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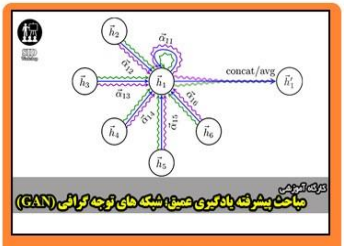


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Original Article

# Effects of Weak and Strong Cation Exchange Resins on Moisture Uptake Behavior of Ranitidine Hydrochloride

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**Abstract**

The aim of the present research was to study the effects of weak cation exchange resins, polacrilex with exchangeable $H^+$ and polacrillin potassium and strong cation exchange resin sodium polystyrene sulfonate on water uptake behavior of ranitidine hydrochloride. Drug resin complexes (DRC) were prepared and evaluated for the percentage of moisture gain when placed in a humidity chamber at $40 \pm 2$ °C and $75 \pm 5$% RH for 17 h as compared to drug and free resins under the same condition. Equilibrium moisture content (EMC) under different humidity conditions and the rate and extent of moisture uptake in the presence (15 watt florescence light) and absence of light under $40 \pm 2$ °C and $75 \pm 5$% RH were also calculated for DRCs, drug and unloaded resins. DRC 264 (containing polacrilex with $H^+$) gained minimum weight (10.22%) maintaining free flowing characteristics whereas other resinates showed higher weight gain and formation of sticky mass while ranitidine HCl turned liquid with gain of 28.11% weight. The rate of moisture uptake by ranitidine HCl was found to increase in the presence of light with slight difference in extent, whereas moisture uptake rate was independent of light in the case of resins. Even though DRC 264 contained ranitidine HCl, the moisture uptake rate was unaffected by light and saturation in moisture gain was seen just at 6 h. Thus, loading ranitidine HCl on polacrilex resin with exchangeable $H^+$ significantly improves its moisture resistance and may not require very tight environmental controls during its formulation.

*Keywords:* Drug-resin complex; Equilibrium moisture content; Hygroscopicity; Ranitidine HCl; Polacrilex resin.
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## 1. Introduction

Hygroscopicity and deliquescence in pharmaceuticals is a cause of concern for many reasons including chemical instability, poor flow, change in dissolution characteristics, and change in appearance [1]. Some drugs are sensitive to moisture in the environment to such an extent that if left in contact with moist air for even short periods of time, crystalline materials turn into problematic paste or even liquid. Typically, the pharmaceutical industry has sought to control this effect by using very

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tight environmental controls in their manufacturing and formulation areas. Loading a drug onto a functional polymer-resin imparts some of the characteristics of the polymer-resin to the resulting resinate, in particular, the physical properties of a fine free flowing powder.

It is known that ranitidine hydrochloride, an $H_2$ receptor antagonist is subject to degradation upon aging and that such degradation is accelerated by moisture and light [2]. The most popular method for dealing with such stability problem of ranitidine is film coating of tablets with suitable polymers. A report states that polymorphic form II of this drug is less hygroscopic than form I and has better drying characteristics [3]. Complexation of ranitidine HCl with cyclodextrin has proved to have improved drying characteristics and decreased hygroscopicity [4].

In the present work, effects of weak cation and strong cation exchange resins on the moisture uptake behavior of ranitidine HCl in the presence and absence of light was studied to assess their ability in protecting ranitidine HCl from moisture.

## 2. Materials and methods

### *2.1. Materials*

Ranitidine hydrochloride was a gift sample from Neon Laboratories Ltd., Palghar, India (Batch no. RH 8681204). The resins used were gifts from Ion Exchange India Ltd., Mumbai, India. Weak cation resins were Polacrilex resin with exchangeable $H^+$ (Indion 264) and Polacrillin potassium (Indion 234). Strong cation exchange resin was sodium polystyrene sulfonate (Indion 254). Resins were purified prior to use by successive washing in deionised water, 95% and 50% ethanol, and finally deionised water, and dried at the room temperature.

### *2.2. Preparation of drug resin complexes (DRC)*

Complexes containing ranitidine HCl and different resins were prepared using the batch method under varying conditions like drug-resin ratio (1:1, 1:2, 1:3, 2:3 and 2:1), temperature (10, 30, 40 and 50 °C), pH (1.0, 1.5, 2.0, 6.5, 7.0, 8.0 and 10.0) and drug concentration (3, 6 and 12 mg/ml) to get the optimum condition for maximum drug loading. During preparation, the drug and

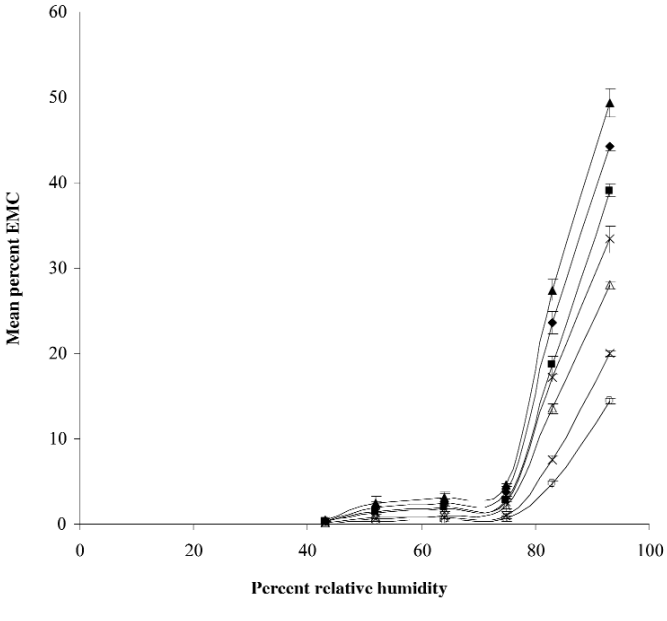


**Figure 1:** Equilibrium moisture content of ranitidine HCl, resins, and DRCs under different RH conditions at 25±1°C. Results are the mean of three determinations ±SD. Symboles: (♦Ranitidine HCl; (▲) Indion 234; (×) Indion 264; (*) Indion 254; (■)DRC 234; (✙) DRC 264; (△) DRC 254.

resin were stirred at 400-500 rpm. Resinates for further study were prepared under optimized condition.

*2.3. Drug content in resinates*

Accurately, 100 mg of resinate was stirred with 200 ml 2 N NaCl at 500-600 rpm on a magnetic stirrer. After every 2 h, the solution was replaced with fresh 2 N NaCl solution until no further drug was detected in solution. Total drug eluted was determined spectrophotometrically at 313 nm [5]. The drug content per 100 mg resinate is shown in Table1.

*2.4. Storage stability of drug, resins and resinates*

One gram of the dry resins and ranitidine HCl and resinates equivalent to 1 g of ranitidine HCl were weighed accurately in aluminium dish and dried for two h at 60 °C before study. They were then placed in the humidity chamber at 40±2 °C and 75±5% RH for 17 h. Physical changes were noted and the percentage of increase in weight was calculated thereafter [6].The results are summarized in Table 2.

2.5. *Determination of equilibrium moisture content*

Initial moisture content of ranitidine HCl, resin and resinate was determined using a moisture balance (Model no. EB 340 MOC, Shimadzu Corporation, Singapore). EMC determinations were made by placing 0.1 g of ranitidine HCl and resins while resinates equivalent to 0.1 g of ranitidine HCl in aluminum dish, which were then kept in desiccators for a period of 7 days. A liberal amount of the saturated salt solution (with excess crystal) was placed in the desiccators to maintain constant humidity condition.

**Table 1:** Drug content in different resinates.

| Resinates | Ranitidin (mg/100 mg) of DRC[a] |
|---|---|
| DRC 234 | 53.13 ± 0.45 |
| DRC 264 | 54.39 ± 0.88 |
| DRC 254 | 54.57 ± 0.94 |

[a]DRC: Dry-resin complex.

Studies were done in triplicate and accordingly three desiccators were employed for each humidity condition. The desiccators were maintained at the constant temperature of 25±1 °C in a stability chamber. After 7 days, samples were removed and an increase in weight of samples was determined.

EMC was calculated with the following formula:

$$P = \frac{(W \times A/100) + B \times 100}{W-(W \times A/100)} \qquad (1)$$

where P is the percent of moisture on dry basis, A is the initial moisture content, W is the initial weight of sample and B the change in weight in g after equilibrium has been attained (After storage for 7 days at 25 °C). EMC values were calculated from P with the aid of equation given below:

$$\%EMC = \frac{P}{P + 100} \times 100 \qquad (2)$$

*2.6. Evaluation of hygroscopicity*

The study was carried out according to method described by Kaur *et al*. [7]. One g of ranitidine HCl, resins and 1.83 g of resinates (equivalent to 1 g of ranitidine HCl) were exposed to high humidity (75±5% RH) and temperature (40±2 °C) in a humidity chamber. Increase in weight was recorded after 2, 4, 6, 8, 10, 12, 14 and 16 h in the absence and presence of light (15 watt florescence light × 2). The moisture isotherms are depicted in Figures 2 and 3.

## 3. Results and discussion

*3.1. Drug-resin complexation studies*

All of the parameters, viz. drug-resin ratio, temperature, pH and drug concentration, affected either the rate or the extent of loading of ranitidine HCl on weak and strong cation exchange resins. Study on the effect of drug-resin ratio suggests a higher drug loading for all of the resins in drug-resin ratio of 1:3 than 1:2, but the difference was little, therefore, drug-resin ratio of 1:2 was selected as the optimized ratio. Increase in the temperature

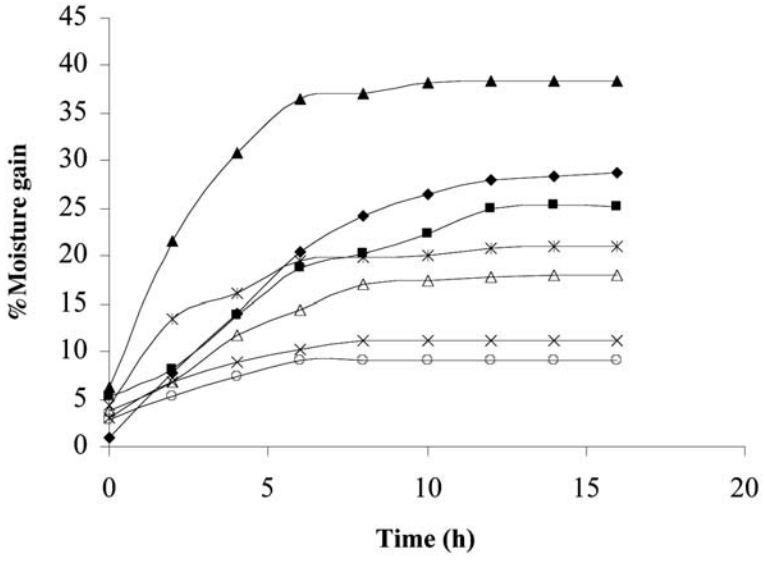


**Figure 2**: Moisture uptake of ranitidine HCl, resins and resonates under 40±2 °C and 75±5 % RH in the absence of light. Symboles: (♦)Ranitidine HCl; (▲) Indion 234; (×) Indion 264; (*) Indion 254; (■)DRC 234; (⊕) DRC 264; (△) DRC 254.

during complexation increases the ionization of drug and resin. However, this effect is more pronounced in poorly water soluble and unionizable drug. High temperature tends to increase the diffusion rates of ion by decreasing the thickness of the stationary layer. However, Frank and Koebel [8] reported that cationic exchange resins are not affected as significantly by temperature changes as anionic exchange resins. In the case of drug-resin complex formation, water-soluble drugs completely ionize at the room temperature, and continuous stirring in batch process does not allow development of thick executive zone. As ranitidine HCl is water-soluble and all of the resins are cationic, therefore, in all of the cases loading was good at 30 °C. Decrease in the loading at higher temperature was found which may be due to pronounced disruptive effect.

Ranitidine HCl possess two Pka values 2.7 and 8.2 while the weak cationic exchange resins (Indion, 234 and 264) have Pka in the range of 4-6, and the strong cationic resin (Indion 254) has Pka between 1-2. Therefore, when drug was complexed with weak cation exchange resins, maximum drug loading was observed at pH 6.5 as at this pH the weak cation exchange resins and dimethyl amino group of ranitidine HCl, which is responsible for Pka of 8.2, remained in the ionized form to the maximum extent. While strong cation exchange resin with Pka 1-2 can't remain ionized to a greater extent at pH 6.5, therefore, the maximum loading was observed at the pH 1.5 where both the strong resin and drug remain ionized to a greater extent. High ionization of the drug at pH 1.5 may be attributed to the ionization of the side chain of ranitidine responsible for Pka of 2.3. Higher loading was observed for the concentration of 6 mg/ml than 3 mg/ml because of more availability of drug for binding. However, further increase in concentration to 12 mg/ml showed decreased loading owing to saturation and more competition between drug-drug ions for the active binding site on resins.

### *3.2. Storage stability of drug, resins and resinates*

Storage stability under 40 ± 2 °C and 75 ± 5% RH for 17 h showed ranitidine HCl to be deliquescent as it converted into liquid upon moisture gain, while all resins were

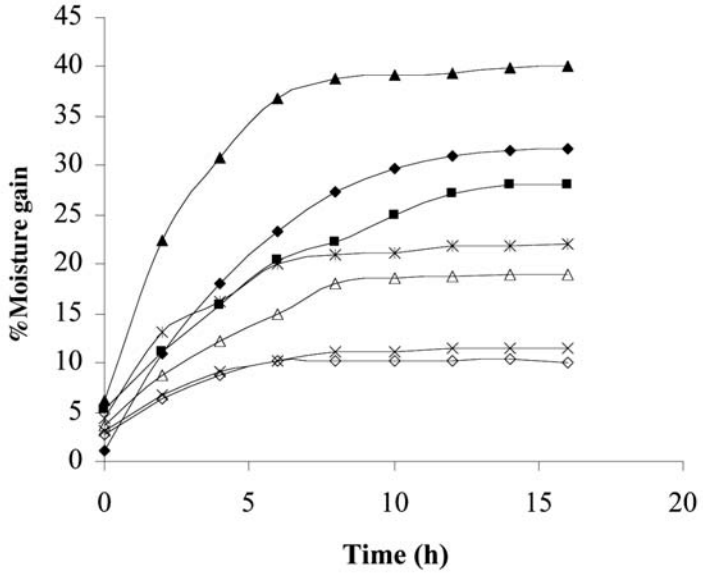


**Figure 3:** Moisture uptake of ranitidine HCl, resins and resinates under 40 ± 2°C and 75 ± 5 % RH in the presence of light. Symboles: (♦)Ranitidine HCl; (▲) Indion 234; (*) Indion 264; (*) Indion 254; (▪)DRC 234; (✣) DRC 264; (△) DRC 254.

hygroscopic but not deliquescent (Table 2). Among the resonates, the percentage of weight gain was minimum in DRC 264 (10.22%), and it retained its free flowing characteristics; however, other resinates showed reduced flow and formation of sticky mass. More interestingly, the percentage of moisture gain by resinates was slightly less than that of the resins. Minimum weight gain by DRC264 may be due to the properties of resin itself which gained only 11.03% moisture under 40±2 °C and 75±5% RH after17 h. Another reason for less moisture gain by DRC264 may be because it consists of $H^+$ form of resin having more resistance to the moisture than $K^+$ form (Indion 234) and $Na^+$ form (Indion 254). $K^+$ and $Na^+$ forms of resin swell to a greater extent in the presence of water.

**Table 2.** Physical changes and % of weight gain by ranitidine HCl, resins and resinates after storage under 40±2 °C and 75±5% RH for 17 h.

| Samples | Physical Changes | | % Weight gain |
|---|---|---|---|
| | Initial | Final (After 17 h) | |
| Ranitidine HCl | Crystalline powder with moderate flow | Yellowish brown syrupy liquid | 28.11±0.95 |
| Indion 234 | Dry poor flowing powder | Clumpy mass, with no flow | 39.17±1.04 |
| Indion 264 | Dry free flowing powder | Powder with reduced flow | 11.03±0.91 |
| Indion 254 | Dry free flowing powder | Powder with reduced flow | 18.09±0.44 |
| DRC 234 | Dry free flowing | Sticky mass with poor flow | 25.41±0.55 |
| DRC264 | Dry free flowing | Dry free flowing resinate | 10.22±0.17 |
| DRC 254 | Dry free flowing | Resinate with reduced flow | 17.32±0.33 |

Results are the mean of three determinations ±SD.

*3.3. Equilibrium moisture content*

Ranitidine HCl demonstrated more than 40% EMC above 80% RH but negligible below 50% RH. It seems that below 50% RH the water molecules were adsorbed onto the crystal surface, whereas above 60% RH, the powder dissolved into liquid. Teraoka *et al*. [9] reported that ranitidine HCl posses a critical relative humidity at 67% RH, therefore, moisture is of critical concern for its stability, and moisture at 60% RH may cause severe degradation of the drug. All of the resinates showed less moisture content than ranitidine HCl. DRC 264 showed only 14.44% moisture content at 93% RH and negligible moisture content 0.64% at 75% RH (Figure 1), thus it improves moisture resistance of the drug ($p<0.01$).

*3.4. Evaluation of hygroscopicity*

Hygroscopicity study of ranitidine HCl, resins and resinates in the presence and absence of light suggests that both the rate and extent of moisture gain by the resinates were less than by ranitidine HCl. DRC 264 showed significant ($p<0.01$) improvement in moisture resistance with saturation in moisture gain at 6 h only, and the percentage of moisture gain of about 9.12 % (Figure 2). However, Indion 234 showed maximum rate and extent of moisture gain even greater than ranitidine HCl. This might be due to more hygroscopic nature of this resin itself owing to $K^+$ form which is having more affinity for water.

Comparison of moisture uptake rate of drug resins and resinates clearly shows that the rate of moisture uptake by ranitidine HCl increases in the presence of light with only slight difference in the extent of moisture uptake whereas moisture uptake rate was independent of light in the case of resins. More interestingly, even though the DRC 264 contained ranitidine HCl, the moisture uptake rate was not affected by light (Figure 3) which conclusively demonstrates protective effect of DRC 264 both in the presence and absence of light. Thus, resinate of deliquescent drug ranitidine HCl retained the properties of resin and remained free flowing.

## 4. Conclusion

Out of the three resins tested for reducing moisture uptake by ranitidine HCl, polacrilex resin with exchangeable $H^+$ (Indion 264) was proved better than polacrillin potassium (Indion 234), and the strong cation exchange resin sodium polystyrene sulfonate (Indion 254). Thus loading ranitidine HCl on polacrilex resin with exchangeable $H^+$ may not require very tight environmental controls during its formulation.

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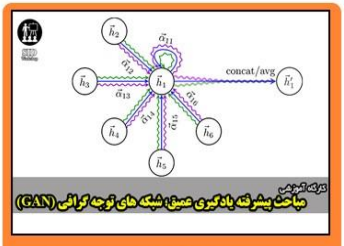


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