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Research Article

Development and Evaluation of Artemether Taste Masked Rapid Disintegrating Tablets with Improved Dissolution Using Solid Dispersion Technique

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Abstract. The purpose of this research was to mask the intensely bitter taste of artemether (ARM) and to formulate a rapid-disintegrating tablet (RDT) of the taste-masked drug. Taste masking was done by solid dispersion with mono amino glycyrrhyzinate pentahydrate (GLY) by solvent evaporation method. To characterize and formulate taste masked rapid disintegrating tablets (RDTs) of ARM, the 1:1M solid dispersion was selected based on bitterness score. Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray powder diffraction (XRPD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. RDTs were evaluated for weight variation, disintegration time, hardness and friability. *In vitro* drug release studies were performed for RDTs at pH 1.2 and 6.8. Bitterness score was evaluated using mini-column method and compared with gustatory sensation test. FTIR spectroscopy and DSC showed no interaction while XRPD showed amorphization of ARM in GLY solid dispersion. RDTs prepared using solid dispersion, (RDT3), showed faster disintegration (within 28 s) and complete bitter taste masking of ARM. In addition, RDT3 exhibited better dissolution profile at both pH 1.2 and 6.8, than RDTs prepared from pure ARM (RDT5). Taste evaluation of RDTs in human volunteers rated tasteless with a score of 0 to RDT3 and 3 to RDT5. Mini-column revealed that RDT5 showed increase in number of persons who sensed bitterness with increased amount of ARM release while RDT3 sensed no bitterness. Thus, results conclusively demonstrated successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity with improved dissolution.

KEY WORDS: artemether; rapidly disintegrating tablet; solid dispersion; taste masking.

INTRODUCTION

β-Artemether (ARM) is one of the artemisinine derivatives, which has proved to be efficient against acute uncomplicated and severe falciparum malaria (1,2) and can clear the parasite faster even in multiple drug-resistant falciparum malaria (3). ARM has poor aqueous solubility, and thus resulting in incomplete absorption after oral administration. This is due to a large fraction of the dose remaining undissolved for absorption upon reaching, the non-absorbable site in the large intestine. Under such conditions, the bioavailability can be increased by using, a more water soluble formulation. Attempts to develop more water soluble formulations are still continuing (4).

Further ARM has an extremely unpleasant bitter taste. The exact mechanism of bitterness is unknown. However it has been reported that the drugs like ARM bind to the membrane receptor, present on the apical taste cells and produces bitterness (5).

Masking of bitter taste of the ARM is an extremely important factor in the formulation of rapidly disintegrating tablets (RDTs) to ensure patient compliance (6,7). RDTs are useful in patients, such as pediatric, geriatric, who may face difficulty in swallowing conventional tablets or capsules and liquid orals or syrup (8–11).

Many reported techniques such as polymer coating, microencapsulation, use of lecithins and related substances, liposomes and various polymeric materials mask the bitterness by controlling drug release at salivary pH (12). However it is a major challenge to develop taste masked RDTs with improved drug release.

Glycyrrhizin, which is also known as glycyrrhizinic acid, is an oleanane-type triterpene glycoside whose use as sweeteners has been reviewed. This compound is extracted from the rhizomes and roots of licorice (*Glycyrrhiza glabra* L. Fabaceae) and other species in genus Glycyrrhiza (13,14). In USA, ammoniated glycyrrhizin is included in the generally recognized as safe (GRAS) list of approved natural flavoring agent (15). Ammoniated glycyrrhizin has been rated as approximately 50 times the sweetness of sucrose (13,16). Monosodium glycyrrhyzinate together with flavors has been used to mask the bitter taste of guaifenesin (17) and extract containing pogostemi herba (18).

Thus in the present study an attempt has been made to formulate taste masked RDTs of ARM with improved

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dissolution so as to prepare a "patient-friendly dosage form" using Mono amino glycyrrhyzinate pentahydrate (GLY) as the hydrophilic carrier. Furthermore, the study undertakes to investigate solid-state characterization, and attempts to see the possible mechanism of taste masking and improved dissolution rate.

MATERIALS AND METHODS

Materials

Artemether (ARM) was a gift from Ajanta Pharma Ltd, (Mumbai, India). Mono amino glycyrrhyzinate pentahydrate (GLY) was received as gift sample 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 302, FMC Biopolymer, Ireland), and spray-dried lactose (Lactopress, Friesland, The Netherlands). The superdisintegrants were crospovidone (Kollidon CL, BASF, Germany), croscarmellose sodium (Ac-Di-Sol, FMC Biopolymer, Ireland). Talc and magnesium stearate were purchased from ACS chemicals (Ahmedabad, India) and Suvidhinath laboratories (Baroda, India), respectively. All reagents and solvents used in the study were of analytical grade.

Preparation of ARM-GLY Solid Dispersion

The solid dispersion of ARM and GLY in 1:0.5 and 1:1M was carried out using solvent evaporation method. Accurately weighed quantity of ARM (500 mg in 5 ml) was dissolved in methanol. Previously dissolved GLY (1.41 g in 5 ml) in water was added with constant stirring on magnetic stirrer. The solid was dried to a constant weight in hot air oven at 70 °C for 48 h. Dried powder was passed through sieve no. 44 (ASTM no. 45) and stored in desiccator until further evaluation.

The physical mixtures of ARM and GLY in 1:0.5 and 1:1 M were prepared by mixing individual components geometrically that had previously been sieved through sieve no. 44 (ASTM no. 45), together with a spatula.

CHARACTERIZATION OF SOLID DISPERSIONS

Solubility Studies

An excess of ARM was added to screw-capped vials containing GLY solution (0.5% to 2.5% *w/v* concentration range), prepared in phosphate buffer, pH 6.8. Vials were shaken mechanically at 28±0.5 °C for 24 h. At equilibrium after 2 days, aliquots were withdrawn, filtered (0.22 μm pore size) and UV spectrophotometrically (Shimadzu UV visible spectrophotometer 1601) assayed for drug content at 256 nm.

Fourier Transform Infra-Red Spectroscopy (FTIR)

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

Differential Scanning Calorimeter (DSC)

Differential scanning calorimetry study was performed using differential scanning calorimeter (Mettler Toledo, DSC 822). Samples were heated in an open aluminum pans at a rate of 5 °C per min^{-1} in a 30 to 330 °C temperature range under a nitrogen flow of 40 ml/min.

X-Ray Powder Diffractometry (XRPD)

X-Ray powder diffraction patterns were recorded on a X-ray diffractometer (Philips X'Pert MPD, Eindhoven, The Netherlands) using Ni-filtered, CuKα radiation, a voltage of 40 kV, and a 25-mA current. The scanning rate employed was $1°min^{-1}$ over the 10 to 30° diffraction angle (2θ) range.

TABLET FORMULATION AND CHARACTERIZATION

Rapid disintegrating tablets (RDTs) containing equivalent of 50 mg of ARM were compressed on an eight-station single rotary tabletting press (GMC, Mumbai, India) using a

Table I. Formulation and Physical Properties of RDTs

Drug/Excipients	RDT1	RDT2	RDT3	RDT4	RDT5	RDT6
ARM (mg)	–	–	–	–	50	50
GLY (mg)	–	–	–	–	–	141
Solid dispersion eq. to 50 mg ARM (mg)	191	191	191	191	–	–
Microcrystalline cellulose (Avicel PH 302; mg)	185	–	185	–	326	185
Lactose (Lactopress; mg)	–	185	–	185	–	–
Croscarmellose sodium (mg)	–	–	20	20	20	20
Crospovidone (mg)	20	20	–	–	–	–
Magnesium stearate (mg)	4	4	4	4	4	4
Physical properties of RDTs						
Weight (mg)	398.47	399.12	401.28	398.86	402.71	400.63
Disintegrating time (s)	56	42	28	53	32	37
Hardness (kg)	2.67	3.11	3.16	3.26	3.53	3.23
Friability (%)	0.63	0.59	0.54	0.56	0.48	0.51

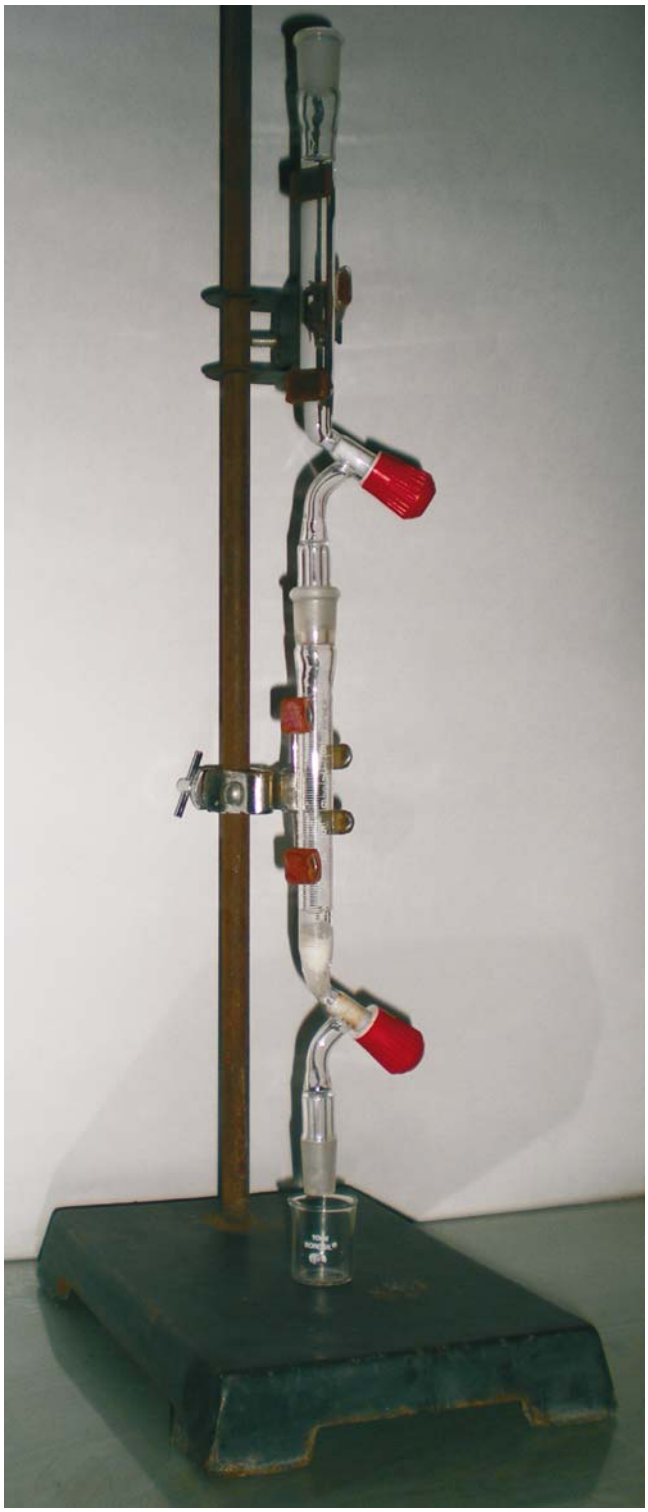

Fig. 1. Mini-column apparatus for evaluation of bitterness

9-mm flat punch with break line by direct compression technique (7).

Two different superdisintegrants, croscarmellose sodium and crospovidone were tried to achieve rapid disintegration of tablets. Granular microcrystalline cellulose (Avicel PH 302) and lactose (Lactopress) were tried to achieve the hardness. The formula of different RDTs prepared is summarized in Table I.

Prepared RDTs were evaluated for thickness (Varnier Caliper), hardness (Monsanto hardness tester), friability (Roche Friabilator), disintegration time (Electrolab disintegrating apparatus) and weight variation. The bitterness score was evaluated *in vitro* using mini-column method and further compared with human gustatory sensation test.

In Vitro Drug Release Study

In vitro drug release study was performed at 37±0.5 °C, using six-station USP XXII apparatus (TDT-50, Electrolab, Mumbai, India) with paddle rotating at 50 rpm. The drug release study was carried out in phosphate buffer, pH 6.8 because the pH of the saliva is in the range from 6.3 to 7.2. Further the drug release study was performed in hydrochloric acid buffer, pH 1.2 to demonstrate the availability of 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 1601) at 256 nm. 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 (19).

Gustatory Sensation Test

Gustatory sensation test was carried out according to the method described by Mou-ying *et al.* (20) 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 15 s. 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 was used with the following values: 0 = tasteless, 0.5 = very slightly bitter, 1 = slightly bitter, 1.5 = slight to moderate bitter, 2 = moderately bitter, 2.5 = moderate

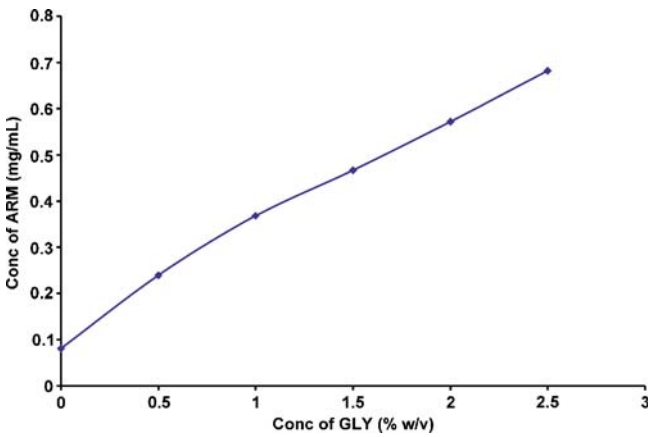

Fig. 2. Solubility diagram of ARM in presence of GLY

to strong bitter, 3 = strongly bitter, 3+ = very strong. This numerical scale was validated by testing samples randomly. The oral cavity was rinsed with distilled water three times to avoid bias. Wash out period between testing different samples was 15 min.

RDTs were evaluated for taste masking by keeping in mouth till it disintegrated. For comparison, RDTs of pure ARM were also subjected to taste evaluation by the panel and the results were compared. The threshold of bitterness was determined as point at which maximum number of the volunteers described the taste as bitter or slightly bitter.

Mini-column Method

Yajima *et al*. reported a mini-column method for evaluation of bitterness in dry syrup (21). This method has been modified for evaluation of bitterness in tablets. 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.

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 three, ten 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 two separate columns, upper and lower as shown in Fig. 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. 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 three 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 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 1601) at 256 nm. The bitterness score of mini-column was compared with gustatory sensation test.

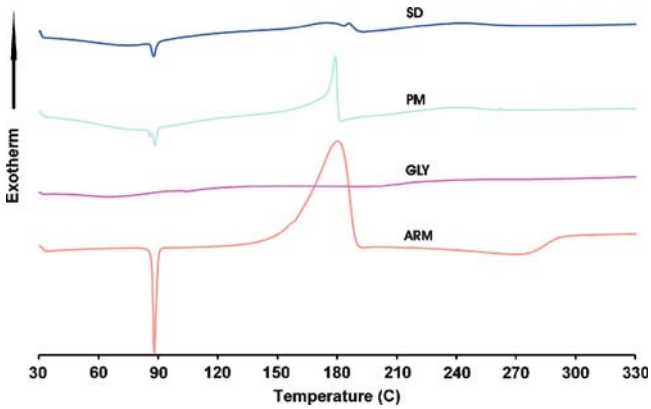

Fig. 4. DSC curve of ARM, GLY, physical mixture (PM) and solid dispersion (SD)

RESULTS AND DISCUSSION

Characterization of Solid Dispersions

Solubility Studies

The phase solubility diagram of the ARM-GLY system is shown in Fig. 2. Intrinsic solubility of ARM in phosphate buffer (pH 6.8) is found to be 8.1 µg/ml, which is in good accordance with literature (22). The solubility of ARM was enhanced using increasing concentrations of GLY phosphate buffer (pH 6.8), a phenomenon that can probably be explained by improved wettability of the hydrophobic surface of ARM by the carriers.

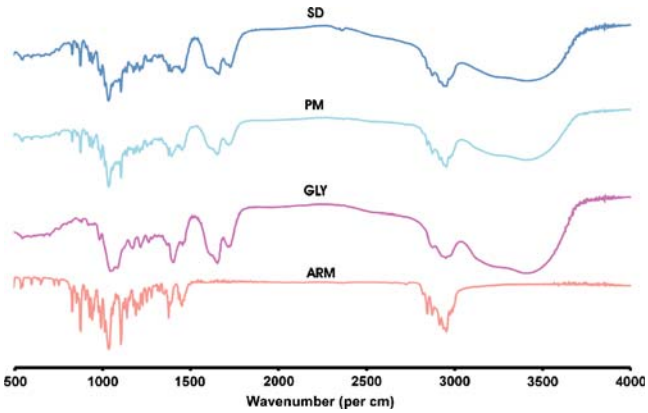

Fig. 3. FT-IR spectra of ARM, GLY, physical mixture (PM) and solid dispersion (SD)

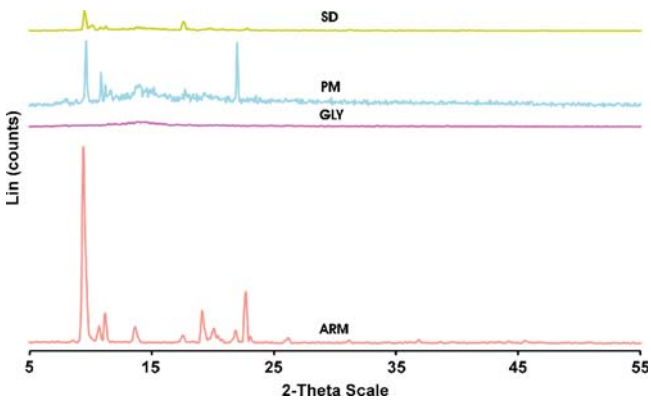

Fig. 5. XRPD pattern of ARM, GLY, physical mixture (PM) and solid dispersion (SD)

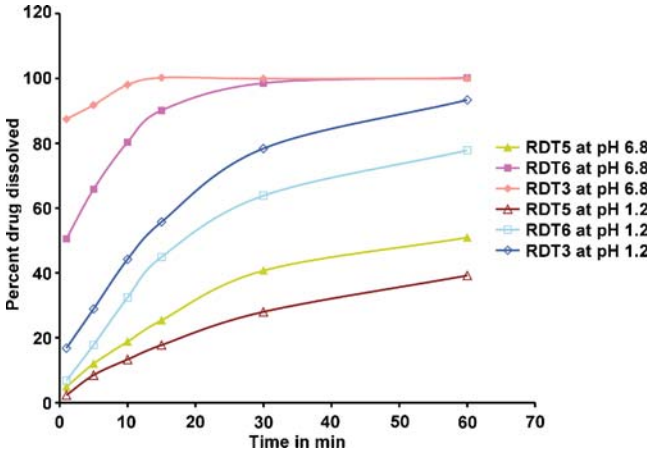

Fig. 6. Dissolution profile of RDTs prepared from ARM, physical mixture and solid dispersion

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR studies were performed to detect the possible molecular interaction between ARM and GLY in the solid dispersion system. FTIR spectra of ARM, GLY and its binary systems in 1:1 M are presented in Fig. 3. The characteristic peaks of ARM at 2,873 cm^{-1} are assigned to C–H stretching vibration in CH_3, CH_2. In addition, the absorption peak at 2,844 cm^{-1} can be assigned to C–H stretching vibration in C–O–CH_3. The peak at 1,137 cm^{-1} can be assigned to C–O stretching vibration in C–O–C. The peaks at 2,953 and 2,916 cm^{-1} are assigned to C–H stretching in –CH_3. All the above characteristic peaks of ARM appears in the spectra of all binary systems at same wavenumber indicating no modification or interaction between the drug and carrier.

Differential Scanning Calorimetry (DSC)

Thermal behavior of pure drug and corresponding drug carrier system in 1:1 M are depicted in Fig. 4. The pure ARM shows a sharp endothermic peak at 87.94 °C, followed by exothermic peak at 180.28 °C. The characteristic endothermic peak corresponding to melting peak of ARM was shifted towards lower temperature, with reduced intensity in physical mixtures as well as solid dispersions. This could be attributed to higher GLY concentration and uniform distribution of ARM in the crust of GLY, resulting in complete miscibility of molten drug in GLY. Moreover, the data also indicate there seems to be no interaction between the components of binary system. No significant difference in DSC pattern of solid dispersion and physical mixture suggests that interaction could not induce at molecular level even in the solvent evaporation process and solid dispersion formed is a physical mixture with highly dispersed drug crystals in carrier.

X-Ray Powder Diffractometry (XRPD)

XRPD analysis was performed to confirm the results of FTIR and DSC studies. XRPD patterns of ARM, GLY and binary systems in 1:1 M are shown in Fig. 5. X-Ray diffractogram of ARM showed sharp peaks indicating the presence of crystalline drug while solid dispersion showed sharp peaks with reduced intensity. The XRPD patterns of ARM, GLY, and solid dispersion showed a total 11, three, and five peaks, respectively. The XRPD of solid dispersion exhibits nine peaks less than the sum of the number of peaks of ARM and GLY in their pure forms. This suggests that crystallinity of ARM is reduced in the solid dispersion. Decrease in crystallinity of the drug may contribute to enhancement of dissolution of the drug.

TABLET PREPARATION AND CHARACTERIZATION

To formulate a rapid disintegrating tablet (RDT) of ARM, the 1:1 M binary mixture was selected, based on its bitterness score.

RDTs containing croscarmellose sodium and granular microcrystalline cellulose (RDT3) showed the fastest disintegration (28 s) 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 GLY (RDT6). Tablet characteristics of RDTs are summarized in Table I.

In Vitro Drug Release Studies

Drug release profiles of pure ARM and drug-carrier binary systems are presented in Fig. 6. It is evident that the solid dispersion technique has improved the dissolution rate of ARM to a great extent. Table II summarizes percent drug dissolved in 5 min (DP5), dissolution efficiency at 15 min (DE15), and dissolution efficiency at 60 min (DE60) for ARM and its binary systems with GLY.

In vitro drug release studies for RDT3 confirmed the results obtained with solid binary mixtures. RDT3 showed excellent dissolution efficiency (DE60=97.83%) and rapid dissolution (DP5=91.77%) at pH 6.8. Similarly RDT3 showed improved dissolution efficiency (DE60=68.55%) and rapid dissolution (DP5=28.89%) at pH 1.2. When

Table II. Percent Dissolution and Dissolution Efficiency of ARM From Binary Systems in Comparison with Pure Drug

	DP5		DE15		DE60	
Formulation	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	8.50	12.09	10.32	14.91	25.10	34.89
RDT6	17.80	65.80	24.76	69.94	55.18	90.75
RDT3	28.89	91.77	35.49	91.48	68.55	97.83

DP5 percent drug dissolved at 5 min, *DE15 and DE60* dissolution efficiency at 15 and 60 min

Table III. Bitterness Evaluation by a Panel of 20 Human Volunteers

	Number of Volunteers Rating the Preparation as							
Formulation	0	0.5	1	1.5	2	2.5	3	3+
Pure ARM						1	17	2
Physical mixture			4	13	3			
Solid dispersion	19	1						
RDT5						3	13	4
RDT6		2	16	2				
RDT3	20							

compared with pure ARM formulation, RDTs formulated with the binary mixture clearly perform better and a significant enhancement in dissolution characteristics.

This enhancement of dissolution of ARM from drug–carrier systems can be ascribed to several factors. It has been reported that GLY has structural similarity to triterpenes and show surfactant action (23,24). 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 (25). RDT6 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 ARM. The results are in agreement with that obtained from solubility studies, DSC and XRD.

Bitterness Evaluation

Bitterness evaluation results made by the consents of human volunteers are listed in Table III. It has been reported that the bitter drug like artemether seem to bind G-protein coupled receptors, present on the apical taste cell membrane and produce bitterness (5). GLY is astringent in nature and hence might be directly interacting with G-proteins and paralyzing them, resulting in reduced taste transduction and thus reduced bitterness score.

ARM was uniformly distributed in the crust of GLY, which avoids contact of ARM with G-protein coupled receptors. Further the sweet taste of GLY imparted additive effect (13). This results in complete taste masking of ARM in GLY solid dispersion. Though the physical mixing of ARM with GLY brings the drug in close contact with carrier, ARM was not uniformly distributed in GLY as that of solid dispersion. This might be the reason for not complete masking the bitter taste of ARM in GLY physical mixture.

RDT5 was rated as moderate to strong bitter by 20% and strongly bitter by 80% while RDT3 was rated as tasteless by 100% of volunteers of panel.

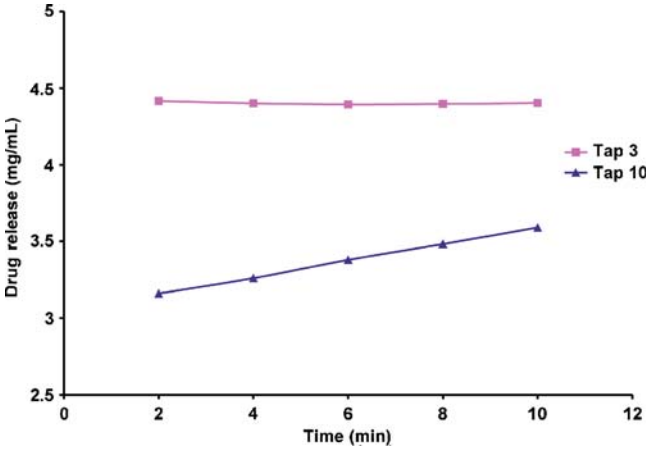

Fig. 7. Effect of tapping frequency on the release of ARM from RDT43 with 1 ml/min flow rate

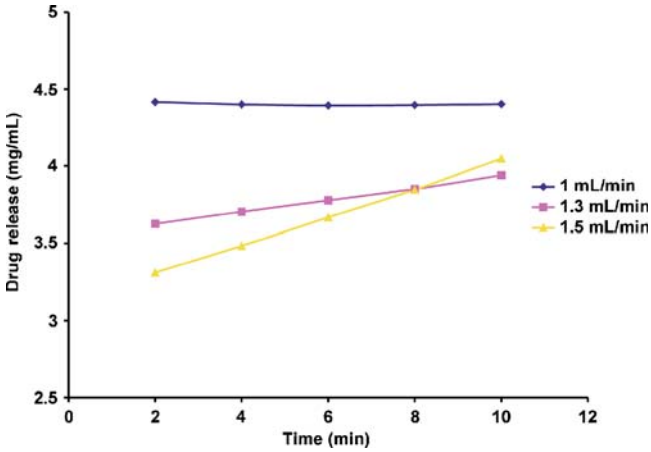

Fig. 8. Effect of flow rate on the release of ARM from RDT43 with three times tapping frequency

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 three, ten and 30 times. The effect of tapping frequency on the release rate is shown in Fig. 7.

When the tapping frequency was 30 times, the amount of ARM release from RDT was difficult for the test solution to penetrate the RDT. The release rate increased when the tapping frequency was three times. However the release rate decreased when the tapping frequency was ten 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 Fig. 8. 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

Table IV. Relationship Between Amount of Release and Results of Sensory Test of RDTs Using Mini-column Method

	Time (min)				
Formulations	2	4	6	8	10
RDT5	0.311	0.333	0.330	0.326	0.325
Bitterness score	3	3	3	3	3
RDT6	3.162	3.147	3.154	3.121	3.092
Bitterness score	1	1	1	1	1
RDT3	4.416	4.401	4.394	4.397	4.403
Bitterness score	0	0	0	0	0

optimized, based on maximum drug release, at 1 ml/min and three times, respectively.

Table IV shows the results of the sensory tests and amount of ARM released after 2 min interval with the mini-column method. RDT prepared from pure ARM showed increased number of persons who sensed bitterness with increased amount of ARM released. RDT prepared from solid dispersion sensed no bitterness with 4.42 mg/ml. The value (0.33 mg/ml) was about 14 times larger than that of pure ARM.

CONCLUSION

The study conclusively demonstrated the complete taste masking of ARM with improved dissolution by solid dispersion technique. ARM-GLY solid dispersion along with use of superdisintegrant could be considered for formulation of taste masked RDTs of ARM. This may be of value for the pharmaceutical industries dealing with bitter drugs to improve patient compliance and thus effective pharmacotherapy.

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