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Article

# Characterization and quantification of pH sensitive polymers used in drug targeting by inverse-phase gas chromatography and dynamic vapour sorption techniques

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## ABSTRACT

Surface energies and dynamic vapour sorption (DVS) plays an imperative role in drug polymer interaction in the formulation development for a number of applications. Powdered films of two pH sensitive polymers namely hypromellose phthalate (HPMCP) and methacrylic acid copolymer NF (Eudragit L30-55) were studied for surface energy analysis employing inverse-phase gas chromatography (IGC) which is a well-known physical technique in acquiring significant information about surfaces of pharmaceutical powder or film. The mean surface energies of Eudragit L30D-55 and HPMCP films were found to be 40.48 mJ/m$^2$ and 55.03 mJ/m$^2$ respectively and significantly different from each other. Due to this difference, tablets were coated separately with HPMC and Eudragit L30D-55 in equal amount and were subjected to Near-Infra Red FTIR (NIR) equipped with DVS analyser for measuring DVS changes versus relative humidity (RH) in both coated tablets. Initial NIR and changing RH (25–75% up to 90%) of coated tablets were recorded after 15 minutes throughout the experiment. Eudragit L30-55 coated tablets showed no changes in NIR up to 90% of RH. However, HPMCP showed significant changes in NIR at 90% RH, indicating interaction of moisture with drug due to greater surface energy of HPMCP compared to Eudragit. These results confirmed good correlation between surface energy and relative humidity of two polymeric films and coated tablets. The study also shows quantification of drug and polymer by *in vitro* release of phthalyl group.

**Keywords:** HPMCP, Eudragit L100-55, IGC, DVS, FTIR, Relative Humidity, Coating, Salbutamol Sulphate.

## 1. INTRODUCTION

The interactions between pharmaceutical solids, liquids or gases is governed by their surface properties which are described in terms of surface free energy or simply surface energy. In general, higher surface energy is related to increased probability of interaction for instance, drug powders having high surface energies were found to adhere more with inert particles than those with lower surface energy.[1] The use of IGC is increasing rapidly in the pharmaceutical field, due to its potential for studying single component powder and blends of different surface energies,[2] batch to batch variability,[3] and the influence of humidity on surface free energy of powders.[4, 5]

In IGC, the unknown is the column packed with powder for testing and the known is the column where different vapours are to be injected. Similar surface energies of

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pharmaceutical powders with different chemical nature have been reported.[6] Whilst most pharmaceutical solids have multiple surface energies because of varying forms, crystal faces and impurities contents or physical defects, among others, therefore IGC is suited for amorphous forms as well.[7, 8] For amorphous and semi-crystalline polymers, main difference in their properties is bulk absorption of water.[9–11] Powder vapour interactions can now be studied by gravimetric method with availability of automated temperature and humidity controlled microbalance system equipped with near infrared FTIR spectrophotometer (NIR). It has been reported that the most important cause of variability in powder properties may be due to the changes in their surface properties.[12] The surface characterizations of the pharmaceutical polymers was also reported in the literature. However, not much attention has been paid to correlating IGC measurements with the behaviour of powders like polymers or other powdered excipients in particular processes or dosage forms design. Hodson et al. proposed in their study that the initial anhydrous material was converted to more stable hydrate form on exposure to high humidity.[13] Das et al. found that the total surface energy of the powder increased during storage at high RH due to the adhered surface moisture.[14] Umang et al. highlighted the effect of milling temperatures on powder surface energetics, and its contribution to cohesion. The surface energy of powders milled at both cryogenic and room temperatures was found to increase with increasing milling cycles.[15]

In the existing literature, very limited studies have focused on the surface energy of polymers and their relationship with relative humidity of the polymeric films. In this study, surface energies of commonly used pH sensitive polymeric films in drug targeting (HPMCP and Eudragit L30-55) were measured using IGC. Drug loaded tablets were then coated with HPMCP and Eudragit L30-55 separately and examined the whole tablets using dynamic vapour sorption (DVS) analyser equipped with NIR-FTIR in order to establish any correlation between surface energy and relative humidity. In addition, *in vitro* dissolution, for simultaneous quantification of polymers and drug was studied.

## 2. EXPERIMENTAL DETAILS

### 2.1. Materials

Different chemicals namely salbutamol sulphate (Sigma Aldrich chemicals, UK), Polyvinylpyrrolidine (K-30, USA), talc BP (Merck, Germany), triethyl citrate (Morflex Inc., USA), HPMCP HP-55 (ShinEtsu, Japan), Eudragit L100-55, Eudragit L30-55 (Rohm Pharma, Germany) ethanol (BDH, UK) were used in this study. The salts used to prepare buffers were of analytical grade and obtained from VWR chemical Ltd., Pole, UK.

### 2.2. Preparation of pH Sensitive Polymeric Films

Aqueous dispersion of Eudragit L30-55, containing 10% polymer, plasticized with 10% triethyl citrate based on dried polymer weight, was poured into Teflon plates and dried at room temperature. The films were subsequently removed and further dried at 50 °C for 24 h to remove any residual water content. After complete drying, the films became hard and were easily broken into pieces and crushed to form powder. The powder was passed through sieve No. 40 and collected in an air tight container until subjected for the different properties evaluation. The above procedure was used for preparing films of Eudragit L100-55 and HPMCP using ethanol: water (9:1) mixture.

### 2.3. Surface Energy Determination

About 800–900 mg powder of polymeric film was packed in silanized glass columns having 30 cm length and 3 mm internal diameter. Even packing was achieved by charging the column with small amount of powdered film at a time and tapping. Column ends were loosely closed with silanized glass wool. The packed columns were then placed on an automated IGC system with flame ionization and thermal conductivity detectors (SMS, London, UK). Columns were conditioned at 30 °C at 0% RH for an hour under helium flow prior to the surface energy determinations to remove any adsorbed or absorbed water and other gases from the sample. Helium, a noble gas that does not chemically interact was used as carrier gas at a flow rate of 6 sccm (standard $cm^3$/min) at which good elution and pressure drop across the column was achieved. Used Solvents or probes (decane, nonane, heptane, hexane, pentane comprised apolar probes while acetonitile, acetone ethyl acetate and dioxane as acid/amphoteric probes) were HPLC-grade and were held at 30 °C throughout experiments. Methane was used as non interacting marker in order to correct for dead volume in the column. Triplicate measurements were made on each column and the results were averaged. Surface energy calculations were performed using SMS IGC Analysis software version 1.3.

### 2.4. Tablet Coating with Enteric Polymer

First, blank tablets were prepared using standard formula comprising Avicel, lactose and stearic acid for direct compression and then drug-loaded tablets were produced by applying salbutamol sulphate-PVP solution onto 25 g blank tablets (Av. wt. 215 mg). Talc was also used in drug-binder solution with continuous stirring before and during the application. Solution of HPMCP as one of the commonly used enteric polymers was subsequently applied onto both blank tablets and drug loaded tablets separately to get blank coated and drug coated tablets using Fluidized-bed coater. There was no difference in the time of coating except processing time for each batch. One batch of blank tablets was double coated with HPMCP solution. In addition, both blank tablets and drug loaded

**Table I.** Formulae for applying drug solution onto blank tablets.

| Ingredients | I | II |
|---|---|---|
| Blank tablets (g) | 25 | 25 |
| Salbutamol sulphate (g) | – | 0.5 |
| Polyvinylpyrrolidine (K-30) (g) | 0.05 | 0.05 |
| Talc BP (g) | 0.05 | 0.05 |
| Ethanol (ml) | 40 | 40 |
| Distilled water (ml) | 10 | – |
| Amber coloured water (ml) | – | 10 |

tablets in equal amounts were also coated with similar coating solutions and processing parameters. Processing parameters used for drug-loading and polymer coating are as follow: inlet air temperature (55–60 °C), atomizing air pressure (1.0 bar), spray rate (1.0–1.5 ml/min) and spray nozzle diameter (1.0 mm). The standard formulae for drug-loaded tablets and polymer coating are shown in Tables I and II.

### 2.5. Dissolution Study

Both blank coated and salbutamol coated tablets were assessed by *in vitro* testing using BP Method II paddle apparatus (model PTWS, Pharma Test, Hainburg, Germany). The distance of $25 \pm 2$ mm between the bottom of the paddle blade and the inside bottom of the vessel was maintained during the test. The volume of the dissolution media was 450 ml maintained at $37 \pm 0.5$ °C and paddle speed of 50 rpm was set. The phthalyl content of HPMCP and salbutamol sulphate from the blank coated and drug coated tablets was determined by an in-line UV spectrophotometer (Cecil 2020 model, UK) with 1 mm flow cells at 280 nm in pH 5.8 buffer. As UV readings were automatically recorded at the interval of every 2 minutes, no loss of media occurred throughout the dissolution test. In addition to testing of tablets in buffer, tablets were also tested in 0.1 M HCl for 2 h to simulate the average gastric residence and then transferred to the pH 5.8 buffer.

### 2.6. Water Vapour Sorption Study

Water uptake study was carried out using a dynamic vapour sorption analyser equipped with near infrared spectrophotometer (DVS-NIR, SMS Ltd., London, UK). Both the blank coated tablets and drug coated tablets were exposed separately to 25 °C at 25% relative humidity (RH). When the variation in the sample mass was less than 0.0010 wt%, equilibrium was assumed and humidity was changed to 50% until again equilibrium was reached. Similarly, RH was changed to maximum of 90% and then back to 75%, 50% and 25% RH (half cycle). The amount of water absorbed was expressed as the mass percentage of water relative to the dry sample mass.

**Table II.** Formulae for applying polymer solution onto both blank and drug loaded tablets.

| Ingredients | I | II | III |
|---|---|---|---|
| Salbutamol tablets (Amber coloured) (g) | 25.0 | – | 12.5 |
| Blank tablets (white) (g) | – | 25.0 | 12.5 |
| HPMCP HP-55 (g) | 5.0 | 5.0 | 5.0 |
| Triethyl citrate (g) | 0.5 | 0.5 | 0.5 |
| Talc BP (g) | 1.0 | 1.0 | 1.0 |
| Ethanol (ml) | 80 | 80 | 80 |
| Distilled water (ml) | 20 | 20 | 20 |

## 3. RESULTS AND DISCUSSION

### 3.1. Surface Energy of Polymeric Films

In this study, the dispersive energies of powdered films of HPMCP, Eudragit L30D-55 and Eudragit L100-55 were determined using IGC measurements and are shown in Table III. Mean dispersive energy of Eudragit L30D-55 was 40.48 mJ/m$^2$ compared to 37.96 mJ/m$^2$ of Eudragit L100-55, while mean dispersive energy of Eudragit L100-55 had been found to be slightly lower due to its pure and amorphous powder nature, used for film formation. Eudragit L30D-55 was in dispersion form and contains other dispersive agents for preparation of this polymeric dispersion. It was observed that there was no remarkable difference in the dispersive energy if determined in the form of pure powder or making powder after film formation. On the other hand, dispersive energy of HPMCP film was found to be 55.03 mJ/m$^2$ and was significantly different from that of L100-55 or Eudragit L30D-55. There are no reported values in the literature for comparison with those obtained in this study. The surface energy of poly(lactic acid) (40 mJ/m$^2$) and polycaprolactone (30 mJ/m$^2$) have been successfully determined by Cava et al.[16] However, IGC has become a widely used method for determining the surface free energy of solids. These data are helpful in predicting the technical performance of materials such as polymers and fibers.[17, 18]

### 3.2. Absorbance of Salbutamol Sulphate

Various concentrations of salbutamol sulphate and HPMCP were dissolved separately in phosphate buffers having pH 5.8 and UV-scanned between wavelength of 400–200 nm (Figs. 1 and 2). Maximum absorbance of salbutamol sulphate was found to be in between 276 to 280 nm and close to maximum absorbance of phthalyl contents of various cellulose derivatives such as HPMCP, PVAP and CAP at 280 nm. As both HPMCP and salbutamol sulphate has maximum absorbance at 280 nm

**Table III.** Dispersive surface energy of various polymeric films.

| Polymeric films | 1 | 2 | 3 | Mean | SD |
|---|---|---|---|---|---|
| Eudragit L30-55 | 41.73 | 40.36 | 39.34 | 40.48 | 1.2 |
| Eudragit L100-55 | 39.74 | 37.22 | 36.93 | 37.96 | 1.55 |
| HPMCP HP-55 | 55.62 | 54.44 | – | 55.03 | 0.83 |

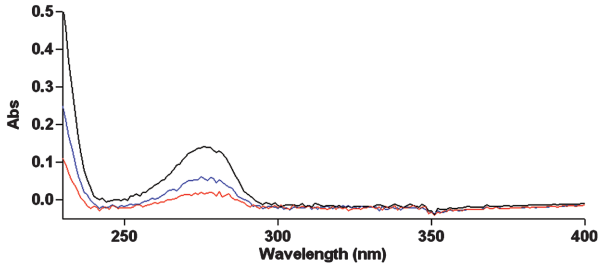


**Fig. 1.** UV-scan of known concentrations of Salbutamol Sulphate solution at wavelength between 400–200 nm.

therefore it was hypothesized to quantify phthalyl content indirectly by coating with HPMCP solution separately onto blank or drug loaded tablets as well as together with equal amount of blank (white) and drug loaded tablets (Amber colour) using similar coating parameters. After coating, both types of tablets were sorted out from the coated tablets i.e., mixture of blank and drug coated tablets and stored separately for further dissolution studies. Figure 3 shows *in vitro* release of phthalyl group from blank tablets coated with single and double coat of HPMCP. It is apparent from the figure that the release of phthalyl group from the single or double coat reaches its highest value at almost similar time intervals (14 min), while the amount released is almost half in case of single coat compared to double coat and was confirmed using standard curve of known concentrations of HPMCP in pH 5.8 solutions. Figure 4 shows *in vitro* release of phthalyl group from blank tablets and combined release of salbutamol sulphate along with phthalyl group from coated tablets. Most of the HPMCP coat was completely converted to phthalyl group at pH 5.8 within 14 minutes from both blank and drug coated tablets. After that more, than 80% of salbutamol sulphate from drug coated tablets was released within 6 minutes. The combined amount released from the drug coated tablets was almost doubled than the amount released from the blank coated tablets and the difference representing the amount of drug which was loaded on the surface of the blank tablet prior to polymer coating. Therefore, amount of the drug released from the coated tablets can be determined by subtracting the

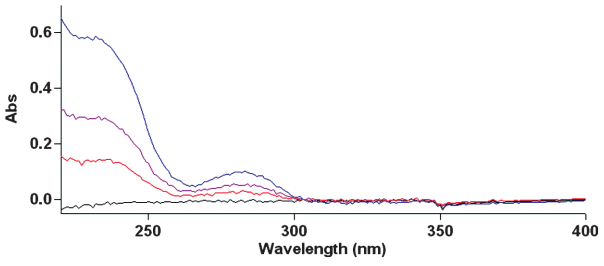


**Fig. 2.** UV-scan of known concentrations of HPMCP solution at wavelength between 400–200 nm.

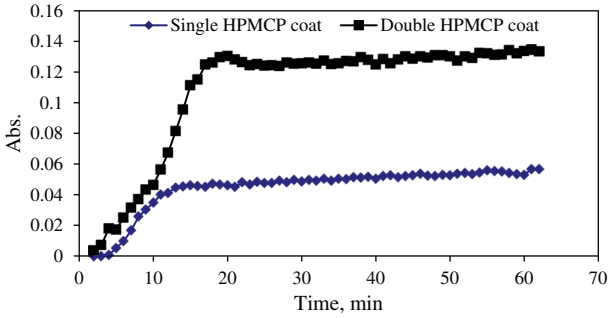


**Fig. 3.** *In vitro* release of HPMCP in pH 5.8 from blank tablets coated with two different coats of HPMCP.

polymer release in the blank coated tablets from combined drug-polymer release in coated tablets.

### 3.3. Water Vapour Sorption-NIR Spectra

Figure 5 shows DVS changes in mass versus RH in blank coated tablets and changes in NIR versus RH respectively. As the percent RH increases, there was a gradual increase in the mass of coated film and after reaching highest value at about 90% RH, it turns down at low percent RH. It was observed that as the RH increases more and more water molecules are adsorbed on the surface of the coated polymeric film to increase the weight of coated tablet. NIR spectra of both blank coated and drug coated tablet was taken separately in the beginning and at each step of changing RH after 15 minutes throughout the experiment. NIR spectra of blank coated tablets taken at various RH (overlay) is shown in Figure 6, while NIR spectra of coated tablets containing salbutamol taken at 25–75% and 90% RH are shown in Figures 7 and 8 respectively. The NIR spectra in Figures 7 and 8 are not distinguishable except for small changes in the region at 1940 nm related to adsorption of water where O–H stretching and deformation is prominent. Although the pattern of NIR spectra is different in both coated tablets but no change in NIR of blank coated tablet is apparent throughout various RH (25–90%). On the other hand, no change in NIR spectra of coated tablet was observed at three different RH

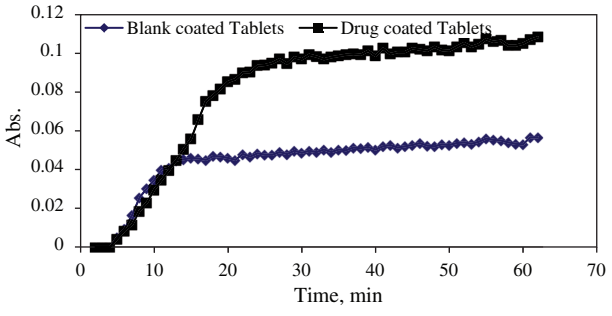


**Fig. 4.** *In vitro* release of both salbutamol and HPMCP from drug coated tablets and release of HPMCP from blank coated tablets in pH 5.8.

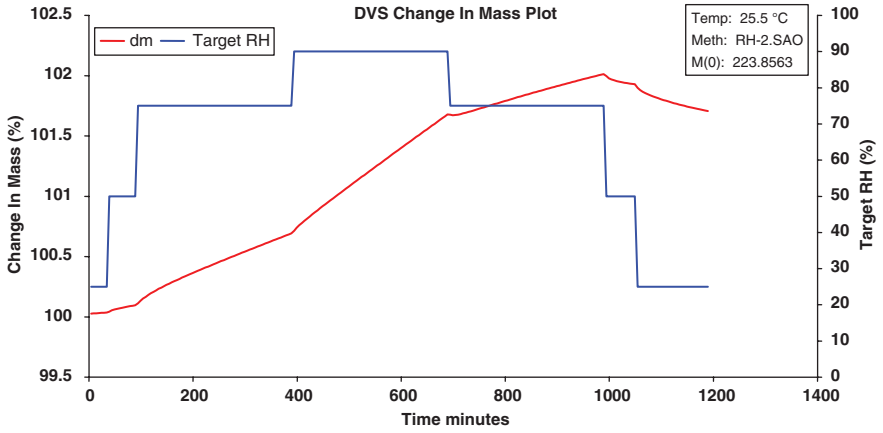


**Fig. 5.** Increase in percent weight of coated tablet with an increase of relative humidity.

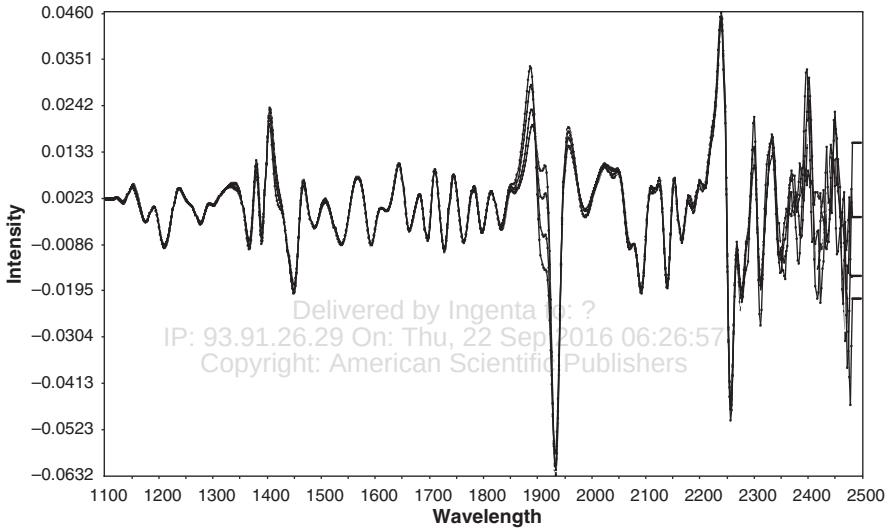




**Fig. 6.** Near FTIR spectra of drug loaded tablet taken at 25, 50, 75 and 90% relative humidity.

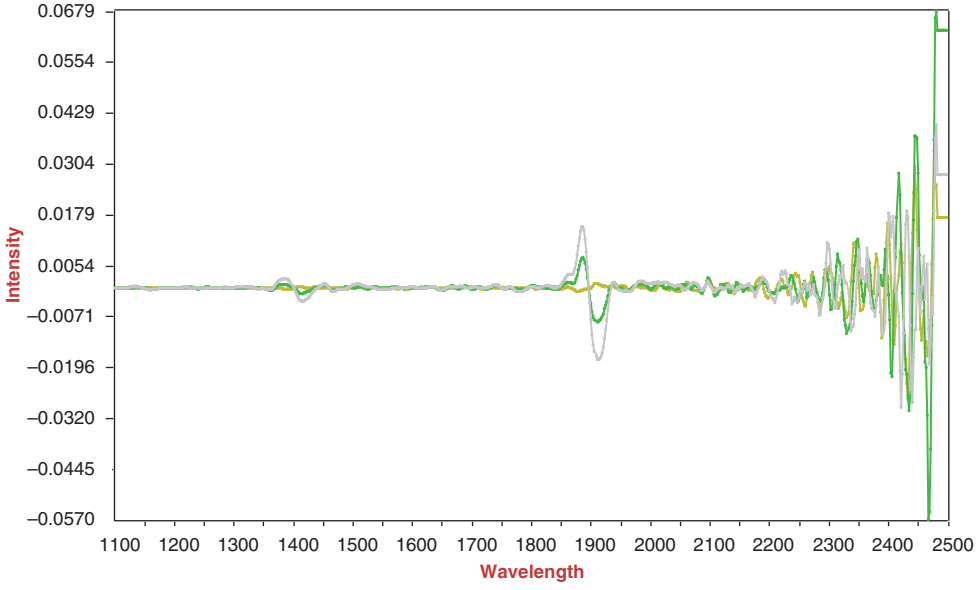


**Fig. 7.** Near FTIR spectra of HPMCP-coated tablet taken at 25, 50, and 75% relative humidity.



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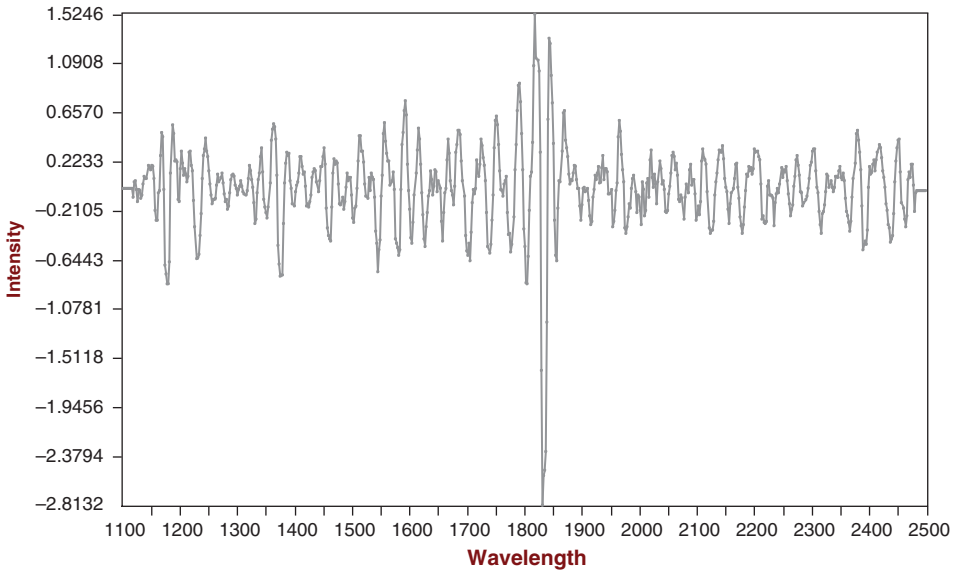


**Fig. 8.** Near FTIR spectra of HPMCP-coated tablet taken at 90% relative humidity.

(25%, 50% and 70%) but total change is quite apparent at 90% RH (Fig. 8). Such changes in the spectra of coated tablet indicated possibility of water molecules to penetrate into the polymeric film at 90% RH and dissolved the drug layer on the surface of the tablet. Therefore, NIR spectra at 90% RH is most probably of salbutamol sulphate solution formed in coated tablet in contrast to spectra of polymeric film up to 70% RH. Thus higher surface energy of HPMCP caused instability of the coated tablets at 90% RH. This helps to establish relationship between higher surface energy and RH and can be considered in formulation development. The influence of humidity on surface energetics and flow behavior of fine pharmaceutical powders was investigated by Karde and Ghoroi. The specific component of surface energy was found to increase with increasing RH for hydrophilic excipients.[19] The increase in surface free energy values of polymers (polypropylene, polyethylene and polyvinyl alcohol) was found to cause a decrease in water contact angles of polymers due to high adhesion interactions between the solid surface and the water droplet.[20]

## 4. CONCLUSION

The above results proves that HPMCP film having higher surface energy is sensitive at higher humidity areas and can interact with active as well as inactive components of coated dosage forms. Therefore, IGS technique is reliable analytical tool in determining the surface energy of polymeric films and can be employed in preformulation and stability studies of pharmaceutical products. Moreover, in addition to HPMCP, the phthalyl contents of other cellulose derivatives such as poly vinyl acetate phthalate and cellulose acetate phthalate can be determined by UV spectrophotometer at 280 nm.

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