DiluCap

The right excipient for your capsules

www.fagron.com

Fagron
personalizing medicine

Summary

1. THE IMPORTANCE OF THE EXCIPIENTS FOR A DOSAGE FORM

Excipients are essential for compounding pharmaceutical dosage forms.

The word excipient comes from the Latin *excipere*, which means "to receive" (the excipient "receives" the active pharmaceutical ingredient, API). For a long time, it was believed that excipients were pharmacologically inert substances used solely to optimize the handling of powders, to protect the API or to facilitate its transport.

Currently, in addition to their traditional functions, the excipients need to play the role of an adjuvant, assisting the API to promote its activity through influence on the release from the pharmaceutical dosage form. Therefore, it is considered an essential ingredient for the formulation's good performance, ensuring correct bioavailability, solubility, stability, dose accuracy, and improvement of organoleptic characteristics. In addition, it is yet favoring greater adherence to treatment **(Figure 1)**.

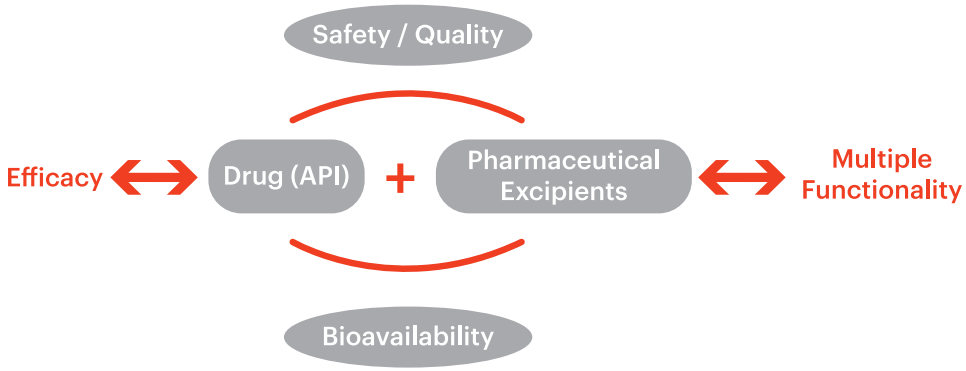


Figure 1. Joint effects of active pharmaceutical ingredients (API) and excipients on the final characteristics of a dosage form. Adaptaded.[1]

2. DILUCAP: THE RIGHT EXCIPIENT FOR YOUR CAPSULES

Choosing the right excipient is paramount for the adequate clinical performance of a robust dosage form. This choice needs to be based on technical parameters of both the API and the functionality of the dosage form itself – therefore science needs to be on the backbone of such process.

As an example of the importance of the excipient's role on the dosage form performance, we can consider the case of an intoxication that occurred in Australia in the late 1960s: epileptic patients who were taking phenytoin capsules experienced intoxications due to the replacement of the diluent. Calcium sulphate (low solubility in aqueous media, which prolongs the release of the API) was changed by lactose (high solubility in aqueous media, which triggers immediate release of the API), and this led to an increase of the mean serum concentration of phenytoin (a narrow therapeutic index drug) by a factor of 4.5, beyond the toxic threshold.

Therefore, properties such as bioavailability and stability of the dosage form are largely dependent on the use of the right excipient. Given this, Fagron developed a line of excipients with a large number of studies to guarantee performance and safety of compounded capsules: DiluCap.

DiluCap is a line of excipients specially developed so that you can compound every capsule formulation with ease and trust in its final characteristics. All excipients were developed following scientific criteria and were extensively tested to prove their performance.

For each API, there is a right DiluCap excipient:

DiluCap SLD | DiluCap PSD | DiluCap SR

DiluCap Hygro | DiluCap Antioxi | DiluCap OD

Advantages of choosing to standardize your capsules' excipients with DiluCap include:

- Avoidance of segregation between API and other formulation components;
- Preservation of API stability;
- Dose accuracy, as they facilitate the distribution of particles from the API;
- Modulation of the solubility and bioavailability of API;
- Good flux properties;
- Absence of allergens such as lactose, gluten, soy, and others;
- Proven functionality;
- No need for other adjuvants;
- Developed based on the biopharmaceutical classification;
- Physiologically inert;
- Reduction of process time and the number of items in stock;
- Batch-to-batch reproducibility.

3. THE SCIENCE BEHIND DILUCAP

3.1. Excipients for hard-shell capsules

The availability of excipients on the market represents a very expressive number: more than a thousand different excipients are available as individual ingredients, for diverse dosage forms. **Table 1** demonstrates the main excipients for hard-shell capsules, according to their function in the formulation.

Table 1. Classification of excipients for hard-shell capsules according to their function.

Excipient class per function	Properties	Examples
Diluent	Inert filling substances used to provide adequate volume and weight, flow properties, or compression characteristics.	Lactose, starch, pregelatinized starch, microcrystalline cellulose, mannitol, isomalt, talc, and others.
Lubricant	Used to reduce friction during the tablet compression process, preventing the powder from adhering to the punch of the tablet press. When preparing capsules, lubricants reduce the adherence between powders and the parts of the filling capsules device/machine. Lubricants also improve the flow properties of powder mixtures, facilitating their flow.	Magnesium stearate, talc (magnesium silicate).
Glidant	Agents used in capsules formulations to improve the flow properties of powder mixtures.	Colloidal silicon dioxide.
Wetting agent	Substances that increase the penetration of water and the wetting of solid particles, which are present in compacted solid dosage forms such as tablets and capsules, favoring the disintegration, and dissolution of poorly soluble APIs.	Sodium lauryl sulfate, sodium docusate, polysorbate.
Disintegrant	Used to break the compacted mass of powders inside the capsule into smaller particles that disperse or dissolve more quickly.	Sodium croscarmellose, sodium starch glycolate.
Stabilizer	API stability enhancer. ***Absorbents***: Agents that are capable of capturing other molecules within them and used to prevent the formation of eutectic mixtures and decrease the hygroscopy of some solid substances. ***Antioxidants***: inhibit oxidation and are used to prevent the degradation of preparations by oxidative processes	***Absorbents***: Light magnesium oxide, light magnesium carbonate, kaolin. ***Antioxidants***: Butylated hydroxytoluene (B.H.T.), butylated hydroxyanisole (B.H.A.),sodium metabisulfite.

3.2. How to define the correct excipient blend for each formulation

Defining an excipient blend for your hard-shell capsules is not always a direct process, and it can be time-consuming as you would need to evaluate the performance in a trial-and-error way. When choosing the excipient composition, it is important to consider its role and several other technical criteria according to the specific formulation to be prepared.

Some of the parameters that need to be considered during this excipient-selection process include the API stability profile, the API-excipient compatibility, powder flowability and packing, powder mixing process and its critical factors, disintegration and dissolution rate, powder hygroscopicity, desirable release profile, patient adherence and API bioavailability profile.

All those factors impact on the dosage form performance, which is reflected on its bioavailability.

Regarding drug bioavailability and its relationship with capsules formulation, the creation of the **Biopharmaceutical Classification System** (BCS) by Amidon et al.[3] provided a very important step towards the standardization and automatization of the decision process for excipients **(Figure 2)**. The BCS scheme was designed to correlate *in vitro* drug product dissolution and *in vivo* bioavailability, based on two criteria: drug dissolution (solubility) and gastrointestinal permeability, which are the fundamental parameters controlling rate and extent of drug absorption. Table 2 lists the BCS class of some selected APIs, to exemplify such classification.

Solubity	Biopharmaceutical Classification System Class	Permeability
HIGH	I	HIGH
LOW	II	HIGH
HIGH	III	LOW
LOW	IV	LOW

- **Class I** - high solubility and high permeability (amphipathic). They have few bioavailability problems; therefore, they have few requirements for the excipient choice.
- **Class II** - low solubility and high permeability (lipophilic). They present dissolution as a limiting factor for absorption. Therefore, it is recommended to opt for excipients that aid in dissolution, in addition to the use of wetting and disintegrating agents.
- **Class III** - high solubility and low permeability (hydrophilic). They have limited absorption by permeability, therefore an excipient that contains ingredients that overcome this barrier is needed.
- **Class IV** - low solubility and low permeability (hydrophobic). They can present many difficulties to oral bioavailability, therefore an excipient that contains ingredients that overcome this barrier is needed.

Figure 2. Biopharmaceutical Classification System classes, based on the solubility and gastrointestinal permeability of the APIs.

Table 2. Biopharmaceutical Classification System (BCS) class of selected Active Pharmaceutical Ingredients (APIs).

API	Solubility (mg/mL) *	Biopharmaceutical class
Aceclofenac	0.01	II
Acetazolamide	0.1	IV
Acetylsalicylic acid	3.33	III
Acyclovir	10	III
Allopurinol	0.1	IV
Amiloride, hydrochloride	1	III
Atenolol	26.5	III
Benserazide	33	III
Biperiden, hydrochloride	1	I

API	Solubility (mg/mL) *	Biopharmaceutical class
Buspirone	33	I
Carvedilol	0.01	II
Celecoxib	0.01	II
Clonidine, hydrochloride	80	I
Diazepam	0.01	II
Diclofenac sodium	0.1	II
Doxycycline	0.1	IV
Escitalopram	10	I
Ethinylestradiol	0.01	I
Fluoxetine, hydrochloride	33	I
Glibenclamide	0.01	II
Hydralazine, hydrochloride	40	III
Isoniazid	125	III
Levamisole	33.0	I
Lorazepam	0.08	I
Methotrexate	0.01	III
Metoprolol, tartrate	1000	I
Nadolol	0.64	III
Nitrofurantoin	0.19	IV
Oxcarbazepine	0.01	IV
Oxybutynin, chloride	100	I
Prednisolone	0.1	I
Propranolol, hydrochloride	33	I
Quetiapine, fumarate	1.0	II
Risperidone	0.01	II
Spironolactone	0.01	II
Tacrolimus	0.01	II
Tetracycline, hydrochloride	33	III
Ursodeoxycholic acid	0.01	II
Verapamil, hydrochloride	83	I

**Solubility measured in 250 mL water at 37ºC over the pH range 1 - 7.5*

3.3. Using the Biopharmaceutical Classification System to create a decision tool for excipients

The knowledge on the BCS allowed for the extension on the knowledge on how to improve bioavailability of solid oral formulations by adjusting the excipient composition. Using this, we have created the Algorithm for Choosing Excipients for Hard-Shell Capsules **(Figure 3)**, which was the base for the development of our whole DiluCap line. In other words, the DiluCap line was science-based developed to aid on the performance of all types of APIs for oral use on solid dosage forms.

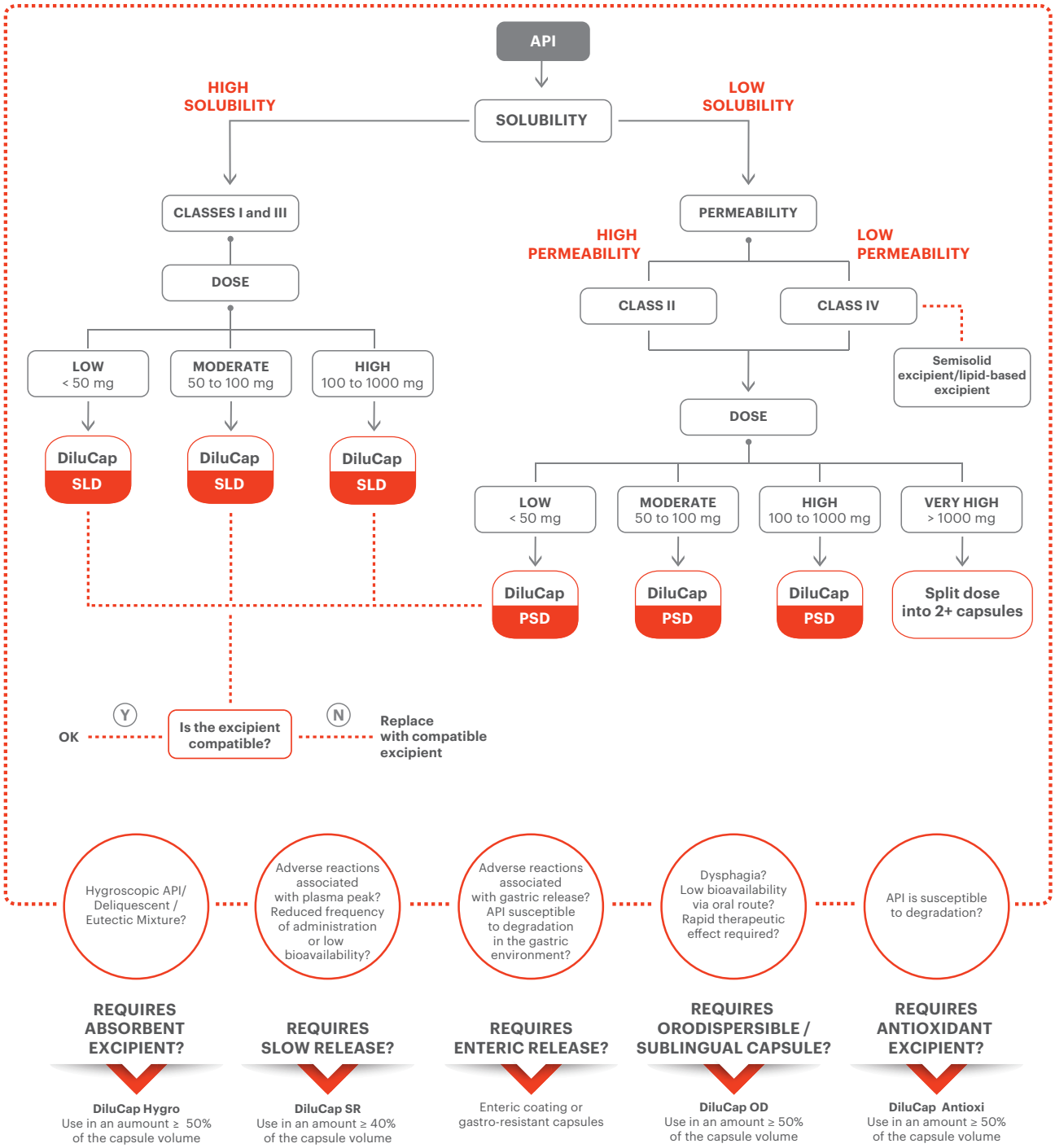


Figure 3. Algorithm for Choosing Excipients for Hard-Shell Capsules, using the DiluCap line (patent: PI0705377-0 A).

3.4. DiluCap: a line of excipients developed using the Biopharmaceutical Classification System

Table 3. DiluCap line of excipients.

DiluCap	Indication	Functionality	APIs examples
DiluCap SLD	Soluble APIs Class I and III (BCS)	Promotes the disintegration without negative impact on dissolution.	Fluoxetine Fluconazole Gabapentin
DiluCap PSD	Poorly soluble APIs Class II and IV (BCS)	Favors the disintegration and dissolution of the API.	Ivermectin Finasteride Orlistat
DiluCap SR	APIs requiring modified release (*Slow release*)	Reduces the disintegration and release rate of the API, promoting its slow release. Prevents plasma peaks responsible for adverse effects.	Nicotinic acid Pentoxifylline Bupropion
DiluCap Hygro	Hygroscopic or deliquescent APIs	Absorbent. Reduces hygroscopicity, deliquescence and eutectic mixture formation.	Herbal dry extracts Chelates minerals Amino acids
DiluCap Antioxi	APIs susceptible to oxidation	Chemical stabilizer. Antioxidant. Reduces water activity, reducing chemical degradation.	Lovastatin Simvastatin Captopril
DiluCap OD	Orodispersible APIs (*Sprinkle capsules*) or candidate APIs for sublingual administration	Sweetener. Flavoring. Promotes transmucosal permeation.	Coenzyme Q10 Hydroxytriptophan Vitamin B12

HOW TO USE DILUCAP	
DiluCap SLD	For a better performance of the excipient in the formulation, it is recommended that the amount used represents at least 30% of the filled volume of the capsule.
DiluCap PSD	For a better performance of the excipient in the formulation, it is recommended that the amount used represents at least 30% of the filled volume of the capsule.
DiluCap SR	At least 40% of the capsule volume must be filled with DiluCap SR. Handle only on capsules with a size equal to or greater than 1.
DiluCap Hygro	For a better performance of the excipient in the formulation, it is recommended that the amount used represents at least 50% of the filled volume of the capsule.
DiluCap Antioxi	For a better performance of the excipient in the formulation, it is recommended that the amount used represents at least 30% (and ideally 50%) of the filled volume of the capsule.
DiluCap OD	For a better performance of the excipient in the formulation, it is recommended that the amount used represents at least 50% of the filled volume of the capsule.

3.4.1. Special DiluCap excipients: DiluCap Antioxi and DiluCap OD

Usually, DiluCap SLD and DiluCap PSD can be considered for most APIs provided that they do not require special handling characteristics: if they are very hygroscopic, DiluCap Hygro is more advisable; if they require extended-release, DiluCap SR.

However, there are still two special situations that require attention from the pharmacist: when the API is very sensitive to oxidation and when an oral absorption is required. For those cases, we have developed DiluCap Antioxi and DiluCap OD, respectively.

DiluCap Antioxi

Oxidation is a process that leads to raw material decomposition, with subsequent loss of function. Light, air, heat, contaminants in the medium (catalysts → heavy metals) and medium pH are triggering agents of this process. The oxidation mechanism begins with the formation of so-called free radicals.

Antioxidants are substances that preserve the formulation of any oxidative process. They inhibit the oxidative deterioration (destruction by oxygen action) of pharmaceutical products, interfering with the development of oxidative rancidity in oils and fats or the inactivation of medications.

Antioxidants are then substances that act by disrupting the formation of free radical chains. They act by slowing or inhibiting the oxidation of organic or inorganic compounds, preventing the initiation and spread of oxidation reactions.

Considering the development of solid pharmaceutical dosage forms for oral use with the presence of APIs with potential susceptibility to oxidation, the use of excipients containing antioxidants represents a rational way to maintain the preparation stability throughout the use and storage of the drug.

DiluCap Antioxi is an antioxidant excipient for the preparation of hard-shell capsules, specially developed to prepare formulations containing APIs sensitive to oxidation.

It represents a practical solution for preparing stable and effective capsule formulations. Its composition includes excipients with an antioxidant role and desirable free-flow characteristics when filling hard capsules.

DiluCap OD

Capsules with patient-friendly appeal and aiming to circumvent the swallowing difficulty or dysphagia of conventional pills, such as sprinkle capsules, sublingual or orodispersible capsules, represent an attractive alternative to increase adherence due to their convenience.

Within this context, sprinkle capsules are a new generation of patient-centric hard-shell capsules. They consist of hard capsules that offer the administration possibility either by swallowing them or opening it, so that their contents are sprinkled over semi-solid foods (e.g., yogurt, puree, pudding, milk jam) or liquids (e.g., water or juice). This allows the API administration for children, elderly and dysphagic patients. “Sprinkle” formulations provide virtually the same dose flexibility and ease of ingestion as liquid formulations. In addition, when the medication is sprinkled and ingested with food, its unpleasant taste or smell can also be masked, increasing the patient's adherence to the treatment.

Additionally, the sprinkle capsule formulation has the convenience of being opened before sprinkling its contents on the food or liquid. As a solid dosage form, sprinkle formulations ensure greater stability during the drug's storage period when compared to liquid formulations. Therefore, the sprinkle capsules are specifically designed to be opened by patients and caregivers, allowing the administration of the encapsulated internal content (API + excipients) consistently and concomitantly with food or beverages, without compromising quality, safety, or efficacy. In this way, they can overcome various challenges associated with the administration and development of medications for pediatric and geriatric patients.

Another convenient option is the sublingual route, which provides a way of administering drugs through the mouth through the highly vascularized sublingual oral mucosa that favors the permeation of specific drug molecules. It allows bypassing the passage through the digestive tract and effects of the first-pass metabolism in the liver. Then, it favors the administered API to directly reach the bloodstream, resulting in a rapid therapeutic effect and greater bioavailability.

Sublingual capsules can be compounded by using small capsules with shells made of orodispersible materials (e.g., Pullulan capsules). Those capsules can be placed directly under the sublingual region without prior opening. They need to contain soluble excipients that allow their rapid disintegration and sublingual dissolution together with the APIs.

DiluCap OD is an excipient from the DiluCap family that was specifically developed to prepare sprinkle capsules or sublingual capsules.

It contains soluble, palatable excipients that promote the permeation of active ingredients through the oral and sublingual mucosa. It also has excellent flow properties and broad compatibility with active ingredients conveyed, providing the pharmacy with the practicality and convenience of a ready-to-use excipient.

4. DILUCAP PERFORMANCE: EXTENSIVE TESTING TO ENSURE THE BEST QUALITY

DiluCap line of excipients was extensively tested to ensure that all performance parameters are adequate for the different BCS classes of APIs.

4.1. Flow Properties

Angle of repose

The angle of repose is used to measure frictional forces in the form of a loose powder. It is measured as the angle relative to the flat base of the conical pile, produced when a granular material is poured onto a horizontal surface. The angle of repose can range from 0° to 90°. By decreasing the angle of repose, the flow property is improved. The angle of repose is calculated according to Eq. 1, and classified according to **Table 4**.

Eq. 1 $$\theta = \tan^{-1}(h/r)$$

in which **h** = stack height, **r** = stack base radius, and **θ** = angle of repose.

Carr's compressibility index

The Carr's compressibility index, also known as Carr index, is a measure of the compressibility of a powder and it is frequently used in pharmaceutical studies. A small numerical Carr index means that the bulk density and the tapped density are close in value. A large Carr index, on the other hand, indicates that the interparticle interactions are significative, leading to considerable differences between the bulk and the tapped densities.

The Carr index is calculated according to Eq. 2, and classified according to **Table 5**.

Eq. 2 $$C = 100\,\frac{\rho T - \rho B}{\rho T}$$

in which ρT = tapped density and ρB = bulk density.

Table 4. Angle of repose classification.[4]

Angle of repose	Flow properties
< 25º	Very good
25º - 30º	Good
30º - 45º	Limited (Acceptable)
>45º	Poor

Table 5. Carr's compressibility index (CI) as indicator of capsule-filling properties.[4]

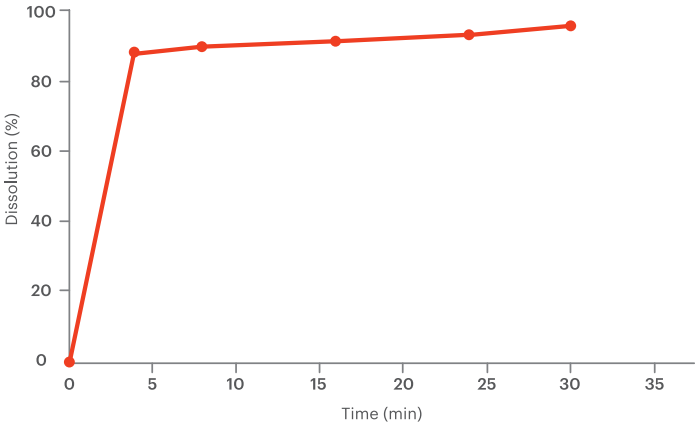
% Carr index	Flow type
< 15	Free flowing
15-25	Good
25-35	Acceptable / poor
> 35	Extremely poor / no flow

Table 6. Flowability of the DiluCap line of excipients.

Excipients	Bulk density (g/mL)	Tapped bulk density (g/mL)	Carr Index (%)	Flow type	Angle of repose (°)	Flow type
DiluCap SLD	0.5045	0.5766	12.50	Free flowing	28.89	Good
DiluCap PSD	0.4261	0.5114	16.68	Good	31.70	Acceptable
DiluCap SR	0.3833	0.4815	20.39	Good	32.17	Acceptable
DiluCap Hygro	0.4971	0.5800	14.29	Free flowing	31.83	Acceptable
DiluCap Antioxi	0.4620	0.5429	14.90	Free flowing	35.15	Acceptable
DiluCap OD	0.4463	0.4892	8.8	Free flowing	28.72	Good

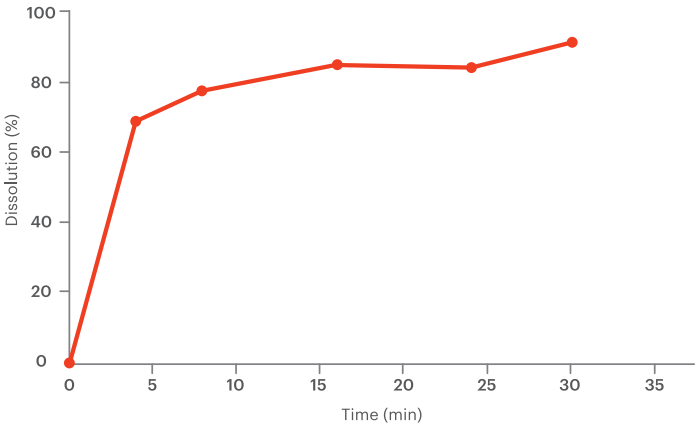
4.2. Dissolution profiles (*biopharmaceutical studies*)

4.2.1 DiluCap SLD



Time (min)	Dissolution (%)
4	87.97
8	89.61
16	90.97
24	92.98
30	95.61

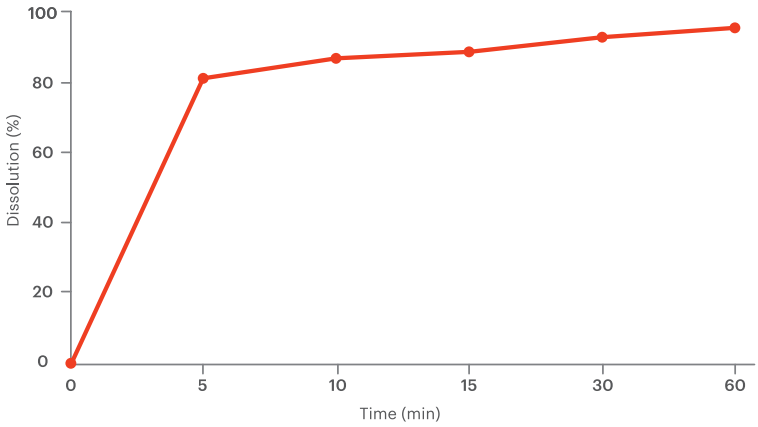
Figure 4. Dissolution profile of amlodipine (besylate) (BCS III/I) 5 mg capsules compounded with DiluCap SLD. Tolerance: minimum of 75% of the labeled amount is dissolved.



Time (min)	Dissolution (%)
4	69.05
8	77.51
16	84.97
24	84.32
30	91.45

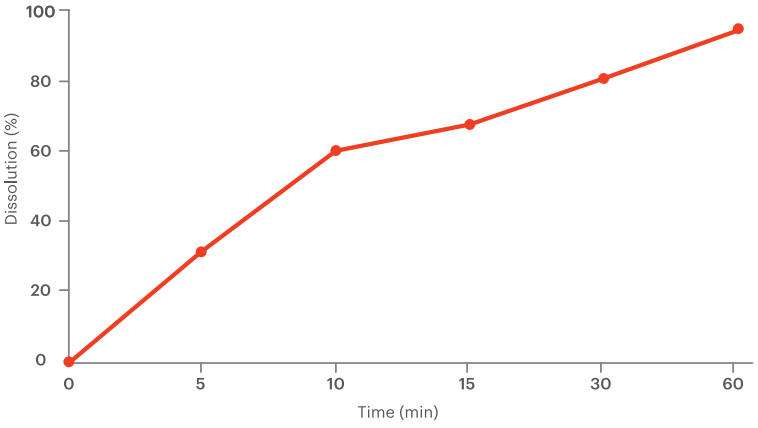
Figure 5. Dissolution profile of doxazosine mesylate (BCS I) 4 mg capsules compounded with DiluCap SLD. Tolerance: minimum of 70% of the labeled amount is dissolved.

4.2.2 DiluCap PSD



Time (min)	Dissolution (%)
5	81.95
10	87.42
15	89.38
30	93.39
60	96.33

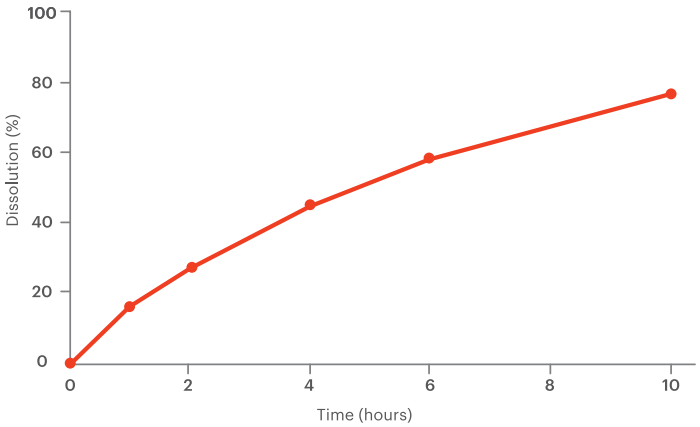
Figure 6. Dissolution profile of furosemide (BCS IV/II) 40 mg capsules compounded with DiluCap PSD. Tolerance: minimum of 80% of the labeled amount is dissolved.



Time (min)	Dissolution (%)
5	31.75
10	60.51
15	67.65
30	80.75
60	94.97

Figure 7. Dissolution profile of carbamazepine (BCS II) 200 mg capsules compounded with DiluCap PSD. Tolerance: minimum of 75% of the labeled amount is dissolved.

4.2.3. DiluCap SR



Time (hours)	Dissolution (%)
1	16.28
2	27.27
4	45.10
6	58.23
10	76.66

Figure 8. Dissolution profile of diclofenac sodium 50 mg capsules compounded with DiluCap SR. Tolerances: in 1h a maximum of 28% of the labeled amount is dissolved; in 2h, 20% to 40%; in 4h, 35% to 60%; in 6h, 50% to 80%; in 10h, a minimum of 65%.

4.3. Water uptake (*hygroscopicity*)

4.3.1 DiluCap Hygro

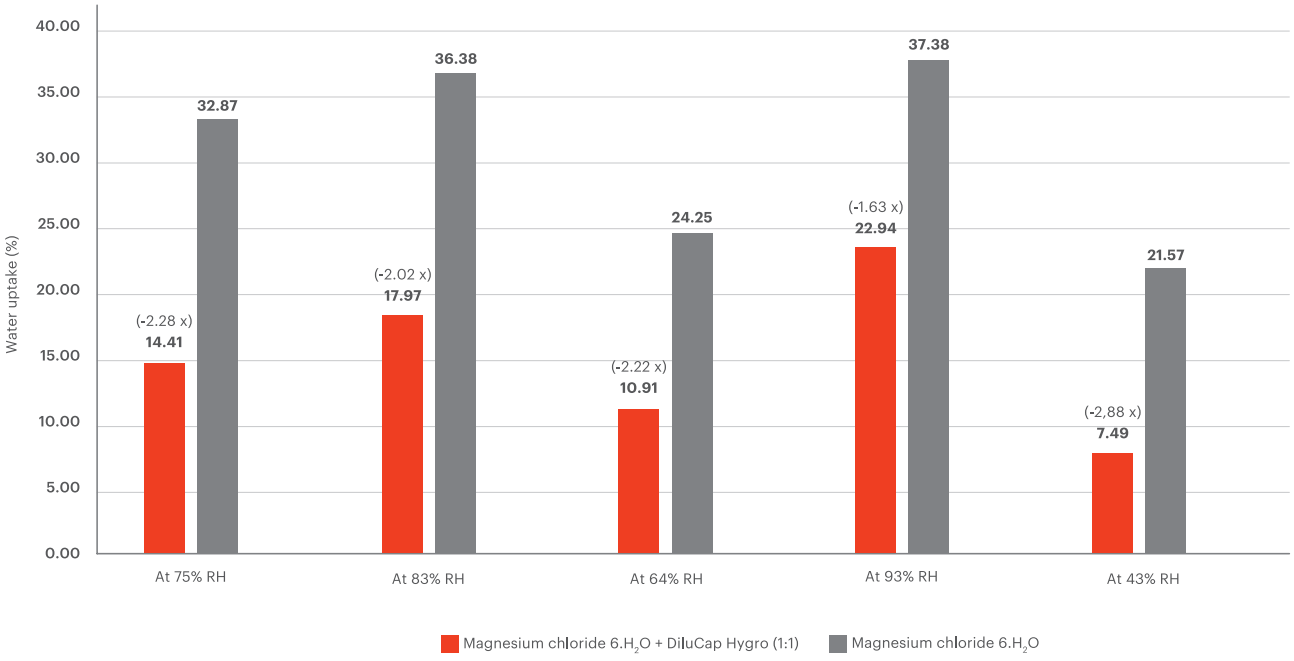


Figure 9. Differences in water uptake by magnesium chloride hexahydrate when standalone or in a mixture 1:1 with DiluCap Hygro, in different humidity conditions.

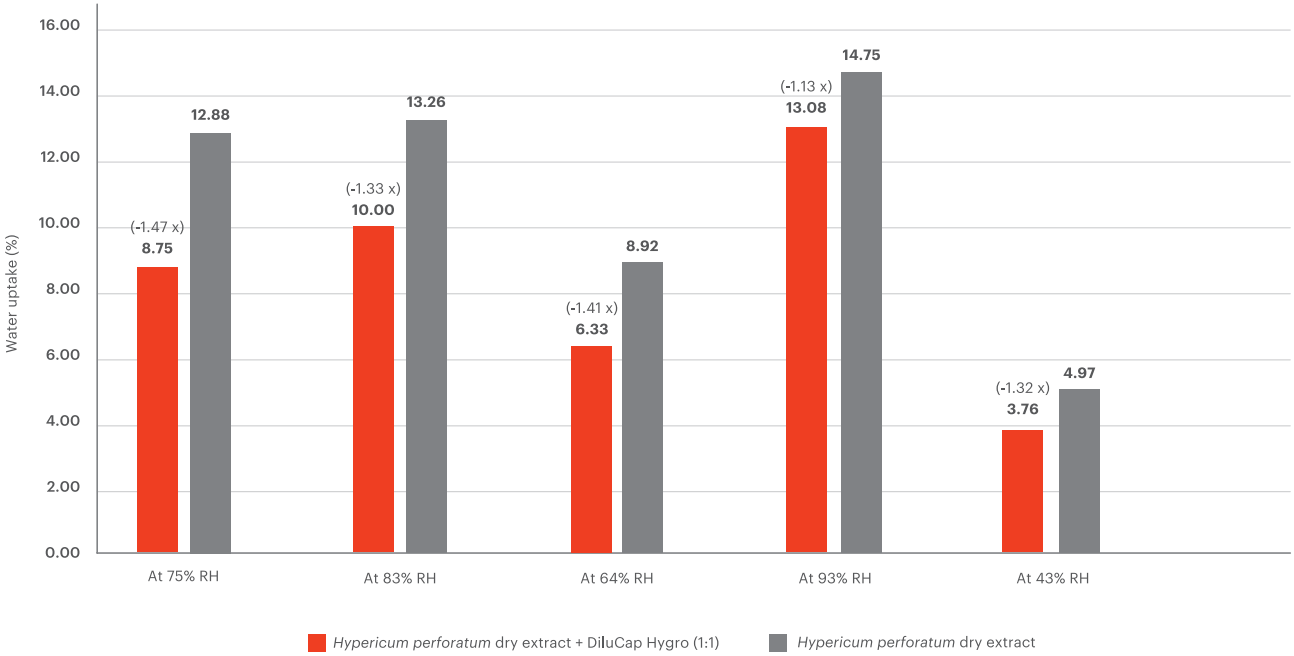


Figure 10. Differences in water uptake by *Hypericum perforatum* (dry extract) when standalone or in a mixture 1:1 with DiluCap Hygro, in different humidity conditions.

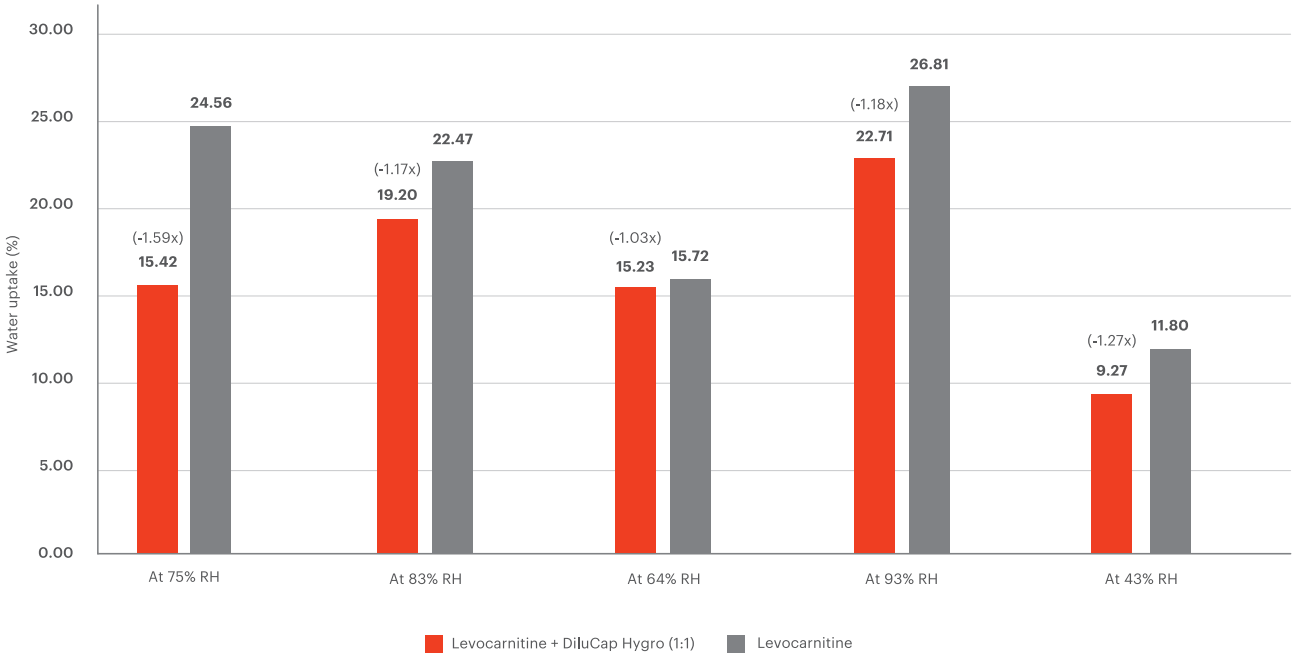


Figure 11. Differences in water uptake by levocarnitine when standalone or in a mixture 1:1 with DiluCap Hygro, in different humidity conditions.

4.4. Equilibrium Moisture Content

The Equilibrium Moisture Content (EMC) of a material inserted in different environments with specific relative humidity reflects the moisture content at which the material is neither gaining nor losing moisture. The EMC is calculated according to Eq. 3, and classified according to **Table 7**.

$$\text{Eq. 3} \qquad EMC = \frac{P}{P + 100} \text{ X } 100$$

where **P** is the moisture percentage on the dry basis, calculated according to Eq. 4.

$$\text{Eq. 4} \qquad P = \frac{\left[W \text{ x } \frac{A}{100}\right] \pm B \text{ x } 100}{W - \left[W \text{ x } \frac{A}{100}\right]}$$

where **W** is the initial sample weight (in grams), **A** is the initial moisture percentage, and **B** is the equilibrium weight change (in grams).

Table 7. Classification of powders according to their Equilibrium Moisture Content.[6]

Class	Characteristic
I (non-hygroscopic)	Essentially no moisture increases occur at relative humidities below 90%. Furthermore, the increase in moisture content after storage for one week above 90% R.H. is less than 20%.
II (slightly hygroscopic)	Essentially no moisture increases occur at relative humidities below 80%. The increase in moisture content after storage for one week above 80% R.H. is less than 40%.
III (moderately hygroscopic)	Moisture content does not increase above 5% after storage at relative humidities below 60%. The increase in moisture content after storage for one week above 80% R.H. is less than 50%.
IV (very hygroscopic)	Moisture increase may occur at relative humidities as low as 40 to 50%. The increase in moisture content after storage for one week above 90% R.H. may exceed 30%.

4.4.1 DiluCap OD

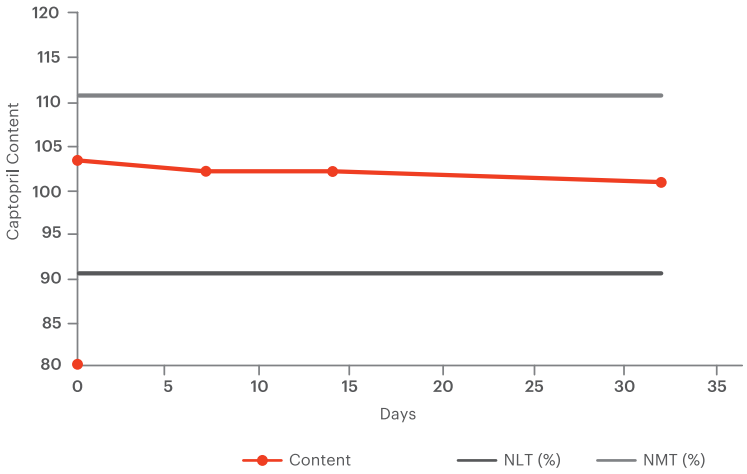
Table 8. Results of the Equilibrium Moisture Content study (EMC) for DiluCap OD.

Equilibrium Moisture Content (EMC) – Humidity uptake						
Humidity condition	33% RH	43% RH	64% RH	75% RH	83% RH	93% RH
Dilucap OD	0.25%	0.42%	0.32%	0.04%	0.02%	<0.01%

*DiluCap OD can be considered Class I according to the EMC classification, therefore it is **non-hygroscopic** (increase in weight in environments with RH lower than 90% is <20%).*

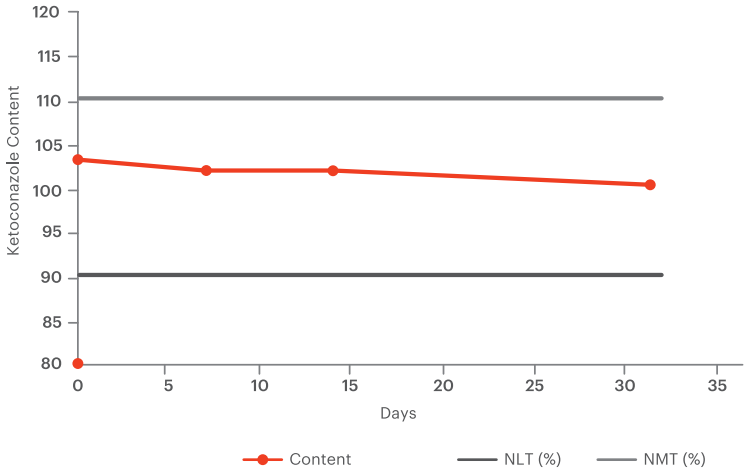
4.5. Stability study

4.5.1 DiluCap Antioxi



Days	Average Content (%)
0	104.22
7	103.08
14	103.91
32	102.58

Figure 12. Accelerated stability of captopril 50 mg capsules compounded with DiluCap Antioxi.Study conducted at 55°C and 75% RH. Specification: captopril capsules contain not less than (NLT) 90.0% and not more than (NMT) 110.0% of the labelled amount of captopril ($C_9H_{15}NO_3S$).[4] Considering the temperature and humidity conditions of the climatic chamber used and the evaluation period of the accelerated study, **a minimum shelf-life of at least 186 days is estimated** (Q_{10}=1.8) for the captopril 50 mg capsules compounded with DiluCap Antioxi.[7]



Days	Average Content (%)
0	102.77
7	101.70
14	101.69
32	100.36

Figure 13. Accelerated stability of ketoconazole 200 mg capsules compounded with DiluCap Antioxi. Study conducted at 55°C and 75% RH. Specification: ketoconazole capsules contain not less than 90.0% and not more than 110.0% of the labelled amount of ketoconazole ($C_{26}H_{28}Cl_2N_4O_4$). Considering the temperature and humidity conditions of the climatic chamber used and the evaluation period of the accelerated study, **a minimum shelf-life of at least 186 days is estimated** (Q_{10}=1.8) for the ketoconazole 200 mg capsules compounded with DiluCap Antioxi.[7]

References

1. Chan M. The Effect of a Source Change for an Active Pharmaceutical Ingredient (API) or Excipient on the Finished Drug Product. Published online 2016.
2. Chavda H, Neerumalla SK, Patel A, Poptani S. Excipients: The Real Players behind Robust Formulation. Indian Journal of Pharmaceutical Education and Research. 2019;53(1):5-7. doi: 10.5530/ijper.53.1.2 2.
   Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical Research*. 1995;12(3):413-420. doi:10.1023/A:1016212804288.
3. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical Research*. 1995;12(3):413-420. doi:10.1023/A:1016212804288.
4. Podczeck F, Jones B. Pharmaceutical Capsules. 2nd ed. Pharmaceutical Press; 2004.
5. United States Pharmacopeial Convention. *United States Pharmacopeia and National Formulary*. 2021.
6. Callahan, J. C. et al. Equilibrium moisture content of pharmaceutical excipients. Drug Development and Industrial Pharmacy, v. 8, n. 3, p. 355-369, 1982.
7. NEN - Royal Netherlands Standardization Institute. *ASTM F1980- 07.*; 2011.

Together
we create the future
of personalizing medicine.

Fagron BV
Fascinatio Boulevard 350
3065 WB Rotterdam
The Netherlands

T +31 88 33 11 288
F +31 88 33 11 210
www.fagron.com

Fagron
personalizing
medicine