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Research Article

SUSPENSION OF ISONIAZID FORMULATED USING CATIONIC RESIN FOR PEDIATRIC USE

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ABSTRACT

The purpose of this research was to develop and evaluate pediatric formulation by masking the bitter taste of Isoniazid.Non-compliance of therapy of tuberculosis which is mostly associated with bitter taste can lead to worsening of diseased condition in children. Cationic resin utilized to mask the bitter taste of Isoniazidby preparing resinate complex. Syrup preparation evaluated for drug content, *in vitro* drug release, viscosity, taste masking, Infra red spectroscopic studyand stability study. Ion exchange resin method using KYRON T-134 proved as a alternative method to prepare suitable pediatric formulation.

Keywords: Isoniazid, Taste masking, Ion-exchange resin, Pediatrics.

INTRODUCTION

It has been estimated by the World Health Organisation (WHO) that worldwide there are 490,000 cases of active Tuberculosis (TB) and sickness in children, and 64,000 deaths of children from TB each year [1]. The risk of progression to TB disease is greatest when the child is less than four years old, and to a lesser extent when they are less than ten years old[2]. Challenges for National Tuberculosis Programs (NTPs); diagnosing TB in children is difficult as children are less likely to have obvious symptoms of TB, and samples such as sputum are more difficult to collect from young children[3,4]. Even when sputum can be collected, it may have very few TB bacteria in it (paucibacillary smear-negative disease) [5].

Report of National Institute of Child Health and FDA Pediatric Advisory Committee meeting held on January 31, 2012 at Gaithersburg, MD declared a list of drugs which are lacking a pediatric formulation that include Isoniazid (INZ)[[6]].INZ is an antimycobacterial agent widely used in first-line therapy for tuberculosis which is bitter in nature. The drug is characterized by a short half-life ranging from 1-4 h, depending on the rate of metabolism [7]. Long-term continuous therapy with INH leads to hepatotoxicity and peripheral neuritis therefore pyrodoxine should be given concurrently.

Because of bitter or unpleasant taste of medicament children are frequently failed to take medications properly. Non-compliance can lead to worsening of diseased condition. Number of taste masking technologies have been used to address the problem of patient compliance [8]. 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 [9,10].

Ion exchange resin (IER) approach utilize weak cation exchange or weak anion exchange resins for taste masking, depending on the nature of drug. Drug-resin complex formed is such that the pH of saliva which is 6.8 and cation concentration of about 40meq/L in the saliva are not able to break the drug resin complex therefore it is absolutely tasteless with no after taste[11]. At the same time the complex is weak enough to break down by hydrochloric acid present in the stomach thus its bioavailability is not affected [12].

MATERIALS AND METHODS

Materials

INZ, Sorbitol solution, citric acid and potassium sorbate were obtained from PAR LABORATORIES (Gozaria, India). Kyron T-134 was obtained as gift sample from Corel PharmaChem, (Ahmedabad, India). All the others reagents were of analytical grade.

Methodology

Purification of ion exchange resin

Resins were purified using the method reported by Irwin [13]. The resins 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 (resinates)

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 INZ in to step 1 & stir it for 4 to 5 hr. continuously under stirrer. Step 3: Filter out prepared resinate and dry at atmospheric air [14,15].

Syrup preparation of resinates

Step 1: Add specified amount of sorbitol solution 70% into separate baker and stirred continuously under mechanical stirrer. Step 2: Add Citric acid monohydrate and potassium sorbate gradually into soritol solution with continuous stirring until dissolved completely. Step 3: Now add specified amount of prepared resinates gradually into solution prepared above with contineous stirring until uniform dispersion achieved.

Characteristics of INZ formulation

Molecular dispersion study using DSC

DSC scans of powdered samples of all ingredients individually and of melt granules were recorded using DSC- Shimadzu 60 with TDA trend line software[16,17]. All samples were weighed (8-10 mg) and heated at a scanning rate of 20°C/min under dry air flow (100 ml/min) between 50 and 300° C. Aluminum pans and lids were used for all samples.

Determination of pH

The pH value conventionally represents the acidity or alkalinity of an aqueous solution. The pH value of a solution was determined potentiometrically by means of glass electrode. A digital pH meter was allowed to stabilize. Then the pH meter was standardized using buffer tablets. The suspension formulation was placed in the pH meter [18]. The reading was noted when there is no fluctuation in the pH meter.

Determination of Viscosity using Brook Field Viscometer

The Viscometer was allowed to stabilize and zero error was checked. Then viscosity of the suspension was determined using LV model

spindle 3 at 60 rpm at 25°C. The viscosity calculations were made based on the correction factor values given by manufacturer in the table for various mobles and spindles.

Drug content

Transfer accurately a quantity of formulation equivalent to 100 mg Isoniazid to a 500-mL volumetric flask with the aid of 200 mL of water. Shake by mechanical means for 30 minutes, add water to volume, and mix. Filter, and discard the first 20 mL of the filtrate [19,20]. Dilute a portion of the filtrate quantitatively and stepwise, if necessary, with a 3 in 100 mixture of 0.1 N hydrochloric acid and water to obtain a solution containing about 10 µg per mL. Determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 263 nm, with a suitable spectrophotometer, using water as the blank.

Determination of 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 [21].

$F = V_u / V_O$ ---------- (1)

Where, V_u = final or ultimate volume of sediment

V_O = original volume of suspension before settling.

In-vitro release of suspension

Suspension equivalent to 100 mg of the INZ were added to the 500 ml dissolution medium 1: 0.1 N Hydrochloric acid and medium 2: 6.8 pH phosphate buffer. Stirred at 50 rpm using paddle apparatus at 37°C ±0.5°C [22]. Withdraw 10 ml sample from dissolution media at every 10 mins time interval until drug dissolved completely. Filtered it (0.22 µm) and finally dilute and analyzed using UV spectrophotometer.

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 [13]. About 5 ml suspension containing 100 mg of drug was placed on tongue and taste evaluated after 15 s.

Fourier-transform infrared spectroscopic study (FTIR)

Infrared spectra of DRC, drug, and physical dispersion (optimized ratio) thereof were obtained using Fourier-transform infrared (FTIR) spectroscopy (Jasco V5300, Tokyo, Japan)[[24]]. 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 (Figure 3).

Accelerated Stability Study

INZ suspension 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, 30, 60 and 90[[25]]. The analyses comprised chemical testing of quantifiable parameters, which could possibly change during storage, such as viscosity, pH, drug contents, sedimentation volume.

RESULT AND DISCUSSION

Formulation have pH around 5.6 and viscosity observed 116 centipoises which complies with requirements. Drug content was found near to 100 % and sedimentation volume ratio found near to 1 which proved good dispensability of syrup which was due to the optimum viscosity of syrup (table 2).

The taste of suspension was evaluated by panel method and result showed in table 3.The study protocol was explained and written consent were obtained from volunteers. For this purpose, 10 human volunteers were selected. About 5 ml suspension containing 100mg of drug was placed on tongue and taste evaluated after 15 s. Compilation of taste revealed that when they are asked for taste of formulation containing same excipients without resinate formation revealed that 6 out of 10 volunteers went with extremely bitter taste while remaining volunteer indicated bitter or unpleasant taste. When volunteers asked for formulation masked with ion exchange resin they agreed that formulation have successfully masked the bitter taste and now they found palatable taste.

In vitro dissolution of suspension equivalent to 100 mg of the INZ was carried out in two different media 0.1 N Hydrochloric acid and 6.8 pH phosphate buffer, 500 ml at 37°C ±0.5°C using paddle apparatus at 50 rpm. In 0.1N HCl more than 80% drug was released at initial time point of 10 mins which confirm the replacement of drug molecule from resinate by H^+ ion (Figure 1). While dissolution in 6.8 pH phosphate buffer showed no released upto 10 mins, which also reveal that drug would not be released in mouth (6.8 pH) when taken it orally and thus it avoid bitter taste of drug (figure 2).

The DSC study confirms the complexation of INZ with kyron T-134. FTIR study signifies that during DRC formation there was interaction of the amino group of drug with the carboxylic group of kyron (figure 3).

The infrared spectra of Kyron T-134, Isoniazide and Isoniazide-Kyron T-134 complex are depicted in Figure 4. Drug spectrum shows a prominent peaks at 3500 - 3300 nm 3375.2 cm−1 corresponding to the NH stretching in a primary amine and secondary amine. Kyron T-134 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. Figure 6 shows peaks corresponding to –COOH dimerization 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. Numbers of overtone peaks were observed at 2308 and 2347 cm−1. The absence of peak at 3375 cm−1 in DRC confirms the complexation of the 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. IR study thus revealed that the interaction of the amino group of drug which is responsible for bitter taste, with the carboxylic group of Kyron T-134 convert into effective masking of bitter taste of drug.

Result of accelerated stability study for 3 month is depicted in table 4. Study was conducted on taste masked syrup formulation showed that all the parameters i.e drug content, sedimentation volume ratio, pH and viscosity were remained unchanged which indicate adequate stability of formulation.

Table 1: Formulation of suspension

S. No.	Ingredients	Concentration in 5 ml
1	Isoniazid USP	100 mg
2	Sorbitol solution 70% USP	4.9 ml
3	Citric acid monohydrate USP	50 mg
4	Potassium sorbate USP	5 mg
5	Kyron T-134	200 mg

Table 2: Result of pH, viscosity, drug content and sedimentation volume

S. No.	Parameters	PD2
1	PH	5.6 ± 0.2
2	Viscosity (Centipoises)	116 ± 2
3	Drug content %	99.92 ± 0.4
4	Sedimentation volume	0.98 ± 0.05

**n=3*

Table 3: Result of taste of suspension

Volunteers	Drug-Resin complex formulation	Formulation without resin
1	D	A
2	D	B
3	C	A
4	D	A
5	D	A
6	D	A
7	D	A
8	D	A
9	D	B
10	D	A

A: Very bitter, B: Bitter, C: Tasteless, D: Palatable/Sweet

Table 4: Accelerated stability study result

Parameters	Initial	1 Month	2 Month	3 Month
Drug Content	99.91	99.88	99.81	99.85
Sedimentation volume	0.97	0.96	0.96	0.96
pH	5.6	5.6	5.6	5.6
Viscosity (Centipoises)	116	113	113	112

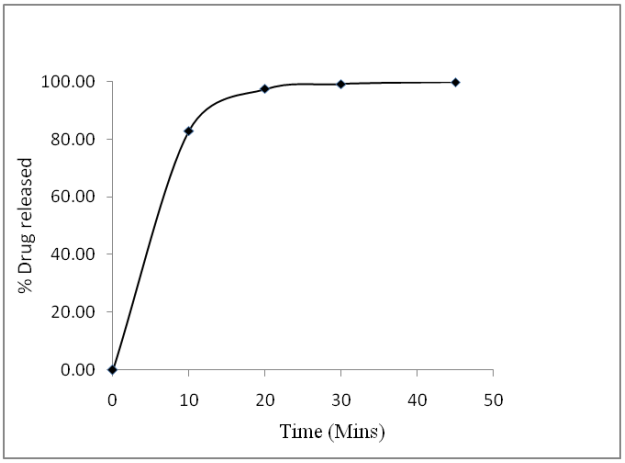

Fig. 1: %Drug released in 0.1N HCl

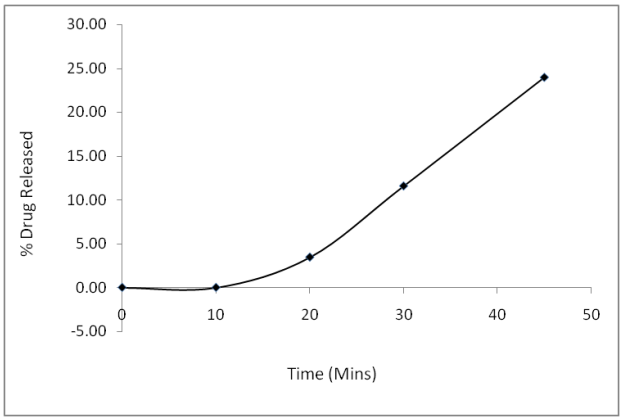

Fig. 2: % Drug released in 6.8 pH phosphate buffer

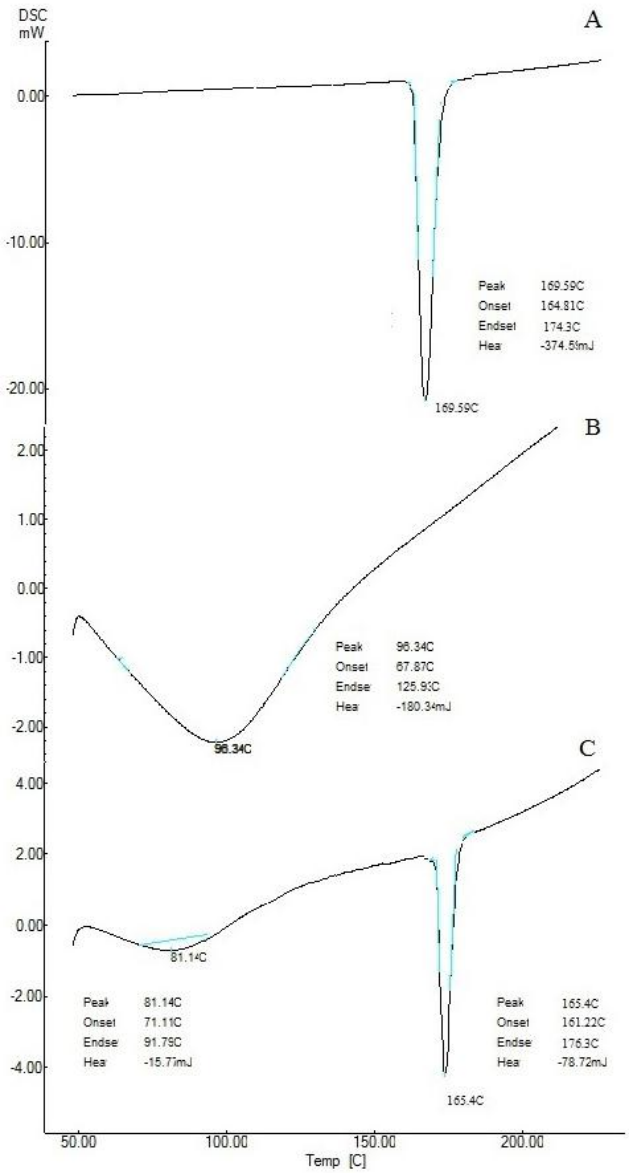

Fig. 3: DSC of A (INZ), B (KYRON T-134), and C (INZ-KYRON T-134)

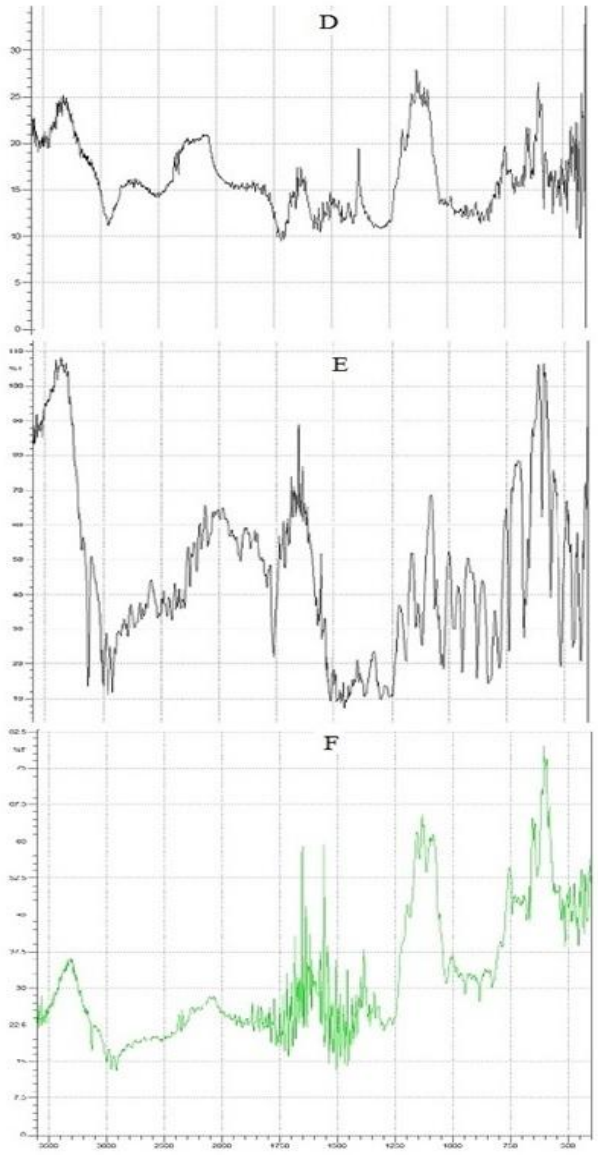

Fig. 4: IR data of D (KYRON T-134), E (INZ) and F (KYRON T-134-INZ)

DISCUSSION

The high affinity of resins for 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]. Experimental study disclosed that among the different resin utilized to prepare complex with INZ, KYRON T-134 showed greater potential in terms of drug entrapment efficiency. Optimized syrup formulation of INZ-KYRON T-134 (1:2) including sorbitol solution 70%, citric acid and potassium sorbate. Formulation was evaluated by DSC study, pH, Viscosity, sedimentation volume, particle size, taste determination, in-vitro release and FTIR study. DSC study, FTIR and taste evaluation by panel method confirm the taste masking of INZ by ion exchange resin. In vitro released studies revealed negligible release at 6.8 pH which is essential for masking. Accelerated stability studies conducted confirms god stability of syrup formulation. Results obtained in this work shows that drug-resin complexes effectively masked bitter taste of highly bitter drug. 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, this “patient-friendly dosage form” of bitter drug INZ would be very useful especially for pediatric, geriatric, bedridden, and non cooperative patients.

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