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Research Article

FORMULATION AND EVALUATION OF TASTE MASKED SUSPENSION OF METRONIDAZOLE

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ABSTRACT

Non-compliance which is mostly associated with bitter taste can lead to worsening of diseased condition The purpose of this research was to prepare palatable liquid formulation by masking the intensely bitter taste of metronidazole (MNZ). Taste masking was done by complexing of MNZ with different rasins Kyron T-114, Kyron T-134 and Indion 234 in different ratios. Prepared suspensions were tested for drug content, *in vitro* drug release, taste masking, stability study, and molecular properties. Kyron T-134 at pH 8 showed potential to prepare palatable formulation with MNZ. Thus to overcome taste problem of traditional paediatric dosage form, IER is dominating method to prepare palatable liquid formulation of MNZ.

Keywords: Metronidazole, Taste masking, Ion-exchange resin, Pediatrics

INTRODUCTION

Children are frequently failed to take medications properly because of unpleasant taste of medicament. Non-compliance can lead to worsening of diseased condition. Numbers of taste masking technologies have been used to address the problem of patient compliance. 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 [1]. Similarly, microencapsulation of potent bitter active agents such as azithromycin is insufficient to provide taste masking of liquid oral suspensions [2].

In Ion exchange resin (IER) method 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[3]. Thus the drug resin complex is absolutely tasteless with no after taste, and at the same time, its bioavailability is not affected. Children under the age of 8 are typically prescribed liquid medications because of smaller structure of a child's esophagus [3, 4]. MNZ is a highly bitter drug, used in the treatment of intestinal protozoal infection like amoebiasis, giardiasis, trichomonas vaginitis etc [4].

MATERIALS AND METHODS

Materials

Metronidazole benzoate was gift sample from Lincoln Pharmaceuticals Ltd.,(Ahmedabad, India). Kyron T 104 and Kyron T 134 was obtained as gift sample from Corel Pharma Chem, (Ahmedabad, India). Indion 234 was 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. [5]. 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 [6, 7, 8]

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 MNZ 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.

Characteristics of MNZ resinates

a) Determination of drug content in resonates [9].

MNZ resinate (200 mg) was placed in a beaker to which 0.1N HCl (50 ml) was added for eluting MNZ from the resinate. The volume of eluate was measured and assayed for the content of MNZ by spectrophotometry at wavelength of 277 nm.

b) In-vitro release of suspension [9, 10]

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 [11]. 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 200 mg of drug was placed on tongue and taste evaluated after 15 seconds.

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[11, 12].

f) Sedimentation volume [13]

Sedimentation volume (F) is a ratio of the final or ultimate volume of sediment (Vu) to the original volume of sediment (V_0) before settling. It can be calculated by following equation.

$$F = V_u / V_0 \text{ ---------- (1)}$$

Where, V_u = final or ultimate volume of sediment
V_0 = original volume of suspension before settling.

g) Accelerated stability study

MNZ suspensions were packed in 60 ml glass bottle. The packed bottles were placed in stability chamber maintained at 40 + 2 °C and 75 + 5% RH for 3 month. Samples were collected at days 0, 5, 15, 30, 60 and 90. [14, 15] 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.

RESULTS AND DISCUSSION

Formulation M1 was prepared without resin, which may provide clear distinction between actual taste of drug before masking and taste after masking by making complex with various resins in different ratios. Formulation M2, M3 and M4 were prepared using kyron T-114 at different drug: polymer ration 1:1, 1:2 and 1:3 respectively. Prepared suspensions showed satisfactory physical properties. Drug loading for M2, M3 and M4 were 34.45, 44.41 and 42.78 % respectively [table 2]. Formulation M3 showed some level of acceptance but it was not sufficient to prepare pediatric formulation. Formulation M5, M6 and M7 were prepared using kyron T-134 at different drug: polymer ration 1:1, 1:2 and 1:3 respectively. Prepared suspensions showed satisfactory physical properties. All showed superior drug loading [table 2]. Taste evaluation by panel method showed palatable taste in M6 and M7 [table 3]. Formulation M7, M8 and M9 were prepared using Indion 234 at different drug: polymer ration 1:1, 1:2 and 1:3 respectively. Drug loading were very less compare to other resins at same condition. Panel method indicates insufficient taste masking of MNZ by using Indion 234 [table 3].

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.[16] 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 MNZ was seen onto Kyron T-114, Kyron T-134 and Indion 234 (data not shown). Effect of drug:resin ratio on % drug content per gram of resinate are shown in [table 2]. Results shows that using kyron T-114 and kyron T-134 maximum drug loading were observed at 1:2 drug-rasin ratio. 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[17, 18]. When the resin is highly crosslinked, fewer functional groups are available inside the particle, resulting in low ion-exchange capacity.

Dissolution profile of optimized formulation M6

In vitro release 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 M6 formulation. In general, strong acid type resins showed greater sustained release than weak acid type resins in *in vitro* dissolution tests [19]. Some drug molecules released accumulated around the surface of the resinates to form an aqueous boundary layer. Stirring can be introduced to 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 M6 is shown in [Table 4]. Study revealed that prepared formulation can be remain intact for a long period of time without major changes in assay, viscosity and sedimentation volume[20]. It was found that formulation was remained palatable without any appearance of microbial growth in agar plates.

Table 1: Formulation of MNZ suspension with different resins

Ingredients	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Complex preparation										
MNZ (mg)	200	200	200	200	200	200	200	200	200	200
Kyron T 114	-	200	400	600	-	-	-	-	-	-
Kyron T 134	-	-	-	-	200	400	600	-	-	-
Indion 234	-	-	-	-	-	-	-	200	400	600
Purified water (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Syrup preparation										
Sucrose (gm)	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
Glycerine (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 (ml)	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.13
Quinoline yellow color (mg)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Purified water uo to (ml)	5	5	5	5	5	5	5	5	5	5

(200 mg metronidazole = 321.6 mg metronidazole benzoate)

Table 2: Evaluation parameter of MNZ suspension with different resins

Parameters	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Drug loading of dry resinates (%)	-	34.45	44.41	42.78	39.42	47.65	44.86	39.56	41.37	38.47
Color	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow
Viscosity (mPa s)	258.4	282.3	312.7	342.5	301.8	319.3	322.4	278.4	309.9	312.4
pH	8	8	8.1	7.9	7.8	8	7.9	8	8	7.9
Sedimentation volume (F)	0.98	0.98	0.95	0.98	0.97	0.98	0.98	0.98	0.95	0.97
Redispersibility	+++	+++	++	+++	+++	++	++	+++	+++	+++
Assay %	101.3	99.41	98.49	97.17	98.28	99.83	98.38	99.55	98.93	99.27

Table 3: Evaluation of taste of suspension

Formulations	Volunteers									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
M1	3	4	4	4	3	4	4	4	3	3
M2	2	3	3	2	3	2	3	3	2	2
M3	1	0	0	0	0	1	0	0	1	0
M4	0	1	0	1	1	0	0	0	0	1
M5	2	3	3	2	3	2	3	3	2	2
M6	0	0	1	0	0	1	0	0	0	0
M7	0	1	2	0	1	1	1	0	2	0
M8	2	3	3	2	3	2	3	3	2	2
M9	2	2	2	3	2	2	3	2	2	3
M10	2	1	0	2	3	1	3	2	3	2

0=Palatable, 1= Normal, 2=Slightly bitter, 3=bitter, 4= Extremely bitter

Table 4: Accelerated stability study

Parameters	Time periods initial (0 Day)	1 month	2 month	3 month
Assay %	99.83 %	99.7 %	99.56%	99.4%
Viscosity (mPa s)	319.3	315.29	317.7	313.23
Ph	8	7.9	7.9	7.9
Sedimentation volume	0.98	0.98	0.97	0.97
Redispersibility	+++	+++	+++	+++
Taste	Palatable	Palatable	Palatable	Palatable

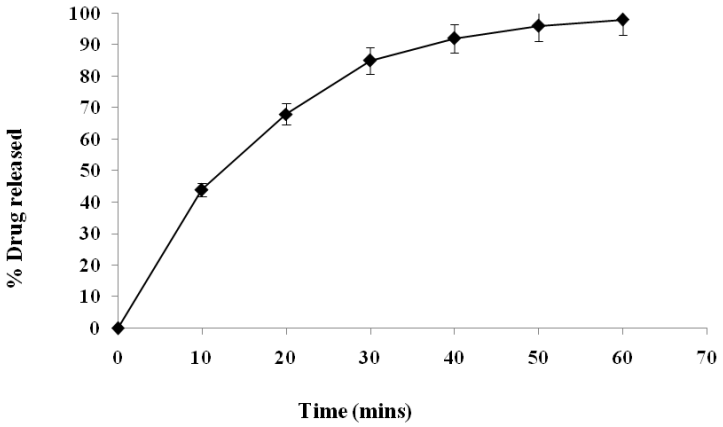

Fig. 1: *In-vitro* dissolution profile of M6

CONCLUSION

Many parents are faced with the daily challenge of getting their children to take a medicine. The unpleasant flavor of the medicine can thwart the benefits of even the most powerful drug, and failure to consume medication may do the child harm, and in some cases, may be life-threatening. Use of weak cation exchange resin offers superior method for preaparing taste-masked substrates of MNZ. Results obtained in this work shows that drug-resin complexes effectively masked bitter taste of MNZ. While liquid formulation provide easier way to administer and getting the child to swallow. Better understanding of the scientific basis for distaste, and how to ameliorate it, is a public health priority for advancing availability of formulations of drug products that will be accepted by children.

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