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Development of Taste Masked Liquid Formulation of Tinidazole Using Ion-exchange resin Complexes

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Abstract

The purpose of this research was to mask the intensely bitter taste of tinidazole (TNZ) 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 TNZ with Kyron T-114, Kyron T-134 and Indion 214 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-Kyron T-134 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 noncooperative patients, can be successfully formulated using this technology.

Keywords: Taste masking; Ion-exchange resin; Tinidazole; Resinate

Introduction

The problem of providing pediatric and geriatric patient with drug dosage forms that are palatable has been around for long time. Children and infants in particular, are most sensitive to bitter and sweet tastes than adults. Because of unpleasant taste children are frequently fail to take medications properly. Non-compliance can lead to worsening of diseased condition.

Different taste masking technologies have been used to address the problem of patient compliance. Conventional taste masking techniques such as the use of sweeteners, amino acids and flavoring agents alone are often inadequate in masking the taste of highly bitter drugs. Coating is more efficient technology for aggressively bitter drugs even though coating imperfections, if present, reduce the efficiency of the technique. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions.

Ion exchange resin (IER) provide alternative method for taste masking. In witch weak cation exchange or weak anion exchange resins are used for taste masking, depending on the nature of drug. The nature of the drug resin complex formed is such that the average pH of 6.7 and cation concentration of about 40meq/L in the saliva are not able to break the drug resin complex but it is weak enough to break down by hydrochloric acid present in the stomach. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected.

Until a child is around 8 years old, swallowing tablets can be challenging. This is often due to the smaller structure of a child's esophagus. Therefore, children under the age of 8 are typically prescribed liquid medications. TNZ is a orally absorbed drug used in the treatment of intestinal protozoal infection. Being a highly bitter drug TNZ posses a challenge particularly in the formulation of a pediatric dosage from.

Materials and Methods

Materials

TNZ was gift sample from Lincoln Pharmaceuticals Ltd.,(Ahmedabad, India). Kyron T-114 and Kyron T-134 was obtained as gift sample from Corel Pharma Chem, (Ahmedabad, India). Indion 214 purchased from Ion exchange India limited (Mumbai, India). Sucrose, Sorbitol, Glycerine, Xanthane gum, Aspartame, Methyl paraben and Mangocandy 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. 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 50^0C 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 TNZ in to 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. 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.

Evaluation of taste masked suspension

a) Determination of drug content in resinates

TNZ resinate (50 mg) was placed in a beaker to which 0.1N HCl (50 ml) was added for eluting TNZ from the resinate. The volume of eluate was measured and assayed for the content of TNZ by spectrophotometry at wavelength of 277 nm.

b) 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 37^0C ± 0.5^0C), which was stirred with a rotating paddle at 50 rpm. At suitable time intervals, 10 ml samples were withdrawn, filtered (0.22 µm), diluted and analyzed at 277 nm using UV spectrophotometer.

c) Determination of Viscosity

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

d) 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. About 5 ml suspension containing 500 mg of drug was placed on tongue and taste evaluated after 15 s.

e) Assay of suspension:

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.

f) Sedimentation volume:

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

$$F = V_u / V_O \text{ ---------- (1)}$$

Where, V_u = final or ultimate volume of sediment

V_O = original volume of suspension before settling.

g) Accelerated Stability Study

Suspension were packed in 60 ml glass bottle. The packed bottles were placed in stability chamber maintained at 40 $\pm$ 2^oC and 75 $\pm$ 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.

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. At pH 8 maximum loading of TNZ was seen onto Kyron T-114, Kyron T-134 and Indion 214 (data not shown).

Table 1: Effect of drug: resin ratio on drug loading

Resinate	Code	Drug:Resin	Drug loading (% w/w)
TNZ and Kyron T-114 resinates	F1	1:01	32.2 ± 2.14
	F2	01:01.5	34. 4 ±1.21
	F3	1:02	41.3 ± 1.30
	F4	01:02.5	28. 3 ± 1.92
Tinidazole-Kyron T-134 resinates	F5	1:01	39.2 ± 1.24
	F6	01:01.5	43. 4 ±1.76
	F7	1:02	47.6 ± 1.44
	F8	01:02.5	36. 3 ± 2.10
Tinidazole-Indion 214 resinates	F9	1:01	41.1 ± 0.74
	F10	01:01.5	40.4 ±1.370
	F11	1:02	33.6 ± 1.59
	F12	01:02.5	29.3 ± 1.73

Data are mean ± SD, n =3.

Effect of drug:resin ratio on % drug content per gram of resinate are shown in [Table 1]. It shows that for kyron T-114 and kyron T-134 maximum drug loading were observed at 1:2 drug-rasin ratio while 1:1 was observed for indion 214. As the crosslinking 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 crosslinked, fewer functional groups are available inside the particle, resulting in low ion-exchange capacity.

Table 2 : Evaluation of taste of suspension

Code	Volunteers									
	1	2	3	4	5	6	7	8	9	10
F1	3	2	3	3	3	2	3	3	2	3
F2	1	1	1	3	1	1	2	2	1	1
F3	2	0	1	2	2	2	1	0	2	1
F4	0	1	0	1	1	0	0	0	0	1
F5	2	3	3	2	3	2	3	3	2	2
F6	2	2	1	2	2	1	1	2	2	2
F7	0	1	2	0	0	1	1	0	0	0
F8	0	1	0	0	0	0	1	0	0	0
F9	2	2	2	3	2	2	3	2	2	3
F10	2	1	0	2	3	1	3	2	3	2
F11	0	0	0	1	0	2	1	2	1	0
F12	0	0	1	0	0	0	0	1	0	0

0=Normal, 1=Slightly bitter, 2=bitter, 3= Very bitter

Results of taste evaluation by panel method [Table 2] revealed that Kyrpn T-114, Kyron T-134 and Indion 214 mask the bitter taste of drug completely at 1:2 and 1:2.5 ratios.

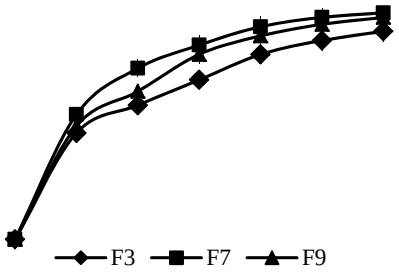

Figure 1: In vitro dissolution profile of
F3 (TNZ-Kyron T-114, 41.7% drug loading)
F7 (TNZ-Kyron T-134, 47.6% drug loading)
F9 (TNZ-Indion 214, 41.1% drug loading)

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 F7 formulation. In general, strong acid type resins showed greater sustained release than weak acid type resins in *in vitro* dissolution tests. 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

Table 3: Accelerated stability study

Parameters	Time periods			
	Initial (0 Day)	1 month	2 month	3 month
Assay	100.40%	99.70%	99.80%	99.40%
Viscosity (mPa s)	335.34	331.29	334.7	332.23
pH	7.8	7.7	7.7	7.7
Sedimentation volume	0.96	0.95	0.93	0.94
Redispersibility	+++	+++	+++	+++
Taste	Palatable	Palatable	Palatable	Palatable

surface of the resinates to form an aqueous boundary layer. Stirring can be introduced to the diminish this layer. However, higher crosslinked resins display a more sustained release effect than lower crosslinked resins. Slight distinction between release profile of formulations may be due to various crosslinking ratio of resins.

Accelerated stability study of F7 is shown in [Table 3]. Study revealed that prepared formulation (F7) can be remain 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 TNZ. Results obtained in this work shows that drug-resin complexes effectively masked bitter taste of TNZ. While liquid formulation provide 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 noncooperative patients, can be successfully formulated using this technology.

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