Effect of two different superdisintegrants on combination dispersible tablets of isoniazid and rifampicin for oral treatment of tuberculosis

Vikesh Shukla¹*, F.V. Manvi¹

Abstract
Oral route of administration have wide acceptance up to 50-60% to total drug forms. Fast disintegrating drug delivery system has number of advantage such as faster onset of action, attractive elegance, ease of administration. In this study, an attempt has been made to study direct compression method, for formulation of fast disintegrating tablets of Isoniazid and Rifampicin, an anti-tubercular drug in view of enhancing bioavailability. These formulations have sufficient hardness and can be manufactured by commonly used equipment. Prior to formulation the pre-compression parameters were characterized for flow properties and prepared formulations were evaluated for physico-chemical parameters, X-ray powder crystallography, SEM and in-vivo bioavailability. All four formulations possessed good disintegration properties with total disintegration time of 25 to 40 seconds. The effects of different superdisintegrants and process variables on drug release profile and disintegration property were evaluated and results revealed the better drug release with different superdisintegrants such as Ac-di sol and Polyplastadone XL. All formulations are rapidly disintegrated in oral cavity as well as all formulations possess good anti-tubercular properties. SEM Showed the mechanical strength of the formulations affected the morphological changes after compression. Hence, it is evident from this study that fast dispersible tablets could be a promising delivery system for Isoniazid, Rifampicin and their combination with good mouth feel and improved drug availability with better patient compliance.

Keywords: Isoniazid; Rifampicin; Superdisintegrants; Direct compression method; Bioavailability.

Introduction
Oral administration is the most popular route among all the routes to ease ingestion, pain avoidance, versatility (to accommodate various types of drug candidates) and most importantly patient compliance [1]. Dispersible tablets are uncoated tablets that produce uniform dispersion in water. The rate of absorption of a drug from a tablet depends upon its ability to disintegrate quickly and dissolve. Dispersible tablets have found wide acceptance today replace conventional suspension and dry syrup dosage form [2]. Recently pharmaceutical industry has become increasingly aware of the need that elderly be considered as a separate and unique medicare population. Thus, oral dispersible tablets are gaining more demand and popularity from last few years [3]. Isoniazid is chemically 4-Pyridinecarboxylic acid

Corresponding author:
Vikesh Shukla
KLES College of Pharmacy, JNMC Campus, Belgaum
590010, India
Tel: +91 9368054741
Email: vikeshg2002@gmail.com
hydrazine, and the usual daily dose is 300 gm daily. Isoniazid is used in the treatment of primary treatment of pulmonary and extra pulmonary tuberculosis. Rifampicin is chemically \((12Z,14E,24E)-(2S,16S,17S,18R,20R,21S,22R,23S)-1,2\text{ dihydro-5.6.9, 17, 19- heptamethyl-8-(4-methyl-peprazine-1-ylinomethyl)-1,11,13-triemo}neptho[2,1-b] furan 21-yl acetate and the usual daily dose is 4500 gm daily. IsoRifampicin is used in the treatment of primary treatment of pulmonary and extra pulmonary tuberculosis. Ac-di-sol is basically cross linked sodium carboxymethyl cellulose and this is used in oral pharmaceutical formulations as a disintegrant for capsules, tablet and granules. Polyplasdone XL is chemically 2-pyrroolidinone, 1-ethyl-homopolymer1-vinyl-2-pyrroolidinone-polymer and pharmaceutically this is used as superdisintegrant, tablet binder, sweetening agent and pharmaceutical excipients. Explotab is chemically starch carboxymethyl ether, sodium salt and this is used as a disintegrant in tablet/capsule formulation [4-6].

Tuberculosis is an infectious disease caused by several species of mycobecteria. M. Tuberculosis is a slender, or slightly curved bacillus, ranging from 1-4 \(\mu m\) length, they are acid-fast bacilli. Oral tuberculosis lesions may be either primary or secondary. Primary oral tuberculosis lesions are extremely rare and generally occur in younger patients associated with cervical lymphadenopathy. The primary lesion remains painless in the majority of cases. The secondary lesions, on the contrary, are more common and are seen mostly in older persons. The lesions are seen as superficial ulcers, patches indurated soft tissue lesions, or even lesions in the jaws that may be in the form of tuberculous osteomyelitis, or simple bony radiolucencies. Of all these oral lesions, the ulcerative form is the most common and is often painful with no associated caseation of the dependent lymph nodes [7-10].

An attempt has been made, in the present work, to develop dispersible tablet of Rifampicin by direct compression method, using a bland of disintegrants such as crosscarmellose sodium (Ac-di-sol) and Polyplasdone XL. The objectives of the study were to investigate the performance of superdisintegrants and effect of other process variables on the characteristics of the Isoniazid and Rifampicin dispersible formulations.

Isoniazid and Rifampicin were procured from Macload Pharmaceuticals Ltd, Mumbai, India. Polyplasdone XL ware procured from Sun Pharmaceuticals Ltd, Baroda, Gujarat, India. Crosscarmellose sodium (Ac-di-sol) sample was obtained from FMC Biopolymer, USA and Explotab (SSG) sample was procured from Forum Biosciences, England (U.K.). All other Chemicals and solvents were of analytical grade and purchased from local market in India.

**Preparation of combination dispersible formulations [11,12]**

Different Isoniazid and Rifampicin combination dispersible formulations were prepared by direct compression technique according to the formula given in table 1.

**Table 1. Composition of INH and Rifampicin combination dispersible formulations.**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Avicel pH102</td>
<td>108</td>
<td>108</td>
</tr>
<tr>
<td>Ac-di-sol</td>
<td>17.5</td>
<td>--</td>
</tr>
<tr>
<td>Polyplasdone XL</td>
<td>--</td>
<td>17.5</td>
</tr>
<tr>
<td>Mannitol</td>
<td>17.5</td>
<td>17.5</td>
</tr>
<tr>
<td>Sodium Saccharine</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Flavor</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Blank space indicate that those components not present in the formulations.

The concentration of disintegrants was developed as optimal concentration under experimental formula and conditions of preparation. A total of 6 formulations were prepared. All the ingredients were passed through 60 mesh sieve separately and collected. The drug and Avicel pH 101 were mixed in a small portion of both and each time blended to get a uniform mixture in a geometrical order. The tablets were then compressed using 10 mm size punches to get a tablet of 100 mg Rifampicin and 100 mg Isoniazid using hydraulic press with suitable standard
punches and stored in a well-closed container till use. In the first set 2 batches of Isoniazid and Rifampicin fast dispersible tablets were prepared using different concentration of sodium starch glycolate and other super disintegrants.

**Evaluation parameters of combination dispersible formulations**

**a) Pre-compression parameters [13]**

**i) Bulk density:** Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of sample (20 gm) was transferred into a 25 ml measuring cylinder. The volume of packing was recorded. The measuring cylinder was then tapped 100 times on a plane hard wooden surface and the tapped volume of packing was recorded. LBD and TBD were calculated by the following formula:

\[
\text{LBD (Loose bulk density)} = \frac{\text{Weight of granules}}{\text{Volume of packing}}
\]

\[
\text{TBD (Tapped bulk density)} = \frac{\text{Weight of granules}}{\text{Tapped volume of packing}}
\]

**ii) Compressibility index:** Percent compressibility of granules as determined by Carr’s compressibility index was calculated by the following formula:

\[
\text{Carr’s Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100
\]

**iii) Angle of repose (θ):** The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

\[
\text{Tan} \theta = \frac{h}{r}
\]

\[
\theta = \tan^{-1} \left( \frac{h}{r} \right)
\]

Where \( \theta \) = Angle of repose, \( h \) = height, \( r \) = radius

Values of angle of repose \( \leq 30^\circ \) indicate free flowing granules and \( \geq 40^\circ \) suggest poorly flowing material.

**b) Post-compression parameters [14-17]:**

**i) Thickness and diameter:** The tablet dimensions were measured using a calibrated dial caliper. 5 tablets of each batch were picked randomly and its thickness and hardness were measured individually. Tablet thickness should be controlled within \( \pm 5 \% \) variation of a standard value.

**Table 2. Pre-compression parameters: characterization of formulation powder**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Angle of Repose (θ)</th>
<th>Loose Bulk Density (gm/cm³)</th>
<th>Tapped Bulk Density (gm/cm³)</th>
<th>% Compressibility</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>29.32</td>
<td>0.57</td>
<td>0.68</td>
<td>16.17</td>
<td>Reddish white</td>
</tr>
<tr>
<td>F2</td>
<td>27.01</td>
<td>0.55</td>
<td>0.64</td>
<td>14.06</td>
<td>Reddish white</td>
</tr>
</tbody>
</table>

**ii) Weight Variation:** The procedure described in IP 1996 was employed to determine the weight variation of the tablets. Ten tablets were randomly selected from each batch and weighed on a electronic balance and the mean weight taken. Each tablet was then weighed individually and the standard deviation in weight was calculated for each batch.

**iii) Hardness:** Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm². Five tablets were randomly picked from each batch and the hardness of the tablets was determined. The mean and standard deviation values were calculated for each batch.

**iv) Friability:** Friability of the tablets were determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_initial) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions, and then the tablets were weighed again (W_final). The loss in tablet weight due to abrasion or fracture was the measure of tablet friability.

% Friability was then calculated by:

\[
F = \frac{W(\text{initial}) - W(\text{final})}{W(\text{initial})} \times 100
\]

% Friability of less than 1% is considered acceptable.
Table 3. Post-compression parameters: evaluation of tablets.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Uniformity of Thickness* (mm)</th>
<th>Hardness* (kg/cm²)</th>
<th>Weight** (mg)</th>
<th>Drug Content Uniformity* (mg)</th>
<th>Friability (%)</th>
<th>Test of dispersion</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>2.278±0.0647</td>
<td>4.63±0.13</td>
<td>361±2.36</td>
<td>97.27±0.47</td>
<td>0.67</td>
<td>Passed</td>
</tr>
<tr>
<td>F2</td>
<td>2.238±0.098</td>
<td>4.48±0.04</td>
<td>361±2.86</td>
<td>99.06±0.21</td>
<td>0.65</td>
<td>Passed</td>
</tr>
</tbody>
</table>

*vTests performed, n=3,**Tests performed, n=10

v) Disintegration test: - Introduced one tablet in to each tube. The disc was added to each tube. The assembly was suspended in Beaker containing buffer and operated the apparatus for 3 min. Water is used as medium at temperature of 26°C.

Table 4. Post-compression parameters: wetting time, water absorption ratio (mean±SD, n=3).

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Wetting Time (Seconds)</th>
<th>Water Absorption Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>224.76 ± 1.48</td>
<td>25.14 ± 1.76</td>
</tr>
<tr>
<td>F2</td>
<td>224.58 ± 1.67</td>
<td>24.98 ± 1/54</td>
</tr>
</tbody>
</table>

vi) Uniformity of dispersion: - this test is applicable only for dispersible tablets. Placed 1 tablet in 100 ml of water and stirred gently until completely dispersed. A smooth dispersion was obtained which passes through a sieve screen with a nominal mesh aperture of 710 μm (Sieve no. 22).

viii) Scanning electron microscopy [21]: SEM has been used to determine particle size distribution, surface topography, texture and to examine the morphology of fractured or sectioned surfaces. The SEM is most commonly used for generating three dimensional surface relief images derived from secondary electrons. The examination of the surface of polymeric drug delivery systems can provide important information about the porosity and microstructure of the device.

Table 5. Post-compression parameters: in vitro dispersion time, dissolution report.

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Disintegration Time (Second)</th>
<th>Dispersion Time (Second)</th>
<th>% Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>27.52 ± 1.72</td>
<td>146.76 ± 1.0</td>
<td>INH-99.99</td>
</tr>
<tr>
<td>F2</td>
<td>28.43 ± 1.14</td>
<td>172.16 ± 0.86</td>
<td>INH-96.72</td>
</tr>
</tbody>
</table>

ix) Powder X-ray diffraction [22,23]: The powder X-ray diffraction measurement were conducted over a 5-40° 2Ө range on a Siemans model D5000 diffractometer, equipped with monochromatic CuKa (α1=1.54060 A, α2=1.54438A) X-ray. The step width was 0.020° 2Ө/min with a time constant of 0-5 sec. the integration of the crystalline reflections was achieved using the Diffrac™ plus diffraction software (Eva, version 2.0, Siemans Energy and automation, Inc. Madison, WI). The degree of crystallinity of samples was expressed as the percentage ratio of the integrated intensity of the sample to that of hydrocellulose, a crystalline standard prepared from cellulose by treating with 2.5 N HCl at boiling temperature.
Stability study [24,25]: The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions and shelf-lives to be established. ICH specifies the length of study and storage conditions:-
Long term testing $25^\circ\mathrm{C} \pm 2^\circ\mathrm{C}$/$60\%\,\mathrm{RH} \pm 5\%$ for 12 months,
Accelerated testing $40^\circ\mathrm{C} \pm 2^\circ\mathrm{C}$/$75\%\,\mathrm{RH} \pm 5\%$ for 6 months.

Biodistribution study [26-28]: Isoniazid and Rifampicin combination tablets

In vivo studies were conducted using albino rats (Wister Rats) and the plasma concentration time profile of Isoniazid and Rifampicin combination was determined using UV spectrophotometry. In this study, Isoniazid and Rifampicin combination dispersible tablets administered orally to rats and every 30 minute drug concentration were determined in serum. The method used for determination is as follows:

Extraction procedure for Isoniazid

Albino Rats (Wister Rats) were divided in 7 groups. One group was kept as a control. 6 groups of animal were given Isoniazid dispersible tablet prepared in PBS. Drug solutions were administered through the oral route with the help of canula. The blood samples were collected from retro-orbital eye plexus. All blood samples were centrifuged at 3000 rpm for 15 min. The supernatant (plasma) was deproteinized by adding acetonitrile (1 ml/ml of plasma). The samples were again centrifuged and 2 ml of these supernatant was diluted to 10 ml with PBS pH 7.4. Then 1 ml of this diluted blood serum was then made up to the mark (10 ml) with PBS, then analyzed spectrophotometrically at 266 nm for drug content against a similarly treated blood sample of control rats after proper dilution. The observations are recorded and drug content in the plasma was determined.

Extraction procedure for Rifampicin

Albino Rats (Wister Rats) were divided in 7 groups. One group was kept as a control. 6 groups of animal were given Rifampicin dispersible tablet prepared in PBS. Drug solutions were administered through the oral route with the help of canula. The blood samples were collected from retro-orbital eye plexus. A 0.5 ml aliquot of sample (plasma sample) was added 2 ml of 0.5M sodium dihydrogen phosphate. The mixture was shaken mechanically with 7 ml of chloroform for 10 min. after centrifugation at 3000 rpm for 15 min, the upper aqueous phase was aspirated off using syringe and 5 ml of the lower organic phase were taken to dryness at 40 °C under reduced pressure. The residue was dissolved in 0.5 ml of the mobile phase and Rifampicin level was determined using UV spectrophotometry at 340 nm. Both drugs are extracted separately and analyzed as per above described methods separately.

Table 7. In vivo bioavailability studies of isoniazid from combination formulation (f-1) and free drug in blood.

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>Isoniazid dispersible tablet</th>
<th>Pure Isoniazid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug content (mg)</td>
<td>% Drug content</td>
</tr>
<tr>
<td>1</td>
<td>0.52</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>0.48</td>
<td>18.46</td>
</tr>
<tr>
<td>3</td>
<td>0.51</td>
<td>19.61</td>
</tr>
<tr>
<td>4</td>
<td>0.49</td>
<td>18.84</td>
</tr>
<tr>
<td>5</td>
<td>0.50</td>
<td>19.2</td>
</tr>
<tr>
<td>Mean</td>
<td>-</td>
<td>19.22</td>
</tr>
<tr>
<td>t(SE)</td>
<td>0.3005</td>
<td>-</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Isoniazid DT was compared with pure Isoniazid group applying student ‘t’ test. Dose Injected Per Mice-2.6 mg
Results and discussion

The FTIR spectra of pure Isoniazid indicated the characteristic absorption stretch for Strong C=O Stretch band (Amide II) at 1560 cm\(^{-1}\) and broad bands between 3300 and 3000 cm\(^{-1}\) for bonded N-H and C-H, stretch are obtained. The fingerprint region FTIR spectra showed a characteristic sharp peak at 1670 and 1610, 1500 cm\(^{-1}\) for C=O, ring C=C and C=N. In comparison with the pure Isoniazid, the absorption peak of the spectra for Isoniazid in its formulations showed no shift and no disappearance of characteristic peaks suggest that there is no interaction between Isoniazid and other additives. No degradation of Isoniazid molecule was observed during its formulation development, hence the drug-excipient combinations used in the formulation development were compatible under given set of experiments (Figure 1).

Figure 1. FTIR study of the prepared rifampicin dispersible formulations (a) pure isoniazid (b) pure rifampicin (c) Formulation F-1 (d) Formulation F-2.
Similarly, the FTIR spectra of pure Rifampicin indicated the characteristic absorption stretch for C=O group at 1572 cm\(^{-1}\) and broad bands for N-H stretch was obtained between 2800 and 2300 cm\(^{-1}\). The fingerprint region of FTIR spectra showed a characteristic sharp peak at 1281 and 1040 cm\(^{-1}\) for C-O-C acetyl group. In comparison with the pure Rifampicin, the absorption peak of the spectra for Rifampicin in its formulations showed no shift and no disappearance of characteristic peaks suggest that there was no interaction between Rifampicin and other additives or no degradation in Rifampicin molecule during formulation development (Figure 1).

The result of angle of repose was found to be in the 29.32° and 27°.01'. Both formulations showed angle of repose within 30° which indicates good flow of powder mixture. Angle of repose little higher above 30° is indicative of fair flow behavior of powder. The loose bulk density and tapped bulk density for both formulations varied from 0.57 gm/cm\(^3\) to 0.55 gm/cm\(^3\) and 0.68 gm/cm\(^3\) to 0.64 gm/cm\(^3\) respectively. The values obtained lies within the acceptable range and not large differences found between loose bulk density and tapped bulk density. The percent compressibility for all the four formulations lies within the range of 16.17 and 14.06. All formulations showed good compressibility hence can be directly compressed (Table 2).

Table 3 depicts the physical parameters (hardness, weight variation, thickness, drug content and friability) and drug content of all fabricated tablets. Table 4 reflects the wetting time and uniformity of dispersion of these tablets. All the tablet formulation showed acceptable pharmaco-technical properties and complied with pharmacopoeial specification for weight variation, drug content (%), friability, disintegration and uniformity of dispersion (UOD). Hardness was maintained to be within 4.48 kg/cm\(^2\) to 4.63 kg/cm\(^2\). Since fast disintegrating tablets are less hard then conventional ones, due to a lower compression employed (Hardness is usually 3KPa.), these tablets can therefore be fragile and need individual packaging. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness. To obviate the difference in the hardness, superdisintegrants are added in the formulations. In fact, a fast disaggregating tablet must disintegrate in the saliva; harder tablets need a de-aggregating agent of a superior ability. In this case Ac-Di-sol, and polyplastadone XL were employed. Tablet disintegration was affected by the wicking and swelling of the disintegrant, and the wicking property would be closely related to the pososity. Both the porosity and average pore size of tablets in all formulation decreased with increase of the tablet hardness.

![Figure 2](image-url)
The wicking property may also correlate to the wetting behavior of the tablet. Rapid dispersion within seconds has been observed in all the formulations. On the basis of the de-aggregation time of the tablets, according to the EP IV Ed., almost all the formulations developed can be defined “Fast dispersible”: the limit for de-aggregation is in fact suggested as within 3 min. The direct compressed tablets consumes less wetting time and all formulation passes test for dispersion.

![Figure 3. Scanning electron microscope (SEM) study of the prepared dispersible formulations. (a) and (b) are of F-1 formulation; (c) and(d) are of F-2 formulation.](image)

The high ratio of water absorption was found in tablet containing disintegrants such as crosscarmmellose sodium (Ac-di-sol), Polyplasdone XL, which is due to hydrophilicity and swelling capacity. All formulated dispersible tablets gave faster and rapid dissolution of Rifampicin. The results are reported in table 5 and formulations follow zero order release kinetics. The graphs were plotted as time Vs percentage (Figure no.2) drug release for all the formulations. Among all, the tablet formulated by employing Explotab (SSG) disintegrated rapidly and gave faster dissolution of Isoniazis(INH) and Rifampicin (RIFA).

All formulations were subjected to Scanning Electron Microscopy (SEM) to examine the surface topography, texture of the formulations, morphology of fractured or sectioned surfaces, that can provide important information about the porosity of the device in the matrix of the formulations by subjecting the formulations to SEM in dry state at the different magnifications, X500, X1000 using a JEOL JSM-T330A. SEM images are shown in figure no.3. After examination the photographic results obtained from SEM, it was observed that formulation F2, contained particles of similar microscopic geometric which reflects the particles sizes of the parent potato starches of the range of 10-100 µm. Additionally, examination at higher magnification suggested that the surfaces of the particles contained small, micron size, features. However, in case of Ac-di-sol formulations (F1) no cracks were observed, suggesting that the formulations had good mechanical properties. The small increase in drug release may not necessarily be attributed to surface rupturing or creak formation.

The particles on the tablet surface were more compressed then those inside, there existed many empty spaces between the particles throughout the tablet where water could be absorbed by capillary forces. At higher magnification, a detailed distribution of pores can be observed. Upon contact with water or saliva, the particles could easily dissociate, and the whole tablet disintegrated to form a paste, which is easy to swallow. As the compression pressure increased, the pores become smaller. The porous structure of the tablet was especially hard to observe.

X-ray powder diffractometry (XRPD) is a powerful technique for the identification of the crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. The X-ray powder diffraction (XRD) spectra of Rifampicin showed characteristic
Characteristic peaks of Rifampicin were detectable in the formulations (F-1 to F4). It is very difficult to identify the presence of Avicel pH 102 or superdisintegrants in the XRPD spectra as they are polymers with amorphous structure and no sharp peaks are apparent at particular 2θ, due to the very low crystallinity of these components.

Figure 4. XRD study of the prepared rifampicin dispersible formulations (a) pure isoniazid (b) pure rifampicin (c) Formulation F-1 (d) Formulation F-2.
X-ray powder diffractometry spectra are shown in XRD Figure No.4. The anti-tubercular activity of the formulations is investigated in the Lawenstain-Jensen’s medium (L.J. medium). H37Rv strain is used for the anti-tubercular activity and formulations are evaluated in two concentrations i.e. 100 µl and 300 µl. The result indicates that all formulation active against the H37Rv strain, and possess the anti-tubercular activity.

Table 8. In vivo bioavailability studies of rifampicin from combination formulation (F-1) and free drug in blood.

<table>
<thead>
<tr>
<th>No. of animals</th>
<th>Rifampicin dispersible tablet</th>
<th>Pure rifampicin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug content (mg)</td>
<td>% Drug content</td>
</tr>
<tr>
<td>1</td>
<td>0.46</td>
<td>17.6</td>
</tr>
<tr>
<td>2</td>
<td>0.43</td>
<td>16.53</td>
</tr>
<tr>
<td>3</td>
<td>0.48</td>
<td>18.46</td>
</tr>
<tr>
<td>4</td>
<td>0.46</td>
<td>17.69</td>
</tr>
<tr>
<td>5</td>
<td>0.44</td>
<td>16.92</td>
</tr>
<tr>
<td>Mean</td>
<td>-</td>
<td>17.44</td>
</tr>
<tr>
<td>±SEM</td>
<td>-</td>
<td>0.5568</td>
</tr>
<tr>
<td>p value</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Rifampicin DT was compared with pure Isoniazid group applying student ‘t’ test. Dose injected per mice-2.6 mg.

The result of screening is tabulated in table 7. The formulations F1 was selected for stability studies on the basis of their high cumulative % drug release studies. The stability studies were carried out at 25°C/60% RH and 40°C/75% RH for all the selected formulations up to 6 months. For every 1 months time interval the tablets were analyzed for in vitro disintegration time. These formulations showed not much variation in any parameter. The accelerated stability study shows no degradation in all the tablet formulations during study. The combination formulation of Isoniazid and Rifampicin (F-1) was also studied for bioavailability in the blood. The average bioavailability of Isoniazid from combination dispersible tablets was found to be 19.22 % of the injected dose, whereas the concentration of pure Isoniazid was 14.82 % in the blood. Similarly, the average bioavailability of Rifampicin from combination dispersible tablets (F-5) was found to be 17.44 % of the injected dose in blood, whereas the concentration of pure Isoniazid was 13.37 % in the blood. Dispersible formulations were compared with pure Isoniazid, Rifampicin group applying Student ‘t’ test, the statistical results showed that the probability value was highly significant P<0.0001 (Table 8). These results reveal that dispersible formulations showed preferential drug bioavailability in the blood. It was also revealed that as compared to pure drug, higher concentration of drug was bio-available to the blood after administering the dose in form of dispersible formulations.

Thus, it can be concluded that dispersible table can be formulated by employing disintegration agents containing disintegrants such as crosscarmellose sodium (Ac-di-sol), and Polyplasdone XL. Further, Long term stability studies and in-vivo studies need to be carried out for establishing the existing products.

Acknowledgements
Authors wish to thank Macleod Pharmaceuticals Ltd, Mumbai, India for providing gift sample of Rifampicin and Principal, KLES’s College of Pharmacy, Belgaum, for providing all the necessary facilities required for the research work.

References


