Characterization Requirements for New Excipients

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Abstract Summary

Novel excipients can play a major role in innovation processes, but physicochemical properties, performance and safety must be adequately demonstrated. Characterization requirements for novel excipients are discussed and illustrated with two examples, polyethyleneglycol-polyvinyl caprolactam polyvinyl acetate grafted copolymer (Soluplus®) and methyl methacrylate and diethylaminoethyl methacrylate copolymer dispersion (Kollicoat® Smartseal 30 D).

Introduction

With the recent advancements in pharmaceutical technology, drug formulations have evolved from traditional medicinal products into drug delivery systems. This progress was brought forward with the use of new technologies in the pharmaceutical industry as well as by the introduction of new or novel excipients.

Table 1: Main categories of new excipients. Trademark rights are with the companies mentioned in the table.

Category	Examples (launched since 2006)
Modified excipients	Polyplasdone® Ultra (ISP) Lutrol® micro 68 & 127 (BASF) Swelstar™ Mx1 (Asahi Kasei) GalenIQ™ 721 (Palatinit)
Co-processed excipients	Specrablend™ HS (Sensient) Prosolv® ODT (JRS) Ludiflash® (BASF) Aquarius® (Ashland) Starcap 1500® (Colorcon)
Novel excipients	Soluplus® Kollicoat® Smartseal 30 D (both BASF)

ICH Guideline M4Q defines an excipient to be novel if it is used for the first time in a drug product or if it is used by a new route of administration.

Regulatory filings should include full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical and/or clinical) according to the drug substance format [1].

But excipients as such are not approved or rejected by health authorities. They are reviewed only in the context of a drug product application. This puts a significant regulatory burden on the excipient user, particularly in Europe, due to the lack of an excipient master file system.

Novel excipients require a thorough characterization with focus on three aspects:

- Functionality: Performance in the drug product e.g. drug delivery properties.
- Physicochemistry: Chemical assessment including physicochemical properties, impurities and stability.
- Safety: Toxicological assessment very similar to new active ingredients.

The development of a novel excipient requires a strong commitment of the manufacturer.

Case Studies

1. Kollicoat® Smartseal 30 D

Methyl methacrylate and diethylaminoethyl methacrylate copolymer dispersion for taste masking and moisture protection.

Functionality

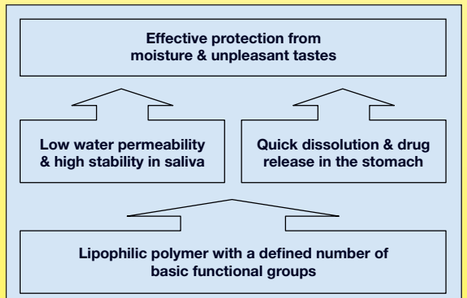

Figure 1: Development goal for a new protective coating agent

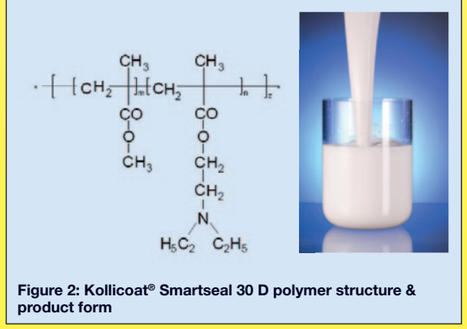

Figure 2: Kollicoat® Smartseal 30 D polymer structure & product form

The performance as taste masking agent was evaluated by a human taste panel. This assessment correlates very well with results from in vitro dissolution tests at pH 6.8, which proved to be a reasonable substitute [2]. The results demonstrate that coating levels of 4–5 mg/cm² of a Kollicoat® Smartseal 30 D based formulation can effectively mask the unpleasant taste of quinine hydrochloride tablets [3].

Physiochemistry

Table 2: Selected Physico-chemical characteristics of Kollicoat® Smartseal 30 D

Parameter	Kollicoat® Smartseal 30 D
Molecular weight (SEC light scattering)	~ 200 000 Da
Viscosity	2–50 mPas
Particle size (laser scattering)	~ 150 nm
pH value	7.5–10.0
Residual monomers	Max 100 ppm
Glass transition temperature (Tg)	~ 57 °C
Minimum film forming temperature (MFT)	~ 57 °C

A variety of different analytical techniques is necessary to describe structure, composition and impurity levels of a new polymer. Specific tests are selected for routine Quality Control and stability testing.

2. Soluplus®

Polyethyleneglycol- polyvinyl caprolactam- polyvinyl acetate grafted copolymer is a polymeric solubilizer with an amphiphilic structure. It has a capability to form solid solutions and is suitable for hot melt extrusion processes.

Functionality

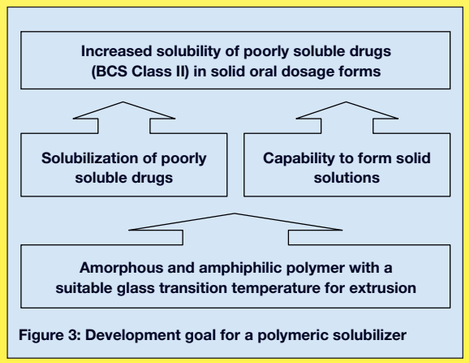

Figure 3: Development goal for a polymeric solubilizer

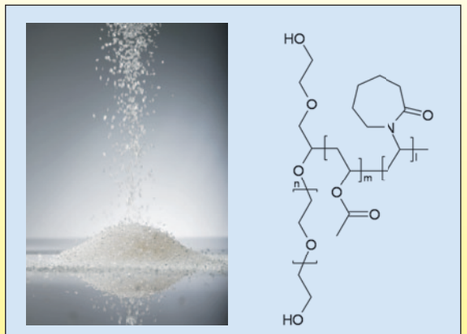

Figure 4: Soluplus®: Polymer structure & product form

Solid solutions of poorly soluble active ingredients can lead to a significant increase in bioavailability. Studies with itraconazole demonstrate a 20 to 30 fold increase in the area under the curve (AUC) compared to crystalline or physical mixture formulations [4].

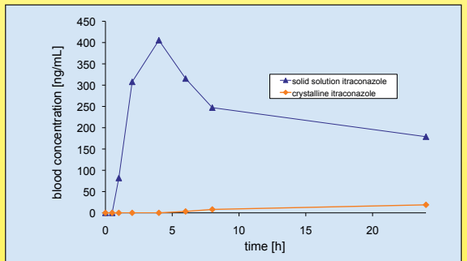

Figure 5: Bioavailability of itraconazol in beagle dogs

Physicochemistry

At extrusion temperatures of up to 160 °C, Soluplus® forms nearly colorless extrudates. The results shows that even after extrusion at a temperature of 180 °C Soluplus® is stable and the amount of impurities remains unchanged [Table 3].

Safety

The pharmacokinetics and the pre-clinical safety of both excipients, Kollicoat® Smartseal 30 D and Soluplus® is adequately documented by *in vitro* and *in vivo* studies. The program includes acute, subacute, subchronic and chronic, reproductive and developmental toxicitiy studies in rodents and/or dogs and *in vitro* and *in vivo* mutagenicity studies. The studies were in line with the current international guidelines, regulations and recommendations.

Table 3: Physicochemical properties of Soluplus® and after extrusion at 180 °C

Test Parameter	Powder	Extrudate at 180 °C
Identification	complies	complies
pH value	4.1	3.9
Ester value	197 mg KOH/g	196 mg KOH/g
Vinyl acetate	< 2 ppm	< 2 ppm
Vinyl caprolactam	< 10 ppm	< 10 ppm
Caprolactam	0.3%	0.3%
Ethylene glycol	< 100	63
Acetic acid/acetate	365 ppm	396 ppm
Peroxide	< 20 ppm	< 20 ppm
Molecular weight	118 000	116 000

Conclusion

- Novel excipients foster innovation in drug delivery and can play a major role in the development of better drugs.
- Novel excipients have to be characterized with regard to their functionality, physicochemistry and safety like active pharmaceutical ingredients.
- A registration process for novel excipients that is independent of a drug product registration would be desirable for the industry. It could mitigate the risk of a delayed drug product registration for first time users.

References

[1] ICH Guideline M4. The Common Technical Document.
[2] Krause, J.: Novel Paediatric Formulations for the Drug Sodium Benzoate. Thesis. Heinrich-Heine University, Düsseldorf 2008.
[3] Kolter, K. et al.: Physicochemical Characteristics of a New Aqueous Polymer Designed for Taste Masking & Moisture Protection. AAPS Annual Meeting and Exposition, November 2010, New Orleans, USA
[4] Hardung et al.: Combining HME & Solubilization. Soluplus® – The solid solution. Vol 10, 3 Drug Delivery Technology (10) 3, 2010

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