Challenges and solutions for moisture sensitive API formulation

Introduction

Today, formulators are looking for alternative processes to reformulate existing products or to formulate New Chemical Entities (NCEs) since most of them are poorly water-soluble. More and more, formulators want to develop new galenics and textures, to have specific release kinetics, to formulate several actives in the same finished dosage form... Moreover, pharmaceutical industries want to develop forms targeting specific population such as children and elderly people. Improvement of drug performance is also strategic for formulators. The improvement of bioavailability, safety, the reduction of toxicity & side effects, the controlled release are some key parameters for formulators.

In formulation, one of basic requirements is that the pharmaceutical active ingredient (API) remains stable in the finished dosage form until the end of its shelf life to ensure efficacy and patient safety.
The degradation of the API can occur through thermal degradation, oxidation, UV, microorganisms or hydrolysis [1].
The physical and chemical properties of pharmaceutical solids are critically dependent on the presence of water: *e.g.* flow, compaction, dissolution, stability, storage, processing into formulations and final product packaging [2].

Moisture has a real impact on the formulation stability due to its influence in the glass transition temperature of the compounds.
Atmospheric humidity is one of the main sources of moisture that influences chemically or physically the active ingredient. Many APIs but also excipients are hygroscopic in nature and need to be protected from moisture.
Specific attention needs to be given when formulating such ingredients in order to prevent degradation due to hydrolysis [3].

In the following paper we will describe different ways of protecting the API through formulation using either a moisture absorbent, a film coating designed to prevent moisture uptake or lipid solvent-free solutions.

1. Protection from the inside

Caking of powder mixes has been an issue in the industry for many years [4].Basically the mechanism for caking is the absorption of moisture by one ingredient resulting in the agglomeration of particles. Formation of caked powder has a negative impact on product manufacturability and quality and can lead to the hydrolysis of the API.

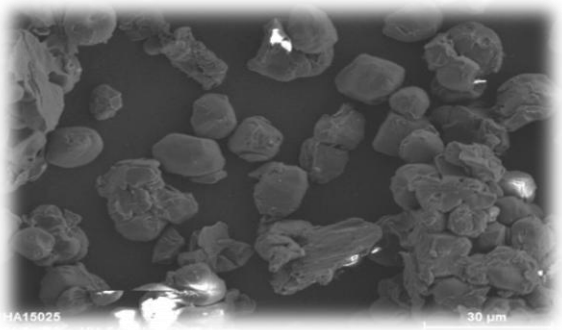
One way to protect the formula from moisture is to use a tabletting excipient designed to absorb water in the place of the active in order to prevent its degradation.

Amongst such excipients we can find magnesium aluminium silicate, carboxymethylcellulose or calcium carbonate [5]. All those excipients have porous structure and the ability to bound water.

SEPPIC's Partially pre-gelatinized starch Sepistab™ ST 200 possess those characteristics as well and hence can play the role of anti-caking agent in a tablet formula. On top of that Sepistab ST 200 compressibility is very good compared to the other anti-caking agents.

1.1 Product characteristics

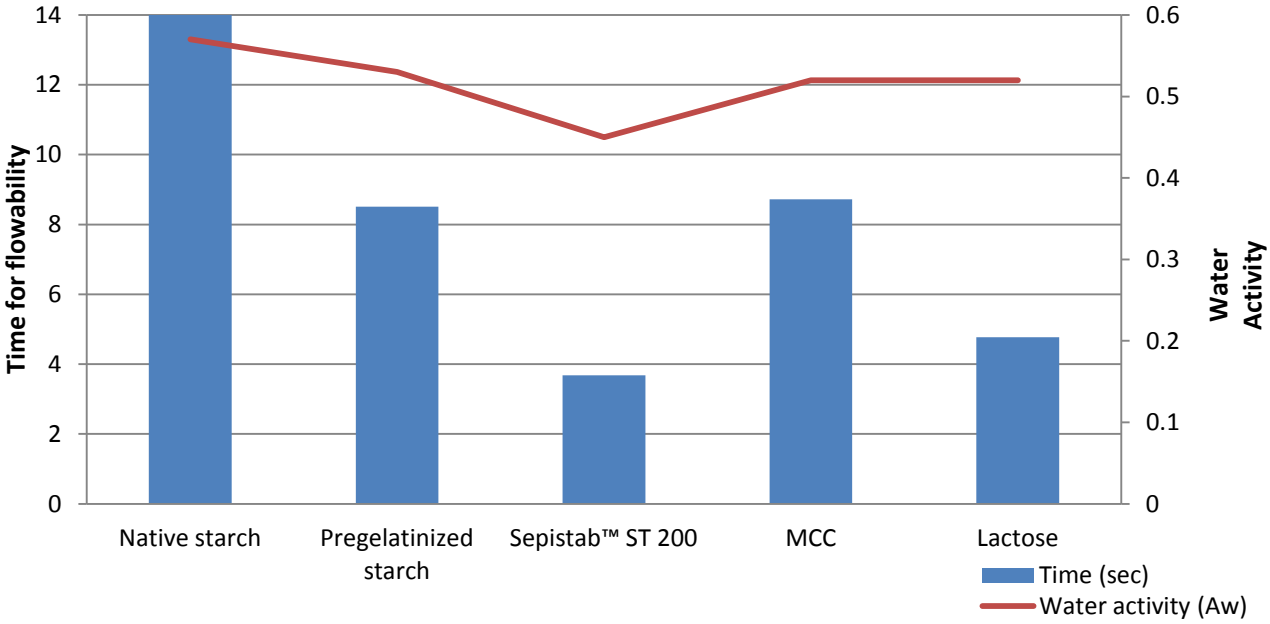
Sepistab™ ST 200 is a co-processed excipient that contains native and pre-gelatinized starch. As a consequence it combines the benefits of both ingredients. In addition to its excellent flowability and compactability behavior, its specific surface area at 0.5 m²/g -compared to around 0.25m²/g for the others partially pre-gelatinized starches- as well as its low water activity makes Sepistab™ ST 200 a good candidate for moisture absorption.



Picture 1: MEB image of Sepistab™ ST 200

The spherical shape of Sepistab™ ST 200 gives the excipient very good flowability as we can see in *Graph 1*. Moreover Sepistab™ ST 200 water activity (a_w) is the lowest of the excipients tested. A low a_w indicates that the excipient contains less free water. The water it contains is trapped inside the structure – it is referred to as bound water. Only free water is available to potentially hydrolyze the API.

This parameter together with a porous structure makes Sepistab™ ST 200 a perfectly versatile excipient also adapted to moisture adsorption.



Graph 1: Flowability of various excipients according to EP 2.9.16 and their a_w

1.2 Conditions of use

Sepistab™ ST 200 level of use is generally 10 to 30 % in a formula as it can replace several excipients at once. It is adapted to capsule filling and tablets manufacturing.
Sepistab™ ST 200 is currently used in many marketed drugs worldwide.

2. Film Coating

Another solution for protection of a finished drug product is through packaging. Although efficient it does not exclude moisture uptake during multiple openings. Protecting the cores with a moisture barrier film is appropriate, since it also eliminates this problem. An ideal moisture barrier coating should exhibit low permeability to water vapor without compromising its dissolution functionality [6]. For a film-coating to be able to protect the core, it must contain a hydrophobic ingredient. This ingredient can be the polymer itself or a hydrophobic plasticizer.

2.1 Sepifilm™ LP - Product characteristics

SEPPIC's Sepifilm™ LP range has been used for over 30 years for moisture protection purpose. Sepifilm™ LP is a ready-to-use film coating range of excipients containing stearic acid that prevents the moisture from reaching the core of the dosage form.
Sepifilm™ LP products can be applied on powder, pellets or tablets at various weight gain depending on the hygroscopicity of the formula and the protection to be achieved.

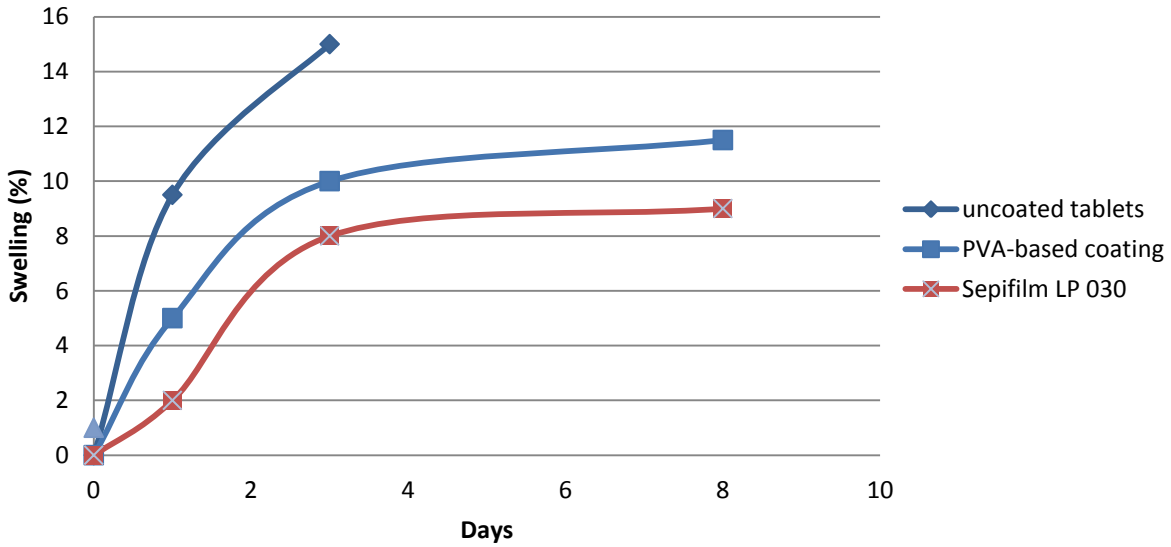
2.2 Sepifilm™ LP performances

500 mg Ranitidine tablets (*Table 1*) were coated with various ready-to-use solutions in order to test the products performances regarding moisture protection.
PVA-based coating designed for moisture protection was compared to Sepifilm™ LP 030.
5% weight gains were applied for all film-coating using the vendors recommendation for application and the swelling of the tablets was measured during 8 days at 25°C and 75 %RH.

Ingredient	% in the tablet
Ranitidine	33.4
Microcrystalline cellulose	32.75
Lactose	32.55
Magnesium stearate	0.5
Silica	0.8

Table 1: Composition of ranitidine tablets

The results in *Graph 2* show that ranitidine tablets coated with Sepifilm™ LP 030 swelled less than the other tablets, indicating that the coating prevents moisture from entering the core. Uncoated tablets became too soft to be handled after 3 days.



Graph 2: Ranitidine tablets swelling with different coatings, 25°C, 75 %RH

2.3 Sepifilm™ LP Dynamic Vapor Sorption

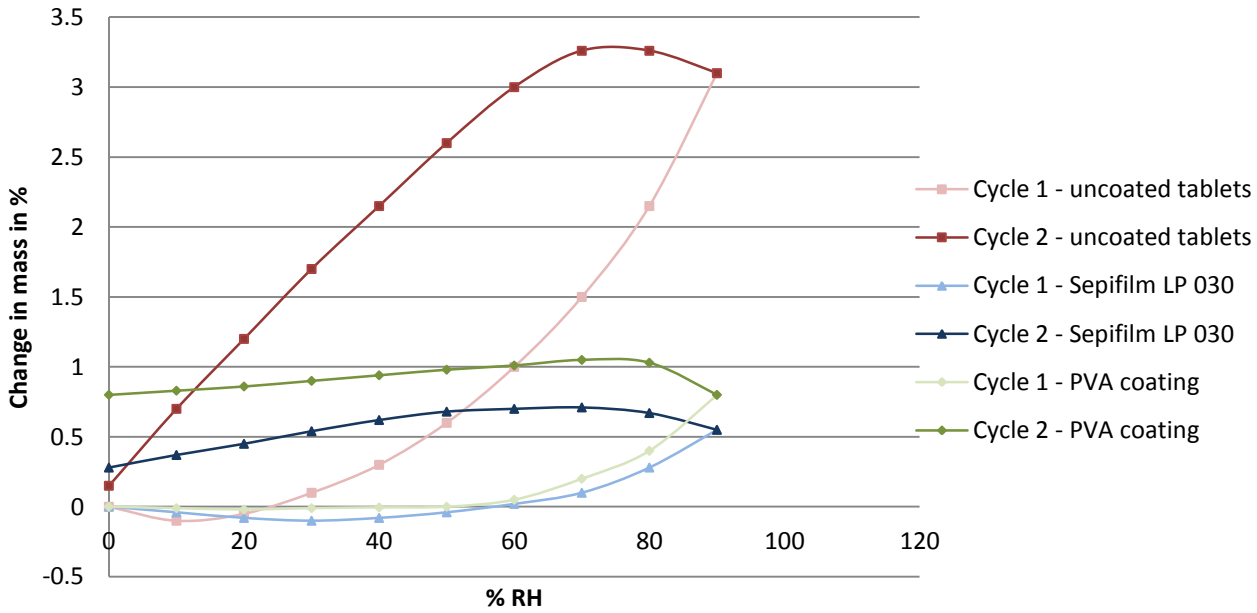
Dynamic Vapor Sorption (DVS) is a gravimetric technique that measures how quickly and how much of a solvent is absorbed by a sample such as dry powder absorbing water. It does this by varying the vapor concentration surrounding the sample and measuring the change in mass which this produces.

500 mg SEPIFIT™ Protect tablets, a hygroscopic nutraceutical active (*Table 2*) containing polyphenols were coated with various ready-to-use solutions in order to test the products performances regarding moisture protection.

Ingredient	% in the tablet
SEPIFIT™ Protect	33.4
Microcrystalline cellulose	35
Calcium diphosphate	34
Crospovidone	3
Magnesium stearate	1

Table 2: SEPIFIT™ Protect tablets composition

Tablets were placed in the DVS measuring device. The percentage of relative humidity was gradually increased from 0%RH up to 90%RH (sorption cycle) and then decreased (desorption cycle). The weight variation of the tablet was recorded continuously thanks to a microbalance.
The maximum weight variation is an important parameter because it reflects the water uptake of the tablet. The final weight variation is the second parameter we take into account since it represents the amount of water trapped inside the core and that can possibly hydrolyze the API.



Graph 3: DVS recording of tablets coated with different coatings

Uncoated tablets adsorb much more moisture than coated ones but they dry more as well. The maximum water uptake is 3.26% but the final moisture content is 0.15%. On the contrary coated tablets absorb less moisture but the moisture remains a more inside the core. It is due to the fact that the coating forms a barrier to prevent the water from entering the core. However, coating being a process where water is used, there is always some amount of water brought to the core. The aim of moisture protection film-coating is to include as less water as possible.

We can notice that tablets coated with Sepifilm LP 030 absorb less water than PVA-based coated tablets but moreover the remaining water content is lower, making Sepifilm LP 030 the best choice for moisture protection in that case.

It is possible to combine both anticaking agent and moisture protection coating to improve the formulation.

2.4 Solvent based coatings

If the tablets are too sensitive to be coated with a water based process there are solutions using solvents (ethanol most of the time). In that case SEPPIC's proposal would be to use Sepifilm™ LP 914 based on HPC or Sepifilm™ SN based on shellac gum. Both coatings can be used in 100% solvent and give excellent core sealing for extremely hygroscopic APIs.

3. Lipid-based solid oral formulations

3.1 A growing interest of lipid-based solid oral formulations

Pharmaceutical products can be administrated by different routes of administration. There are three main routes of administration: oral, topical and injectable. The oral route of administration represents the principle market share for the pharmaceutical drug products. Each route of administration has its benefits and drawbacks and has specific requirements. For the oral route, the main benefits are ease of use and cost efficiency.

However, oral administrations are limited by problems related to physic-chemical properties of the drug, including poor solubility, low permeability, instability and rapid metabolism. All of these parameters decrease oral bioavailability.

To overcome these problems lipid-based formulations have gained interest in pharmaceutical formulators in the recent years. These formulations improve the solubility and bioavailability of poorly water soluble drugs. Lipid-based excipients are formulated as carriers for delivery of drugs. Today, various lipid-based excipients are available with acceptable regulatory and safety profiles and allow improved solubility and enhanced oral bioavailability.

Substances containing a fatty acid in their chemical structure are referred to as lipid-based excipients. Waxes, vegetable oil and its derivatives, polyoxylglycerides, fatty acids, monoacylglycerides, diacylglycerides, triacylglycerides, animal fats, polyglycerides, PEG fatty acid esters, sucrose fatty acid esters. [9]

Lipid-based excipients are integrated in various types of formulations: solutions, SEDDS (Self Emulsifying Drug Delivery System) for example and can be used in various technologies such as melt granulation, extrusion and coating, spray congealing and drying, adsorption on solid carriers; processing solid liquid nanoparticles.[7]

Lipid formulations can be classified depending on their composition:

Type	Composition	Characteristics	Commercial example
I	Oil : 100%	No/limited dispersion Requires digestion	Dustasteride (Avodart®)
II	Oil : 40-80% Surfactant (low HLB) : 20-60%	SEDDS Emulsion Will be digested	Alfacalcidol (One-Alpha®)
III	Oil : <20-80% Surfactant (High HLB): 20-50% Cosolvents : 0-50%	SMEDDS/SNEDDS Fine emulsion Transparent dispersion Digestion may not be necessary	III A : Ritonavir (Norvir®) III B : Cyclosporin A (Neoral) ®
IV	Surfactant (Low HLB): 0-20% Surfactant (High HLB): 30-80% Cosolvents : 0-50%	Lipid-free Micellar solution Limited digestion	Amprenavir (Agenerase®)

Table 3: The Lipid Formulation Classification System [8]

The main factors that determine the choice of excipients for lipid-based formulations are miscibility, solvent capacity, self dispersibility, behavior in the digestive system, regulatory issues, toxicity, chemical stability, melting point… [7]

Lipid formulations can be also used for coating either to modify drug release characteristics or to protect against humidity for example.

Lipidic coating is an alternative to aqueous and solvent-based coating. Lipidic coating provides eco-friendly, cost-effective and time-saving processes.
Lipid coat increases the hydrophobicity of the final product, inhibiting the uptake of moisture from environment and improving stability of the product.
When lipid-based formulations are used, it is necessary to take into account some characteristics such as lipid crystallinity changes which can affect the product performance overtime. [9]

3.2 Hot Melt Coating

3.2.1 Description

Hot Melt Coating technique is the application of a fine layer of coating material over a substrate. The coating materials are in molten state when it is applied on the substrate, then solidified by cooling.

No solvent is used in hot melt coating process, therefore, solvent elimination, treatment is not required. HMC is cost effective, efficient, precise, simple and allow easy compliance with regulatory requirements.

Various substrates can be coated with Hot Melt Coating: powders, tablets, pellets, capsules, granules, etc. with different characteristics. The substrate can be lipophilic or hydrophilic in solid or liquid form. The mean particle size of capsule is included between 20 and 1500µm and a high loaded of API is possible (i.e up to 90%).

Regular forms (i.e tablets, capsules) as well as innovative forms like orodispersible granules (ODGs) in stick packs can be obtained with Hot Melt Coating.

3.2.2 Raw Materials

Different lipid-based excipients can be used in Hot Melt Coating like vegetable oils and its derivatives, waxes or surfactants. Excipients are carefully chosen depending on their melting point, their behavior in the digestive system or the functionality that they can offer (i.e controlled release, taste masking). Lipid-based excipients, thermostable with a relatively low melting point (< 80°C) are used in Hot Melt coating. These excipients are functional, safe and have a well-established history of use in oral dosage form.

3.2.3 Process

The Hot Melt Coating process is easy. It is composed of the following steps:

- Preparation of the equipment and materials (increase of temperature)
- Lipid excipient is heated to be melted (5-10°C above their melting points) and the substrate is heated
- Lipid excipient is sprayed onto the substrate which is suspended
- Cooling of the system to room temperature to congeal the lipid excipient on the substrate to obtain solid hard waxy shell

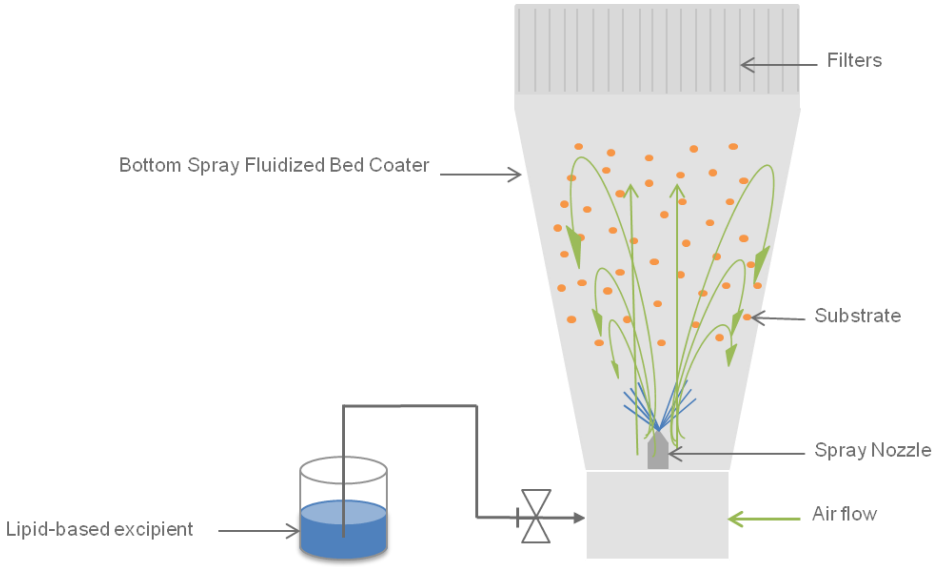


Diagram 1: Diagram for Hot Melt Coating Process in bottom spray fluidized bed coater

3.2.4 Equipment

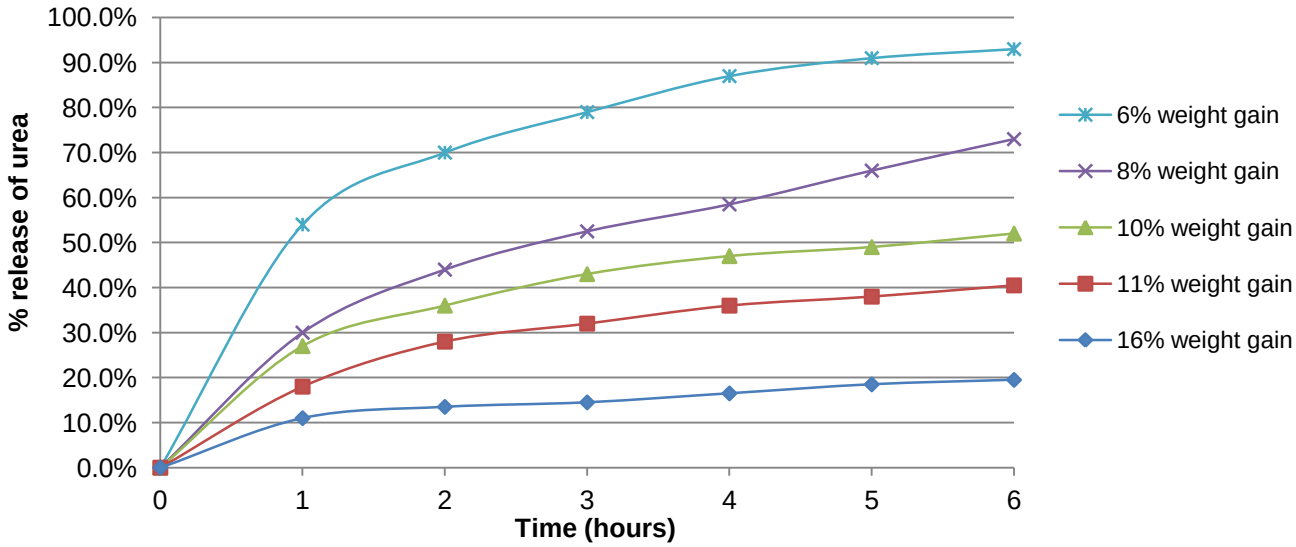
There are various Hot Melt Coating techniques but commonly used equipments are bottom spray fluidized bed coaters.
Alternative for bottom spray are top spray or tangential spray fluid bed coaters.
Pan coater can be also used for Hot Melt Coating as alternative equipment to fluidized bed coaters.

3.2.5 Some applications

Hot Melt Coating is a multi-purpose technology and can be used for various applications:

- To obtain desired modified release profiles: immediate; sustained; delayed releases
- To mask taste of API which have a bad or bitter taste
- To protect drug from environmental factors like humidity or light
- To combine several actives
- To improve bioavailability of poorly aqueous drugs or swallowability (for patient compliance)

SEPPIC developed solutions for Hot Melt Coating technology for taste masking and/or controlled release. These solutions are mixtures composed of waxes and surfactants. By modifying the coating thickness, the desired controlled release profile can be obtained.



Graph 4: Release of urea coated with wax/surfactants blend by HMC (37°C & pH 6)

Conclusion

While developing a formulation for a moisture sensitive drug, the following strategies need to be considered during the entire development process:

- Designing the dosage form with non-hygroscopic/low water-activity excipients
- Use anti-caking excipients
- Providing the dosage form with a moisture protective coating (either water-base solutions or lipid-based coatings)
- Packaging the dosage form with an appropriate moisture-resistant material.

SEPPIC is your partner of choice for the formulation of moisture sensitive APIs in Oral Solid Dosage Forms. Thanks to our many years of expertise we can provide data, trainings, technical visits as well as all documents required for the registration of you finished dosage form.

For contact or more information visit us on our website, www.seppic.com

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