
Research Article

Effects of Thermal Curing Conditions on Drug Release from Polyvinyl Acetate–Polyvinyl Pyrrolidone Matrices

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Abstract. This study aimed to investigate the effects of dry and humid heat curing on the physical and drug release properties of polyvinyl acetate–polyvinyl pyrrolidone matrices. Both conditions resulted in increased tablet hardness; tablets stored under humid conditions showed high plasticity and deformed during hardness testing. Release from the matrices was dependent on the filler's type and level. Release profiles showed significant changes, as a result of exposure to thermal stress, none of the fillers used stabilized matrices against these changes. Density of neat polymeric compacts increased upon exposure to heat; the effect of humid heat was more evident than dry heat. Thermograms of samples cured under dry heat did not show changes, while those of samples stored under high humidity showed significant enlargement of the dehydration endotherm masking the glass transition of polyvinyl acetate. The change of the physical and release properties of matrices could be explained by the hygroscopic nature of polyvinyl pyrrolidone causing water uptake; absorbed water then acts as a plasticizer of polyvinyl acetate promoting plastic flow, deformation, and coalescence of particles, and altering the matrices internal structure. Results suggest that humid heat is more effective as a curing environment than dry heat for polyvinyl acetate–polyvinyl pyrrolidone matrices.

KEY WORDS: aging; drug release; physical stability; polyvinyl acetate–polyvinyl pyrrolidone; pycnometric density; thermal curing.

INTRODUCTION

The success of the process of development of a drug delivery system (DDS) is highly dependent on the appropriate selection and processing of a carrier material capable of exerting the desired control on the onset and rate of drug delivery (1).

A significant proportion of carriers in oral DDSs are polymeric materials fabricated in matrix-type systems. A matrix device is a simple design consisting of a drug dispersed and/or dissolved homogeneously throughout a polymeric matrix (1,2). This simple, but adaptable, design allows a polymer-based matrix DDS to deliver wide variety of drugs at controlled rates. In addition, the ease of manufacture, versatility, cost-effectiveness, and the fact that dose dumping is a highly unlikely event, since the drug is dispersed homogeneously in the matrix, contribute to matrix-type devices being amongst the most successful in the field of drug delivery.

In such systems, drug release is preceded by the penetration of the dissolution medium into the porous matrix

to dissolve the drug, followed by diffusion of the dissolved molecules out of the matrix.

An erosional component may be present and contributing significantly to the drug release depending on the solubility-swelling properties of the polymer, the degree of agitation and composition of the dissolution medium, and the type and level of filler excipients used (3–5).

The use of polymeric materials in sustained/controlled drug delivery is best exemplified by hydroxypropyl methylcellulose (HPMC) which is probably the most commonly used matrix former in pharmaceutical formulations (6).

Other matrix formers include carbomers (7), ethyl cellulose and related derivatives (8), methacrylate esters copolymers (9), and various natural gums (10).

The co-processed excipient, Kollidon® SR, is probably the latest addition to the limited list of commercially available matrix formers. It is a co-processed polymeric combination consisting of 80% polyvinyl acetate (PVAc) having a molecular weight of about 450,000 and 19% polyvinyl pyrrolidone (PVP) Ph.Eur./USP (Kollidon® 30). About 0.8% of sodium lauryl sulfate and about 0.6% of silica are used as stabilizers (11).

PVAc–PVP-based matrices were found to provide sustained release of model compounds. Certain formulation and processing variables were found to play an important role in controlling release kinetics, such variables include the compression force, drug loading, level of the polymeric material in the matrix, excipient level, as well as the nature of the excipients (water soluble vs. water insoluble) (12,13).

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On the other hand, sensitivity of PVAc–PVP-based tablets to temperature and humidity has been pointed out in the pharmaceutical literature. One group (13) reported a decrease in the dissolution rate along with an increase in hardness of diphenhydramine HCl tablets prepared with a high level of PVAc–PVP without diluents or with 15% diluent (lactose, Emcompress®) and subjected to accelerated stability conditions. At higher levels of Emcompress® (25%), no changes occurred (13).

Another group (14) reported that PVAc–PVP-based tablets demonstrated reproducible drug release patterns when stored at 25°C/60% RH and 30°C/70% RH for up to 6 months. On the other hand, drug release from matrix tablets stored at 40°C/75% RH decreased slightly (14). A similar observation was made with PVAc–PVP mini-tablets stored under the same conditions (15).

Since the stability of the performance of a DDS during long storage periods is one of the most important considerations in choosing a carrier material, this physical aging phenomenon constitutes an important limitation to the use of PVAc–PVP as a controlled release matrix former despite it having excellent flow, compression, and release-controlling properties.

Drug release from systems susceptible to such a thermal-aging phenomenon has been stabilized using post-processing thermal treatment or curing (16–18). Curing involves the exposure of the dosage form (matrix system or polymer coated reservoir system) to temperatures above the glass transition temperature (T_g) of the polymeric component for a determined period of time so that adjacent polymer chains and segments can diffuse past each other leading to coalescence of polymeric particles producing a more homogenous, less porous system.

A post-compression curing step was suggested to stabilize drug release from PVAc–PVP matrices (13). However, only dry heat was used for curing and used at one level only (60°C), the inadequacy of such a condition has been pointed out by the same group (19) where they reported that it was found; as a result of a stability chamber malfunction whereby the temperature had temporarily reached 90°C; that tablets were further strengthened into a hardness range beyond the readout capacity of a typical hardness tester.

This gap in our knowledge of optimal curing procedures for PVAc–PVP matrices has prompted us to investigate the effects of exposure to elevated temperature with or without humidity, as candidates for curing conditions, on the drug release and physical properties of PVAc–PVP matrices prepared using different filler excipients.

Our study also aimed to understand the mechanisms mediating such an effect to allow formulation scientists to rationally suggest suitable curing conditions and formulation components necessary to ensure the stability of the quality of PVAc–PVP containing formulations.

MATERIALS AND METHODS

Materials

Chlorpheniramine maleate (CPM), $C_{16}H_{19}ClN_2$, was used as a water-soluble model drug and was generously donated by United Pharmaceutical Manufacturing Co. Ltd., (Amman, Jordan).

PVAc–PVP-based excipient, Kollidon® SR (lot: 6998298800) was generously donated by BASF (Germany);

microcrystalline cellulose (MCC), Avicel PH-101® (lot: 249557 186), was purchased from FMC (Switzerland); anhydrous dibasic calcium phosphate (DCP; lot: 73218/1), was purchased from Janssen Chimica (Belgium); D (+)-lactose monohydrate (LAC; lot and filling code: 436197/112303242), was purchased from Fluka BioChemika (Switzerland); colloidal silica powder, Aerosil® (lot: 9888370), was purchased from BDH chemicals Ltd (England); and magnesium stearate was purchased from Unichema International (Malaysia).

Methods

Tablet Preparation

PVAc–PVP matrix tablets with a target weight of 300 mg and CPM content of 20 mg were prepared by direct compression. The formulation composition is shown in Table I. Twelve different formulations were prepared using different weight ratios (8:2, 6:4, 4:6, and 2:8) of PVAc–PVP to specific filler excipients (MCC, DCP, and LAC).

The formulas were labeled using the letters LAC, MCC, or DCP indicating the type of diluent used in combination with the numbers 8:2, 6:4, 4:6, or 2:8 to denote the weight ratio of PVAc–PVP to the specific diluent.

CPM, PVAc–PVP, the specific filler excipients used (LAC, MCC, or DCP), and colloidal silica were passed through a 25-mesh sieve (710 μ m) and then blended manually in a plastic bag for 10 min. Afterwards, Mg stearate, sieved through a 25-mesh sieve, was added and mixed for an additional 2 min.

The blend was compressed on a Manesty Model F single punch tableting machine (Thomas Engineering Inc., Hoffman Estates, IL, USA) using 9 mm round-shaped flat punches to a target tablet hardness of 100–200 N.

Neat PVAc–PVP tablets were prepared in order to study the physical properties and response to thermal curing of a PVAc–PVP matrix without interference from the fillers. The neat PVAc–PVP tablets were prepared by compressing accurately weighed 300 mg portions of PVAc–PVP using 9 mm round-shaped flat punches in a hydraulic press (Karl Kolb, Germany) at a compression force of 10 kN for 10 s. The punches were lubricated with 5% (w/v) magnesium stearate suspension in methanol before each compression and allowed to dry.

Exposure to Thermal Stress Conditions

Tablets from the 12 prepared formulas were put in open Petri dishes and split in two groups. The first group was placed in a stability chamber (Binder KBF 240, Binder, Germany) pre-equilibrated to 60°C/75% RH. The second

Table I. Formulation Composition of Polyvinyl Acetate–Polyvinyl Pyrrolidone-Based Tablets

Component	Milligrams/tablet	Percentage
Chlorpheniramine maleate	20	6.67
Colloidal silicon dioxide	3	1.00
Magnesium stearate	3	1.00
PVAc–PVP + filler excipient	274	91.33
Total	300	

group was placed in a dry heat oven at 60°C (Philip Harris Ltd, Shenstone, England).

At predetermined time points (1 day, 4 days, 1 week, 2 weeks, 1 month, 2 months, and 3 months), samples of tablets were collected and stored in closed glass bottles for dissolution testing and hardness measurements.

Weight measurements were performed on the same set of 20 tablets from each formula throughout the study.

Dissolution testing, weight, and hardness measurements were performed after the tablets were allowed to cool down to room temperature.

Neat PVAc–PVP tablets and PVAc–PVP powder were also stored under the abovementioned thermal conditions for periods up to 1 month. At predetermined time points (1 day, 1 week, and 1 month), samples were withdrawn for density measurements using helium pycnometry and thermal analysis using differential scanning calorimetry (DSC).

Tablet Testing

Tablet weight variation. Twenty tablets from each formula were selected, individually weighed (Shimadzu AY120 analytical balance, Japan), put in open Petri dishes, and placed under thermal stress conditions (*previous section*). At predetermined time points (*previous section*), the tablets were withdrawn and reweighed. The average weights and standard deviations were calculated.

Tablet hardness. Hardness was determined for ten tablets (of known weights) of each formula at zero time and at predetermined time points during the thermal stress studies (*previous section*) using Dr. Schleuniger Hardness tester (Schleuniger Pharmatron AG, Solothurn, Switzerland). The average hardness and standard deviation were calculated.

Tablet dissolution testing. Dissolution studies were conducted in a USP dissolution apparatus II (Erweka DT600, Germany) over a 12-h period using 900 mLs of deionized water as dissolution medium. The stirring rate and temperature were adjusted to 100 rpm and 37±0.5°C, respectively.

At predetermined time intervals, 5 mL samples were withdrawn for analysis and immediately replaced with an equal volume of fresh medium maintained at the same temperature. Samples were filtered using 0.45 µm syringe filters before the absorbance of CPM was measured at 261 nm (SpectroScan® 80D, SpectroScan, USA). CPM concentration was calculated from linear calibration plots. The dissolution tests were performed in triplicates, and the mean values as well as standard deviations were calculated.

In order to quantify the changes in the drug release profiles as a function of the duration and type of thermal exposure, the release profiles were fitted to the Higuchi square root of time model (20) given in Eq. 1:

$$\frac{M_t}{M_\infty} = kt^{0.5} \quad (1)$$

where M_t/M_∞ is the fraction of drug released at time t , and k is the apparent release rate constant.

One of the most important assumptions in the Higuchi model is that the only release mechanism is diffusion of the

dissolved drug through a reasonably intact matrix. Although the model may be less than ideal for describing a “real” matrix system, it is still considered the most famous and most often used mathematical equation to describe the release rate of drugs from such systems. This is probably due to its simplicity in describing the release process using a single value of the apparent release rate constant (21).

This simplicity is of great value in our situation where we are not interested in the mechanism of the drug release as we are in a quantitative measure of the drug release in the form of an apparent release rate constant.

The percentage change in the apparent release rate constant after storage under elevated temperature conditions was calculated according to Eq. 2.

$$\Delta k(\%) = \left(\frac{k_t - k_f}{k_f} \right) \times 100 \quad (2)$$

where k_t is the apparent release rate constant from tablets stored for time t , and k_f is the apparent release rate constant from freshly prepared tablets.

Differential Scanning Calorimetry

The evaluation of the thermal properties was performed on PVAc–PVP powder and neat PVAc–PVP tablets after storage, gently triturated in a porcelain mortar, using Mettler Toledo DSC 823 (Mettler, Switzerland).

Samples (4–5 mg) were weighed and sealed into aluminum pans with pierced lids. The samples were heated from 25°C to 250°C at a heating rate of 10°C/min under nitrogen purge (80 ml/min).

Helium Pycnometry

Density measurement of neat PVAc–PVP tablets was carried out using Ultrapycnometer 1000 (Quantachrome Instruments, USA). Before use, the instrument was allowed a minimum of 1 h for warm-up and thermal equilibration; a circulating water bath was used to provide constant temperature conditions (25°C).

The instrument was calibrated before measurements using a small calibration sphere (volume, 7.0699 cm³ in a sample holder with a nominal volume of 10.8 cm³).

For measurement, three to four neat PVAc–PVP tablets were weighed using an analytical balance (SHIMADZU AY120, Japan) then placed in the sample cell after removing the calibration sphere, a minimum of six runs were used to obtain accurate results, and averages and standard deviations were calculated. The same procedure was applied to PVAc–PVP powder.

RESULTS AND DISCUSSION

Tablets were successfully prepared from all of the prepared formulations. Due to different compaction properties of the used filler excipients, it was decided not to use a constant compression force for the preparation of the tablets but instead targeting an acceptable level of hardness (between 100 and 200 N). Tablets of consistent target hardness were most successfully prepared when LAC was used as a filler excipient, while in tablets containing MCC or DCP as fillers, the hardness

decreased with increasing the content of the filler excipient in the mixture even when using high compression forces.

The prepared tablets were then placed under humid or dry thermal stress conditions ($60^{\circ}\text{C}/75\% \text{RH}$ and 60°C , respectively). These are relatively harsher conditions than the ones usually used for the curing of film coatings; however, they were decided upon considering the fact that they are intended to modify a thick polymeric matrix rather than a thin film on the surface of a tablet or a pellet. Interestingly, a recent report (22) showed that similar, unconventionally

harsh, curing conditions ($60^{\circ}\text{C}/75\% \text{RH}$ or 80°C) were successful in improving the storage stability of Aquacoat-coated pellets at accelerated stability test conditions in comparison to other “milder” curing conditions.

Tablet Weight and Hardness

Figure 1 shows the percentage change in the tablet weight as a function of thermal exposure time under dry and humid conditions.

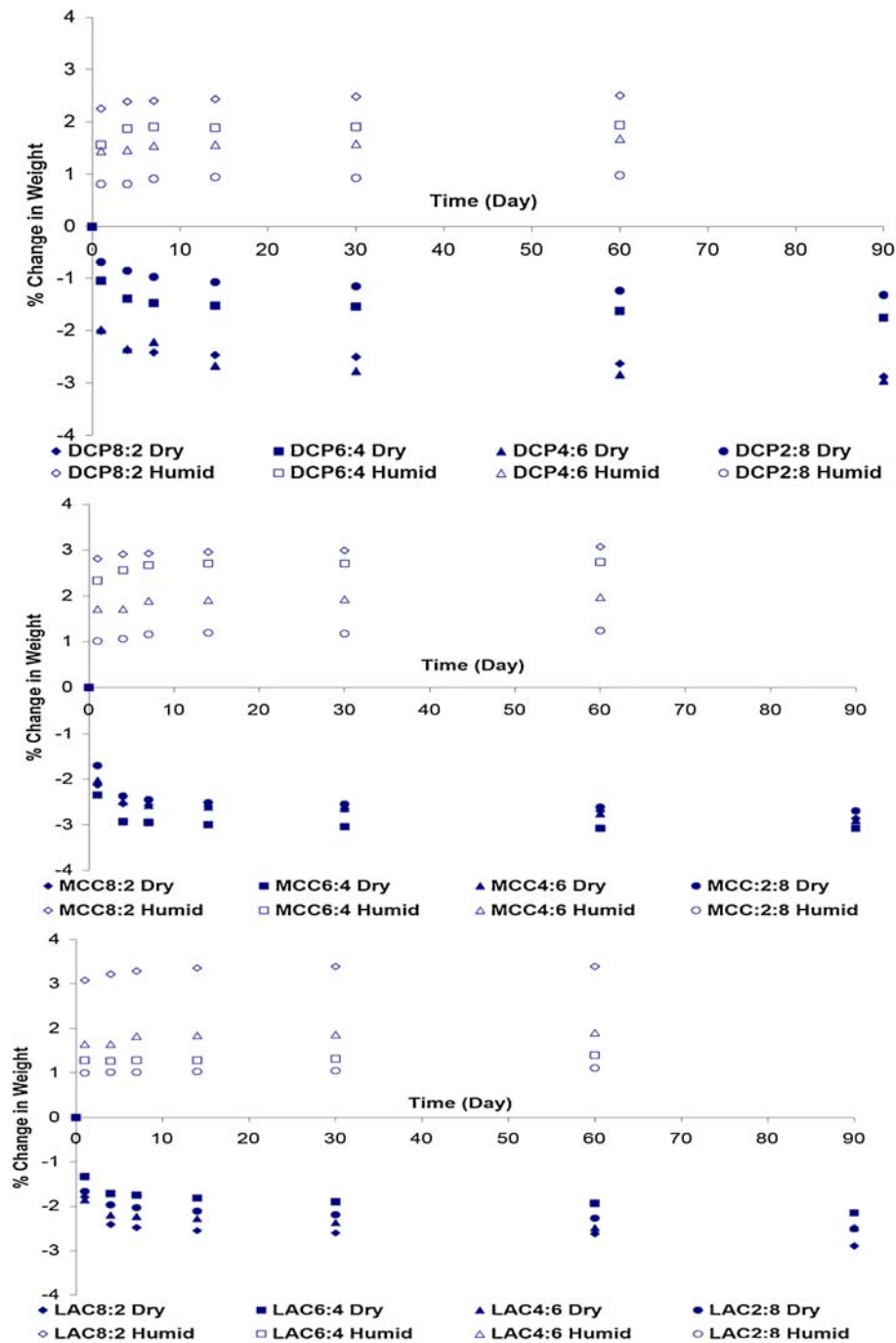


Fig. 1. Effect of storage under dry heat (60°C) and humid heat ($60^{\circ}\text{C}/75\% \text{RH}$) conditions on the weight change of polyvinyl acetate-polyvinyl pyrrolidone-based tablets

Tablets exposed to dry heat conditions showed a reduction in their mass corresponding to removal of residual moisture associated with the tablet components. This process of weight loss is fastest in the early stages of thermal exposure reaching an average value for all formulations of 66.49% (± 7.03) and 82.85% (± 7.53) of the 90-day (plateau) level after 1 and 4 days, respectively.

On the other hand, tablets stored under high temperature and humidity conditions showed an increase in their weight with time as a result of water sorption. Similar to the weight loss process, the tablets showed a quick weight gain in the early stages of exposure to high humidity with an average weight gain for all formulations reaching 86.98% (± 3.91) and 90.48% (± 4.59) of the 60-day (plateau) level after 1 and 4 days, respectively.

In addition, the weight gain seems to show a direct linear relationship with the content of PVAc–PVP in the tablet formulations as can be seen in Fig. 2. The linear relations have R^2 values of 0.9905, 0.9825, and 0.9912 for matrices prepared using MCC, DCP, and LAC as filler excipients. This points to PVAc–PVP as the main water sorping component of the tableted formulas which is expected based on the high hygroscopicity of the PVP component in PVAc–PVP (23,24).

These results are in agreement with the previous reports where tablets with highest level of PVAc–PVP exhibited greatest moisture uptake (19).

Tablets prepared with DCP as a filler excipient showed the smallest percentage weight gain in comparison to those prepared with MCC and LAC, this may be explained by the nonhygroscopicity of DCP in comparison to the hygroscopic MCC and LAC.

In regards to the tablet hardness, the storage under dry heat resulted in an increase in the tablet hardness as can be seen in Fig. 3. The increase in the tablet hardness was related

directly to the PVAc–PVP content in the tablets indicating that a change in the structural properties in the PVAc–PVP component of the matrix is responsible for the increased mechanical strength of the tablets.

However, the most pronounced change in hardness was observed in the case of the tablets stored under elevated temperature and humidity conditions. Tablets with high PVAc–PVP content exposed to high temperature and humidity conditions for periods as short as 1 day showed increased hardness and exhibited pronounced elasticity; no reading was recorded by the hardness tester for those tablets.

The change in tablet hardness as a function of the storage time under humid heat conditions is shown in Fig. 4.

Differential Scanning Calorimetry

DSC was used to detect possible changes in the glass transition of the rate controlling PVAc component of Kollidon® SR which is expected to contribute to the molecular mobility of polymeric chains, plastic flow of polymeric particles, internal structural changes, as well as hardness and drug release changes of the Kollidon® SR matrices.

Fresh samples of PVAc–PVP powder showed a distinctive endothermic peak at around 40°C followed by a broad peak extending from around 50°C to 100°C. This observation is in accordance with the reported behaviors of the two polymeric components of the polymeric system with the first one corresponding to the glass transition temperature of PVAc (11,25,26) and the second one corresponding to dehydration of the hygroscopic PVP.

The thermograms of PVAc–PVP powder samples stored in open containers at 60°C for periods up to 1 month (Fig. 5) did not show significant change as expected.

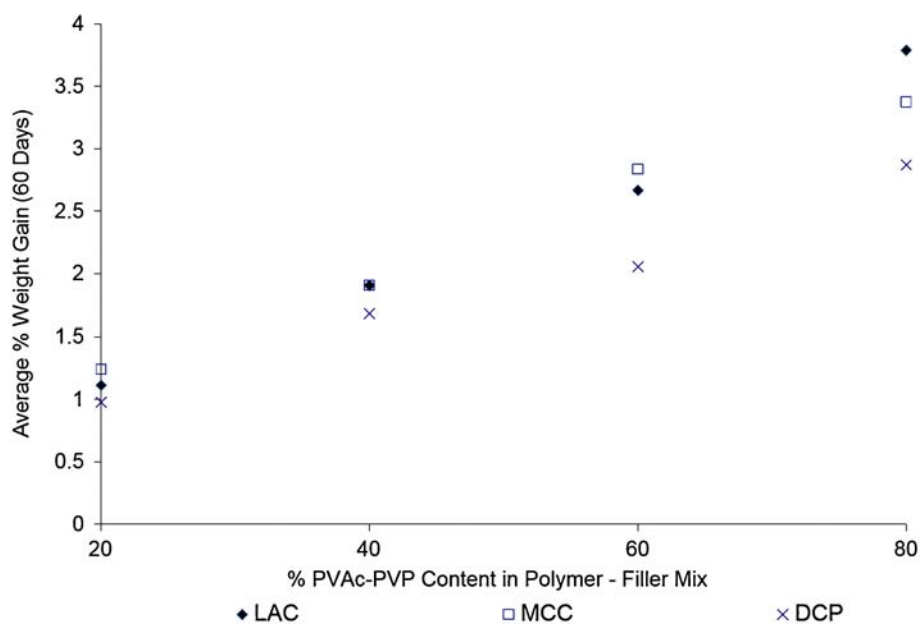


Fig. 2. Effect of polyvinyl acetate–polyvinyl pyrrolidone content on the average weight gain by tablets stored under high temperature–high humidity conditions (60°C/75% RH)

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