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Original Article

PREPARATION AND EVALUATION OF A TASTE-MASKED ARTEMETHER ORAL SUSPENSION

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ABSTRACT

Objective: The antimalarial drug Artemether is bitter in taste. The purpose of this work is to construct a taste-masked Artemether resinate employing ion exchange resins.

Methods: The process for drug resin complexation was adjusted in terms of drug resin ratio and medium pH. FTIR and DSC measurements were used to characterise the taste-masked complex. As an ion exchange resin, Indion 204 was used. It was combined with medication in various ratios: Indion was generated at various times and pH values and the extent of complexation was determined.

Results: The result indicates that a 1:1 ratio of Indion 204 to resin resulted in the largest amount of complexation after four hours of mixing. These resinate then converted into granules and they exhibit an angle of repose, bulk density, and flow characteristic values that are acceptable. The loading of drugs was greater than 99 percent. Based on drug content, a suitable amount of drug-resinate was taken for formulation. Then Suspension was studied for general appearance, viscosity, sedimentation ratio, drug release, resuspendability. The release test showed that 92.46% of drug were release within 120 min.

Conclusion: Hence we can conclude that Indion 204 has been proved to be useful as a taste-masking agent. Thus we are able to achieve our objectives of preparing a taste-masked suspension of Artemether with minimum excipients and a simple method of manufacturing.

Keywords: Artemether, Taste-masked, Oral suspension

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INTRODUCTION

Artemether is a malaria medicine (fig. 1). Rather than quinine, the injectable version is used exclusively for severe malaria. It may not be as efficient as artesunate in adults. It is injected into a muscle. Additionally, marketed in conjunction with lumefantrine. Artemether is a chloroquine-resistant *Plasmodium falciparum and vivax* antimalarial medication used to treat uncomplicated malaria. Artemether is also effective in the treatment of critical cases. Uncomplicated *Plasmodium falciparum* infections should be treated with artemisinin-based combination therapy, according to the WHO. It is possible to avoid Plasmodium vivax or *Plasmodium ovale* malarial parasite relapse and complete cure with lumefantrine and a 14-day primaquine regimen. Schistosomiasis trematode infections can be treated and prevented with a combination of artemether and praziquantel. Artemisinin, an antimalarial medicine produced from the herb *Artemisia annua*, is the active ingredient in artemether. While it is commonly known as dihydroartemisia, its correct nomenclature is (+)-artemisinin methyl ether. It's also called dihydroartemisia. It is a lipophilic and unstable medicine that generates reactive free radicals and interferes with the membrane transport mechanism of the plasmodium organism [1, 2].

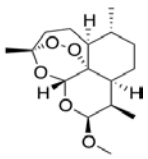

Fig. 1: Chemical structure of artemether

The purpose of this study was to produce a flavor-masked formulation of Artemether, which has an extremely bitter taste and is a major issue, particularly in the paediatric population. Thus, in order to improve the drug's palatability, it is required to disguise the flavour and design a dose form that promotes patient compliance and adherence to treatment. To address the aforementioned issue, we attempted to design an Artemether suspension that was bitter. Suspension is advantageous for children and the elderly who have difficulties swallowing regular tablets and capsules [3].

MATERIALS AND METHODS

Materials

Artemether was graciously provided by IPCA Labs, Ratlam, India, as a gift sample. Ion Exchange India Ltd., Mumbai, provided Indion 204 as a free sample. Doshion Ltd., Ahmedabad, Gujarat, India, acquired Doshion P551 as a gift sample. Thermax Limited, Pune, India, acquired Tulsion 335 as a gift sample. Xanthan gum, glycerine, orange flavour, and tartarazine yellow colour were obtained from Pallav Chemicals and Solvents Pvt. Ltd., Boisar, India; Methyl Paraben and Propyl Paraben were obtained from Research Lab Fine Chem Industries, Mumbai, India.

Methods [4-6]

Preparation of calibration curve of artemether

Spectrophotometry is widely employed for routine drug analysis. Artemether was determined spectrophotometrically at 205 nm using the published method and a JASCO-V520-UV VIS spectrophotometer. Ten milligrammes of medication were accurately weighed and dissolved in five millilitres methanol. The volume was then increased to ten millilitres with distilled water. One millilitre of this solution was diluted to ten millilitres. A series of dilution were made from the above stock solution to get the solution of concentration ranging from 10-100 µg/ml. additionally, the procedure was replicated using phosphate buffer pH 6.8 and 0.1 N HCL.

Preparation of taste-masked drug resin complexes by the batch method using ion-exchange resin

The batch procedure was used to prepare the drug resin complexes. In 25 ml distilled water, a precisely weighed amount of ion exchange resin (100 mg) was dissolved. The solution was then added to a

known weight (100 mg) of Artemether and stirred on a magnetic stirrer. The time required to reach equilibrium was measured by testing distilled water on a periodic basis. The resulting resin was filtered and washed with 10 ml methanol. UV spectroscopy was used to determine the drug concentration in the final filtrate. The amount of drug absorbed was calculated as the difference between the concentration of drug in stock solution and the concentration remaining in the filtrate at the end of equilibrium. Resinate was dried overnight at 50 °C in a hot air oven and then stored in a desiccator.

Selection of drug: resin ratio

Four batches were made with a ratio of 1:0.5, 1:1, 1:1.5, and 1:2 drug-resin. For four hours, the slurry was churned. The resulting resins were filtered, rinsed with copious amounts of deionized water, and the drug content assessed.

Effect of pH on drug loading

We prepared a series of 100 ml of a dispersion containing 1 mg/ml Artemether. The pH of these solutions was adjusted to 2,3,4,5,6,7 using 0.1 N hydrochloric acid; 100 mg ion exchange resin was added to each beaker and swirled for 4 h. The resulting resin was filtered and rinsed with ten millilitres pure water. UV-spectroscopy was used to determine the drug concentration in the final filtrate.

Evaluation of taste-masked products

To determine the drug content, 100 mg of a taste-masked substance was added in 100 ml of 0.1 N HCL and agitated at 100 rpm for one hour. The solution was filtered using Whatman filter paper and diluted further with 0.1 N hydrochloric acid. Artemether's drug concentration was evaluated spectrophotometrically at 205 nm, using 0.1 N HCl as a blank.

Taste evaluation was conducted in two stages

a) Determination of threshold bitterness concentration

Various concentration (10-50 µg/ml) of drug were prepared in phosphate buffer pH 6.8. Six healthy volunteers were selected for the study and they are instructed to provide score from 0-3 for taste perception, where 0=tasteless, 1=slightly bitter, 2= Bitter, 3= very bitter taste perception. Mouth was rinsed with solution and then, 10 ml of most dilute solution was tasted by swirling it in the mouth mainly near the base of the tongue for 30 seconds. If the bitter sensation was no longer felt in the mouth after 30 seconds, the solution was spat out and waited for 1 minute to ascertain whether this is due to delayed sensitivity. Then mouth was rinsed with safe drinking water. The next highest concentration should not be tasted until at least 10 minutes had passed. The threshold bitter concentration is the lowest concentration at which a material continues to provoke a bitter sensation after 30 seconds. After the first series of tests, mouth was rinsed thoroughly with safe drinking water until no bitter sensation remained. Interval of at least 10 minutes was observed between two tests.

b) *In vitro* evaluation of the bitter taste of resinates

A precisely weighed taste-masked product and ten millilitres of pH 6.8 phosphate buffer were placed in a series of volumetric flasks and swirled at 50 revolutions per minute. At various time intervals (0,20,40,60,120 sec.), the stirring was stopped, the dispersion was filtered, and the concentration of Artemether in the filtered resinate was calculated. The time required for resinate to reach a concentration equivalent to the threshold bitterness in 10 ml phosphate buffer was determined.

Characterization of taste-masked products of artemether

Fourier transform infrared spectroscopy (FT-IR): Fourier transform infrared spectroscopy (FT-IR) spectrum investigations were conducted on FT-IR Bruker Alpha II series Using Attenuated Total Reflectance Technique. Scanning was done from 4000 to 400 cm^{-1}

Differential scanning calorimetry study (DSC)

A Mettler Toledo Differential Scanning Calorimeter (DSC) 821 (Mettler Toledo, Greifensee, Switzerland) equipped with an intercooler and a refrigerated cooling system was used to determine the thermal properties of Artemether, Indion 204, and a physical mixture of Artemether and Indion 204, DRC (1:1) in hermetically sealed flat aluminium crucibles over a temperature range of 30 to 300 °C. Calibration of the DSC temperature was performed using an indium standard. Nitrogen was purged at a rate of 40 and 100 ml/min using a cooling device.

a. *In vitro* drug release from DRC (Drug resin complex)

The dissolution of DRC (1:1) in 0.1 N HCl was evaluated using a USP class II dissolving device. The DRC equivalent to 15 mg Artemether was properly weighed and added to 900 ml 0.1 N HCl at a temperature of 37 °C 0.5 °C. For 120 min, the drug was released at a speed of 50 rpm. At 15 minute intervals, aliquots of medium (5 ml) were obtained, filtered, and the absorbance at 205 nm was determined using UV Spectroscopy. The medium was replaced with a fresh dissolving medium in an equivalent volume.

Formulation of oral suspension of taste masked resinate of artemether

Table 1: Formulation of oral suspension of taste masked resinate of artemether

Ingredient	Drug: Indion (1:1) D1	Drug: Indion (1:1.5) D2	Drug: Indion (1:2) D3
Equivalent wt. of drug present in complex (mg)	180	180	180
Sucrose (gm)	4.50	4.50	4.50
Glycerine (ml)	1	1	1
Xanthan gum (mg)	40	40	40
Methyl paraben (mg)	20	20	20
Propyl paraben (mg)	8	8	8
Orange flavour (ml)	Quantity sufficient	Quantity sufficient	Quantity sufficient
Tartarazine (yellow colour) (mg)	Quantity sufficient	Quantity sufficient	Quantity sufficient
Purified water (ml)	Up to 60 ml	Up to 60 ml	Up to 60 ml

Evaluation of suspension

Viscosity

A Brookfield Viscometer DV I+Viscometer model coupled with appropriate spindle and guard arrangement was used to record the viscosity of suspension at room temperature using small sample adapter.

Separation ratio

The separation ratio is defined as the ratio of the length of the upper clear separated layer to the overall suspension column's initial length. Phase separation was determined at 1-day intervals for the first week and then at 7-day intervals for one month. Calculation of the separation ratio as:-

Separation ratio= Hs/Ho

Where Hs= height of upper clear layer in mm and Ho= sample column's initial height in mm. graph was plotted of calculated separation ratios and time of storage.

Re-suspendabilty

The re-suspensionability of the suspension was determined by the number of shakes necessary to redisperse the settled layer formed

after one month at room temperature storage. After a month of storage at room temperature, the number of shakes necessary increases. The table 1 shows the number of shakes necessary for suspension and the characteristics of the settled layer of suspension.

Stability study

The stability period of a pharmaceutical preparation is measured in time from the date of formulation manufacture until the chemical or biological activity is at least 90% of the stated potency and the physical features of the preparation have not altered significantly.

Organoleptic evaluation

The colour, flavour, and taste of the formulation were examined. They were determined to be visually appealing and palatable in taste.

***In vitro* drug release profile**

Artemether was dispersed in suspension *in vitro* for 120 min using a USP Type II dissolving device and 900 cc of 0.1 N HCl as the dissolution medium. The trial used 5 ml of suspension corresponding to 15 mg of Artemether. The temperature was maintained at 37 °C+/-0.5 °C. The rotational speed was maintained at 50 revolutions per minute. At 15 minute intervals, aliquots of medium (10 ml) were obtained, filtered, and the absorbance at 205 nm was determined using UV spectroscopy. The medium was changed with fresh dissolving fluid in an equivalent volume.

RESULTS AND DISCUSSION

Batch synthesis of taste-masked drug resin complexes method (DRC) using ion-exchange resins [7]

Selection of resins

The selection of resins for flavour masking needs the consideration of a variety of features. For an acidic medicine anion exchange resins are utilised for a basic drug cationic exchange resin are employed. In the present experiment, a weak cation exchange resin, i.e. Indion 204, tulsion 335, doshion p551 was utilised for the taste masking of Artemether. Weak cationic exchange resins are used here because of their weak binding ability and the basic character of medicine; consequently, they were selected for the immediate release flavour masking formulation. It was noticed that stirring for 4 h is required to attain drug loading equilibrium, so all the sample were swirled for 4 h. The % drug loading was shown in table 2 [7].

Table 2: Effect of artemether: resin ration drug loading

Resin	Drug: resin	% drug loading
Indion 204	1:0.5	95.06±0.61%
	1:1	99.20±0.51%
	1:1.5	99.32±0.12%
	1:2	99.21±0.09 %
Tulsion 335	1:0.5	84.8±0.53 %
	1:1	90.51±0.88 %
	1:1.5	90.96±0.68 %
	1:2	91.86±0.49 %
Doshion p551	1:0.5	86.3±0.98 %
	1:1	88.25±1.01 %
	1:1.5	89.60±0.43 %
	1:2	92.22±1.01 %

The % drug loading with Indion 204, all the ratios show loading of drug above 99%. These all DRC were prepared by batch method.

Table 3: Drug contents of different ratios of drug: resin complex

Resins	Ratios	Drug content
Indion 204	1:0.5	57.09±0.72 %
	1:1	50.14±0.58 %
	1:1.5	45.43±1.29 %
	1:2	41.62±0.48 %
Tulsion 335	1:0.5	46.13±0.76 %
	1:1	41.35±1.05 %
	1:1.5	35.69±0.65 %
	1:2	28.30±0.67 %
Doshion p551	1:0.5	33.77±0.99%
	1:1	32.92±1.01%
	1:1.5	25.6±0.78 %
	1:2	21.20±0.56 %

Effect of Artemether: resin ratio on drug content

Different drug: resin ratios were prepared, such as 1:0.5, 1:1, 1:1.5, 1:2 were studied. The Artemether: Indion 204 in 1:1 ratio gives best drug loading 99.47% and drug content 50.14%. As the ratio of resin is increased but drug content show fluctuation in result.

The effect of pH on drug loading

Cationic Artemether loading on ion exchange resin is an equilibrium process dependent on the presence of the medication. The loading efficiency may be modified by the pH of the solution, which in turn affects the amount of medication ionised. With the following parameters in place, 0.1 N HCL is added to the drug to modify its pH: resin to resin ratio of 1:1. (Indion 204: Artemether).

Table 4 illustrates that different pH levels have a distinct influence on drug loading. The drug loading is higher at pH 5 than it is at any other pH [8].

Table 4: Effect of pH on % drug loading

pH	% drug loading
2	80.81±0.52 %
3	82.53±0.53 %
4	90.56±0.56 %
5	93.60±0.56 %
6	89.75±0.62 %
7	87.28±0.70 %

Effect of stirring time on % drug loading

The resin soaked in water for 30 min with continuous stirring. Then add specific amount of drug to the slurry. And continue stirring for 1h, 2h, 3h, 4h, 5h. The % drug loading can be calculated by taking the absorbance of the filtrate.

Evaluation of taste-masked products [8, 9]

Determination of the drug's concentration

The concentration of the medication was evaluated spectrophotometrically at 205 nm using 0.1 N HCL as a blank. The medication content of DRC with Indion 204 shows better result than Tulsion and Doshion. The drug content of drug: Indion 1:1 ratio shows 50.14% [8].

Table 5: The influence of stirring duration on drug loading percentage

Stirring time	% drug loading
1 h	92.70±1.24 %
2 h	93.33±0.73%
3 h	95.21±0.61%
4 h	98.73±0.39%
5 h	99.43±0.47 %

The maximum drug loading occurs after 4 and 5 h. But there is not very difference in % drug loading of 4 and 5 h. So all the DRC were prepared with stirring for 4 h.

Characterization of DRC

FTIR study: Artemether

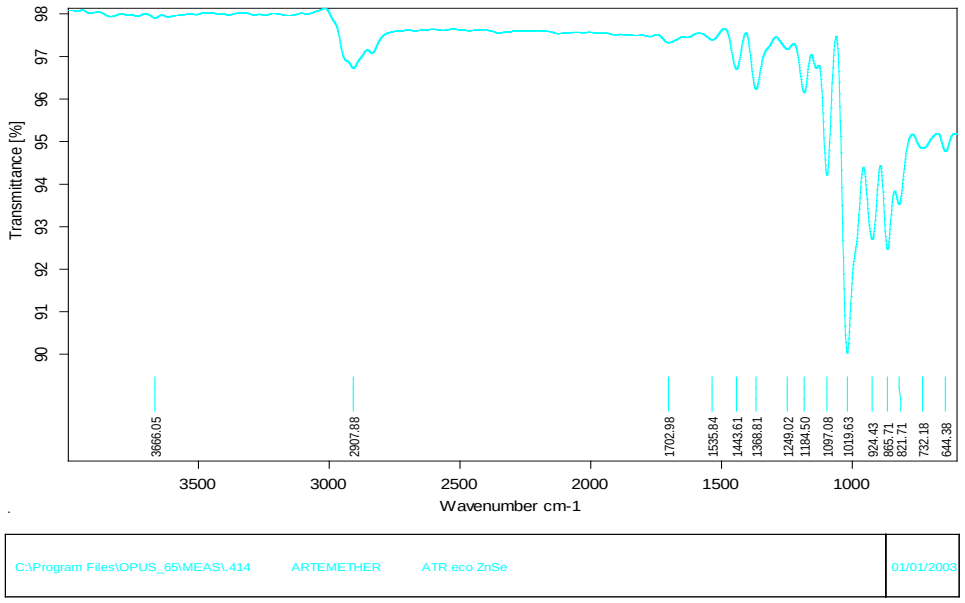

Fig. 2: FTIR spectra of artemether, Artemether: Indion 204 (1:1) ratio

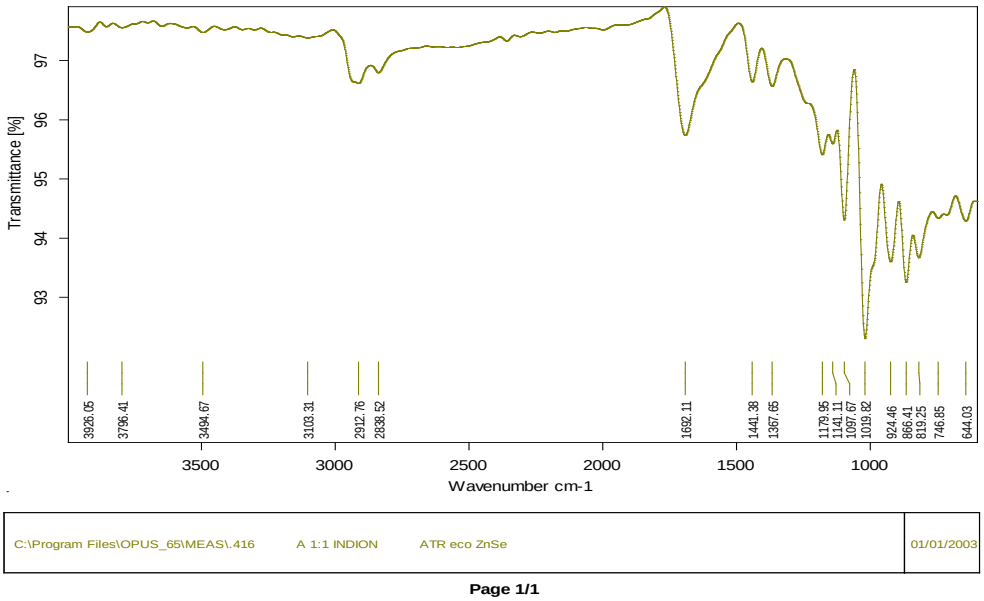

Fig. 3: FTIR spectra of Artemether: Indion 204 (1:1), Indion 204

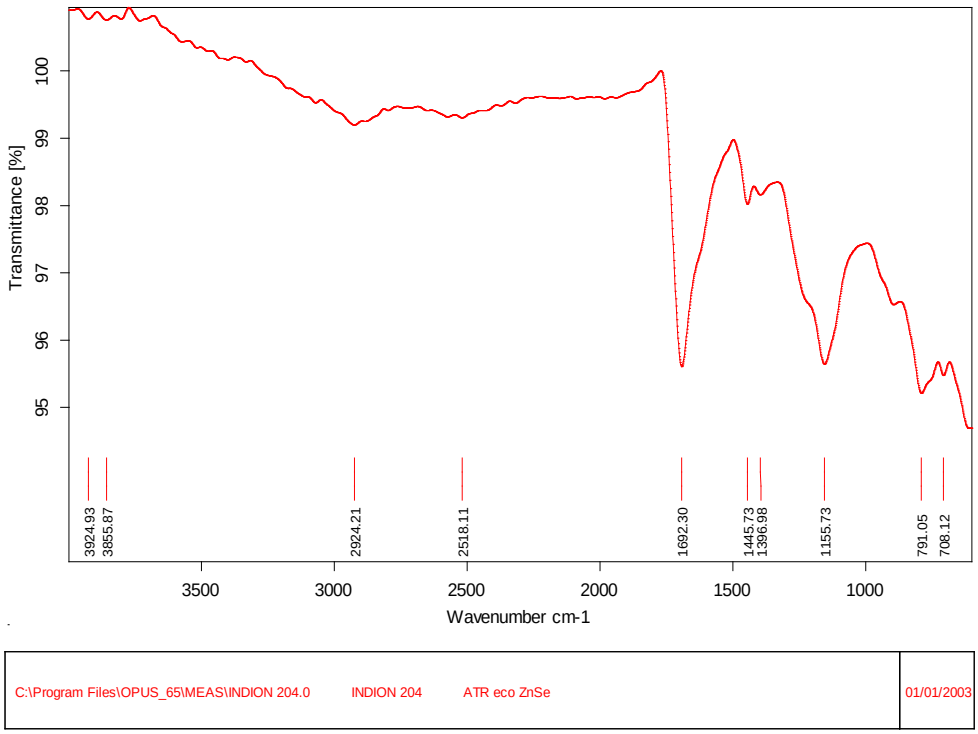

Fig. 4: FTIR spectra of Indion 204

In Artemether's FTIR graphs, O-H stretching vibration has a peak at 3666 cm-1, while C-H stretching vibration has a peak at 2907.88 cm-1, and the bending vibration of C-O-O-C has a peak at 1184.50 cm-1, while the bending vibration of C-O has a peak at 1097.08 cm-1, the bending vibration of C-H has a peak at 1019.63 cm-1.

For the Artemether: Indion complex, an FT-IR spectrum showed that the drug form had not changed, and hence the resin had been chosen correctly. Drug-resin complexes had new peaks detected, but the drug peak remained unchanged, showing that complexes had formed and the drug's composition had not changed.

DSC study: artemether

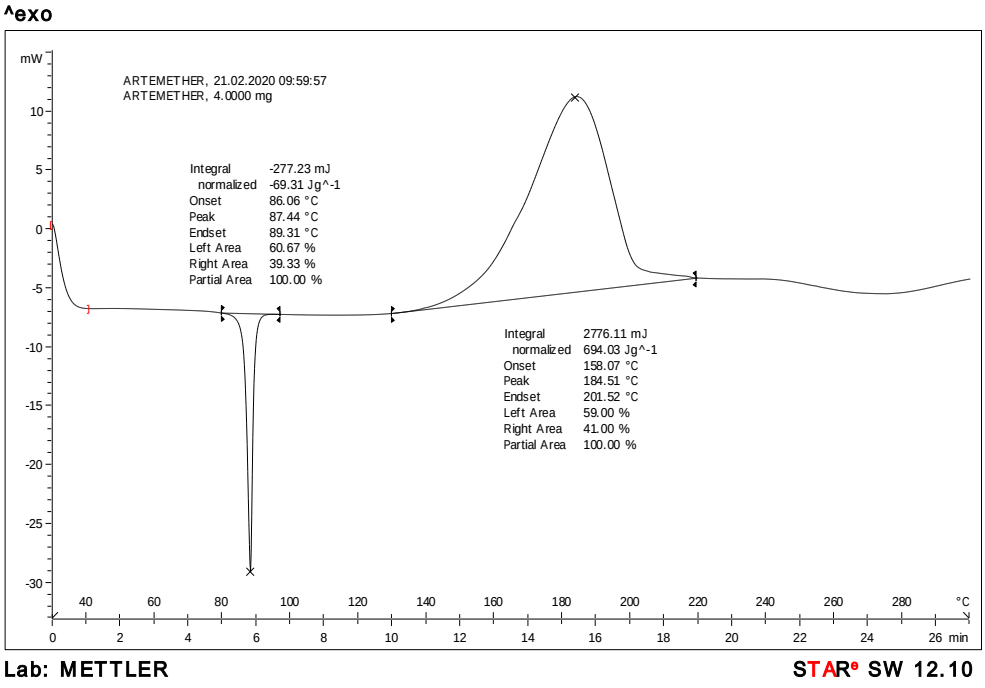

Fig. 5: DSC study of artemether

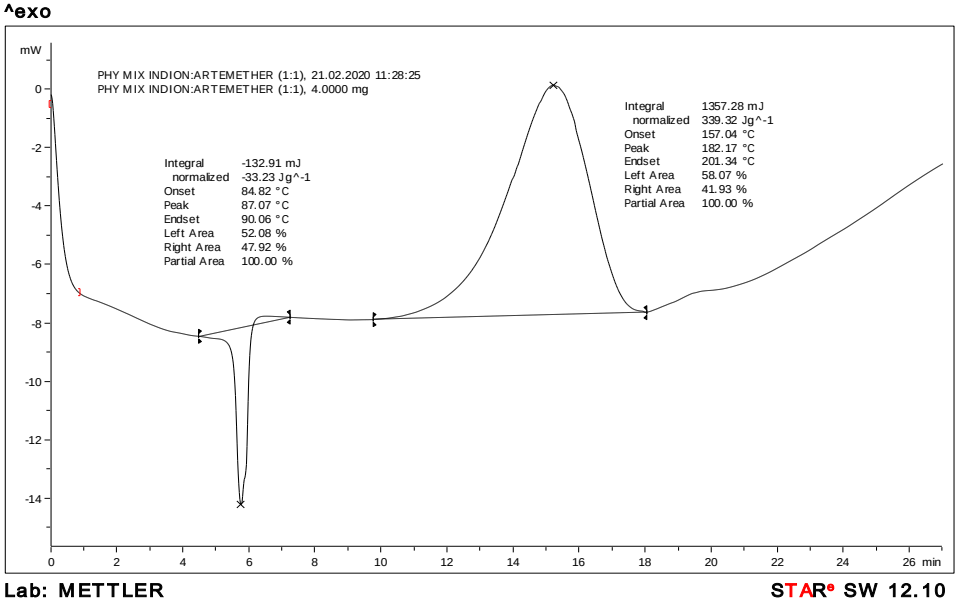

Fig. 6: DSC study of physical mixture

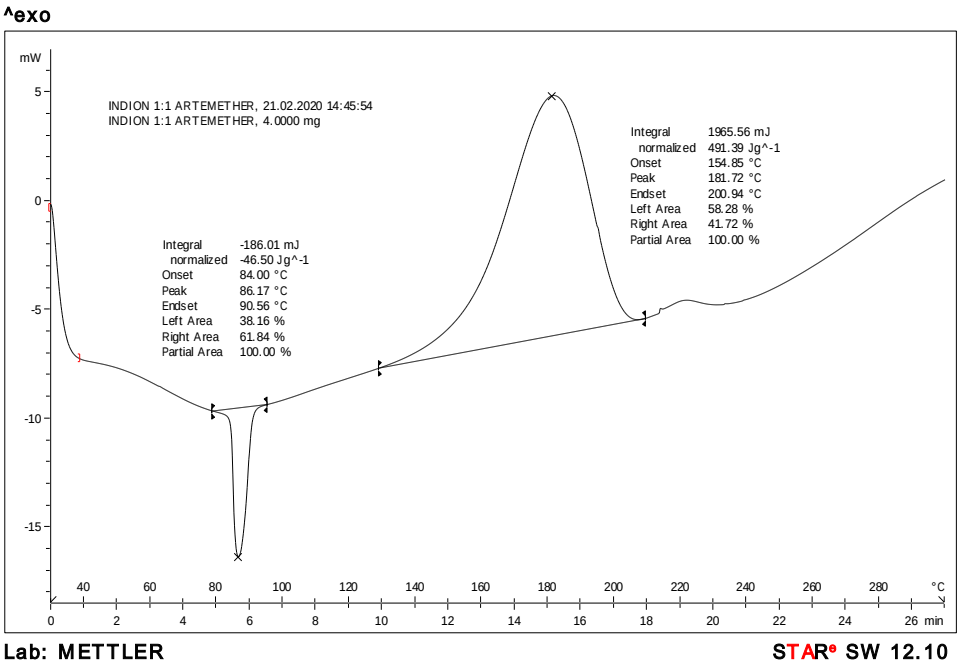

Fig. 7: DSC study of Artemether: Indion (1:1)

Table 6: Cumulative % drug release from drug resin complex

S. No.	Drug: resin ratio	Cumulative % drug release from DRC
1	Indion 1:0.5	80.51±1.30 %
2	Indion 1:1	90.20±1.18 %
3	Indion 1:1.5	82.67±1.24 %
4	Indion 1:2	85.19±1.32 %
5	Tulsion 1:0.5	73.88±1.22 %
6	Tuision 1:1	77.42±1.26 %
7	Tulsion 1:1.5	72.30±1.32 %
8	Tulsion 1:2	77.80±1.25 %
9	Doshion 1:0.5	79.41±1.33 %
10	Doshion 1:1	73.10±1.16 %
11	Doshion 1:1.5	70.63±1.28 %
12	Doshion 1:2	74.40±1.14 %

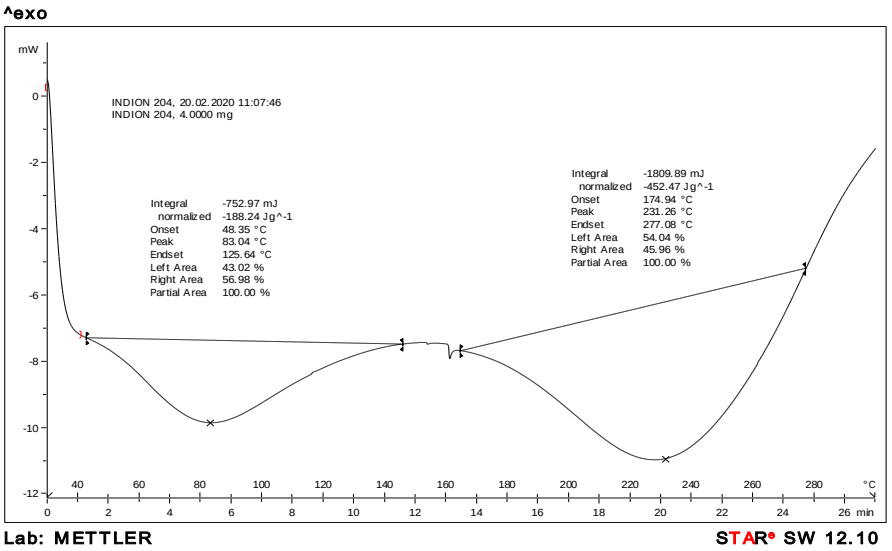

Fig. 8: DSC study of Indion 204

From the DSC study, Artemether shows melting point at 87.44 °C and Indion shows 83.04 °C. The complex formation between Artemether and Indion were showed by shifting of thermogram towards 86.17 °C. (fig. 5, fig. 6, fig. 7, fig. 8))

***In vitro* drug release from DRC**

The batch-prepared drug resin complex was dissolvable in 0.1 N HCL using a USP type 2 equipment at 100 rpm and 37 °C, indicating that the drug was released within 120 min.

Table 6 summarises the cumulative percent medication release over 120 min [9].

From the above results, Indion shows better results than Tulsion and Doshion (fig. 9). So, for preparation of suspension Indion 204 is selected. From the drug content and cumulative % drug release, the 3 ratio of Indion is selected for preparation of suspension.

Taste evaluation of the taste-masked product

Determination of threshold bitterness concentration

The threshold bitterness concentration of Artemether was established to be 15 µg/ml using a panel of six healthy humans. The time required to reach the threshold bitterness concentration was not within 120 seconds (table 7).

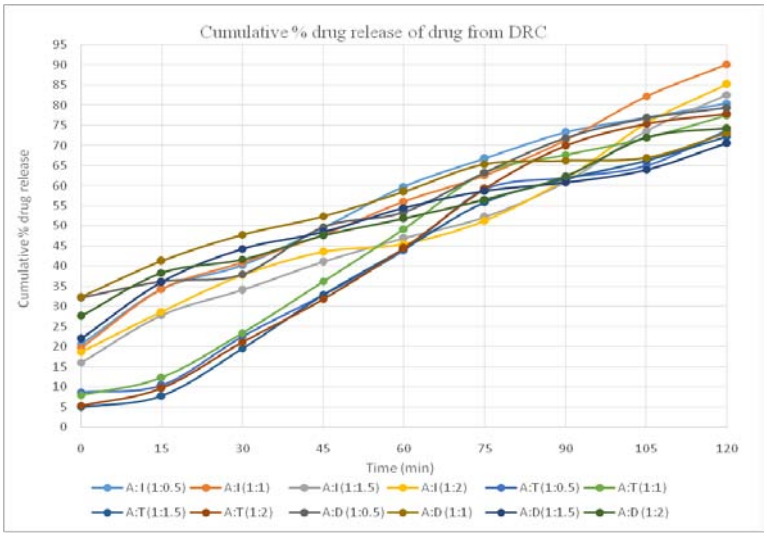

Fig. 9: Cumulative % drug release

Table 7: Determination of threshold bitterness concentration

No. of candidates	Concentration of drug (µg/ml)					
	5	10	15	20	25	30
1	0	0	1	2	2	3
2	0	0	1	2	2	3
3	0	0	1	2	2	3
4	0	0	1	2	2	3
5	0	0	1	2	3	3
6	0	0	1	2	2	3

Scale: 0 = tasteless, 1= slightly bitter, 2=bitter, 3 = very bitter.

Sensory Evaluation of taste-masked resinate

When the taste masked resinate was evaluated for its taste by human volunteers, the volunteers does not feel any bitter taste after keeping the resinate in mouth for 30 sec, from which conclude that bitter taste of the Artemether was masked successfully. Six volunteers were asked as per scale i.e. 0 = tasteless, 1 = slightly bitter, 2 = bitter, 3 = very bitter. (table 8).

Table 8: Sensory evaluation of taste-masked resinate

No. of candidates	Mark rating to preparation	
	Drug substance	Taste masked resinate
1	3	0
2	3	1
3	3	0
4	3	0
5	3	0
6	3	1

Scale: 0 = tasteless, 1 = slightly bitter, 2 = bitter, 3 = very bitter.

Time for attainment of threshold bitterness concentration *in vitro* of DRC, (1:1-Artemether: Indion)

Table 9: Time required to reach the bitterness threshold *in vitro* of DRC

Time (sec)	Concentration of drug (µg/ml)mean(n=3)±SD
0	0.46±1.25
20	1.77±1.45
40	1.91±1.34
60	1.95±0.91
120	2.08±1.54

The duration required to reach the threshold bitterness concentration was determined *in vitro* in a buffer of salivary pH, indicating that the medication may not be instantly released in saliva from the complex, thereby disguising the bitter taste is satisfactory (table 9).

Evaluation of suspension

The Indion 204 shows better results as compared to the other two resins, so for preparation of suspension the 3 ratio of Drug: Indion were selected. The various evaluation parameter related to suspensions were studied and iven in table 10.

Table 10: Evaluation parameters of the suspension

Evaluation parameter	F1	F2	F3
Viscosity (cps)	2.89	4.2891	4.690
pH	5.2	5.1	4.9
Sedimentation ratio	1	1	0.98
Resuspendability (no. of tilts)	2	2	2

*F1= drug: Indion (1:1), F2= drug: Indion (1:1.5), F3= drug: Indion (1:2). The formulation F1 was optimized and further studied on their viscosity. The viscosity of the formulation F1 was such that it will be easily pourable from the container.

Accelerated stability study

The accelerated stability study does not show any significant drug loss or changes in the viscosity, pH, sedimentation ratio and Resuspendability of the taste-masked suspensions at the end of 3 mo (table 11). Therefore, the taste-masked suspension was considered to be stable under ambient storage condition for 3 mo.

Table 11: Accelerated stability study of suspension

Evaluation parameter	Suspension (F1)			
	Initial	One Month	Two Months	Three Months
Colour	Yellow	Yellow	Yellow	Yellow
Viscosity (cps)	2.89	2.88	2.85	2.83
pH	5.2	5.2	5.1	5.0
Sedimentation ratio	1	1	1	1
Resuspendability (No. of tilts)	2	2	2	2

***In vitro* taste evaluation of suspension**

The release of the medication in a pH 6.8 phosphate buffer was evaluated in an *in vitro* taste masking evaluation study. The release of drug from taste masked suspension at 0, 20, 40, 60, 120 second was concentration less than the cutoff value in 6.8 phosphate buffer (table 12). This result shows that satisfactory taste masking was done [10-12].

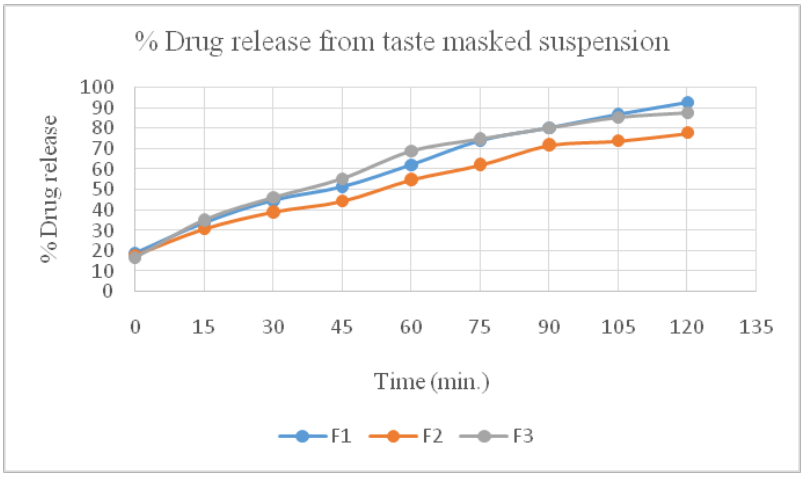

Fig. 10: *In vitro* drug release profile

CONCLUSION

The scientists have faced barriers in formulating a suitable product of undesirable and non-pleasant APIs. There are varied concepts that substantially mask the unpleasant taste of the drug, but they must be used with care so that the bioavailability of the drug is not compromised. According to the literature, the ion exchange resin technique is a relatively easy and practical strategy to masking the bitter taste of various bitter flavour medicaments, hence enhancing patient compliance. The prime objective of any drug formulation is always to serve as a better patient-compliance system with optimum therapeutic dose. Hence, Taste masked formulations of Arte-mether were prepared and evaluated for various parameters. Results obtained were statistically significant.

ETHICS APPROVAL

None

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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