RESEARCH ARTICLE
ISSN: 2278 - 2818

FORMULATION AND EVALUATION OF TASTE MASKED ORAL DISINTEGRATING TABLETS OF DIHYDROARTEMISININ

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ABSTRACT

The oral route is considered the most convenient and easy route of drug delivery. Yet, patient noncompliance, termed "intelligent noncompliance," due to feeling better, bad taste, etc., which is reasoned out by the patient but may not necessarily be wise, is one of the key causes of failure of oral dosage regimen. The aim of the present research work was to mask the intensely bitter taste of Dihydroartemisinin and to formulate an orally-disintegrating tablet (ODT)) of the taste-masked drug. Dihydroartemisinin(DHA) with Tulsion 344 complex were prepared by using physical mixture and kneading technique. The prepared tablets were evaluated for post compression parameters. The study conclusively demonstrated significant taste masking of DHA by kneading method and rapid disintegration and dissolution of ODT was within standard protocol. Taste masked ODTs of DHA are more palatable and patients compliance for gastroparesis, having symptoms of vomiting and fullness of GIT. From this study the taste masked Dihydroartemisinin oral disintegrating tablets can be successfully prepared by Tulsion 344 as taste masking agent (1:3) and disintegrate as it has shown 100% drug release with in 20 mins.

KEYWORDS

Oral disintegrating tablets(OTD), Dihydroartemisinin(DHA), Tulsion 344

INTRODUCTION

The oral route still represents the popular method of administration due to its many benefits and high patient compliance compared to many alternative routes. The bitterness of medicines plays a essential role in patient compliance, because the oral administration of bitter medication is usually hampered by their unpleasant style that results in non compliance and further worsening of diseased condition. [2] Taste masking of the medication that is bitter in taste has been well-tried to be accepted for paediatric and geriatric patients. Several taste masking options are available, including coating ion exchange resins, microencapsulation etc.

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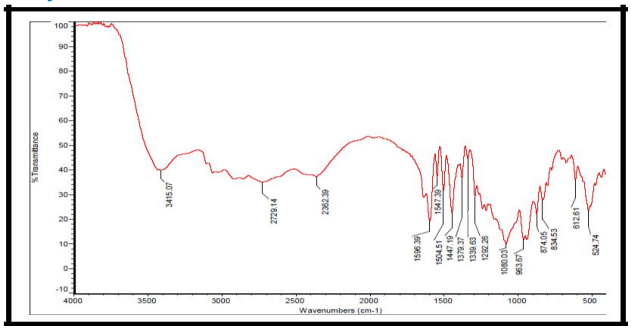
Figure 1. FT-IR Spectra of Kneading Complex Dihydroartemisinin with Tulsion 344



Dihydroartemisinin is an anti-malarial drug with bitter taste. So the present research work was aimed to mask the bitter taste of drug by using resins and formulate into Oral dispersible tablet for better patient compliance. [4]

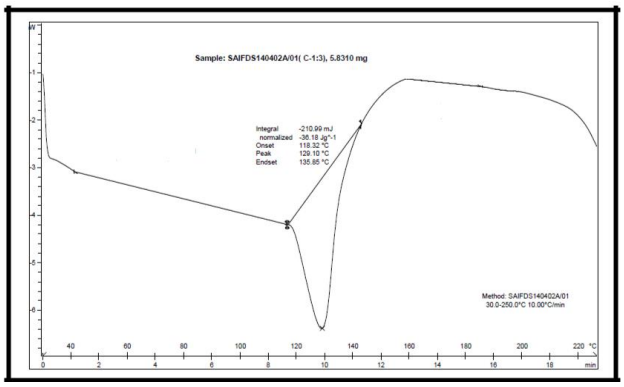
MATERIALS AND METHODS

Materials

Dihydroartemisinin was gift samples from Ajanta Pharma,Mumbai. Sodium starch glycolate & Tulsion 334 & were gift samples from Fisher Scientific, Mumbai. Mannitol, Microcrystalline cellulose, Magnesium stearate were obtained from Loba

Chemicals Mumbai. All the reagents were of analytical grade.

Figure 2. DSC Thermogram of Kneading Complex of Dihydroartemisinin with Tulsion 344



Method

Wavelength of maximum absorbance (λ_{max}) for the solution of the Dihydroartemisinin prepared in distilled water was found to be 217 nm.

Preparation of Dihydroartemisinin – Tulsion 344 Complex

Dihydroartemisinin with Tulsion 344 complex were prepared by using physical mixture and kneading complex method. [17,18] The drugs to resin ratios (1:0.5 to 1:3) were used. The prepared drug-resin complex (DRC) was evaluated for drug content, *in-vitro* and *in-vivo* taste evaluation, and physical properties. On the basis of this evaluation drug to resin ratio of 1:3 was optimized. Further, it was evaluated for molecular properties by IR spectroscopy, Differential scanning calorimetry. [18, 19]

Preparation of Tablet Blend

The optimized complex was mixed with microcrystalline cellulose and magnesium stearate with the help of spatula. [11]

Compression of Tablet Blend

Tablets were prepared by direct compression method. The composition used for preparation of ODT are given in the Table 1.

Table 1. Composition of Tablet Formulation

Ingredients	Quantity (mg / 1 tab)
Kneading Complex	54
Sodium starch glycolate	3
Mannitol	15
Microcrystalline cellulose	75
Magnesium Stearate	3
Total	150

Evaluation of Tablet Blend

The tablet blend was evaluated for following parameters before compression. [4,5]

Table 2. Bitterness Score of Dihydroartemisinin and Tulsion 344

Numerical Scale	DHA	Complex					
		1:05	1:1	1:1.5	1:2	1:2.5	1:3
0	-	-	-	-	-	-	5
0.5	-	-	-	-	1	4	1
1	-	-	2	3	4	2	-
1.5	-	3	4	3	1	-	-
2	-	2	-	-	1	-	-
2.5	1	-	-	-	-	-	-
3	1	1	-	-	-	-	-
3+	5	-	-	-	-	-	-

I. Angle of Repose

It is used to find the flow properties of powder and calculated using following equation:

$$\textbf{Tan } \theta = \textbf{tan-1 (h/r)}$$

where, θ is the angle of repose, H is the height in cm, R is the radius in cm.

Table 3. Tablet Blends Evaluation

Parameters	Result
Angle of Repose (θ)	33.22±3.35
Bulk Density (gm/ml)	0.58±0.028
Tapped Density (gm/ml)	1.15±0.07
Hausner's Ratio	1.98±0.21
Percentage Compressibility (%)	49.03±5.51

II. Bulk Density

Bulk density of the powder blend was determined by pouring gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. The powder was carefully levelled without compacting it and the apparent volume was measured (V_o). Bulk density was calculated by following equation:

$$\textbf{BD (g/ml) = M/V}_o$$

where, M = mass of powder, Vo = apparent unstirred volume

III. Tapped Density

The tapped density was determined by pouring 25 gm sample through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume obtained. Volume occupied by the sample after tapping was recorded and tapped density was calculated by following equation:

$$TD\ (g/ml) = M/V_f$$

where,M = weight of sample powder, V_f = tapped volume

IV. Compressibility Index

It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density by following equation:

$$Carr's\ Index\ (CI) = (TD - BD) / TD\ x100$$

V. Hausner Ratio

It provides an indication of the degree of densification that could result from Vibration of feed hopper. Lower the Hausner ratio better is the flowability. Hausner ratio was calculated by following equation:

$$Hausner's\ Ratio\ (H) = TD / BD$$

Post compression Parameters

The tablets were evaluated for following parameters

I. Weight Variation Test

Twenty tablets of each formulation were weighed individually using an electronic balance. The average weight was calculated and individual tablet was compared with the average value and the deviation was recovered.

II. Content Uniformity of Tablets

Ten tablets were weighed and crushed in a small mortar. The fine powder equivalent to 100 mg of Dihydroartemisinin was transferred to 100 ml volumetric flask containing 20 ml of Methanol and dissolved. The volume was made up to 100 ml with water. The solution was filter through 0.45 µm membrane filter paper. One ml of this solution was diluted 10 times with Methanol and water and the absorbance was measured at 220 nm.

Table 4. Percentage Drug Release Profile in Distilled water, pH 1.2 and pH 6.8

Time(Minute)	% Release in Distilled water	% Release in pH 1.2	% Release in pH 6.8
20	49.17±1.17	51.39±0.86	73.55±0.48
40	52.14±1.90	56.66±0.36	76.84±0.81
60	55.64±1.44	58.72±0.18	83.57±0.46
80	60.53±2.74	60.79±0.29	90.87±0.39
100	67.06±3.73	62.41±0.25	96.48±0.57
120	72.01±4.01	66.16±0.31	98.41±1.22

III. Friability Test

Friability testing was done using Roche friabilator. Ten tablets of each formulation were carefully dedusted and accurately weighed. These tablets were placed in the rotating drum of friabilator. Drum was operated for the 100 revolutions. The tablets were removed and dedusted and reweighed. Percentage weight loss was calculated. A loss of less than 0.5 to 1 % in weight was generally acceptable.

IV. Hardness

Tablet hardness and resistance to powder and friability are necessary requisites for acceptance. The Pfizer hardness tester was used for hardness testing.

V. In vitro disintegration time

Disintegration time is the time taken by the tablet to break into smaller particles. The disintegration test is carried out using USP disintegration test apparatus.

VI. Dissolution study

The prepared formulation was subjected to In vitro dissolution studies.

Dissolution medium	:	pH 1.2, 6.8 and distilled water
Volume of fluid	:	900 ml
Sample size	:	≡100 mg of Dihydroartemisinin
Temperature	:	37±0.5°C

Samples of 10 ml were withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometrically.

RESULTS AND DISCUSSIONS

Taste evaluation was done using the time intensity method by a panel of six healthy volunteers from whom informed consent was first obtained Drug perceives the taste buds as bitter at the concentration of 2-12 µg/ml. Then based on scores, the best taste masked (1:3) complex of Dihydroartemisinin and Tulsion 344 were selected as optimized as shown in Table 2.

The values for angle of repose were found to be within the range of 33.22°C±3.35°C. Bulk densities and tapped densities were found to be within the range of 0.58±0.028 (gm/ml) and 1.15±0.07 (gm/

ml) respectively. The Hausners ratio was within the range of 1.98±0.21 as shown in Table 3. From the result it was concluded that the powder blends have good flow properties which confirms the uniform filling during compression into tablets.

Table 5. FT-IR Peaks and Functional Groups of Dihydroartemisinin, Tulsion 344 and Kneading Complex of DHA with Tulsion 344

Material	Peaks (cm^{-1})	Characteristic Functional Group
Dihydroartemisinin	933.58	C-H Bending vibration
	1188.19	C-O Stretching vibration
	1377.22	C-H Bending vibration
	2723.58	C-H Bending vibration
	3377.47	N-H stretching vibration
Tulsion 344	970.23	C-H Bending vibration
	1226.77	C-O Stretching vibration
	1599.04	C=C Stretching vibration
	2852.81	C-H Stretching vibration
Kneading complex (DHA with Tulsion 344)	963.67	C-H Bending vibration
	1080.03	C-O Stretching vibration
	1379.37	C-H Bending vibration
	2729.14	C-H Stretching vibration
	3415.07	N-H stretching vibration

Hardness for all the formulations were in range of 2.375±0.125 kg/cm², it indicated that all the formulations possess sufficient mechanical strength .Weight variation was found to be within IP limits. Friability values were found to be less than 1% indicated that within the IP limits.

In order to investigate the effect of optimized kneading complex for the drug release rate from the prepared formulation, *in-vitro* dissolution study was carried out. Percentage Drug Release Profile in Distilled water, pH 1.2 and pH 6.8 was shown in Table 4.

CONCLUSION

In this investigation, Styrene divinyl benzene polymer Tulsion 344 was used to mask the bitter taste of drug. The study conclusively demonstrated significant taste masking of DHA by kneading method and rapid disintegration and dissolution of ODT was achieved.

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