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Original Research Paper

TASTE MASKING FORMULATION AND EVALUATION OF CIPROFLOXACIN HCL USING ION EXCHANGE RESINS

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ABSTRACT

Some drugs are bitter and unpleasant in taste and taking orally very difficult for children and some adults. Non-compliance can lead to worsening of diseased condition. Numbers of taste masking technologies have been used to address the problem of patient compliance. The purpose of this research was to mask the intensely bitter taste of Ciprofloxacin HCl and to formulate a palatable liquid formulation of the taste-masked drug, by novel Ion Exchange Resin (IER) method to overcome taste problem with traditional system. Taste masking was done by complexing Ciprofloxacin HCl with Tulsion 335, Indion 254 and Indion 414 in different ratios. Formulation containing resinates were tested for drug content, *in vitro* drug release, taste masking, stability study, and molecular property. The resinates prepared with drug- Indion 254 ratio (1:2) at pH 8, gave maximum drug loading. Suspension containing above resinates showed more than 80% In vitro drug release within 30 min. Prepared formulation also showed good stability and can retain its palatable taste. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non-cooperative patients, can be successfully formulated using this technology.

Keywords: Taste masked suspension, Ciprofloxacin HCl, Taste masking, Resinate, Formulation.

INTRODUCTION

Antibiotics are among the most frequently prescribed medications in modern medicine. Antibiotics are used to treat a wide range of infections like respiratory tract infection, urinary tract infection, soft tissue infection, useful in prophylaxis of patients undergoing surgery, in curing gonorrhea, as well as effective in treatment of typhoid, etc. Most of the antibiotics are bitter in taste and resulting in patient noncompliance while administering. Fluoroquinolones are especially effective against aerobic gram negative bacteria. Ciprofloxacin HCl is first generation antibiotics (as shown in figure 2) is effective again many gram negative enteric bacteria specially in typhoid fever, tissue abscess, upper respiratory tract and urinary tract infections. Ciflaloxacin HCl is bitter in taste so the drug is prepared with the use of ion exchange resin to mask the taste of active drug. Novel drug delivery technologies are revolutionizing drug discovery and development. The challenge in the area of drug delivery is to deliver both existing and emerging drug technologies in a manner that benefits patients. Good mouth feel of formulation helps to change the basic view of medication from "bitter pill" to "better pill". Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that is encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Also, such pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliance and quality of life of such

patients. Thus, the problem of bitter and obnoxious taste of drug in pediatric and geriatric formulations is a challenge to the pharmacist in the present scenario. Patient expects the oral dosage form to be pleasantly flavored and palatable. This change in patient attitude is due to the advances made by flavoring and pharmaceutical industries. Several oral pharmaceuticals and bulking agents have unpleasant, bitter-tasting components. Thus, any pharmaceutical formulation with a pleasant taste would definitely be preferred over another product and would translate into better patient compliance and therapeutic value. The desire of improved palatability in these products has prompted the development of numerous formulations with improved aesthetic appearance and performance. The application of drug delivery technology to any molecule is based on market needs, product differentiation, and patient compliance. The time to get the new chemical entity to the market eats up a majority of the patent life cycle of the drug. Taste masking technologies are very helpful in adding value/timeline to the patent.[1-10]

MATERIALS AND METHODS

2.1 Materials

Ciprofloxacin HCl was gift sample from Sun Pharma Ltd., (Jammu, India). Tulsion 335 and Indion 254 was obtained as gift sample from Corel Pharma Chem, (Ahmedabad, India). Indion 414 purchased from Ion exchange India limited (Mumbai, India). Sucrose, sorbitol, glycerine, xanthane gum, aspartame, methyl paraben and mango candy flavour were purchased from S. D. Fine chemicals (Mumbai, India). All other chemicals/solvents were of analytical grade.

Methodology

Purification of ion exchange resin

Resins were purified using the method reported by Irwin *et al.*[12] The resins (5 g) were washed successively with distilled water, methanol (50 ml), benzene (50 ml), methanol (50 ml) and several times with distilled water to eliminate organic and color impurities. Then, the wet resins were activated by 0.1 M HCl 50 ml and washed several times with distilled water. All resins were dried overnight in hot air oven at 500 C and kept in an amber glass vial.

Preparation of drug-resin complex

Drug-resin complex were prepared by batch process. Step 1: Weigh all the ingredient accurately. Now add weighted quantity of resin in specific quantity of water and stir it for 15 min. under mechanical stirrer. Step 2: Now add weighted quantity of Ciprofloxacin HCl into step 1 & stir it for 4 to 5 hr. continuously under stirrer. Step 3: Take specific quantity of water boil it dissolve sugar & filter it. Now cool the syrup at room temperature and add sorbitol and glycerin in it & add into step 2 under continuous stirring.[13-15] Step 4: Take water & add xanthane gum and stir it to form a paste. Add this paste in step 3 slowly under stirring. Step 5: Take warm water dissolve methylparaben, propylparaben & aspartame in to it & add in to above solution under stirring. Step 6: Now add coloring, flavoring agent in step 5 & make volume of suspension up to required quantity by using purified water, pH of resin solution was adjusted to 8 by using 1 M KOH.[16]

Evaluation of taste masked suspension

- *Determination of drug content in resonates*

  Ciprofloxacin HCl resinate (50 mg) was placed in a beaker to which 0.1N HCl (50 ml) was added for eluting Ciprofloxacin HCl from the resinate.[17] The volume of eluate was measured and assayed for the content of Ciprofloxacin HCl by spectrophotometry at wavelength of 272 nm.

- *In-vitro release of suspension*

  Dissolution studies of above samples were performed using USP XXIII apparatus type 2. Suspension equivalent to 400 mg of the drug were added to the dissolution medium (500 ml 0.1N HCl at a temperature of 37 ^{0}C ± 0.5^{0}C), which was stirred with a rotating paddle at 50 rpm.[18] At suitable time intervals, 10 ml samples were withdrawn, filtered (0.22 µm),

diluted and analyzed at 272 nm using UV spectrophotometer

- *Determination of viscosity*

The viscosity of gel was determined at ambient condition (DV III+, Brookfield Programmable Rheometer) using adequate amount of the sample.[19]

- *Taste evaluation*

The taste of suspension was checked by panel method. The study protocol was explained and written consent was obtained from volunteers. For this purpose, 10 human volunteers were selected.[17] About 5 ml suspension containing 500 mg of drug was placed on tongue and taste evaluated after 15s. Take 10 ml of suspension in 100 ml volumetric flask & make up the volume up to 100 ml with 0.1N HCl. Now take 2 ml solution from flask & add in to 200 ml volumetric flask. Make up the volume up to 200 ml with 0.1 N HCL filter it & measure the absorbance at wavelength 277 nm in U.V. Spectrophotometer & compare it with standard. Calculate % drug content by using following formula.

- *Sedimentation volume*

Sedimentation volume (F) is a ratio of the final or ultimate volume of sediment (Hu) to the original volume of sediment (H_0) before settling. It can be calculated by following equation.

$$F = \frac{H_u}{H_o} \text{ ---------- (1)}$$

Where, H_u = final or ultimate volume of sediment

H_0 = original volume of suspension before settling.

- *Accelerated stability study*

Suspensions were packed in 60 ml glass bottle. The packed bottles were placed in stability chamber maintained at 40 + 2 ^oC and 75 + 5% RH for 3 month. Samples were collected at days 0, 5, 15, 30, 60 and 90. The analyses comprised chemical testing of quantifiable parameters, which could possibly change during storage, such as viscosity, pH, drug contents, sedimentation volume, redispersibility, taste and any kind of microbial or fungal growth.[14,20]

RESULT AND DISCUSSION

For preparation of resinates, batch method was preferred because of its convenience. Equilibrium was reached within 6 h. The high affinity of resins to hydrogen ions can yield fast desorption of bound ions when they are exposed to an acidic environment such as the stomach. When the pH is lower than 4, the resin exists in the Free State. Therefore, drug/resin complex formation needs to be carried out at pH 6 or higher. Higher concentration of competing ions at lower pH may inhibit the interaction of resins.[21] At pH 8 maximum loading of Ciprofloxacin HCl was seen onto Tulsion 335, Indion 254 and Indion 414 (data not shown). Effect of drug: resin ratio on % drug content per gram of resinate are shown in (table 2). It shows that for Tulsion 335 and Indion 254 maximum drug loading were observed at 1:2 drug resin ratio while 1:1 was observed for indion 414. As the cross linking ratio and particle size increased, the drug loading and release rate decreased due to the reduced effective diffusion coefficient and surface area. When the resin is highly cross linked, fewer functional groups are available inside the particle, resulting in low ion-exchange capacity.[22,23] Results of taste evaluation by panel method (table 3) revealed that Tulsion 335, Indion 254 and Indion 414 mask the bitter taste of drug completely at 1:2 and 1:2.5 ratios. In vitro release profile of resinates prepared using different resins is shown in (figure 1). Study was carried out in 0.1 N HCL using USP paddle apparatus at 50 rpm. More than 80% of drug was released within 30 min from C7 formulation. In general, strong acid type resins showed greater sustained release than weak acid type resins in in vitro dissolution tests.[17,24] In general, drug is released from the resinate by exchanging with ions in a surrounding release medium, followed by drug diffusion through the polymer matrix of the resinates. Some drug molecules released accumulated around the surface of the resinates to

form an aqueous boundary layer. Stirring can be introduced to the diminish this layer. However, higher cross linked resins display a more sustained release effect than lower cross linked resins. Slight distinction between release profile of formulations may be due to various cross linking ratio of resins. Accelerated stability study of C7 is shown in (table 4). Study revealed that prepared formulation (C7) can be remaining intact for a long period of time without major changes in assay, viscosity and sedimentation volume. It was found that formulation was remained palatable without any appearance of microbial growth in agar plates.

CONCLUSION

Use of weak cation exchange resin offers superior method for preaparing taste-masked substrates of Ciprofloxacin HCl. A result obtained in this work shows that drug-resin complexes effectively masked bitter taste of Ciprofloxacin HCl. While liquid formulation provides easier way to administer and getting the child to swallow. Also to overcome problem with non compliance with child especially around 8 years old for whom swallowing other dosage form can be challenging. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non cooperative patients, can be successfully formulated using this technology.

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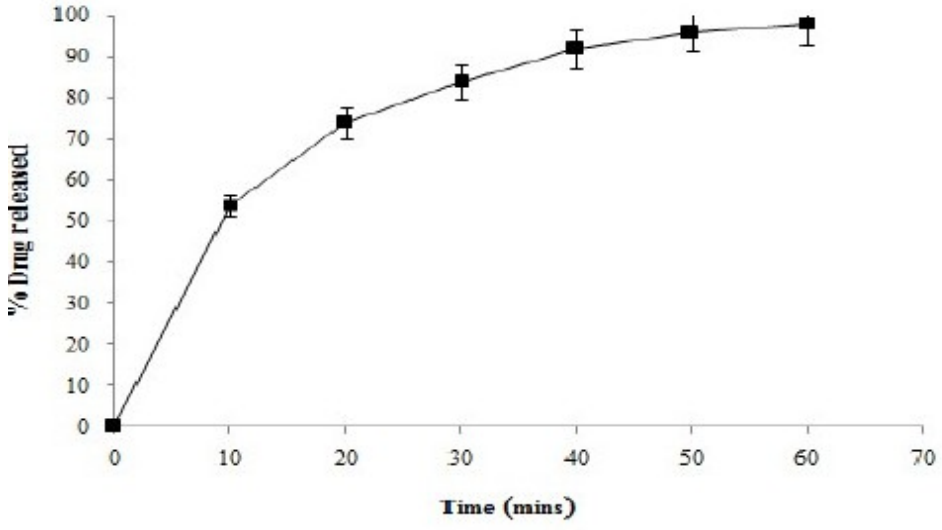

Figure 1: In vitro dissolution profile of C7 (Ciprofloxacin HCl-Indion 254, 46.3% drug loading)

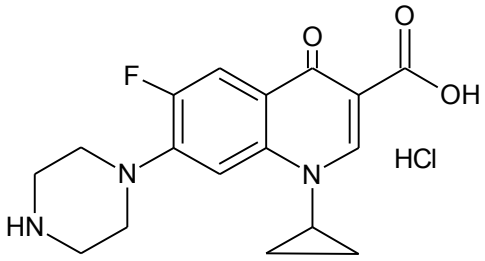

Figure 2: Structural formula of Ciprofloxacin HCl

Table 1: Formulation of Ciprofloxacin HCl suspension with different resins

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Complex formation										
Ciprofloxacin HCl [mg]	500	500	500	500	500	500	500	500	500	500
Tulsion 335	300	600	900	-	-	-	-	-	-	-
Indion 254	-	-	300			300	600	-	-	
Indion 414	-	-	-	-	-	-	-	300	600	900
Purified water	25	25	25	25	25	25	25	25	25	25
Syrup preparation										
Sucrose [gm]	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Glycerin [ml]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Xanthan gum [mg]	20	20	20	20	20	20	20	20	20	20
Methyl paraben [mg]	10	10	10	10	10	10	10	10	10	10
Propyl paraben [mg]	4	4	4	4	4	4	4	4	4	4
Aspartame [mg]	15	15	15	15	15	15	15	15	15	15
Mango candy flavor	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
Quinoline yellow color	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Purified water [ml]	5	5	5	5	5	5	5	5	5	5

Table 2: Evaluation parameter of Ciprofloxacin HCl suspension with different resins

Parameters	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
Drug loading of dry resinate	-	32.15	41.46	42.28	39.42	43.95	46.42	39.58	38.45	43.25
Color	Pale	Pale	Pale	Pale	Pale	Pale	Pale	Pale	Pale	Pale
Viscosity	298.2	296.58	302.45	304.23	296.25	304.58	300.52	297.42	304.2	306.
pH	7.8	8	7.6	8	7.9	7.5	8.1	7.8	7.8	8
Sedimentation volume	0.98	0.97	0.95	0.97	0.98	0.96	0.92	0.95	0.93	0.96
Redispersibility	++	++	+++	++	++	+++	+++	++	++	++
Assay	99.47	100.02	99.75	99.88	100.65	99.58	99.98	98.96	100.1	99.87

Table 3: Evaluation of taste of suspension

Code	Volunteers									
	1	1.	2.	3.	4.	5.	6.	7.	8.	9.
C1	3	2	3	3	2	3	3	2	3	3
C2	2	2	3	1	0	2	1	0	3	1
C3	1	2	0	1	0	3	2	1	2	0
C4	0	1	0	2	3	1	2	1	3	0
C5	20	1	3	2	1	0	1	3	2	2
C6	1	2	0	1	2	1	3	2	0	1
C7	0	3	1	2	3	0	2	1	2	3
C8	2	0	2	1	2	1	2	3	1	0
C9	1	2	1	3	1	2	1	0	2	1
C10	2	1	2	0	3	2	1	0	3	2

0 = normal, 1 = slightly bitter, 2 = bitter, 3 = very bitter

Table 4: Accelerated stability study of C7

Parameters	Time periods			
	Initial one day	One month	Two month	Three month
Assay %	100.42	99.85	99.35	99.23
Viscosity	335.54	334.25	333.52	334.54
pH	7.8	7.7	7.7	7.65
Sedimentation volume	0.97	0.96	0.96	0.95
Redespersibility	+++	+++	+++	+++
Taste	Palatable	Palatable	Palatable	Palatable

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