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CENTRAL COMPOSITE DESIGNED TASTE MASKED ION EXCHANGE RESINATES FOR DEVELOPMENT OF AZITHROMYCIN DISPERSIBLE TABLETS

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ABTRSACT

Purpose: The purpose of the present investigation was to formulate taste masked dispersible tablets of azithromycin using complexation by ion exchange resin applying the central composite design.

Methodology: The basic methodology behind the present work was the application of ion exchange resin complexation for masking the bitter taste of azithromycin. The central composite design (CCD) was applied to study the effect of two critical factors i.e. swelling time (X_1) and stirring time (X_2) on percent drug complexed and cumulative percentage drug release. ANOVA was applied to percent drug complexed and cumulative percentage drug release to study the fitting and the significance of the model. The drug resinate was finally formulated into dispersible tablets by direct compression method.

Findings: The drug resin ratio of 1:3 and pH 6 were found to have maximum drug loading onto the resin (Tulsion 335). The maximum drug release was found at high values of swelling and stirring time. The techniques of differential scanning calorimetry (DSC), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) clearly indicated the formation of drug resin complex. Further, the formulated tablets were found to be within the pharmacopoeial limits.

Originality: The present work is a novel attempt to prepare optimized taste masked formulation of extremely bitter drug azithromycin to overcome the problem of swallowing conventional tablets in case of paediatric patients.

Conclusion: The technique of ion exchange resin complexation was successfully applied to prepare the taste masked azithromycin dispersible tablets. Data revealed that the developed dispersible tablets showed better taste profile when compared with the marketed formulation and were found to be stable.

Keywords: *azithromycin; acidic cation exchange resin; taste masking; tulsion-335; central composite design; dispersible tablets.*

INTRODUCTION

The oral route of drug administration is a popular, convenient and widely accepted method of administering the drugs[1]. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance. However, taste is an important factor in the success of oral dosage form; the bitter taste drugs often present formulation problems and affect the patient compliance[2]. According to reports, more than 50% of patients do not take their medications as prescribed, costing the pharmaceutical industry an estimated U.S. $30 billion annually from prescriptions that are not filled or refilled[3-4].

Numerous techniques have been described in academic and patent literature for masking of bitter or undesirable taste of drugs like addition of flavors, sweetener and amino acids, microencapsulation, inclusion complexation with cyclodextrin, complexation with ion exchange resin, salt preparation, group alteration and prodrug approach[5-9].

Ion exchange resin complexation has emerged as a simple, efficient and viable technique for taste masking of a number of bitter tasting drugs. The basic mechanism involved in this technique is the attachment of bitter tasting drugs to oppositely charged resin substrate resulting in formation of drug resinate. The salivary environment with an average pH of 6.8 and a cation concentration of 40 meq/L does not allow the drug to be disassociated from the resin complex. This primarily is the reason for masking of unpleasant taste of bitter drugs. Immediately after the drug reaches the gastric environment, it is broken down due to large concentration of hydrogen ions. The hydrogen ions in the stomach displaces the drug from the complex and cause rapid elution from or disintegration of ion exchange resin drug complex and release the drug in the gastric content. The free drug is now available, which can be easily absorbed from the GIT. Thus, taste masking of a drug is achieved without affecting the release of drug[10].

Azithromycin, a macrolide antibiotic is extremely bitter in taste, which makes its formulation very challenging. It was, therefore, considered worthwhile to develop a taste

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Taste masked dispersible tablets of azithromycin

masked azithromycin dispersible tablets especially for children for whom swallowing of tablet may be difficult. However, the designing of taste masked preparation for drug with unpleasant taste is difficult because of usual need to incorporate two contradictory characteristics in the product, i.e., masking of unpleasant taste for patient compliance and complete releasing of the drug from dosage form to avoid lowering of bioavailability[11].

In the present investigation, an attempt has been made to formulate taste masked dispersible tablets of azithromycin, using the technique of complexation with ion exchange resin. Ion exchange resin complexation is a simple, efficient and proven technique for taste masking of a number of bitter tasting drugs and does not interfere with the release of the drug[12-15]. The objective behind the present work was to study the effect of two critical variables - swelling time (X_1)and stirring time (X_2) on the percentage drug complexed and percent cumulative drug release (% CDR) using central composite design.

MATERIALS AND METHODS

Azithromycin was received as gift sample Vishal Pharma., Kurukshetra, India; Acidic cation exchange resin Tulsion-335 was a kind gift from Thermax Limited, Chemical Division, Pune, India and aspartame was a kind gift sample from Martin and Brown Pharmaceuticals Ltd., Hisar, India. All other chemicals were of analytical reagent grade and used as received. The solvents used for HPLC analysis were HPLC grade.

Purification and activation of resin

Tulsion 335 was purified by washing with distilled water. The wet resin was activated by 0.1M HCl 300 mL followed by washing with distilled water. The resin was then dried in vacuum oven at 60°C till the moisture content came below 5% confirmed by Karl Fisher titration. The purified resin was stored in an air tight glass vial[16].

Optimization of drug resin ratio

The different quantities of activated resin were transferred to 20 ml of deionised water and allowed to swell for 30 min. The accurately weighed quantity of azithromycin was added separately to each beaker to obtain different ratios of drug: resin (1:1, 1:2, 1:3 and 1:4) and stirred using a magnetic stirrer for 3 hrs at room temperature. The mixtures were filtered and residues were washed with 5 ml of deionised water. The unbound drug in the filtrate was estimated by HPLC using Agilent 1200 series on Reverse Phase C-18 column operated at 50°C using 80% methanol and 20% buffer (Phosphate buffer was prepared by dissolving potassium dihydrogen phosphate in 1000 ml of water (0.3 M), adjusted to pH 7.5 with 10% sodium hydroxide solution) as mobile phase, flow rate maintained at 2.0 ml/min and detection was carried out at 210 nm[17].

Optimization of effect of pH on complexation

Buffer solutions of different pH ranging from 3 to 9 were prepared as per USP specifications. The drug resin mixing was carried out at different pH to study the effect of pH on drug loading.

Preparation of drug resin complex (DRC)

DRC was prepared by batch process, using central composite design at an optimized drug to resin ratio and pH. Resin was allowed to swell in 20 ml water under magnetic stirring for 25-60 min at room temperature. Azithromycin was added to swelled resin slurry at maximum drug: resin ratio under magnetic stirring and the resultant mixtures were stirred for 0-7 hrs. The drug–resin complex was separated by filtration and residue was washed with 5 ml of deionized water to remove any uncomplexed drug, and finally dried at room temperature. The complex was stored in an air tight glass vial.

Optimization of process parameters

Statistically designed experiments using Central composite design (Design-Expert 8, version 8.0.7.1) were performed to study the effect of two critical factors – swelling time (X_1) and stirring time (X_2) on percent drug complexed and percentage cumulative drug release (% CDR). The central-composite design utilizes orthogonal arrays from design of experiments theory to study a large number of variables with a small number of experiments. Further, this design has an added advantage of determining the quadratic response surface, not determinable using a factorial design at two levels[18]. The study of two factors at three levels (-1, 0, +1) using central composite design leads to twelve complexes of drug and resin (ARC1-ARC12).

Characterization of optimized drug – resin complex

Differential Scanning Calorimetry (DSC) characterization of samples

The thermal behavior of each drug resin complex (DRC) was examined by differential scanning calorimeter (DSC Q10, TA Instruments, USA). Sample 3-4 mg was run at a scanning rate of 10°C/min over a temperature range of 45 to 250°C in nitrogen environment.

Fourier transform Infrared Spectral (FTIR) study

Drug resin complex was powdered and transferred to zirconium crystal window and then their IR spectra (Alpha 1206 0280 FTIR Spectrohotometer, Brukers, Netherlands) were recorded over the region 400–4000 cm^{-1}.

X-ray Diffraction (XRD) characterization of samples

X-ray diffractometer (Xpert Pro's Pan Analytical Instrument, Model Philips PW 3040/60, Germany) was employed to study the crystalline form of the drug in the complex. The X-ray copper target tube K_α (λ=1.5465980 A°) was operated at Crystal monochromator voltage of 45mV and current 30 mA. The scanning was carried out over 2θ range of 8° to 60°C.

In Vitro Dissolution Rate Studies

Dissolution studies of complexes were performed according to USP XXIII Apparatus II (LabIndia DS 500, India) by adding complex equivalent to 125 mg of azithromycin in 900 ml of dissolution media (buffer solution prepared by adding to 6 litres of 0.1 M dibasic sodium phosphate about 40 ml of hydrochloric acid to adjust the pH to 6.0, adding 600 mg of trypsin, and mixing). The temperature was maintained at 37±0.5°C

with rotation speed of 50 rpm[19]. The samples were withdrawn at various time intervals and analyzed by HPLC. The test was carried out in triplicate.

Taste evaluation study

The bitterness evaluation test was performed with human volunteers according to a method described by Kawano *et al.,* after clearance from human ethical committee [Approval # PHY/HEC/13/421 dated 26.4.13]. Test was carried out on a trained taste panel of six human volunteers, from whom informed consent was first obtained. The volunteers rinsed their mouths thoroughly before and after the tasting. Each sample was held in the volunteers' mouth for 30 sec and then expectorated, and the taste was evaluated and assigned a numerical value according to the following scale: 0- Tasteless, 1- Slight bitter, 2- Moderate bitter, 3- Strong bitter. The lower score indicated a greater masking effect[20].

Preparation of dispersible tablets

Azithromycin dispersible tablets were prepared using optimized DRC by direct compression method. A total number of eight formulations were prepared. All the ingredients were passed through #60 sieve. Firstly, Avicel 102 (directly compressible microcrystalline cellulose)/Pearlitol SD200 (directly compressible mannitol), super disintegrating agents and DRC were mixed together for 25 min using double cone blender. Finally to this blend aspartame, lemon flavor and lubricants were added and mixed further for 10 min. The tablets were then compressed using 13 mm size round faced punches to obtain tablet of 700 mg weight by 16-station rotary tablet making machine (Cadmach Machinery Co. Pvt. Ltd., India).

Evaluation of blend for dispersible tablets

Before tablet preparation, the mixture blend of all the formulations was evaluated for various pre compression parameters, such as angle of repose, bulk density, tapped density, carr's compressibility index etc[21].

Evaluation of tablets

The formulated dispersible tablets were evaluated for different parameters like, weight variation hardness, friability, drug content, disintegration time, *in vitro* dissolution and taste evaluation.

Drug content

The drug content was determined by transferring one finely powdered tablet to a 100 ml volumetric flask. To this 2 mL of 5N HCl was then added and the volume was made with distilled water. The volumetric flask was stirred in a sonicator for 30 min with intermittent shaking. The samples were diluted suitably and filtered and analyzed by HPLC at 210 nm. The test was carried out in triplicate.

Weight variation

The USP weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The weight variation tolerances for uncoated tablets differ depending on average tablet weight.

Hardness

Tablets were evaluated for hardness using Monsanto hardness tester. The tablet was placed in contact with the lower plunger and a zero reading was taken. The upper plunger was then forced against a spring by turning a threaded bolt until the tablet fractures. The force of fracture was recorded and the zero force reading was deducted from it.

Friability

Friability was determined using Roche friabilator which consist of a circular plastic chamber, divided into 2-3 compartments. Twenty tablets were weighed and placed in the apparatus which was rotated at 25 rpm for 4 min. After revolution the tablets were dusted and weighed. The friability is given by the formula:

$$F = (1 - W/W_o) \times 100 \quad \text{.....eqn (1)}$$

Where W_o = weight of the tablets before test

W = weight of the tablets after test

The weight loss should not be more than one per cent.

Disintegration time

The disintegration time of tablets from each formulation was determined by using digital tablet disintegration apparatus. *In vitro* disintegration test was carried out at 37±2 °C in 900 ml distilled water.

Taste evaluation study

Bitterness evaluation test was performed to evaluate the taste of the prepared tablet to that of pure drug. The test was carried out as per procedure mentioned in taste evaluation of DRC. The mean bitterness score of three tablets was considered.

In vitro dissolution rate study of dispersible tablet

The drug release studies were performed using USP XXII type II tablet dissolution apparatus (DS-500, Labindia Instruments Pvt. Ltd., Mumbai). Tablets consisting of the azithromycin resin complex equivalent to dose of azithromycin (125 mg) was taken in 900 ml of a buffer solution as used in case of dissolution rate study of resin complexes. The temperature and speed of the apparatus were maintained at 37±0.5°C and 100 rpm, respectively. Aliquots were withdrawn at time interval of 5, 10, 20, 30, 45 and 60 min, filtered with Whatman # 41 filter paper and analyzed at 210 nm by HPLC. The test was carried out on six tablets.

Stability study

Stability study was conducted at 40°C±2°C/75%±5% RH for three months. The tablets were individually weighed and wrapped in an aluminium foil and packed in black PVC bottle and kept under conditions specified above for three months. At one month interval, the tablets were evaluated for drug content, hardness, disintegration time, weight variation and *in vitro* dissolution[22].

RESULT AND DISCUSSION

The selection of an ion exchange resin for a particular drug delivery application is generally based on its functional group characteristics. In the present work, the drug azithromycin is a free base for which a weak acid cation exchange resin is useful for taste masking. From the different variety of the cation exchange resins, Tulsion-335 grade chemically known as Polacrilex resin which is a weakly acidic polyacrylic copolymer was chosen as a cation exchange resin for taste masking of azithromycin. Tulsion-335 uses the hydrogen ion as an exchange ion which helps it in adsorbing the drug in its base form. On exposure to acidic pH of stomach, desorption of drug takes place due to high affinity of the resin for the hydrogen ion.

Purification and activation of resin

The resin was purified for removal of the adsorbed impurities associated with large scale manufacturing of resins and adsorbed during storage and handling. The purpose of activating the resin is to ensure that more exchangeable groups are available for maximum and rapid loading.

Optimization of drug: resin ratio

Complexation of drug with Tulsion was studied for optimum drug to resin ratio for maximum loading. The values of percentage drug complexed showed an increasing trend with the increase in resin content which is attributed to the increased interaction between the drug molecules and the resin particles. The values for percentage drug complexed for the drug to rein ration of 1:1, 1:2, 1:3, 1:4 and 1:5 was found to be 64.48, 76.06, 84.56, 85.24. and 85.64 respectively. One way ANOVA was applied to compare the effect of different drug to resin ratios on drug loading. In case of ratios 1:1 and 1:2 drug bound was less than, 1:3, 1:4 and 1:5 as shown by the result of one way ANOVA where the p value ($p< 0.05$) indicated significant difference. The ratio of 1:3, 1:4 and 1:5 did not indicated significant difference ($p>0.05$). Since, the increase in % drug complexed is negligible after 1:3 ratios, increasing the resin amount for a negligible increase in drug loading is not economically justifiable. Therefore, drug: resin ratio of 1:3, was selected for further investigation.

Optimization of effect of pH on complexation

The percentage drug complexed at pH 3, 4, 5, 6, 7, 8 and 9 was found to be 12.24, 22.46, 76.68, 92.24, 92.06, 84.68 and 82.64 respectively. The exchangeable cation in Tulsion 335 is hydrogen ion. In an acidic environment (below pH 4), the resin exists as free acid in an essentially nonionic state and hence the percentage drug complexed was found to be minimum (12.24%) at pH 3. On increasing the pH from 4.0 to 6.0, an increase in loading efficiency was observed with maximaum laoding of 92.24% at pH 6. Above pH 4, the Tulsion 335 resin's carboxyl group liberates hydrogen ions resulting in protonation of weakly basic drug azithromycin which binds to resin's anionic carboxylic group by an ionic bond to form a water insoluble complex. As the pH is increased to 6, a greater quantity of drug is solubilized and the equilibrium concentration of drug substance shifts to complex the solubilized drug with the resin.

Above pH 6, the drug loading became constant and above pH 8, it slightly decreased. This can be explained on the basis of pKa of drug which is 7.4. If the pH is higher than pKa of drug, the drug remains mostly in nonionized form. At pH 6, both the drug and the resin are ionized in sufficient quantity which resulted in maximum resinate formation. Thus the pH 6 was found to be an optimum pH for complex formation

Optimization of process parameters

A central-composite statistical design with two factors at three levels was chosen as the experimental design. The key factors studied were X_1-swelling time; X_2 – stirring time at three levels (-1, 0 and +1) and twelve formulations (ARC1- ARC12) of drug resin complex were prepared by keeping drug to resin ratio (1:3) and pH 6.0 constant in all formulations as shown in Table 1. To determine the magnitude of contribution of different factors towards percentage drug complexed and cumulative percent drug release, multiple linear regression analysis (MLRA) was performed. It was found that percent drug complexed was maximum at high level of both the swelling time (X_1) and stirring time (X_2). It shows that high levels of swelling and stirring are required for maximum binding of the drug with the resin.

Table 1. *Percent drug complexed and % CDR of azithromycin from batches ARC1-ARC12*

F.Code	X_1(Swelling time)	X_2(Stirring time)	Percent drug complexed	%CDR (after 60 min)
ARC-1	-1(30 min)	+(6 hr)1	94.98±1.26	90.24±1.48
ARC-2	-1(30 min	)-1(1 hr)	65.46±0.98	85.14±1.03
ARC-3	+1(1 hr)	+1(6 hr)	96.54±1.08	94.45±2.54
ARC-4	+1(1 hr)	-1(1 hr)	74.09±0.76	89.89±1.61
ARC-5	-1.414(24 min)	0(3.5 hr)	76.41±1.45	89.80±1.72
ARC-6	+1.414(66 min)	0(3.5 hr)	81.08±1.28	91.70±1.69
ARC-7	0(45 min)	-1.414(0 hr)	29.04±0.84	89.75±1.73
ARC-8	0(45 min)	+1.414(7 hr)	93.82±2.12	90.51±1.22
ARC-9	0(45 min)	0(3.5 hr)	71.87±1.46	92.42±1.91
ARC-10	0(45 min)	0(3.5 hr)	73.47±0.94	87.41±3.00
ARC-11	0(45 min)	0(3.5 hr)	75.15±1.34	89.41±2.12
ARC-12	0 (45 min)	0 (3.5 hr)	76.40±0.88	89.50±2.59

The model, developed from multiple linear regression to estimate % drug complexed can be presented mathematically as:

$$\mathbf{Y = 75.69 - 2.10\,X_1 + 17.95\,X_2} \quad \text{.....eqn (2)}$$

Where Y = % Complexed drug; X_1 = swelling time; X_2 = stirring time

ANOVA was applied on cumulative percentage of drug released to study the fitting and significance of model. F-test was carried out to compare the regression mean square with residual mean square [Table 2]. The ratio F = 13.72 shows regression to be significant.

The model, developed from multiple linear regression to estimate cumulative percent drug release can be presented mathematically as:

$$\mathbf{Y = 90.02 + 1.46\,X_1 + 1.34\,X_2} \quad \text{.....eqn (3)}$$

Where Y = % Complexed drug; X_1 = swelling time;
X_2 = stirring time

Table 2: *ANOVA of the regression (% drug complexed and % CDR (after 60 min)*

	% drug complexed			% CDR (after 60 min.)		
	Total	Regression	Residual	Total	Regression	Residual
Degree of freedom	11	02	09	11	02	09
Sum of squares	3468.85	2612.26	856.59	59.90	31.36	28.54
Mean square	-	1306.13	95.18	-	15.68	3.17
F	-	13.72	-	-	4.94	-
F-significance	-	0.0018*	-	-	0.0356*	-

** Values of "Prob > F" less than 0.0500 indicate model terms are significant.*

ANOVA was applied on cumulative percentage of drug released to study the fitting and significance of model as shown in Table 2. The ratio F = 4.94 shows regression to be significant.

The 3D Surface and Contour plots were developed for % drug complexed and % CDR employing Design Expert® software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN) and given in Figures 1-4.

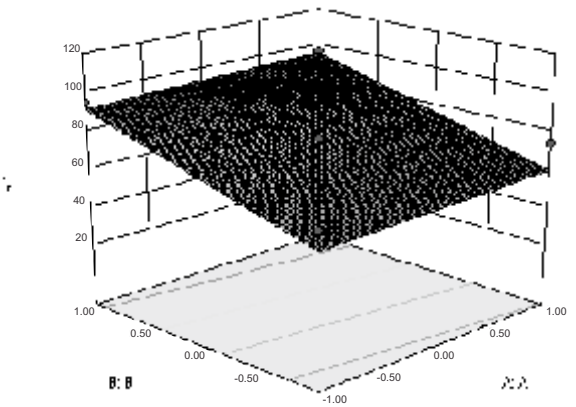

Fig. 1: *3-D Response surface for percentage drug complexed*

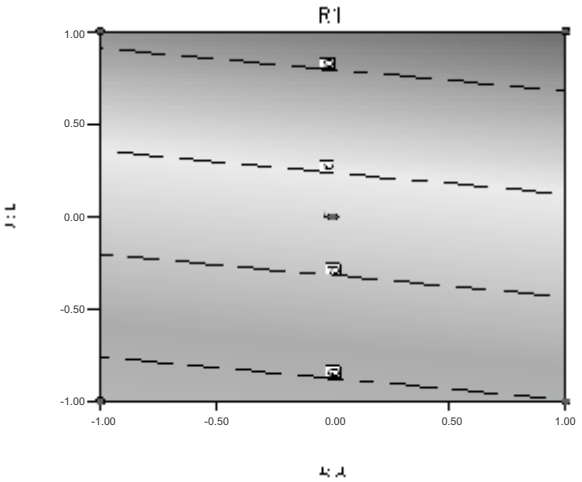

Fig. 2: *Contour Plot for percent drug complexed*

Characterization of drug resin complexes

Differential Scanning Calorimetry Evaluation

The pure drug, resin, physical mixture of resin and the optimized drug resin complex (ARC-3) was subjected to thermal characterization and the overlay of thermograms is presented in Figure 5. The DSC thermogram of physical mixture of azithromycin and resin showed independent peaks of drug and the resin indicating that the drug existed in crystalline form in the physical mixture. However, in case of optimized drug resin complex (ARC-3) no peak related to azithromycin was observed which clearly suggested that the drug has undergone physical changes from crystalline to amorphous which confirms the formation of complex.

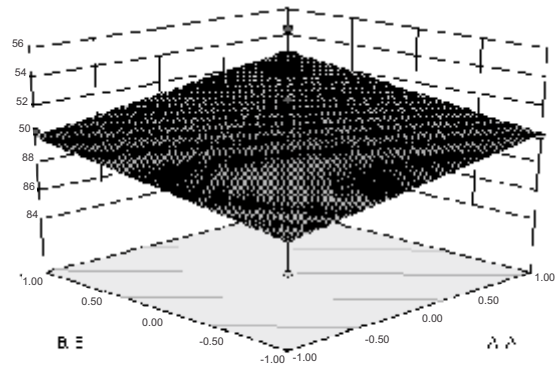

Fig. 3*: 3-D Response surface for cumulative percentage drug released (60 min.)*

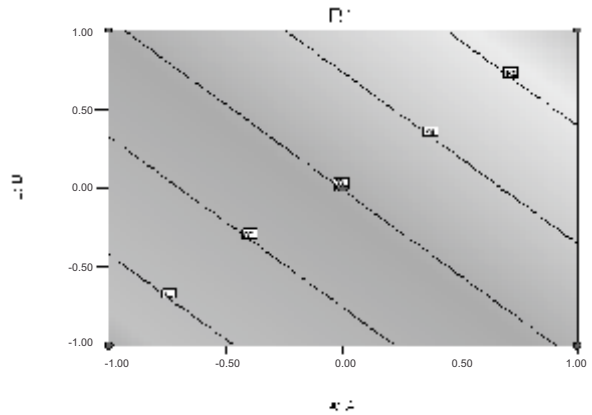

Fig. 4*: Contour Plot for cumulative percent drug released (60 min.)*

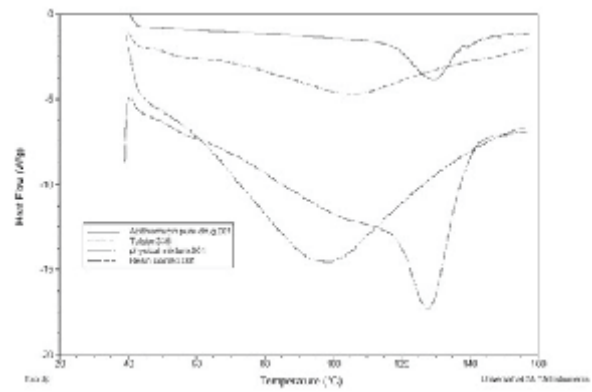

Fig. 5*: DSC thermograms of azithromycin, tulsion-335, physical mixture and drug resin complex- ARC 3*

FTIR studies

FTIR Spectra as shown in Figure 6 was employed to study the interaction between azithromycin and Tulsion 335. The IR spectrum of azithromycin exhibits five characteristic transmission peaks at 3490, 1720, 1453, 1377 and 1183 cm^{-1}, attributed to stretching vibration of O-H, C=O, CH_3-O, C-N and C-O-C respectively. The FTIR spectrum of tulsion-335 exhibits characteristic peak at 1696, 1162 and 797 cm^{-1}. The FTIR spectrum of physical mixture was similar to synthetic spectra produced by addition of azithromycin and Tulsion 335. This indicated that there was no interaction between azithromycin and Tulsion 335. The spectrum of complex was different from that of physical mixture and characteristic peaks of azithromycin were absent in case of complex indicating transformation of the drug from crystalline to amorphous form. The possible mechanism behind the complex formation is resin adsorption on to the drug by exchange of ions. In the present study, the -OH group of azithromycin and functional group -COOH of Tulsion 335 interacted to form the complex.

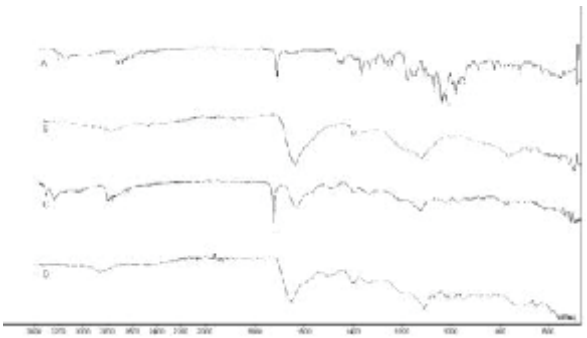

Fig. 6*: FTIR Spectra of (a) azithromycin, (b) tulsion-335, (c) physical mixture and (d) drug resin complex -ARC-3*

X-ray diffraction studies

Powder X-ray diffraction pattern of azithromycin, Tulsion 335, physical mixture of azithromycin and Tulsion 335 and optimized drug resin complex (ARC-3) are shown in Figure 7. The result of X-ray diffraction showed that the pure drug exhibited crystalline property, while Tulsion 335 exhibited amorphous pattern. Physical mixture of azithromycin with Tulsion 335 exhibited crystalline property of azithromycin indicated that the drug has not undergone any physical change while the complex displayed amorphous pattern. All the peaks of azithromycin were absent in case of the complex. It proved the drug was changed into amorphous form after the preparation process of complex.

Bitterness evaluation study

The results of taste evaluation as shown in Table 3 indicates that there is very little or no bitterness imparted with ARC-1, ARC-3 and ARC-8 (mean taste score of 0.33±0.002,0.16±0.001 and 0.83±0.002 respectively) with reference to pure drug (3.00±0.000) since a person is not able to keep the pure drug in the mouth in 30 sec. One way ANOVA was applied for

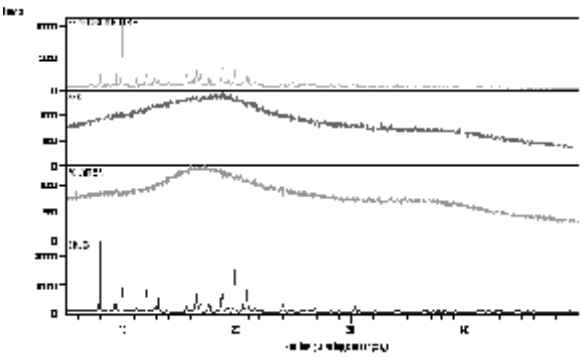

Fig. 7*: X-ray diffraction pattern of (a) physical mixture, (b) drug resin complex- ARC 3(c) resin and (d) azithromycin*

Table 3*: Bitterness evaluation study of resin complexes*

Sr. No.	Product Code	Volunteers score						
		I	II	III	IV	V	VI	Mean Score
1	Pure drug	3	3	3	3	3	3	3.00±0.000
2.	ARC-1	0	0	1	0	0	1	0.33±0.002
3.	ARC-2	2	2	1	2	2	1	1.66±0.036
4.	ARC-3	0	0	0	0	1	0	0.16±0.001
5.	ARC-4	2	1	1	2	1	2	1.50±0.024
6.	ARC-5	1	2	2	1	1	1	1.33±0.018
7.	ARC-6	1	1	1	1	2	1	1.16±0.014
8.	ARC-7	3	2	2	2	3	3	2.50±0.048
9.	ARC-8	1	1	1	1	1	0	0.83±0.002
10.	ARC-9	2	2	2	1	1	2	1.66±0.028
11.	ARC-10	2	1	2	1	2	1	1.50±0.024
12.	ARC-11	2	2	2	1	1	2	1.66±0.016
13.	ARC-12	2	2	2	2	1	1	1.66±0.034

comparing the results of taste study for different drug resin complexes. Out of various drug resin complexes ARC-1, ARC-3 and ARC-8 showed better taste masking ability than other resin complexes (p< 0.05 indicating significant difference).

The taste score of ARC-3 was lower than ARC-1 and ARC-8 and hence the azithromycin resin complex ARC-3 was found to be the optimized complex in terms of taste study and was taken up for further characterization and formulation of dispersible tablets.

Formulation of dispersible tablets

The optimized batch of resin complex (ARC-3) which showed the best release profile and taste was used for the formulation of taste masked azithromycin dispersible tablets by direct compression method. Batches F1-F8 as shown in Table 4 were prepared to obtain the formulation with best disintegrating properties. Different diluents (microcrystalline cellulose and mannitol) and disintegrants (Ac-di-sol, crospovidone and sodium starch glycolate) in varying concentration were employed to optimize the formulation with best disintegrating and organoleptic properties.

Before tablet preparation, the mixture blend of all the formulations was evaluated for various pre compression parameters such as angle of repose, bulk density, tapped density, carr's compressibility index and the

results are shown in Table 5. The formulations were found to have good flow characteristics as evident by the angle of repose which was less than 30 indicating excellent flow characteristics. Similarly the value of carr's index was in the range of 12-14 indicating excellent flow and compressibility.

***Table 4**: Formulation of azithromycin dispersible tablets F1-F8*

Formulation Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
DRC(Equivalent to 125 mg of azithromycin)	500	500	500	500	500	500	500	500
Avicel 102 (DC Microcrystal Cellulose)	138.4	138.4	138.4	-	-	-	69.2	92.27
Pearlito SD 200 (Mannitol)	-	-	-	138.4	138.4	138.4	69.2	46.13
Ac-di-sol	28	-	-	28	-	-	28	28
Crospovidone	-	28	-	-	28	-	-	-
Sodium Starch Glycolate	-	-	28	-	-	28	-	-
Aspartame	21	21	21	21	21	21	21	21
Lemon flavour	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1
Magnesium Stearate	7	7	7	7	7	7	7	7
Aerosil	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5

***Table 5**: Pre-compression characteristics of formulations F1-F8*

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Angle of repose	22.54±0.4	24.62±0.7	25.46±0.2	28.13±0.4	26.42±0.2	26.22±0.5	25±0.18	24±0.68
Bulk Density gm/cm^3	0.58±0.01	0.58±0.01	0.59±0.01	0.58±0.02	0.56±0.01	0.58±0.01	0.55±0.02	0.58±0.21
Tapped density gm/cm^3	0.68±0.00	0.67±0.01	0.67±0.01	0.67±0.00	0.66±0.01	0.67±0.01	0.65±0.01	0.68±0.01
Carr's index	12.46±0.2	13.84±0.4	12.88±0.5	13.86±0.4	14.08±0.8	13.66±0.4	13.48±0.5	12.98±0.7

Evaluation of dispersible tablets

After the compression, the dispersible tablets were evaluated for various parameters like weight variation, hardness, friability, drug content, disintegration time and *in vitro* drug release. The results are tabulated in Table 6. The dispersible tablets were found to pass weight variation test as per I.P. (700 ± 7.5). The hardness was found to be 4.0 kg/cm^3, which is sufficient to withstand mechanical shocks of handling in manufacture, packaging and transportation. The batch F1 containing crosscarmellose sodium as the disintegrating agent exhibited best disintegrating time of 15±0.24 sec and % friability was 0.35±0.0, which is acceptable.

***Table 6**: Evaluation of dispersible tablets F1-F8*

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Drug content (%)	98.42±1.24	96.86±1.68	97.24±2.06	97.48±1.88	98.12±1.66	97.42±1.44	98.24±1.88	95.46±1.28
DT (In sec)	15±0.24	18±0.12	25±0.2	240±0.42	45±0.26	52±0.24	42±0.18	35±0.68
Hardness (kg/cm^2)	4±0.12	3.8±0.26	4.2±0.16	4.8±0.22	4.2±0.86	4.8±0.72	4.5±0.26	4.6±0.12
Friability (%)	0.35±0.01	0.56±0.08	0.76±0.02	0.68±0.06	0.48±0.04	0.58±0.16	0.72±0.14	0.58±0.18
Weight Variation	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

In vitro dissolution rate study of dispersible tablets

In vitro drug release studies were performed in the dissolution media (buffer solution prepared by adding to 6 litres of 0.1 M dibasic sodium phosphate about 40 ml of hydrochloric acid to adjust the pH to 6.0, adding 600 mg of trypsin, and mixing). The temperature was maintained at 37±0.5°C with rotation speed of 50 rpm and was compared with the marketed formulation (tablet) in the same media. The azithromycin dispersible tablets showed 94.76 % release after 60 min whereas for marketed formulation drug release values for azithromycin were 91.24 %.

Batch F1 showed the best disintegration time and cumulative release and hence was selected as best formulation and subjected to stability testing and comparison with marketed tablet in terms of taste profile.

Taste evaluation study

The developed tablet was found to have mean taste score of 0.42±0.002 which was less than marketed tablet having taste score of 0.86±0.002 which clearly indicated that the developed dispersible tablet was better in taste in comparison to marketed tablet.

Stability studies

The tablets were found stable after three month study as no appreciable change was observed in the value of drug content, hardness, disintegration time, weight variation and *in vitro* dissolution rate as shown in Table 7.

***Table 7**: Stability profile of azithromycin dispersible tablets*

Evaluation Parameters	1 month	2 month	3 month
Drug content (%)	98.42±1.24	96.86±1.44	95.24±1.66
Disintegration time (In sec)	15±0.24	18±0.12	18±0.22
Hardness (kg/cm^2)	4±0.12	3.8±0.26	3.6±0.16
Friability (%)	0.35±0.01	0.56±0.08	0.66±0.02
% CDR (After 60 min.)	94.76±1.48	94.06±1.76	92.76±2.08
Weight Variation	Pass	Pass	Pass
Taste	No bitterness	No bitterness	No bitterness

CONCLUSION

Taste masking has gained immense significance in formulation of dispersible tablets. In the present work, an effective taste masking of azithromycin was achieved by ion exchange resin complexation. Data revealed that swelling of resin and stirring time play critical role in the complex formation. The maximum drug release was found at high values of swelling and stirring time. The model developed in the present study can be further utilized as response surface for cumulative percent of drug release from drug resinate. Thermal study, FTIR and XRD studies confirmed the formation of complex. From the *in vitro* dissolution and taste evaluation studies, it was concluded that taste masking was achieved for azithromycin without affecting the release of drug. The dispersible tablets showed better release and taste profile when compared with the marketed formulation. These formulations can be further taken up for scale up.

CONFLICT OF INTEREST

The authors report no conflict of Interest.

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