Pharma Solid Knowledge Report

Bioavailability of low soluble API – formulation solutions in capsules

One of the major challenges in pharmaceutical formulation development is the increasing number of active pharmaceutical ingredients which belong to the low solubility categories of the Biopharmaceutical Classification System (BCS). Therefore Active pharmaceutical ingredients (APIs) need support on their way through the human organism. So-called carriers or excipients transport the pharmaceuticals and make sure the body absorbs APIs more easily. Liquid carriers are particularly effective – and a specialty of the chemical company BASF, headquartered in Ludwigshafen, Germany. Together with Bosch Packaging Technology and using the GKF machine and dosing technology, BASF investigated how these excipients can be efficiently filled in hard gelatine capsules.
Beside the well-known powder, pellet, inhalation, tablet and special customized dosing technologies the different GKF platforms offer also a flexible and accurate liquid dosing technology. Based on a servo-controlled liquid pump, which provides stepless control of the fill volume for high-precision dosing and a constant temperature control via a fully automated product heating system a wide viscosity range (oil to paste) can be filled in the capsules. Special features do avoid product spillage during dosing and control the so called “last drop” safely.

New liquid formulation approach

▶ Investigation of different liquid matrices and formulations in lab scale for automatic hard gelatin capsule filling

▶ General Idea

Simplification

- Ideally, the API is suspended or dissolved in a matrix and filled into the hard-shell capsules

▶ Merely 3 components need to be declared: API, matrix, capsule (e.g. gelatin)

Product safety

- Dissolving the API in the liquid matrix leads to a homogeneous distribution

▶ An improved content uniformity for low dose drugs can be expected

Time to market

- Screening of the formulation components is rather simple and quickly done in lab scale

▶ Due to simplicity, potential interactions are limited and upscaling is easy

GKF LIQUID FILLING TECHNOLOGY

- Two integrated heating circuits for product hopper and pump block
- Setup control via servomotor
- Analog ultrasonic level sensor – product level displayed on screen
- Servo drive for pistons and nozzles
- Single pump for all bores
- Viscosity Range: 5 – 12,000 cps
- No spillage and full control of last drop

Pharma Solid Knowledge Report – Automated Process Development

FEASIBILTY STUDY WITH EXCIPIENTS AND LOPERAMIDE HYDROCHLORIDE

- 3 melted excipients (solidification in the capsule, no banding needed) and 1 liquid (sealing or banding needed) tested
- Study with low soluble Loperamide Hydrochlorid

UNIFORMITY OF DOSAGE UNITS (N = 60) WITH EXCIPIENTS

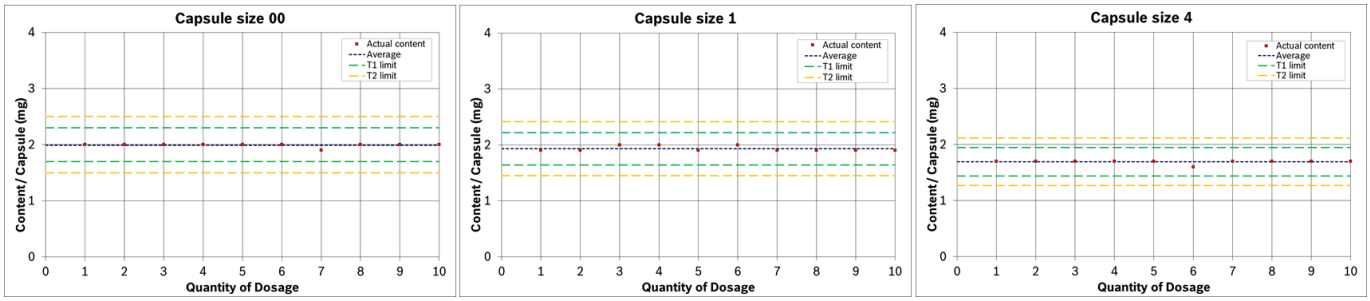
Product	Kolliwax® S			Kolliphor® P 188			Kolliphor® CS12			Kollicream® 3C	
Capsule size	00	1	4	00	1	4	00	1	4	00	1
Capsule type	ConiSnap®	ConiSnap®	ConiSnap®	ConiSnap®	ConiSnap®	ConiSnap®	ConiSnap®	ConiSnap®	ConiSnap®	LiCaps®	LiCaps®
GKF speed (cpm)	60	85	120	85	120	120	85	120	120	85	85
Mean weight (mg)	593.4	324.0	138.8	741.6	403.8	173.6	697.2	378.8	175.6	596.9	323.3
Standard deviation (mg)	0.6	0.7	0.3	0.5	0.3	0.3	0.4	0.3	0.3	1.1	0.6
Variation coefficient (%)	**0.1**	**0.2**	**0.2**	**0.1**	**0.1**	**0.2**	**0.1**	**0.1**	**0.2**	**0.2**	**0.2**
Minimum (mg)	592.6	322.7	137.8	740.6	403.0	173.0	696.3	378.0	174.9	595.2	321.8
Maximum (mg)	595.1	325.5	139.9	742.9	404.7	174.3	698.6	379.5	176.5	598.9	324.5
Weight range (mg)	2.5	2.8	2.1	2.3	1.7	1.3	2.3	1.5	1.6	3.7	2.7

UNIFORMITY FOR LOPERAMIDE

Capsule size	00	1	4
Capsule type	ConiSnap®	ConiSnap®	ConiSnap®
GKF speed (cpm)	85	120	120
Mean weight (mg)	699.6	380.0	172.5
Standard deviation (mg)	0.4	0.4	0.3
Variation coefficient (%)	**0.1**	**0.1**	**0.2**
Minimum (mg)	698.3	379.0	171.5
Maximum (mg)	700.5	380.7	173.2
Weight range (mg)	2.2	1.7	1.7

Bosch GKF liquid filling system is suited for various types of solid and liquid matrix excipients and expected high dosing accuracy

Content uniformity for Loperamide HCl and Kolliphor® CS12



- Active ingredient content for two component mixture is uniform

CONCLUSION

- **Liquid dosing into hard capsules allows for efficient formulation development, addressing various formulation challenges**
- **Scale-up from lab scale to automatic filling via the GKF liquid dosing technology is quick and easy**
- **Results of mass variation and content uniformity prove that this formulation approach works very well**
- **BASF pharma excipients offer a great ‚tool box' for efficient formulation of poorly soluble drugs, modified release products or low dose products (content uniformity)**
- **The Bosch GKF liquid station is well suited for filling various types of liquid formulations**
- **Cooperation of formulation and filling specialist helps in marketing new drugs**

PLEASE CONTACT US

Our team "Engineering Pharmaceutical Service" will be available with all our experience of over 50 years.

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