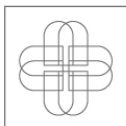


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Stability of Powder-Filled Hard Gelatin Capsules Stored in Standard I.C.H. Conditions T3086

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Poster presented at the 2010 Annual Meeting and Exposition of the American
Association of Pharmaceutical Scientists.
New Orleans Louisiana
November 14-18, 2010



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PURPOSE

The work presented hereafter illustrates that the selection of the blister type is crucial to document the stability of product filled in hard gelatin capsules when tested under the standard I.C.H. conditions.



Photo 1: Capsugel Coni-Snap® capsules.

Coni-Snap® hard gelatin capsule (Photo 1) is proposed in different sizes, colors, and from different gelatin origins (porcine, bovine, fish) since more than 50 years to encapsulate powders, pellets, tablets and other solid-like products.

With the expansion of the variety of products filled into hard gelatin capsules, the stability studies are more and more important. We decided to focus on blister (Photo 2).



Photo 2: Examples of blister.

Name	PVC	PVC/Pvdc (250/40)	PVC/Pvdc (250/90)	PVC/PE/Pvdc	PVC/Pvdc/PVC	PVC/Aclar/PVC	PVC/Aclar/PVC	PVC/Aclar/Pvdc
Commercial name	PVC	Alfoil P5G	Alfoil X5G	Alfoil T5G	Alfoil ES03	Aclar PA 503	Aclar PA 503	Kp Max 504
Thickness (µm)	PVC= 250	PVC= 250 Pvdc= 25	PVC= 250 Pvdc= 54	PVC= 250 PE= 30 Pvdc= 57	PVC= 127 Pvdc= 71	PVC= 127 Aclar= 51	PVC= 127 Aclar= 76	PVC= 127 Aclar= 102 Pvdc= 96 PVC= 127
Total thickness (µm)	250	275	304	337	325	312	337	452
Water Vapor transmission rate (g/m2.d)	3.1	0.75	0.35	0.25	<0.14	0.11	0.08	<0.035

Table 1: Porosity of various blister is depending on their composition. Aluminum/Aluminum is our reference with almost “zero” water transmission.

The purpose of this study is to determine the design space for gelatin hard capsules filled with acetaminophen tablets in blisters of variable porosity and stored under I.C.H. [1] storage conditions.

METHOD

Product description

The capsules studied are Coni-Snap® hard gelatin capsules size#0 white opaque, filled with 500mg acetaminophen tablets.

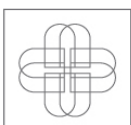
Testing protocol

Capsules were packed in blister with variable porosity (Table 1) and in moisture-tight aluminum blister to compare the effect of packaging. The blisters were stored under I.C.H. conditions, namely 25°C.60%RH, 30°C.65%RH, 30°C.75%RH and 40°C.75%RH and analyzed after 1 month and 3 months.

Measurements performed

During the stability study, capsules are characterized by:

- Dimensions: 10 capsules are visually inspected and their closed length measured. Specification is 21.7mm (+/-0.3).
- Dissolution profile[2]: 6 capsules are submitted to USP dissolution method for Acetaminophen capsules (Apparatus II paddle, 50 rpm, demi water at 37°C).



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Tolerances—Not less than 75% (Q) of the labeled amount of Acetaminophen is dissolved in 45 minutes.

- Gelatin semi-crystalline structure[3]: 3 capsules are cut in small pieces and 10mg randomly analyzed using differential scanning calorimetry (Mettler Toledo, DCS1 Stare System) Result of interest here is the melting enthalpy expressed in mJ/g of product equilibrated at 50%RH.
- Water content: water content is evaluated from glass transition temperature from calibration curve done with LOD Method (105°C for 18h).

RESULTS

Capsule water content: The overall results are consistent with expectations (Fig.1& 2): water content remains stable in blisters except at 40°C and 75%RH, where it increases significantly in porous blisters such as PVC and PVC/PVdCs.

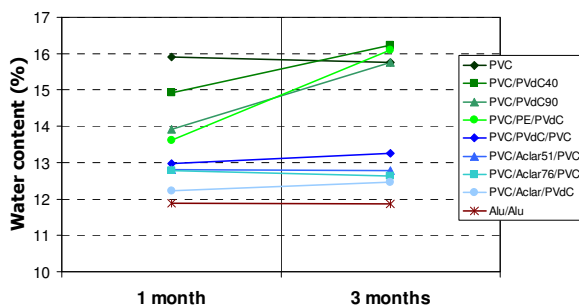


Fig. 1: Evolution of water content in capsules after storage in accelerated condition 40°C/75%RH for 1 and 3 months. For information, Initial water content in capsules is 14.2%.

Capsule dimension: the length of closed capsules after storage remains within specifications (21.7mm+/-0.3) whatever the blister porosity, except the case of porous

blisters (PVC, PVC/PVdCs) stored at 40°C/75%RH (Table 2).

Storage	25°C/65%RH		30°C/65%RH		30°C/75%RH		40°C/75%RH	
Blister	PVC	PVC/Aclar/PVdC	PVC	PVC/Aclar/PVdC	PVC	PVC/Aclar/PVdC	PVC	PVC/Aclar/PVdC
Shrinkage of closed length after 3 months (mm)	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	0

Table 2: Closed length of capsules after storage in ICH conditions

Capsule dissolution: dissolution profile of capsules filled with APAP and stored in all I.C.H. conditions remain stable for 3 months, except the capsules stored in PVC and PVC/PVdCs blister in accelerated conditions 40°C/75%RH (Table 3).

Blister	PVC	PVC/PVdC (250/40)	PVC/PVdC (250/90)	PVC/PE/PVdC	PVC/PVdC/PVC	PVC/Aclar/PVC	PVC/Aclar/PVC	PVC/Aclar/PVdC	Alu / Alu
25°C - 60%RH	PASS	not tested	PASS	not tested	not tested	not tested	not tested	PASS	not tested
30°C - 65%RH	FAIL	not tested	PASS	not tested	not tested	not tested	not tested	PASS	not tested
30°C - 75%RH	FAIL	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
40°C - 75%RH	FAIL	FAIL	FAIL	FAIL	PASS	PASS	PASS	PASS	PASS

Table 3: Dissolution results versus blister & ICH conditions

We documented in Fig.2 that capsules are stable in accelerated conditions, even in open conditions; blisters containing PVC induced in our study gelatin cross-linking in hot and humid conditions.

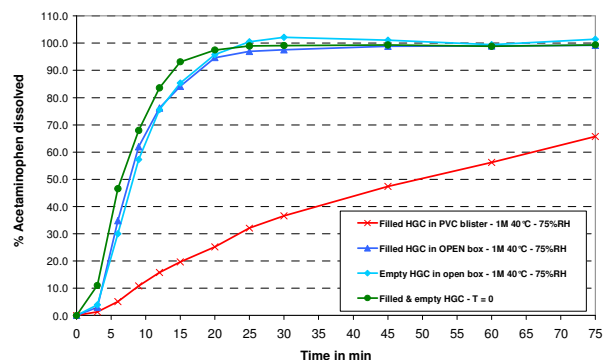
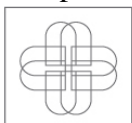


Fig.2: Example of dissolution profile of HGC capsules stored at 40°C/75%RH for 1 month: (v) filled and stored in PVC blisters, (▲) filled and stored in open bottle, (●) empty and stored in open bottle, (●) reference before storage



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Gelatin structure in capsule: After 3 months storage, gelatin structure does not change. In accordance with above water content results, glass transition decreases in gelatin stored in porous blisters (PVC, PVC/PVdCs) and accelerated conditions.

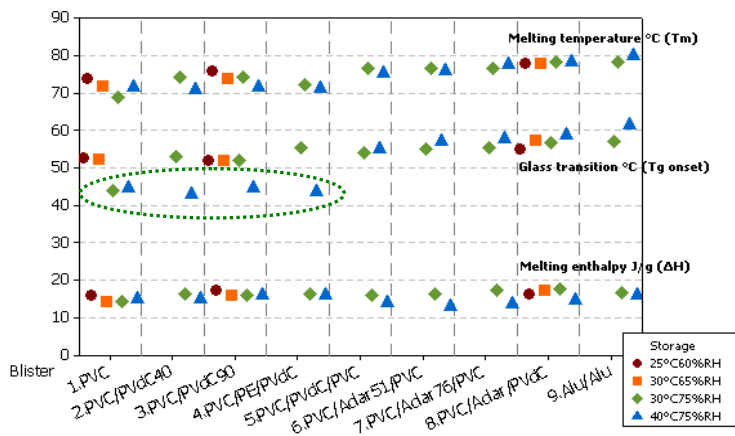


Fig. 3: Gelatin structure after 3 months storage: melting temperature (above), glass transition temperature (middle) and melting enthalpy (bottom).

CONCLUSIONS

We demonstrated that hard gelatin capsules are stable in all I.C.H. conditions provided that blisters are adequately selected: capsule dimensions, gelatin water content and structure and dissolution profile are preserved after 3 months.

We detected anomalies in porous blisters such as PVC and PVdCs that may affect

capsule dimensions or dissolution profile, under hot and humid conditions.

We recommend customers to select tight blisters such as aluminum/aluminum blisters to preserve the active and the capsule, whatever the storage conditions.

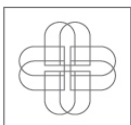
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ACKNOWLEDGEMENT

We wish to acknowledge the teams from the Colmar Chemical R&D, Strasbourg PDC and Dr. Keith Hutchison for their support and discussions.

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