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Temperature/Humidity Sensitivity of Sustained-Release Formulations Containing Kollidon® SR

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ABSTRACT

The effects of temperature and humidity on tablets containing Kollidon® SR have been evaluated using diphenhydramine HCl as a model drug. Exposure of tablets to ICH accelerated stability condition (40°C/75%RH) in an open dish resulted in rapid increases in tablet hardness, accompanied by step-wise decreases in dissolution rate. Such a change can be observed as fast as an hour upon exposure. The tablet matrix appears to rapidly absorb atmospheric moisture, as demonstrated by tablet weight gain and moisture adsorption isotherms. Exposure to 25°C/60%RH similarly resulted in increases in tablet hardness, although with minimal impact on dissolution. Potential implications of such rapid moisture uptake during aqueous film-coating were further evaluated by spraying either water or an Opadry solution in a coating pan. Exposure of Kollidon SR tablets to the aqueous coating process indeed resulted in noticeable changes in both hardness and dissolution. Application of the Opadry solution appears to affect tablet behavior to a lesser degree, compared to water, most likely due to protection via formed barrier film. Attention needs to be paid to the extreme sensitivity of Kollidon SR matrix tablets to temperature and moisture during product development.

Key Words: Diphenhydramine HCl; Kollidon® SR; Matrix tablets; Polyvinylacetate; Sustained release.

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INTRODUCTION

Kollidon® SR is a directly compressible polymeric blend composed primarily of polyvinylacetate (PVAc) and povidone (PVP).[1,2] The amorphous nature of PVAc coupled with its unusually low glass transition temperature of 28–31°C[3] imparts certain unique characteristics to this binary matrix. Upon compression, this material forms a matrix block releasing the host drug through channels created by the gradual leaching of the water-soluble PVP component.

In our previous work,[4,5] Kollidon SR and Kollidon SR 30D were found to provide a sustained release effect for a highly water-soluble model compound, diphenhydramine HCl. However, such tablets require a post-compression curing step, in order to stabilize drug release. Curing can typically be accomplished thermally at 60°C. Recently, it was unexpectedly discovered that at a temperature higher than 60°C, Kollidon SR tablets were further strengthened into a hardness range beyond the readout capacity of a typical hardness tester. This was found as a result of a stability chamber malfunction, whereby the temperature had temporarily reached ~90°C.

Aberrant exposure of drug product intermediates to high temperature and humidity conditions is expected, either intentionally done to evaluate stability or inherently associated with certain manufacturing unit operations. One such unit operation is the aqueous film-coating process, wherein core tablets are exposed to relatively high temperature and humidity environments for periods upto several hours. It was, therefore, our objective to further examine the effects of extreme storage and processing conditions on drug release from Kollidon SR matrix tablets.

MATERIALS AND METHODS

Materials

Diphenhydramine hydrochloride USP was internally sourced from Pfizer Inc., Consumer Healthcare Division. Kollidon® SR was obtained from BASF Corporation (Mount Olive, NJ). Lactose monohydrate, Fast-Flo® grade, was obtained from Foremost Farms USA (Baraboo, WI). Calcium phosphate dibasic dihydrate (Emcompress®) was purchased from JRS Pharma (Patterson, NY). Magnesium stearate of non-bovine origin was obtained from Mallinckrodt Inc. (St. Louis, MO). Opadry Clear (05B19141) was obtained from Colorcon (West Point, PA).

Tablet Preparation

Diphenhydramine HCl, Kollidon® SR, with or without a selected diluent were blended in an 8-qt. Patterson-Kelly (East Stroudsburg, PA) V-blender for 5 minutes. Magnesium stearate was passed through a 30-mesh screen and added to the V-blender. Mixing was continued for an additional 5 minutes. The blend was compressed on a Manesty Betapress (Thomas Engineering Inc., Hoffman Estates, IL) using oval-shaped tooling with a dimension of $0.750'' \times 0.390'' \times 0.062''$ to produce tablets with a hardness range of 14–18 kp. Tablets were compressed to a target weight of 800 mg containing 300 mg of diphenhydramine HCl. Detailed compositions are shown in Table 1.

Exposure to Stability Conditions

Tablets were put into 90-cc high-density polyethylene bottles and placed inside humidity chambers (Tabai Espec Corp., Osaka, Japan) preequiliberated to 25°C/60% RH and 40°C/75% RH respectively. At predetermined timepoints (1 hour to 4 weeks), a bottle was pulled from the oven and tested for hardness by Distek HC97 (EL Ektronik Gmbh, Germany) and dissolution. Dissolution testing and hardness measurements were performed after the tablets were allowed to cool down to room temperature for overnight or longer.

Dissolution Methodology

Dissolution testing was performed using an automated Distek 2000 apparatus (North Brunswick, NJ) equipped with a model HP8453A diode-array spectrophotometer (Hewlett Packard, Palo Alto, CA) using a detection wavelength of 258 nm. Paddle method (USP Apparatus II) was used with 900 mL purified water as the medium, at a water bath temperature of 37°C, and a paddle speed of 50 rpm. Six tablets were used in each run.

Drug Release Modeling

To determine the release kinetics of diphenhydramine HCl from Kollidon® SR-based tablets, attempts were made to fit the data corresponding to $\leq 80\%$ of release using the following equation:[6,7]

$$Q = kt^n \quad (1)$$

where Q is the percentage of drug released at time t, k is the release rate constant, and n is the release

Table 1. Compositions of diphenhydramine HCl tablets (800 mg tablet weight).

	%w/w		
Ingredients	Formulation 1	Formulation 2	Formulation 3
Diphenhydramine HCL	37.5	37.5	37.5
Kollidon SR	62.0	47.0	47.0
Lactose	–	15.0	–
Calcium phosphate dibasic dihydrate	–	–	15.0
Magnesium stearate	0.5	0.5	0.5
Total	100	100	100

exponent. For matrix tablets, an n value of $\sim$0.5 indicates diffusion-controlled mechanism while an n value of $\sim$1.0 indicates erosion-controlled release. Intermediate values suggest dual mechanisms of both diffusion and erosion.[6] $T_{50\%}$, the time to reach 50% of drug release, was then calculated from the above fitted equation for each formulation, by using mean dissolution data.

Moisture Adsorption Studies

Tablet weight gains were monitored either gravimetrically or by a VTI Vapor Sorption Analyzer (SGA-100, VTI Corporation, Hialeah, FL) pre-equilibrated to 40°C/75%RH. The vapor sorption analyzer was programmed to acquire weight data every 2 minutes, after the tablet has been loaded onto the microbalance.

Film Coating Process

Flim-coating was done in a Hi-Coater HCT-30 (Vector Corporation, Marion, IA) by spraying water alone for simulation purpose or an Opadry Clear solution (15%w/w). Pan parameters were 700 gm pan load, inlet air temperature set at 85°C, pan speed at 14 rpm, 1.5 bar atomization pressure, 4″ gun-to-bed distance, and a flow rate of 5 g/min. The spray time was limited to 45 minutes. Exhaust temperature was between 37.9 to 41.9°C during spray and $\sim$43°C at the end of a 5 minute drying cycle.

RESULTS AND DISCUSSION

Open Dish Exposure to Accelerated and Long-Term Stability Conditions

Tablets manufactured using Formulation 1 (no diluent) were first placed in open bottles and put inside both 40°C/75%RH and 25°C/60%RH chambers. At 40°C/75%RH, tablets hardened as quickly as 1-day (Table 2). Extending exposure time does not appear to further increase tablet hardness. A similar trend was also observed at 25°C/60%RH, although it appeared to have taken several days for the tablets to harden completely.

A second study was then carried out to examine shorter periods of exposure. Samples pulled following as fast as an hour exposure already revealed significant hardening effect (Table 2). Within a few hours, such hardening effect appeared to have plateaued.

Dissolution results for samples pulled at different exposure times are shown in Fig. 1. Pronounced changes in both the rate and extent of drug release have been found, even as early as 1 hour following exposure at 40°C/75%RH. Unlike changes with hardness, dissolution curves appeared to trend down without plateauing even after a 4 week exposure time. Exposure to 25°C/60%RH only resulted in very minor

Table 2. Hardness values of diphenhydramine HCl-kollidon SR tablets on storage.

	Hardness (kp)	
Time	25°C/60%RH	40°C/75%RH
Initial	16.2±2.6	16.2±2.6
1 hour	N.D.	22.4±2.3
4 hours	N.D.	26.2±1.9
8 hours	N.D.	27.5±1.7
1 day	21.8±1.1	29.9±1.4
4 days	21.4±1.8	28.8±2.4
7 days	27.5±1.8	32.9±3.5
2 weeks	27.3±1.2	25.9±2.7
4 weeks	27.0±2.3	26.6±4.1

Notes: Results are the means±SD of 10 determinations. N.D.—not determined. $P<0.001$ by t-test for all values compared to initial.

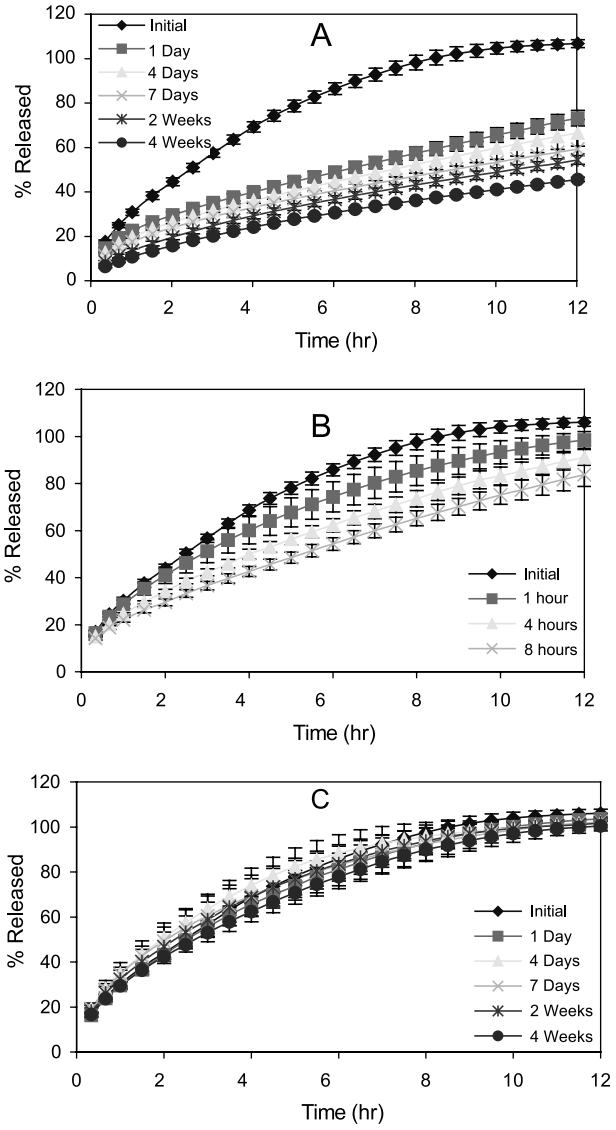

Figure 1. Release profiles of diphenhydramine HCl from Kollidon SR matrix tablets placed open on stability. Values are means ± SD (n = 6). A and B—40°C/75%RH; C—25°C/60%RH.

changes in dissolution rate. Therefore, temperature and humidity impact tablet hardness and dissolution to different extents.

Mean dissolution data were then fitted into Eq. 1 and results are listed in Table 3. All profiles were well fitted as shown by the excellent correlation coefficients. Since the release exponent (n) is close to 0.5 in all cases, release of this highly water-soluble drug appears to be by diffusion-controlled mechanism, as proposed by BASF.[1] Exposure to 40°C/75%RH over time resulted in steady decreases in the kinetic release constant (k), a phenomenon very similar to our observation with Kollidon SR30D-coated nonpareil beads.[5]

Table 3. Kinetic parameters based on Eq. 1.

Exposure time to 40°C/75%RH	k (hr^{-n})	n	r^2	$T_{50\%}$(hr)
Initial	30.6	0.569	0.998	2.4
1 hr	28.9	0.525	0.999	2.8
4 hrs	24.7	0.514	0.997	3.9
8 hrs	22.1	0.509	0.990	5.0
1 day	21.6	0.464	0.993	6.1
4 days	18.9	0.483	0.995	7.5
7 days	17.0	0.485	0.998	9.2
2 weeks	13.3	0.557	0.999	10.8
4 weeks	10.4	0.587	0.999	14.5

Notes: k—release kinetic constant; n—release exponent; r^2—correlation coefficient squared; $T_{50\%}$—the time for 50% drug to be released.

Moisture Uptake

Tablet weight gain as a function of exposure time was also monitored. As shown in Fig. 2, upto 7% weight gain was found for tablets exposed to 40°C/75%RH for 10 days. At 25°C/60%RH, ~1% weight gain was found within 1 day. Very little increase was found thereafter.

To better study the moisture adsorption kinetics, isotherms were generated on a VTI Vapor Sorption Analyzer for all three formulations (Fig. 3). These data confirmed the weight gain trend measured gravimetrically. Furthermore, Formulation 1 containing the

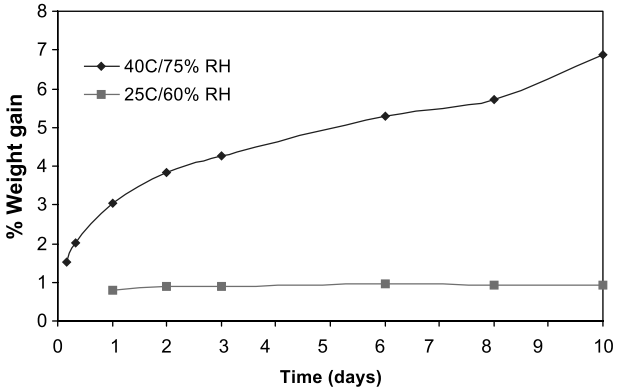

Figure 2. Tablet weight gain as a function of exposure time (Formulation 1).

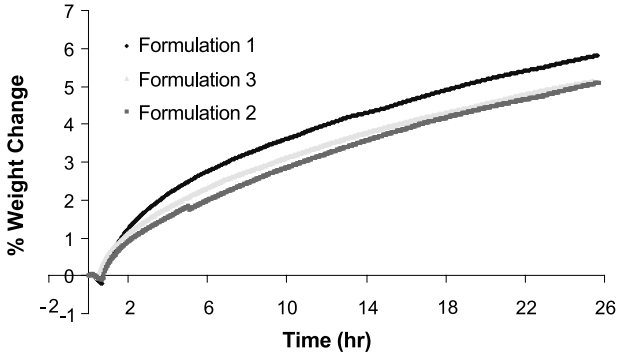

Figure 3. Moisture adsorption isotherms at 40°C/75%RH.

highest level of Kollidon SR exhibited greatest moisture uptake.

Effect of Film-Coating Process

The rapid moisture absorption potential of tablets containing Kollidon SR calls for the investigation of routine manufacturing stresses on product quality. One such stress is the heat/moisture encountered during film-coating. A weight gain of 3–4% (as a result of film coating) was obtained in the case of Opadry coating.

Formulation 1 containing a higher level of Kollidon SR showed significant size expansion and extensive surface erosion. Testing of finished product was not performed. Formulations 2 and 3 were successfully sprayed without tablet integrity being compromised. Hardness values before and after coating operations are shown in Fig. 4. Spraying water onto tablet bed indeed resulted in significant increases in tablet hardness ($p<0.001$ by t-test for both formulations), regardless of

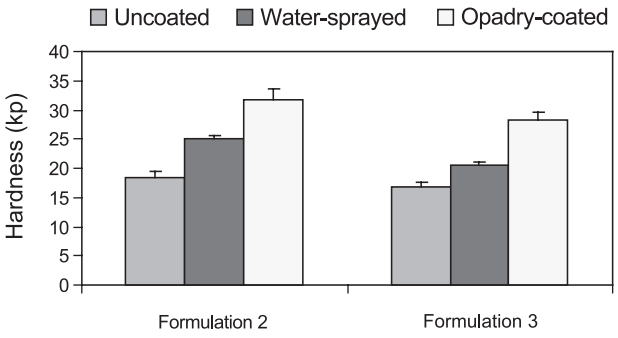

Figure 4. Tablet hardness increases as a result of coating process.

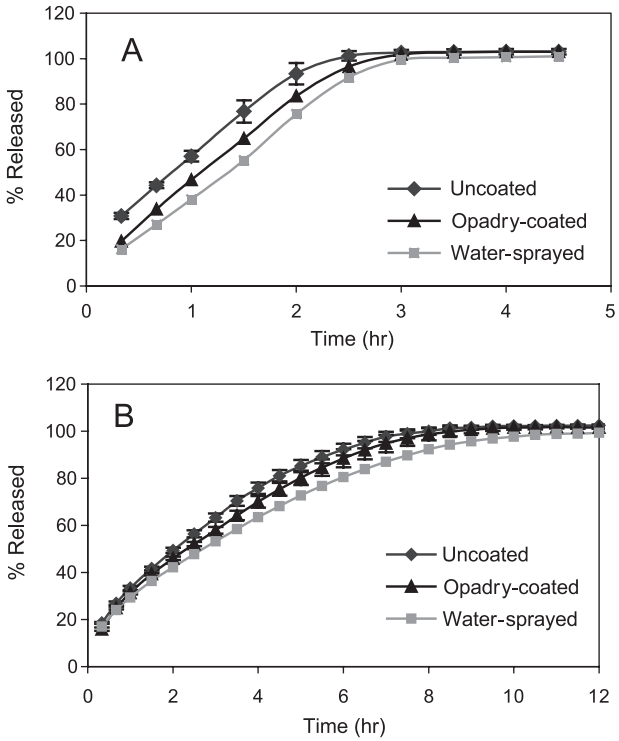

Figure 5. Release profiles of diphenhydramine HCl from Kollidon SR formulations after spraying with water or Opadry solution in a coating pan. Values are means±SD (n=6). A—Formulation 2; B—Formulation 3.

the type of diluent (lactose or Emcompress) present. It is likely that the additional hardness increase obtained after the application of the Opadry coating is due to the strengthening effect of the applied coating.

Dissolution profiles before and after coating are shown in Fig. 5. Spraying water onto tablets has, in each case, a discernable effect on dissolution. Coating with Opadry resulted in a lesser impact on dissolution. The deposited HPMC film may have protected the cores from further moisture penetration during coating.

CONCLUSIONS

Sustained-release tablets composed of Kollidon SR have been shown to be heat/moisture sensitive. Increases in tablet hardness and decreases in the release kinetic constant have been observed depending upon environmental conditions. Caution should be exercised in certain unit operations like aqueous film-coating. Such thermal-responsiveness of polymeric excipients of

low glass transition temperatures, however, should be further exploited to benefit controlled-release dosage form design.

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