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Taste Masking of Clarithromycin using Complexation with Ion exchange resin

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Abstract: Clarithromycin, an antibacterial agent, is extremely bitter in taste. The present research communication deals with development of taste masked resinate of clarithromycin using Tulsion-335, an acidic cation ion exchange resin. The drug resin complexes were prepared by batch process by taking drug to resin ratios of 1:1, 1:2, 1:3 and 1:4. The drug resin complexation procedure was optimized with respect to parameters like selection of suitable resin, mixing time, drug to resin ratio, effect of pH on drug loading and taste of complex. The drug resinate were evaluated for the drug content, taste, drug release and molecular properties. The resinate formation was confirmed using the techniques of Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC) and X-ray diffraction (XRD). There is very little or no bitterness imparted with drug resin complexes with reference to pure drug. Dissolution rate studies of the taste masked drug resin complexes were carried out in Phosphate buffer pH 6.8 (Salivary pH). Dissolution rate studies in phosphate buffer pH 6.8 showed that more than 75 % of pure drug was dissolved in 10 minutes, while in the same period the dissolution of clarithromycin from drug resin complex in 1:3 ratio was below 50%. The dissolution of clarithromycin is thus reduced at salivary pH from the resinate. This reduction of dissolution rate of clarithromycin from the resinate is responsible for reduction of the bitterness of drug. These finding can be utilized to formulate a non bitter dosage form for clarithromycin without affecting the rate of dissolution.
Keywords: Clarithromycin, Acidic Cation Exchange Resin, Taste Masking, DSC, FTIR, X-ray Diffraction, Tulsion-335 (Polacrilex resin).

Introduction and Experimental

The macrolide antibiotic, clarithromycin is extremely bitter in taste and effective in the treatment of various infections in children and elderly patients, which often experience difficulty in swallowing solid oral dosages forms. For these patients the drugs are mostly provided in liquid dosage forms or in the form of chewable tablet or fast dispersible tablet. These dosage forms usually lead to perceptible exposure of active drug ingredient to the taste buds. Taste masking is an important factor in these dosage forms for greater patient compliance [1].

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[2-6]. The high bitterness intensity of clarithromycin has led to development of various approaches for its taste masking in pharmaceutical formulations[7-9]. Although there are several methods reported for the taste masking of clarithromycin but *complexation with ion exchane resin* technique was chosen for the present work as the bitter tasting drugs can be easily attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding[10]. Since while passing through the mouth the drug remains in complex form, no or very little taste is imparted. This suitably masks the unpleasant taste of drugs. Immediately after ingestion, ions in the body (especially in the lower pH of the stomach) cause rapid elution from or disintegration of ion exchange resin drug complex and dissolve the drug in the gastric content. The free drug is now bioavailable, which can be easily absorbed from the GIT. The ion echange resin is eliminated or biodegraded from or at the site of delivery.

Complexation with ion exchange resin is a simple, efficient and proven technique for taste masking of a number of bitter tasting drugs[11-15]. Thus the objective of the present study was to utilize this technique to mask the bitter taste of clarithromycin, using Tulsion-335 which is a weak acid cation exchange resin.

Experimental Materials

Clarithromycin was received as gift sample from Ranbaxy PDR, Gurgaon, India. Acidic cation exchange resin Tulsion-335 was a kind gift from Thermax Limited, Chemical Division, Pune, India. All other chemicals were of analytical reagent grade and used as received.

Purification of resin

Tulsion 335 was purified by washing with distilled water. The wet resin was activated by 0.1M HCl 300ml followed by washing with distilled water. The resin was then dried in vacuum oven at 60^{o}C till the moisture content came below 5% which was checked by Karl Fisher titrator. The purified resin was stored in an air tight glass vial.

Preparation of drug resin complex

Clarithromycin was mixed with Tulsion-335 in the drug: resin ratio of 1:1, 1:2, 1:3 and 1:4. Two hundred ml of distilled water was added to the mixtures and stirred for 5 hours with magnetic stirrer to allow complete complexation of drug with resin. The drug resin complex so obtained was filtered by vacuum filtration and the residue was washed with distilled water. The prepared resinate was dried in vacuum oven at 60°C till the moisture content was below 5%.

Drug Content and percentage bound drug

An accurately weighted amount of drug resin complex was transferred to a 100 ml volumetric flask to which 2ml of 5 N HCl was added and finally the volume was made with distilled water. The volumetric flask was stirred in a sonicator for 30 minutes and was kept aside for 2 hrs with intermittent shaking. The samples were diluted suitably, filtered and absorbance was measured at 270.4 nm. Percentage drug bound, defined as total amount of drug in complex form divided by initial weight of drug added to resin slurry, was then calculated from % assay and total amount of complex obtained.

Optimization of conditions for complexation

Mixing time: For optimization of mixing time the stirring of drug resin mixture was carried out for 1h, 2h, 3h, 4h and 5h at room temperature on a mechanical shaker to allow maximum possible loading. The sample was then evaluated for drug loading after each time interval.

***Effect of pH*:** Buffer solutions of different pH ranging from 4 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.

Differential Scanning Calorimetry (DSC) characterization of samples

The thermal behavior of each drug resin complex was examined by differential scanning calorimeter (DSC Q10 V9.0, Build 275 model, Water Ltd.). 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.

Fourier transform Infrared Spectral (FTIR) study

Drug resin complex was crushed to make KBr Pellets (0.5%, w/w) and then their IR (IR 200 Spectrometer, Thermo Electron Corporation) spectra were recorded over the region 400–4000 cm−1

X-ray Diffraction(XRD) characterization of samples

An X-ray diffractometer (Xpert Pro's Pan Analytical Instrument, Model Philips PW 3040/60) 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.

In-Vitro Dissolution Rate Studies

Dissolution studies of complexes were performed according to USP XXIII Apparatus II in Phosphate Buffer pH 6.8 (simulating salivary pH) by adding complex equivalent to 125 mg of clarithromycin in 900 ml of dissolution media. The temperature was maintained at 37±0.5°C and the rotation speed was 50 rpm. 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 previously described method[16]. Test was carried out on a trained taste panel of 6 human volunteers (3 males and 3 females, with a mean age of 25 years), 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' mouths for 30s 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.

Result and Discussion

Selection of resin

The selection of an ion exchange resin for a particular drug delivery application is generally based upon its functional group characteristics. In the present work the drug clarithromycin 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 available in the market, Tulsion, a reputed brand of ion exchage resins of Thermax India Ltd. was used for taste masking. Tulsion-335 grade chemically known as Polacrilex resin uses the hydrogen ion as an exchange ion which helps it in adsorbing the drug in its base form. On exposure of acidic pH of stomach desorption of drug takes place due to high affinity of the resin for the hydrogen ion. In acidic environment, Tulsion-335 is in nonionic state and exists as the free acid. Hence drug loading onto this cation exchange resin is carried out at higher pH. Since the physiochemical properties of Tulsion -335 grade were best suited for the needs of present formulation and hence it was selected as the ion exchange resin for the present work. The drug resin complex thus prepared was optimized with respect to drug to polymer ratio, effect of drug to resin ratio on drug loading, effect of pH for drug resin complexation and mixing time on drug resin complexation.

Selection of drug to resin ratio

As presented in (Table 1) the complexation of drug with Tulsion gave efficient binding. Complexation of drug with Tulsion was studied for optimum drug to resin ratio for maximum loading. The values of percentage drug bound to resin 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. 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 and 1:4 as shown by the result of one way ANOVA where the *p* value ($p< 0.05$) indicated significant difference. The ratio of 1:3 and 1:4 did not indicate significant difference ($p>0.05$). Hence the ratio of 1:3 was selected as the optimum ratio because increasing the resin amount for an insignificant increase in drug loading is not an economically viable approach.

Table 1: Drug loading in different drug to resin ratios

Resin to drug ratio	Percent drug bound[a]
DRC1(1:1)	83.75 ±0.49
DRC2(1:2)	90.47±1.42
DRC3(1:3)	92.52 ±0.78
DRC(1:4)	92.88±0.54

[a]Mean±SD for n=3

Differential Scanning Calorimetry Evaluation

Complex prepared using different drug to polymer ratios were also subjected to thermal characterization and taste evaluation**.** (Figure 1) shows the DSC scan of complexes prepared with different ratios of drug to resin. From the figure it is evident that drug has been partially complexed in case of 1:1 ratio because their DSC pattern contains feeble peak characteristics of clarithromycin. But in case of 1:2, 1:3 and 1:4 no peak related to clarithromycin has been observed which shows drug has undergone physical changes from crystalline to amorphous which confirm the formation of complexes.

Taste Evaluation study

From the results of Taste evaluation as shown in (Table 2**)** it is evident that there is very little or no bitterness imparted with 1:2, 1:3, and 1:4 drug resin complex with reference to pure drug since a person is not able to keep the pure drug in the mouth in 30 sec. One way ANOVA was applied for comparing the results of taste study for different drug to resin ratios. Out of these three taste masking complex 1:3 showed better taste masking ability than 1:2($p< 0.05$ indicating significant difference) and is comparable with 1:4($p> 0.05$ indicating insignificant difference). Hence the ratio of 1:3 was found to be the optimized ratio.

Effect of mixing time on drug resin complexation

As shown in (Figure 2) the maximum drug has been complexed in 4 hr. and there was no further increase in complexation of drug. Thus 4 hr to 5 hr of total mixing time could be considered as sufficient for maximum complexation.

Effect of pH for drug resin complex formation

The effect of pH on drug loading is shown in Figure 3. At acidic pH the Tulsion -335 is available as unionized free acid which results in decreased drug loading. As the pH increases above 4, an increase in drug loading is observed. This is attributed to the liberation of hydrogen ions by the resin's carboxyl group. This leads to the protonation of the clarithromycin which binds to the resin's anionic carboxylic group by an ionic bond to form a complex. The maximum loading efficiency was observed at pH 6.8 as both the drug and resin are ionized sufficiently. At more alkaline pH a decrease in loading efficiency was observed which could be due to presence of unionized drug at alkaline pH.

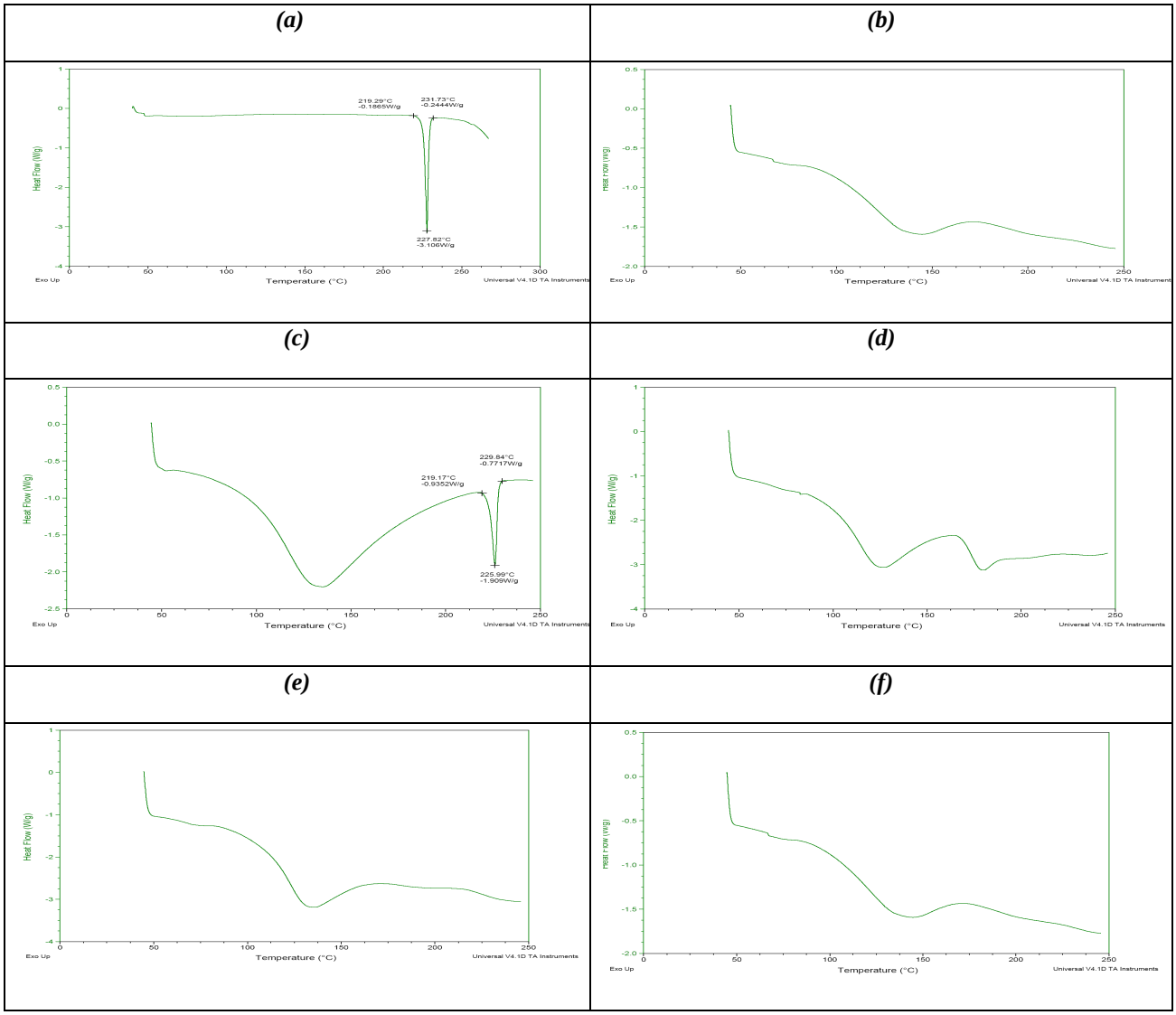

Figure 1: DSC thermograms of (a)Clarithromycin, (b)Tulsion Ion Exchange resin 335, (c) complex of clarithromycin with Tulsion 335 in (1:1), (d) complex of clarithromycin with Tulsion 335 in (1:2): (e) complex of clarithromycin with Tulsion 335 in (1:3) and (f) complex of clarithromycin with Tulsion 335 in (1:4)

Table 2: Bitterness evaluation by taste panel

Type of Product		Volunteers Score					
		I	II	III	IV	V	VI
Pure Drug	30 s	4+	4+	4+	4+	4+	4+
DRC1(1:1)	30 s	2	2	2	2	1	1
DRC1(1:2)	30 s	1	1	1	1	1	1
DRC1(1:3)	30 s	0	1	0	1	0	0
DRC(1:4)	30 s	0	0	1	0	0	0

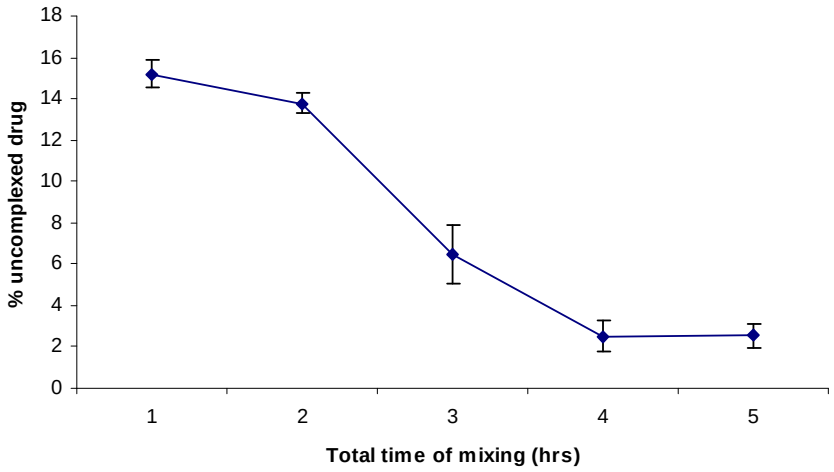

Figure 2: Effect of mixing time on complexation

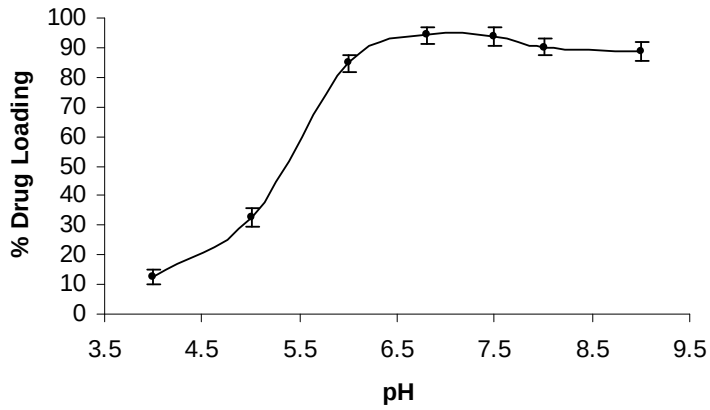

Figure 3: Effect of pH on drug loading

Molecular properties of drug resin complexes

FTIR Spectra and X-ray diffraction was employed to study the interaction between Clarithromycin and Tulsion 335. The FTIR spectrum of physical mixture was similar to synthetic spectra produced by addition of Clarithromycin and Tulsion 335 (Figure 4). This indicated that there was no interaction between Clarithromycin and Tulsion 335. The spectra of complex was different from that of physical mixture and exhibited marked variation in some bands (broadening and intensity reduction) which can be interpreted assuming change in hydrogen bonds of drug due to interaction with Tulsion 335 . Interaction between Clarithromycin and Tulsion 335 would be inhibitory and/or retardatory factor in the crystallization and cause Clarithromycin to be precipitated out in an amorphous form. Powder X-ray diffraction pattern of Clarithromycin, Tulsion 335, Physical mixture of Clarithromycin and Tulsion 335 and Taste masked complex (1:3) are shown in Figure 5. The result of X-ray diffraction showed that the pure drug exhibited crystalline property, while Tulsion 335 exhibited amorphous pattern. Physical mixture of Clarithromycin with Tulsion 335 exhibited crystalline property of clarithromycin indicated that drug has not undergone any physical change while the complex displayed amorphous pattern. All the peaks of clarithromycin were absent in case of the complex. It proved the drug was changed into amorphous form after the preparation process of complex.

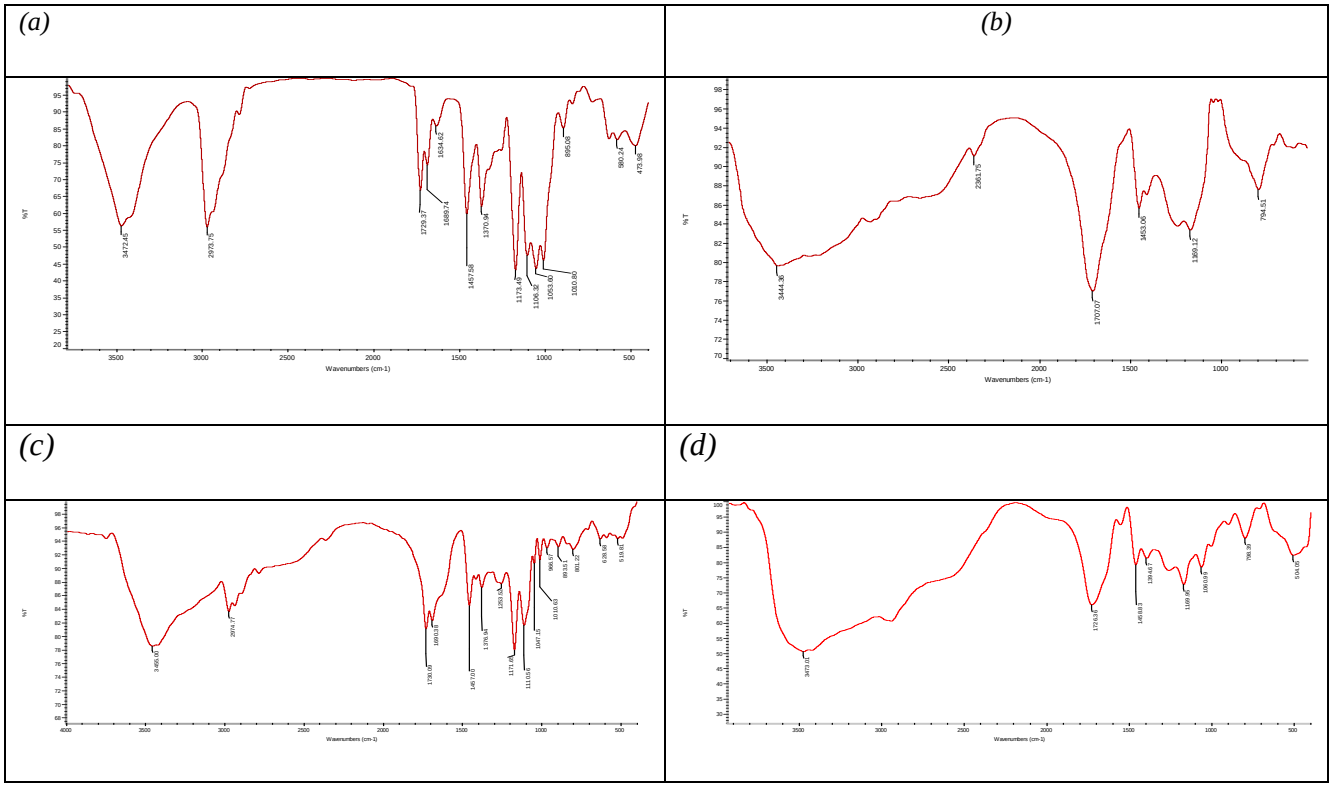

Figure 4: FTIR spectra of (a) Clarithromycin ,(b) Tulsion 335, (c) Physical Mixture of Clarithromycin and Tulsion 335, (d) FTIR Spectra of taste masked drug resin complex (1:3)

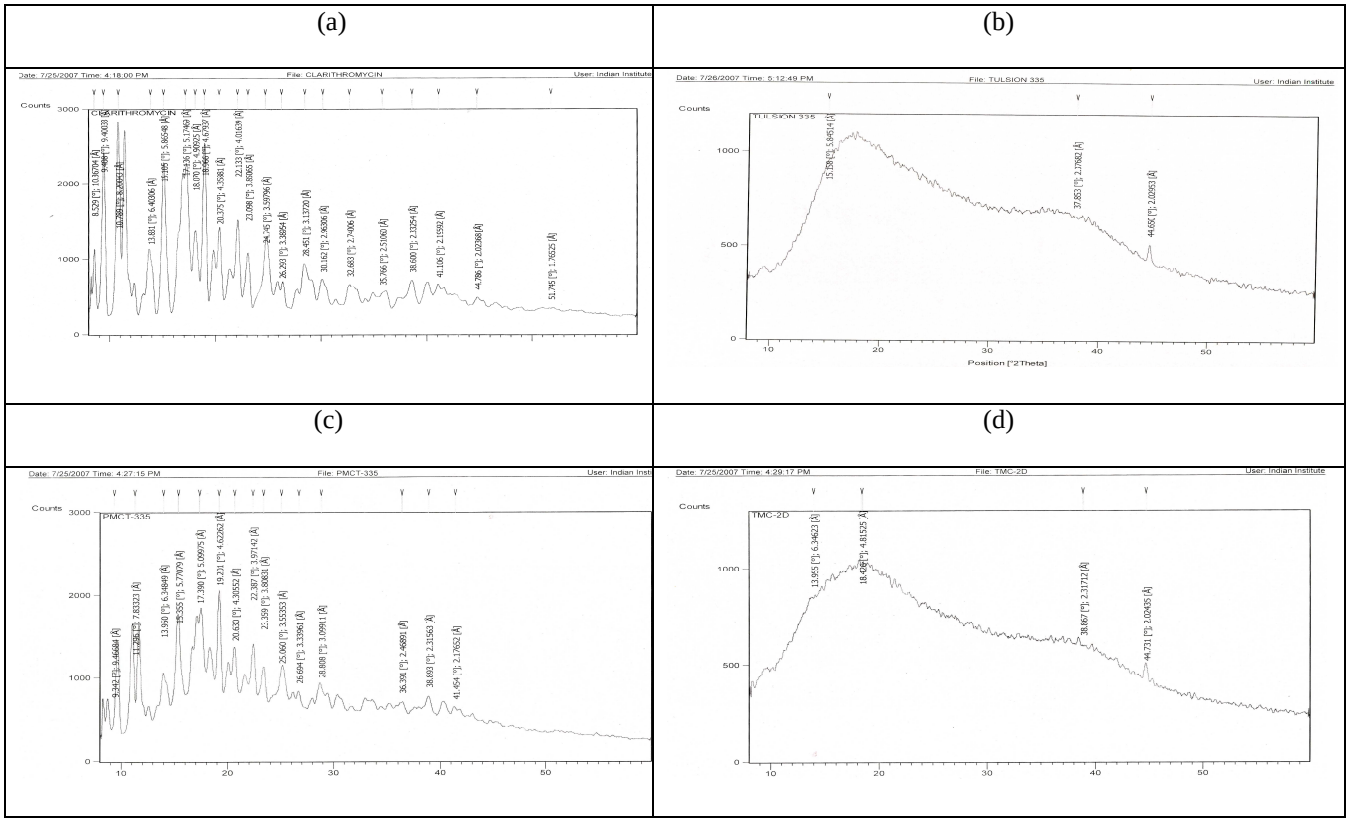

Figure 5: Powder X-Ray Diffraction Pattern of (a) clarithromycin, (b) Tulsion 335, (c) physical mixture of Clarithromycin and Tulsion 335, (d) taste masked drug resin complex (1:3)

Drug Release Study

The dissolution rate study was designed to assess whether the dissolution rate is retarded during the initial period in order to suppress the bitterness. The dissolution rate studies in phosphate buffer pH 6.8 showed that approximately 75 % of drug was dissolved in 5 minutes, while in the same period the dissolution of clarithromycin from drug resin complex in 1:3 ratio was below 50% (Figure 6). The dissolution of clarithromycin is thus reduced at salivary pH from the complex. The reduction in drug release in the initial period clearly suggests that upon development of taste masked complex into some stable dosage formulations such as rapidly disintegrating tablets or suspensions, where the contact time of drug with taste buds will be very less, this retardation of drug release will be very significant. Hence this reduction of dissolution rate of clarithromycin from the complex is responsible for reduction of the bitterness of the drug which is further proved by the taste masking studies.

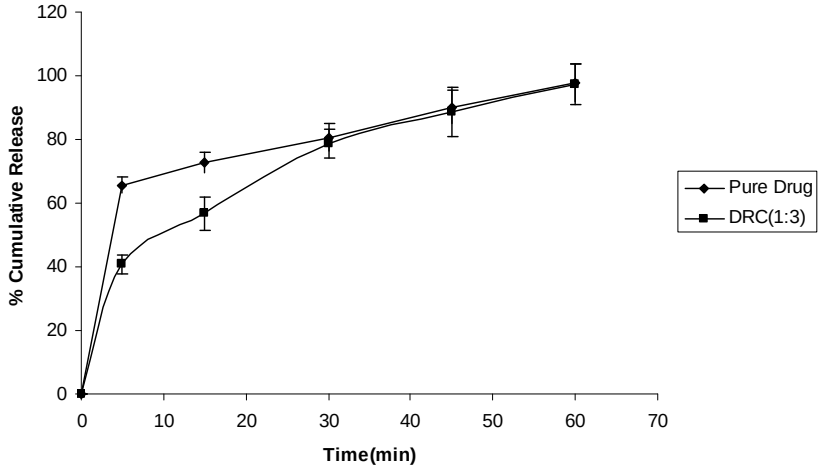

Figure 6: Dissolution profiles of pure drug and drug resin complex (1:3)

Conclusion:

From the in-vitro dissolution and taste evaluation studies it was concluded that effective taste masking was achieved for clarithromycin using the technique of complexation with ion exchange resin without affecting the bioavailability of drug. Ion Exchange resin complex can be formulated as granules, dry syrup or suspension and can be taken for scale up after carrying out requisite studies.

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