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A METHOD FOR IMPROVING HANDLING PROPERTIES OF RANITIDINE HCl

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ABSTRACT
Ranitidine is widely used H_2 receptor antagonist in clinical practice; however its deliquescent character is major challenge during formulation. In this study we have explored one of the possible uses of ion exchange resins to reduce hygroscopicity of ranitidine through complexation with commercially available resin Indion 234 and thereby improve handling properties.
Ranitidine, resin and resinate (complex of resin and ranitidine) was exposed to 75% relative humidity at 40º C and the plot of % moisture content (obtained by weight gain) Vs time was used to determine the hygroscopic nature. The effect of drug content of resinates on moisture uptake was also studied. The moisture content was also determined by Karl Fischer titration. Thermogravimetric analysis and differential thermal analysis (TG - DTA) plots were used to compare drying characteristics of ranitidine, resin and resinate. Resinate showed less equilibrium moisture content and moisture uptake rate compared to ranitidine and resin. Moreover the ranitidine content and moisture uptake showed inverse relationship.
To conclude that resinates of ranitidine have less moisture uptake rate and moisture content than resin and ranitidine alone and can be used to improve handling of ranitidine.

Keywords: *Hygroscopicity, cation exchange resin, Ranitidine*

INTRODUCTION

Water absorption during the manufacturing of dosage forms results in processing problems such as stickiness, clumping poor release from dies, poor flow, chemical instability , variable assay moreover absorption During storage the absorption of water causes changes in dissolution behavior, change in crystalline form and deterioration of appearance.[1]
Callahan et al. [2] have classified the degree of hygroscopicity into four classes:

1. Non-hygroscopic solids: no increase in water content at < 90% RHs, and increase after storage for one week above 90% RH is less than 20%.
2. Slightly hygroscopic solids: no moisture increase at < 80% RHs and increase after one week storage less than 40% at > 80% RH
3. Moderately hygroscopic solids: moisture increase d" 5% after storage at below 60% RH, and after storage for one week at > 80% RH is less than 50% moisture.
4. Very hygroscopic solids: moisture content increase may occur at 40-50% RH and increase may exceed 30% after storage for one week > 90% RH.

Hygroscopic substances either absorb or adsorb water from surrounding; the absorption of water is because of hydrate formation or specific site adsorption [3]. Frequently, a problem of poor drying characteristics is associated with hygroscopic materials. There have been attempts to address the aforementioned problems by the use of salt formation [4], additives such as magnesium and calcium compounds [5], cetyl alcohol and cetostearyl alcohol [6], hydrate forms such as pentahydrate of sodium pamidronate which is not deliquescent to amorphous forms that are deliquescent, adsorbent[7] and complexation with Cyclodextrins[8] .
Ion exchange resins are polymeric materials that contain basic or acidic groups that interact with ionisable molecules and form insoluble salts. The mechanism of action of ion exchange resin is well understood and the drug-resin interaction can be manipulated to create desirable effects. The resins are insoluble solids that are not absorbed by the body, so are very safe[9].
These resins are useful as active ingredients in drug formulations as well as excipients for effecting tablet disintegration, taste masking, controlled / extended release and drug stabilization; and in pharmaceutical manufacturing for drug isolation, drug purification and catalysis of reaction [10, 11].
The drug-resin complex known as resinate can be used in suspension or isolated as a dry, solid, free flowing stable compound. The drug is released from resinate upon exposure to physiological fluids.

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EXPERIMENTAL

Materials

Weak cation exchange resin Indion 234 was obtained from Ion Exchange India Ltd. Mumbai, India as gift sample. Ranitidine was obtained from Dr Reddys Laboratories, Hyderabad, India as gift sample.

Methods

Estimation of ranitidine

An UV spectrophotometric method based on the measurement and absorbance at 229 nm in 0.1 N HCl, Jassco V- 530 spectrophotometer was used for the analysis of ranitidine.

Preparation of resinates

Preformulation work showed that the ranitidine : resin ratio of 1:1 shows best drug loading and further increase in resin does not show significant improvement in drug loading. Hence, resinate of ranitidine was prepared by employing drug- resin ratio 1:1 with Indion 234 using batch method [12]. The drug and resin were stirred as slurry for sufficient time to attain ion exchange equilibrium. The samples were withdrawn at definite 30 min intervals till the constant amount of drug was detected in bulk solution, which indicated attainment of equilibrium. The amount of drug complexed was determined as the difference between amount of drug present in stock solution and amount remaining in filtrate at the end of equilibrium. Resinates were formed by stirring the drug and resin for different time intervals filtered, washed with deionised water and dried.

Characterization of resinate

FTIR studies A Jasco FTIR spectrophotometer (Jasco FTIR- 401, Japan) was used for infrared analysis of samples. About 1-2mg of sample was mixed with dry potassium bromide and the samples were examined at transmission mode over wave number range of 4000 to 400cm^{-1}.

X Ray powder diffraction was carried out to ascertain the formation of resinate complex. The X- ray diffraction patterns for Ranitidine HCl, 234 and resinate were obtained. The instrument was Phillips Analytical X-ray BV (PW 1710) using cu anode, 40 kv voltage and current of 30 mA

Moisture uptake studies

Weighed quantities of ranitidine, resin and resinate were dried to constant weight at 50 ^{0}C and were exposed to humidity environments of 75%, 60% and 40% RH maintained in stability chamber (Make Remi CHM6S) in the cabinet with and without fluorescent light source. The % moisture content of all the materials was determined as function of %RH. The samples were weighed periodically over a period of 24 h. % moisture content Vs. time (moisture uptake rate) was plotted to obtain the water uptake kinetics of each sample. The moisture content was also confirmed using Karl Fischer titration.

Thermal studies

TG-DTA plots performed on Mettler Toledo SD TA 851 were used to compare drying characteristics of resin, resinate and drug.

Dissolution test

The resinate equivalent to therapeutic dose of ranitidine was subjected to dissolution testing in 0.1 M HCl using USP dissolution apparatus II (Veego D A 6D) at 50 rpm at 37± 0.5 ºC.

RESULTS AND DISCUSSION

The UV analytical method was validated for linearity accuracy precision and interference. Beer's law was obeyed over 2-14 µg concentration range (Fig 1). When a standard drug solution was repeatedly assayed (n=6), the relative error and the coefficient of variation were found to be 0.78% and 1.2 % respectively. No interference by the excipients used in the study was observed.

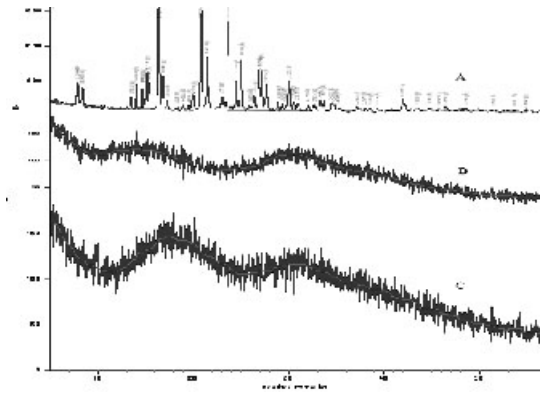

Fig. 1: *X ray diffraction pattern for A) Ranitidine B) Indion 234 and C) Resinate*

The ranitidine content of resinates increased with stirring time, the content at 30 min was 3.06% which gradually increased with stirring time and maximum was noted at 120 min. (Table 1). From the results of moisture uptake study it can be seen that moisture uptake by ranitidine and resin is higher than resinates while the moisture uptake was reduced with increased drug content in resinate. Hygroscopic nature of drug and also resin was reduced upon complexation and this might be due to the interaction of hydrophilic groups in the structures, which also contribute to the moisture absorption behavior[13].

Table 1. *Ranitidine content on resinate and % moisture content.(n=3)*

Parameter	Resinate IV (120 min)	Resinate III (90 min)	Resinate II (60 min)	Resinate I (30 min)
Ranitidine content in resinate (%w/w)	29.84	17.22	10.97	03.06
% moisture content upon exposure to 75% RH determined by KF titration	15.8	17.22	18.9	24.36

The X–ray diffraction pattern for ranitidine hydrochloride contained number of sharp peaks (A), while the resin showed a diffused peak or halo pattern (B). where as only a diffused peak was observed in X–ray powder diffraction patterns for the resinate (D). (Fig 1)

According to this data molecular state of ranitidine hydrochloride is crystalline, but that of resin is amorphous. The molecular state of ranitidine hydrochloride prepared as drug resin complexes was changed from crystalline state to amorphous state. This shows that entrapped drug molecule is monomolecularly dispersed in resin bead.

In the IR spectra ranitidine hydrochloride shows peak at 3349 cm^{-1} corresponding to the N-H stretching in a secondary amine (Fig 2). The absence of peak at 3349 cm^{-1} in resinate confirms the complexation of the secondary amine group in the drug with resin.The peaks representing amino group of the drug (3349 $cm^{-1)}$ and the peak at 2976 cm^{-1} corresponding to –CH stretching in drug are absent in resinate, which is signifies that during resinate formation there was interaction of the amino group of drug with the sulfonic group of resin.

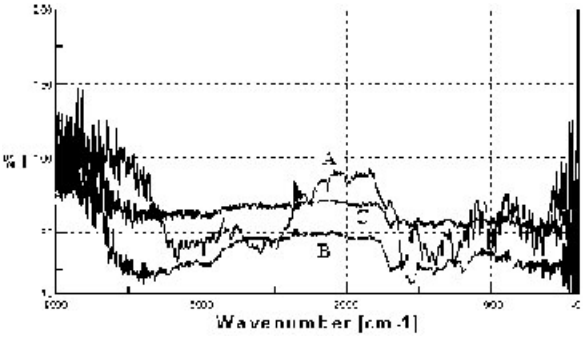

Fig. 2: *The infra red spectrum of A) Drug B) Indion 234 and C) Resinate*

Moisture uptake rate as depicted in Fig. 3 is a plot of mean % moisture content of the samples as a function of time. At equilibrium, Ranitidine absorbed enough moisture presenting syrupy appearance, resin absorbed water to greater extent and was a swelled mass with no flow properties but resinates remained as powders with reduced flow properties. For complex IV, the weight gain at saturation was minimum (13%) as compared to resin and ranitidine (Fig 3c). It was seen that in presence of light the MUR of hygroscopic materials was increased but final moisture content didn't change which proves that the complex is not hygroscopic. Similar observations are reported in previous study. [14]

Results of moisture content determination by Karl Fisher analysis (Table 2) are in good agreement with moisture content values determined by weight gain.

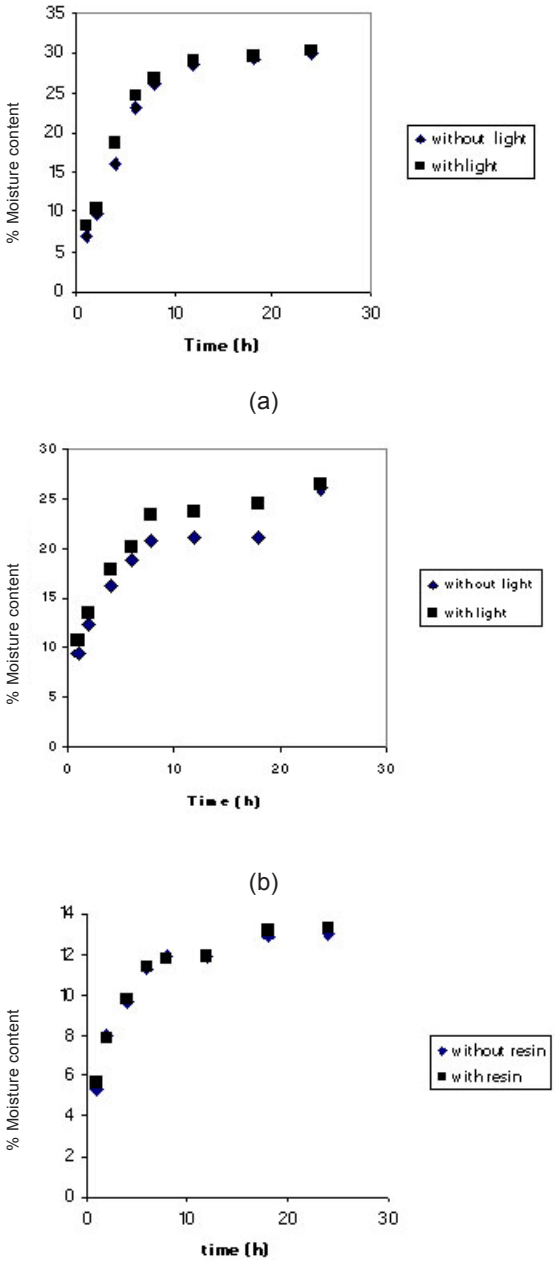

Fig. 3: *Moisture uptake rate of a) ranitidine b) resin and c) resinate at accelerated conditions of temperature and humidity in presence and absence of light. (n=3)*

Table 2. *Moisture content determined by Karl Fischer analysis of samples*

Results for TG-DTA analysis are displayed in fig 3 and 4. Resin and resinate displayed initial moisture loss in TG analysis and corresponding endothermic valley extending to about 120^0 C in DTA curve. Exothermic peak from about 220 to 300^0 C was also observed in resin and resinate DTA, probably indicating decomposition, marked by corresponding weight loss displayed in TGA. Weight of drug sample continued to decline up to about 300^0 C, with no distinguished stages for moisture loss and decomposition. However such decomposition was evident in corresponding DTA, displayed by exothermic peaks at about 180 and 110^0 C. The reason for degradation peaks of drug in resinate DTA was unclear.

Ranitidine released in 45 min was 92.3% this complies with official limit for dissolution. [14]

From above findings it can be interpreted that hygroscopic character of ranitidine HCl is reduced upon complexation with ion exchange resin.

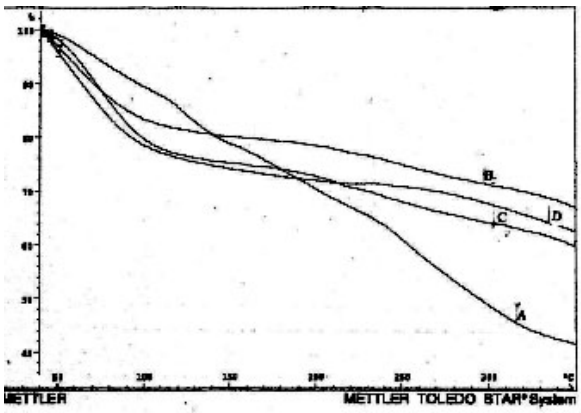

Fig. 4: *T G A of A) Indion 234 B) Ranitidine and C) Resinate IV*

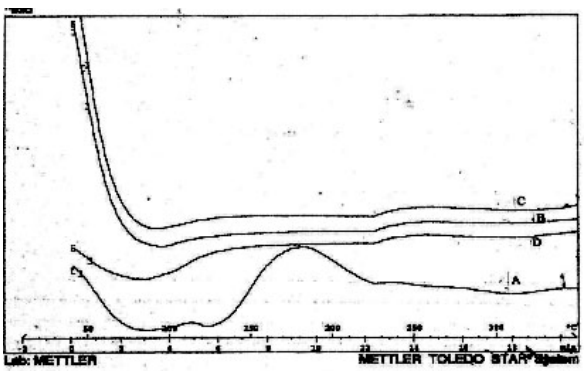

Fig. 5: *DTA of A) Indion 234 B) Ranitidine C) Complex I and D) Complex II*

CONCLUSION

Resinate showed less moisture content and moisture uptake rate as compared to resin and ranitidine both. The drug release from this resinates also fulfills Pharmacopoeial requirement. Thus formation of resinate can be a useful means to make the handling of ranitidine easier.

Rate and extent of moisture uptake was found to decrease considerably with increased proportion of drug in resinate. This shows that ion exchange resins are useful excipients, which can be used for solving problems associated with handling of hygroscopic drugs.

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