



Received on 12 May, 2015; received in revised form, 08 June, 2015; accepted, 10 September, 2015; published 01 November, 2015

EFFECT OF RELATIVE HUMIDITY ON ACETAMINOPHEN TABLET PROPERTIES PREPARED BY DIFFERENT TECHNIQUES USING POLYVINYLPIRROLIDINE DERIVATIVES AS BINDER

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Keywords:

Dissolution,
Moisture Uptake,
Direct Compression,
Wet Granulation,
Tablet Hardness, Powder Rheology

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ABSTRACT: Amount of moisture content present in solid dosage forms plays a major role in influencing the physicochemical properties of tablets such as dissolution rate, disintegration time, hardness, etc. The aim of the current study was to investigate the effect of relative humidity (RH) exposure on various properties of acetaminophen tablets manufactured by direct compression and wet granulation methods. Microcrystalline cellulose was used as diluent and Plasdone™ K-29/32 and Kollidon® 90F as binder in different formulations. Wet granulation end point was determined using thermal effusivity measurements. Compressed tablets were exposed to 2%, 22%, 52% and 75% RH for 48 hours at room temperature ($26 \pm 1^{\circ}\text{C}$). Powder rheometer was used to evaluate the flow properties of granules after RH exposure. USP dissolution apparatus II was used to study the *in-vitro* drug release profiles after humidity exposure compared to reference. Thermal properties of different humidity exposed granules were examined by modulated differential scanning calorimetry. Tablets were further analyzed for hardness and disintegration time. The observed results suggested that the initial drug release was retarded for the directly compressed tablets with increase in RH exposure compared to wet granulated tablets where no major difference was observed. Viscosity of binder solution also played a significant role in the moisture uptake. Hardness of the directly compressed tablets was higher and also decreased with humidity exposure. The results show a comparative aspect of the influence of relative humidity on tablets manufactured by various techniques and different excipients on the performance properties of tablets.

INTRODUCTION: Granulation is an agglomeration process of smaller powder particles to form larger granules having uniform size and shape with the help of granulation binders to improve the dissolution rates, bulk density, flow properties etc.

Wet granulation involves addition of aqueous or alcoholic binder solution to form larger particles whereas direct compression refers to dry addition and uniform mixing of all the required ingredients followed by compression to form tablets¹. Determination of optimum region for wet granulation end point has always been a challenge and many techniques have been used traditionally like near infrared spectroscopy², power consumption³, acoustic emission monitoring⁴, focused beam reflectance measurement⁵, etc. Recently, Dugar and Dave et al showed the use of thermal effusivity measurements to successfully and accurately determine the optimum region of wet granulation end point⁶.

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| <p>QUICK RESPONSE CODE</p>  | <p>DOI: 10.13040/IJPSR.0975-8232.6(11).4629-38</p> |
| <p>Article can be accessed online on: www.ijpsr.com</p> | |
| <p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(11).4629-38</p> | |

Tablets have been one of the most convenient and simplest ways of administering drugs into the body and physicochemical properties of tablets such as dissolution rate, disintegration time and hardness are highly influenced by formulation contents and amount of moisture present in the formulation⁷. Wet granulation has been a widely used technique for tablet manufacturing but direct compression have also been used to a large extent because of the advantages it provides over wet granulation^{8, 9}.

Acetaminophen (APAP) has been chosen as model drug in the current study due to its extensive use and studying its characteristics being important. It is chemically N-acetyl-p-aminophenol and its molecular weight is 151.16 g/mole belonging to BCS class III¹⁰⁻¹². It is known for its analgesic and antipyretic properties and thus is widely used in the pharmaceutical world. APAP is a weekly basic drug having a water solubility of 12.78 mg/ml¹³. It has a half-life of 1 to 4 hours¹⁴. Due to its ease of administration, it has a wide variety of formulations available in the market namely tablets, capsules, liquids, suppositories, etc.¹⁵

Microcrystalline cellulose PH 101 (Avicel® PH 101) is one of the major excipients which is used as diluent in pharmaceutical industry and is known to possess excellent compressibility properties^{16, 17}. Binders used in granulation process are important in governing the physical properties of tablets and thus makes an considerable contribution in dictating the performance of granules and tablets^{6, 18}. Plasdone™ K-29/32 is used as a tablet binder and whitening or stain removal agent in the oral care products. Kollidon® 90F is high molecular weight polymer which is comparatively less soluble in water and is also used as a binder in various formulations.

Dissolution methodology has been traditionally used to predict and understand the *in-vivo* release behavior of active pharmaceutical ingredients^{11, 19, 20}. Drug dissolution is a kinetic phenomenon which gives the rate of drug leaving the matrix of the dosage form and entering into solution under standardized conditions. It is used to predict the performance of drug in body after administration. It is used for bio-waiver for many generic formulations²¹⁻²³. US Pharmacopoeia recommends

use of USP dissolution apparatus II (Paddle) for Acetaminophen tablets.

Humidity conditions make an important contribution in the maintenance of stability and quality of tablets while storage^{24, 25}. Adsorbed moisture during storage can affect lot of tablet properties which could lead to performance failure²⁶. Designing an appropriate range of humidity conditions for storage of tablets at room temperature is essential for longer stability and achieving desired dissolution rate in body²⁷.

The present study focuses on comparing the effect of RH conditions on the two mentioned techniques used for formulation of tablets with different binders and ultimately its effect on performance properties of tablets.

MATERIALS & METHODS:

Microcrystalline Cellulose PH 101 (Avicel® PH 101, Lot # P112824635) was a generous sample provided by FMC Biopolymer Corp., Philadelphia, PA, USA. Acetaminophen (Batch # 12G26-U08-005520) was kindly supplied by Fargon Inc., St. Paul, Minnesota, USA. Kollidon® 90F (Lot # 92831316K0) was provided by BASF Corporation, Ludwigshafen, Germany. Plasdone™ K-29/32 (Lot # 032307239) was purchased from ISP Technologies Inc., Wayne, NJ, USA. De-ionized water (Barnstead Nanopure, Thermoscientific, Model# 7119) was collected fresh and utilized when needed.

UV spectroscopy calibration curve:

Stock solution of acetaminophen in simulated intestinal fluid without enzymes having pH=6.8 (100 µg/ml) was scanned through 200-400nm wavelength to determine the λ_{max} . Standard curve was prepared using different concentrations (1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 µg/ml) in triplicates. Filter binding studies were also performed for drug solution using 0.45µm polytetrafluoroethylene (PTFE) syringe filters.

Blending:

32.5% w/w APAP was blended with MCC to make 500 grams of pre-blend in a V-blender for 15 min at 12 RPM and samples (top, middle and bottom) were collected initially at regular intervals and

blend uniformity was confirmed by UV spectroscopy. 5, 10 and 15 mm from the bottom of the V-shell were considered as bottom, middle and top sampling points respectively. Blending time was validated to be used for all the batches. Final blend was stored in tightly sealed containers for wet granulation and direct compression.

Wet granulation:

Binder solution was made by adding 3 grams of dry binder to 97 grams of constantly stirred deionized water to make 3% w/w binder solution. Prepared binder solution was added to the pre-blended APAP in MCC in a ratio of 1:1 w/w for both binders in Cuisinart mixer for the first 30 seconds at a constant rate and then was allowed to mix for 3 minutes at 100 revolutions per minute (rpm) for uniform mixing and granulation. Obtained granules were further dried in a gravitational convection oven at 70°C until constant loss on drying (LOD) values was obtained. Dried granules were passed through sieve no. 12 in order to obtain uniform granules and then were stored in sealed containers for further immediate processing.

Direct compression:

Direct compression is the process of blending the active pharmaceutical ingredient with other excipients to get a uniform mixture followed by compaction to get tablets. Direct compression blend was prepared by blending 3% w/w dry binder to the pre-blended mixture of APAP in MCC to keep a similar amount of binder that was used in wet granulation approach assuming complete water loss during drying. This blend was stored in sealed containers for powder rheology studies and was later compressed to form tablets.

Thermal effusivity:

Thermal effusivity is a dynamic property that takes into account the thermal conductivity, density and heat capacity of the material as shown in equation below. Thermal effusivity measurements were conducted using the thermal conductivity probe (Mathis Instruments, Canada) which was calibrated prior to testing using polymethylsiloxane as a standard. Principle behind the working of this probe is that it transmits heat to the material surface and measures the heat that is not absorbed by the material to give the thermal effusivity reading as

per the formula below. Constant volume of test sample was ensured in order to minimize any density variations. Above concept has been previously used to determine the optimum region for wet granulation end point⁶. Measurements were done on small 10g batches and were confirmed later on with the actual batches (500g) in triplicates. Measurements were performed until slurry formation for all the batches.

$$Effusivity = \sqrt{k \times \rho \times C_p}$$

Where,

$$k = \text{Thermal conductivity } \left(\frac{W}{m.K} \right)$$

$$\rho = \text{Density of the material } \left(\frac{Kg}{m^3} \right)$$

$$C_p = \text{Heat capacity } \left(\frac{J}{Kg.K} \right)$$

Modulated differential scanning calorimetry (MDSC):

MDSC analysis was used to study the thermal properties of all samples using the Q100 (TA instruments, New Castle, DE) instrument with nitrogen (50ml/min) as a purge gas. Indium was used for calibration of equipment for temperature and cell constant before performing experiments. Baseline and heat capacity calibration were also conducted by heating the empty cell and using sapphire respectively. Different RH exposed granules within a sample size of 9±3 mg were analyzed using the pin-holed hermetically sealed aluminum pans. Heating rate of 5°C/min was used for a range of 20°C to 250°C with a modulation of ±1.06°C every 40s. Obtained thermograms were integrated to analyze the change in enthalpy (ΔH) and in crystallinity of acetaminophen.

Tablet compression and evaluation:

Dried granules and direct compression blend using different binders were compressed using a single station Carver tablet press (Indiana, USA) at a force of 2500 pounds using “B” type tooling and concave punches with a tablet weight of 1000±10 mg for all the batches. Tablets were stored in tightly sealed containers and were then exposed to different relative humidity conditions for further studies. Twenty tablets from each batch were tested

for evaluating tablet hardness using Schleuniger tablet tester 6D. Disintegration test was carried out on six tablets for each batch in 200 ml of deionized water in USP disintegration apparatus.

Relative humidity exposure:

Dried granules, direct compression blend and compressed tablets were subjected to 2%, 22%, 52% & 75% RH conditions in tightly sealed chambers for 48 hours at room temperature until equilibrium was achieved. Saturated salt solutions prepared with distilled water were used for simulating different RH conditions in glass chambers. Saturated salt solution of potassium acetate, magnesium nitrate and sodium chloride were used to generate 22% (± 0.32), 52% (± 0.22) & 75% (± 0.14) respectively²⁸. Reference of 2% (± 0.5) RH condition was used for comparison and was generated using a desiccator. A digital hygrometer was used to further confirm the established RH conditions.

Powder rheology:

FT4 powder rheometer (Freeman technology, UK) was used to evaluate and compare the rheological properties of various humidity exposed granules and blends. Torque, force, spindle and height calibrations were previously done for the instrument to ensure accuracy. Basic flow ability energy (BFE) & Specific energy (SE) measurements were performed on all samples. 48 mm stainless steel blade and 50mm x 160ml glass vessel was used for testing. BFE is the work done by the downward anti-clockwise motion of the rheometer blade at a tip speed of 100mm/sec to displace constant volume of the conditioned powder from top to bottom of the vessel. SE is the energy required for the upward clockwise motion of the blade in an unconfined low stress environment. Volume variation of test samples for different batches was minimized using the split vessel. Tests were done in triplicate immediately after humidity exposure.

Loss on drying (LOD):

All the granules and tablets were subjected to Loss on drying analysis immediately after RH exposure to determine the moisture uptake using an Ohaus MB25 moisture analyzer with a halogen lamp. The

samples were dried at 105°C until a constant %LOD was obtained.

In-vitro dissolution testing:

For dissolution studies, USP dissolution apparatus II was used to study the *in-vitro* drug release profile of acetaminophen tablets. Compressed tablets having different binders were separately exposed to above mentioned relative humidity conditions for 48 hours. Testing was carried out in simulated intestinal fluid without enzymes (pH=6.8) at paddle speed of 50 rpm at $37 \pm 0.5^\circ\text{C}$. Samples were taken at pre-determined sampling intervals of 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes. 5 ml of sample was withdrawn at the particular sampling time point and was replaced by fresh media simultaneously. Collected samples were filtered through 0.45 μm PTFE filters and were further diluted 20 times with media before analyzing in UV spectrophotometer at a wavelength of 243 nm. Cumulative percentage drug released was noted against time to understand and compare the *in-vitro* drug release profiles. All samples were done in triplicates and average was considered.

The f_2 similarity factor was calculated for each formulation at each humidity exposure condition to test the similarity or dissimilarity in the profiles considering tablets stored at 2% RH conditions as reference. Dissolution profiles having value of f_2 equal to or greater than 50 were considered as similar and ones having value below 50 were considered statistically different from the reference. The f_2 values were calculated using the formula below as per US FDA guidelines^{11, 29, 30},

$$f_2 = 50 \times \log_{10} \left\{ 1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right\}^{-0.5} \times 100$$

Where,

n = number of sample time points

R_t = Percent dissolved of reference (2% RH)

T_t = Percent dissolved of sample (22, 52, 75% RH)

RESULTS & DISCUSSION:

UV spectroscopy calibration curve:

λ_{max} for the stock solution of acetaminophen was found to be 243 nm. Data for the calibration curve from UV spectroscopy is shown in **Fig. 1**. The graph follows a linear pattern with R^2 value of

0.9997. Equation for the line is shown in Fig. 1 which was used for further analysis of acetaminophen tablets. Absorbance readings taken after filtering the samples through 0.45µm PTFE

filter did not show any statistically significant difference confirming that the drug did not bind to the filters extensively.

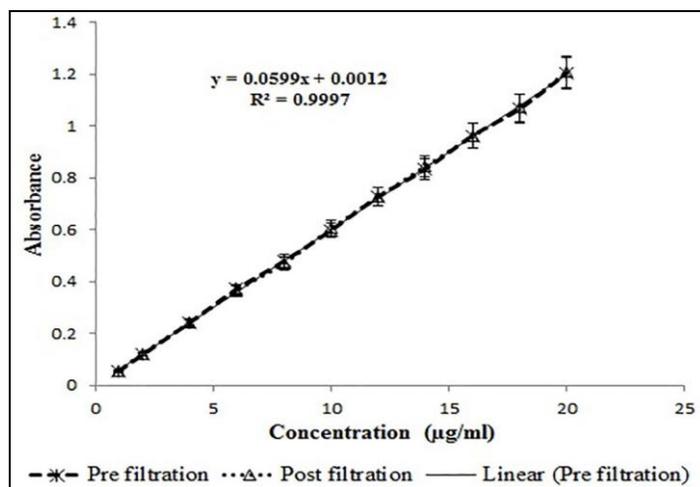


FIG.1: UV SPECTROSCOPY CALIBRATION CURVE FOR ACETAMINOPHEN

Blending:

Blending time was validated to be 15 min at a constant speed of 12 rpm, respectively by repetitive iterations and confirming uniformity by UV

spectroscopy. Samples were taken from three distinct areas (top, middle and bottom) of the V-shell blender and data is shown below in Table 1 at different time points.

TABLE 1: VALIDATION OF BLENDING TIME

| Time (Min.) | Percent amount of APAP | | | | | |
|-------------|-------------------------|--------|--------|---------------------|--------|--------|
| | Plasdone™ K-29/32 Blend | | | Kollidon® 90F Blend | | |
| | Top | Middle | Bottom | Top | Middle | Bottom |
| 5 | 30.83 | 31.24 | 31.05 | 30.08 | 30.19 | 30.93 |
| 10 | 30.75 | 30.88 | 30.11 | 32.05 | 32.14 | 32.25 |
| 15 | 32.58 | 32.44 | 32.66 | 32.68 | 32.33 | 32.55 |

Thermal effusivity:

It has been observed in all batches that thermal effusivity value increases gradually with the increase in amount of liquid binder solution until certain point and then beyond that point, a sudden rise in effusivity value is observed as seen in Figure 2. The point before this sudden rise is considered to be the optimum region for wet granulation end point³¹. 50% w/w binder solution was found to be the optimum region for both binders. It has also been noticed that slurry formation occurs on further addition of binder solution to powder blend. The sudden rise in effusivity values was further justified by over-granulation or slurry formation which takes place due to excess addition of binder solution. At this stage, the probe measures the effusivity value close to that of binder solution.

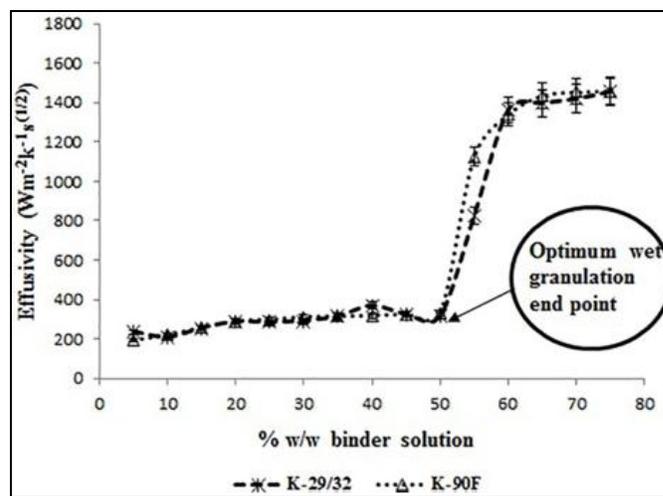


FIG. 2: THERMAL EFFUSIVITY AS A FUNCTION OF % BINDER SOLUTION

MDSC measurements:

Thermograms obtained by MDSC analysis for direct compression blend and dried granules (before and after humidity exposure) were integrated to compute the enthalpy change. These values for all the batches are shown in **Table 2** (Direct compression) and 3 (Wet granulation). Melting point of pure acetaminophen was found to

be 169.89°C. As can be seen, there was a slight change in enthalpy after humidity exposure for all the samples and thus confirming that the observed dissolution profile changes were due to the probable matrix formation phenomenon and not due to changes in crystallinity of drug as discussed below in dissolution results.

TABLE 2: ENTHALPY VALUES OF DIRECT COMPRESSION BLEND AS A FUNCTION OF %RH EXPOSURE

| Sample | Direct Compression | | | |
|-----------|--------------------|----------------|------------------|----------------|
| | Plasdone™ K-29/32 | | Kollidon® 90F | |
| | ΔH (J/g) | Peak Temp (°C) | ΔH (J/g) | Peak Temp (°C) |
| Pure APAP | 210.9 | 169.89 | 210.9 | 169.89 |
| 2% RH | 37.97 | 170.11 | 47.02 | 169.86 |
| 22% RH | 38.37 | 169.71 | 41.89 | 169.95 |
| 52% RH | 31.81 | 170.24 | 43.91 | 169.94 |
| 75% RH | 38.19 | 170.05 | 51.08 | 170.39 |

TABLE 3: ENTHALPY VALUES OF DRIED GRANULES AS A FUNCTION OF %RH EXPOSURE

| Sample | Wet Granulation | | | |
|-----------|-------------------|----------------|------------------|----------------|
| | Plasdone™ K-29/32 | | Kollidon® 90F | |
| | ΔH (J/g) | Peak Temp (°C) | ΔH (J/g) | Peak Temp (°C) |
| Pure APAP | 210.9 | 169.89 | 210.9 | 169.89 |
| 2% RH | 36.99 | 167.33 | 33.79 | 170.79 |
| 22% RH | 33.89 | 170.37 | 37.16 | 171.05 |
| 52% RH | 38.56 | 169.85 | 34.75 | 170.67 |
| 75% RH | 34.36 | 169.80 | 36.26 | 170.53 |

Powder rheology:

BFE values for direct compression powder blend with the two binders are shown in **Fig.3(A)**. As can be clearly seen from the graph, the energy required for flow of powder bed decreased with increasing humidity conditions making the blend easier to flow for both binder batches. It can be inferred that the adsorbed moisture on the dry blend acts as a lubricant and thus offers less resistance to the blade to move through the powder bed and thus requires less energy.³¹

On the other hand, BFE values for both batches of granules prepared by wet granulation doesn't show any accountable change as shown in **Fig. 3(B)** indicating the negligible sorption of moisture due to change in relative humidity conditions. This observation is seen due to the hygroscopic nature of MCC which interlocks lot of moisture during granulation and hence, it does not have much affinity to moisture in the humidity chambers and hence negligible amount of moisture uptake.³² Direct compression blend containing dry MCC has lot of affinity and thus adsorbs moisture from

environment. It is also observed that the SE values for all the batches of dry powder as well as wet granules remain constant suggesting that there is a little effect of humidity conditions on the unconfined flow properties as seen in **Fig.3**.

Tablet evaluation:

Fig. 4(A) shows the hardness values of compressed acetaminophen tablets for all batches after being exposed to different relative humidity conditions. It can be seen from the data that tablet hardness shows a negative correlation with the humidity conditions.

Also, tablets prepared by direct compression have relatively higher hardness than the ones made by wet granulation. These results are further supported by disintegration test results shown in **Fig.4(B)** which also shows a similar trend for all the tablets made by different techniques. Tablets prepared by wet granulation exhibit quicker disintegration in comparison due to their increased wettability.

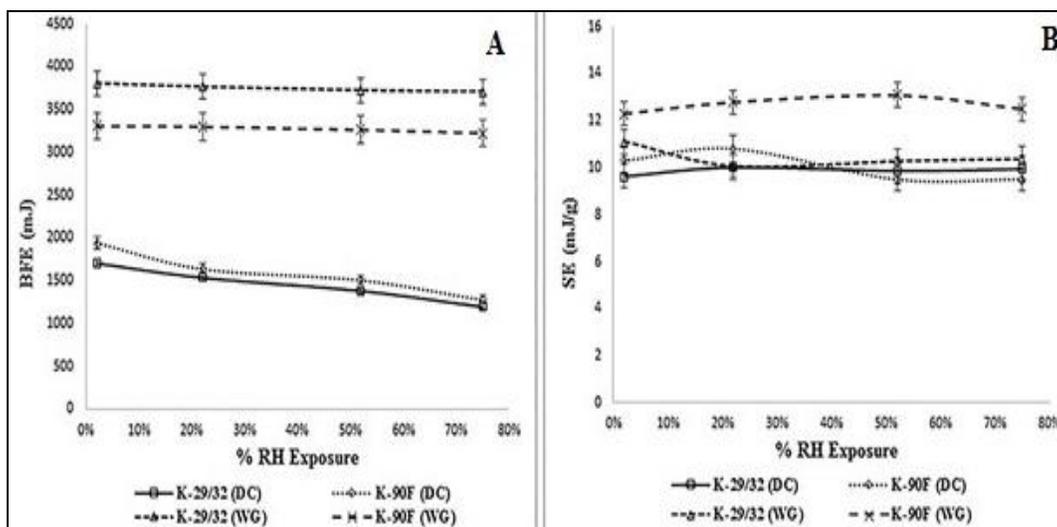


FIG.3: BASIC FLOWABILITY ENERGY (BFE) AND SPECIFIC ENERGY (SE) AS A FUNCTION OF % RH EXPOSURE

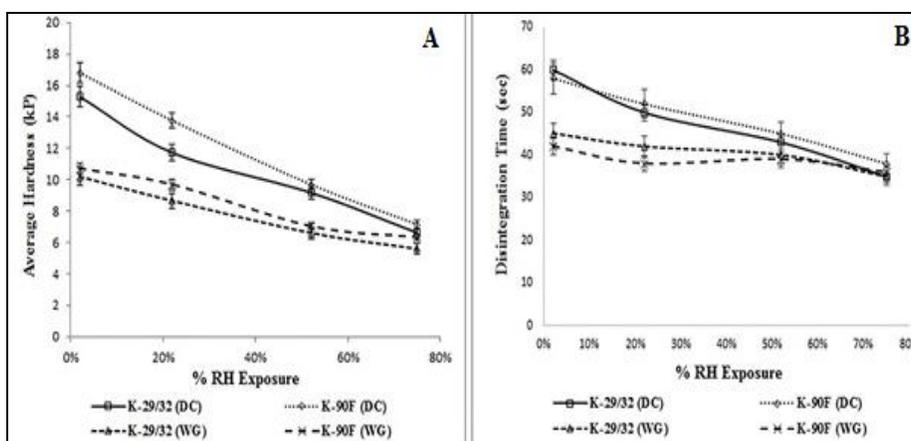


FIGURE 4: COMPARISON OF HARDNESS AND DISINTEGRATION TIME OF TABLETS

Loss on drying (LOD):

Results from the loss on drying experiments are shown in Table 4 (Direct compression) and 5 (Wet granulation). As can be seen from the values, the granules and tablets prepared from direct

compression show greater sorption of moisture as compared to the ones prepared by wet granulation. This confirms the rheology behavior of granules and *in-vitro* dissolution data of tablets.

TABLE 4: PERCENT LODVALUES OF DIRECTLY COMPRESSED POWDER AND TABLETS

| RH Exposure | Direct Compression(%LOD) | | | |
|-------------|--------------------------|---------|---------------|---------|
| | Plasdone™ K-29/32 | | Kollidon® 90F | |
| | Blend | Tablets | Blend | Tablets |
| 2% RH | 1.83 | 2.02 | 2.11 | 2.22 |
| 22% RH | 5.84 | 3.26 | 3.46 | 3.03 |
| 52% RH | 6.13 | 4.35 | 4.16 | 3.56 |
| 75% RH | 9.24 | 6.95 | 7.89 | 4.39 |

TABLE 5: PERCENT LODVALUES OF WET GRANULATION GRANULES AND TABLETS

| RH Exposure | Wet Granulation(%LOD) | | | |
|-------------|-----------------------|---------|---------------|---------|
| | Plasdone™ K-29/32 | | Kollidon® 90F | |
| | Granules | Tablets | Granules | Tablets |
| 2% RH | 3.74 | 3.59 | 3.33 | 3.81 |
| 22% RH | 3.96 | 3.46 | 3.49 | 4.06 |
| 52% RH | 4.08 | 3.89 | 3.53 | 4.18 |
| 75% RH | 4.15 | 4.03 | 3.68 | 4.22 |

In-vitro dissolution testing:

Standard curve and the linear equation obtained as shown in **Fig.1** were used to calculate the unknown concentration of acetaminophen in the dissolution samples. Percent cumulative drug release profiles for tablets prepared by direct compression are shown in **Fig.5** for Plasdone™ K-29/32 and Figure 6 for Kollidon® 90F. Similarly, profiles for tablets prepared using wet granulation technique are shown in Figure 7 for Plasdone™ K-29/32 and Figure 8 for Kollidon® 90F. A comparison of humidity exposure on the different tablets is shown above and the effect of moisture sorption was studied and evaluated.

From the dissolution profiles, it can be clearly inferred that after exposure to humidity, the initial dissolution rate slowed down for tablets prepared by direct compression where significant retardation was seen after 75% humidity exposure for Plasdone™ K-29/32 containing tablets. This observation indicated that sorption of moisture on directly compressed tablets possibly created a matrix after combining with the polymer which slowed down the release of APAP. The phenomenon of matrix formation was more pronounced for low viscosity binder Plasdone™ K-29/32 as compared to Kollidon® 90F which is the low viscosity binder.

The f_2 similarity factor values for all samples are shown in **Table 6** (Direct compression) and 7 (Wet granulation). It confirms that dissolution profile was statistically different after 75% RH exposure compared to reference. On the other hand, dissolution profiles for humidity exposed tablets prepared by wet granulation for both binder solutions did not show any significant difference. These values for all formulations prepared by wet granulation were above 50 except for 75% RH exposure for Kollidon® 90F batch which was also only marginally lower than 50. There was little sorption of moisture for these tablets and phenomenon of matrix formation was not that prominent as can be seen from the LOD values. Possible reason for the above results is due to the hygroscopic nature of MCC which absorbs water during wet granulation and hence, there was not much moisture uptake. Powder rheology and tablet

physical properties confirmed the above phenomenon and similar results were obtained.

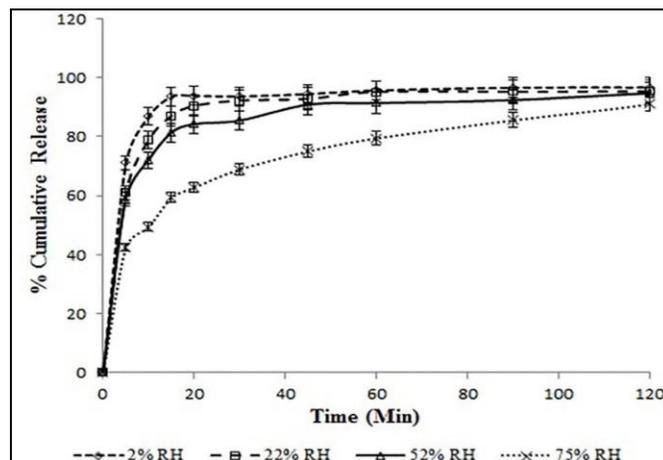


FIG. 7: DISSOLUTION PROFILE OF DIRECTLY COMPRESSED TABLETS WITH PLASDONE™ K-29/32 AT DIFFERENT %RH EXPOSURE

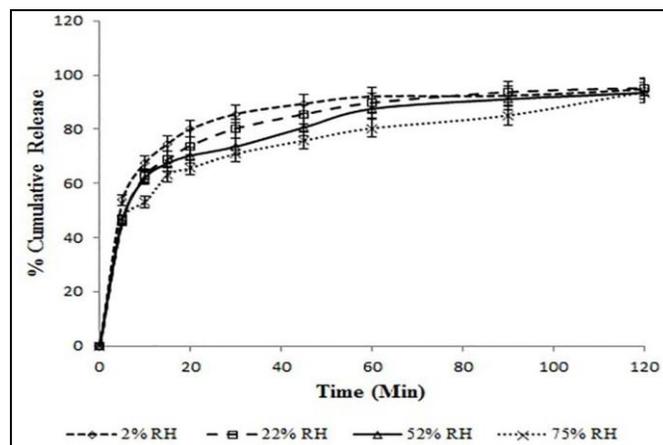


FIG.8: DISSOLUTION PROFILE OF DIRECTLY COMPRESSED TABLETS WITH KOLLIDON® 90F AT DIFFERENT %RH EXPOSURE

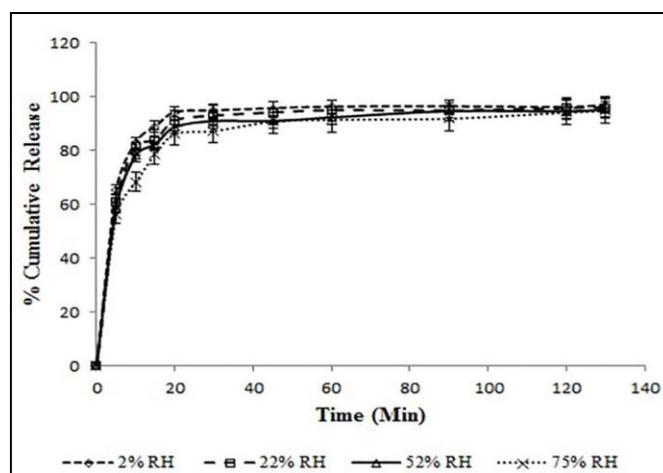


FIG. 9: DISSOLUTION PROFILE OF WET GRANULATED TABLETS WITH PLASDONE™ K-29/32 AT DIFFERENT %RH EXPOSURE

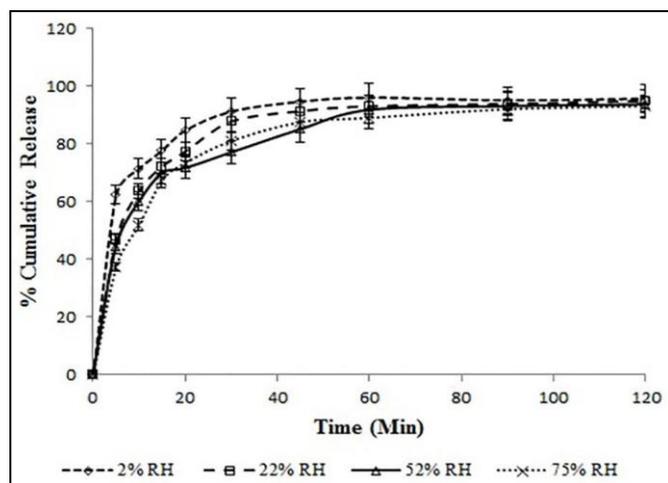


FIG. 10: DISSOLUTION PROFILE OF WET GRANULATED TABLETS WITH KOLLIDON® 90F AT DIFFERENT %RH EXPOSURE

TABLE 6: F₂ VALUES FOR DISSOLUTION PROFILES OF DIRECTLY COMPRESSED TABLETS

| % RH Exposure | F ₂ Values (Direct Compression) | |
|---------------|--|---------------|
| | Plasdone™ K-29/32 | Kollidon® 90F |
| 22% | 66.469 | 67.703 |
| 52% | 54.329 | 58.779 |
| 75% | 32.006 | 48.913 |

TABLE 7: F₂ VALUES FOR DISSOLUTION PROFILES OF WET GRANULATED TABLETS

| % RH Exposure | F ₂ Values (Wet Granulation) | |
|---------------|---|---------------|
| | Plasdone™ K-29/32 | Kollidon® 90F |
| 22% | 79.267 | 60.242 |
| 52% | 68.255 | 50.979 |
| 75% | 56.836 | 46.748 |

CONCLUSION: Moisture uptake affects the tablet properties and can lead to batch failures post storage of formulation. Above research explains this phenomenon on two different manufacturing techniques and its effect on moisture sorption. Composition variation is also an integral part of current pharmaceutical practice and it affects the stability of formulation in many ways. Above work gives an insight into this aspect and will help formulation scientists to develop more stable formulations.

ACKNOWLEDGEMENT: The authors are thankful to Division of Pharmaceutical Sciences, Long Island University to provide an opportunity to conduct the above research.

CONFLICT OF INTEREST:

The authors report no conflict of interest.

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How to cite this article:

Dugar RP, Gupta P and Dave RH: Effect of Relative Humidity on Acetaminophen Tablet Properties Prepared by Different Techniques Using Polyvinylpyrrolidone Derivatives as Binder. *Int J Pharm Sci Res* 2015; 6(11): 4629-38. doi: 10.13040/IJPSR.0975-8232.6(11).4629-38.

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