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 pyridoxine should be given concomitantly.

Because of bitter or unpleasant taste of medicament children are frequently failed to take medications properly. Non-compliance can lead to worsening of disease 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 oral liquid suspensions [9,10].

Ion exchange resins (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 40 meq/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 (Goa, India). Kyron T-134 was obtained as gift sample from Corel PharmaChem (Ahmedabad, India). All the others reagents were of analytical grade.

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 disease condition in children. Cation resin utilized to mask the bitter taste of Isoniazid by preparing resinate complex. Syrup preparation evaluated for drug content, in vitro drug release, viscosity, taste masking, Infrared spectroscopic study and stability study. Ion exchange resin method using KYRON T-134 proved as an alternative method to prepare suitable pediatric formulation.

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

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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 (V0) to the original volume of sediment (Vo) before settling. It can be calculated by following equation [21].

\[ F = \frac{V_o}{V_f} \]

Where, \( V_o \) = final or ultimate volume of sediment
\( V_f \) = 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. 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 diluted 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 100 mg 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 release up to 10 mins, which also reveal that drug would not be released in mouth (6.8 pH) when it taken 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 3: Result of taste of suspension

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>Drug-Resin complex formulation</th>
<th>Formulation without resin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>D</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>D</td>
<td>A</td>
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<td>D</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>D</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>D</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>D</td>
<td>A</td>
</tr>
</tbody>
</table>

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

Table 4: Accelerated stability study result

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Initial</th>
<th>1 Month</th>
<th>2 Month</th>
<th>3 Month</th>
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</thead>
<tbody>
<tr>
<td>Drug Content</td>
<td>99.91</td>
<td>99.88</td>
<td>99.81</td>
<td>99.85</td>
</tr>
<tr>
<td>Sedimentation volume</td>
<td>0.97</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>pH</td>
<td>5.6</td>
<td>5.6</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Viscosity (Centipoises)</td>
<td>116</td>
<td>113</td>
<td>113</td>
<td>112</td>
</tr>
</tbody>
</table>

Fig. 1: % Drug released in 0.1N HCl

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