Characterization of a New, Co-processed Excipient (CombiLac®) for Direct Compression by Dynamic Vapor Sorption (DVS)

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Purpose: Many APIs are susceptible to water uptake, leading to changes in physical form, functional performance, or chemical stability (e.g. degradation by hydrolysis). Appropriate excipient selection can significantly reduce or prevent these changes, which could impact solid dosage form development and manufacture with regard to API performance. The objective of this study was to examine water sorption characteristics of a new, co-processed, directly compressible excipient (CombiLac®) comprising α-lactose monohydrate (70 %), MCC (20 %) and native maize starch (10 %), in comparison to various physical admixtures (PAMs) having equivalent composition.

Methods: Moisture up-take of different samples (ca. 2.5 g) was monitored gravimetrically by Dynamic Vapor Sorption (SPSx-1μ Advance moisture sorption test; ProUmid®) over a range of 0 and 90% + 0.6 % R.H. at 20°C + 0.5°C. Each sample was dried at 0 % R.H. until constant mass was reached. Two cycles were performed on each sample changing R.H. by 5 % increments from 0 % to 90 %, returning to 0%. As an equilibrium parameter, a relative mass per time unit change (dm/dt) of < 0.01% within 15 min. was established. Figure 1 shows a typical DVS relative mass change (water sorption) versus R.H. change. Materials examined included three CombiLac® lots (Meggle: lots L160586, L160587, and L160588) and three PAMs with equivalent composition: PAM 1: spray-dried (SD) lactose (Meggle FlowLac® 90: lot L1432 A4982), MCC (JRS Pharma VIVAPUR® 200: lot 5620000612), and pregelatinized starch (Colorcon Starch® 1500: lot IN 528947); PAM 2: SD lactose (FlowLac® 90), MCC (JRS Pharma VIVAPUR® 102: lot 5610230545), and pregelatinized starch; and PAM 3: milled lactose grade (Meggle GranuLac® 230: lot L1424 A4202), MCC (JRS Pharma VIVAPUR® 101: lot 6610144435), native maize starch (Roquette: lot E6388).

Results: Moisture uptake reproducibility (30, 50, 90% R.H.) of three co-processed lactose-based excipient (CombiLac®) lots resulted in good agreement (RSD_{max} <3%). A performance comparison for the change (dm [%]) plot showed that co-processed excipient demonstrated superior moisture uptake capacity compared to the PAMs. This effect was clearly evident over the entire water sorption range investigated using equilibrium and non-equilibrium conditions. A ranking in dm [%] of the corresponding PAMs could be established: PAM1, PAM2 > PAM3. This was attributed to the individual component physical properties, including particle size. Kinetics in dm [%] after leaving equilibrium conditions have been recorded and fitted for various relative humidities.

Conclusions: DVS results showed that co-processing lactose, MCC, and maize starch was successful in creating an excipient having improved moisture sorption properties superior to a physical admixture having equivalent composition. Water sorption behavior may be tailored to enhance the protective performance of an excipient, which may provide greater API stability.

INTRODUCTION

Water adsorbed by active pharmaceutical ingredient(s) (API) and/or surrounding formulation matrix can result in unexpected phase transformations, leading to biopharmaceutical, functional, physicochemical, and storage-related instabilities. Because excipients frequently comprise large dosage form content, special attention must be given to water effects and water-driven interactions during development and manufacture. Appropriate excipient selection is a key factor in balancing variability and reducing moisture-associated impact to individual formulation components, particularly APIs.

Co-processed excipients (CPEs), an ingredient subgroup typically developed and manufactured using intelligent combinations of compendial excipients, are increasingly considered during formulation development, significantly enriching formulators' options. This results from creating functional performance synergies, simplifying DoE in support of QbD, and adding convenience and efficiency, which reduces cost. CPE manufacturing processes typically affect the individual components' physical state; however, little was known about co-processing impact on moisture sorption and storage properties at various relative humidities (RH).

This study's objective was to examine water sorption characteristics of a new, co-processed, directly compressible excipient (CombiLac®) comprising α-lactose monohydrate (70%), MCC (20%), and native maize starch (10%). In this experiment, CombiLac® was compared to various physical admixtures (PAMs) having equivalent composition, and assessing moisture sorption variability across all ingredient systems. Using this approach, the impact of specific manufacturing processes, such as spray-drying (SD) on water sorption capacity, was evaluated.

MATERIALS & METHODS

Excipients examined included three CPE lots (MEGGLE CombiLac® lots L160586, L160587, and L160588) and three PAMs having equivalent composition (Table 2).

Table 2 – PAM Composition

Ingredient	PAM 1	PAM 2	PAM 3
FlowLac® 90	70%	70%	
GranuLac® 230			70%
VIVAPUR® 200	20%		
VIVAPUR® 102		20%	
VIVAPUR® 101			20%
Starch 1500®	10%	10%	
Maize starch			10%

Materials used in PAM preparation included two lactose types, three MCC grades, pregelatinized and native maize starch (Table 1). 500 g PAMs were prepared using Turbula® blender. Individual ingredients were dispensed, transferred to mixing vessel, and blended for 5 min.

Table 1 – Materials used for PAM preparation

Ingredient	Manufacturer	Trade name and Grade	Lot number
Spray-dried lactose	MEGGLE	FlowLac® 90	L1432 A4982
Milled lactose	MEGGLE	GranuLac® 230	L1424 A4202
MCC	JRS PHARMA	VIVAPUR® 200	5620000612
		VIVAPUR® 102	5610230545
		VIVAPUR® 101	6610144435
Pregelatinized starch	Colorcon	Starch 1500®	IN 528947
Maize starch	Roquette		E6388

Moisture uptake was performed using 2.5 g samples, monitored gravimetrically by DVS using ProUmid® SPSx-1µ Advance moisture sorption test over a range of 0 and 90% + 0.6% RH at 20°C + 0.5 °C (Figure 1).

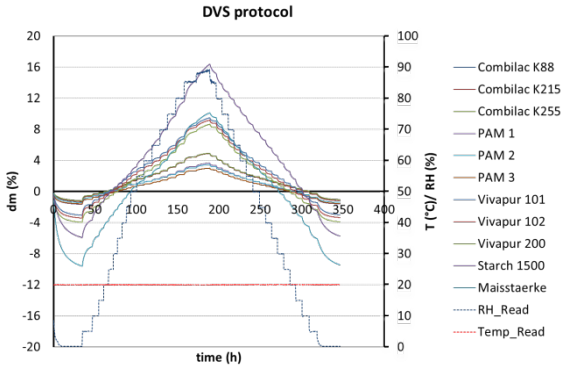

Figure 1: DVS protocol rel. change in mass and water sorption for co-processed excipient CombiLac®, its corresponding physical admixtures (PAM 1-3), and the individual MCC and starch components at 20 ± 0.5 °C.

Each sample was dried at 0% RH until constant mass was reached. Two cycles were performed on each sample changing RH by 5% increments from 0% to 90%, returning to 0%. As an equilibrium parameter, relative mass per time unit change (dm/dt) of < 0.01% within 15 min was established.

RESULTS & DISCUSSION

CPE (CombiLac®) moisture uptake reproducibility at 30%, 50%, and 90% RH showed little sorption variability for the samples assessed. The dm (%) values resulted in good agreement, expressed by an RSD_{max} of <3% (n=3 / each RH).

All investigated samples showed hysteresis behaviour in DVS relative mass change (water sorption) versus RH (%). CombiLac® demonstrated an overall superior moisture uptake capacity. The PAMs showed a ranking according to: PAM 1, 2 > PAM 3 (Figure 2).

If the time-dependent mass change, dm (%), is plotted for four different moisture conditions (35%, 45%, 60%, and 80% RH) with a 0 and 0.8 h (48 min) exposure, CombiLac®, demonstrated an overall superior initial moisture uptake capacity compared to the PAMs.

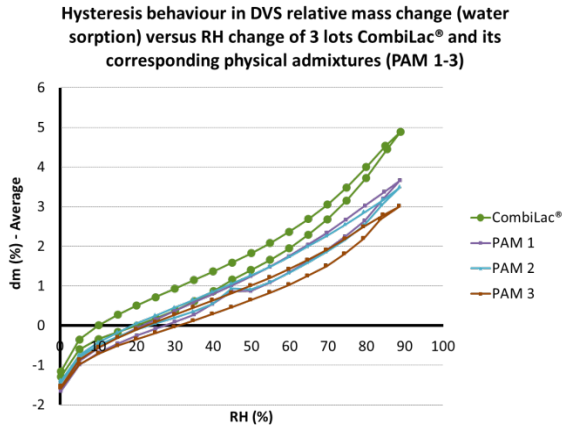

Figure 2: CombiLac® demonstrated an overall superior moisture uptake capacity (green line). The PAMs showed a ranking according to: PAM 1, 2 (pink, blue line) > PAM 3 (brown line).

The highest absolute values in humidity induced weight gain dm (%) were observed for CombiLac® after 0.8 h exposure at 80% RH with a 0.36% dm, followed by the corresponding PAMs (Figure 3).

Given the results, PAMs were ranked as follows: PAM 1, PAM 2 > PAM 3. This could be explained by the individual component physical properties, specifically SD lactose (typically 15% amorphous content) and pregelatinized starch water uptake tendencies in PAM 1 and PAM 2, having an impact. PAM 3 was dominated by less moisture absorbing milled α-lactose monohydrate and native corn starch.

Component particle size seemed to be of minor importance. However, without BET analysis, it is difficult to predict if surface area contributed to the observation. If water uptake kinetics were traced between 0 and 0.8 h time, three divisions were visible: (i) within the first 0.25 h, a moderate increase in dm (%) was observed, independent from the tested sample and applied RH. (ii) Additional exposure (0.25 - 0.5 h) resulted into a CombiLac® & PAM 2 and PAM 1 & PAM 3 differentiation.

CombiLac® and PAM 2 exhibited greater time dependent water uptake at RH > 60%. PAM 1 and PAM 3 showed similar performance over the whole investigated time period (up to 0.8h).

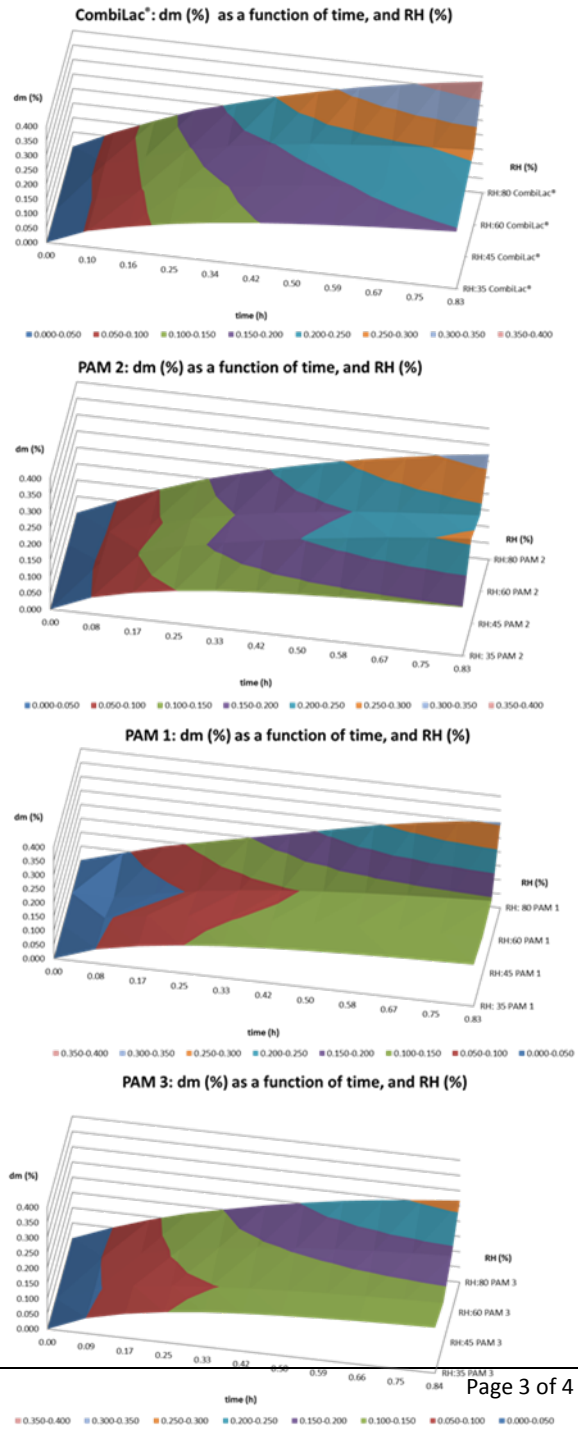

Figure 3: Water uptake kinetics for a CPE (CombiLac®) and its corresponding PAMs at 35%, 45%, 60%, and 80% RH.

This behavior is well understood for PAM 3, as the blend possessing the lowest reactivity. A possible explanation for the reduced PAM 1 sorption may have resulted from MCC particle size. (iii) After 0.5 h at an 80% RH CombiLac® PAM 2 water uptake is most distinct.

CONCLUSION

DVS results showed that co-processing α-lactose monohydrate, MCC, and maize starch was successful in creating an excipient possessing improved moisture sorption properties superior to PAMs having equivalent composition.

Water sorption behavior can be tailored to enhance the excipient protective performance, which may provide greater API stability. Further tests monitoring the stability of appropriate APIs are necessary to evaluate this protective potential.

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