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Research Article

Formulation Optimization and Evaluation of Taste Masked Azithromycin Tablets

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ABSTRACT
The aim of the present study was to mask the bitter taste of azithromycin by ion exchange resin complexation using Tulsion-335 resin and to formulate the resinates into dispersible tablets. The objective behind the study was to investigate the effect of swelling time (X_1) and stirring time (X_2), on percent drug complexation and percent cumulative drug release (% CDR) of azithromycin using central composite design. 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 dissolution rate. Taste masking has gained immense significance in formulation of dispersible tablets. The ion exchange resin complexation were successfully applied to prepare taste masked azithromycin dispersible tablets Thermal study FTIR and XRD studies were instrumental in the characterization and confirmed the formation of azithromycin ion exchange resin 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 mathematical models developed in the optimization study can be utilized to design complex with desired % complex with desired entrapment efficiency. The optimized azithromycin resin complex was further formulated into dispersible tablets. 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.

KEYWORDS: Taste masking, azithromycin, Ion exchange, Bitter Taste, Design-Expert

INTRODUCTION

The oral route of drug administration is popular, convenient and widely accepted method of administering the drugs because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance (Lachman and Liberman, 2013). The major foucs of the formulation scientist is to develop formulations for oral application of newly synthesized drugs since they can be self-administered by the patient. The characteristics of drug, the application desired and the need for any special effects than dictates the type of oral dosage form to be developed (Roy, 1990). The monophasic liquids such as syrups, solutions, elixirs, biphasic liquids such as suspensions, emulsion etc. and solid dosage forms like tablets and capsules and liquid filled capsules are the common types of oral formulations.

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Taste masking is a viable and practical strategy to improve the patient compliance, especially for bitter drugs, whereby, a number of methodologies may be adopted to deliver a taste masked palatable formulation. Various techniques based on different principles have been investigated and 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. In the present work, the techniques of ion exchange resin complexation and spray drying have been employed for masking the bitter taste of medicament.

Taste is one of the most important and most challenging parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs.

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 of6.8 and a cationconcentrationof40 meq/L does not allow the drug to be disassociated from the resin complex. This is primarily 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 (Singh et al., 2007). 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 bioavailable, which can be easily absorbed from the GIT. Thus, taste masking of a drug is achieved without affecting the release of drug (Shukla et. al., 2009), The aim of present work was to develop taste masked pharmaceutical dosage form of bitter drug(s) by using the technique of ion exchange resin complexation and spray drying. The objective behind the study was to investigate the effect of swelling time (X1), and stirring time (X2), on percent drug complexation and percent cumulative drug release (% CDR) of azithromycin using central composite design (CCD) for ion exchange resin complexation technique.

MATERIAL AND METHOD

Materials

Azithromycin, Tulsion-335 Eudragit, Methanol, Acetonitrile, Sodium Starch Glycolate, Microcrystalline Cellulose, Crospovidone, Aspartame, Magnesium, Stearate, and Talc all excipient used as analytical grade.

Estimation of Azithromycin by HPLC:

Several methods based on different techniques have been reported for analysis of azithromycin in pharmaceutical dosage forms [14,15,16]. For the present study, a simple and validated HPLC method as reported by Al-Rimawi & Kharoaf, 2010 was employed for estimation of azithromycin. This reported method demonstrated good linearityover the range of 0.3–2.0 mg/mL of azithromycin. The accuracy of the method was 100.5% with a relative standard deviation of 0.2%. HPLC analysis was performed using Agilent technologies 1200 series, Germany (Reverse phase C-18 column, UV detector dual wavelength) utilizing the parameters as enlisted in the Table 1.

Table 1: HPLC Parameters for analysis of azithromycin

Parameter	Conditions
Apparatus	AgilentTechnologies,1200,Germany
Mobile phase	80% Methanol & 20% buffer (Phosphate buffer was prepared by dissolving potassium dihydrogen phosphate in 1000 ml of water (0.3M)
Detection wavelength	210nm
Flow rate	2.0ml/min
Column	ReversePhaseC-18
Detector	VariableWave length Detector (VWD)
Retention time	5-7min
Column Temperature	50^0C
Linearity range	0.3-2.0mg/ml

Preparation of stock solution of azithromycin

Stock solution was prepared by dissolving 500 mg of azithromycin in50 ml of mobile phase to obtain a solution having a known concentration of 10 mg/ml. Nominal standard solution was prepared by diluting 5 ml of stock standard solution to 50 ml mobile phase to obtain a solution having known concentration of 1.0 mg/ml azithromycin[17].

Preparation of calibration curve of azithromycin

Firstly, the column was washed with mixture of methanol and acetonitrile with decreasing ratio of methanol and varying flow rate for half an hour[18]. Then the column was saturated with the mobile phase with the flow rateof2.0 ml/min for half an hour and afterwards with the sample of standard drug to wash off the column. Standard solutions were prepared by diluting specific volume of stock solution to obtain several concentrations (0.3, 0.4, 0.5, 0.6, 0.8, 1.0. 1.2, 1.6; and 2.0 mg/ml). The samples of each drug dilutions (20 µl) were injected and run for 10 min. Then, these standards were chromate graphed using UV detector at 210 nm. The retention time of drug was found between 5.0-7.0 min.Three runs were performed for every concentration. The peak response i.e. peak area were recorded and plotted versus standard concentrations to obtain standard plot[19].

Determination of Bitter Taste Threshold Value

The bitter taste threshold value of azithromycin was determined after due approval from Human Ethical Committee by six volunteers. Aseries of aqueous solutions were prepared at different concentrations (5, 10, 15, 20, 25, 30, 40, 50 µg/ml). One ml of each standard solution was placed on the centre of the tongue and retained there for so seconds, and then the mouth was thoroughly rinsed

with distilled water. The lowest concentration at which the bitter taste perceived by the human volunteers was then recorded to obtain bitter threshold value[20].

Purification and Activation of Resin

Tulsion335 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 60ºC till the moisture content came below 5% confirmed by Karl Fisher titrator. The purified resin was stored in an air tight glass vial [21].

Optimization of Drug Resin Ratio

The different quantities of activated resin were transferred to20ml of deionised water and allowed to swell for 30 min[22]. 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 50ºC using 80% methanol and 20% buffer Phosphate buffer 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[23].

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 complexation.

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 (9 gm) was allowed to swell in 20 ml water under magnetic stirring for 25-60min at room temperature. Azithromycin (3 gm) was added to swelled resin slurry at maximum drug: resin ratio under magnetic stirring and the resultant mixtures were stirred for 0-7 hrs[24]. 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 percentagecumulative drug release (% CDR). The central-composite design (CCD) utilizes orthogonal arrays from design of experiments theory to study a large number of variables with a small number of experiments[25]. Further, this design has an added advantage of determining the quadratic response surface, not determinable using a factorial design at two levels. The study of two factors at two levels using central composite design resulted in twelve complexes of drug and resin (ARC1-ARC12) as shown in Table 2

Table 2: Optimization of azithromycin resin complex by CCD

Formulation Code	X1(Swelling time)	X2 (Stirring time)
ARC-1	-1(30min)	+1(6h)
ARC-2	-1(30min)	-1(1h)
ARC-3	+1(1h)	+1(6h)
ARC-4	+1(1h)	-1(1h)
ARC-5	-1.414(24min)	0(3.5 h)
ARC-6	+1.414(66min)	0(3.5 h)
ARC-7	0 (45min)	-1.414(0h)
ARC-8	0 (45min)	+1.414(7h)
ARC-9	0 (45min)	0(3.5 h)
ARC-10	0 (45min)	0(3.5 h)
ARC-11	0 (45min)	0(3.5 h)
ARC-12	0 (45min)	0(3.5 h)

Characterization of Azithromycin Resin Complex

Percent drug complexed

Percentage drug complexed was determined by transferring an accurately weighted amount of drug resin complex to a 100 ml volumetric flask. To this 2 ml of 5 N HCl was 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, filtered and analyzed by HPLC at 210 nm. The drug content and the weight of complex were then used to calculate the percent drug complexed[26].

***In-Vitro* dissolution rate studies**

Dissolution studies of complexes were performed according to USP XXIII Apparatus II (Lab India DS 500, India) by adding complex equivalent to 125 mg of azithromycin in 900 ml of dissolution media (buffer solution prepared by adding to 6litres of0.1 M dibasic sodium phosphate, ~ 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. The samples were withdrawn at various time intervals and analyzed by HPLC[27].

Taste evaluation study

The bitterness evaluation test was performed with human volunteers according to a method described by Kawano *et al.,* after due clearance from human ethical committee[28]. 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.

Differential scanning calorimetry (DSC) study

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 a nitrogen environment [29].

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 Kα (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°.

***In vitro* taste evaluation of optimized drug resin complex**

The optimized drug resin complex was placed in a volumetric flask with 25 ml of phosphate buffer pH6.8(salivary pH)and stirred for 60 sec.The mixture was filtered, and the filtrate was analyzed by HPLC to determine the drug content. This value was then compared with the bitter threshold value[30].

Preparation of Azithromycin Dispersible Tablets

Azithromycin dispersible tablets were prepared using optimized DRC by direct compression method. A total number of eight for mulations were prepared as shown in Table 3. All the ingredients were passed through # 60 sieves. Firstly, Avicel 102 (directly compressible microcrystalline cellulose)/Pearlitol SD200 (directly compressible mannitol), superdisintegrating agents and DRC were mixed together for 25 min using double cone blender[31]. 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 a tablet of 700 mg weight by 16-station rotary tablet making machine (Cadmach Machinery Co. Pvt.Ltd., India).

Table 3: Formulation of azithromycin dispersible tablets (batch F1-F8)

Formulation Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
DRC(Equivalent to 125mg of azithromycin)	500	500	500	500	500	500	500	500
Avicel102 (DC Microcrystal Cellulose)	138.4	138.4	138.4	-	-	-	69.2	92.27
PearlitoSD200 (Mannitol)	-	-	-	138.4	138.4	138.4	69.2	46.13
Ac-di-sol	28 (4 %)	-	-	28 (4 %)	-	-	28 (4 %)	28 (4%)
Crospovidone	-	28 (4%)	-	-	28 (4%)	-	-	-
Sodium Starch Glycolate	-	-	28 (4 %)	-	-	28 (4 %)	-	-
Aspartame	21	21	21	21	21	21	21	21
Lemonflavour	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1
MagnesiumStearate	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

*Value in bracket indicated the percentage of superdisintegrant used

Preformulation Studies for Azithromycin Dispersible Tablets[32,33]

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

Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane and is explained by an equation:

$\theta=\tan^{-1}h/r$

where h is the height of pile; r is radius of the base of the pile; θ is the angle of repose.

Apparent bulk density: Bulk density is an important pre-formulation parameter and is explained by an equation:

Bulk density (ρ)=mass of a powder(w) /bulk volume(Vb)

About 50 gm of blend was passed through a standard sieve # 20 and introduced into a 100 ml graduated cylinders fixed on the bulk density apparatus.The blend wasleveled without compacting and the final volume was noted which was bulk volume (Vb). Then bulk density was calculated using equation 2.

Tapped density:
Tapped density was determined by USP method II. The powder sample under test was screened through sieve # 18 and 20 g of tablet blend was filled in 100 ml graduated cylinder of tap density tester. The mechanical tapping of the cylinder was carried out using tapped density tester at a nominal rate of 250 taps per minute for 500 times initially and the initial tapped volume (Va) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated. Tapping was continued in increments of 1250 taps until difference between volumes of subsequent tapings was less than 2%. The volume was noted as, the final tapped volume (V_b). The tapped density (Dt) was calculated in g/ml by the formula,
$Dt=M/V_b$
Where, M was the weight of sample powder taken; $V_b$was tapped volume. The mean value of three determinations was considered.

Compressibility:
Carr's index = [(tapped density - fluff density)/tapped density] × 100
property is also known as *compressibility*. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics. *Fluff* (poured) *density* is the ratio of mass of powder to the fluff volume. Fluff volume was the volume occupied by acerta in mass, when gently poured into a measuring cylinder.

Tapped density is the ratio of mass of powder to the tapped volume. Tapped volume was the volume occupied by the same mass of the powder after a standard tapping of a measure.

Evaluation of Azithromycin Dispersible Tablets [35,36]
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 5 N 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 not 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[37].

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 25rpmfor 4min. After revolution the tablets were dusted and weighed.
The friability is given by the formula:
$F=(1-W/Wo)\times100$
Where Wo=weight of the tablets before test; W= weight of the tablets after test
The weight loss should not be more than one percent.

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 24˚C in 900 ml distilled water[38].

In-vitro dissolution rate study of azithromycin dispersible tablet
The drug release studies were performed using USP XXII type II tablet dissolution apparatus (Lab India DS-500, India). 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±0.5ºC and 100 rpm, respectively. Aliquots were withdrawn at time intervalof5, 10,20, 30, 45and 60min, filtered with whatmann filter paper and analyzed at 210 nm by HPLC. The test was carried

out on six tablets (Azithromycin tablets, Indian Pharmacopoeia 2014).

Azithromycin Release Kinetics Study

In order to understand the mechanism of drug release and kinetics of drug release from tablets, the *in vitro* drugrelease study were fittedto various kinetics equations in DD Solver 1.0 correlation and correlation coefficient (R^2) values were obtained. The release rates were analyzed by the following models:

- Zero order release kinetics(Cumulative drug release(%) vs.time),
- First order release kinetics(Log drug remaining(%)vs. time),
- Higuchi model (Cumulative drug release (%) vs. Square root of time) and
- Korsmeyer-Peppas model (Log cumulative drug release (%) vs. log of time)

R^2 values were calculated for the linear curves obtained by regression analysis of the above plots.

Comparison with Marketed Formulation

The formulated azithromycin dispersible tablets were compared with the marketed formulation of azithromycin (AZEE-DT, Cipla Ltd., India) in terms of *in vitro* drug release study and taste profile[39].

Stability study of azithromycin dispersible tablets

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 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[40]

RESULT AND DISCUSSION

Estimation of azithromycin by HPLC

Area under curve (AUC) obtained from HPLC curve (prepared with the help of software Agilent Chem Station is shown in Table 4 and calibration curve was prepared as shown in Figure 1. The HPLC curves are shown in Annexure III (vi- xiv)

Table 4: HPLC (Area under Curve) data of standard solution of azithromycin

Drug concentration (mg/ml)	Area under curve	Statistics
0.3	318.0	**Slope=932.7**
0.4	410.0	**Intercept=34.06**
0.5	461.9	**Correlation coefficient= 0.998**
0.6	591.1	
0.8	800.27	
1.0	980.0	
1.2	1160.96	
1.6	1543.36	
2.0	1876.21	

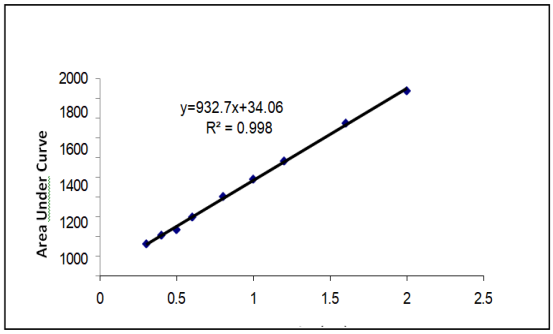

Figure 1: Standard curve of azithromycin

The curve was found to be linear in the concentration range of 0.3-2.0 µg/ml which confirms its validity with the Beer's law as evident by Figure 1. The value of Correlation co efficient was 0.998, which is in accordance to the value reported[41]

Determination of bitter taste threshold value of azithromycin

The threshold value for azithromycin bitterness was selected on the basis of the lowest concentration that had a bitter taste as shown in Table 5.

Table 5: Determination of bitterness threshold value of azithromycin

Concentration(µg/ml)	Volunteers					
	I	II	III	IV	V	VI
5	N	N	N	N	N	N
10	N	N	N	N	N	N
15	N	Y	Y	N	Y	Y
20	Y	Y	Y	Y	Y	Y
25	Y	Y	Y	Y	Y	Y
30	Y	Y	Y	Y	Y	Y
40	Y	Y	Y	Y	Y	Y
50	Y	Y	Y	Y	Y	Y

Y-Recognition of bitter taste, N-No perception of bitter taste

The threshold value for bitter taste was found to be 15-20 µg/ml as it was the lowest concentration of azithromycin that was perceived as bitter by the human taste panel study.

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 was to ensure that more exchangeable groups

are available for maximum and rapid loading [42].

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. In case of ratios 1:1 and 1:2 drug bound was less than, 1:3, 1:4 and 1:5. The ratio of 1:3, 1:4 and 1:5 did not indicate significant difference. Since, the increase in % drug complexed is negligible after 1:3 ratio, 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[43].ptimization of effect of pH on complexation

The percentage drug complexed at pH 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 9.0 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 non-ionic 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 maximum loading of 92.24% at pH 6.0. Above pH 4.0, the Tulsion 335 resin's carboxyl group liberates hydrogenions 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[44].

Above pH 6, the drug loading became constant and above pH 8.0, it slightly decreased. This can be explained on the basis of pKa of drug (pKa= 7.4).If the pH is higher than pKa of drug, the drug remains mostly in nonionized form. At pH 6.0, 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

Acentral-composite statistical design with two factors at two levels was chosen as the experimental design. The key factors studied were X1-swelling time; X2 –stirring time at two levels 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 (Table 2.8). 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 drugcomplexed 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 6: Percent drug complexed and % CDR of azithromycin (ARC1-ARC12)

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

S.D.=Standard deviation

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

$$Y = 75.69 - 2.10X_1 + 17.95X_2$$

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

ANOVA was applied on percent drug complexed to study the fitting and significance of model. F-test was carried out to compare the regression mean square with residual mean square (Table 7). The ratio F = 13.72shows regression to be significant.

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

$$Y = 90.02 + 1.46X_1 + 1.34X_2$$

Where Y=% CDR; 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 as shown in Table 7, The ratio F = 4.94shows regression to be significant.
The 3D Surface and Contour plotswere developed for % drug complexed and %CDR employing Design Expert® software (Version 8.0.7.1, Stat-Ease Inc., Minneapolis, MN) and given in Figures 2 -5.

Table 7: ANOVA of the regression (% drug complexed and cumulative % CDR 60min)

	% 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.

Design-Expert® Software Factor Coding: ActualR1 Design points above predicted value Design points below predicted value 96.54

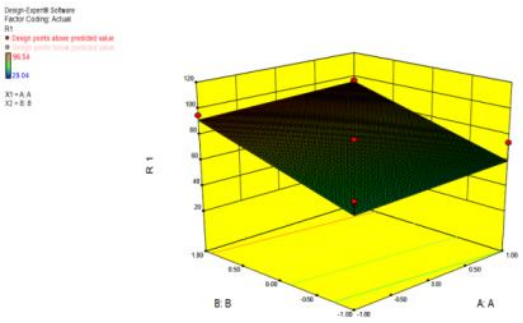

Figure 2: 3-D Response surface for percent drug complexed of azithromycinres in complex

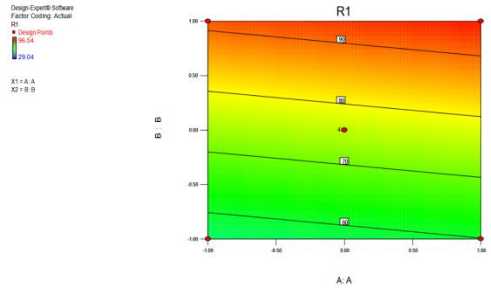

Figure 3: Contour plot for percent drug complexed for azithromycin resin complex

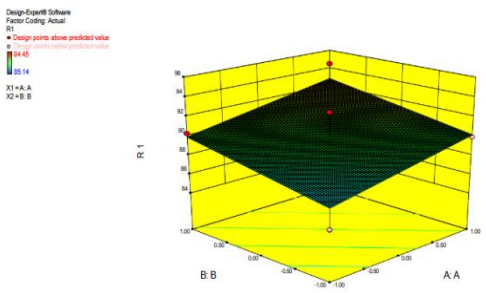

Figure 4: 3-D Response surface for % CDR (60 min) of azithromycin resin complex

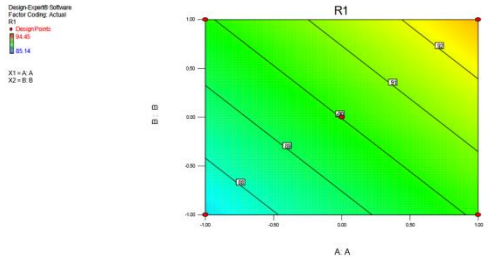

Figure 5: Contour plot for % CDR (60min) of azithromycin resin complex

Characterization of Drug Resin Complexes: Percent drug complex
The percent drug complex for azithromycin resin complexes (batch ARC1-ARC12) is shown in Figure 6.

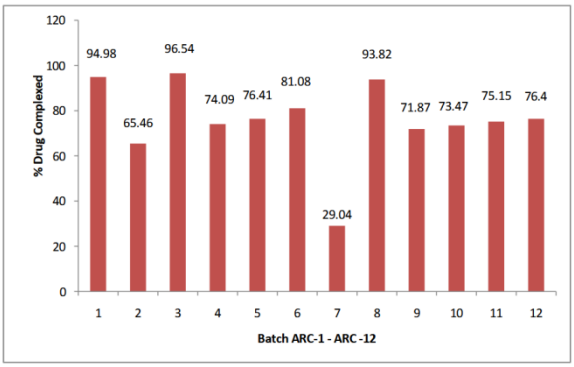

Figure 6: Percent drug complexed of azithromycin resin complex (ARC1-ARC12)

The results of % drug complexed showed that batch ARC3 with 6 h of stirring time and 1h of swelling time of resin has maximum percent drug complexation of 96.54. Batch ARC7 and ARC2 with low level of stirring and swelling time showed low values of 29.04 and 65.46 percent drug complexation, respectively. This clearly demonstrated that high level of swelling and stirring time is required for obtaining maximum % drug complexation.

***In-Vitro* dissolution rate studies**

In vitro drug release studies of azithromycin resin complexes were performed in the dissolution media specified for azithromycin in Indian Pharmacopoeia 2007. The result are shown in Table 8.

Table 8: *In vitro* drug release study of drug resin complex (batch ARC1-ARC12)

Code	% cumulative drug release					
	10min±S.D.	15min±S.D.	20min±S.D.	30min±S.D.	45min±S.D.	60min±S.D.
ARC-1	24.68±0.10	33.73±0.72	50.53±0.91	55.21±0.89	82.59±1.44	90.24±1.48
ARC-2	32.50±0.23	39.02±1.35	58.41±0.58	81.21±1.18	84.20±0.57	85.14±1.03
ARC-3	25.60±0.32	40.93±1.33	54.21±1.19	58.09±1.35	82.74±1.03	92.45±2.54
ARC-4	29.01±1.40	40.33±0.49	65.26±1.86	75.33±0.73	85.99±1.52	89.89±1.61
ARC-5	28.42±0.98	40.85±0.67	56.11±0.84	74.12±1.14	82.07±1.83	89.80±1.72
ARC-6	26.33±0.87	39.21±2.32	56.77±2.48	64.55±0.50	82.42±1.49	91.70±1.69
ARC-7	35.80±0.93	47.43±2.32	58.25±1.68	82.64±0.66	85.14±1.63	89.75±1.73
ARC-8	27.65±1.31	37.47±0.71	50.66±1.38	70.40±2.29	86.18±1.90	90.51±1.22
ARC-9	30.49±1.50	44.11±0.40	57.12±1.12	64.95±1.28	81.52±1.46	92.42±1.91
ARC10	27.05±0.52	38.37±0.99	55.02±1.23	65.02±1.26	80.66±2.86	87.41±3.00
ARC11	29.26±0.46	38.33±0.89	62.52±3.78	66.76±1.36	83.59±2.64	89.41±2.12
ARC12	28.28±1.15	38.67±1.92	54.58±1.84	64.48±0.61	83.59±2.64	89.50±2.59

S.D.=Standard deviation

Taste evaluation study of azithromycin resin complexes

The taste evaluation of pure drug and drug resin complex were carried out by human taste panel and the results are shown in Table 9. .The taste score of various azithromycin resin complex indicated 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 for 30 sec. Out of various drug resin complexes ARC-1, ARC-3 and ARC-8 showed better taste masking ability than other resin complexes.

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.

Table 9: Taste evaluation study of resin complexes (batch ARC1-ARC12)

S. No.	Product Code	Volunteers score						
		I	II	III	IV	V	VI	Means core± S.D.
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

S.D.=Standard Deviation

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 over lay of thermo grams is presented in Figures 7-8. The DSC thermogram of azithromycin showed a sharp endothermic peak at 129oC while the resin Tulsion 335 showed endothermic peak at 105oC which corresponds to its glass transition temperature (Tg). The DSC pattern of physical mixture contains peak characteristics of both azithromycin and Tulsion 335. However, in case of optimized drug resin complex (ARC-3) no peak related to azithromycin at 129°C was observed which clearly indicated that the drug has undergone physical changes from crystalline to amorphous which confirms the formation of complex.

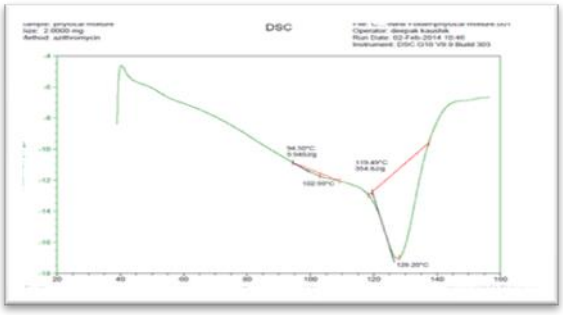

Figure 7: DSC thermo gram of physical mixture of azithromycin and Tulsion-335

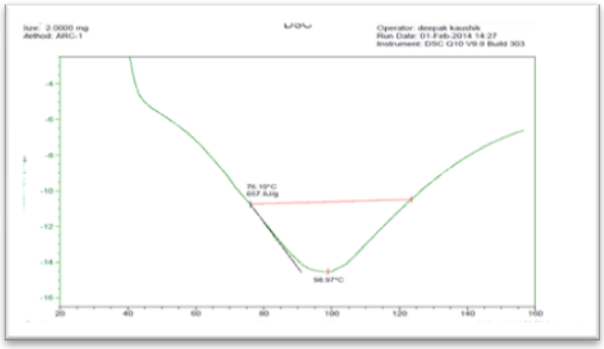

Figure 8: DSC thermo gram of azithromycin resin complex (batch ARC3)

FTIR studies

FTIR Spectra were employed to study the interaction between azithromycin and Tulsion 335. The IR spectrum of azithromycin exhibited three characteristic absorption peaks at 3490, 1720, 1453, 1377 and 1183 cm^{-1}, attributed to stretching vibration of O-H, C=O, CH_3-O, CH_2-O and C=O=C respectively (Table 10). The FTIR spectrum of tulsion-335 exhibited characteristic peak at 1696, 1162 and 797 cm^{-1} (Table 11).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. During the process of complex formation the NH^- group of azithromycin and functional group COO^- of tulsion 335 interacted to form the complex.

Table 10: Major IR peaks of azithromycin

Types of Peaks	Peaks of pure drug
O=H Stretching(Carboxylic acid)	1675cm^{-1}
C=O Stretching(Carboxylic acid)	3171cm^{-1}
CH_3-O Stretching (Aliphatic)	1543cm^{-1}
C-NStrectching	3171cm^{-1}
C-O-C Stretching(Straight chain)	1361cm^{-1}

Table 11: Major IR peaks of Tulsion-335

Types of Peaks	Peaks of resin
C=O Stretching(Carboxylic acid)	1696cm^{-1}
C-O Stretching(aliphatic)	1162cm^{-1}
C-H Stretching (Out of plane)	797cm^{-1}

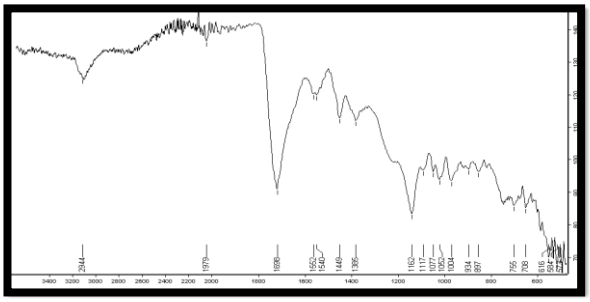

Figure 9: FTIR spectra of physical mixture of azithromycin and tulsion 335

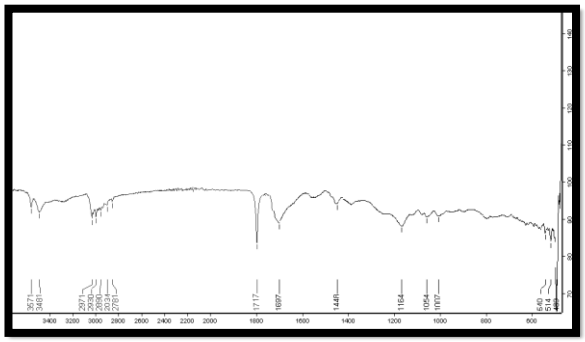

Figure 10: FTIR Spectra of azithromycin resin complex (batchARC-3)

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 Figures 11and 12, respectively.

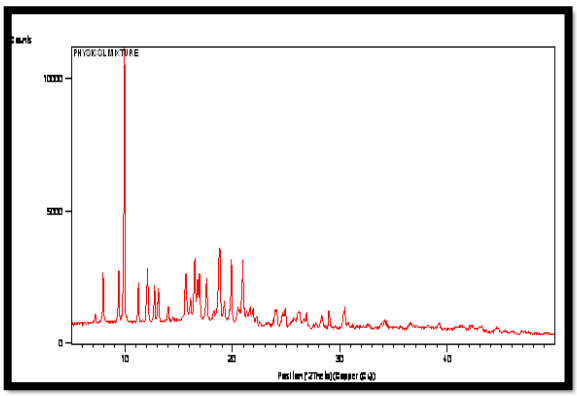

Figure 11: XRD of physical mixtureofazithromycinandTulsion-335

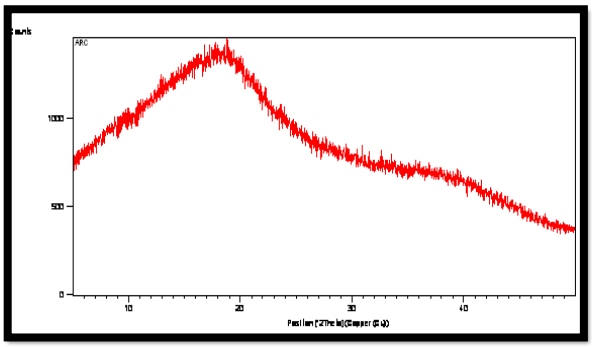

Figure 12: XRD of optimized azithromycin resin complex (batchARC3)

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.

In-vitro taste evaluation of optimized drug resin complex:

The drug release in pH 6.0 phosphate buffer was studied to evaluate taste masking. The drug release from drug resin complex (ARC-3) was found to be 10.8µg/ml which was below the threshold value for bitter taste (15µg/ml).The bitter threshold value of azithromycin recognized by the human volunteers was between 15-20 µg/ml. The drug concentration dissolved in phosphate buffer pH 6.0 from the drug resin complex (ARC-3) after stirring for 60 seconds was below the threshold value. Hence no bitter taste could be identified by the taste buds.Based on result of drug release and taste studies, batch ARC-3 was selected as an optimum batch and taken up further for formulating azithromycin dispersible tablets.

Formulation of Azithromycin 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 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.

Pre-formulation Studies of Azithromycin Dispersible Tablets

Before tablet preparation, the mixture blend of all the formulations was evaluated for various pre-formulation parameters such as angle of repose, bulk density, tapped density, carr's compressibility index and the results table 12. The formulations were found to have good flow characteristics as evident by the angle of repose which was in the range of 22-25 indicating excellent flow characteristics. Batch F1 showed lowest value of angle of repose (22.54±0.4). Similarly the value of carr's index was in the range of 12-14 indicating excellent flow and compressibility.

Batch F1 and F8 showed lowest value of carr's index (12.46±0.2 and 12.98±0.7 respectively) indicating excellent flow and compressibility characteristics in these batches.

Evaluation of Azithromycin 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 13.

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 containg crosscarmellose sodium as the disintegrating agent exhibited best disintegrating time of 15±0.24 sec and % friability was 0.35±0.01, which is acceptable. The drug content and other parameters were also found to within the pharmacopoeial limits.

***In vitro* Dissolution Rate Study of Azithromycin Dispersible Tablets**

In vitro drug release studies of azithromycin dispersible tablets was performed in the dissolution media specified for azithromycin tablets in IP 2007. The results are shown in Table 14. Batch F-1 showed maximum release of 94.76±1.48 % in 60 min.

Azithromycin Release Kinetics Study

The release mechanism of azithromycin dispersible tablets was investigated by fitting their release data to classic drug-release kinetics models. Kinetic Analysis of azithromycin dispersible tablets is shown in Table 15 and R^2 values from different models are given in Table 16. The drug release patterns from models are shown in Figure. Highercorrelation coefficient (0.990)was observed

Table 12: Pre-formulation characteristics of azithromycin dispersible tablets (batchF1-F8)

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Angle of repose± S.D.	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±S.D.	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± S.D.	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 ± S.D.	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

S.D.=Standard deviation

Table 13: Evaluation of azithromycin dispersible tablets (batchF1-F8)

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Drug content(%) ±S.D.	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) ± S.D.	15±0.24	18±0.12	25±0.22	40±0.42	45±0.26	52±0.24	42±0.18	35±0.68
Hardness (kg/cm2) ±S.D.	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 (%)±S.D.	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 ± S.D.	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

Table 14: In vitro release profile of azithromycin dispersible tablets (batch F1-F8)

Code	% cumulative drug release						
	5min±S.D.	10min± S.D.	15min±S.D.	20min±S.D.	30min±S.D.	45min±S.D.	60min±S.D.
F1	8.26±0.10	20.42±0.68	34.62±0.88	50.06±0.82	60.24±0.78	84.72±1.24	94.76±1.48
F2	10.12±0.22	18.64±0.18	32.42±0.36	47.24±0.64	58.16±0.82	81.28±0.94	91.68±1.84
F3	9.48±0.16	19.22±0.32	31.87±0.44	46.84±1.66	57.66±0.84	82.46±0.88	91.06±2.24
F4	11.24±0.28	22.56±0.46	33.56±0.78	45.84±0.94	58.68±0.66	81.44±1.46	89.46±1.84
F5	10.46±0.10	17.68±0.64	30.42±0.66	42.74±0.84	53.48±1.64	79.66±1.24	88.48±2.06
F6	10.22±0.28	19.46±0.78	32.46±0.46	41.28±0.88	56.66±0.76	82.20±1.44	90.78±1.78
F7	8.42±0.66	18.34±0.86	30.42±0.92	40.46±1.06	53.56±1.22	80.12±1.76	90.42±1.84
F8	9.34±0.18	22.24±0.36	32.46±0.68	42.32±0.88	56.24±1.06	83.27±0.94	92.42±1.92

S.D.=Standard Deviation

Table 15: Kinetic Analysis of the azithromycin dispersible tablets

S.No.	Time (min.)	Log of Time (min.)	Square Root of Time(min.)	%Cumulative Drug released	Log of% Cumulative Drug Released	Log of% Cumulative Drug Remaining
1	5	0.698	2.236	8.26	0.916	1.962
2	10	1	3.162	20.42	1.310	1.900
3	15	1.176	3.872	34.62	1.539	1.815
4	20	1.301	4.472	50.06	1.699	1.698
5	30	1.477	5.477	60.24	1.779	1.599
6	45	1.653	6.708	84.72	1.927	1.184
7	60	1.778	7.745	94.76	1.976	0.719

Table 16: Correlation Coefficient from different models

Release Model	Correlation Coefficient
Zero Order	0.950
First Order	0.975
Higuchi Release Model	0.915
Korsemeyer Peppas Model	0.990

in the Koresmeyer- peppas model (Table 15). For planery geometry, the value of n=0.5 indicates a Fickian diffusion mechanism, for 0.5<n<1.0, indicates anomalous (non-Fickian) and n=1 implies class II transport. Both dissolution and diffusion profile of the drug from the resin complex showed fitting to Koresmeyer-peppas plot and indicated non-fickian diffusion mechanism for the release of the drug from the complex

Comparison with marketed formulation

The optimized batch F1 was compared to marketed formulation (AZEE-DT, Cipla Ltd., India) in terms of *in vitro* drug release and taste profile. The optimized batch F1 of azithromycin dispersible tablets showed 94.76±1.48 % of drug release, whereas for marketed form6ulationdrug release values for azithromycin were 91.24±2.48 %.The taste score of formulated dispersible tablet was 0.42±0.002 in comparison to 0.86±0.002 for commercial tablet. Thus, a remarkable improvement in the taste was observed in the formulated tablets in comparison to marketed tablet without a significant difference in the release of drug. The results of comparison are shown in Table 17.

Table 17: Comparison of formulated azithromycin tablets with marketed tablets

Name of product	Mean bitterness core	%CDR(60min)
Azithromycin dispersible tablets (Batch F1)	0.42±0.002	94.76±1.48
AZEE-DT(Marketed product) BatchNo.D412205	1.16±0.002	91.24±2.48

Table 18: Stability profile of azithromycin dispersible tablets

Evaluation Parameters	1 month	2 month	3 month
Drug content(%)± S.D.	98.42±1.24	96.86±1.44	95.24±1.66
DT(Insec)±S.D.	15±0.24	18±0.12	18±0.22
Hardness(kg/cm^2)±S.D.	4±0.12	3.8±0.26	3.6±0.16
Friability(%)±S.D.	0.35±0.01	0.56±0.08	0.66±0.02
%CDR (After60min.)±S.D.	94.76±1.48	94.06±1.76	92.76±2.08
Weight Variation	Pass	Pass	Pass
Taste	No bitterness	No bitterness	No bitterness

SUMMARY&CONCLUSION

Taste masking is defined as a perceived reduction of an undesirable taste that would otherwise exist.". Taste is one of the most important parameters governing patient compliance. A wide variety of active pharmaceutical agents exhibit the bitter taste either during or immediately after oral administration resulting in poor compliance. Poor drug compliance due to bitter tasting oral drugs is true for all patient populations, but is especially true for pediatric and geriatric medications. The poor palatability and bitter taste were found to be one of the main reasons for noncompliance. This further result in discontinuities in therapy as the bitter taste causes resistance in swallowing oral drugs there by losing the beneficial effects of the drug. Low loyalty to OTC brands, frequent medication switch and overall loss in revenues are the other issues arising out of low compliance. Therefore, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company (Sohi *et al.*, 2004). The desire of improved palatability in these products has prompted the development of numerous bitter taste masked formulations with improved performance and acceptability.

Inspite of the fact that taste is an important factor in the development of dosage form; still it is that arena of product development that has been overlooked and undermined for its importance. The development of age adapted dosage forms and taste masking of bitter tasting drugs administered orally for children, are formidable challenges for formulation scientists. 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

The aim of present work was to develop taste masked pharmaceutical dosage form of bitter drug(s) by using the technique of ion exchange resin complexation and spray drying.

The objective behind the study was to investigate the effect of swelling time (X1), and stirring time (X2), on% drug complexation and % cumulative drug release (% CDR) of azithromycin using central composite design(CCD) in case of ion exchange complexation technique.

Ion exchange resin complexation was chosen as one of the technique for taste masking of extremely bitter drug azithromycin. It is a simple, efficient and viable technique for taste masking of a number

of bitter tasting drugs in which taste masking of a drug is achieved without affecting the release of drug. 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 anaverage 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 is primarily 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 (Singh *et al.,* 2007). The hydrogen ions in the stomach displaces square with residual mean square. The ratio F = 13.72 in case of % drug complexed shows regression to be significant. Similarly the ratio F = 4.94 in case of % CDR also shows regression to be significant. It was observed that the % drug complexation of batch ARC-3 (96.54) was highest with highest % CDR (94.45±2.54). Thus the swelling time (1 h) and stirring time (6 h) were found to be optimum for the drug resin complexation. The estimated model, therefore, may be used as response surface for the % drug complexation and % CDR.

The results of taste evaluation indicated 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). Out of various drug Resin complexes ARC-3 showed better taste masking ability than other resin complexes. Hence, ARC-3 was chosen for further characterization and formulation of azithromycin dispersible tablets.

The pure drug, resin, physical mixture of resin and the optimized drug resin complex (ARC-3) were characterized by DSC, FTIR and XRD. The DSC pattern of physical mixture contained peak characteristics of both azithromycin and Tulsion-335. However, in case of optimized drug resin complex (ARC-3) no peak related to azithromycin was observed which clearly indicated that the drug has undergone physical changes from crystalline to amorphous which confirms the formation of complex. The IR spectrum of azithromycin exhibited 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 exhibited 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 Tulsion335. 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.

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.

The drug release in pH 6.8 phosphate buffer (simulating salivary pH) was studied to evaluate *in vitro* taste masking. The drug release from drug resin complex (ARC-3) was found to be 12.8 µg/ml and the threshold value of bitter taste for azithromycin was 15- 20 µg/ml. The drug released in phosphate buffer pH 6.8 from the microspheres (ARC-3) after stirring for 60 sec was below the threshold value. Hence no bitter taste could be identified by the taste buds.

The optimized batch of resin complex (ARC-3) which showed the maximum release of 92 % and lowest bitter taste score of 0.16 was selected for the formulation of taste masked azithromycin dispersible tablets by direct compression method. Eight batches (F1-F8) 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 formulation parameters such as angle of repose, bulk density, tapped density and carr's compressibility index. The formulations were found to have good flow characteristics as evident by the angle of repose which was in the range of 20-25 indicating excellent flow characteristics. Similarly the value of carr's index was in the range of 12-14 indicating excellent flow and compressibility. 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 dispersible tablets were found to pass weight variation test as per I.P. (700 ± 7.5 mg). 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

containg crosscarmellose sodium as the disintegrating agent in 5% concentration exhibited best disintegrating time of 15±0.52 sec and % friability of 0.35±0.06 which was well within the limits.

In vitro drug release studies were performed using USP Type II apparatus in the dissolution media specified for azithromycin in Indian Pharmacopoeia 2007. The temperature was maintained at 37±0.5°C with rotation speed of 50 rpm. The azithromycin dispersible tablets (batch F1) showed maximum release of 94.76% after 60 min dissolution rate study. Batch F1 showed the best disintegration time and cumulative drug release and hence was selected as best formulation and subjected to drug release kinetics study, stability testing and comparison with marketed tablet in terms of taste profile.

The optimized batch F1 was compared to marketed tablet (AZEE-DT, Cipla Ltd., India) in terms of in vitro drug release and taste profile. The optimized batch F1 of azithromycin dispersible tablets showed 94.76±1.48 of drug release, whereas for marketed tablet, drug release values for azithromycin were 91.24±2.48. The taste score of formulated dispersible tablets was 1.16 ± 0.002 in comparison to 0.86 ±0.002 for marketed tablet. Thus a remarkable improvement in the taste was observed in the formulated azithromycin dispersible tablets in comparison to marketed tablet without a significant difference in the release of drug. The tablets were subjected to stability testing and 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.

The mathematical models developed in the optimization study can be utilized to design complex with desired % complex with desired entrapment efficiency. The optimized azithromycin resin complex was further formulated into dispersible tablets. 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.

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