

PURPOSE

To provide data on the compatibility of hard two-piece capsules and liquid or semi-solid excipients performed by means of stability test at accelerated environmental conditions.

Liquid or semi-solid based dosage forms have attracted considerable interest for their features which could be used to enhance bioavailability and solve difficulties caused by raw material properties such as poor water-solubility, low dose, high potency, low melting point or critical stability profile<sup>1</sup>.

Two-piece hard capsules are a suitable solid oral dosage form for liquid filling. However, their use for this application has not been sufficiently studied.

This investigation shows the fundamental compatibility data of two-piece hard capsule and liquid or semi-solid excipients used for liquid formulation.

METHOD

PROCEDURE

1. Capsules were filled with 0.3mL of liquid or semi-solid excipients. Semi-solid excipients were melted at 80°C before filling.

2. The capsules were band-sealed with their own formulation material in order to prevent possible leakage in the case of low viscous liquids..

3. Accelerated storage tests were conducted at 40°C 75%RH in closed glass bottles for 4 months. The capsules were evaluated by visual inspection and measurement of force at break.

Materials

Capsules (Three types of opaque capsule, #2 size, Qualicaps Co, Ltd.)

Quali-G™ (Bovine gelatin)

Quali-G™ PEG (Bovine gelatin & PEG)

Quali-V® (Hypromellose)

Liquid/Semi-solid Excipients (32 species, referred to table)

Rupture Test Methods

Room conditions25°C 50%RH

Sample treatment before testing

Placed in room conditions to cool down.

Test equipment & condition

EquipmentTexture analyzer (EZ-test, Shimadzu)

Press Rod & speedFlat-head (φ30mm) , 50mm/min

Number of sample : 10

Test pass criterion : 50N (on average)

Reference of test method & criterion

Test methods referred to in literature were used to evaluate the push-through strength of capsules from blister packages<sup>2,3,4</sup>.

The pass criterion was set from the literature results.

Test image

Ruptured sample

RESULT

Table : Test results after 4 months at 40°C / 75%RH in closed glass bottle

Hydro/Lipophilic Property	Group name	Brand name	HLB	Quali-G™			Quali-G™ PEG			Quali-V®			
				Assess-ment	Visual	Force at break (N) <sub>300</sub>	Assess-ment	Visual	Force at break (N) <sub>600</sub>	Assess-ment	Visual	Force at break (N) <sub>150</sub>	
Hydrophilic Excipients (Water Soluble)	Glycerol (Gly)			No	Def	N/A	No	Def	N/A	No	S	N/A	
	Propylene Glycol (PG)			No	Def	N/A	No	Def	N/A	No	Def	N/A	
	PEG, POE	PEG400		No	S	N/A	Yes	+	220	No	Def	N/A	
		PEG600		No	S	N/A	Yes	+	211	No	Def	N/A	
		PEG1540*		Yes	+	189	Yes	+	435	Yes	+	112	
Hydrophilic Surfactants (HLB>9)	Citric Acid Ester	Citroflex 2 (Triethylcitrate)		Yes	+	159	Yes	+	312	No	Def	N/A	
		BL-25*	19.5	Yes	+	222	Yes	+	383	Yes	+	137	
		BL-9EX	14.5	Yes	+	121	Yes	+	303	Yes	+	82	
	POE - Alkyl Ether	BL-2	9.5	Yes	+	139	Yes	+	311	No	S	N/A	
		PEG - Fatty Acid Ester	MYS-40MV*	17.5	Yes	+	299	Yes	+	506	Yes	+	145
		POE - Sorbitol Ether	Polysorbate20	16.7	Yes	+	94	Yes	+	272	Yes	+	90
	Gly - Fatty Acid Ester - PEG Ether	Polysorbate80	15	Yes	+	117	Yes	+	301	Yes	+	73	
		Koliphor EL	12-14	Yes	+	107	Yes	+	288	Yes	+	85	
		HCO-60*	14	Yes	+	149	Yes	+	232	Yes	+	99	
	Polyoxy glyceride	Labrasol	14	Yes	+	159	No	Den	N/A	No	Def	N/A	
Lipophilic Surfactants (HLB≤9)		Gelucire 44/14*	11-14	Yes	+	216	Yes	+	398	Yes	+	79	
		Gelucire 50/13*	11-14	Yes	+	247	Yes	+	466	Yes	+	114	
PG - Fatty Acids Ester	Labrafil M2125CS	9	Yes	+	190	Yes	+	243	No	Den	N/A		
	SEFSOL-218		Yes	+	180	Yes	+	303	No	Def	N/A		
	SEFSOL-228		Yes	+	150	Yes	+	315	Yes	+	74		
Sorbitol - Fatty Acid Ester	Labrafac PG	1	Yes	+	168	Yes	+	268	No	S	N/A		
	SO-15MV	4	No	Den	N/A	No	Den	N/A	No	Den	N/A		
	SO-30V	2	Yes	+	184	Yes	+	321	Yes	+	85		
Vegetable Oil	Vitamin E		Yes	+	158	Yes	+	271	Yes	+	73		
	Oleic Acid		No	S	N/A	No	Den	N/A	No	Den	N/A		
	Lipophilic Excipients (water Insoluble)		Mineral Oil (Liquid Paraffin)		Yes	+	162	Yes	+	288	Yes	+	78
Triglyceride	Triester F-810 (MCT)		Yes	+	168	Yes	+	335	Yes	+	78		
	Cotton Seed Oil		Yes	+	166	Yes	+	309	Yes	+	78		
	Sesame Oil		Yes	+	165	No	Den	N/A	Yes	+	69		
Vegetable Oil	Corn Oil		No	Den	N/A	No	Den	N/A	Yes	+	86		
	Soy Bean Oil		Yes	+	161	Yes	+	300	Yes	+	81		
					Yes	+	170	Yes	+	307	Yes	+	73

Abbreviations




Visual +:No-change, Def: Deformed, Den: Dent, S:Sweating. \*:Solid excipients in room temperature, N/A: Not available

Brand name: Generic name

BL-2: Polyoxyl 2 Lauryl ether, BL-9EX: Polyoxyl 9 Lauryl ether, BL-25: Polyoxyl 25 Lauryl ether, MYS-40MV: Polyoxyl 40 stearate, Koliphor EL: Polyoxyl 35 Castor oil, HCO-60: Polyoxyl 60 Hydrogenated Castor oil, Labrasol: Caprylocapryl polyoxyl-8 glycerides, Gelucire 44/14: Lauroyl polyoxyl-32 glycerides, Gelucire 50/13: Stearoyl polyoxyl-32 glycerides, Labrafil M2125CS: Linoleoyl polyoxyl-6 glycerides, SEFSOL-218: Propylene glycol monocaprylate, SEFSOL-228: Propylene glycol dicaprylate, Labrafac PG: Propylene glycol dicaprolate/dicaprate, SO-15MV: Sorbitan sesquioleate, SO-30V: Sorbitan trioleate

CONCLUSIONS

Visual Defects

Property	Deformed	Dent	Sweating
Capsule shape	Deformed	Deformed	No-change
Excipient	Leakage	No-leakage	Leakage
Picture			

Force at break (N)

Quali-G™ PEG shows the highest required force at break among these three capsules.

Within the same capsule type, the force at break results of liquid-filled capsules are considered to have a consistent and homogeneous distribution.

Higher force at break results were observed for the semi-solid filled capsules in relation to those of liquid-filled ones. An additional force from the inner solid substance is considered to be the reason.

Summary

Selection of capsule type required depends on the liquid or semi-solid fills.

For hydrophilic excipients, Quali-G™ PEG capsules would be most suitable. For hydrophilic surfactants, either could be used, with the exception of Labrasol which requires Quali-G™.

Overall Quali-G™ PEG supports more pressure as shown by the higher rupture pressure values.


REFERENCE

1. A.Roberson, “Formulating with liquids: Two-piece or softgel Capsules?”,Tablet & Capsule, 10-13, January, 2016

2. A.Yamashita *et.al.*, Japan Journal of Pharmaceutical Health Care Science, 27(6), 576-582, 2001

3. Eric Chiang, “how strong your blister pack?”, Brookfield, 2012

4. “Measurement of strength of the press through package and tablet”, Shimadzu application news, No.i243, 2011



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