

ExAct

No. 9, October 2002

Excipients & Actives for Pharma

Calendar

8th to 14th November, 2002

AAPS (American Association of Pharmaceutical Scientists) Annual Meeting
Toronto*, Canada

16th to 18th April, 2003

CPhI Japan
Tokyo*, Japan

18th to 23rd July, 2003

30th International Symposium on Controlled Release of Bioactive Materials
Glasgow*, Scotland

27th to 29th October, 2003

CPhI Worldwide
Frankfurt*, Germany

23rd to 30th October, 2003

AAPS (American Association of Pharmaceutical Scientists) Annual Meeting
Salt Lake City*, USA

29th May to 3rd June, 2004

2nd Pharmaceutical Sciences World Conference
Kyoto, Japan

Summer, 2004

31st International Symposium on Controlled Release of Bioactive Materials
Orlando*, USA

*: BASF will be represented.

Dear reader,

The last issue of ExAct already focussed on Kollicoat® IR, an innovative instant release coating recently introduced by BASF. Several different BASF research departments collaborated to develop this product, a polyvinyl alcohol polyethylene glycol graft copolymer. Two articles in ExAct No. 8 featured the physicochemical characteristics and application properties of Kollicoat® IR.

Scaling up is one of the most challenging tasks in pharmaceutical production. Up to now, Kollicoat® IR has mainly been tested in small batch sizes. As a number of companies are currently testing the properties of the polymer, we are presenting detailed information in this ExAct issue on the quality of tablets after spraying in different coaters up to production scale size. We are confident that Kollicoat® IR will rapidly become a synonym for fast and economic instant release coating.

Our research on new pharmaceutical excipients is dedicated to discovering highly innovative, new products such as Kollicoat® IR.

Yours sincerely,

**BASF Aktiengesellschaft
Strategic Marketing
Pharma Solutions**



Charles Dods



➤ **Scale-up of an Instant Release Film Coating Process with Kollicoat® IR**
page 2-3

➤ **Suitability of additives to reduce the tack of Kollicoat® EMM 30 D coatings**
page 4-5

➤ **Applications of Solutol HS 15 – A Potent Solubilizer with a Low Toxicity**
page 6-8

➤ **Contract Manufacturing is getting bigger**
page 9

➤ **BASF sets up ExAct Pharma Solutions Technical Center for Asia Pacific**
page 10

➤ **New Pharma Solutions Website Launched**
page 11

➤ **New Media**
page 12

➤ **Preview**
page 12

➤ **Contact**
page 12

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BASF

Scale-up of an Instant-Release Film-Co

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Purpose

Kollicoat IR, a new polyvinyl alcohol – polyethylene glycol graft copolymer, offers the means to improve the coating of instant-release tablets [1]. To date, the polymer has only been tested in small batch sizes. In this study, the scale-up from lab to production scale was investigated with special emphasis on the process parameters and tablet properties.

Methods

A 40 mg propranolol HCl tablet made by direct compression (weight 250 mg, diameter: 9 mm, biconvex) was coated in batches of 5 kg and 15 kg using a 24" Accela Cota (Manesty) and in a batch of 250 kg using a Driacoater 900 (Driam). A standard coating formulation with Kollicoat IR as film forming polymer (Table 2) was applied in a coating weight of 4.8 mg/cm², or a weight gain of 3.8 %. Spraying rates, inlet air volumes and temperatures were varied. The dissolution rate, disintegration time, hardness and appearance of the coated tablets were determined.

Table 1: Tablet composition

		[mg]
Propranolol HCl	BASF	40.0
Ludipress	BASF	97.5
Avicel PH 102	FMC	97.5
Kollidon VA 64	BASF	12.5
Magnesium stearate	Bärlocher	2.5
Tablet weight		250.0

Table 2: Coating formulation

		[%]
Kollicoat IR	BASF	16.0
Talc	Riedel de Haen	4.5
Titanium dioxide	Kronos	3.0
Sicovit red 30	BASF	1.5
Water		75.0
Total solids		25.0

Table 3: Coating parameters

		Accela Cota 5 kg A	Accela Cota 5 kg B	Accela Cota 15 kg	Driacoater 250 kg
Batch size	[kg]	5	5	15	250
Spraying rate	[g/min]	14	30	42	700
Relative spraying rate	[g/min/kg cores]	2.8	6.0	2.8	2.8
Inlet air volume	[m ³ /h]	83	191	223	4400
Relative inlet air volume	[m ³ /h/kg cores]	16.6	38.2	14.9	17.6
Inlet air humidity	[%]	5	4	5	–
Outlet air humidity	[%]	15	13	14	–
Inlet air temperature	[° C]	71	69	73	70
Outlet air temperature	[° C]	47	48	50	47
Product temperature	[° C]	45	44	45	–

Results

The coating experiments were started with the smallest batch size and a moderate absolute spraying rate of 14 g/min corresponding to a relative spraying rate of 2.8 g/min/kg cores. The scale-up of tablet coating with Kollicoat IR proved to be easy without any need for adjustment of the inlet air temperature, relative spraying rate (g/min/kg cores) or relative inlet air volume (m³/h/kg cores). The experiments show that if these parameters are maintained, the outlet air temperature, product temperature and outlet air humidity do not change. A 50-fold increase in batch size with the use of a larger coating machine was possible without any problem.

In the Accela Cota 5 kg-batch, the spraying rate could be increased to 6 g/min/kg cores by increasing the inlet air volume proportionately. As the inlet air volume in the Driacoater was at its maximum and could not be further increased, it was not possible to increase the spraying rate without overwetting the cores. However, compared with common instant-release coatings like HPMC, the coating process with Kollicoat IR was extremely fast: 24 min in the Accela Cota at 6 g/min/kg cores and 55 min in the production scale Driacoater at 2.8 g/min/kg cores. While the tablets from the production scale trial had a slightly better

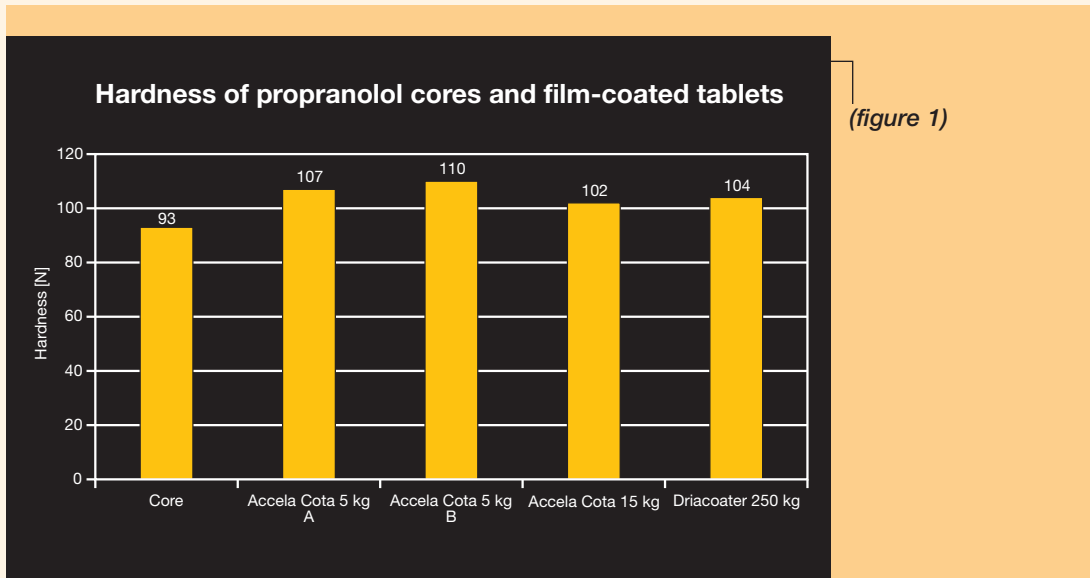
appearance, there was no difference in the properties such as hardness, friability, disintegration or dissolution.

The coating process slightly increased the hardness of the cores as expected, but the disintegration and dissolution remained unchanged showing that the dissolution rate of the coating is extremely fast.

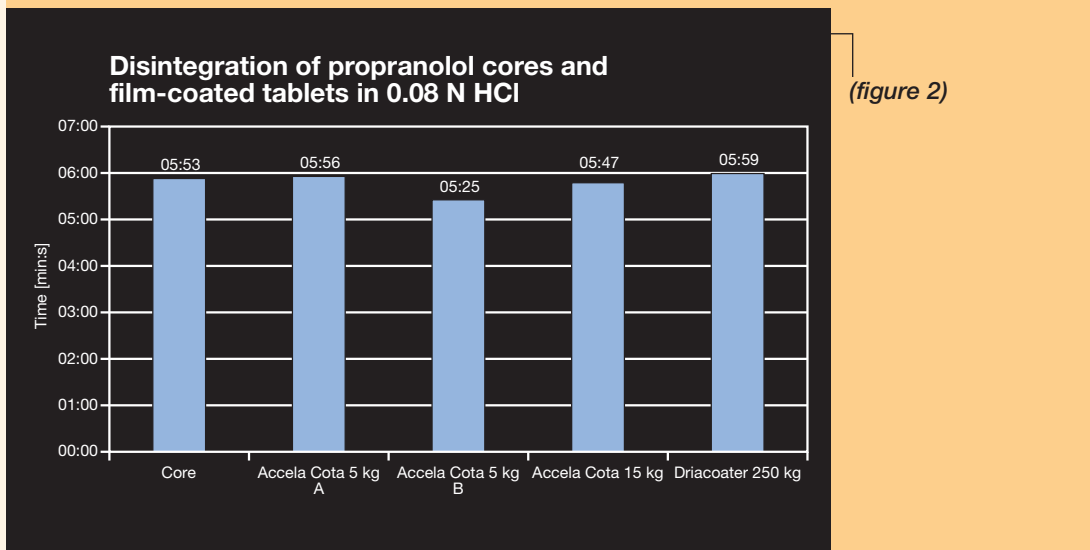
General rule

If a coating process is to be scaled up, one has to know the maximum inlet air volume of the coating machine and the usual batch size. The same relative inlet air volume (m³/h/kg cores) should be set in the small coater and increasing spraying rates should be tested until overwetting effects are observed. A moderate relative spraying rate should be used for the scale-up trials.

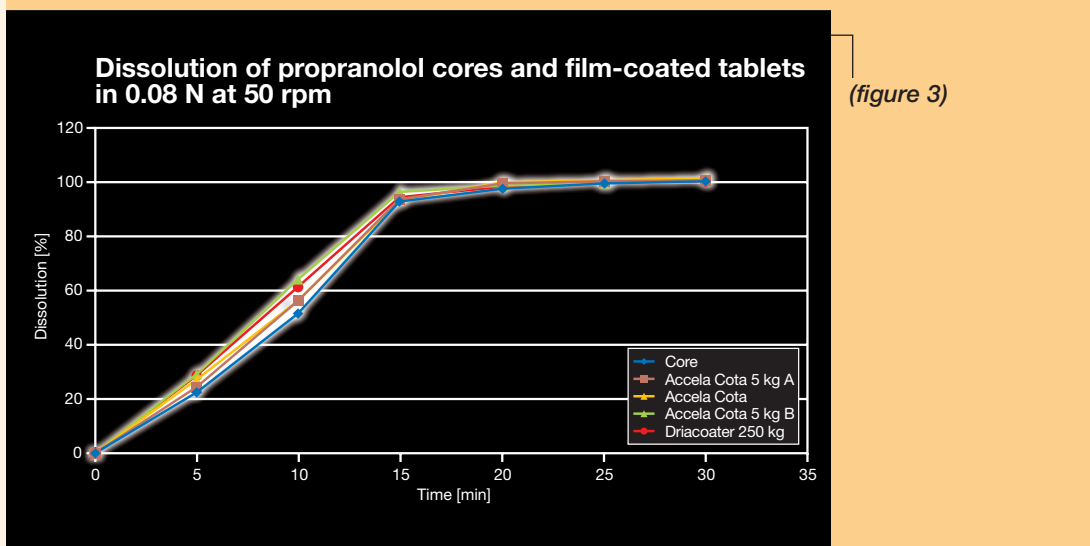
Coating Process with Kollicoat® IR



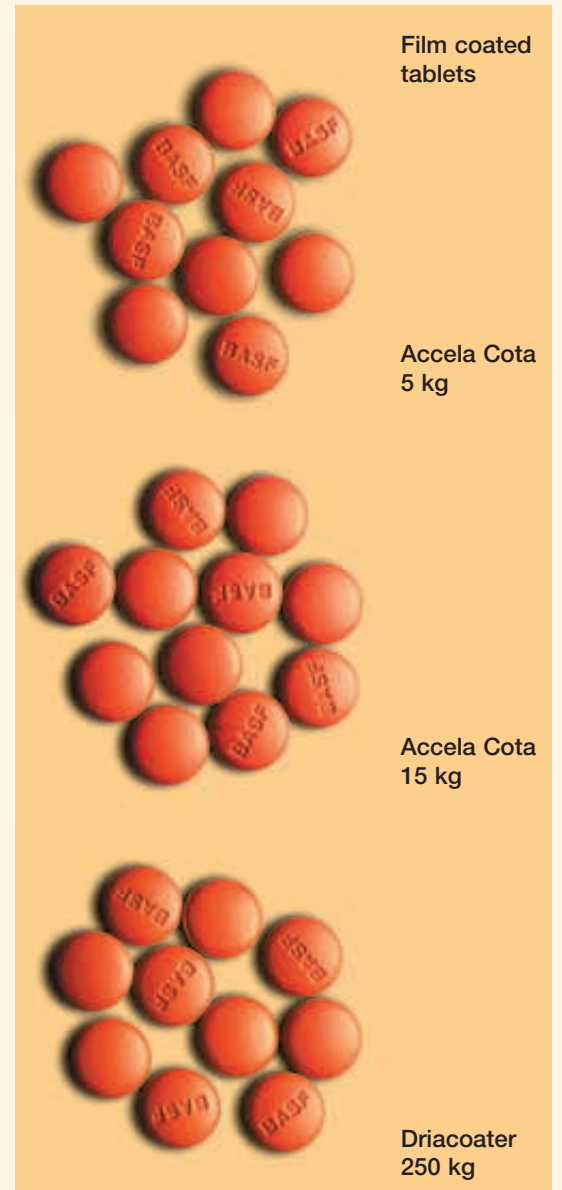
(figure 1)



(figure 2)



(figure 3)



Conclusions

- The coating process with Kollicoat IR can easily be scaled up from lab to production scale.
- The tablet properties remain unchanged.
- The coating process was extremely fast, even with a 250 kg batch.
- In scaling up, the inlet air temperature, relative spraying rate and relative inlet air volume should be kept constant.
- The newly developed method for determining the film dissolution time gives reliable and reproducible results.

References

- [1] Technical Information Kollicoat IR, BASF Aktiengesellschaft, October 2001.

Suitability of Additives to Reduce the Tackiness of Pellets

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Introduction

Kollicoat® EMM 30 D is a copolymerisate based on ethyl acrylate and methyl methacrylate in a 2:1 ratio and is increasingly used in the manufacture of coated oral sustained-release formulations. Because of its very low minimum film-forming and glass transition temperature, this product has a tendency to tackiness necessitating the addition of antitack agents.

The tack effects have an adverse effect on product processibility both during the spraying process and subsequent pellet storage.

Additives such as talc, magnesium stearate, kaolin, Aerosil 200 or glycerol monostearate are widely used in practice to minimize tack effects, talc being the most popular agent.

The purpose of this study was to

- reduce the tendency of Kollicoat® EMM 30 D to tackiness by adding suitable excipients and thereby optimize processibility,
- ensure flowability of the coated pellets also after storage,
- avoid significantly influencing dissolution on addition of antitack agents.

Experimental Methods

• Materials:

Kollicoat® EMM 30 D (BASF AG, Ludwigshafen), propranolol HCl (Knoll AG, Ludwigshafen), antitack additives see Figure 1.

• Apparatus:

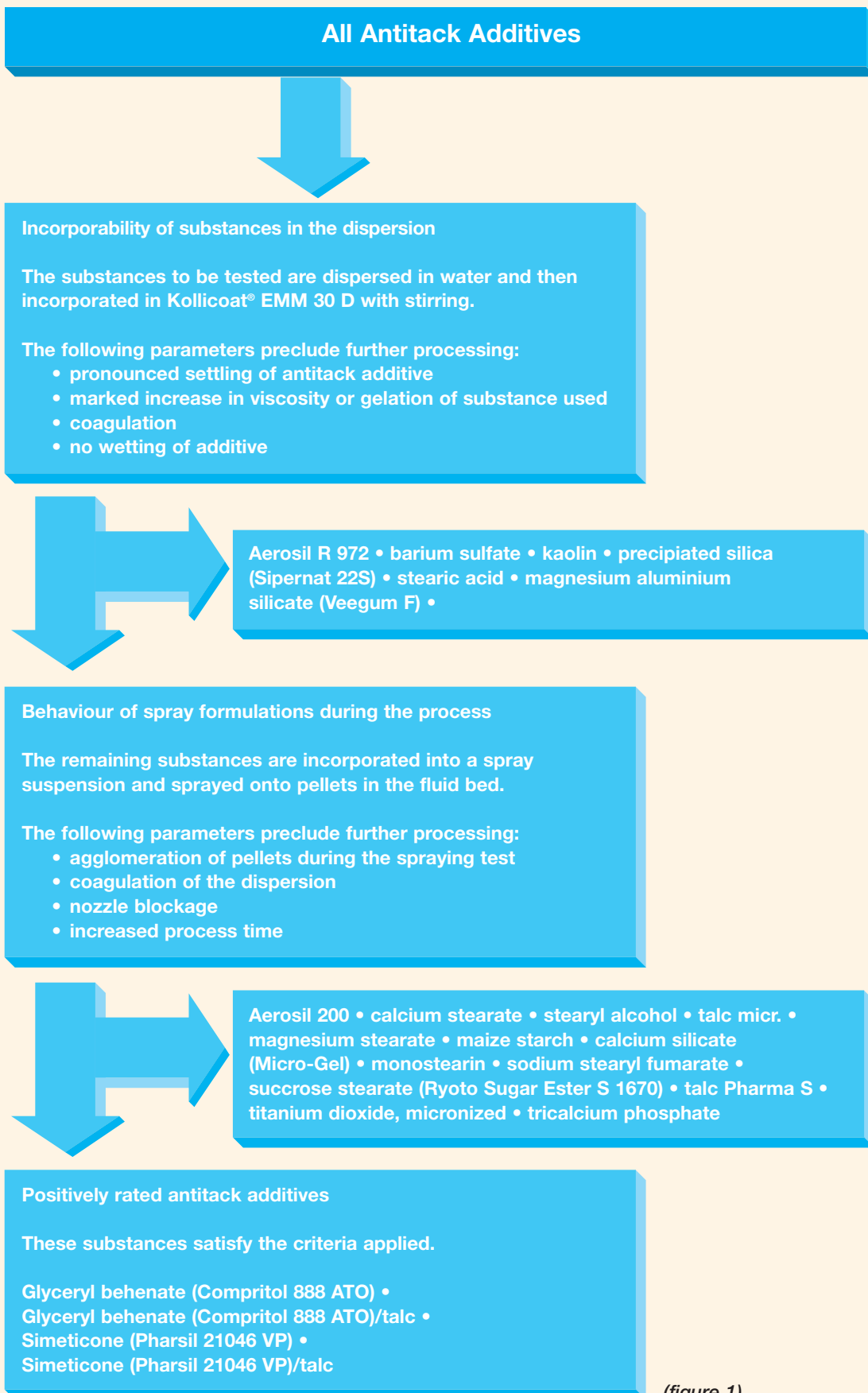
Ultra Turrax (IKA Labortechnik), corundum disc mill (Fryma Maschinenbau GmbH), fluid bed coater (Aeromatic-Fielder), dissolution tester (Pharmatest Apparatebau)

• Preparation of isolated films:

The spray suspension is sprayed onto a preheated rotating teflon roller and dried with a blower.

• Determination of tackiness:

The isolated films are fixed on a glass plate and stored for 12 h at the condition of interest. Testing is then performed by the Hössel method [1].



(figure 1)

ck of Kollicoat® EMM 30 D Coatings

• Coating formulation:

Propranolol-HCl-pellets:

propranolol-HCl	30.00 %
Avicel PH 101	46.66 %
Granulac	20.84 %
Kollidon VA 64	2.50 %

Spray suspension:

Kollicoat®	
EMM 30 D	39.30 %
Pharmacoat 603	1.40 %
Kollidon 30	0.50 %
Sicovit Rot 30	0.50 %
talc	4.72 %
water	53.58 %

Results and Discussion

In this study the substances listed in Figure 1 were tested for suitability as antitack additives, using concentrations between 2.5 and 12.5 % with reference to polymer solids.

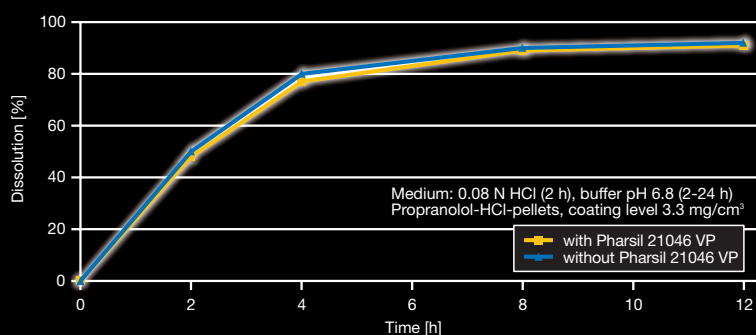
Figure 1 shows all the materials ruled out on the basis of incorporability into the dispersion and those with which a spraying test was performed.

The antitack additives listed in the lowest box and their combinations proved suitable. Storage trials with the coated pellets show that pellet flowability also does not decrease after storage. The Pharsil/talc combination was found to be optimal. Figure 2 demonstrates that the addition of Pharsil has no impact on dissolution.



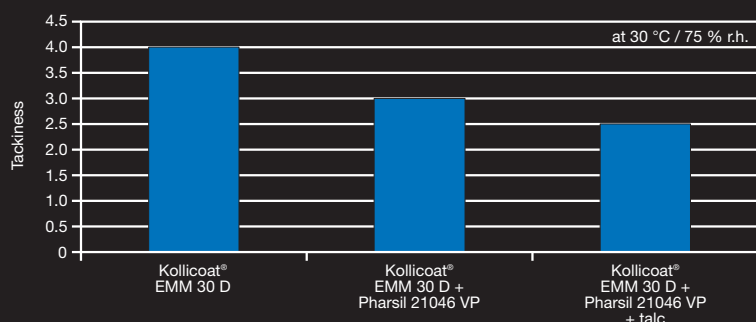
Dependence of dissolution on antitack additive

(figure 2)



Tackiness of Kollicoat® EMM-films with different additives (0: not tacky, 5: tacky)

(figure 3)



Conclusions

- Some of the substances studied are unsuitable due to unsatisfactory incorporability or stability of the dispersion, as well as processing problems during the spraying test.
- Compritol 888 ATO and Pharsil 21046 VP as well as their combinations with talc were found to be suitable, with Pharsil/talc being the preferable option.
- The Pharsil/talc combination effective as antitack agent has no impact on dissolution and thus allows optimization of formulations practically without problems.

References

- [1] P. Hössel, Cosmetics and Toiletries 111 (8), 73ff (1996)

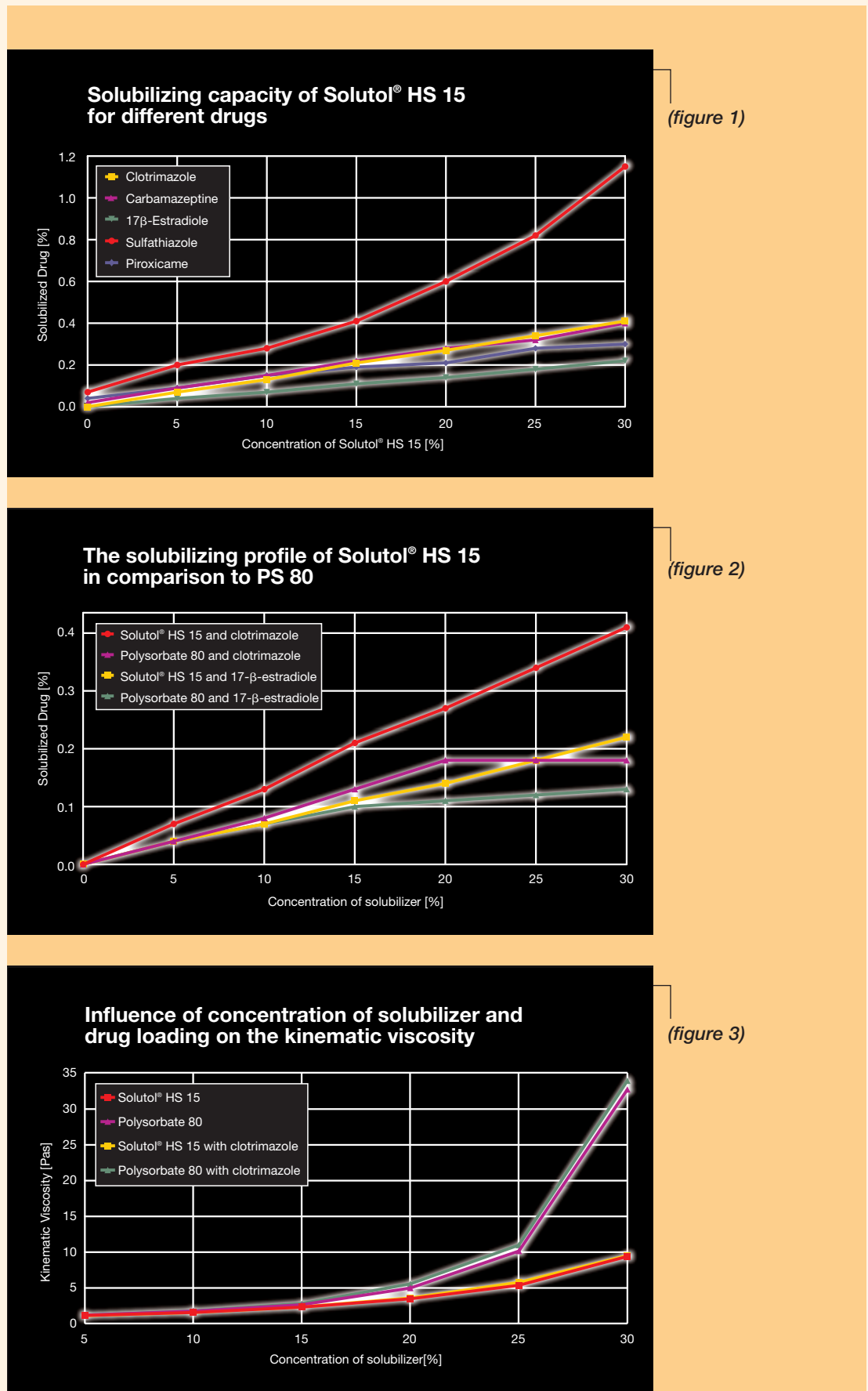
Applications of Solutol® HS 15 - A Pote

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Introduction

An increasing number of potent drugs is poorly water-soluble and the trend of developing new drugs with lipophilic character is still continuing. To dissolve these drugs for parenteral administration is a common problem [1]. Thus, the incorporation of drugs into micelles using solubilizing agents is often a favourable method to yield a sufficient and suitable drug solution [2]. However, when using amphiphilic non-ionic surfactants for solubilizing purposes the physiological tolerability and compatibility as well as the physicochemical properties of the solubilizers have to be taken into account. The relatively new solubilizer Polyethylene glycol-660-hydroxystearate, Solutol® HS 15, meets the requirements of an effective modern solubilizer and was recently approved for human injectables in Canada. There is a formulation with Phytonadione on the market. When using Solutol® HS 15 as solubilizer the reversal of the multi drug resistance of tumor cells to anticancer drugs could be realized as a positive side effect of the substance [3,4]. The objective of the present study was the detailed determination of the formulation properties of Solutol® HS 15 and its physiological tolerance in comparison to polysorbate 80 (PS 80).



nt Solubilizer with a Low Toxicity

Materials and Methods

With Solutol® HS 15 (Batch No. 51-1772, BASF) and Polysorbate 80 (Batch No. 516851, ICI) solubilizes were prepared by using carbamazepine, clotrimazole, 17- β -estradiole, piroxicam, sulfathiazole (ST) and tocopherolacetate as model drugs.

Preparation method: The drug was suspended in the molten solubilizer under stirring at 65 °C. Phosphate buffer (PB) pH 7.0 (USP XXIII) was added dropwise at the same temperature. The mixtures were cooled to room temperature under stirring. The dispersions were filtered through a 0.22 μ m membrane resulting in clear / opalescent solutions.

Drug content: The amount of solubilized drug was measured using a photometer after diluting the solubilizes with a 1:1 mixture of methanol / PB. The tocopherol-acetate was analyzed by means of a HPLC-method.

Kinematic viscosity: Equilibrating the solutions for at least 30 min. at 25 °C a capillary viscosimeter (Ubbelohde, Germany), capillary No.1 was used.

Sterilization process: The solubilizes were sterilized by steam sterilization for 20 min at 121 °C and afterwards analyzed with regard to fat values with commonly used methods (Ph. Eur. 1997).

Haemolytic activity: The solubilizers were incubated over a wide concentration range with isolated erythrocytes of rabbits for 60 min. The degree of damage of the red blood cell membranes was quantified by spectrophotometry of released haemoglobin [5].

Blood histamine level in dogs: The manufactured solubilizers of Solutol® HS 15 and PS 80 in concentration of 5 % in an aqueous solution of 10 % sorbitol were administered intravenously to beagle dogs in a concentration of 100 mg / kg. The blood histamine level was monitored by sampling the blood in intervals over a period of 60 min. The amount of released histamine was analyzed using an ELISA test.

Table 1: Influence of a sterilization process on analytical parameters of Solutol® HS 15

[mg/g KOH]	untreated	20 min/121 °C
Acid value	0.2	0.2
Saponif. value	60	60
Hydroxyl value	99	99



Table 2: Influence of a sterilization process on solubilizes of Solutol® HS 15

	20 % HS 15		20 % HS 15 + 7.5 % Tocoph.-acetate	
	untreated	20 min/121 °C	untreated	20 min/121 °C
Acid v. [mg/g KOH]	0.1	0.1	0.1	0.1
Saponif. v. [mg/g KOH]	13.0	13.2	21.0	21.0
pH-value	6.0	5.5	5.75	5.63
Micelle dm [nm]	13.0	13.0	24.6	24.1
Turbidity [FTU]	5.1	5.0	26.0	26.0

	20 % HS 15 + 0.6 % ST in H ₂ O		20 % HS 15 + 0.6 % ST, PB pH 7	
	untreated	20 min/121 °C	untreated	20 min/121 °C
Acid v. [mg/g KOH]	1.4	1.4	1.5	1.3
Saponif. v. [mg/g KOH]	13.0	14.0	14.0	14.0
pH-value	5.9	5.6	7.0	7.0
Micelle dm [nm]	12.9	12.8	12.4	12.5
Turbidity [FTU]	4.7	4.7	5.0	5.0

Table 3: Haemolytic activity of rabbit erythrocytes and serum histamine level in dogs after i.v. application

	Haemolytic activity [% Haemolysis]			Serum histamine level [nM]		
	0.1 %	1 %	10 %	0 min	15 min	60 min
HS 15	0	0	8.7	5	220	8
PS 80	0	0	11.1	3	>50000	247

Results and Discussion

The solubilizing capacity for the tested drugs increased almost linearly with enlarging concentration of solubilizing agent (Fig.1) due to the formation of spherical micelles even at high concentrations of Solutol® HS 15. It seemed that the formation of mesomeric phases did not take place at concentrations up to 30 %. As shown in Fig. 2 the slope of solubilizing capacity of PS 80 declined at higher concentrations in contrast to the constant slope of Solutol® HS 15. Additionally a higher amount of drug - in this case clotrimazole and estradiol - could be dissolved when using Solutol® HS 15. Evaluating the viscosity data it can be shown (Fig.3) that solubilized drugs did not have any influence on the kinematic viscosity. The viscosity increased with increasing amount of solubilizer. However, in contrast to Solutol® HS 15 the viscosity of PS 80 strongly increased at higher concentrations, whereas the viscosity of Solutol® HS 15 remained fairly low. Therefore a painless administration of a 30 % solution of Solutol® HS 15 is possible. The steam sterilization process (121 °C / 20 min) of pure Solutol HS 15 revealed

no changes of different fat values or other properties indicating that no considerable hydrolyzation processes took place (Table 1). The sterilization process performed with solubilizates of 20 % Solutol® HS 15 in demineralized water and a drug loading of 7.5 % tocopherolacetate respectively 0.6 % sulphathiazole did not influence the properties of the solubilizates except a minor change of pH-value. After the sterilization process a phase separation occurred which can be overcome by shaking the solutions moderately. Even the micelle diameter remained unchanged. Steam sterilization of Solutol® HS 15 solubilizates is possible. Therefore expensive aseptic manufacturing could be avoided (Table 2). As can be seen in Table 3 the haemolytical activity of both solubilizers is moderately low, but the increase of the blood histamine level of PS 80 after i.v. application is dramatically high. In contrast to PS 80 the histamine release after administration of Solutol® HS 15 was only slightly increased indicating the better physiological tolerability of Solutol® HS 15.

Conclusions

- Solutol® HS 15 meets the requirements of a potent modern low toxicity solubilizer. The solubilization capacities enclose a wide range of drugs. The formulations can be sterilized with a steam sterilization process. There are great advantages of Solutol® HS 15 in comparison to PS 80.

References

- [1] Sweetana, S., Akers, M.J. Pharm. Sci. & Technol. 5, (1996), 330-342.
- [2] K.H. Frömming et al., Acta Pharm. technol. 36 (4), 1990, 214-220.
- [3] J.S. Coon et al., Cancer Res. 51 (3), 1991, 897-902.
- [4] J.S. Coon, Proc. Am.Assoc. Cancer Res. 33, 1992, 484.
- [5] D. Hoover et al., Fundam. Appl. Toxicol. 14 (1990), 589 pp.



Contract Manufacturing is getting bigger

A. Germani

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Our group has changed, but not our commitment to our customers.

Since April Mr. Ing. Daniele Piergentili has joined the group as account manager for the west coast of the US, UK and Italy. The other account managers are: Dr. Martin-Jochen Klatt, who is responsible for USA (East Coast), Canada and Japan and Wolfgang Falkenberg, who takes care of Europe (except Italy and UK).

The group is getting bigger in order to offer more expertise and experience in contract development and manufacturing services.

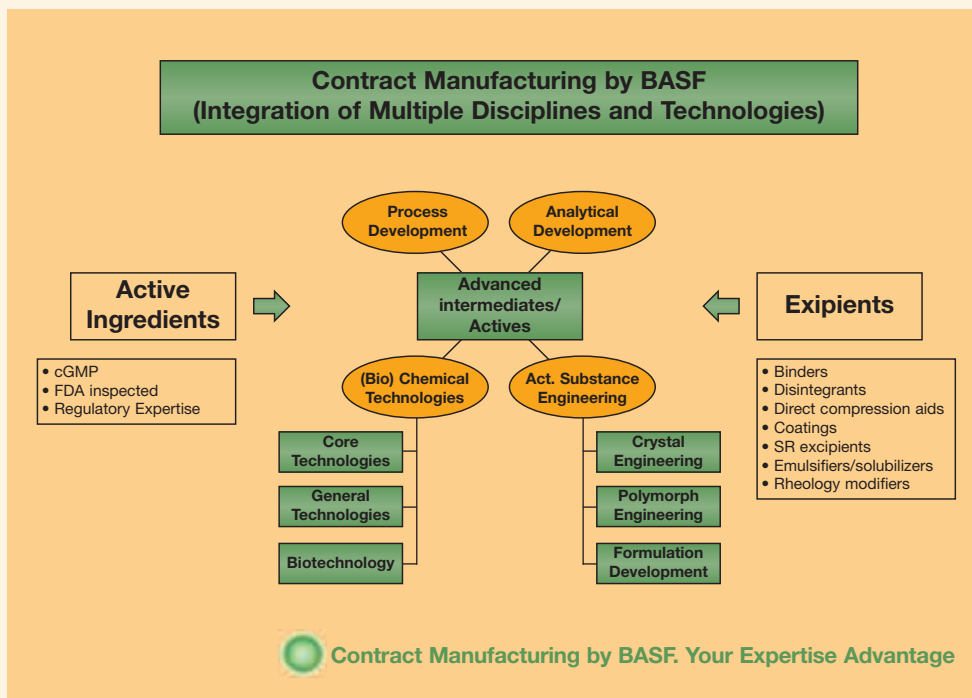
Contract Manufacturing is exclusively dedicated to providing world-class pharma solution and contract development services to the pharmaceutical world.

Further as part of BASF Fine Chemical global division we have access to the broadest and special list of technologies, capabilities and resources of the group (see right).

Of course it is our dedicated people who really make us special.

Our motto is: Try to do something new more than something better that others already do.

Let's process your ideas together



Our Team



BASF sets up ExAct Pharma Solutions Technical Center for Asia Pacific



BASF's newly established Pharma Technical Center is aptly called "ExAct", an integration of the special range of Excipients and Actives which BASF manufactures for the pharmaceutical and human nutrition industry. The center is strategically located in Yokkaichi, Japan and is housed with the other BASF technical centers for competence in chemicals. The pharma center joins the food and the cosmetic technical centers, which are also part of the BASF network.

The thrust of the center is to offer innovative pharma solutions to customers in the Asia Pacific region. It aims to match research-based solutions to current customer needs. It also augments the technical platform of the recently formed Asia Pacific Regional Business Management for Pharma Solutions based in Singapore. Core to the center's services is an application laboratory, which offers practical solutions for development and manufacture of pharmaceutical dosage forms. Among others, it has facilities for analysis and testing formulations including prototype manufacturing. The center is run by qualified chemists, pharmacists and specialists, who provide the necessary expertise in pharmaceutical formulation and drug manufacturing technology. The technical team is coordinated by the regional management in Singapore through its Technical Manager, Mr. Sang Jun Lee.

Picture from left to right:

Mr. Hiroshi Sumitani, Mr. Hiroshi Kasai, Mr. Yoshitomi Kakiguchi, Mr. Mitsunori Tanabe, Mr. Sang Jun Lee, Mr. Kunihiko Yokota, Dr. Danilo Mercado

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New Pharma Solutions Website Launched

At the beginning of August the new website for the Pharma Solutions Division of BASF was launched. The contents have been completely revised and tailored to meet our customer needs. We are now offering downloads for Technical Information Sheets of our active ingredients and excipients.



In addition to that we are presenting our contract manufacturing group and their services in detail.



Please visit us at <http://www.pharma-solutions.basf.com>

Preview

Innovative Single-Unit Drug Delivery Systems Using Kollicoat® SR 30 D-Coatings

In general sustained release coatings are applied on multiparticulate formulations and seldom on single-unit dosage forms in order to avoid the risk of dose dumping. OROS-systems represent a special type of coated sustained release single-unit dosage form that is very costly to produce.

Besides other topics ExAct No. 10 will inform about the development of a coated single-unit delivery system exhibiting a strong release effect following zero order kinetics, which can be manufactured more easily than an OROS-system.

Should you require information in advance, please contact your local BASF company or one of our regional marketing offices.

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New Media

New booklet on BASF excipients published

In this first edition of the booklet an overview is given on the functions of our excipients in the pharmaceutical technology. On 101 pages it deals with the different dosage forms (tablets, capsules, solutions, suspensions, semisolid forms, diagnostics etc.) and describes a multitude of applications of our Kollidon®, Kollicoat®, Ludipress®, Lutrol®, Solutol® and Cremophor® grades using typical formulations as examples for the demonstration of their function in the different fields. It starts with binders in tablets and finally ends with stabilizers in diagnostics. An excellent impression of the technical advantages of our pharmaceutical excipient range can be obtained.

Three books on one CD-ROM

The 4th edition of this CD-ROM now combines three new or revised books:

- „Functions and Applications of BASF Pharmaceutical Excipients“ (1st edition 2001, presentation see left)
- „Kollidon® - Polyvinylpyrrolidone for the pharmaceutical industry“ (6th edition 2002, including Kollidon® SR as chapter 5)
- „Generic Drug Formulations“ (4th edition 2001)

These books give an excellent overview on the technical possibilities offered by our excipients, active ingredients and vitamins for the development of drugs and vitamin preparations.

