Studies of Moisture Absorption and Development of Stable Ranitidine Hydrochloride Tablets

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ABSTRACT

In this study, an investigate effect of moisture absorption by ranitidine and resinates used to improve stability of ranitidine hydrochloride tablets. Moisture absorption by ranitidine at three different level of relative humidity (RH) has been studied. Percentage of moisture absorption at 22% was low as compared to 57% and 75% RH. To eliminate deliquescent tendency of drug, weak cation-exchange resins Indion 204, Indion 264 and Indion 254 were used in formulation as complexing agent. The drug loading process was optimized with respect to drug: resin ratio and pH of loading solution. The complexes were evaluated for bulk density, angle of repose, stability and in-vitro drug release. Optimum drug loading was at pH of 4.0 in drug: resin ratio of 1:1. In-vitro drug release studies showed more than 90% drug release from the optimized formulation within 30 min. X-Ray diffraction studies revealed ranitidine hydrochloride to be present in amorphous form in resinates. Tablets were prepared containing Indion 204: drug complex using different diluents. Tablets containing resinates and commercial products were exposed to 75%RH to observe their effect on moisture absorption. The type of dosage form also influenced moisture absorption. Uncoated tablets absorbed maximum amount of moisture, capsule intermediate while coated tablets absorbed minimum. Formulated tablets containing microcrystalline cellulose absorbed minimum amount of moisture as compared to formulations containing lactose and mannitol. Tablets containing resinates exhibited similar dissolution profile with commercial tablets. Indion 204 was found to be better complexing agent for reducing the hygroscopicity and to design stable ranitidine hydrochloride tablets.

Keywords: Ranitidine hydrochloride, % relative humidity (RH), moisture absorption, cation-exchange resin

INTRODUCTION

Moisture plays remarkable negative role in pharmaceutical product, particularly for solid dosage forms. Both physical and chemical stability of some drugs are affected by moisture. Moisture is absorbed on the surface of solid drugs and increases the rate of decomposition causes agglomeration and dissolution of drugs [1]. Presence of moisture possesses a critical challenge on drug stability. Moisture accelerates the hydrolysis of drug as well as facilitates reaction with other excipients, thereby affecting stability and shelf life of the final product [2]. Generally, the initial moisture level as well as the inherent tendency of the active ingredients and excipients to uptake water from the surrounding environment governs the moisture absorption pattern of the final product. The hygroscopic nature of excipients and active ingredients should be considered in designing the formulation. Water sorption or adsorption by drugs and excipients is not always reversible and absorbed moisture may not be easily removed during drying which directly affects the drug stability. Moisture can affect the way in which a system accepts aqueous granulating solutions. The moisture content and rate of moisture uptake are the functions of temperature and humidity. Moisture affects the tableting characteristics in granulation process.

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Ranitidine hydrochloride is extensively used as anti-ulcerant, gastroesophageal reflux disease and conditions where the stomach produces too much acid, such as Zollinger-Ellison syndrome. Over-the-counter ranitidine is used to prevent and treat symptoms of heartburn associated with acid indigestion and sour stomach. Ranitidine hydrochloride is an H₂ blocker which decreases the amount of acid produced in the stomach [3]. For a hygroscopic drug ranitidine, which absorbs moisture from the environment, its physical and chemical instability in the presence of moisture has a major impact on the choice of formulation excipients, the selection of processing method, and the design of the product package [4, 5]. Investigators have described moisture uptake rate of various commercial brands of ranitidine in the rate and extent of moisture absorption [6]. The development of a dosage forms containing a moisture sensitive drug is subject to those high temperatures and high humidity during the manufacturing process. Therefore, it is important that the formulation be composed of excipients that will help prevent the drug from decomposing. Stability of moisture sensitive drugs can be improved by enlisting different techniques. Since humidity in the air can be absorbed by the product, the manufacturing area can be humidity controlled to keep moisture at a low level. Protective packaging, such as foil-foil blisters can be used to prevent transmission of moisture through the package. These two methods are typically very expensive. The selection of ingredients within the dosage form can be optimized in order to reduce the
hygroscopicity and to reduce the activity of the water within the product. There have been attempts to address problem of hygroscopicity by salt formation, use of additives such as magnesium and calcium compounds for choline salicylate, cetyl alcohol and cetostearyl alcohol with becampicillin and use of pentahydrate of sodium pamidronate [7]. Also, exchange resins-drug complexation can be used to withstand higher humidity environments. Ion-exchange resins are solid and suitably high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. Ion-exchange resins have versatile properties as drug delivery vehicles and have been extensively studied in the development of novel drug delivery systems [8].

Ion-exchange resins i.e. Indion 204, Indion 264 and Indion 254 were chosen as a carrier to provide stability to the drug product. Recently found that resinates of deliquescent and highly hygroscopic drugs retain the properties of resin and are not deliquescent and remain free flowing powders. Manek and Kamat evaluated Indion CRP-244 and CRP-254 resins as sustained release and taste masking agents [9]. The aim of the present study was to investigate the effect of % relative humidity on moisture absorption by ranitidine and focus on one of the important application of ion-exchange resins by formation of drug-resin complex to develop stable tablet. The literature survey revealed that no work has been reported for stability using these ion-exchange resins.

**MATERIALS AND METHODS:**

Ranitidine hydrochloride was provided as a gift sample by J. B. chemical & pharmaceutical ltd. Mumbai, India. Indion 204, Indion 264 and Indion 254 were gifted by Ion-exchange (India) Ltd. Mumbai. All other reagents used were of analytical grade.

**Moisture uptake study by ranitidine at different relative humidity:**

A controlled humidity environment was produced using laboratory desiccators containing saturated solutions of various salts. Potassium acetate, sodium bromide, and sodium chloride were used to provide a RH of 22, 57 and 75%, respectively at 25°C. Percentage of RH was measured by a hygrometer. 1 gm ranitidine hydrochloride was taken in a glass petridish and spread uniformly in the petridish in a thin layer. The petridish was then placed in the 75% RH chamber to observe the moisture uptake. The weight increase due to moisture absorption was measured by taking weight at different intervals such as intervals of 10, 20, 30, 60, 90, 120, 150 and 180 min by an electronic balance (Metler, Switzerland). In the same way, 1 gm ranitidine hydrochloride was placed in each 57% RH and 22% RH chamber and amount of moisture absorbed determined [4, 10].

**Moisture content determination of resins:**

Accurately weighed 1g resin samples were kept in oven (previously heated to 100°C) for 24 hours and weighed. The difference in the weight before and after drying gave moisture content [11].

**Preparation of drug-resin complexes (Resinates):**

The resinates were prepared by the batch process. An accurately weighed amount of ranitidine hydrochloride (672 mg) was taken in 100 ml of distilled water. Then a known weight of ion-exchange resin was added in ratio of drug-resin, 1:1, 1:2 and 1:3 to the solution and stirred on a magnetic stirrer until equilibrium was achieved. Time to reach equilibrium was determined by measuring concentration of drug in solution. Resinates obtained were separated by filtration, washed with copious quantity of deionised water to remove uncomplexed drug. The complexes were dried overnight in a hot air oven at 40°C and then stored in tightly closed desiccator. The amount of drug loading was determined by finding the difference between the amount of drug present in the stock solution and the amount remaining in filtrate at the end of equilibrium.

**Optimization of drug loading:**

A series of solution containing fixed quantity of resin and ranitidine hydrochloride were subjected to different pH condition to find the optimum pH condition for loading of drug. Three batches were prepared containing drug-resin ratio 1:1, 1:2 and 1:3 by maintaining pH at 4. The solutions were stirred for 1 hour. Resinate obtained was separated by filtration, washed with copious quantity of methanol and drug content was determined.

**Determination of drug content in the complexes:**

About 100 mg complex was weighed and taken in a 100-ml volumetric flask and volume was made with 0.1 N HCl. The solution in the volumetric flask was then sonicated for 20 min and stirred further for 2 h on magnetic stirrer and then filtered using 0.2-µ membrane filter. From filtrate, 10 ml of solution was pipetted out and diluted up to 100 ml with the 0.1 N HCl, and absorbance was measured at 313 nm using UV double beam spectrophotometer.

**Determination of properties of complexes:**

Prepared complexes were evaluated for shape, angle of repose, bulk density, tapped density. Carr’s index and Hausner’s ratio. Angle of repose was determined by funnel method. Bulk density was determined by taking weighed quantity of material in measuring cylinder tapped on hard surface 100 times and subtracting the volume occupied after tapping from the initial volume [12].

**In-vitro release of ranitidine hydrochloride from resinate:**

Complexes of ranitidine hydrochloride with Indion 204, Indion 264 and Indion 254 were subjected to in-vitro dissolution studies using USP 24 method. Weighed quantity of complexes equivalent to normal dose was suspended in 900 ml of 0.1N HCl using USP type II dissolution apparatus at stirring speed of 50 rpm. After 5 minute interval 5 ml of dissolution medium was withdrawn by pipette for analysis. The volume withdrawn was replaced with fresh quantities of dissolution fluid. The withdrawn samples were filtered and filtrates were analyzed at 313.0 nm using UV spectrophotometer and the quantity of drug released was determined [13, 14].

**Stability studies under the influence of accelerated condition:**

The stability studies were carried out desired weighed quantities of drug, resin and resinate of drug with Indion 204 (1:1 & 1:2 complex) were dried at 50°C and exposed to humidity environment of 75% RH. Equilibrium moisture was determined using desiccators method with saturated salt solution to provide desired relative humidity [15, 16]. The samples were weighed periodically 1, 2, 4, 6, 8, 10, 18 and 24 hour and increases in weight of various samples are noted. A plot of percentage moisture content Vs time was drawn to gives the water uptake kinetics of each sample.

Percentage moisture uptake = \( \frac{W_2 - W_1}{W_1} \) = is weight gain by sample after exposure to humidity.

**Formulation of ranitidine hydrochloride tablets:**

The tablets of ranitidine hydrochloride were prepared by conven-
tional direct compression technique using various diluents like spray-dried lactose, microcrystalline cellulose and mannitol. All ingredients were passed through the sieve no # 80 to produce uniform powder. Required quantity of each was taken for particular formulation and the blend was mixed by tumbling in polythene bag. The composition of each formulation is given in Table 1. The hardness of tablet of each batch kept constant (3.4 kg/cm²). The weight of tablet of each batch was adjusted to 380 mg.

**Post compression parameters:**

After tablets compression, weight variation, friability, content uniformity and disintegration time was determined. In-vitro dissolution studies were carried out in USP dissolution test apparatus type II, using pH 1.2 dissolution fluids at 50 rpm [17, 18].

**Equilibrium water uptake:**

The water uptake by tablets was determined gravimetrically [19]. Tablets were introduced into the swelling media (pH 1.2). At predetermined time intervals (15, 30, 60, 90, 120 and 180 min.) the tablets were removed from the medium, excess water was blotted with tissue paper and immediately weighed (n=3). This procedure was repeated until the tablets reached a constant weight (Equilibrium water uptake). The swelling rates were determined as the slope of plots of water uptake vs time.

**Moisture uptake study of various dosage forms of ranitidine:**

Formulated tablets F1, F2 F3, commercial uncoated tablets, coated tablets and capsules were taken in different glass containers. The containers were then placed in the constant humidity (75% RH) chamber. The weight increase due to moisture absorption was measured by taking weight at different intervals such as 1, 2, 3, 5, 6, 10, 20, 32, 44, 56, 68 and 92 hrs.

**RESULTS AND DISCUSSION:**

Ranitidine hydrochloride absorbs moisture to a sufficient extent that it liquefies. Water absorption during manufacturing or storage causes various problems such as poor flow characteristics and chemical instability. Stability testing is therefore an essential part of product development and there is need to ensure that satisfactory product quality is maintained during practical usage. Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. The step-by-step studies were carried out to ion-exchange resin to provide stability to the drug. The moisture absorption study of ranitidine was conducted in different controlled environment. The weight gain at different time interval was taken as moisture gain. Figure 1 shows moisture uptake profiles for 1 gm ranitidine hydrochloride at three different level of relative humidity such as 75, 57 and 22%. The amount of moisture uptake was seen to be higher for samples exposed to a higher relative humidity for the three-hour time period. The figure indicates that ranitidine exposed to higher relative humidity absorbed maximum amount of moisture. The dependence of moisture uptake on relative humidity has been reported by Li et al which is similar to the present study. The rate of moisture absorption was also calculated from the best fit lines of the Figure 1 and presented as bar diagram (Figure 2).

It has been observed that ranitidine exposed to higher relative humidity showed high rate of moisture absorption whereas the slowest rate was found with ranitidine exposed to lower relative humidity. Form this experiment; it is clear that the rate and extent of moisture absorption by ranitidine depend on relative humidity. So, it is better to select an environment for the manufacturing of ranitidine tablet. It is also noted that all three moisture uptake curves exhibited biphasic characteristics: an initial linear portion followed by a curvilinear segment. This biphasic moisture uptake profile can be further explained with respect to the moisture uptake process. The surface of the particles absorbs moisture rapidly and saturated solution was formed in the adsorbed layer. Then moisture penetrates into the particles slowly and as a result moisture absorption rate decreased forming a biphasic moisture absorption curve.

The moisture content of the resins was obtained and it was found to be in acceptable ranges (Figure 3). For preparation of resins, batch method was preferred because of its convenience. As the reaction is an equilibrium phenomenon, maximum efficiency is best achieved in batch process. Equilibrium time was shorter due to thinner barrier for diffusion of ions, as it is a continuous motion. Also, higher swelling efficiency in batch process results in more surface area for ion-exchanged. Hence the batch process is suitable for smaller particles [20]. Various experimental conditions were optimized to get optimum drug loading. Time to reach equilibrium during drug loading was found to be 6 hrs. To investigate effect of pH on drug loading, the pH of drug-resin solution was varied keeping the drug: resin in the ratio 1:1, and results are recorded in Table 2. The loading of ranitidine hydrochloride on cation-exchange resin is an equilibrium process, which depends upon the presence of the cations in the solution. This is dictated by the pH of solution, which may affect the amount of ionized drug species present in the solution thereby affecting loading efficiency. The results showed that lower loading of ranitidine hydrochloride was observed at low pH, which might be due to the higher concentration of competing ions which may inhibit the interaction of resins. As ion-exchange is equilibrium process the presence of higher number of ionized drug molecules increases drug loading. Similar findings have been reported earlier [21]. At pH 4, maximum loading of ranitidine hydrochloride was obtained. Hence, pH 4 was selected for complexation of ranitidine hydrochloride with Indion 204, Indion 264 and Indion 254. Effect of drug: resin ratio on loading is shown in Figure 4. It shows that 1:1 drug: resin ratio shows maximum drug loading. Increase in the amount of complexing agent increases the amount of drug adsorbed as number of sites increases, but the drug content per gram of the complex decreases. Thus resinate prepared by batch method using Indion in drug: resin ratio of 1:1 at pH 4 gave optimum drug loading. In-vitro release profile of complex is shown in Figure 5. Studies in 0.1 N HCL using USP paddle apparatus at 50 rpm with drug-Indion 204 and Indion 264 complex showed better release than that of drug-Indion 254 complexes. While more than 90% of drug release from Indion 204 and Indion 264 in just 20 min and 25 min respectively. Reichenberg (1953) in his study discussed release of drug from ion-exchange resins. He described release of two types (1) Film diffusion, which is dependent on ingoing ion concentration, and (2) particle diffusion which is independent of concentration of ingoing ions [22]. The complexation was confirmed by carrying out x-ray diffraction studies on Indion 204, Indion 264 and Indion 254 resins, drug, drug complex, and physical mixture of two. The x-ray powder diffraction (XRPD) showed crystalline peak characteristics of drug were masked and characteristic amorphous characteristics of the
Table 1: Formulae of ranitidine hydrochloride tablets prepared

<table>
<thead>
<tr>
<th>Ingredient (mg/tablet)</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Resinate (drug: resin)</td>
<td>300</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>150</td>
</tr>
<tr>
<td>Lactose</td>
<td>-</td>
</tr>
<tr>
<td>Mannitol</td>
<td>-</td>
</tr>
<tr>
<td>Pregelatinised Starch</td>
<td>20</td>
</tr>
<tr>
<td>Talc</td>
<td>6</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
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</table>

Table 2: Effect of pH on Drug Loading

<table>
<thead>
<tr>
<th>pH Ratio</th>
<th>% Drug content per gram of resinate (mean ± S.D., n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>37.25 ± 0.28</td>
</tr>
<tr>
<td>2</td>
<td>40.2 ± 0.61</td>
</tr>
<tr>
<td>3</td>
<td>44.10 ± 0.49</td>
</tr>
<tr>
<td>4</td>
<td>50.12 ± 0.15</td>
</tr>
<tr>
<td>5</td>
<td>42.06 ± 1.42</td>
</tr>
<tr>
<td>6</td>
<td>40.48 ± 0.72</td>
</tr>
</tbody>
</table>

Table 3: Physical Properties of Resins and Resinates

<table>
<thead>
<tr>
<th>Character</th>
<th>Resins</th>
<th>Resinates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape</td>
<td>Irregular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Angle of repose</td>
<td>20.4</td>
<td>28.66</td>
</tr>
<tr>
<td>Bulk density</td>
<td>0.688</td>
<td>0.640</td>
</tr>
<tr>
<td>Tap density</td>
<td>0.776</td>
<td>0.761</td>
</tr>
<tr>
<td>Carr’s index</td>
<td>15.6</td>
<td>16.8</td>
</tr>
<tr>
<td>Hausner Ratio</td>
<td>1.20</td>
<td>1.26</td>
</tr>
</tbody>
</table>

Table 4: Physical properties and dissolution characteristics of ranitidine hydrochloride tablet formulated and marketed samples

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Disintegration time (s)</th>
<th>Weight Uniformity</th>
<th>% Friability</th>
<th>Content Uniformity</th>
<th>T&lt;sub&gt;50&lt;/sub&gt;</th>
<th>DF&lt;sub&gt;50&lt;/sub&gt;</th>
<th>K (min&lt;sup&gt;-1&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>312±1.2</td>
<td>481.2±2.36</td>
<td>0.68</td>
<td>98.85±0.73</td>
<td>22.5</td>
<td>40.18</td>
<td>0.02358</td>
</tr>
<tr>
<td>F2</td>
<td>350±0.25</td>
<td>483.4±1.54</td>
<td>0.87</td>
<td>99.38±0.83</td>
<td>30.5</td>
<td>39.62</td>
<td>0.0230</td>
</tr>
<tr>
<td>F3</td>
<td>327±1.23</td>
<td>482.7±1.12</td>
<td>0.82</td>
<td>98.88±0.62</td>
<td>33.0</td>
<td>51.46</td>
<td>0.0553</td>
</tr>
<tr>
<td>Market Sample</td>
<td>319.2±0.5</td>
<td>301±1.42</td>
<td>0.75</td>
<td>98.7±1.2</td>
<td>20.5</td>
<td>39.62</td>
<td>0.0230</td>
</tr>
</tbody>
</table>

Figure 1: Effect of % RH on the moisture absorption by ranitidine (Mean ± SD, n = 3)

Figure 2: Moisture absorption rate of ranitidine (Mean ± SD, n = 3)

Figure 3: Moisture contents of resins

Figure 4: Percent of ranitidine hydrochloride loaded on resinate ratio (Mean ± SD, n = 3)
Figure 5: In-vitro drug release profile from resinates (Mean ± SD, n = 3)

Figure 6: Moisture uptake rate of various samples at 75% RH

Figure 7: In-vitro drug release from ranitidine hydrochloride tablets (Mean ± SD, n = 3)

Figure 8: Moisture absorption by different dosage form of ranitidine (Mean ± SD, n = 3)

The dissolution parameters of formulated and marketed tablets are summarized in Table 4. No variations were observed in the dissolution characteristics of the tablets formulated and marketed. All dissolution parameters indicated rapid and higher dissolution of ranitidine hydrochloride from formulated tablets than market tablets. Dissolution efficiency (DE) values were calculated as suggested by Khan [23]. Dissolution efficiency (DE) and disintegration time of formulation F2 and F3 was found to be poor than F1. Figure 7 shows that formulated and conventional tablets showed dissolution and percent cumulative drug release at the end of 50 minute was 98%. The extent of moisture absorption by pure ranitidine, conventional
comranitidine capsule, ranitidine coated tablets, ranitidine uncoated tablet and formulated F1, F2, F3 is shown in Figure 8. This figure indicates that pure ranitidine absorbed maximum amount of moisture while different dosage forms of ranitidine absorbed less amount of moisture although inter dosage form variability in moisture absorption is clear. Among the dosage forms uncoated tablet absorbed maximum amount of moisture, capsules and formulated tablets absorbed intermediate amount while coated tablet absorbed minimum. Uncoated tablets melted gradually while the coated tablets became soft. Pure ranitidine absorbed higher amount of moisture than tablet. This is because tablet is a compressed dosage form. Moist air cannot penetrate easily in the tablet core. On the other hand, coated tablet absorbed less moisture than uncoated tablet. Capsule absorbed an intermediate amount of moisture. This is because gelatin cannot prevent the moisture penetration. This study indicates that type of dosage forms and dosage forms containing excipients have also effect on moisture absorption by ranitidine formulation. Formulation F1 containing microcrystalline cellulose as diluent with resinate of ranitidine absorbed minimum amount of moisture while resinate with lactose absorbed maximum (F2). On the other hand, resinate with mannitol (F3) was found to absorbed intermediate amount of moisture. Presence of other excipients like diluent, binder in the formulations of ranitidine absorbed almost double moisture than that of resinates of ranitidine. This is because excipients itself is a hygroscopic material in some extent. Selected formulations were subjected to stability studies for 9 weeks at 40°C and were analyzed after specific time period one week intervals. No significant changes were seen in-vitro disintegration.

The formulation F1 of ranitidine hydrochloride with microcrystalline cellulose as filler was found to be optimum as it shows lowest disintegration time with desired dissolution rate. This study indicates that ranitidine tablet prepared from drug: Indion 204 (1:1) complex might be suitable for commercial supply than uncoated tablet and capsule dosage form.

Different data generated in this experiment indicates that % RH of manufacturing environment has a great effect on the moisture level of ranitidine tablets as ranitidine absorbs maximum amount of moisture at higher % RH. This higher moisture level is responsible for various physical stability problems of ranitidine tablets. Therefore, by controlling the % RH of manufacturing environment, we can overcome the various stability problems of ranitidine tablet manufacturing. Even though, resinate of ranitidine used to control optimum moisture level for ranitidine tablet processing. The batch process of complexing ranitidine hydrochloride with Indion 204 (1:1) produced efficient drug loading. The study also suggests that an ion-exchange resin system is reducing hygroscopicity of drug which helps to produce stable tablets.

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**REFERENCES:**


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