Vol 1 | Issue 1 | Jul –Dec 2010 | 7-13.

Research Article

Taste Masking of Ciprofloxacin by Ion Exchange Resin

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ABSTRACT

Taste is an important parameter in administering drugs orally. Undesirable or bitter taste is one of the important formulation problems that are encountered with many drugs, like Ciprofloxacin. Taste is mainly depending upon the physiology, sensitivity & structure of taste bud of tongue. There are different techniques of taste masking but in modern days the most improved & easy technique is to formulate tasteless complexes of ciprofloxacin with ion exchange resin (Indion 234). After acid activation & swell in water, resin & ciprofloxacin (proper ratio) stirred by magnetic stirrer for definite time, temperature & unbound drug in filtrate were estimated spectrophotometrically and drug-loading efficiency was calculated. The molecular properties of drug complexes by DSC & FTIR study confirm the complexation of ciprofloxacin with Indion 234. The % drug release in pH 6.8 also confirms the masking of bitterness of ciprofloxacin.

Keywords: Ciprofloxacin, Ion Exchange Resin (INDION 234), Complexation

INTRODUCTION

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for health care providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals [1]. Understanding the taste preferences of children is extremely important as palatability of a medication plays a pivotal role in achieving patient acceptance and therefore compliance and treatment success. In paediatric patients, acceptance of a dosage form is primarily dependent on a child's taste preference as any parent who has struggled with administering unpalatable formulations can attest.

Physiology of Taste

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue. The sense of taste is conducted to the brain by a process called taste transduction. This process begins with the interaction of tastant (i.e., food or medicine) with taste receptor cells in the taste buds. The tastant binds with G-protein coupled receptors in the cells, triggering the release of a G-protein called gustducin. Taste sensation begins when gustducin activates the effector enzymes phosphodiesterase 1A or phospholipase C □-2. The effector enzymes then change the intracellular levels of second messengers such as cyclic adenosine monophosphate (cAMP), inositol 1,4,5-tri phosphate(IP3), and idacylglycerol (DAG). The second messengers activate ion channels, including calcium channels inside the cell, and sodium, potassium and calcium channels on the extracellular membrane. This ionization depolarizes the cell, causing the release of neurotransmitters that send a nerve impulse to the brain that carries the signal of taste [2].

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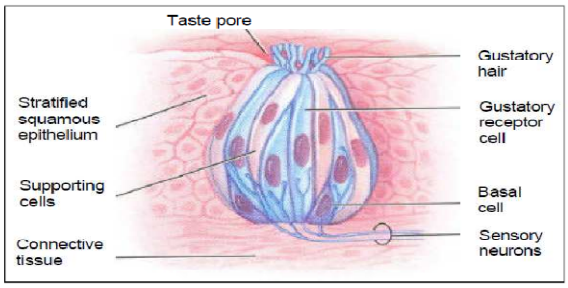

Taste constitutes four primary effects, viz., sweet, sour, bitter and salty. Correspondingly, there are four different kinds of taste buds. Sweet sensations are most easily detected at the tip, where as bitterness at the back of the tongue, but salty sensations are usually detected at the tip and the sides of the tongue. During ingestion, taste buds react to soluble substances. The resulting sensations are transmitted to the brain by the ninth cranial nerve and tastes are detected. The sensitivity of the tongue to different sensations varies widely among individuals.

Different Taste-masking Techniques

- Coating of Drug Particles
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- Fluidized bed coating technique.
- Microencapsulation
- Solid Dispersions
    - Melting method
    - Solvent method
    - Melting-solvent method
- Formation of Salts or Derivatives
- use of Amino Acids and Protein Hydrolysates
- Taste-masking by Viscosity Modifications
- Inclusion Complexes
- Molecular Complexes of Drugs with Other Chemicals
- Prodrugs
- Taste abatement by flavoring

Now-a-days the most popular approach in the development of taste masking is based on **Ion exchange resins (IER)**. The purpose of the research was to formulate ***tasteless complexes of ciprofloxacin with Indion 234*** and to evaluate molecular properties of drug complexes.

Ion exchange resins are solid and suitably insoluble high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with the surrounding medium. The resulting ion exchange is reversible and stoichiometric with the displacement of one ionic species by another.

Being high molecular weight water insoluble polymers, the resins are not absorbed by the body and are therefore inert. They have versatile properties as drug delivery vehicles, equally suitable for drug delivery technologies, including controlled release, transdermal, nasal, topical, and taste masking.

Types of Ion Exchange Resins

Cation exchangers (Anionic resin):- Cation-exchange resin is prepared by the copolymerization of styrene and divinyl benzene and have sulphonic acid groups ($-SO_3H$) introduced into most of benzene rings. The functional group of these resins undergoes reaction (exchange) with the cations in the surrounding medium.

Mechanism: $Resin^- - ex^+ + C^+ \rightarrow Resin^- - C^+ + ex^+$

Where, $Resin^-$ indicates polymer with SO_3^- sites available for bonding with exchangeable cation (ex^+) and C^+ indicates cation in the surrounding solution getting exchanged.

*Anion exchangers (Cationic resin):-*These are the polyelectrolytes undergoing reaction with the anions of the surrounding solutions. They are prepared by first chlor-meythylating the benzene rings of styrene-divinylbenzene copolymer to attach CH_2Cl groups and then causing these to react with tertiary amine such as triethylamine.

Mechanism: $Resin^+ - ex^{-+} A^- \rightarrow Resin^+ - A^- + ex^-$

Where, $Resin^+$ indicates polymer with N^+ sites available for bonding with exchangeable anion ($ex^{-)}$ and A^- indicates cation in the surrounding solution getting exchanged [3].

Some bitter drugs whose taste has been masked by using ion exchange resin are listed below:

Table 1. Bitter Drugs masked by ion exchange resin

Drug	Ion exchange resin
Norfloxacin	Indion 204 (weak cation exchange resin)
Ciprofloxacin	Indion 234 (weak cation exchange resin)
Roxithromycin	Indion 204 (weak cation exchange resin)
Azithromycin	Indion 214 (weak cation exchange resin)
Chloroquine phosphate	Indion 234 (weak cation exchange resin)

MATERIALS AND METHODS

Material:- Ciprofloxacin hydrochloride (batch no. YAAA1528) was a gift sample from WALLACE Pharmaceuticals PVT. LTD. (Ponda, Goa, India). The resin, Indion 234 was procured from Ion Exchange India Ltd (Mumbai, India).

Method:- For 0.1 n HCL, the λmax of Ciprofloxacin is found from the UV is 273.5 nm & In pH 6.8, the λmax is found from UV is 271 nm.

1. Preliminary Evaluation of Resin

Indion 234 particle diameter was measured microscopically. Water absorption time was obtained by keeping 500 mg of Indion 234 in contact with 1 mL of water in a Petri dish. The time required for complete water absorption was recorded.

2. Effect of Resin Activation

Indion 234 (200 mg), placed on a Whatman filter paper in a funnel, was washed with deionized water and subsequently with 1N HCl (100 mL). The resin was rewashed with water until neutral pH was reached. DRC was prepared by placing 100 to 300 mg of acid-activated resin in a beaker containing 25 mL deionized water. Ciprofloxacin (100 mg) was added to resin slurry with magnetic stirring. On filtration, the residue was washed with 75 mL of deionized water. Unbound drug in filtrate was estimated at 273.5 nm. The drug-loading efficiency of activated resin was evaluated spectrophotometrically.

3. Effect of Swelling of Resin on Drug Loading

Separate batches of activated Indion 234 (200 mg) were soaked in 25 mL of deionized water contained in a beaker for 10, 20, 30, and 40 minutes, respectively. The complexation in batch process was performed, and the loading efficiency with resin swollen for different times was determined.

4. Formation of Ciprofloxacin-Indion 234 Complexes

In batch process, take 100 mg of acid activated resin in 25 ml of deionized water in a beaker. Allow to swell for 30 minutes. Then take 100 mg of drug (on that beaker) and stirred (Magnetic Stirring) for 30 minutes. The mixture was filtered and residue was washed with 75 mL of deionized water. Unbound drug in filtrate was estimated at 273.5 nm and drug-loading efficiency was calculated. The same process has been taken for other batches of drug-resin ratio as 1:2 and 1:3.

There is another process of masking the bitterness by resin with using little amount of water. This is done because the above technique need more amount of water incase of large scale production. So in that process, Drug and Resin is taken in a beaker (as 1:1,1:2,1:3 ratio) , mix them well. Then take distilled water drop wise into the beaker with continues stirring with glass rod. The stirring is going on until a wet mass is produce. As resin is insoluble in water, drug has been coated (complexation) with resin.

5. Optimizing Drug Loading

Accurately weighed ciprofloxacin (100 mg) was added to 130 mg of activated resin and slurred in 25 mL of deionized water. Six batches with a stirring time of 5, 10, 15, 20, 30, and 240 minutes were processed. Amount of bound drug at the end was estimated at 273.5 nm. (Blase CM, Shah M, Inventors. Taste masked pharmaceutical suspensions containing xanthum gum and microcrystalline cellulose. European patent 0556057. August 18, 1993) [3,4].

6. Effect of Temperature on Complex Formation

The complexation of 100 mg of drug with 130 mg of activated resin, slurred in 25 mL of deionized water in a 100 mL beaker, was performed at 27°C, 40°C, 60°C, and 80°C using temperature- controlled magnetic stirring for 30 minutes. The volume of filtrate was made up to 50 mL with water washings of DRC. The amount of bound drug was estimated spectrophotometrically (273.5 nm) from the unbound drug in filtrate.

7. Molecular Properties of Drug Resin Complex

Infrared spectra of DRC, drug, and physical dispersion (optimized ratio) thereof were obtained using **Fourier-transform infrared (FTIR) spectroscopy**. The pellets were prepared on KBr press, and the spectra were recorded over the wave number 4000 to 1500 cm−1. The 3 spectra were comparatively analyzed.

A Mettler Toledo **differential scanning calorimeter (DSC)** equipped with an intercooler and a refrigerated cooling system was used to analyze the thermal behavior of ciprofloxacin and DRC. Indium standard was used to calibrate the DSC temperature. Nitrogen was purged at 50 mL/min and 100 mL/min through cooling unit. The thermal behavior of hermetically sealed samples (5-10 mg) heated at 20°C/min is shown.

8. Drug Release From Drug-Indion Complex

DRC equivalent to 500 mg of drug was weighed accurately and added to 900 mL of 0.1 N HCL (pH 1.2) and maintained at 37°C. Drug release was performed at 100 rpm for 2 hours. A 10-mL sample removed from mixtures each kept at 5 minutes was filtered, and the amount of drug was estimated spectrophotometrically at 273.5 nm. The same process was performed replacing 0.1N HCL with pH 6.8 buffer and the filtrates were assayed for drug but in that case only three reading were sufficient for the experiment [5,6,7,8].

RESULTS

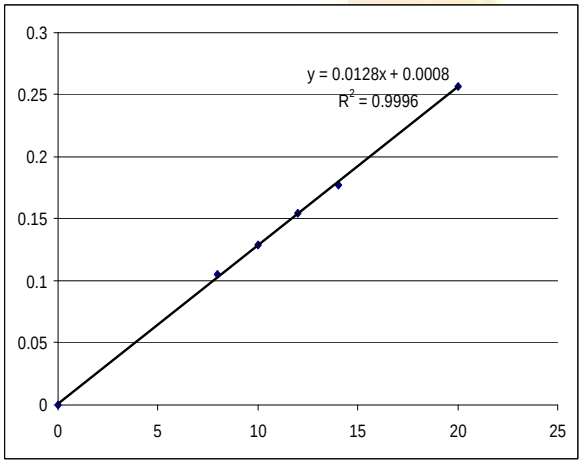
The size of Indion 234 particles obtained, 54 ± 4 µm, was in conformation with the reported size (<150 µm), which is useful for taste masking. The water uptake time of Indion 234 was found to be 45 seconds.

The drug-loading efficiency for a drug-resin ratio 1:1, 1:2, and 1:3 of batch process was 90.61% , 95.54%, and 96.08% wt/wt. A 4% wt/wt increase of loading efficiency was observed in batch process, when drug-resin ratio was changed from 1:1 to 1:1.2. Hence the drug loading performed at intermediate drug-resin ratio of 1:1.3, 1: 1.5, and 1:1.7 was found to be 93.36%, 93.76%, and 93.60% wt/wt, respectively.

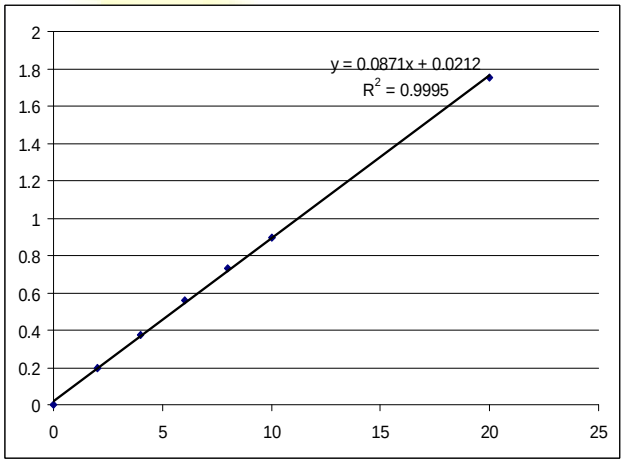
A 30-minute swelling time of Indion 234 in deionized water gave the maximum ciprofloxacin loading of 96.08% wt/wt. The swelling and hydrating properties of Indion 234 affect the rate of ion exchange, which in turn affects the percentage drug loading. In unswollen resin matrix, the exchangeable groups are latent and coiled toward the backbone, hence less drug-loading efficiency. The percentage drug loading (wt/wt) with a stirring time of 5, 10, 15, 20, 30, and 240 minutes was found to be 50.20%, 56.25%, 71.27%, 93.53%, 95.50%, and 95.63%, respectively. Efficient drug loading on Indion 234 occurred uniformly in the experimental temperature range of 27ºC to 80ºC.

Drug Release from Drug-Indion Complex:-

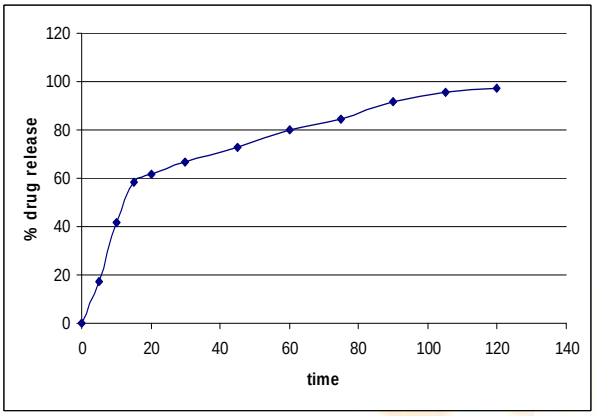
Graph 1. Calibration curve of Ciprofloxacin (Hcl) in 0.1 N HCL by UV



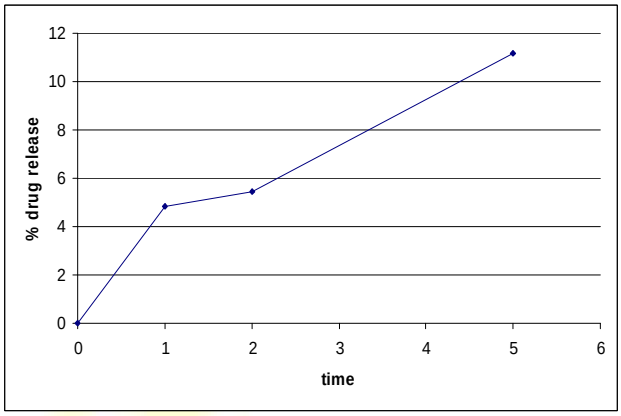
Graph 2. Calibration curve of Ciprofloxacin (Hcl) in pH 6.8 by UV



Graph 3. % Drug release in Gastric pH with time



Graph 4. % Drug release in pH 6.8(saliva) with time



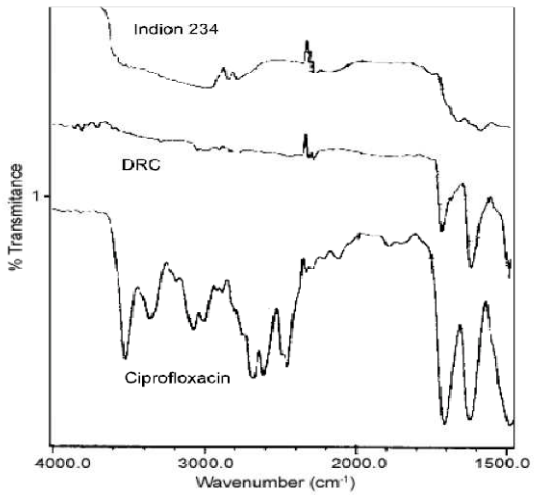


Figure 2. Infrared spectra of Indion 234, DRC, and ciprofloxacin.

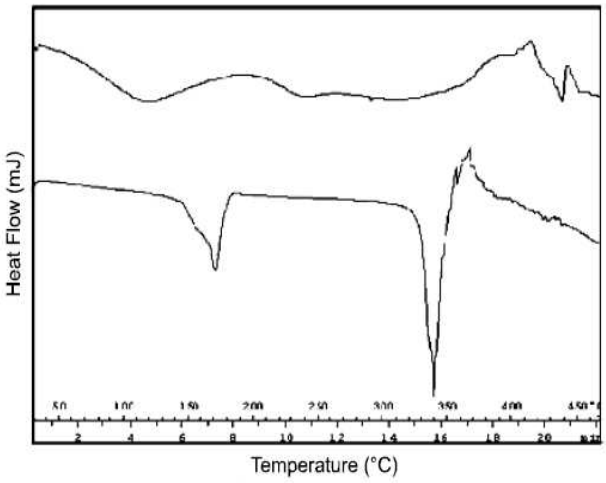


Figure 3. DSC curves for DRC and ciprofloxacin.

DISCUSSIONS

Ciprofloxacin hydrochloride, a broad-spectrum antibiotic, prescribed extensively in both solid and liquid dosage forms, is extremely bitter resulting in poor patient compliance. Complexation with ion exchange resin is a simple and efficient technique of masking the bitterness. The drug being soluble in water has desired ionization power. The resulting size is useful for taste masking. Substantially small size particles are difficult to process and particles greater than 200 µm have a tendency to fracture. Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. As the reaction is an equilibrium phenomenon, maximum efficacy is best achieved in batch process. Equilibration time was shorter due to thinner barrier for diffusion of ions, as it is in continuous motion. Also, higher swelling efficiency in the batch process results in more surface area for ion exchange. Hence, the batch process is suitable for smaller particles. The swelling and hydrating properties of Indion 234 affect the rate of ion exchange, which in turn affects the percentage drug loading. In unswollen resin matrix, the exchangeable groups are latent and coiled toward the backbone, hence less drug-loading efficiency. The equilibrium ion exchange in solution occurs stoichiometrically and hence is affected by stirring time. Drug adsorbate formation may be significantly affected by processing temperature. Increased temperature during complexation increases ionization of drug and resin. The effect is more pronounced for poorly water soluble and un-ionizable drugs. Higher temperatures tend to increase the

diffusion rate of ions by decreasing the thickness of exhaustive exchange zone. It was reported that cation exchangers are not affected as significantly by temperature changes as anion exchange resins [9].

Molecular Properties of Drug-Resin Complexes

The infrared spectra of Indion 234, ciprofloxacin-Indion 234 complex and ciprofloxacin hydrochloride are depicted in ***Figure 2A, B, and C,*** respectively. Drug spectrum shows a prominent peak at 3375.2 cm^{-1} corresponding to the NH stretching in a secondary amine. Figure 2C shows peaks corresponding to –COOH dimerization of drug in the range of 2464.9 to 3091.7 cm^{-1}. Dimerization is a characteristic of acidic functionality, where the compound occurs in the form of dimers of acids due to self-association in the drug molecule through weak van der Waals forces. A peak at 3535 cm^{-1} is due to –OH stretching, which lies in standard range of 3400 to 3600 cm^{-1}. Indion 234 shows characteristic peaks at 1674 cm^{-1}, at 1764 cm^{-1} corresponding to –C = O stretching of aryl acids, and at 1602 cm^{-1} due to aromatic C = C stretching. Numbers of overtone peaks were observed at 2308 and 2347 cm^{-1}. The absence of peak at 3375 cm^{-1} in DRC (1:1.3) confirms the complexation of the secondary amine group in the drug with resin. The absence of peaks (3091-2464 cm^{-1}) due to dimerization of carboxylic acid groups in the drug in DRC denotes the breaking of acid dimers during complexation. The peak at 3535 cm^{-1} in DRC corresponding to –OH stretching is also absent, which signifies that during DRC formation there was interaction of the amino group of drug with the carboxylic group of Indion [11].

Figure 3, shows DSC curves for DRC (top) and pure ciprofloxacin hydrochloride (bottom). The thermal behavior of the pure drug shows endothermic at 168.88°C and 335.00°C corresponding to loss of water of crystallization and melting of pure drug. The thermal behavior of DRC shows fractional loss of water between 100°C and 140°C and melting endothermic of drug at 335°C. However, the DRC curves show a small gradual exothermic at 428°C indicating onset (endothermic- exothermic inversion) and gradual decomposition of the optimized complex. The study confirms the complexation of ciprofloxacin with Indion 234 [10].

Drug Release from Drug-Indion Complex

Ciprofloxacin release from drug-resin adsorbate was observed in average salivary pH of 6.8, and at gastric pH of 1.2, separately. In vitro drug release in average salivary pH of 6.8 was 4.86% within 60 seconds, 5.46% within 120 seconds and 11.17% within 180 seconds. The presence of exchangeable ions of ionizable electrolytes in the salivary fluid may be responsible for this release. The DRC is stable in salivary pH for a period of administration. The amount released is insufficient to impart bitter taste while the formulation passes through the mouth to further parts of the gastrointestinal (GI) tract. At gastric pH (1.2), 58.25% of ciprofloxacin was released within 15 minutes, and the release was nearly complete in 120 minutes [9].

The complexation of ciprofloxacin hydrochloride with Indion 234 produces amorphous tasteless drug resonates. When DRC is exposed to a low pH, it causes dissociation of the complex. The presence of H^+ ion in the medium causes displacement of ciprofloxacin, thus facilitating drug release. This finding has been well supported by DSC data and confirmed by in vitro drug release in salivary pH [9,10,11,12].

CONCLUSION

Taste masking of bitter drugs has been a challenge to the scientist. This method could be suitable for taste masking of bitter drugs-Ciprofloxacin. The method described in this review can be used for bench scale as well as pilot scale also. There are numbers of technologies available which effectively mask the objectionable taste of drugs but require skillful application which does not affect the bioavailability of drug. Recent trends of patient oriented practice demand design of patient oriented dosage form to achieve patient compliance. Taste masking of bitter drugs has significantly improved the quality of treatment provided to suffering patient, especially children.

Pharmaceuticals complexes using ion exchange resins have shown improved organoleptic performance of pharmaceuticals. They are used to mask the bitter taste, improve processing characters of drug molecules, modified release and physicochemical stabilization. Moreover, they are proved for their therapeutic application as hypolipidemic agent. In conclusion, ion exchange resin Indion-234 can be of great value in making tasteless complex of Ciprofloxacin. Ion exchange resins also can be very important for developing new formulations for a variety of drugs and their potential is not fully explored. This is an area opening for high commercial outputs in near future.

ACKNOWLEDGEMENT

Authors are sincerely thankful to Sri. V. Prasad Rao, L.L.M , Director ; Sri Rajsekhar Reddy, M.sc & Dr. S.Vijay Srinivas, Principal, M.Pharm, Ph.D, Department of Pharmaceutics, Prasad Institute Of Pharmaceutical Sciences, for their contribution and facilities provided regarding our Research work.

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