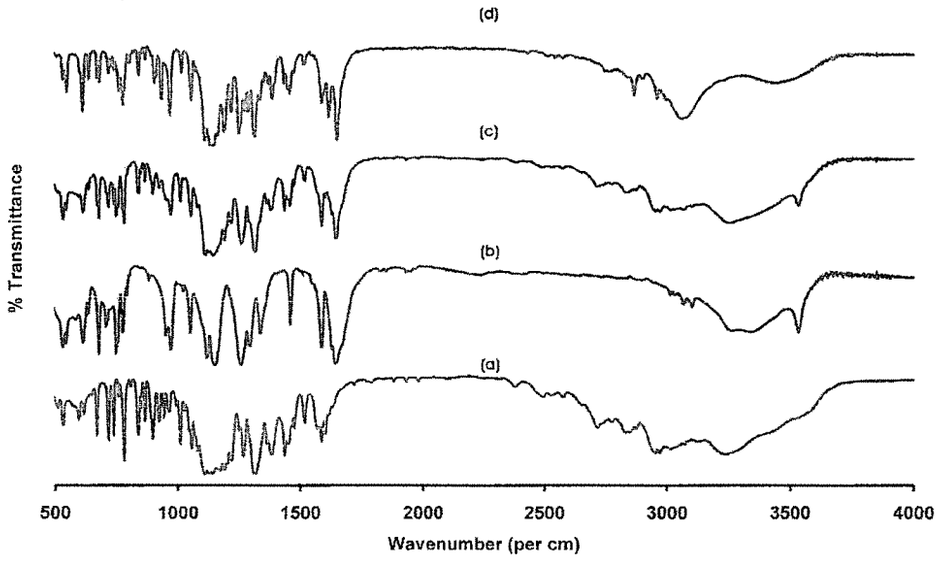

Figure 3.9. FT-IR spectra of (a) MFL, (b) SS, (c) physical mixture and (d) solid dispersion

3.3.2.2. Differential Scanning Calorimetry (DSC)

Figure 3.10 shows the DSC curve of MFL, SS, physical mixture and solid dispersion in 1:1M.

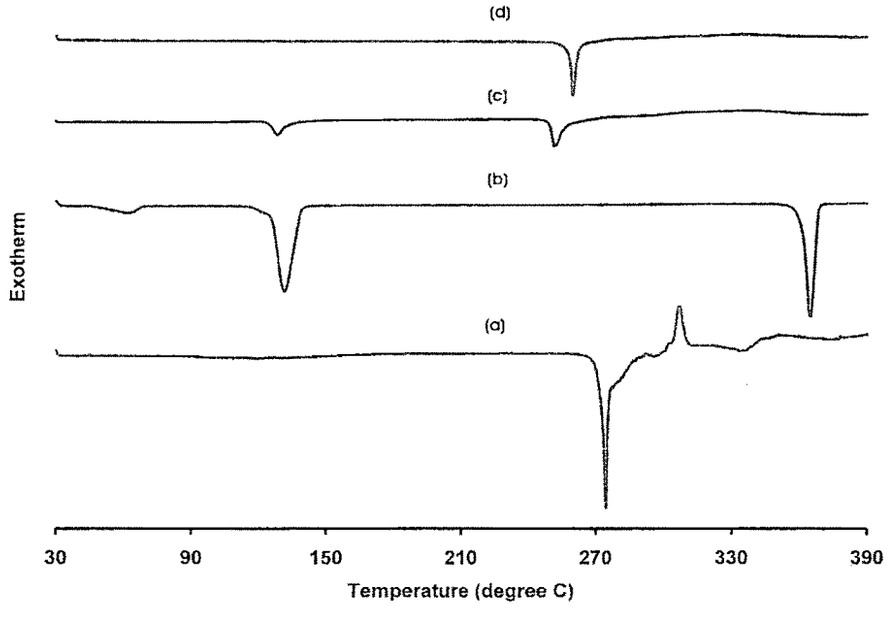

Figure 3.10. DSC curve of (a) MFL, (b) SS, (c) physical mixture and (d) solid dispersion

The pure MFL shows an endothermic peak at 271.38^{0}C, followed by exothermic peak at 308.36^{0}C. The characteristic endothermic peak corresponding to melting peak of MFL was shifted towards lower temperature (260.01^{0}C), with reduced intensity in both physical mixtures as well as solid dispersions. It might be due to the presence of the amorphous form of MFL in the solid dispersion. In addition, the desolvation and melting peak of SS disappeared. This could be attributed to phase transition of MFL during solvent evaporation.

3.3.2.3. X-ray Powder Diffraction (XRPD)

XRPD analysis was performed to confirm the results of DSC studies. XRPD patterns of MFL, SS, physical mixture and solid dispersion in 1:1M are shown in figure 3.11.

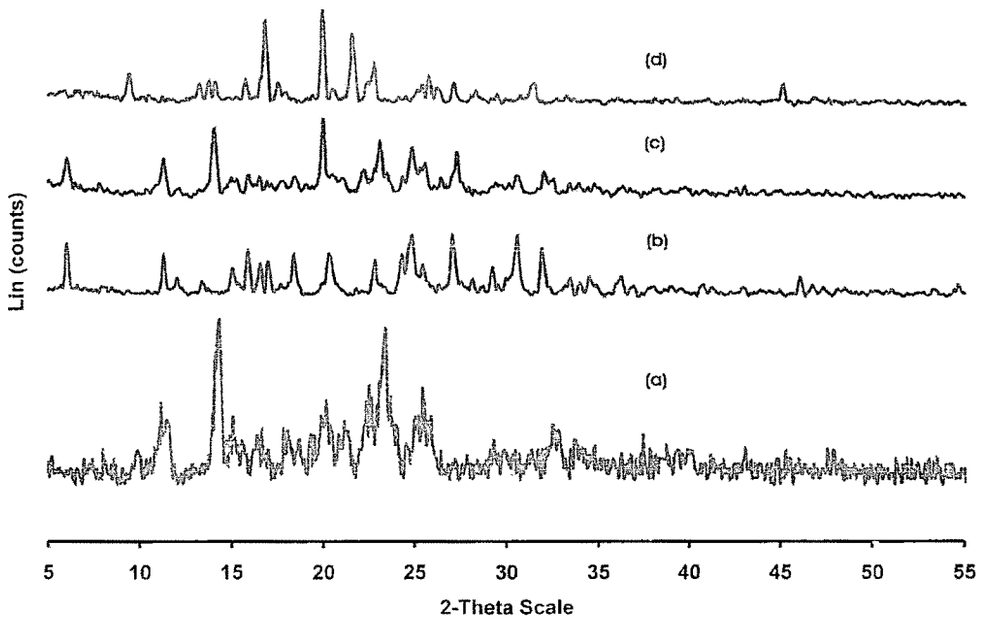

Figure 3.11. XRPD pattern of (a) MFL, (b) SS, (c) physical mixture and (d) solid dispersion

In x-ray diffractogram of MFL, sharp peaks at a diffraction angle (2θ) of 11.52^0, 14.31^0, 16.37^0, 18.03^0, 20.11^0, 21.26^0, 23.37^0, 25.50^0, 32.57^0 indicates the presence of crystalline drug, while solid dispersion shows sharp peaks at 9.43^0, 13.24^0, 13.77^0, 15.75^0, 16.84^0, 19.97^0, 21.60^0, 22.80^0,

25.78^0, 27.14^0, 31.53^0, 45.16^0, 56.14^0. This data revealed that the typical drug crystalline peaks were still detected with reduced intensity in solid dispersion. The XRPD patterns of MFL, SS, and solid dispersion showed a total 11, 15, and 13 peaks, respectively. The XRPD of solid dispersion exhibits 13 peaks less than the sum of the number of peaks of MFL and SS in their pure forms. This suggests that crystallinity of MFL is reduced in the solid dispersion. Further new peaks at 9.43^0 and 15.75^0 were observed in solid dispersion, indicating phase transition of MFL during solvent evaporation.

3.3.2.4. Tablet Preparation and Characterization

To formulate a rapid disintegrating tablet (RDT) of MFL, the 1:1M binary mixture was selected, based on its bitterness score. The formula of different tablets prepared is summarized in Table 3.7.

RDTs containing croscarmellose sodium and granular lactose (RDT14) showed the fastest disintegration (32-38 seconds) with improved hardness and friability. The formula of optimized RDT was used to prepare RDT of pure MFL (RDT15) and physical mixture of MFL and SS (RDT16). Tablet characteristics of RDTs are summarized in Table 3.8.

Table 3.7. Formulation of RDTs

Drug/Excipients	RDT11	RDT12	RDT13	RDT14	RDT15	RDT16
MFL (mg)	-	-	-	-	250	250
SS (mg)	-	-	-	-	-	145
Solid dispersion eq. to 250 mg MFL (mg)	395	395	395	395	-	-
Microcrystalline cellulose (Avicel PH 302) (mg)	68	-	68	-	-	-
Lactose (Lactopress) (mg)	-	68	-	68	213	68
Croscarmellose sodium (mg)	-	-	20	20	20	20
Crospovidone (mg)	20	20	-	-	-	-
Povidone (PVPK-30) (mg)	15	15	15	15	15	15
Magnesium stearate (mg)	2	2	2	2	2	2

Table 3.8. Physical properties of RDTs

Parameters	RDT11	RDT12	RDT13	RDT14	RDT15	RDT16
Weight (mg) ± SD*	500.23 ± 1.19	501.06 ± 1.37	498.73 ± 1.18	499.81 ± 1.24	500.16 ± 1.31	501.08 ± 1.26
Disintegrating Time (sec)	53-56	46-51	56-60	32-38	43-47	38-42
Hardness (kg)	3.4-3.5	3.6-3.7	3.3-3.4	3.7-3.8	3.6-3.7	3.8-3.9
Friability (%)± SD*	0.52 ± 0.12	0.49 ± 0.14	0.58 ± 0.11	0.42 ± 0.10	0.46 ± 0.18	0.49 ± 0.12

**Values represent the mean ± SD of 3 experiments.*

3.3.2.5. *In vitro* drug release Studies

Drug release profiles of RDTs prepared from MFL, physical mixture and solid dispersion are presented in Figure 3.12. It is evident that the solid dispersion technique has improved the dissolution rate of MFL to a great extent. Table 3.9 summarizes % drug dissolved in 5 minutes (DP5), dissolution efficiency at 15 minutes (DE15), and dissolution efficiency at 60 minutes (DE60) for RDTs prepared from MFL and its binary systems with SS. RDT14 showed excellent dissolution efficiency (DE60 = 84.02%) and rapid dissolution (DP5 = 33.40%) at pH 6.8. However RDT14 showed slightly decreased dissolution efficiency (DE60 = 58.45%) and dissolution (DP5 = 15.84%) at pH 1.2. This attributes to the pH-dependent solubility of SS. It has been reported that the SS is more soluble in basic solution than acidic solution (Rowe et al., 2003).

The enhancement of dissolution of MFL from RDT14 at pH 6.8 can be ascribed to several factors. Lack of crystallinity, ie, amorphization, solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, conversion of drug to amorphous state, and a combination of above are the main reasons for improvement of dissolution of MFL (Liu et al., 2004). RDT16 showed increase in drug release, which may be contributed to several factors such as solubilization effect of hydrophilic

carrier, conversion to amorphous state, and improved wettability of MFL. The results are in agreement with that obtained from DSC and XRPD studies.

Table 3.9. Percent dissolution and dissolution efficiency of MFL from binary systems in comparison with pure drug

Formulations	DP5 (%)		DE15 (%)		DE60 (%)	
	At pH 1.2	At pH 6.8	At pH 1.2	At pH 6.8	At pH 1.2	At pH 6.8
RDT15	18.69	21.60	29.23	33.24	65.96	72.37
RDT16	16.11	25.62	27.28	37.99	62.03	76.71
RDT14	15.84	33.40	26.15	46.27	58.45	84.02

DP5 – Percent drug dissolved at 5 min, DE15 and DE60 – dissolution efficiency at 15 and 60 min

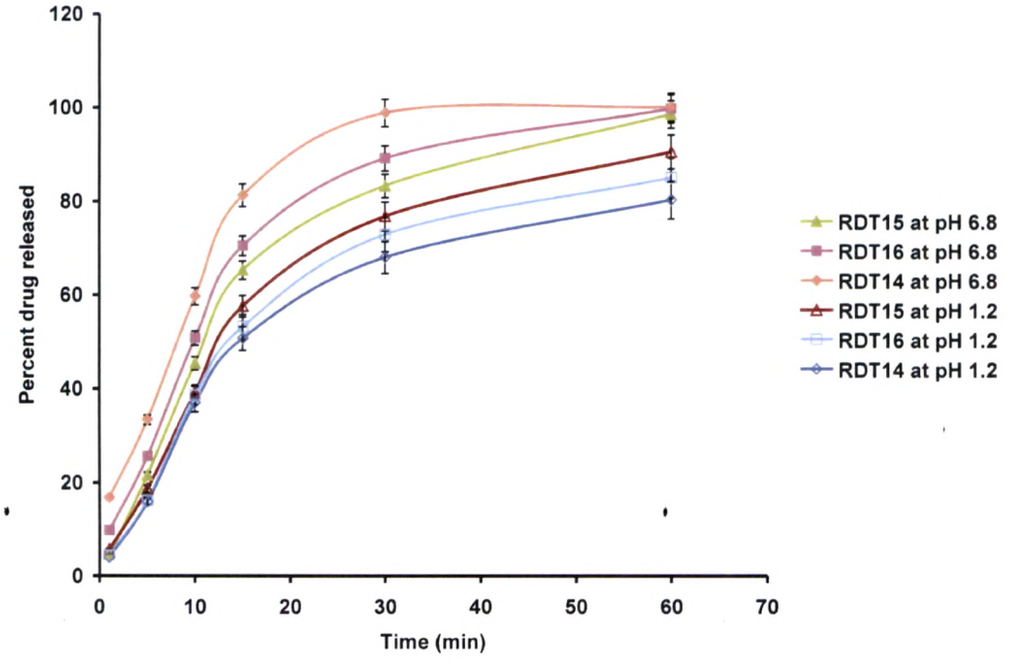

Figure 3.12. Dissolution profile of RDTs prepared from MFL, physical mixture and solid dispersion

3.3.2.6. Gustatory sensation test for RDTs

Bitterness evaluation results made by the consents of trained persons are listed in Table 3.10.

Table 3.10. 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+
Pure MFL						2	15	3
Physical Mixture		3	12	5				
Solid Dispersion	20							
RDT15							18	2
RDT16		5	10	5				
RDT14	20							

No bitterness was reported in solid dispersion with reference to pure drug. It has been reported that MFL depolarize taste cells by closing K^+ channels and produce bitterness (Yamamoto et al., 1998). SS is sweet in taste and inhibits depolarization of K^+ channels, thus producing sweet taste (Yamamoto et al., 1998). This finding suggests the solid dispersion inhibits the depolarization of taste cells through K^+ channels and thus reduces bitterness.

Though the physical mixing of MFL with SS brings the drug in close contact with carrier, MFL was not uniformly distributed in SS as that of solid dispersion. This may not result in complete taste masking of MFL in SS physical mixture, compared to solid dispersion.

RDT15 was rated as strongly bitter by 80% and very strongly bitter by 10% while RDT14 was rated as tasteless by 100% of volunteers of panel.

3.3.2.7. Mini-column Method

The tapping frequency of column and flow rate of test solution were assumed to influence the mini-column results. The tapping frequency was set at 30, 10

and 3 times. The effect of tapping frequency on the release rate is shown in Figure 3.13.

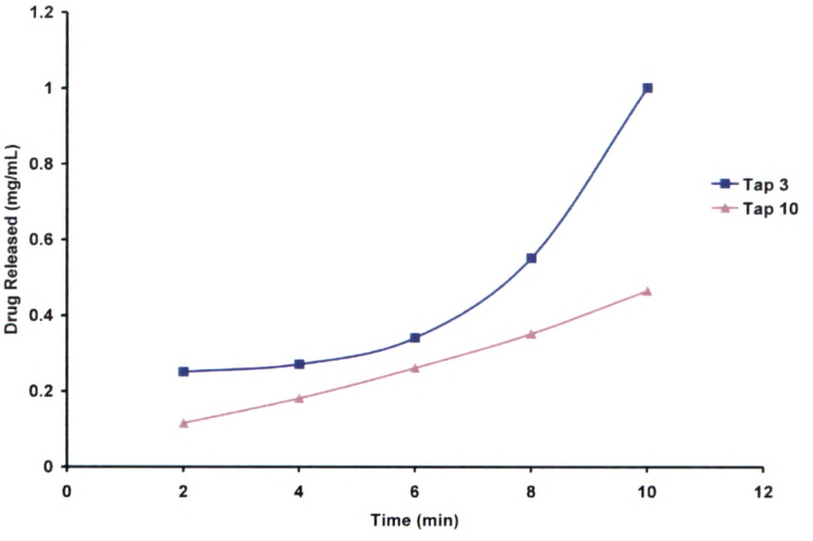

Figure 3.13. Effect of tapping frequency on the release of MFL from RDT14 with 1 mL/min flow rate

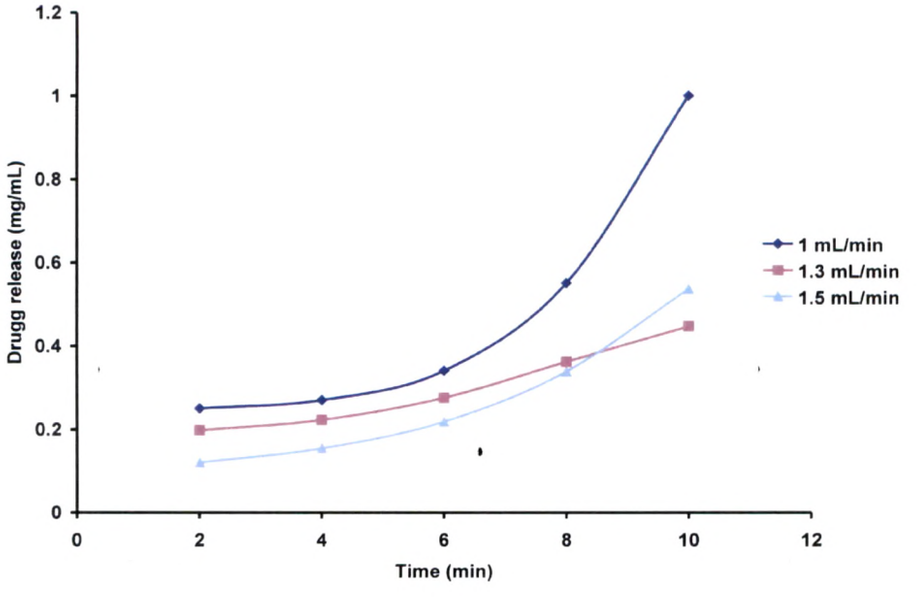

Figure 3.14. Effect of flow rate on the release of MFL from RDT14 with 3 times tapping frequency

When the tapping frequency was 30 times, no release of MFL from compact powdered mass was observed. This might be because of the difficulty for the test solution to penetrate the compact powdered mass. The release rate increased, when the tapping frequency was 3 times. However the release rate decreased, when the tapping frequency was 10 times. The release rate decreased as the tapping frequency increased.

Next, the tapping frequency was set at 3 times and flow rates at 1, 1.3 and 1.5 mL/min. The results are shown in Figure 3.14. When the flow rate increased the release rate decreased. This was probably due to a delay in liquid penetration into the matrix, since the liquid flow rate on the matrix surface increased. The flow rate and tapping frequency were optimized, based on maximum drug release, at 1 mL/min and 3 times, respectively. Optimized flow rate and tapping frequency were further applied to RDT15 and RDT16.

Table 3.11 shows the results of the sensory tests and amount of MFL released after 2 min interval with the mini-column method. RDT15 showed increased number of persons who sensed bitterness with increased amount of MFL released. RDT14 sensed no bitterness with 0.25 mg/mL. The value (0.07 mg/mL) was about 3.5 times larger than that of pure MFL.

Table 3.11. Relationship between amount of release and results of sensory test of RDTs using mini-column method

Formulations	Time (min)				
	2	**4**	**6**	**8**	**10**
RDT15 (mg/mL) ± SD*	0.07 ± 0.03	0.22 ± 0.06	0.50 ± 0.04	0.46 ± 0.08	0.48 ± 0.06
Bitterness score	2.5	3	3+	3+	3+
RDT16 (mg/mL) ± SD*	0.22 ± 0.06	0.24 ± 0.05	0.28 ± 0.09	0.44 ± 0.07	0.57 ± 0.08
Bitterness score	0	1	1	1	1.5
RDT14 (mg/mL) ± SD*	0.25 ± 0.06	0.27 ± 0.06	0.34 ± 0.08	0.55 ± 0.04	1.00 ± 0.09
Bitterness score	0	0	0	0	0

**Values represent the mean ± SD of 3 experiments.*

3.3.2.8. Stability studies

For the RDT14, the similarity factor (f2) was calculated by a comparison of the dissolution profiles in each storage condition with the control at the initial condition.

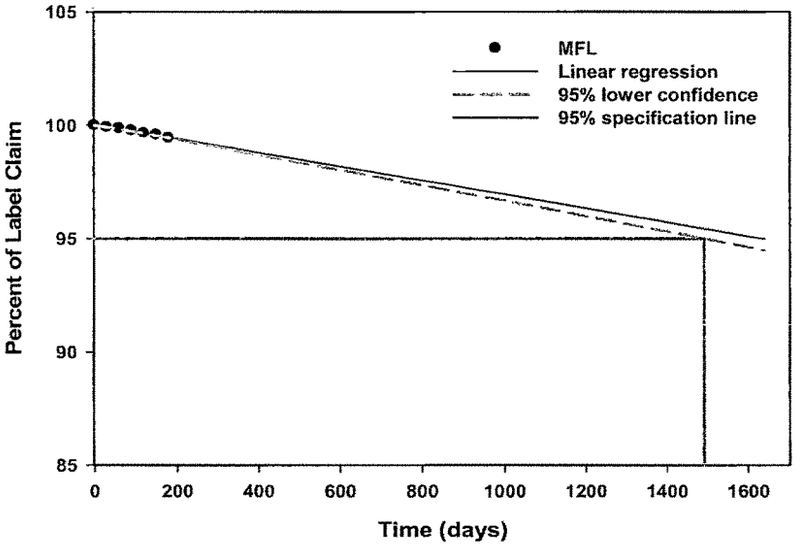

Figure 3.15. Extrapolation of accelerated stability data for shelf life calculation

The f2 values ranged from 89 to 94 with a 2%-3% average difference at pH, 1.2 and 6.8. Evaluation of the shelf life was carried out as per ICH Q1E, step 4 (Evaluation of stability data) guidelines for drug substances intended for room temperature storage. The accelerated stability data showed little change over time, and so a shelf life up to 1490.65 days (49.68 months) can be proposed. The extrapolation to change with time is to determine the time at which 95% one-sided confidence limit for the mean curve intersects the acceptance criterion (not more than 5% change in assay from initial value).

The study conclusively demonstrated the complete masking of bitter taste of MFL with improved dissolution at pH 6.8 by solid dispersion technique. The drug release at pH 1.2 decreased due to pH dependent solubility of SS. The FTIR, DSC and XRPD studies indicated phase transition of MFL in SS solid dispersion, which is favorable for bitter taste masking. MFL-SS solid

dispersion along with use of croscarmellose sodium as disintegrant could be considered for formulation of a stable RDTs of MFL. The use of mini-column, an *in vitro* model, could be applicable to evaluate bitterness score, which simulates the disintegration of tablet in oral cavity.

3.4. Primaquine Phosphate (PRM)

3.4.1. Experimental

3.4.1.1. Materials

Materials used were as mentioned in 3.2.1.1.

3.4.1.2. Preparation of PRM-SS solid dispersion

The solid dispersion of PRM and SS in 1:0.5 and 1:1M was prepared using solvent evaporation method. Accurately weighed quantity of PRM (100 mg in 5 mL) was dissolved in water. Previously dissolved SS (53 mg in 5 mL) in water was added with constant stirring on magnetic stirrer. Acetone was added to obtain a solid mass. The solid obtained after filtration, was further dried to a constant weight in hot air oven at 100^0C. Dried powder was passed through sieve no. 44 and stored in desiccator (Tarsons Products Pvt. Ltd, India) until further evaluation.

The physical mixtures of PRM and SS in 1:0.5 and 1:1M were prepared by mixing individual components geometrically that had previously been sieved through sieve no. 44, together with a spatula.

3.4.1.3. Fourier transform infra-red spectroscopy (FTIR)

FTIR study was carried out as mentioned in 3.2.1.3.

3.4.1.4. Differential scanning calorimeter (DSC)

DSC study was carried out as mentioned in 3.2.1.4.

3.4.1.5. Tablet Formulation and Characterization

Rapid disintegrating tablets (RDTs) containing equivalent of 13.16 mg of PRM (equivalent to 7.5 mg primaquine base) were compressed on an 8-station single rotary tabletting press (GMC, Mumbai, India) using a 5-mm round shaped flat punch with break line by direct compression technique.

Two different superdisintegrants, croscarmellose sodium and crospovidone were tried to achieve rapid disintegration of tablets. Granular microcrystalline cellulose and dibasic calcium phosphate (DCP) were used as diluent. Prepared RDTs were evaluated as mentioned in 3.2.1.6.

3.4.1.6. *In vitro* drug release

In vitro drug release study was carried out as mentioned in 3.2.1.7.

3.4.1.7. Gustatory sensation test

Gustatory sensation test was carried out as mentioned in 3.2.1.7.

3.4.1.8. Mini-column Method

Mini-column method was studied as mentioned in 3.2.1.9.

3.4.1.9. Stability studies

Stability studies were carried out as mentioned in 3.2.1.10.

3.4.2. Results and discussion

3.4.2.1. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of PRM, SS, physical mixture and solid dispersion in 1:1M are presented in Figure 3.16. The characteristic peaks of PRM at 2968 and 2878 cm^{-1} are assigned to C-H stretching vibration in CH_3, CH_2. In addition, the absorption peak at 2844 cm^{-1} can be assigned to C-H stretching vibration in C-O-CH_3. The peak at 1119 cm^{-1} can be assigned to C-O stretching vibration in C-O-C. The peak at 3305 cm^{-1} can be assigned to N-H stretching in primary amines. All the above characteristic peaks appear in the spectra of binary

systems at same wavenumber indicating no modification or interaction between the drug and carrier.

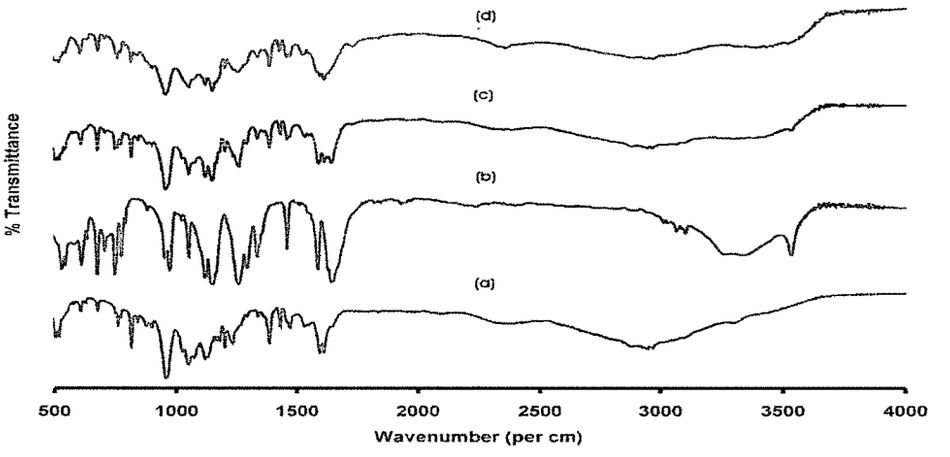

Figure 3.16. FT-IR spectra of (a) PRM, (b) SS, (c) physical mixture and (d) solid dispersion

3.4.2.2. Differential Scanning Calorimetry (DSC)

Thermal behavior of PRM, SS, physical mixture and solid dispersion in 1:1M are depicted in Figure 3.17.

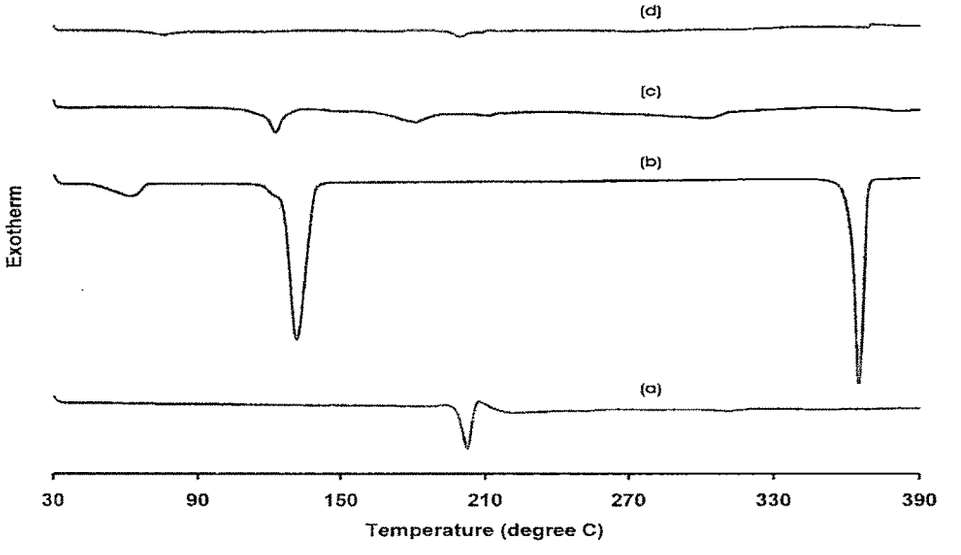

Figure 3.17. DSC curve of (a) PRM, (b) SS, (c) physical mixture and (d) solid dispersion

3.4.2.3. Tablet Preparation and Characterization

To formulate a rapid disintegrating tablet (RDT) of PRM, the 1:1M binary mixture was selected, based on its bitterness score. The formula of different tablets prepared is summarized in Table 3.12.

RDTs containing croscarmellose sodium and granular microcrystalline cellulose (RDT24) showed the fastest disintegration (36-41 seconds) with imprSoved hardness and friability. The formula of optimized RDT was used to prepare RDT of pure PRM (RDT25) and physical mixture of PRM and SS (RDT26). Tablet characteristics of RDTs are summarized in Table 3.13.

Table 3.12. Formulation of RDTs

Drug/Excipients	RDT21	RDT22	RDT23	RDT24	RDT25	RDT26
PRM (mg)	-	-	-	-	13.16	13.16
SS (mg)	-	-	-	-	-	6.96
Solid dispersion eq. to 13.16 mg PRM (mg)	20.12	20.12	20.12	20.12	-	-
Microcrystalline cellulose (Avicel PH 302) (mg)	27.63	-	27.63	-	34.59	27.69
Dibasic calcium phosphate (Emcompress) (mg)	-	27.63	-	27.63	-	-
Croscarmellose sodium (mg)	-	-	2	2	2	2
Crospovidone (mg)	2	2	-	-	-	-
Magnesium stearate (mg)	0.25	0.25	0.25	0.25	0.25	0.25

Table 3.13. Physical properties of RDTs

Parameters	RDT21	RDT22	RDT23	RDT24	RDT25	RDT26
Weight (mg) ± SD*	59.27 ± 1.39	50.34 ± 1.43	50.11 ± 1.33	50.69 ± 1.26	50.42 ± 1.29	51.23 ± 1.32
Disintegrating Time (sec)	41-47	44-49	42-47	36-41	43-47	33-37
Hardness (kg)	3.4-3.5	3.6-3.7	3.5-3.6	3.7-3.8	3.6-3.7	3.7-3.8
Friability (%) ± SD*	0.26 ± 0.10	0.24 ± 0.12	0.27 ± 0.11	0.23 ± 0.09	0.25 ± 0.09	0.21 ± 0.10

**Values represent the mean ± SD of 3 experiments.*

3.4.2.4. *In vitro* drug release Studies

Drug release profiles of RDTs prepared from PRM, SS, physical mixture and solid dispersion are presented in Figure 3.18. It is evident that the solid dispersion technique has negligible effect on the dissolution rate of PRM. Table 3.14 summarizes % drug dissolved in 5 minutes (DP5), dissolution efficiency at 15 minutes (DE15), and dissolution efficiency at 60 minutes (DE60) for RDTs prepared from PRM and its binary systems with SS. RDT24 showed dissolution efficiency (DE60 = 99.24%) and dissolution (DP5 = 100.14%) at pH 6.8. However RDT24 showed decreased dissolution efficiency (DE60 = 66.33%) and dissolution (DP5 = 64.57%) at pH 1.2. This attributes to the pH-dependent solubility of SS. It has been reported that the SS is more soluble in basic solution than acidic solution (Rowe et al., 2003).

The enhancement of dissolution of PRM from RDT24 at pH 6.8 can be ascribed to several factors. Solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of a drug from the dispersion, dissolution of the drug in the hydrophilic carrier, and a combination of above are the main reasons for improvement of dissolution of PRM (Liu et al., 2004).

Table 3.14. Percent dissolution and dissolution efficiency of PRM from binary systems in comparison with pure drug

Formulations	DP5 (%)		DE15 (%)		DE60 (%)	
	At pH 1.2	At pH 6.8	At pH 1.2	At pH 6.8	At pH 1.2	At pH 6.8
RDT25	97.62	100.33	65.84	95.90	69.64	99.54
RDT26	65.83	98.99	63.85	95.56	67.34	98.73
RDT24	64.57	100.14	62.87	96.24	66.33	99.24

DP5 – Percent drug dissolved at 5 min, DE15 and DE60 – dissolution efficiency at 15 and 60 min, respectively.

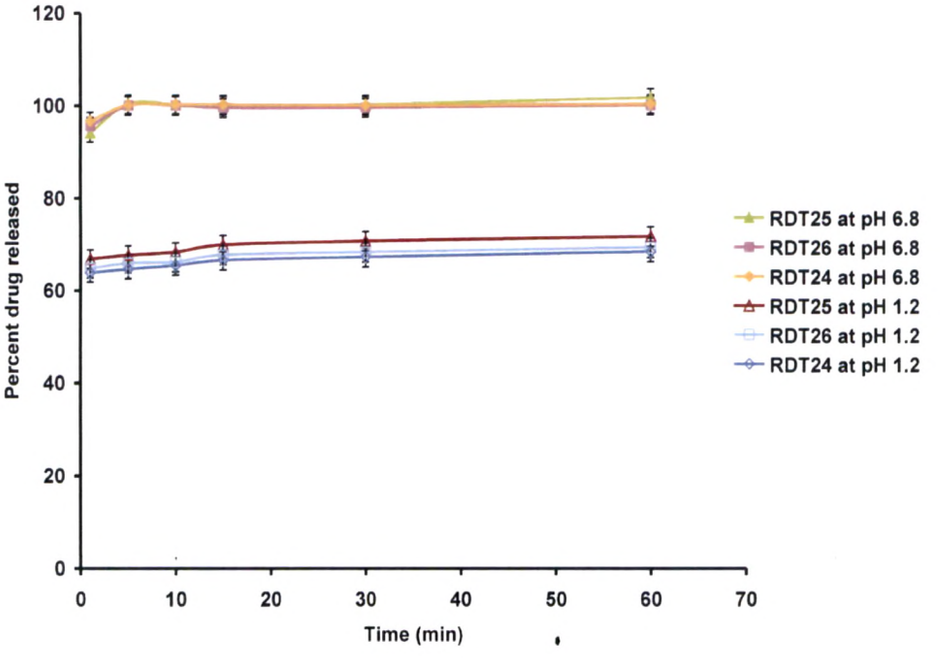

Figure 3.18 Dissolution profile of RDTs prepared from PRM, physical mixture and solid dispersion

RDT26 showed increase in drug release, which may be contributed to several factors such as solubilization effect of hydrophilic carrier, conversion to

amorphous state, and improved wettability of PRM. The results are in agreement with that obtained from DSC studies.

3.4.2.5. Gustatory sensation test

Bitterness evaluation results made by the consents of trained persons are listed in Table 3.15. No bitterness was imparted in solid dispersion with reference to pure drug. It has been reported that PRM depolarize taste cells by closing K^+ channels and produce bitterness (Yamamoto et al., 1998). SS is sweet in taste and inhibits depolarization of K^+ channels, thus producing sweet taste (Yamamoto et al., 1998). This finding suggests the solid dispersion inhibits the depolarization of taste cells through K^+ channels and thus reduces bitterness.

Though the physical mixing of PRM with SS brings the drug in close contact with carrier, PRM was not uniformly distributed in SS as that of solid dispersion. This may not result in complete taste masking of PRM in SS physical mixture, compared to solid dispersion.

RDT25 was rated as very strongly bitter by 5%, moderate to strong bitter by 5% and strongly bitter by 90% of volunteers of panel. RDT24 was rated as tasteless by 100% of volunteers of panel.

Table 3.15. 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+
Pure PRM							19	1
Physical Mixture		4	15	1				
Solid Dispersion	20							
RDT25						1	18	1
RDT26		5	14	1				
RDT24	20							

3.4.2.6. Mini-column Method

The tapping frequency of column and flow rate of test solution were assumed to influence the mini-column method results. The tapping frequency was set at 30, 10 and 3 times. The effect of tapping frequency on the release rate is shown in Figure 3.19.

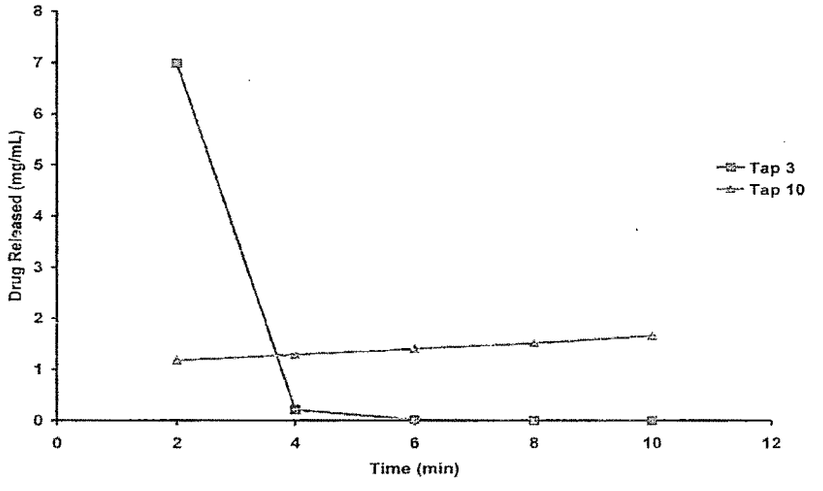

Figure 3.19. Effect of tapping frequency on the release of PRM from RDT24 with 1 mL/min flow rate

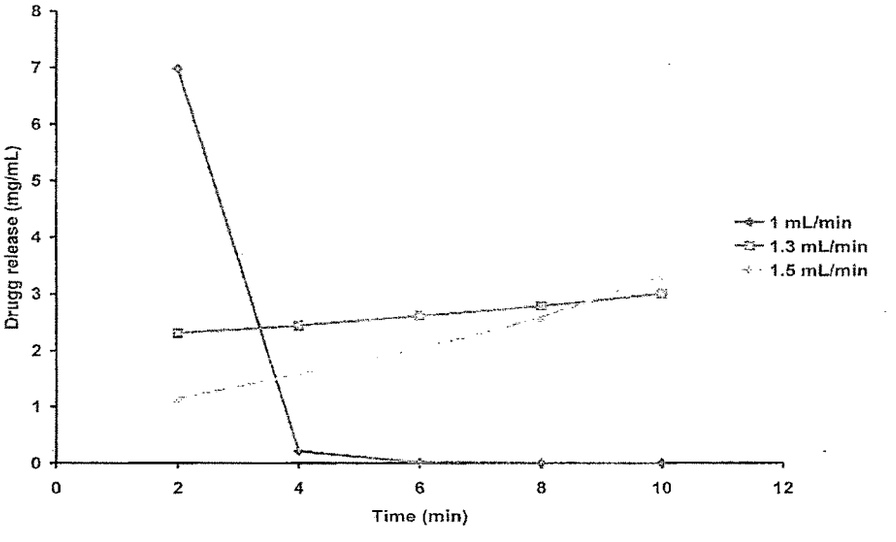

Figure 3.20. Effect of flow rate on the release of PRM from RDT24 with 3 tapping frequency

When the tapping frequency was 30 times, no release of PRM from compact powdered mass was observed. This might be because of the difficulty for the test solution to penetrate the compact powdered mass. The release rate increased, when the tapping frequency was 3 times. However the release rate decreased, when the tapping frequency was 10 times. The release rate decreased as the tapping frequency increased.

Next, the tapping frequency was set at 3 times and flow rates at 1, 1.3 and 1.5 mL/min. The results are shown in Figure 3.20. When the flow rate increased the release rate decreased. This was probably due to a delay in liquid penetration into the matrix, since the liquid flow rate on the matrix surface increased. The flow rate and tapping frequency were optimized, based on maximum drug release, at 1 mL/min and 3 times, respectively. Optimized flow rate and tapping frequency were further applied to RDT25 and RDT26.

Table 3.16 shows the results of the sensory tests and amount of PRM released after 2 min interval with the mini-column method. Initial increased PRM concentration in eluate resulted due to the higher solubility of PRM in pH 6.8. RDT25 showed increased number of persons who sensed bitterness with increased amount of PRM released. RDT24 sensed no bitterness with 6.98 mg/mL. The value (0.55 mg/mL) was about 12 times larger than that of pure PRM.

Table 3.16. Relationship between amount of release and results of sensory test of RDTs using mini-column method

Formulations	Time (min)				
	2	**4**	**6**	**8**	**10**
RDT25 (mg/mL) ± SD*	6.63 ± 0.09	0.55 ± 0.06	0.23 ± 0.08	0.05 ± 0.03	0
Bitterness score	3+	3	2.5	2	0
RDT26 (mg/mL) ± SD*	6.77 ± 0.07	0.31 ± 0.08	0.15 ± 0.04	0	0
Bitterness score	1.5	1	0	0	0
RDT24 (mg/mL) ± SD*	6.98 ± 0.08	0.21 ± 0.05	0.02 ± 0.02	0	0
Bitterness score	0	0	0	0	0

**Values represent the mean ± SD of 3 experiments.*

3.4.2.7. Stability studies

For the RDT24, the similarity factor (f2) was calculated by a comparison of the dissolution profiles in each storage condition with the control at the initial condition. The f2 values ranged from 89 to 96 with a 2%-2.5% average difference at pH, 1.2 and 6.8. Evaluation of the shelf life was carried out as per ICH Q1E, step 4 (Evaluation of stability data) guidelines for drug substances intended for room temperature storage. The accelerated stability data showed little change over time, and so a shelf life up to 1472.95 days (49.09 months) can be proposed. The extrapolation to change with time is to determine the time at which 95% one-sided confidence limit for the mean curve intersects the acceptance criterion (not more than 5% change in assay from initial value).

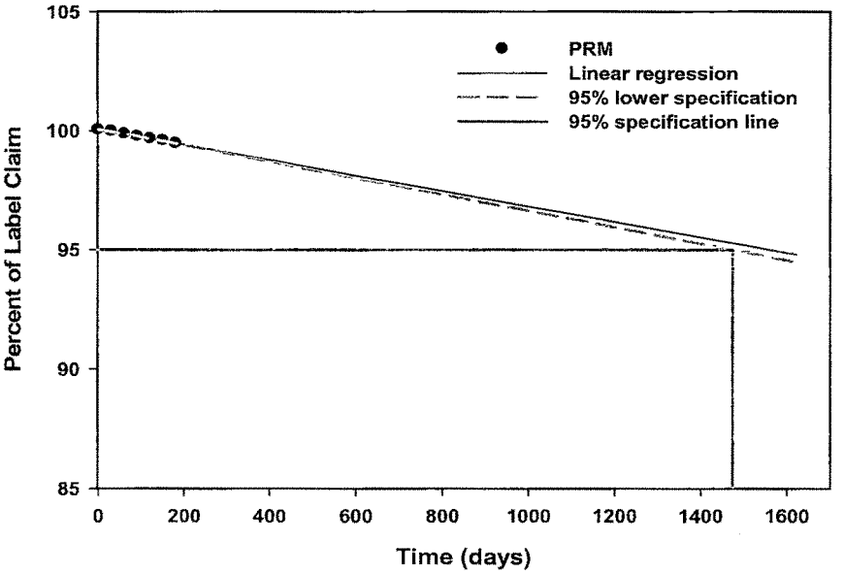

Figure 3.21. Extrapolation of accelerated stability data for shelf life calculation

The study conclusively demonstrated the complete masking of bitter taste of PRM by solid dispersion technique. The drug release at pH 1.2 decreased due to pH dependent solubility of SS. FTIR and DSC studies showed no interaction of PRM with SS in solid dispersion. PRM-SS solid dispersion along with croscarmellose sodium could be considered for formulation of RDTs of PRM.

3.5. Summary

	ARM-SS	MFL-SS	PRM-SS
SS required per tablet	50 mg ARM+ 40.41 mg SS	250 mg MFL + 145 mg SS	13.16 mg PRM + 6.96 mg SS
Mole ratio	1:1	1:1	1:1
Bitterness score (for solid dispersion)	3 (not masked)	0	0
Punch diameter	8 mm round shaped flat	9 mm round shaped flat	5 mm round shaped flat
Weight (mg)	190 mg	500 mg	50 mg
Disintegration Time (sec)	37-42	32-38	36-41
DP5 at pH 1.2 (%)	5.28	15.84	64.57
DP5 at pH 6.8 (%)	29.49	33.40	100.14
DE60 at pH 1.2 (%)	35.16	58.45	66.33
DE60 at pH 6.8 (%)	59.86	84.02	99.24
Hardness (kg)	3.9-4.0	3.7-3.8	3.7-3.8
Friability (%) ± SD*	0.37 ± 0.09	0.42 ± 0.10	0.23 ± 0.09
Bitterness score (for RDTs)	3 (not masked)	0	0
Similarity factor (f2)	85 to 93	89 to 94	89 to 96
Shelf life (months)	43.84	49.68	49.09

**Values represent the mean ± SD of 3 experiments, DP5 – Percent drug dissolved at 5 min, DE15 and DE60 – dissolution efficiency at 15 and 60 min*

3.6. References

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