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Original Article

TASTE ABATEMENT AND CHARACTERIZATION OF DISPERSIBLE TABLETS OF ARTEMETHER PREPARED BY HOT MELT EXTRUSION

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ABSTRACT

Objective: The aim of this study was to formulate and evaluate a taste-masked formulation using hot melt extrusion approach for artemether.

Methods: Taste masking of artemether was done by preparing solid dispersion with coating polymer kollicoatsmartseal 30D using hot melt extrusion. The prepared solid dispersion was subjected to taste masking evaluation like sensory evaluation parameters against five levels set for taste evaluation using artemether as control standard along with *in vitro* release studies in simulated salivery fluid. After taste evaluation of solid dispersion was subjected to the formulation of dispersible tablets by direct compression method. The final taste masking evaluation of dispersible tablets of solid dispersion containing artemether were done by a sensory evaluation panel of nine members along with *in vitro* release study in simulated salivary and gastric fluid.

Results: The percent drug content was found 35.09±0.06 % in solid dispersion. The drug excipients compatibility studies performed with the help of FTIR instrument and DSC that indicates there were no interactions between drug and polymers. Solid dispersions (1:1, 1:2, 1:3 drug polymer ratio) of artemether were evaluated by sensory evaluation panel from which 1:3 drug: polymer solid dispersion was found more palatable. Release rate study in simulated salivary fluid shown no release but shows release of drug in simulated gastric fluids which indicates that the drug was taste masked. The optimized batch of dispersible tablets (F1) were subjected for evaluation parameters like dispersion time (70±1.90), wetting time (63±1.86), etc. Dissolution studies of optimized formulation indicated that the polymer does not allow drug to release in simulated salivery pH 6.8 but shows immediate release in simulated gastric pH which also confirms taste masking efficiency of polymer. Final optimized F1 batch evaluated for taste masking evaluation by sensory evaluation panel using pure drug as control standard found to be palatable.

Conclusion: It may be concluded that kollicoatsmartseal 30D could mask the taste of the drug in salivary pH and shows drug release at gastric pH which confirms its efficiency for taste masking.

Keywords: Artemether, Kollicoatsmartseal 30D, Hot-melt extrusion, Taste masking, Solid dispersion

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INTRODUCTION

Worst the taste of the medication, the better the cure was once the prevailing attitude. Today this trend has changed and great importance is placed on the organoleptic characteristics of pharmaceutical products [1]. Oral administration of pharmaceuticals is one of the most popular method of drug delivery [2]. Organoleptic characteristics of pharmaceutical products, i.e. Taste, odor, and appearance are essential factors in assessing the patient acceptability; out of these organoleptic characteristics of taste is an important parameter governing patient compliance [3]. Some active pharmaceutical ingredients (API's) are generally associated with an unpleasant taste. The formulations containing such APIs are poorly accepted by patients and the adherence to treatment is adversely affected. Bad taste is a primary barrier while administering drugs to children. Most of the pediatricians reported that the taste and palatability were the greatest hurdles to complete treatment. Therefore. It is necessary to discover robust approaches to formulate the dosage forms to mask the unpleasant taste of the API to improve the ease of administration and palatability. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Taste masking in the present day pharmaceutical industry has become a potential tool to improve patient compliance and commercial success of the product [3-6]. The taste of any substance can be improved by two basic manipulations; either by reducing the drug solubility or by altering the ability of the drug to interact with taste receptors [7].

Artemether (ARM) drug used for the prevention of malaria and is included in the WHO list of essential medicines. Artemether is essential for rapid clearance of parasitemia and rapid resolution of symptoms. It reduces parasite numbers by a factor of approximately 10,000 in each asexual cycle, which is more than other current antimalarial (which reduce parasite numbers 100–1000-fold per cycle). Artemether is active against P. vivax as well as chloroquine sensitive and chloroquine resistant strains of P. falciparum and is also indicated in the treatment of cerebral malaria [8-12].

The objective of this study was to developed taste masked formulation of artemether which is intensely bitter in taste and is a critical problem, especially in the pediatric population. Hence, to increase the palatability of the drug it is necessary to mask the taste and to formulate a suitable dosage form to enhance patient compliance and adherence to treatment. On this background, this research was designed to address the question, whether it is possible to mask the intensely bitter taste of the poorly water soluble drug 'Artemether' by hot melt extrusionusing the kollicoatsmartseal 30D as a polymer for taste abatement?

Oro-dispersible tablets (ODTs) entered the market in the 1980s as an alternative to tablets and it also provides an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules [13].

MATERIALS AND METHODS

Materials

Artemether was received as a gift sample from ajanta pharma limited. aurangabad and IPCA laboratories limited. ratlam, India. kollicoatsmartseal 30 D was received as a gift sample from the BASF chemical company, mumbai, India. Potassium dihydrogen phosphate procured from modern Scientifics, nashik-India. Materials were used as received.

Methods

Preparation of drug: polymer solid dispersion by hot melt extrusion (HME)

The HME was optimized by trial and error method with the help of data obtained from previous work. It was optimized first using

several parameters like inlet and outlet temperature (50-60 °c) the batches were taken as placebo, drug: polymers in various ratios (1:1, 1:2, and 1:3). Weigh drug and polymer in 1:1 ratio and prepared granules for the further process before HME. Likewise, all the batches of prepared granules of drug: polymer (1:1, 1:2 and 1:3) was hot melt extruded [14-16].

Characterization of drug-polymer dispersion

Percent drug contained in drug: polymer dispersion

The percentage of drug complexes with polymer was determined by using HPLC analysis. With a stainless steel column 25 cm X 4.0 mm, packed with octadecylsilane bonded to porous silica (5 µm), Mobile phase: a mixture of 62 volumes of acetonitrile, 38 volumes of water, Flow rate1.5 ml per minute, Injection volume 20 µl, Spectro-photometer set at 216 nm.

Attenuated total reflectance spectroscopy (ATR)

Spectra of the drug-polymer dispersion were recorded using Bruker Eco-ATR machine. The spectra were scanned over the wave number range of 3600 to 400 cm^{-1}. ATR was done for pure drug samples and for the drug: polymer dispersion.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed using METTLER calorimeter to study the thermal behavior of dispersion formed and compare it with the DSC curve of the drug sample.

***In vitro* release study**

Release rate study of drug: polymer dispersion

The release of the drug (artemether) from drug-polymer complexes were studied at the pH of the mouth (simulated salivary fluid) pH 6.8, To determine the amount of the drug that would be released in the mouth during the administration of the formulation. The bitterness of the taste is related to the amount of drug released in the mouth, a plain drug was used as a control. In brief the dispersion was accurately weighed (equivalent to 80 mg) and added to 5 ml simulated salivary fluid pH 6.8 placed in the test tube. An aliquot was withdrawn after an interval of 1 min. The sample was filtered and absorbance was measured of Artemether at 216.0 nm. The drug concentration in the sample was determined from the standard curve of the drug in simulated salivary fluid (pH 6.8). The reported values of percent drug release are average values of three readings.

Release rate study at simulated gastric pH

The release rate of the drug and drug: polymer dispersions were studied at gastric pH in simulated gastric fluid and 0.1 N HCl with the help USP dissolution test apparatus II (model: disso 2000 apparatus: labindia). Solid drug: polymer dispersions were weighed accurately and subjected to release rate study. Parameters were set as 75rpm, temperature 37 °c, media volume 900 ml. 10 ml of the aliquot was withdrawn at specific time interval as per requirement and maintained sink condition by adding the same volume of fresh dissolution medium. Each of the 10 ml samples was filtered. The drug concentration in the sample was determined from the standard curve of the artemether in 0.1 N HCl (213.00). The reported values of percent drug release are average values of three readings.

Taste evaluation of solid drug: polymer dispersion

The sample of each drug: polymer complex was subjected to sensory evaluation by a panel of nine members With respect to bitter taste. The pure drug was used as a control having an average bitterness value of 5. Bitterness values were categorized into 5 levels with respect to the bitterness of artemether were at level 5: very strongly bitter, level 4: strongly bitter, level 3: moderately bitter taste, level 2: palatable, level 1: no bitter taste [18].

Formulation and development of dispersible tablet

Dispersible tablets were prepared by using the solid drug: polymer dispersion (1:3) of artemether with kollicoatsmartseal 30 D. The dispersion was taken equivalent to doses of the drug. Four different types of dispersible tablets were formed using a different type of super-disintegrating agents by direct compression method using 10 stations compression machine (REMEK) by using an Oval shape punch of size 10. These super disintegrating agents are crospovidone and sodium starch glycollate. The formulations were coded as formulation F1, F2, F3 and F4 respectively. The composition of formulation batches F1, F2, F3, F4 were shown in table 2.

Table 2. Selected prototype for dispersible tablet preparation

Ingredients	Quantity of ingredients (mg)			
	F1	F2	F3	F4
Artemether	200	200	200	200
Sodium starch glycolate	40	30	30	40
PVPK30	15	15	10	10
Mannitol	63	73	78	68
Microcrystalline cellulose	80	80	80	80
Magnesium stearate	2	2	2	2
Flavor	QS	QS	QS	QS
Total	400	400	400	400

F1, F2, F3 and F4 were formulations code. PVPK30-polyvinylpyrrolidone K30, QS-Quantity sufficient

Evaluation of dispersible tablet

Parameters were evaluated for tablets at, dispersion time, wetting time, wetting volume and uniformity of dispersion

Taste evaluation of dispersible tablet

The sample of each dispersible tablet was subjected to sensory evaluation by a panel of nine members with respect to bitter taste standards (pure drug-artemether).

Release rate study of the formulation

The release rate study of the tablets in 0.1N HCl was carried out using USP II apparatus in 900 ml dissolution media at 75 RPM, to determine the amount of drug that would be released in the stomach after administration of the tablet. The release rate of optimized formulation also carried out in simulated salivary pH 6.8.

RESULTS AND DISCUSSION

Percent drug contained in drug: polymer dispersion

The drug content in the dispersion was calculated using comparisons of an area of peaks obtained by HPLC method. 20 ppm concentration of dispersion shown 35.09±0.06 % drug content with respect to 20 ppm concentration of pure drug (artemether).

Chromatograms were shown in fig. 1. The results indicates sufficient amount of drug entrapped in polymer [24].

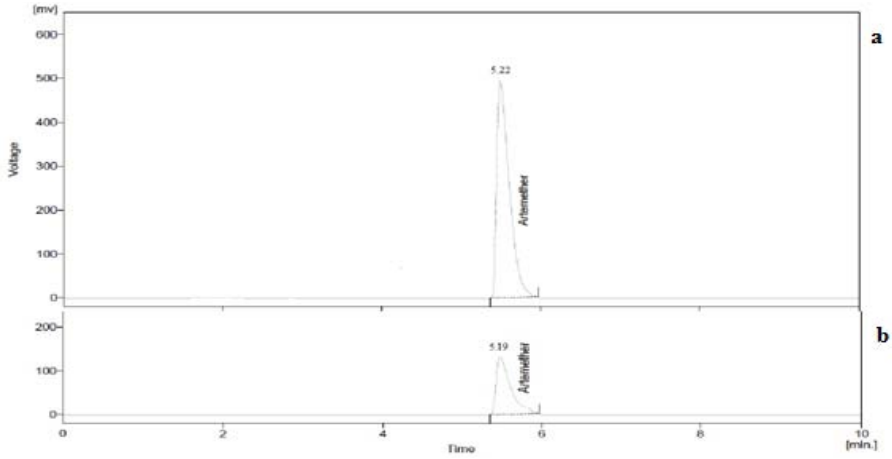

Fig. 1: (a) Is chromatogram of artemether and (b) is a chromatogram of dispersion

Attenuated total reflectance spectroscopy (ATR)

The characteristic peaks of ARM at 2930.13 cm^{-1} are assigned to C–H stretching vibration in CH_3, CH_2. In addition, the absorption peak at 1448.02 cm^{-1} can be assigned to C–H bending vibration in C–O–CH_3. The peak at 1019 cm^{-1} can be assigned to C–O stretching, vibration in, C–O–C. The peaks at 1103.81is assigned to C–O stretching in with low intensity. The peak at 3670. 38 cm^{-1}indicates O-H stretching due to a little amount of moisture may present. All the above characteristic peaks of ARM appear in the spectra of the binary system, i.e. Solid dispersion at same wavenumber with a little shift in peaks indicating no modification or interaction between the drug and polymer. ATR spectra shown in fig. 2. It indicates that the drug and polymer were compatible with each other.

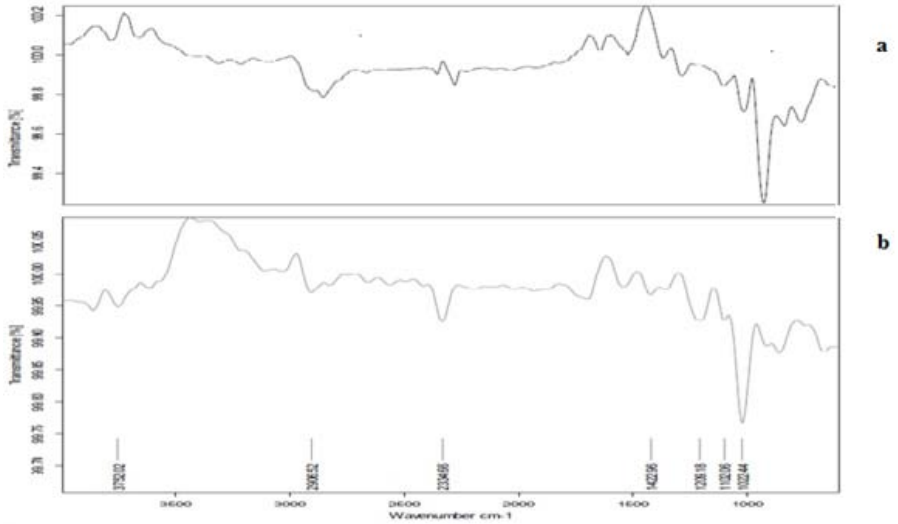

Fig. 2: (a) Is ATR spectra of artemether and (b) ATR spectra of dispersion

Differential scanning calorimetry (DSC)

Thermal behavior of pure drug and corresponding drug dispersion system are depicted in fig. 3. The pure ARM shows a sharp endothermic peak at 88.08 °C, followed by an exothermic peak at 183.04 °C. The characteristic endothermic peak corresponding to the melting peak of ARM was shifted towards lower temperature, with reduced intensity in solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of ARM in the crust of polymer, resulting in complete miscibility of the molten drug in a polymer. Moreover, the data also indicate there seems to be no interaction between the components of the binary system.

***In vitro* release study**

Release rate study of drug: polymer dispersion

The dispersion shows no drug release in phosphate buffer pH 6.8 compared with that of pure drugs. As the polymer does not dissolve above pH 6.8 it will not release the drug in the buffer that means drug not directly come in contact with the taste buds and hence gives prior idea about taste abatement was done or not [26].

Release rate study at simulated gastric pH

The increase in dissolution profile was observed when drug releases of batches 1:1, 1:2, 1:3 was compared with that of pure drugs. The reason behind this could be various instrumental factors like use of hot melt extruder. Percent cumulative drug release in 60 min. Shown as pure drug 32.53 (±0.27), batches 1:1, 1:2, 1:3 shows 45.27 (±0.88), 45.59 (±0.55), 43.97 (±0.37) respectively. Percent cumulative drug release comparison is shown in fig. 4.

Release study in simulated gastric pH confirms that the polymer release drug quickly in acidic media and make drugs available at the site of absorption which is in stomach without any delaying in drug release from polymeric entrapment. The release rate study also confirms the property of polymer. Kollicoatsmartseal 30 D does not allow dispersion of drug to release drugs into simulated salivary phosphate buffer pH 6.8, but quickly release the drug in simulated gastric fluid [29].

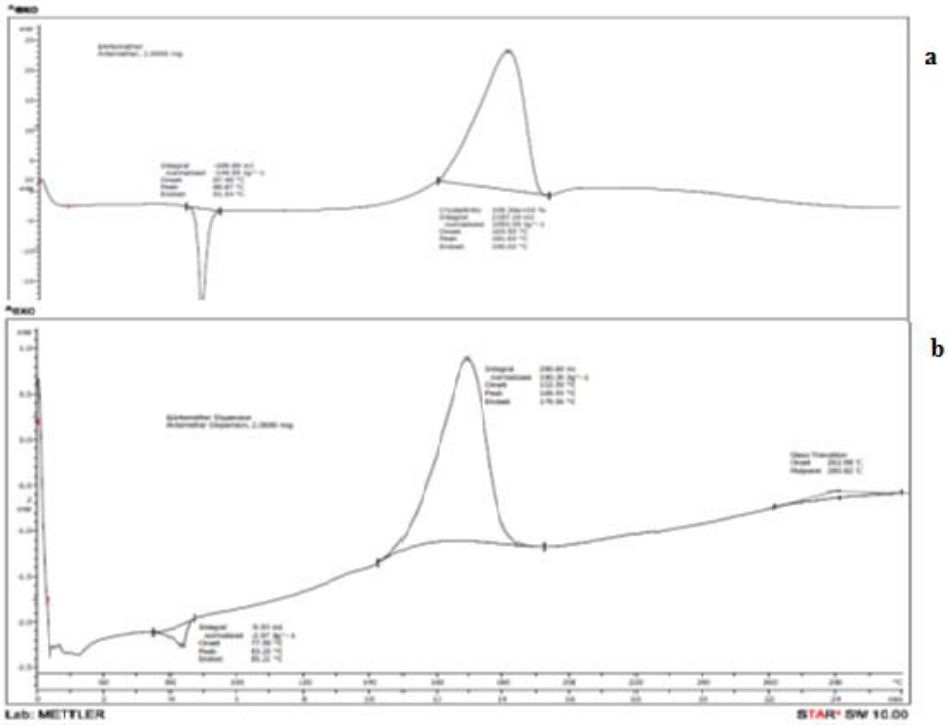

Fig. 3: (a) Is thermogram of artemether and (b) is a thermogram of dispersion

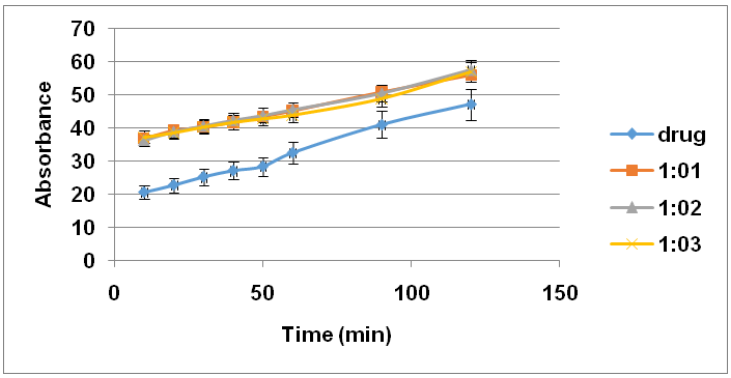

Fig. 4: Percent cumulative drug release (n=3, Data presented as mean±SD)

Taste evaluation of solid drug: polymer dispersion

The drug: polymer dispersion ratio 1:1, 1:2 and 1:3were evaluated against the pure drug by a sensory evaluation panel of nine members. The drug dispersion ratio 1:3 shows the bitterness value score 1.44 which is close to level 1 that is palatable and other dispersions were failing to mask bitterness as compared with 1:3 drug polymer ratio. Hence this dispersion was selected for the formulation of dispersible tablet. Sensory evaluation data shown in table 1. Results shown that polymer masks the bitterness of API by means of forming a coating around drug molecules [18, 26, 28-29].

Table 1: Sensory evaluation data of solid dispersion

Ratio of drug: polymer dispersion	Scores of drug: polymer dispersion									Average bitterness value
	Group I			Group II			Group III			
Pure drug	5	5	5	5	5	5	5	5	5	5
1:1	2	3	3	2	4	3	2	4	3	2.88
1:2	2	1	2	2	1	1	3	2	1	1.66
1:3	1	2	1	1	2	2	1	2	1	1.44

Evaluation of formulation: dispersible tablet

After taste evaluation, drug polymer ratio 1:3 was selected for dispersible dosage form preparation. Dispersible tablets were evaluated against dispersion time, wetting time, wetting volume and uniformity of dispersion. After characterization of tablets F1 batch formulation was selected as best formulation compared with other batches of formulation. Evaluation parameters were shown in table 3.

Table 3: Evaluation of formulations

S. No.	Evaluation parameter	Formulations (*±SD)			
		F1	F2	F3	F4
1	Dispersion time (Sec)	70±1.90	96±1.92	90±2.45	73±2.72
2	Wetting time (Sec)	63±1.86	72±1.78	70±1.53	67±2.66
3	Wetting volume (ml)	2.9±0.554	3.5±0.95	3.4±0.846	3.2±0.22
4	Uniformity of dispersion	Pass	Pass	Pass	Pass

*n=3, Data presented as mean±SD.

Taste evaluation of dispersible tablet

Sensory evaluation of dispersible tablets of optimized formulation batch F1 was done by a human volunteer panel of nine members. From sensory evaluation data bitterness value scores 1.33 which is close to level of bitterness 1 that is palatable. Bitterness value near to 1 indicates that F1 formulation was taste masked dispersible formulation and it confirms the taste masking efficiency of polymer. As compared to drug polymer dispersion F1 formulation shows less bitterness because of ingredients were used in tablet preparationsuch as mannitol, flavors etc. Sensory evaluation data are shown in table 4 [18, 26, 28-29].

Table 4: Sensory evaluation of F1 dispersible tablet formulation

Sample name	Scores of drug: polymer dispersion									Average bitterness value
	Group I			Group II			Group III			
Pure drug tablet	5	5	5	5	5	5	5	5	5	5
Optimized F1 formulation	1	2	1	1	2	1	1	1	2	1.33

Release rate study of the formulation

The optimized formulation F1 shows no drug release in phosphate buffer pH 6.8 compared with that of pure drugs. The polymer does not get solubilized in pH above 6.8 simulated salivary pH, which confirms taste masking of artemether. The increase in dissolution profile was observed when drug release of formulation F1 was compared with that of pure drugs. Which confirms that polymer release drug when it came in contact with gastric fluid pH 0.1 N HCl. Percent cumulative release in 0.1 N HCL was shown in fig. 5 [26-29].

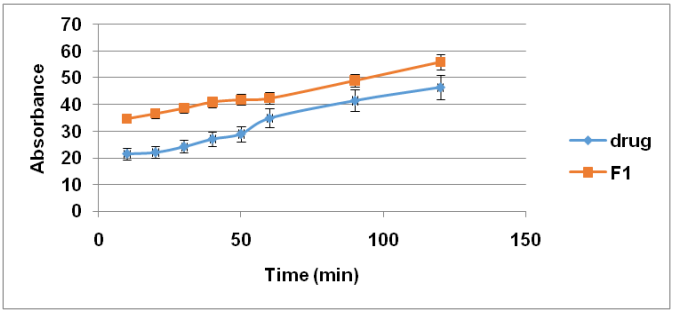

Fig. 5: Percent cumulative drug release of formulation F1 in 0.1 N HCl (n=3, Data presented as mean±SD)

CONCLUSION

It may be concluded that kollicoatsmartseal 30D could mask the taste of the drug in salivary pH and shows drug release at gastric pH which confirms its efficiency for taste masking. From previous studies of taste masking, it is assumed that coating of the bitter drugs with a suitable polymer with no effect on drug release can mask the bitter taste of the drug. Hence an attempt was made to formulate taste-masked formulation of artemether with kollicoatsmartseal 30 D as a coating polymer. The polymer shows no drug release at salivary pH and it dissolves under protonation in acidic media below pH 5.5. As the amount of polymer increases the taste masking efficiency also increases and it was confirmed by sensory evaluation method.

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CONFLICT OF INTERESTS

Declared none

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