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Taste masked resinates of cefpodoxime proxetil using ion exchange resins

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ABSTRACT

Cefpodoxime proxetil is a third generation broad spectrum β-lactam cephalosporin class of antibiotic administered orally in pediatric and adult patients and is extremely bitter in taste. Masking bitter taste is a major challenge for better patient compliance particularly in an antibiotic treatment where dose and duration is important. Among the various techniques available for bitter taste masking, ion exchange resin is a popular approach as it has significant advantages over other techniques. In the present study resinates of cefpodoxime proxetil were formulated using anion exchange resin Duolite AP143 and cation exchange resin Kyron T-104. Resinates were prepared in various drug: resin ratios using batch method. The prepared resinates were characterized for FTIR, DSC, and SEM studies. The release rate of Duolite AP143 resin in the ratio of 1:2 Drug: resin complex showed identical release profile. Taste masking was done with increase in the ratio of resin.

Keywords: Cefpodoxime proxetil, taste masking, resinates, Duolite AP143, Kyron T-104.

INTRODUCTION

Oral administration of pharmaceuticals is one of the most popular methods of drug delivery. Many orally administered drugs elicit bitter taste. Palatability is an exceptionally important factor in ensuring the likelihood that the recipients will intake the pharmaceuticals. A constant problem is in treatment of reluctance to take the bitter drug especially in paediatrics.[1] Acceptability of any drug dosage form mainly depends over its taste that is mouth feel. The drug molecule interacts with taste buds on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. The problem of bitter and obnoxious taste of drug in paediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. Hence it becomes necessary to develop a dosage form that must be suitable in taste to patient especially in case of children or geriatrics. [2] Unpalatability results in patient non-compliance to the medicines especially in case of children and elderly, thereby reducing the effectiveness of the pharmacotherapy. Therefore, it is necessary to lessen or mask the bitterness for enhancing patient compliance and to improve oral palatability of bitter tasting drugs. A number of methods have been reported for masking the bitter taste, such as use of ion-exchange resins, [3] use of inclusion complexes with cyclodextrins,[4] viscosity modifications[5] melt granulation,[6] microencapsulation techniques like spray-drying,[7] spray-congealing,[8] coacervation[9]and solvent evaporation method.**[10]** Ion exchange resins are solid and properly insolubilized high molecular weight polyelectrolytes that can replace their mobile ions of equal charge with the neighbouring medium reversibly. Typically, the ionized drug and the ion exchanger form a stable complex for the relatively short period of exposure, making the drug unavailable for taste sensation. As the formulation passes to the further parts of the GI

tract, the drug is released from the ion-exchanger into the surrounding media due to low pH in the stomach, augmented ionic concentration of the GI tract, larger volume of the surrounding media and/or increased gastric residence time and is, thus, accessible for absorption. Ion exchange resins have been widely used as a drug carrier in pharmaceutical dosage forms for their taste masking and controlled release applications[11]

Cefpodoxime proxetil is a third generation cephalosporin antibiotic given orally which is very slightly soluble in water; freely soluble in dehydrated alcohol. Oral bioavailability is about 50% in fasting subjects and may be increased in presence of food. Peak plasma concentrations of about 1.5, 2.5 and 4 micrograms/mL have been achieved 2 to 3 hours after oral doses of 100,200 and 400 mg cefpodoxime respectively. Plasma protein binding is 20 to 30%. $T_{1/2}$ is about 2 to 3 hours. Cefpodoxime Proxetil has good activity against enterobacteriaceae, Hemophilus spp. and Moraxella spp. and is also active against Gram positive bacteria, especially against streptococci. It has been used most widely in the treatment of respiratory and urinary tract infection. It is also used in children for treating pharyngitis or tonsillitis. It is noncrystalline, slightly basic compound and after oral administration is absorbed from the gastro intestinal tract (stomach and duodenum). It has a better solubility in the acidic pH i.e. in the upper GI region which will further increase its absorption. [12-15]

In order to mask the bitter taste of cefpodoxine proxetil complexation technique using strong cation exchange resin, Tulsion-344 resinates were prepared. The prepared resonates were evaluated for micromeritic properties, taste masking and were characterized using DSC and IR. The resinates were then formulated into sustained release matrix tablets using Hydroxy Propyl Methyl Cellulose(K100). The tablet was found to sustain the release of drug over a period of 12h. [16]

In this study, in order to mask the bitter taste of CP, drug resinates were prepared using two different resins Duolite AP143 and KyronT-104 in order to achieve taste masking of bitter drug and to assess the performance of taste masked resinates of CP in healthy human volunteers.

MATERIALS AND METHODS

Materials

Cefpodoxime Proxetil (CP) was obtained as a gift sample from Dhanuka lab (Mumbai), Duolite AP143 was obtainted as a gift sample from Dow chemical corp /Rohm and Haas(France),

KyronT-104 was obtained as a gift sample from Corel Pharma chem.(Ahmedabad) ,Glycine Merck(Mumbai).All other chemicals used in this study were of analytical grade.

Preformulation study

Analysis of drug candidate

Visual inspection of drug was done and description as per specification was checked. It was found to be white to brownish white powder.

Melting point

Melting point of drug was determined by capillary method. The melting point is found to be 98^0c.

Solubility study

An excess quantity of Cefpodoxime proxetil was placed in 25ml capacity glass flasks containing 25ml of different solutions (Distilled water, 0.1N HCl and phosphate buffer pH 6.8).The samples were sonicated for 10min at room temperature and capped conical flasks were shaken for 24hr at 37^0C using orbital shaking incubator.The supernatant solution was then passed through a whatmann filter paper (Grade 1) and the amount of the drug dissolved was analyzed spectrophotometrically (UV-SL-164 Double beam spectrophotometer Elico, Hyderabad) at 259nm after suitable dilution. This study carried out to select a suitable dissolution medium for the *in-vitro* drug release studies.

Purification of Ion exchange resins

All the resins were pretreated to remove the impurities associated with industrial scale manufacturer. The resins were purified by rinsing 10gm of wet resin with 3 x 5ml portions of deionised water, 1 x 50ml of 95% ethanol and 1 x 50ml of deionised water. Each stage of treatment lasted for about 1hr under magnetic stirring. The resin then conditioned with 60ml of 2M NaOH and 60ml of 2M HCl and was washed with deionised water after each

treatment. Finally the resins were recovered by vaccum filtration, washed thoroughly with deionised water and dried in a tray dryer for 12h at 40^0C then ground and passed through sieve no. 60 to get a uniform size distribution.

Preparation of Drug Resin complexes (Resinates)

Ion exchange resins are cross linked water insoluble polymers carrying ionizable functional groups. Resinate were prepared by Batch process. According to this method, accurately weighed amount of drug and resin is thoroughly dispersed in 50ml of water and was stirred on a magnetic stirrer for 5h to get resinate. In the current studies Duolite AP 143 and Kyron T104 resins were used to prepare resinate. Table 1 and 2 depicts the amount of drug and resin used in various complexes.

Drug resin complexes were prepared by mixing Cefpodoxime proxetil with anion exchange resin Duolite AP 143 and weak cation exchange resin Kyron T-104 in various stoichiometric ratios (1:0.125, 1:0.250, 1:0.5, 1:1, 1:2 and 1:3 of Drug:Resin). Weighed amount of resin was added to distilled water (50ml) in a glass beaker and the suspension was stirred on a magnetic stirrer for 30 min followed by the addition of the drug and the contents of the beaker were allowed to stir for another 5 h at 37 ºC. Resulting drug resinates were then separated by filtration and washed with distilled water to remove the free drug and other ions. Then the resinates were subjected to overnight drying at 40 ºC and the dried resinates were kept in a desicator till further use. Ion exchange resins are solid and suitable high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with surrounding medium reversibly and stochiometrically, they are available in desired size ranges .Bitter cationic drugs can get adsorbed on to the weak cationic exchange resins of carboxylic acid functionally to form the complex which is not bitter. Drugs are attached to the oppositely charged resin substrate or resonate through weak ionic bonding so that dissolution of the drug does not occur under salivary pH conditions. This suitably masks the unpleasant taste and odor of drugs.

Drug loading analysis

Dry drug resinate (100 mg) was extracted with hydrochloric acid (0.1 N HCl, 100 mL) in a sonicating bath for 30 min. The flask was allowed to stand for 1 hour and then an aliquot (1 mL) was diluted to 10 ml with water and filtered. The filtered sample was analyzed by UV spectrophotometry using a double beam spectrophotometer (SL-164, Elico) at 259 nm. For each resinate extractions were carried out in triplicate.

In vitro **dissolution study**

The in-vitro drug release study was performed using (LABINDIA DS 8000,Mumbai) USP type-II paddle apparatus containing 900 mL of Simulated Gastric Fluid(pH 1.2) as dissolution medium mentioned in USP. Aliquots of 5 ml were withdrawn at predetermined time intervals and an equal amount of fresh dissolution medium was added. Test samples were filtered through whatmann filter paper grade 1 (Whatmann Paper Limited, UK), suitably diluted if necessary and assayed at 259 nm using a blank solution as reference with a UV-Vis double-beam spectrophotometer (SL-164, Elico). The cumulative percentage of Cefpodoxime proxetil dissolved was calculated using a regression equation generated from the standard data.

Infrared (IR) spectroscopy

IR spectroscopy was conducted using an FT-IR spectrophotometer (Spectrum BX 1-FT-IR, Perkin Elmer, USA). The spectrum was recorded in the range of 4000-400cm^{-1}.The procedure consisted of dispersing a sample in KBr gentle mixing. The spectrum was scanned at a resolution of 0.15cm^{-1} and scan speed was 20scans/s.

Scanning electron microscopy (SEM)

The surface characteristics of samples were studied by scanning electron microscopy (SEM).Double sided carbon tape was affixed on aluminium stubs .The powder sample was sprinkled onto the tape. The aluminium stubs were placed in the vaccum chamber of a scanning electron microscope (ZEISS, Germany). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 Torr, acceleration voltage: 30.00kv). The particles were observed for surface characteristics.

Taste Evaluation

After taking ethical committee approval all the batches of drug resin complexes were subjected to gustatory sensory evaluation test performed on ten volunteer. The volunteers selected randomly and were instructed to rate the samples as per the taste evaluation scale. Same set of volunteers were employed for the taste evaluation study. Sample equivalent to 50 mg was held in mouth for 15 sec. The evaluation was performed by classifying bitter taste into five

classes: 0-No bitterness, 1-Acceptable bitterness, 2-Slight bitterness, 3-Moderate bitterness, 4-Strong bitterness. Significant differences among different drug resinates were analyzed using the student's unpaired t-test; a value of $p < 0.05$ was accepted as index of a significant difference between samples.

RESULTS AND DISCUSSION

The drug loading analysis was carried out for prepared resinates. The complexation of drug with Duolite AP143 was found to have efficient binding and good resinates were formed. Maximum amount of drug was loaded with 1:3 DRCD ratio which was about 41.82% and minimum was with 1:0.125 DRCD of about 34.65%,when repeated with Kyron T104 more amount of drug was loaded with 1:1DRCK of about 41.59% and was less with 1:3DRCK of about 36.49%. This suggests that increase in the concentration of resin, decreases the drug loading capacity. In-vitro drug release studies were performed for the prepared resinates and as the prepared resinates float on the dissolution medium, the equivalent amount of pure drug is placed in a muslin cloth and tied over the bottom of the paddle. This study was conducted in Simulated Gastric Fluid (pH1.2) using type-II rotating paddle apparatus at 100rpm.

There was decrease and sustainment in the drug release with increasing concentration of resin Duolite AP143. Highest cumulative amount of drug release was observed with 1:2 DRCD resinate and was 77.09% at the end of 6^{th} hr. Pure drug has shown a drug release of 68.82% at the end of 6h. The same was observed with resinates containing Kyron T104and was found to be highest with 1:0.25 DRCK and was 37.92% at the end of 6h. Figures 1 and 2 show the drug release profile of drug from resonates, respectively, at various concentrations of resin. The dissolution rate from both the resonates follows the order 1:2DRCD>1:0.5DRCD>1:0.25DRCK>1:0.125DRCK with cumulative percent drug release order of 77.09%>51.30%>37.92%>37.14%, which suggests extended release pattern caused by ion exchange resin. As the drug is having absorption in entire GIT, even sustained action of resinates are suitable formulations and the results are consistent with this mechanism. The mechanism behind this sustained action depends on fact that, the ion exchange is an equilibrium phenomenon. When the resinate is exposed to a solution of the salts it displace the drug until an equilibrium is reached. At that point no net drug is released. However in the body some of the released drug gets absorbed into the blood. This results in reduction of the amount of drug in solution and so more drug is released from the resinate to compensate. This situation continues until all the drug has been released or the resinate reaches a part of the GIT where drug absorption stops. The FTIR spectra of cefpodoxime proxetil, resin and the resinate mixture 1:2 DRCD are depicted in Figure3,4,5. The pure drug showed characteristic absorption bands cm^{-1} at3448.77 and 3328 (NHstretching), 2987, 2938, 2823 (aromatic CH stretching), 1758, 1679,1623 (C=Ostretching), 1537, 14589 (C=C stretching), 1276,1376 (C-N stretching). The same peaks were observed in the resin and optimized resinate. The absence of any peaks in the resinates indicates that there are no polymorphic changes in the drug substance during the preparation of drug resinates. The FTIR studies revealed that there was no chemical interaction between the drug and the resin(duolite) in the resinate. The surface characteristics of drug, resin and resinate were studied by SEM. Double sided copper tape and stupper coated with gold-palladium in the presence of argon gas was used where the powder sample was sprinkled onto the tape. The aluminium stubs were placed in the vaccum chamber of SE microscope. The samples were observed for morphological characterization using a gaseous secondary electron detector. The particles were observed for surface characteristics. The SEM micrographs of drug, resin and resinate1:2DRCD at different magnifications are shown in Figures 6,7,8. The pure drug was characterized by crystals of bigger size and irregular shape with an apparent smooth surface.

The figure of duolite AP143 depicts that the surface characteristics are of irregular shape with smooth surfaces and that of resinate shows that no porous structures are present upon loading the resin, this is because of cross linking between drug and resin. Spherical resinates are formed.

All the batches of drug resin complexes subjected to gustatory sensory evaluation test by volunteer, and based on their opinion, complexation of cefpodoxime proxetil with anion exchange resin Duolite AP143 was found to increase the acceptability and palatability of the drug. However 1:2 DRCD, 1:3DRCD of Duolite AP143 was found to have better masking properties compared to other ratios of Duolite AP143.

Taste masking properties was found to be good in high resin ratios with Kyron T-104, 1:3 DRCK was found to have better acceptability and palatability. But less taste masking was observed with kyron T104 when compared with Duolite AP143.

The taste masking ability was found to be dependent on concentrations as it improves at higher concentration. This is because at high concentration each and every drug particle comes in contact with the resin network thereby improving taste masking by the resins.

Table 1: Quantities of Drug and Resin taken for different drug to resin ratios (DRCD)

Drug : Resin	Amount of Cefpodoxime proxetil taken (gm)	Amount of resin (DuoliteAP143) taken (gm)	Volume of water taken to disperse (ml)
1:0.125	1	0.125	50
1:0.250	1	0.250	50
1:0.5	1	0.5	50
1:1	1	1	50
1:2	1	2	50
1:3	1	3	50

DRCD= Drug resin complex using Duolite AP143

Table 2: Quantities of Drug and Resin taken for different drug to resin ratios (DRCK)

Drug :Resin	Amount of Cefpodoxime proxetil taken (gm)	Amount of resin (Kyron T 104) taken(gm)	Volume of water taken to disperse (ml)
1:0.125	1	0.125	50
1:0.250	1	0.250	50
1:0.5	1	0.5	50
1:1	1	1	50
1:2	1	2	50
1:3	1	3	50

DRCK= Drug resin complex using Kyron T 104

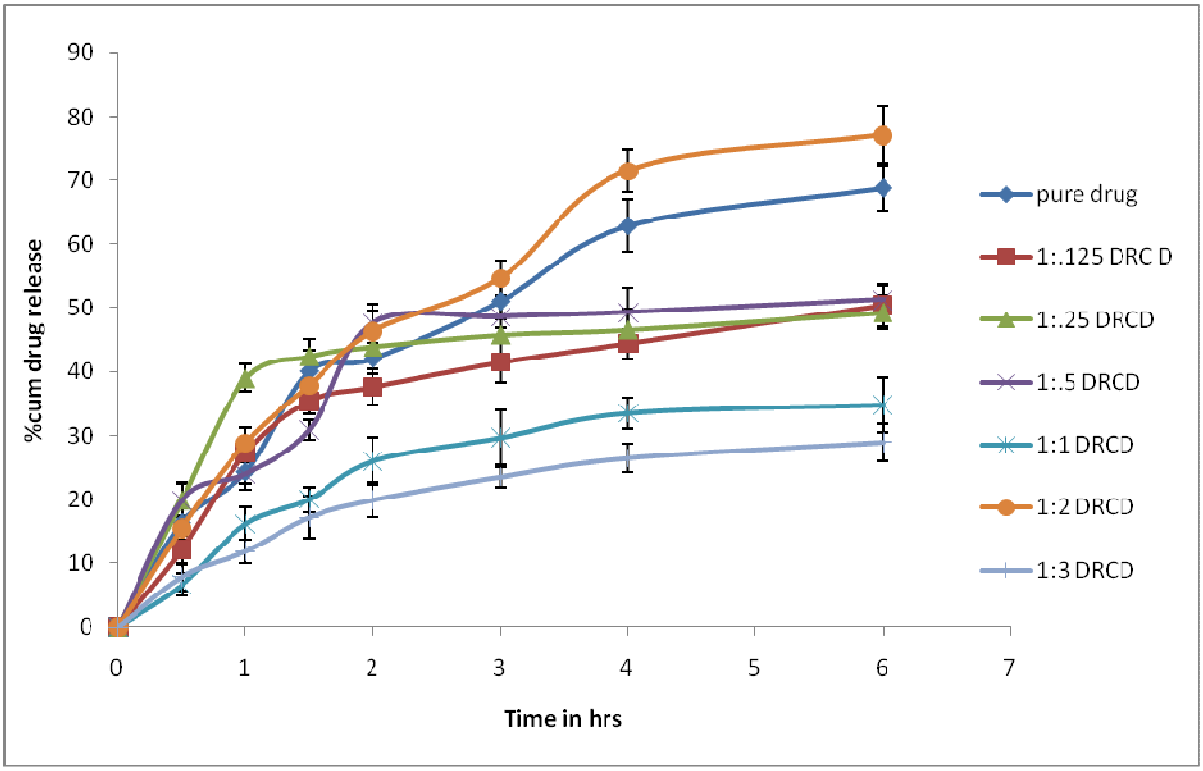

Figure 1: Figure showing comparative release profile from Pure drug and resinates of Duolite AP 143

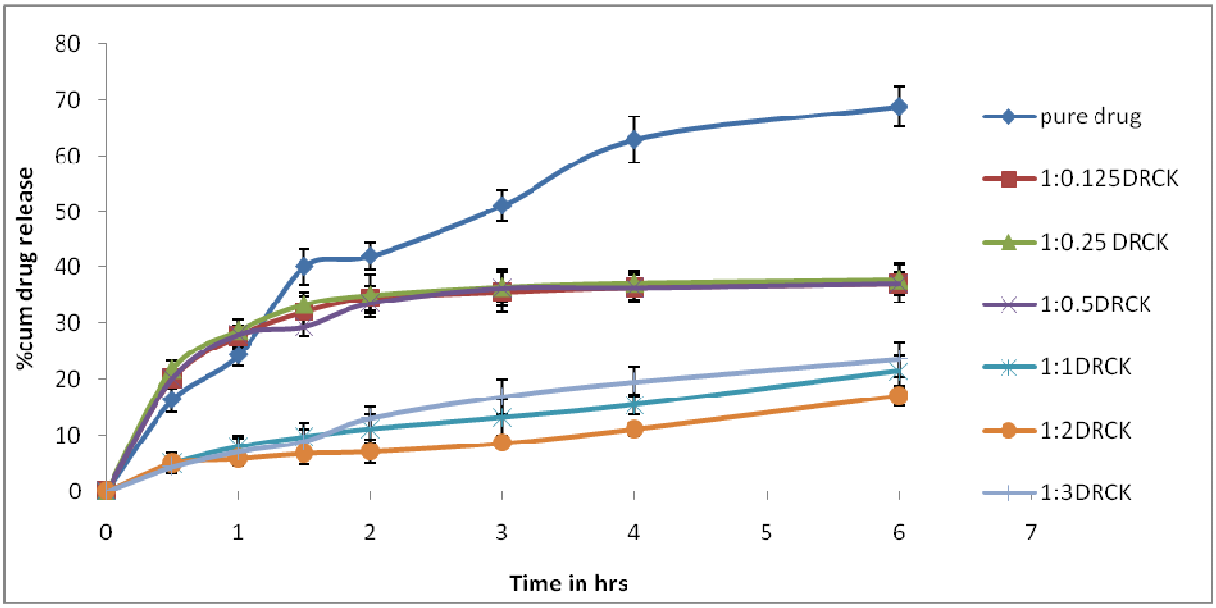

Figure 2: Figure showing comparative release profile from Pure drug and resinates of Kyron T 104

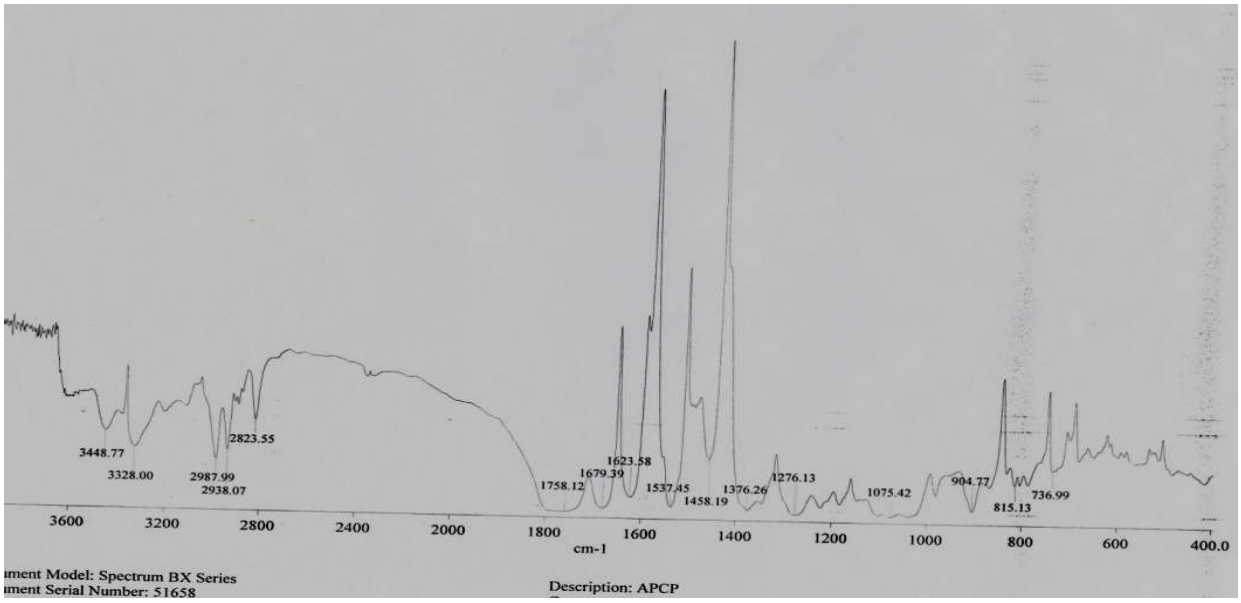

Figure 3: FTIR spectrum of pure Cefpodoxime proxetil

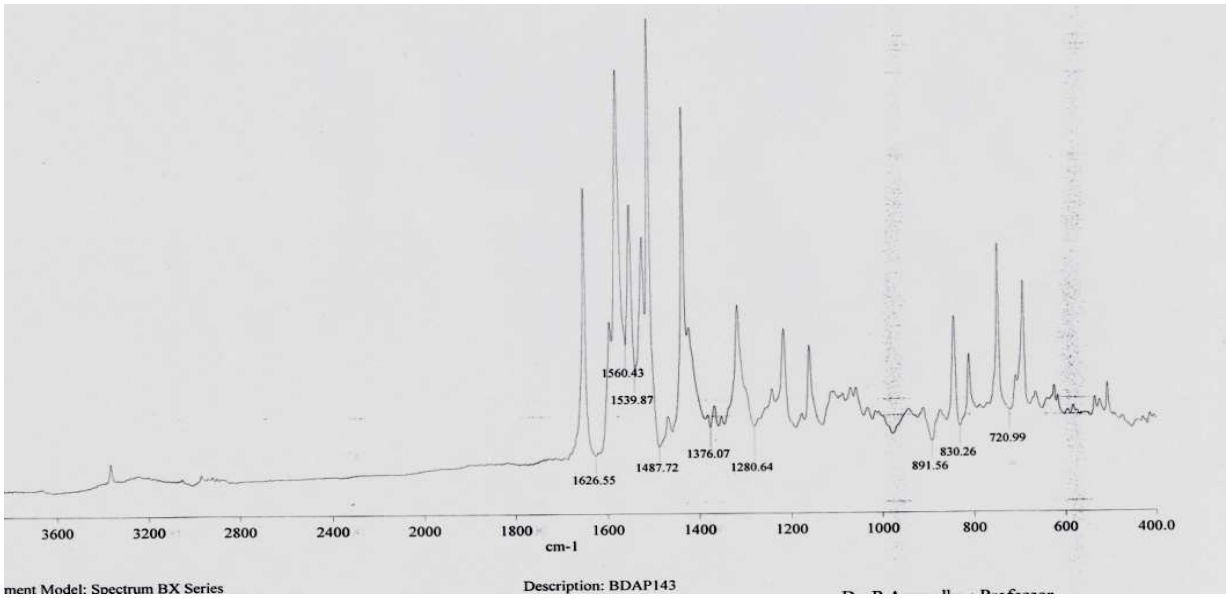

Figure 4: FTIR spectrum of Duolite AP 143

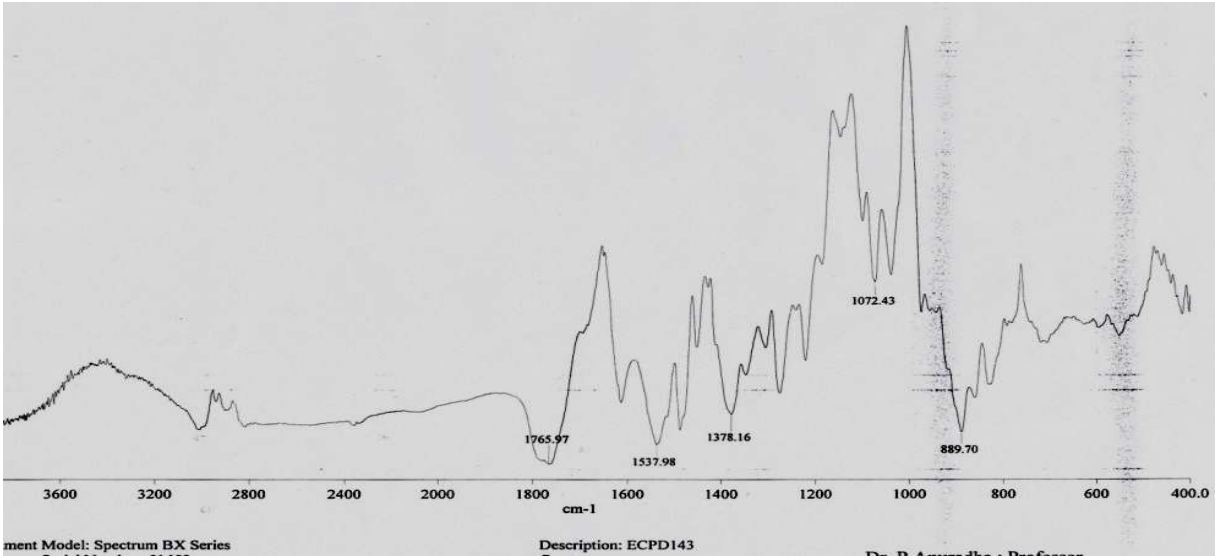

Figure 5: FTIR spectrum of resinate 1:2DRCD

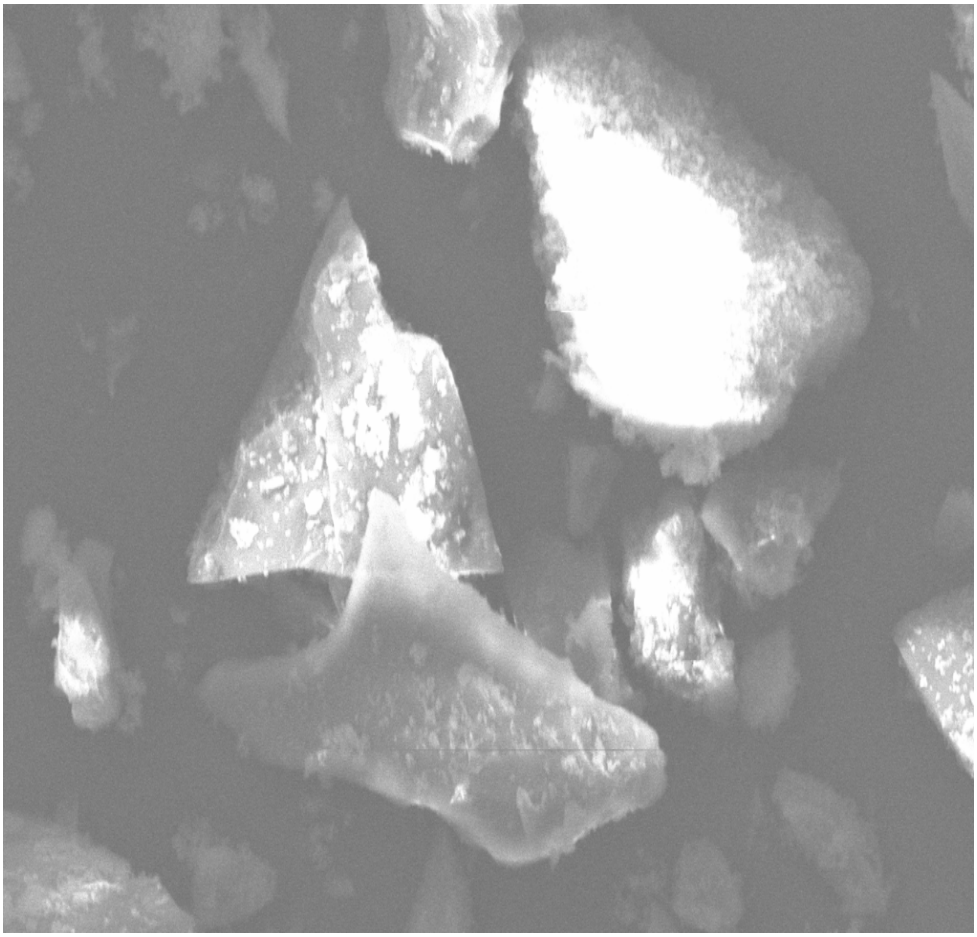

Figure 6: SEM of Pure Cefpodoxime proxetil

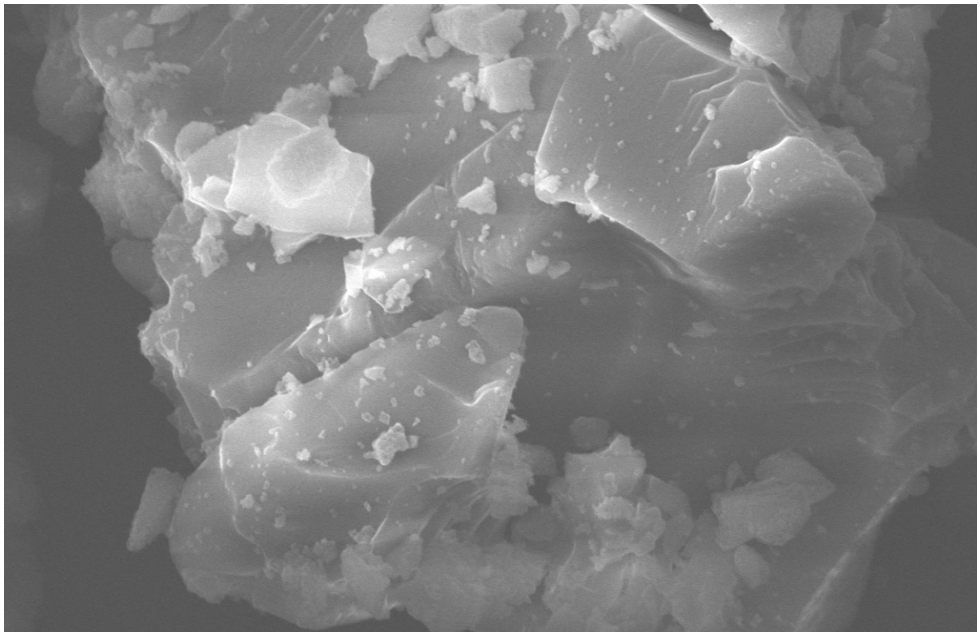

Figure 7: SEM of Duolite AP 14

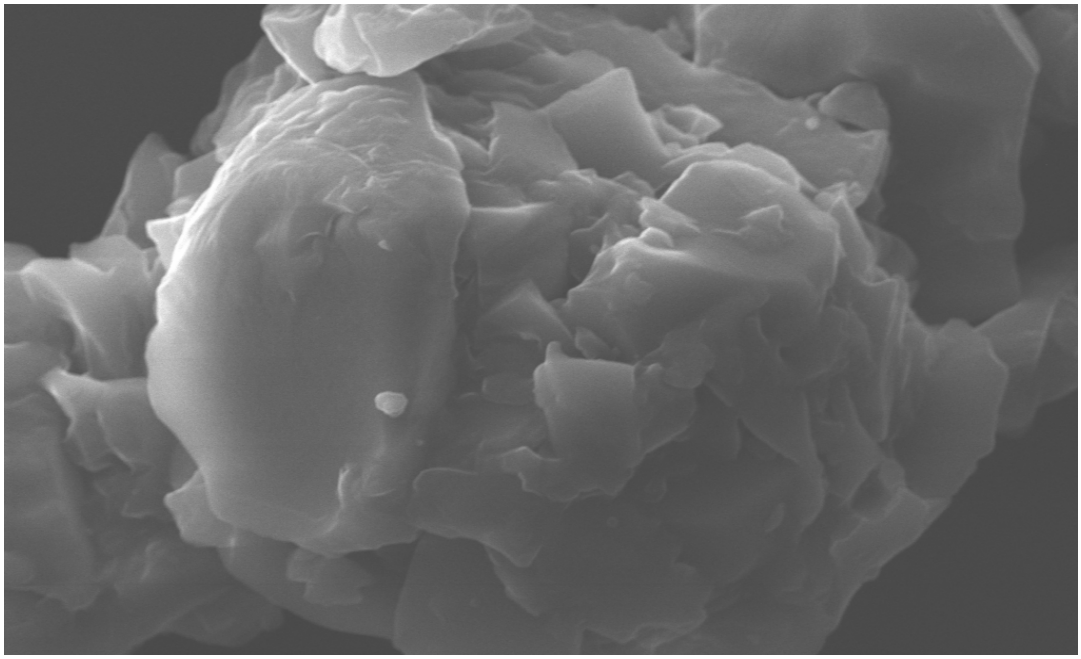

Figure 8: SEM of resinate (1:2DRCD Loaded Drug resin complex)

CONCLUSION

In this work, efforts made to prepare stable resinate for oral bioavailability and taste masking Cefpodoxime proxetil. Resinates of Cefpodoxime proxetil with anion exchange resin (Duolite AP 143) and cation exchange resin (Kyron T104) and observed results found to increase the acceptability and palatability of the drug. An attempt made to enhance the dissolution of Cefpodoxime proxetil with 1:2 DRCD of Duolite AP 143 and it was found to exhibit taste masking and also good *in vitro* drug release property. The taste masking ability of both resins at different concentration exhibited same taste masking property with respect to Duolite AP 143, whereas with Kyron T 104 better acceptability and palatability of drug was observed in 1:3 DRCK. The drug loading was more in lowest concentrations of Duolite AP 143 and Kyron T 104. *In vitro* drug release was more with Duolite AP 143 compare to Kyron T 104.

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