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Dear Reader: Excipient Innovation - What Else?



Each year, numerous new drugs come onto the market to improve drug therapy; but where are the novel excipients which make for better drug delivery systems? Only a few per decade have been developed and successfully launched in the past. This is because of the long development and launch periods required as well as the high costs and considerable risk of failure.

For several years now, BASF has been pursuing a long-term excipient innovation strategy, a policy that differentiates it from many other suppliers. Our intent is to come up with new excipients, thus creating new opportunities for drug delivery systems and making treatments safer and more reliable.

Excellent examples of this strategy are the novel excipients Soluplus® and Kollicoat® Smartseal 30D. Soluplus, – decorated last year with CPhI's Silver Innovation Award – enables highly bioavailable drug formulations to be produced with poorly soluble actives. Soluplus is indeed the first polymeric solubilizer designed for solid solutions. At the AAPS in November 2010, Kollicoat Smartseal 30D, a 30% aqueous dispersion, was introduced as a new polymer for taste-masking and moisture protection. It can

be considered a new milestone in this area since it is easy to apply, allows effective taste-masking and has the lowest vapor permeation rate of all pharma polymers.

With Kollicoat Smartseal 30D, BASF has now completed its range of coating polymers now offering state-of-the-art, instant release, enteric, sustained release and protective coatings.

In addition to an article on Kollicoat Smartseal 30 D, this issue of ExAct also provides valuable information on established products such as Kollicoat MAE 100P, Kollidon® CL grades and poloxamers.

We trust these products will help you to develop even better drug formulations.

Yours sincerely,



Karl Kolter
Head of R&D Pharma Ingredients

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IN FOCUS: COATINGS

Kollocoat® Smartseal 30 D – For active protection

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➤ Providing protection from unpleasant tastes has gained in importance with the increasing popularity of orally dispersible tablets. The taste masking of granules or smaller particles is particularly important and challenging in the development of such dosage forms.

Some active ingredients and certain types of dosage forms (e.g. matrix tablets or formulations with a disintegrant) are moisture-sensitive and must be protected from humidity.

Kollocoat Smartseal 30D is the first film coating agent for taste masking and moisture barrier applications that combines a strong protective effect with simple and economic processing.

Kollocoat Smartseal 30D is an aqueous polymer dispersion containing methyl methacrylate and diethylaminoethyl methacrylate co-polymer stabilized with ~ 0.6% macrogol cetostearyl ether and ~ 0.8% sodium lauryl sulfate. The solids concentration is approximately 30%.

It comes as a milky white liquid with a faint characteristic odor.

The lipophilic polymer is highly impermeable to moisture. It is insoluble at neutral pH (e.g. saliva), but dissolves quickly under protonation in acidic media at pH values of 5.5 and below (e.g. the stomach). Kollocoat Smartseal 30D helps to achieve a strong protective effect, quick release and onset of action of the active ingredients.

An aqueous polymer dispersion, Kollocoat Smartseal 30D is easy to dose and convenient to apply. Table 1 provides an overview of its important physico-chemical characteristics [2].

Due to the minimum film forming temperature of 57°C, a plasticizer must be added to the formulation. Suitable plasticizers, the preparation of the coating suspensions and other handling recommendations are described in the technical information [3].

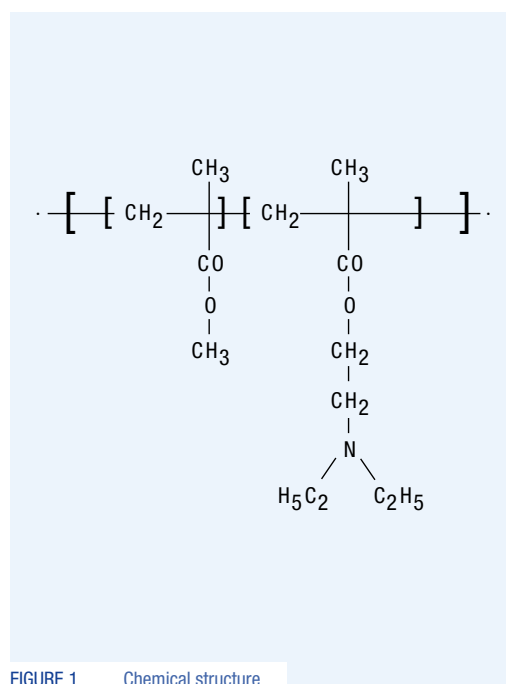


FIGURE 1 Chemical structure



FIGURE 2 The first aqueous dispersion of a protective polymer

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

TABLE 1 Selected physico-chemical characteristics of Kollocoat

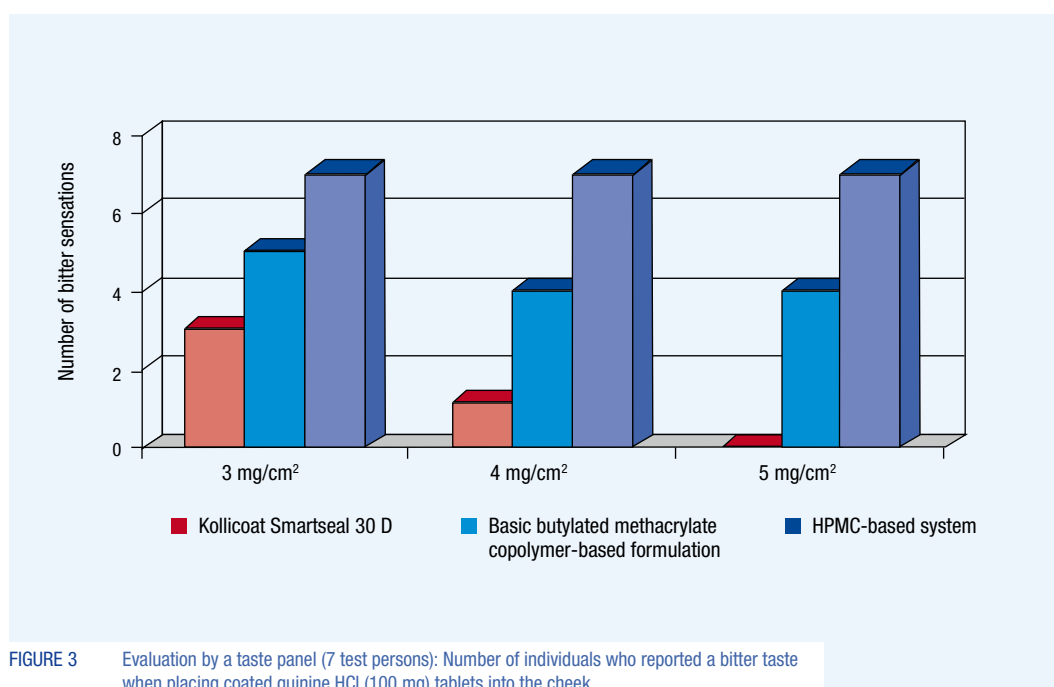


FIGURE 3 Evaluation by a taste panel (7 test persons): Number of individuals who reported a bitter taste when placing coated quinine HCl (100 mg) tablets into the cheek

Smart protection from unpleasant tastes Coating levels of 4-5mg/cm² on tablets can effectively mask the taste of bitter active ingredients such as quinine hydrochloride or caffeine. Results from a human taste panel demonstrate that Kollocoat Smartseal 30D can hide the bitter taste more effectively than other well-known protective coatings.

Kollocoat Smartseal 30D is suitable for tablet, pellet and particle coatings. It can be used at high solid concentrations and high spray rates and therefore contributes to a cost-efficient manufacturing process. The following formulation example was performed with extruded caffeine pellets with a particle size of 0.7-1.4mm. Tables 2 and 3 summarize the composition of the coating suspension and the settings of the coating process.

Ingredient	Content [%]
Kollocoat Smartseal 30 D	33.33
Tributyl citrate	1.50 (15% rel. to polymer)
Butylated hydroxytoluene*	0.10 (1% rel. to polymer)
Talc	8.00
Colorant	0.40
Water	56.67
Total	100.0

Solids content of the spray suspension: 20%

Polymer content in the dried film: 50%

*Antioxidants stabilize the aminoester moiety of the polymer. They help to stabilize dissolution behavior and reduce yellowing under stress conditions.

TABLE 2 Formulation example: Kollocoat Smartseal 30 D-based coating suspension

Machine	Aeromatic Strea 1, Wurster insert
Inlet air temperature	55°C
Batch size	0.5 kg
Product temperature	30 – 34°C
Spraying rate	9 g/min
Nozzle diameter	0.8 mm
Spray pressure	1.5 bar
Final drying	55°C, ca. 10 min (until outlet air temperature has reached 45°C)

TABLE 3 Formulation example: Process parameters

Results from dissolution tests in phosphate buffer (pH 6.8) and diluted hydrochloric acid (pH 1.2) can be attributed to the strong resistance in the saliva and rapid release of the active ingredients in the acidic environment of the stomach.

A coating level of 3 mg/cm² of a Kollicoat® Smartseal 30D-based formulation can prevent dissolution from extruded pellets for more than 60 minutes. On the other hand, caffeine is released quickly and completely at pH 1.2, independently of the coating level.

Effective sealing against moisture Any solid dosage form that is exposed to humidity will take up moisture. A protective coating can significantly delay the time until equilibrium between ambient humidity and moisture content is reached (e.g. during the packaging process or after dispensing the drug product).

Kollicoat Smartseal 30D-based films have an extremely low degree of water vapor permeability [1]. Kollicoat Smartseal 30D can thus prevent the moisture uptake of sensitive cores more effectively than other pharmaceutical film coating agents. Highly hygroscopic sorbitol cores were coated with varying levels of a Kollicoat Smartseal 30D-based formulation. The tablets were stored at 30°C and 70% relative humidity. Water uptake was determined at each test interval. The results demonstrate that Kollicoat Smartseal 30D coatings can significantly reduce moisture uptake during storage. The barrier effect increases with higher coating levels [Figure 6].

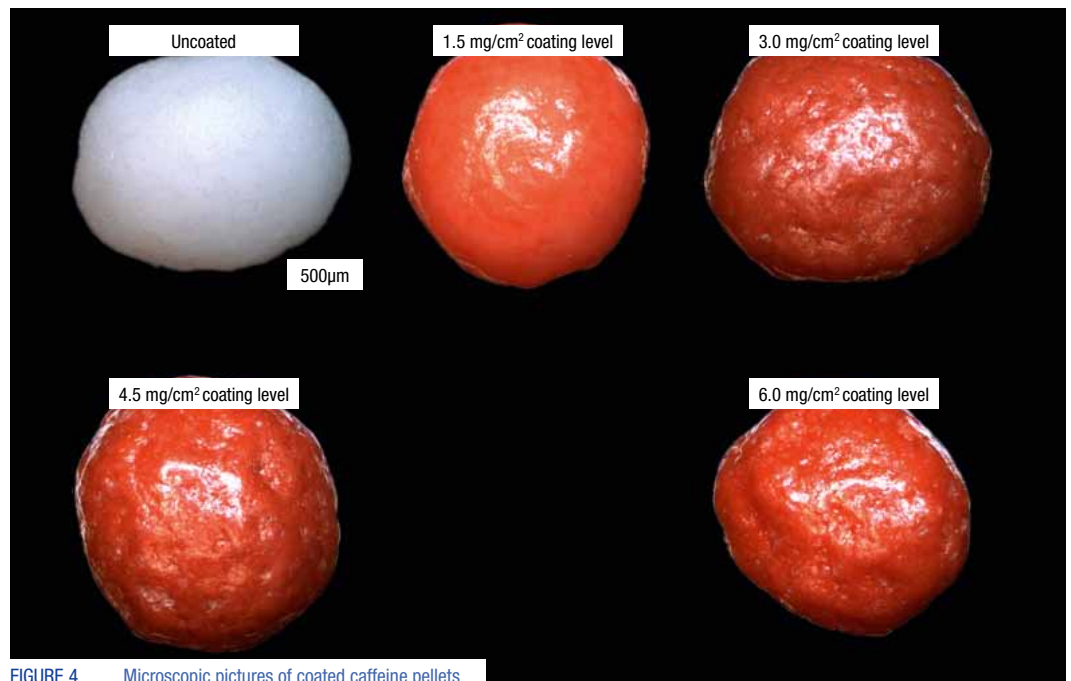


FIGURE 4 Microscopic pictures of coated caffeine pellets

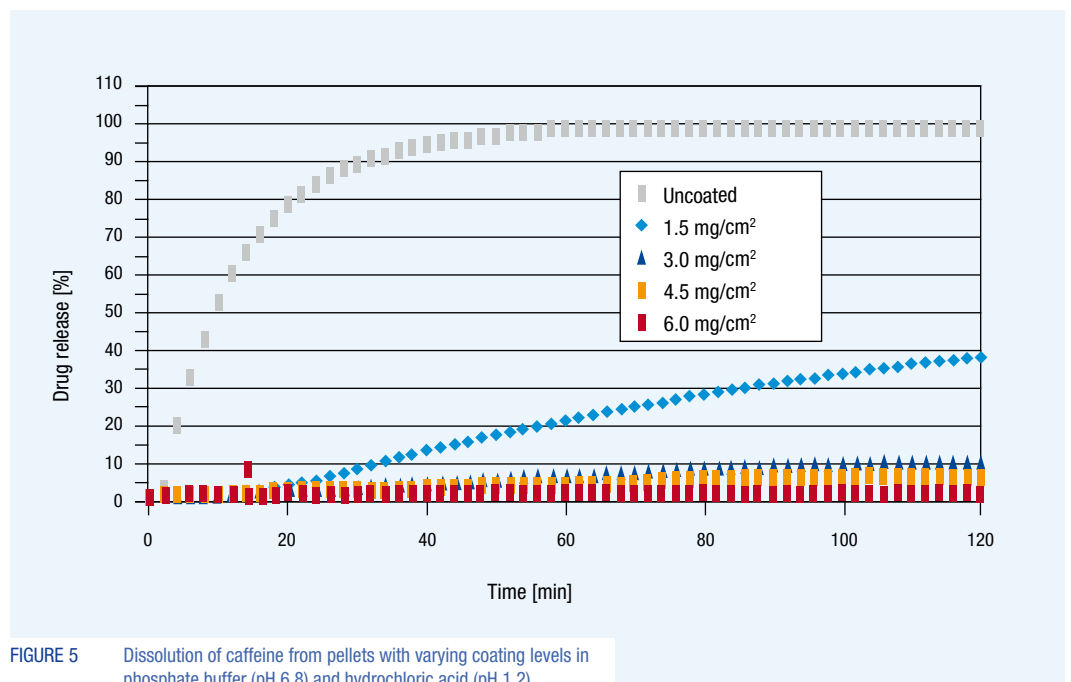


FIGURE 5 Dissolution of caffeine from pellets with varying coating levels in phosphate buffer (pH 6.8) and hydrochloric acid (pH 1.2)

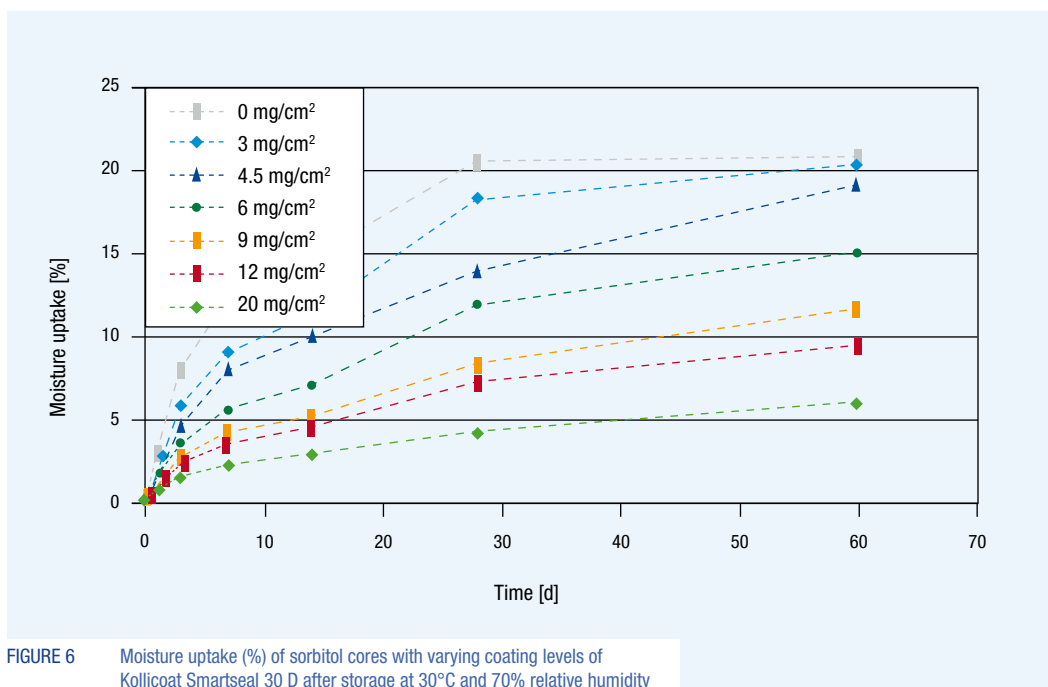


FIGURE 6 Moisture uptake (%) of sorbitol cores with varying coating levels of Kollicoat Smartseal 30 D after storage at 30°C and 70% relative humidity

SUMMARY | Kollicoat Smartseal 30 D is the first water-based polymer dispersion for taste masking and moisture barrier applications. It was developed to simplify and accelerate aqueous film coating operations and opens up new possibilities for the formulation of tablet, pellet and particle coatings. Read more about BASF's Kollicoat portfolio on page 14. ■■

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- [1] BASF Pharma Ingredients & Services, www.kollicoat-smartseal.basf.com
- [2] 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
- [3] Kollicoat Smartseal 30 D, Technical Information

Kollicoat Smartseal 30 D is the first aqueous dispersion for taste masking and moisture barrier combining a strong protective effect with simple and economic processing.

Ingredient	Content [%]
Composition of cores	
Sorbitol (Neosorb® P 60 W)	49.8%
Ludipress®	49.8%
Magnesium stearate	0.2%
Composition of film coat	
Kollicoat Smartseal (polymer)	52%
Talc	40%
Tributyl citrate	6.7%
Butylated hydroxytoluene	1.3%
Coating levels: 0, 3, 4.5, 6, 9, 12 and 20 mg/cm ²	

TABLE 4 Formulation example of moisture protection of sorbitol cores

COATING FORMULATIONS

Comparison of aqueous and non-aqueous enteric coatings of a model drug using Kollicoat® MAE 100 P and Eudragit® L 100-55

Shivesh P Sinha, Vaishali Tawde, Satyajee Narode

INTRODUCTION | Enteric-coated dosage forms are designed to resist the destructive action of the gastric fluid and to disintegrate in the higher pH environment of the intestinal fluid. Polymer for enteric coating can be applied to solid dosage forms (i.e. granules, pellets, or tablets) from aqueous solutions of alkali salts or organic solvent solutions. The most commonly used pH-sensitive enteric coating polymers today include: cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate (HPMCP) and methacrylic acid copolymers).

In recent years, acrylic copolymers have evolved as the preferred materials for enteric coating formulations in terms of performance and overall acceptability. The objective of this study was to investigate the non-aqueous enteric coating properties of Kollicoat MAE 100P, a copolymer of methacrylic acid and ethyl acrylate (1:1 ratio). Kollicoat MAE 100P is a re-dispersible powder produced by spray-drying Kollicoat MAE 30DP. Film coatings prepared from such dispersions are resistant to gastric juice but readily dissolve at a pH above 5.5. We chose propranolol HCl as a model substance because it can be quickly analyzed using UV spectroscopy.

METHODS AND MATERIALS | Materials

Propranolol hydrochloride (C₁₆H₂₁NO₂.HCl) was purchased from IPCA Laboratory, Mumbai, India. Microcrystalline cellulose (Avicel® PH 102; FMC Biopolymers, USA), Ludipress® (lactose monohydrate, a directly compressible agent, BASF India Limited, Mumbai), Kollidon® VA 64 (copovidone, BASF India Limited, Mumbai) and magnesium stearate (Merck, Mumbai) were used as directly compressible excipients. The enteric coating materials Kollicoat MAE 100P and Eudragit L 100-55 were respectively obtained from BASF India Limited, Mumbai and Evonik Industries. Eudragit L 100-55 plasticizer, triethyl citrate, was purchased from Vertellus, India. Anti-tacking agent talc and coating pigment titanium dioxide were purchased from Loba Chemie, Mumbai. Diluents such as isopropyl alcohol and acetone were purchased from Fisher Scientific, Mumbai. All the chemicals used were of analytical grade and obtained from commercial sources.

Preparation of propranolol hydrochloride core (20mg) tablets

Propranolol hydrochloride core (20mg) tablets were prepared by direct compression. All the ingredients (excipients and drug) were properly weighed (Mettler-Toledo India Ltd, Mumbai & Sartorius, Germany) and sieved through a 40-mesh screen, except for magnesium stearate which was sieved through a 60-mesh screen. Propranolol hydrochloride, Ludipress, Avicel PH 102 and Kollidon CL-F were mixed for 5 minutes by tumbling action in a polyethylene bag of suitable size. Finally, the magnesium stearate was added for lubrication and mixed for an additional 5 minutes or until a fine blend of ingredients was obtained. The tablets were produced on an eight-station rotary press (Rimek Mini Press-11 SF, Karnavati Engineering.) using round convex 8 mm punches at an average compaction force of 1000kg.

All the formulations were prepared under the same blending and compression conditions.

Sl No.	Ingredients	F1	F2	F3	F4	F5
1.	Propranolol HCl	20	20	20	20	20
2.	Ludipress (lactose)	41.59	31.59	73.16	33.59	55.37
3.	Avicel PH 102 (MCC)	83.16	63.16	41.59	73.16	55.37
4.	Kollidon CL-F (crospovidone)	4.5	4	4.5	4.25	4.5
5.	Magnesium stearate	0.75	1.25	0.75	1	0.75
6.	Total weight (mg)	150	120	140	132	135

TABLE 1 Formulation of propranolol HCl 20 mg core tablets

The objective of this study was to investigate the non-aqueous enteric coating properties of Kollicoat MAE 100 P, a copolymer of methacrylic acid and ethyl acrylate (1:1 ratio).

Optimization of the propranolol hydrochloride formulation

For optimization purposes, five different formulations of propranolol hydrochloride (20 mg) tablets were developed. The tablets were prepared using the composition as given in Table [1]. Ludipress, Avicel PH 102 and Kollidon CL-F were selected as independent variables and the response was studied regarding tablet weight, hardness, thickness, diameter, friability, disintegration time, assay and dissolution.

Evaluation of the formulated core tablets

After compression, the tablets of all the formulations were evaluated for different parameters. Weight variation was determined using an electronic balance (Sartorius, Germany). Tablet thickness and diameter were measured using digital vernier calipers (Digimatic, Mitutoyo, Japan). Friability was determined using a friabilator (USP EF-2, Electrolab, India). A model USP ED-2, SAPO disintegrator tester (Electrolab, India) was used for disintegration testing. A dissolution station (Jasco-DT 610, Japan) was used for drug release testing. The paddle was operated at 100 rpm using 900mL maintained at 37%. Tablet assay was determined using a UV Spectrophotometer (Perkin-Elmer, Lambda-35, UK) at 289nm.

Choice of the optimized formulation Formulation 1 was selected as an optimized formulation after comparative evaluation of all necessary parameters on tablet weight, hardness, thickness, diameter, friability, disintegration time, assay and dissolution.

Enteric coating of tablets		Formulation of aqueous and non-aqueous enteric coatings				
Sr.No	Function	Ingredients	Qty (w/w%)	Qty (w/w%)	Qty (w/w%)	Qty (w/w%)
1.	Coating polymer	Kollicoat MAE 100 (non-aqueous)	4.5			
2.	Coating polymer	Kollicoat MAE 100 P (aqueous)		15		
3.	Coating polymer	Eudragit L 100-55 (non-aqueous)			4.5	
4.	Coating polymer	Eudragit L 100-55 (aqueous)				15
5.	Plasticizer	Triethyl citrate	0.9	2.25	0.9	2.25
6.	Antitacking	Talc	0.7	4.50	0.7	4.50
7.	White pigment	Titanium dioxide	0.1	0.50	0.1	0.50
8.	Diluent	Isopropyl alcohol	55.45		55.45	
9.	Diluent	Acetone	38.35		38.35	
10.	Stablizer	NaOH (0.1 mol/L)				6
11.	Water	Diluent		77.75		71.25
12.		Total	100	100	100	100

TABLE 2 Formulation of aqueous and non-aqueous enteric coatings

After compression, the tablets of all the formulations were evaluated for different parameters. Formulation 1 was selected as an optimized formulation after evaluation of all these parameters.

Method and process for non-aqueous enteric coating

The compressed tablets were coated with non-aqueous enteric coating polymers (due to the high viscosity of the non-aqueous polymer solution, 4.5% concentrations were selected) of Kollicoat MAE 100P and Eudragit L100-55. For non-aqueous enteric coating, the non-aqueous solvents isopropyl alcohol and acetone were used (60:40 ratio). The tablet coating was produced in an auto coater (Neocota, India). The enteric coating solutions were atomized from the top of the apparatus at a flow rate of 2-5 g/min. The inlet air temperature was set at 30°C. The pan load was 500 gm. The tablets were pre-warmed at reduced coating speed to 30°C. Warm air was introduced into the coating pan (up to 30°C) during the entire coating process. The coating was applied up to 10% weight gain. The coated tablets were dried in the apparatus for 30 minutes after completion of the coating process.

Method and process for aqueous enteric coating

The compressed tablets were coated with aqueous enteric coating polymers (15%) of Kollicoat® MAE 100P and Eudragit® L100-55. The tablet coating was produced in an auto coater (Neocota, India). The enteric coating solutions were atomized from the top of the apparatus at a flow rate of 2-5g/minutes. The inlet air temperature was set at 50°C. The pan load was 500 gm. The tablets were pre-warmed at reduced coating speed to 45°C. Warm air was introduced into the coating pan (up to 50°C) during the entire coating process. The coating was applied up to 10% weight gain. The coated tablets were dried in the apparatus for 30 minutes after completion of the coating process.

WEIGHT GAIN STUDY | This was done using a modified disintegration test method.

Modified disintegration test method for enteric-coated tablets A modified USP disintegration test method using a variety of buffer compositions was used to investigate the impact of elevated pH conditions on propranolol HCl tablets coated with Kollicoat MAE 100P and Eudragit L100-55.

Materials and methods – weight gain – acid uptake testing

Each enteric tablet (n=6) was weighed and six of them were placed in the disintegration tester with the respective buffer medium (0.1 N HCl, acetate buffer pH 3 and pH 4.5, phthalate buffer pH 3 and pH 4) at 37°C. After two hours, the tablets were taken out and any adhering water was removed with a tissue. Each tablet was then reweighed. The difference in the weights was reported as percentage acid uptake. Twelve tablets of each coating formulation were tested in the different buffer media.

EVALUATION OF ENTERIC-COATED TABLETS | Disintegration test of enteric-coated tablets

Six tablets of propranolol HCl enteric-coated tablets were weighed individually and placed in acid phase (0.1 N HCl) for two hours in a USP basket rack assembly (Electrolab-ED-2, SAPO, India) after which they were removed and inspected for cracking or disintegration. The same tablets were then placed in phosphate buffer (pH 6.8) and observed for disintegration.

Dissolution test of enteric-coated tablets

Drug release was measured in a USP dissolution bath (Jasco-DT 610, Japan) using apparatus II at 100 rpm. The dissolution media were 900 mL of 0.1 N HCl and phosphate buffer (pH 6.8) maintained at 37±0.5 °C. The tablets were placed in the acidic medium for two hours and in the basic medium for 45 minutes. The sampling intervals for 0.1N HCl were 30, 60, 90 and 120 minutes and for phosphate buffer (pH 6.8) 5, 10, 15, 20, 25 and 30 minutes. Samples were assayed spectrophotometrically (Perkin-Elmer, Lambda-35, UK) at 289nm.

STABILITY STUDIES

The propranolol HCl tablets were stored in HDPE (high-density polyethylene) bottles (Triveni chemicals, Mumbai) in a dualstability chamber (Thermolab, India) under different storage conditions. Samples designed for intermediate condition were kept at 30±2 °C and 65±5% relative humidity (RH). The samples in the accelerated stability study were kept at 40±2 °C and 75±5% RH in a humidity chamber. A total of four products were tested in the study. Two were aqueous enteric-coated and two were on-aqueous enteric-coated tablets of Kollicoat MAE 100P and Eudragit L100-55. The samples were tested for appearance, disintegration, dissolution and assay using the previously described procedure.

At predetermined time points, the tablets were sampled and tested for physical properties and drug release.

RESULTS AND DISCUSSION | Discussion

Physical appearance, hardness, friability, weight variation and drug content of different tablet formulations were found to be satisfactory under pharmacopoeial standards. It was observed that the incorporation of the superdisintegrant 'crospovidone' greatly improved the disintegration time of all the formulations. An in-vitro disintegration study revealed that the tablets were completely disintegrated within a few seconds. The results obtained from the evaluation of tablet characteristics were utilized in the selection of optimized formulation. Formulation 1 was found to have the best results according to the optimization criteria with dissolution up to 97.89% in basic medium and assay results up to 98.54%. This was finally chosen for the preparation of enteric-coated formulation.

It was observed that incorporation of the super disintegrant "crospovidone" greatly improved the disintegration time of all the formulations.

Evaluation of formulated core tablets All values are expressed as a mean \pm S.D, n=3

Batch code	Wt. of 20 tabs.(20mg)	Fribility (%)	Disint. time (s)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm ²)	Diss. test (%)	Assay 289 nm (%)
F1	150 \pm 0.906	0.280	10	8.095 \pm 0.015	3.307 \pm 0.037	5.583 \pm 0.308	97.89	98.54
F2	120 \pm 0.758	0.080	11	8.095 \pm 0.015	2.999 \pm 0.042	6.867 \pm 0.251	94.25	98.54
F3	140 \pm 0.668	0.142	18	8.092 \pm 0.018	3.220 \pm 0.034	6.027 \pm 0.175	96.22	94.88
F4	132 \pm 0.912	0.156	20	8.095 \pm 0.015	3.211 \pm 0.041	5.959 \pm 0.073	95.51	94.88
F5	135 \pm 0.223	0.171	25	8.095 \pm 0.015	3.110 \pm 0.061	6.990 \pm 0.098	95.12	95.67

TABLE 3 Evaluated data of formulated core tablets

Enteric coating of tablets Tablet coating was carried out in an auto coater (Neocota, India) using a spray-coating technique. Enteric coating of propranolol HCl tablets was carried out up to 10% (7.15mg/cm²) weight gain in the case of both aqueous and non-aqueous Kollicoat MAE 100P and Eudragit L100-55.

WEIGHT GAIN STUDY | Modified disintegration test method for enteric-coated tablets The percentage acid uptake by the enteric-coated tablets after direct exposure to 0.1N HCl (pH 1.2), USP phthalate buffer (pH 3.0 and pH 4.0) and USP acetate buffer (pH 3.0 and pH 4.5) was measured. The acid uptake results for the propranolol HCl enteric-coated tablets are shown in the figure below.

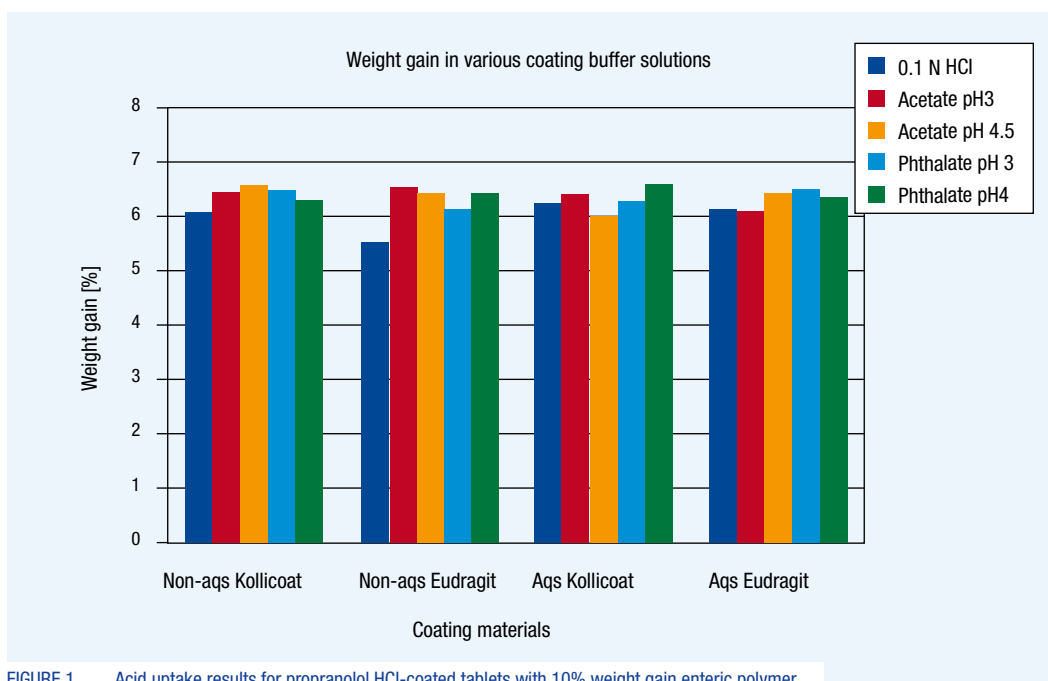


FIGURE 1 Acid uptake results for propranolol HCl-coated tablets with 10% weight gain enteric polymer

Discussion In the weight gain study, all aqueous and non-aqueous Eudragit® L100-55 and Kollicoat® MAE 100P enteric coating formulations were stable at pH 1.2 to pH 4.5 for two hours and no disintegration of the API was detected. The average weight gain of 4.8%–7% is acceptable. Eudragit L grades and Kollicoat MAE grades performed equally well in this test system. There was no significant difference at intermediate pH values. Testing of the enteric dosage forms at intermediate pH (1.2 to 4.5) may also provide information that would be important in achieving bioequivalence.

Evaluation of enteric-coated tablets The enteric-coated tablets were subjected to a tablet disintegration and a dissolution test. The results showed that in the case of both aqueous and non-aqueous enteric-coated tablets, there were no signs of cracking, peeling or disintegration in 0.1 N HCl for two hours; however, the coated tablets were completely disintegrated in 5–7 minutes in pH 6.8 phosphate buffer. Drug release met the criteria outlined in this study, i.e. not less than 75% dissolved after 45 minutes in pH 6.8 phosphate buffer.

Disintegration test The disintegration test of enteric-coated tablets of aqueous and non aqueouscoated tablets of Kollicoat MAE 100P and Eudragit L100-55 with 10% (7.15mg/cm²) weight gain showed both to be comparatively similar in terms of more stability in acidic medium and optimum rate of disintegration in pH 6.8 phosphate buffer. The results showed that there were no signs of cracking, peeling or disintegration in 0.1 N HCl; however, the coated tablets were completely disintegrated in 5–7 min in pH 6.8 phosphate buffer (Table 4).

Formulation	0.1 N HCl (2 hrs)	Disinteg. time in phosphate buffer, pH 6.8
NAK	No disintegration	5 min 55 sec.
NAE	No disintegration	7 min 11 sec.
AK	No disintegration	6 min 34 sec.
AE	No disintegration	6 min 11 sec.

NAK=Non-aqueous Kollicoat, NAE=Non-aqueous Eudragit, AK= Aqueous Kollicoat, AE= Aqueous Eudragit.
(Note: DT was performed in triplicate) The disintegration test of enteric-coated tablets of aqueous- and non-aqueouscoated tablets of Kollicoat MAE 100 P and Eudragit L100-55 with 10% (7.15mg/cm²).

TABLE 4 Disintegration time of enteric-coated tablets

Dissolution test It was found that at a coating of 10% (7.15 mg/cm²), weight gain with both aqueous and non-aqueous coated tablets of Kollicoat MAE 100P polymer, propranolol-HCl tablets exhibited a dissolution rate of <10% after 2 hours in 0.1 N HCl. In phosphate buffer pH 6.8, more than 90% dissolved after 30 minutes. The use of Eudragit L100-55 resulted in similar dissolution characteristics. Thus, drug release met the criteria outlined in this study i.e. not less than 75% dissolved after 45 minutes in pH 6.8 buffer (Figure 2).

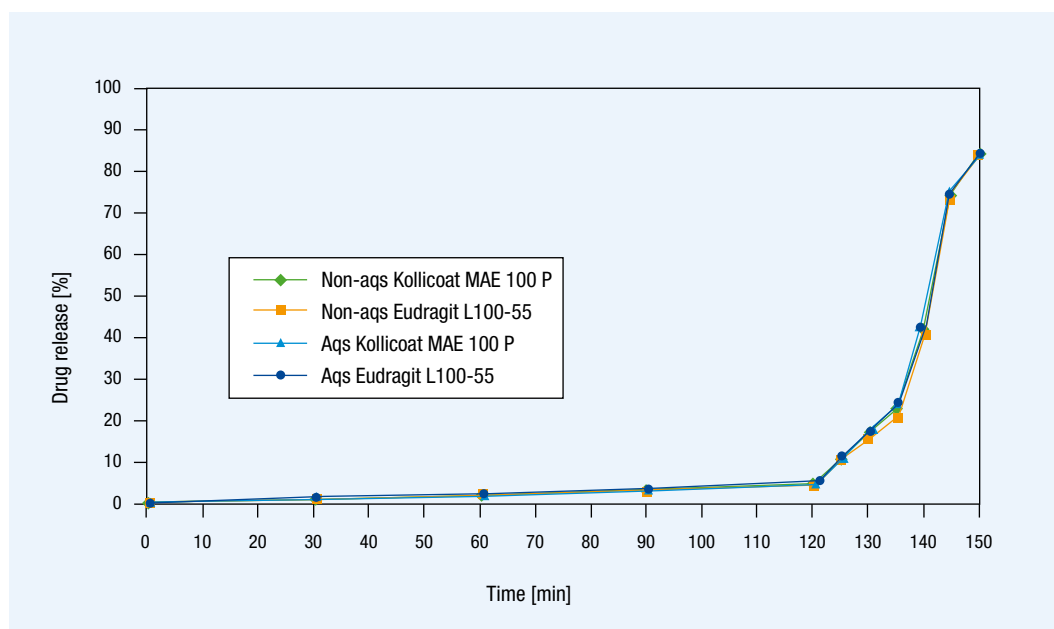


FIGURE 2 Dissolution profile of enteric-coated tablets in 0.1N HCl for 120 min followed by pH 6.8 phosphate buffer for 30 min

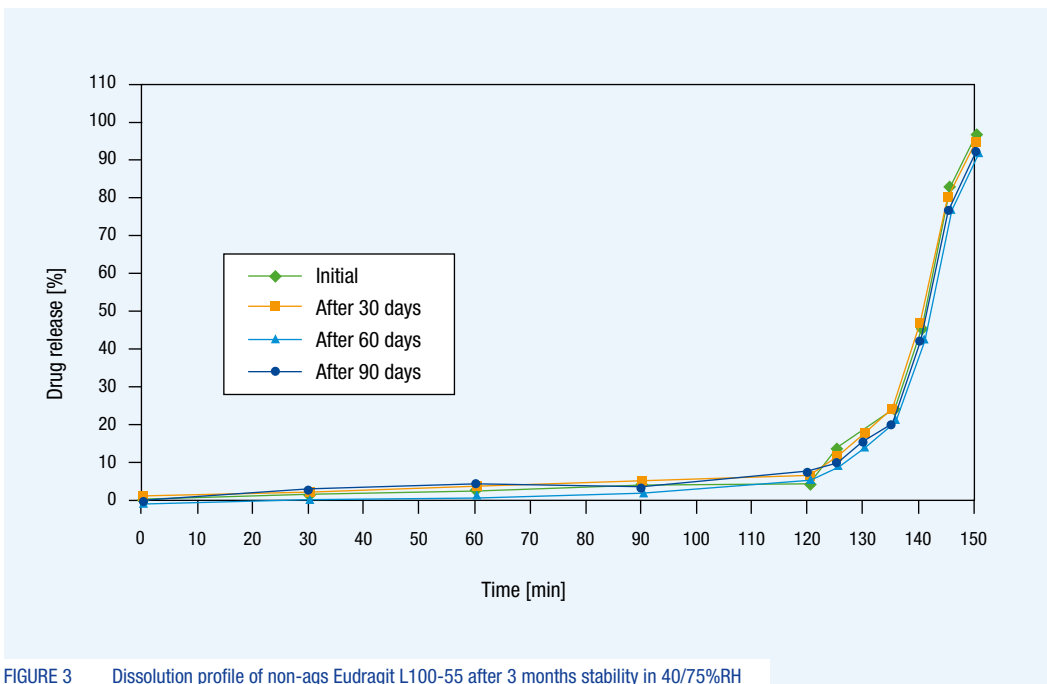


FIGURE 3 Dissolution profile of non-aqs Eudragit L100-55 after 3 months stability in 40/75%RH

STABILITY STUDIES | All samples were evaluated with respect to visual appearance, weight variation, thickness, hardness, drug content and dissolution characteristics. The samples were stored for a total period of 3 months for stability evaluation. The samples were designated as 0, 1, 2 and 3 months for RT and 0, 1, 2 and 3 months for accelerated studies (Figure 3-6).

The results of disintegration and dissolution tests of enteric-coated tablets showed no signs of cracking, peeling or disintegration in 0.1 N HCl for two hours.

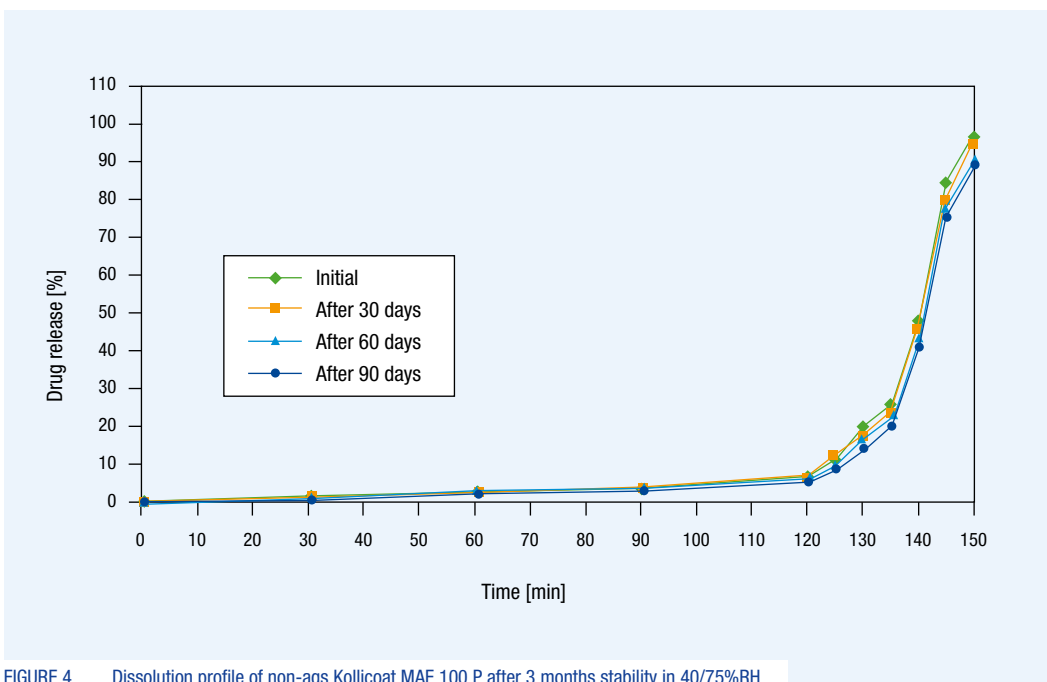


FIGURE 4 Dissolution profile of non-aqs Kollicoat MAE 100 P after 3 months stability in 40/75%RH

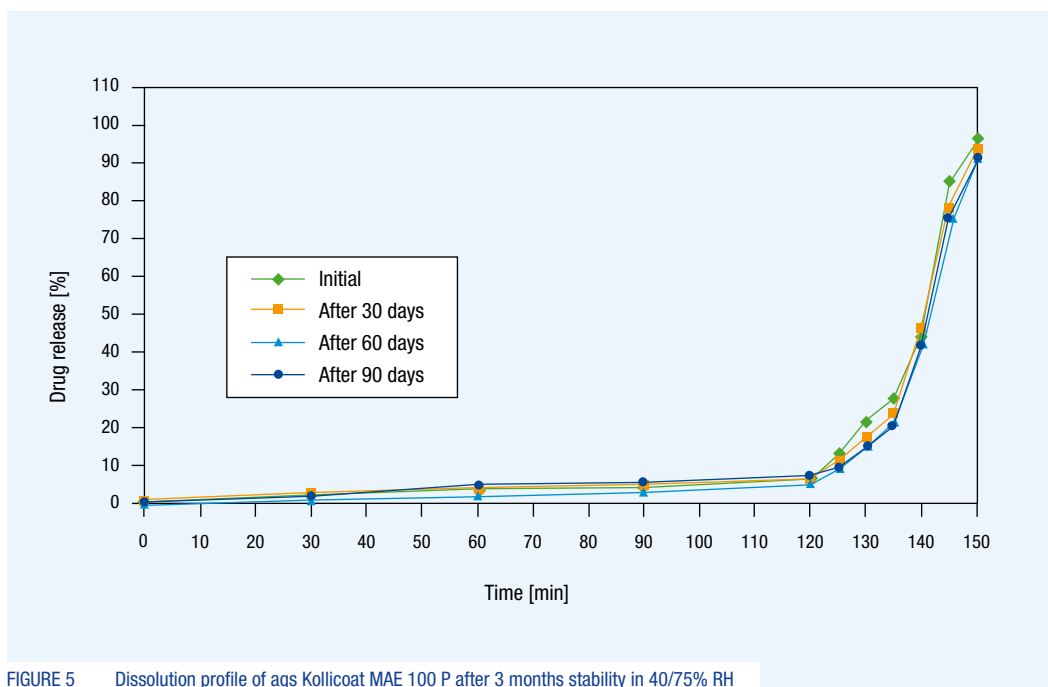


FIGURE 5 Dissolution profile of aqs Kollicoat MAE 100 P after 3 months stability in 40/75% RH

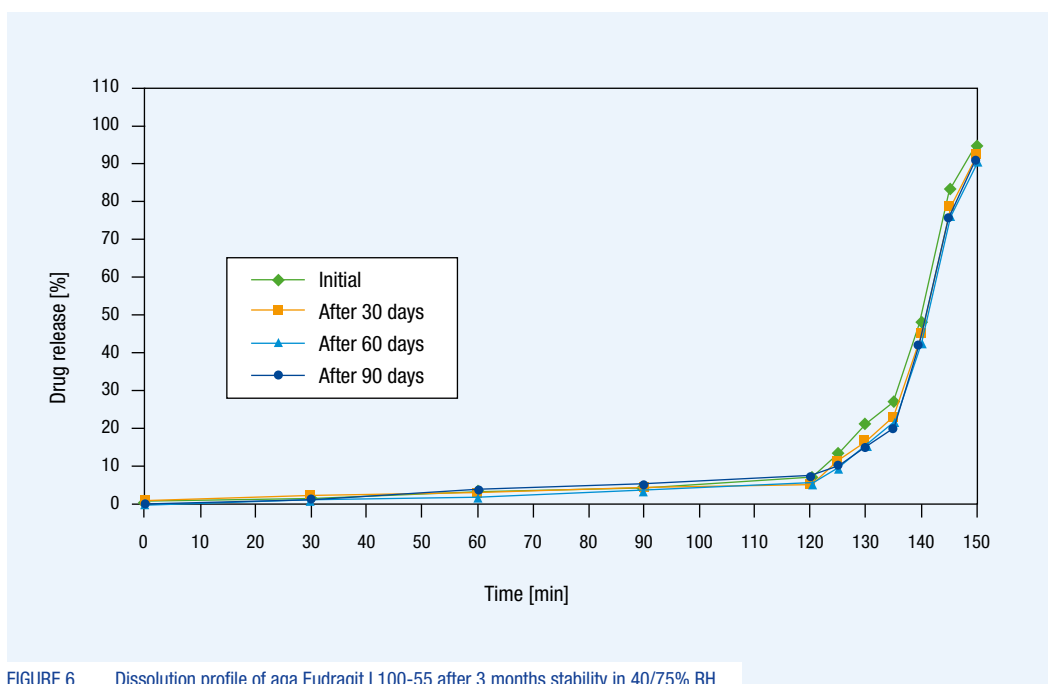


FIGURE 6 Dissolution profile of aqa Eudragit L100-55 after 3 months stability in 40/75% RH

SUMMARY AND CONCLUSIONS | In the weight gain study, all aqueous and non-aqueous Eudragit® L100-55 and Kollicoat® MAE 100P enteric coating formulations were stable at a pH 1.2 to pH 4.5 for two hours and no disintegration of the API was detected. The average weight gain of 4.8%–7% is regarded as acceptable.

It was concluded that IPA:acetone in a proportion of 60:40 with and without pigments showed good results in terms of tablet appearance, surface and uniformity of the coating, provided atomization was carried out at a pressure up to 2 to 3 bar. No coagulation occurred and no spider web formation was observed while coating with Kollicoat MAE 100P at a pressure of 3 bar. It was observed during the studies that Kollicoat MAE 100P can be processed using a wide range of process parameters such as atomizing pressure between 0.8 to 3 bars and a spray rate from 2 to 5 gm/mL. At higher atomizing pressure with Kollicoat MAE 100P, the tablet surface appearance was superior and showed good gloss.

During the studies involving Eudragit L100-55, it was observed that, if an atomizing pressure above 2 bar was applied, spider web formation occurred. In order to avoid this effect, Eudragit L100-55 was processed at an atomizing pressure of 0.8 to 1.2 bars and a spray rate of 2 to 5 gm/mL. As the tablets could only be processed at lower atomizing pressures, their appearance was suboptimal.

The studies show that a non-aqueous coating of Kollicoat MAE 100P can be processed at a solid content of 5-8% whereas Eudragit L100-55 cannot be processed at a solid content exceeding 5%.

Kollicoat MAE 100P in non-aqueous form also showed good performance with plasticizers such as 1,2propylene glycol, polyethylene glycol-6000, triacetin.

Kollicoat MAE 100P and the corresponding Eudragit L100-55 grades performed equally well in enteric coating formulations in terms of weight

gain, disintegration, dissolution and stability. The optimized formulation which was subjected to stability studies was found to be stable after three months.

Conclusion Based on the above studies, it can be concluded that Kollicoat MAE 100 P is a potentially useful excipient for the production of pH-dependent enteric-coated delayed release tablets and can be used for both aqueous and non-aqueous enteric coating. The process is both easy and economical. ■■

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COATING PORTFOLIO

Kollocoat® – Meets all your coating needs

Felicitas Guth, Thorsten Schmeller, Jan Bebbler

➤ In recent years, BASF has continuously expanded its portfolio of film forming excipients, covering both the existing and future needs of pharma formulators. BASF's inherent know-how and expertise in all aspects of chemistry from polymer research to pharmaceutical application technology make it possible to translate pharmaceutical needs into product solutions.

With the most recent launch of Kollocoat Smartseal 30D, BASF now offers the first aqueous dispersion for taste masking and moisture protection, at the same time offering unique performance and processing efficiency (see also page 2).

Kollocoat Smartseal 30D perfectly complements the Kollocoat product line, which now covers all your needs in pharmaceutical film coating – instant release, sustained release, protective and enteric applications as well as colored coating systems.

The coating portfolio overview below will enable you to select the right product for any specific application:

ROBUST AND COST-EFFECTIVE COATING PROCESSES WITH KOLLOCOAT IR |

Kollocoat IR – a water-soluble polyethylene glycol-polyvinyl alcohol grafted copolymer – provides excellent film coating results over a wide range of operating parameters and helps to reduce process times. Kollocoat IR is the basis for BASF's instant release coating agents:

Kollocoat IR for film coating and other instant release applications (e.g. as a binder or protective colloid).

Kollocoat IR Coating Systems for all applications where a readily re-dispersible, flexible and colored instant release coating is required. Seven basic colors help you to create your own color.

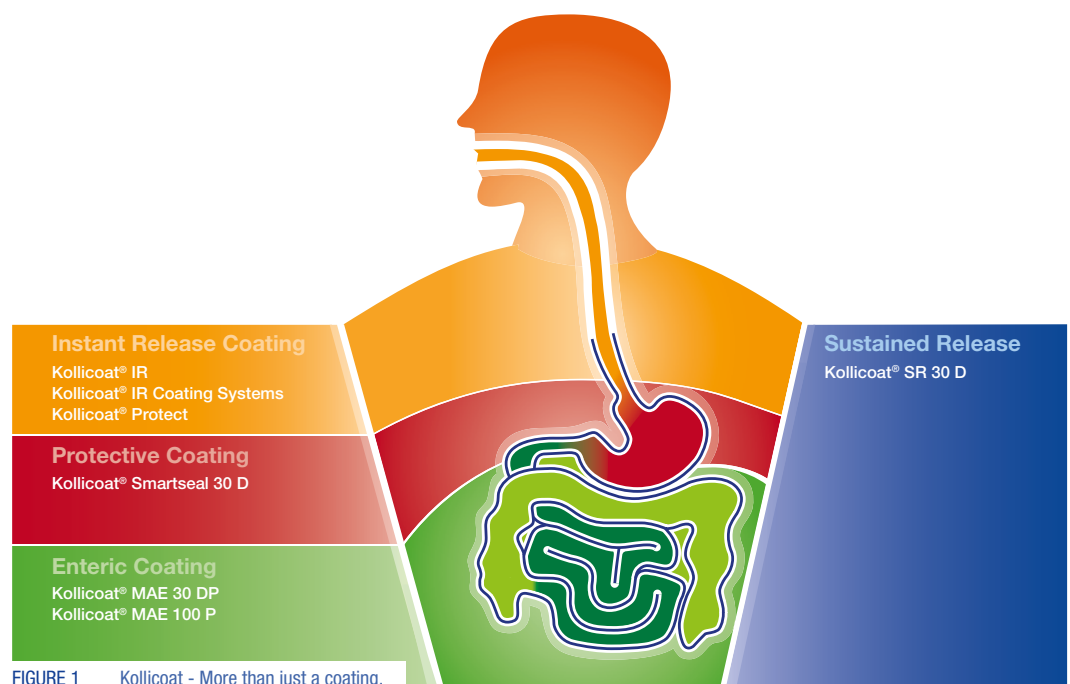


FIGURE 1 Kollocoat - More than just a coating.

Kollocoat goes far beyond delivering excellent coating results. It also helps streamline production processes, boost efficiency and cut manufacturing costs – while ensuring high-quality standards.

Kollocoat Protect is a water-soluble polymer combination that can easily be formulated as a moisture-protective coating without the need for a plasticizer.

ACTIVE PROTECTION WITH KOLLOCOAT SMARTSEAL 30 D |

Kollocoat Smartseal 30D – a methyl methacrylate and diethylaminoethyl methacrylate copolymer dispersion – offers superior protection from moisture and unpleasant tastes and helps to reduce coating levels. It simplifies and accelerates aqueous film coating operations, and opens up new possibilities for the formulation of tablet, pellet and particle coatings. Kollocoat Smartseal 30D is BASF's latest development. We provide support to our customers with comprehensive safety data and regulatory information (read more on page 2).

Effective enteric coating with Kollicoat MAE 30DP and Kollicoat MAE 100P The methacrylic acid and ethyl acrylate copolymer (1:1) is well-known for its reliable gastro-resistant effect. With Kollicoat MAE 30DP and Kollicoat MAE 100P, BASF offers two product forms: the aqueous polymer dispersion with a solid content of approx. 30% and a partially neutralized powder grade that can be re-dispersed easily without the addition of an alkalizing agent.

Strong sustained release effects with Kollicoat SR 30D Kollicoat SR 30D – a polyvinyl acetate dispersion – offers maximum flexibility in drug development and opens up new possibilities in life cycle management. Kollicoat SR 30D can be used as a film or matrix former in sustained release applications.

Our Kollicoat products go far beyond delivering excellent coating results. They also help you streamline production processes, boost efficiency and cut manufacturing costs – while ensuring your high-quality standards. ■■

BASF's inherent know-how and expertise in all aspects of chemistry from polymer research to pharmaceutical application technology make it possible to translate pharmaceutical needs into product solutions.

Evaluation of formulated core tablets All values are expressed as a mean ± S.D, n=3

Product	Application	Ph.Eur.	USP/NF
Kollicoat IR	Instant release coating, binder, protective colloid	Macrogol - poly(vinylalcohol) graft polymer	Ethylene glycol and vinylalcohol graft copolymer
Kollicoat IR Coating Systems	Unique modular system based on seven basic colors for the manufacture of colored instant release tablets	N/a (components have own monographs)	N/a (components have own monographs)
Kollicoat Protect	Polymer combination based on Kollicoat IR and polyvinyl alcohol for moisture barrier applications	N/a (components have own monographs)	N/a (components have own monographs)
Kollicoat Smartseal 30 D	Aqueous polymer dispersion for taste masking and moisture protection	No (new product)	No (new product)
Kollicoat MAE 30 DP	Easy and effective aqueous-based enteric coating	Methacrylic acid - ethyl acrylate copolymer (1:1) dispersion (30 %)	Methacrylic acid copolymer dispersion
Kollicoat MAE 100 P	Easily re-dispersible powder	Methacrylic acid - ethyl acrylate copolymer (1:1) type B	Partially neutralized methacrylic acid and ethyl acrylate copolymer
Kollicoat SR 30 D	Strong sustained release effect for multiple applications	Poly(vinyl acetate) dispersion (30%)	Polyvinyl acetate dispersion

TABLE 2 JPE monograph for Kollicoat MAE 30 DP (methacry (methacrylic acid copolymer LD) JPE monograph for Kollicoat IR under preparation

TROUBLE-SHOOTING – FILM COATING

Trouble-shooting in film coating: selecting the right plasticizer in film coating formulation

Thorsten Agnese, Thorsten Cech, Michael Herting, Florian Wildschek

➤ One of the most important excipients in a functional film coating formulation is the plasticizer. This excipient influences both the minimum film forming temperature (MFFT) of the dispersion and the elasticity of the final coat. As there is a huge variety of plasticizers available, the decision as to which one to take is not very easy. In this investigation, different plasticizers were used in combination with Kollicoat® SR 30D – a film former based on polyvinyl acetate (PVAc) and providing sustained release functionality.

PROBLEM | For the water-insoluble sustained release film forming polymer PVAc, both elongation at break and MFFT depend strongly on the type and amount of plasticizer used in the coating formulation. Since the MFFT is comparably low for PVAc (18°C), this physical characteristic is of minor interest [1]. However, the elongation properties are of huge importance, especially if coated particles are compressed to multiple unit pellet systems (MUPS).

This investigation was intended to consider the suitability of three different plasticizers: polyethylene glycol 6000, 1,2-propylene glycol and triethyl citrate. Isolated films were prepared with a plasticizer content of 10% (m/m) each, calculated on the polymer content of the dispersion. To ensure homogeneous distribution and incorporation within the PVAc dispersion, the mixture was stirred for at least 2 hours. The actual preparation was carried out using a film caster (Coat-master) equipped with a 300µm knife. The film caster allows various temperatures to be used to dry the cast films.

The films were examined visually as a first indication of quality. To determine the mechanical properties, a texture analyzer (TA-XT2i HR) was used. Testing was performed under climatically controlled conditions of 23°C and 54% r.h [2].

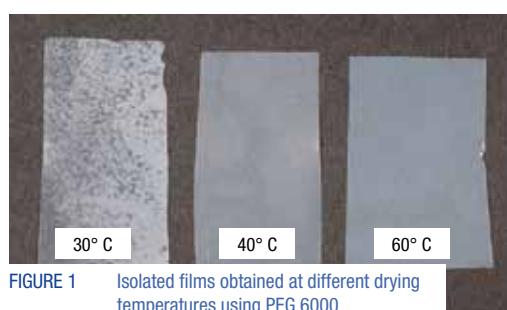


FIGURE 1 Isolated films obtained at different drying temperatures using PEG 6000

The investigation was intended to consider the suitability of three different plasticizers: polyethylene glycol 6000, 1,2-propylene glycol and triethyl citrate.

Polyethylene glycol 6000 On appraising the film visually, a clear dependency of homogeneity on the drying temperature was found. Forming the film at temperatures of about 30°C led to an inhomogeneous distribution of PEG 6000 within the film. As the white sections appearing in the film (Figure 1) can be dissolved in water, it can be concluded that the plasticizer was not properly incorporated in the PVAc matrix.

Using elevated temperatures of 40°C and higher, the distribution of PEG 6000 within the isolated film is visually more homogeneous.

On investigating this effect in detail, a temperature of 36°C could be determined as the necessary minimum temperature to achieve a film without any crystalline areas.

The inhomogeneous distribution of PEG 6000 in the film was confirmed by the results of the texture analysis. In spite of the poor elongation properties of all films tested, differences could still be observed between the films prepared at different temperatures (Fig. 2).

Drying temperatures above 30°C resulted in films showing a higher elasticity/plasticity compared with films dried at 30°C.

PEG 6000 can be considered as a film former in its own right, but it forms very brittle films. Hence, the elasticity of PVAc cannot be increased by means of adding this plasticizer. However, physical properties such as tackiness and tensile strength can clearly be influenced [3]. Due to its poor elongation properties, even at elevated preparation temperatures, PEG 6000 cannot be regarded as a useful plasticizer for PVAc.

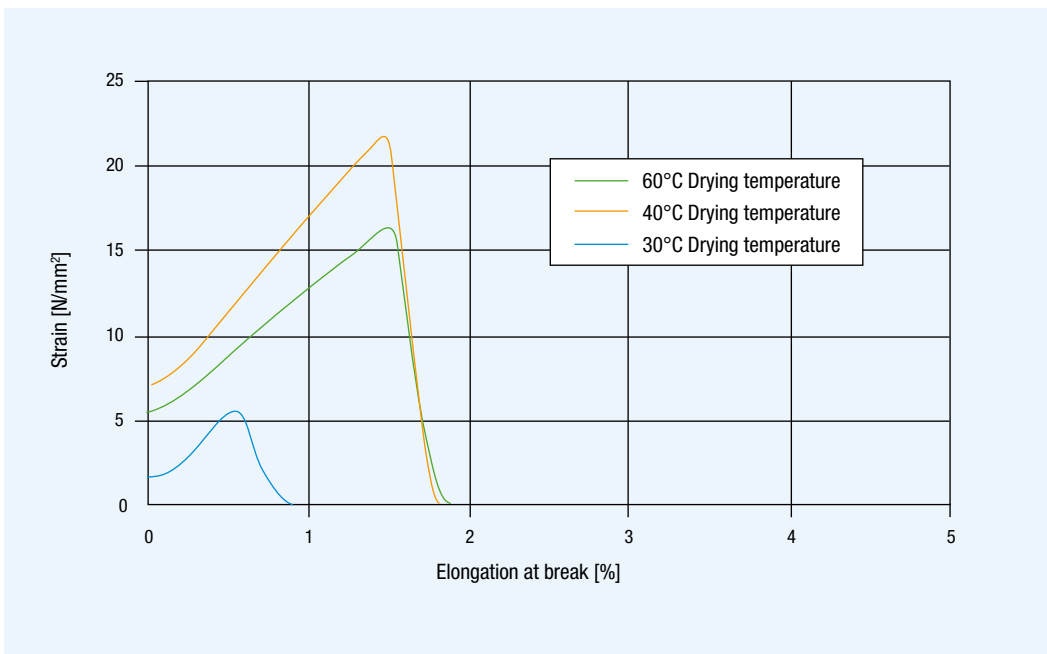


FIGURE 2 Elongation properties of isolated films prepared at different drying temperatures using PEG 6000

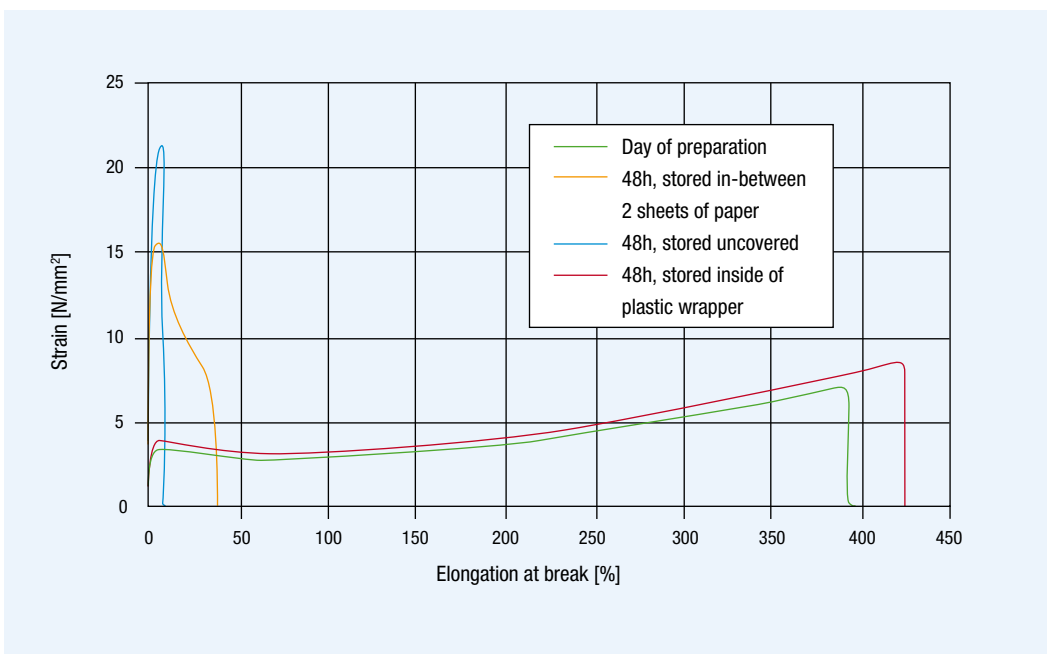


FIGURE 3 Elongation properties of isolated films prepared at different drying temperatures using PG

Propylene glycol The MFFT of a PVAc film containing 10% PG was found to be 14°C [1]. However, independent of the temperature used for the preparation of the isolated films, visible homogenous films could be obtained.

Skultety and Sims stated that huge amounts of PG evaporate during the film coating process [4]. This effect was found while testing the elasticity and plasticity of the isolated films as well. Both characteristics were observed as being extremely high on the day of preparation (Figure 3). However, storing the films openly for 48 hours under controlled conditions of 23°C/54% r.h., the elongation properties changed substantially; the film became more brittle. However, no alteration could be found for samples stored in a closed system.

Additional tests regarding this phenomenon showed that the intensity of the effect depended on the preparation method used and the thickness of the film. Preparing the film with a spray gun led to a less pronounced reduction in elongation at break during storage. In any case, reductions of more than 20% could also be found after 65 hours.

To prove that evaporation of the plasticizer was the cause of the change of the film characteristics, a fabric filter wetted with PG was stored at 23°C/54% r.h. After taking up the amount of water required for equilibrium, a strong decrease in mass was observed (Figure 4). This suggests that PG evaporates under these storage conditions.

From the solely process technology point of view, PG can be used as a plasticizer for PVAc. However, the potential risk of change in its elongation properties has to be closely monitored during stability tests.

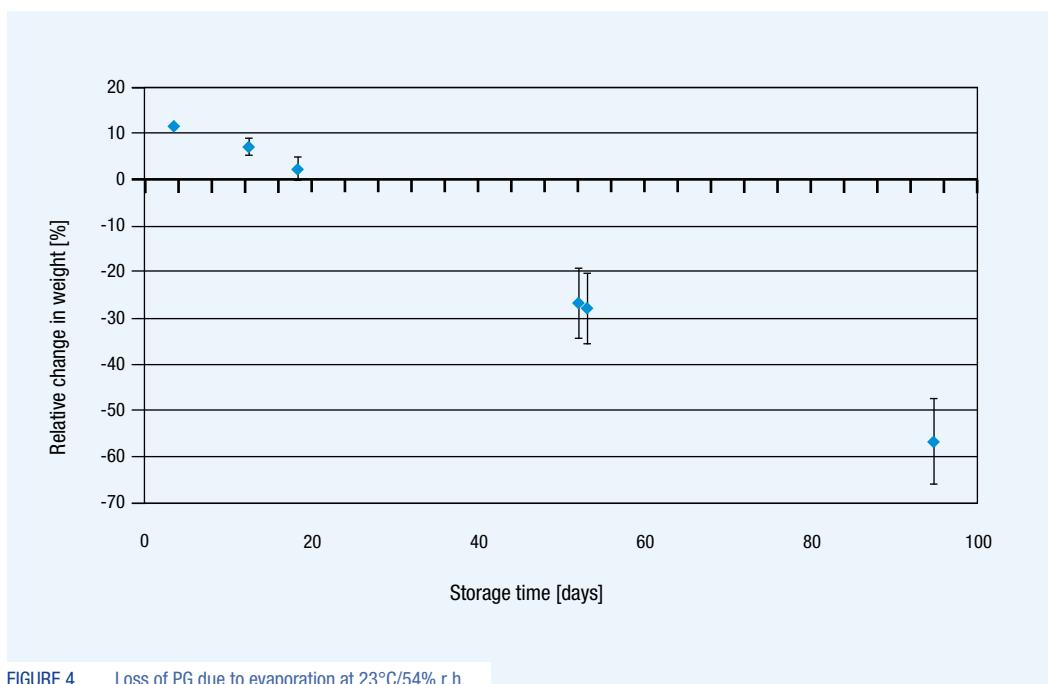


FIGURE 4 Loss of PG due to evaporation at 23°C/54% r.h.

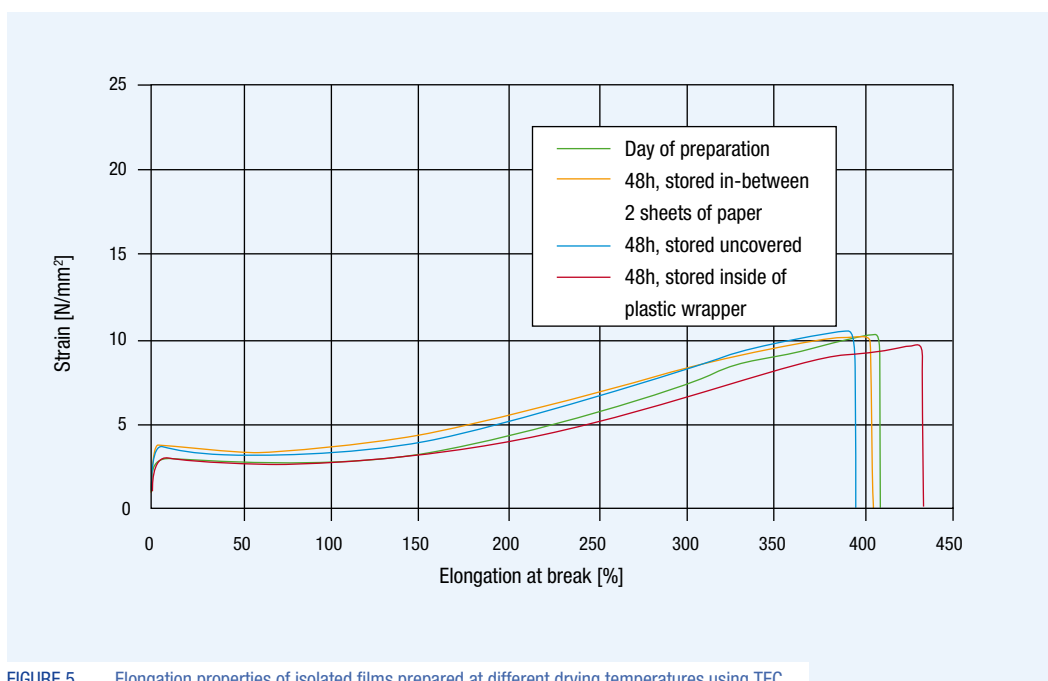


FIGURE 5 Elongation properties of isolated films prepared at different drying temperatures using TEC

Triethyl citrate TEC has a very high effect on the MFFT of PVAc films [1]. An amount of 10% plasticizer lowers the MFFT to 1°C. Similar to PG, it was also found that for TEC, homogeneous films could be prepared, independent of the temperature used for drying. The elongation properties were also found to be very high (Fig. 5).

The elongation properties of the isolated film remain at this high level, even during open storage of the films. This indicates that TEC is not as susceptible to evaporation or migration effects as PG. Therefore, TEC is suggested to be the ideal plasticizer for PVAc. It offers a very low minimum film forming temperature and results in films with excellent elongation properties.

SOLUTION | The plasticizer showing the best results with regard to plasticizing effects and storage stability was triethyl citrate (TEC). This excipient is therefore recommended to be used as a plasticizer for the aqueous dispersion of PVAc (Kollicoat® SR 30D).

A previous investigation showed that the performance of triacetin (TAC) is comparable to TEC, except for tackiness (TAC is less tacky than TEC) [3]. Therefore, TAC could be used alternatively to TEC in similar quantities. ■■

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SOLUBILIZATION

A high-throughput robot for solubilizer screening

Christian Holtze, Ulrike Troppmann, Dejan Djuric, Eva Wagner, Michael Herting

INTRODUCTION | Pharmaceutical scientists increasingly face the challenge of formulating active pharmaceutical ingredients (APIs) that are poorly soluble in water. This trend is likely to continue: new APIs in pharmaceutical research are becoming more and more lipophilic and complex, given that combinatorial chemistry and pharmacological high-throughput screening (HTS) have become standard methods in the industry. Because of their problematic physico-chemical properties such as poor water solubility or low permeability, a large number of new chemical entities show poor bioavailability and consequently fail during the development phase. Therefore, scientists around the world are currently trying to tackle the issue of bioavailability by developing novel strategies for drug formulation.

One particularly appealing way to improve “biopharmaceutical fitness” is to enhance the aqueous saturation solubility of the API. However, to date, scientists have still not been able to relate API structures to the solubilizing activity of excipients. Thus, within the pharmaceutical industry, the solubilization effect is being examined more by “trial and error”. In conventional screening, this leads to long development times and consequently results in high development costs. However, the time required for experiments can be significantly reduced by applying HTS. The use of HTS provides absolutely reproducible and well-documented screening of the solubilization capacity of different solubilizers for various APIs. Moreover, it appears to be the only way of generating a sufficiently reliable data base that allows the general structure-property relationships to be determined for deducing the solubilizing efficacy of solubilizer-active combinations.

The purpose of this study was to set up an HTS robot for the solubilization of poorly soluble APIs. Carbamazepine was used as a model API and the solubilization capacity of various solu-

bilizers for this API was examined. Screens obtained with the help of this robot benefit from automation, miniaturization and parallelization. It can be used to accelerate research projects and to scan various influencing parameters simultaneously. For proof of the concept, the results obtained were compared to the data from manual experiments in the lab.

METHODS AND MATERIALS | Materials

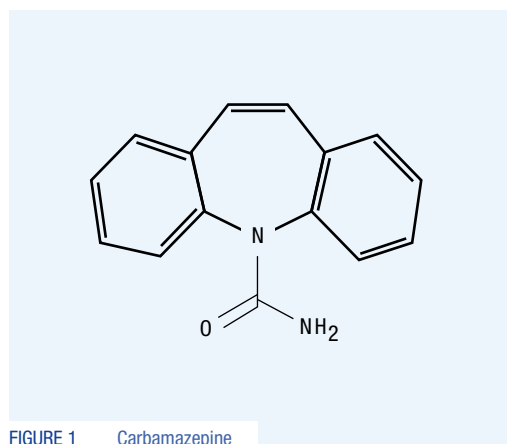


FIGURE 1 Carbamazepine

The experiments showed that the use of an HTS robot for screening trials can help to save development time.

Name	Chemistry	Supplier
Cremonophor® RH 40	Polyoxyl 40 hydrogenated castor oil Macroglycerol hydroxystearate	BASF SE
Cremonophor® EL / ELP	Polyoxyl 35 castor oil Macroglycerol ricinoleate	BASF SE
Solutol® HS 15	Macrogol 15 hydroxystearate	BASF SE
Lutrol® F68	Poloxamer 188	BASF SE
Lutrol® F127 Lutrol® micro 127	Poloxamer 407	BASF SE
Tween® 20	Polysorbate 20	Croda International Plc
Tween® 80	Polysorbate 80	Croda International Plc
Vitamin E TPGS	d-α-Tocopheryl polyethyleneglycol 1000 succinate	Eastman Corp.
Soluplus®	PEG 6000 / vinylcaprolactam / vinyl acetate (13 / 57 / 30)	BASF SE

TABLE 1 Overview of solubilizers tested

Preparation of samples The set-up of the multi-purpose HTS robot allows for the dispensing of liquids and solids. Solubilizer solutions and API powders are dispensed into vials (Fig. 1). The amount of API to be added is set to 10mg and the actual amount added is controlled using a balance (X404S DeltaRange, Mettler Toledo, Germany) and recorded. 0.5mL of the solubilizer solution in phosphate buffer (pH 7.0) is dispensed from a 1% and 5% (w/w) aqueous stock solution.

The 1.0mL vials have standard dimensions and are placed on a standard tray to provide high operational freedom with regard to analytics like UV/VIS spectroscopy or HPLC.

An overview of sample preparation and measurement is given in Figure 3.

Determination of dissolved carbamazepine Following incubation and a filtration step, a 1:100 dilution with a phosphate buffer/methanol 1:1 (v/v) mixture was carried out by the HTS robot. Then, 0.1mL of the diluted sample was analyzed automatically using the incorporated UV spectrometer (DDT3200, Duratec, Germany) at a wavelength of 286nm. In the case of maximal absorbance of greater than 1, an appropriate second dilution step was automatically performed.

In the manual trials, all steps were performed by a lab technician. Evaluation of solubilized carbamazepine for the manually prepared samples was carried out using a Hewlett Packard HP8452A Diode Array UV/Vis spectrometer.



FIGURE 1 Set-up of the multi-purpose HTS Robot at BASF



FIGURE 2 Preparation set-up showing the 3-axis robot arm and balance with vials

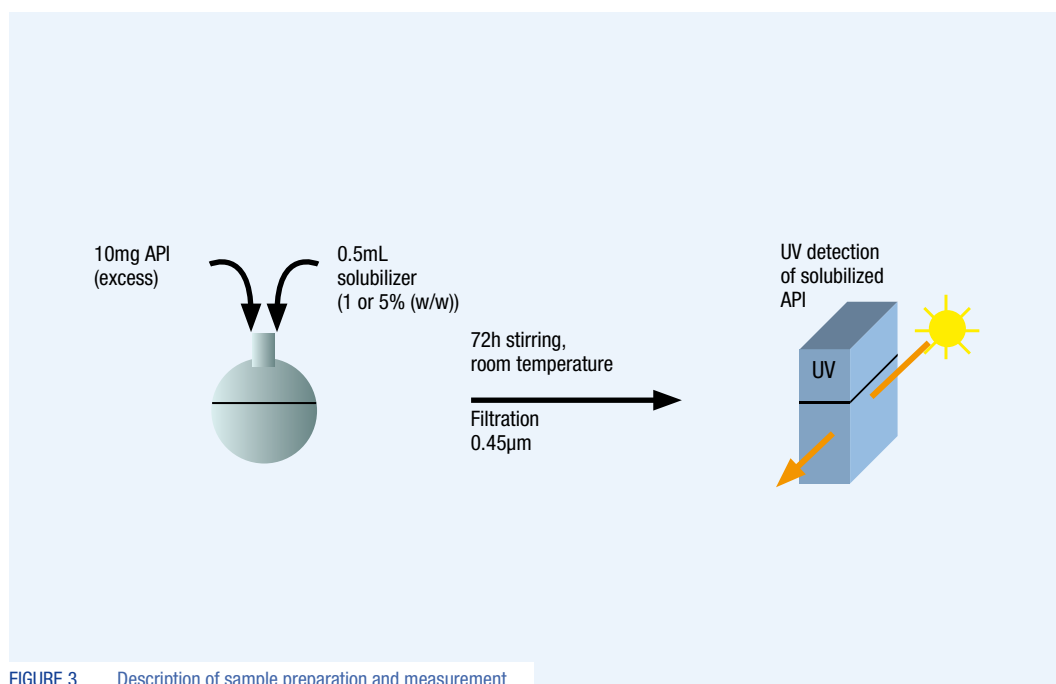


FIGURE 3 Description of sample preparation and measurement

RESULTS AND DISCUSSION | The use of solubilizers resulted in an improvement in the saturation solubility of carbamazepine in all cases. The saturation solubility achieved for the different solubilizers tested ranged from approximately 137ppm using Lutrol F 68 to 806ppm for Soluplus at 1% solubilizer concentration as detected by the UV-Vis spectrometer built into the HTS robot. The solubilization capacity did not change at 5% solubilizer concentration. However, at higher solubilizer concentrations, the saturation solubility of carbamazepine was increased for all solubilizers used. Soluplus proved to be the most efficient solubilizer for carbamazepine, resulting in the highest saturation solubility for the two concentrations used. As expected, there was no difference in solubilization capacity between Cremophor EL and the purified grade Cremophor ELP, nor between Lutrol F127 and micronized Lutrol micro 127. Thus, solubilization capacity was neither dependent on the purity level of the excipient nor on particle size.

In the case of the solubilizer concentrations used (1% and 5% (w/w)), the results obtained from both manual experiments and screening using the HTS robot correlated well (Figures 4 and 5).

The experiments showed that the use of an HTS robot for screening trials can help to save development time. The trials with the HTS robot took two days while the manually performed experiments by one operator took three times as long. As these were the first test trials using the robot, it can be expected that the analyzing speed in future trials can be increased due to process optimization.

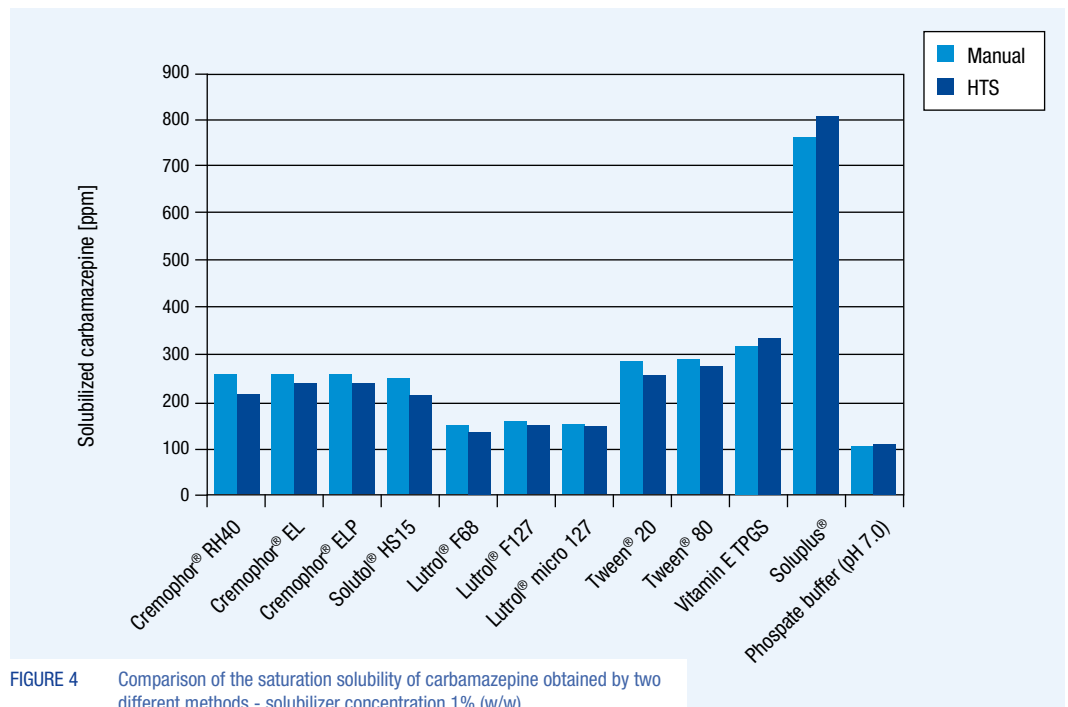


FIGURE 4 Comparison of the saturation solubility of carbamazepine obtained by two different methods - solubilizer concentration 1% (w/w)

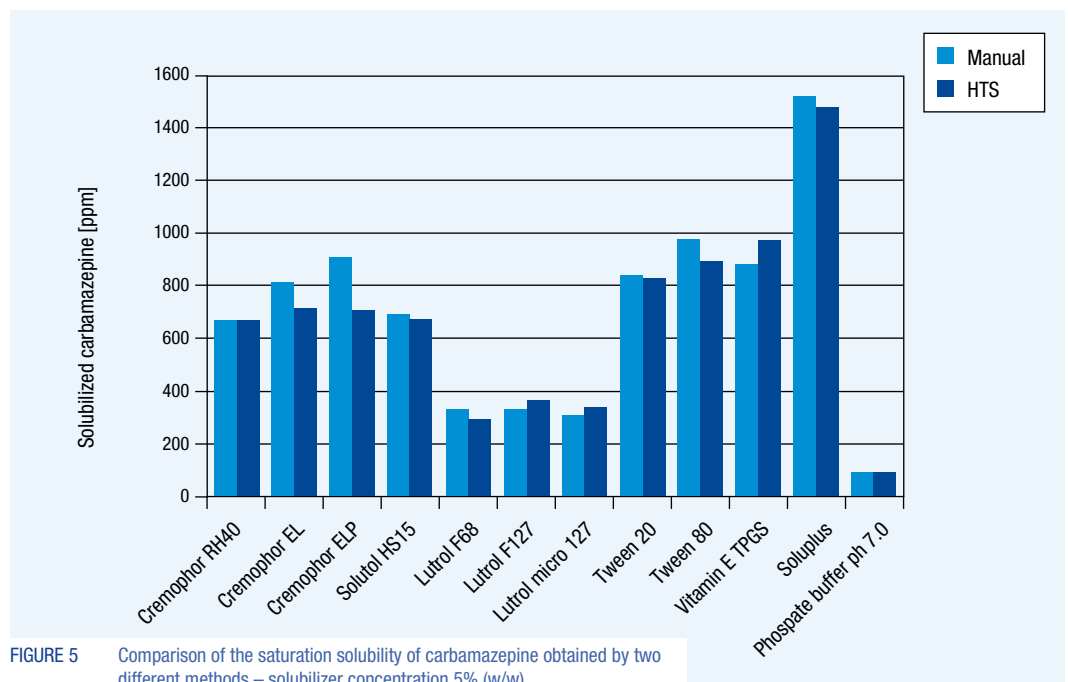


FIGURE 5 Comparison of the saturation solubility of carbamazepine obtained by two different methods - solubilizer concentration 5% (w/w)

An additional benefit compared to manual work is perfect reproducibility of the dispensing steps and the automated documentation of parameters and results in a database. This data can be used in the evaluation step for data mining and statistical analysis to extract correlations and structure-property relationships.

CONCLUSION | The HTS robot was successfully used for the fast screening of different solubilizers with carbamazepine as a model API. The data of this screening were comparable to the manually obtained results. The use of the HTS robot allowed for a large number of data and increased the information output significantly due to the built-in software. Therefore, this approach helps to reduce development time. The benefits are summarized in Table 2.

It is to be expected that using the HTS robot, a comprehensive database will be obtained allowing for the correlation of the API structure and solubilization capacity of different solubilizers for specific APIs.

ACKNOWLEDGEMENTS | The authors gratefully acknowledge the help provided by Markus Müller and Bernd Strubel in setting up the robot and performing the experiments. ■■

	Manual	HTS
Number of screened solubilizers in a given time	Low	High
Amount of work	High	Low
Time requirement	High	Low
Repeatability	Medium	High
Documentation	Unknown	Full

TABLE 2 Comparison of manual screening and screening with an HTS robot

The use of the HTS robot allowed for a large number of data and increased the information output significantly due to the built-in software.

UPDATE ON REGULATORY AFFAIRS

New regulatory requirements for residues of metal catalysts or metal reagents under development

Dorothee-Christine Kriha, Rainer Fendt

Background With the introduction of the current EMA Guideline (CHMP/SWP/4446/2000, published in February 2008, effective from September 1, 2008) and the development of a future harmonized ICH Guideline initiated by the ICH Steering Committee in November 2009 (ICHQ3D), recommendation is given on the maximum acceptable concentration limits of metal residues that arise from the use of metal catalysts or metal reagents during the synthesis of drug substances and excipients. Such metal residues do not provide any therapeutic benefit to the patient and should therefore be evaluated and restricted based on safety and quality criteria.

Nevertheless, manufacturers of pharmaceutical ingredients are facing some major problems when it comes to implementing the EMA Guideline. Therefore, the following comments on the current regulatory requirements are made with the aim of further improving some practical aspects of the guideline. They are also intended to contribute to the further development of ICH Q3D since a harmonized ICH Guideline will help to ensure appropriate control of these impurities, to the benefit of public health.

Introduction and classification The general set of safety limits defined for all (classes of) metals that are currently included in the CHMP-SWP/QWP Guideline is highly appreciated. It is of course especially important to establish appropriate controls for those metals with clearly established toxicological concerns. However, regarding those metals not yet classified as Class 1, 2 or 3, how much scientific literature and toxicology information will be expected by the authority to justify the proposed acceptance criteria? Will summary information be enough if it clearly states the overall safety of the metal? Clarification of the metal's limit calculation is also recommended: has it been taken into account that the toxicology of some metals depends on the state of oxidation?

Analytical procedures The CHMP Guideline states that 'any harmonized procedures for determining the levels of metallic residues as described in the pharmacopoeias should be used, if feasible'. However, the commonly used pharmacopoeial methodology was intended to control metals which form a sulfide precipitate, such as lead or copper, even including metal residues from other sources (e.g., the equipment). The control of these is a task of the GMP/Quality System rather than a problem the pharmacopoeias should deal with. Most analytical methods used to control these extraneous metals are non-specific and have not been developed to detect low-level residues of metal catalysts and reagents as often used in modern synthetic processes. The three major pharmacopoeias have already initiated a revision of their respective chapters, the USP being the most advanced.

The European Pharmacopoeia Commission has decided to align the revision process with the deliberations at the level of the ICH Q3D Expert Working Group in order to ensure consistency. As demonstrated by this decision, it is crucial that pharmacopoeial requirements, which, in contrast to regulatory guidelines, are of a legally binding nature, are consistent with these guidelines. In addition, pharmacopoeial harmonization in this area is vital for a global industry.

Batch results, testing frequency and deletion of tests In the CHMP Guideline, it is implied that synthetic manufacturing processes are known or suspected of leading to the presence of metal residues only due to the simple use of a metal catalyst or metal reagent.

Companies should be allowed to apply their knowledge of the product and the manufacturing process as the production operation may be conducted in a manner that excludes carry-over and results in consistent removal of potential metal residues, e.g. when performing distillation or when heterogeneous gas phase catalysts are used.

In July 2010, the EMA published a new Q&A document on its website (“Impurities – Harmonization of Policies on Setting Specifications for Potentially Genotoxic Impurities, Heavy Metal Catalysts Residues and Class 1 Solvent Residues”) that addresses this issue and clarifies that metals not used or suspected of being present do not need to be included in the specification.

However, in conjunction with the given examples, it remains unclear as to which conditions need to be fulfilled in order to claim that a metal is not suspected of being present. Moreover, example 2 obviously goes beyond the generally accepted approach in demonstrating that a substance is not likely to be present. This is because the not-exceeding 30% of the guideline limit is directly linked to the requirement that the metal be routinely controlled by a suitable limit in a synthesis intermediate. A justification for this more stringent point of view is not provided. We are in agreement that class 1 metals are the prime focus due to their toxicity; however the given statement that “class 2 and 3 metals could be treated similarly but somewhat less strictly” offers too much room for interpretation and requires more precise guidance.

Furthermore, clarification is required as to how the information about the concerned metallic residues should be disclosed to drug manufacturers. It is mentioned that “[...] the test may be deleted from the relevant specification if the drug manufacturer sufficiently demonstrates that the adequate removal of the metal residue from the drug substance or the drug product is guaranteed.”

What is meant by “relevant specification”? Does it refer to the specification of the pharmaceutical ingredient manufacturer or to the substance specification included in the MA application or does it refer to the finished drug product specification?

In the section “REPORTING LEVELS OF METALLIC RESIDUES” it is more clearly stated “[...] that the manufacturers of pharmaceutical substances provide a clear statement on the identity and quantity of all metal residues present in their compounds to the drug product manufacturers.”

It is generally understood that manufacturers of drugs need information about the content of metallic residues in order to comply with the EMA Guideline. Do the requirements in this section allow for issuing a statement on identity and quantity of all metal residues rather than including the information in the supplier’s specification?

It is preferred that, as long as a certain metal is “not likely to be present”, a separate drug manufacturer’s statement is acceptable, and an inclusion in the supplier’s CoA can be avoided. However, compliance with this request by drug manufacturers may undoubtedly result in confidentiality issues concerning this information, for instance in the case of a patented metal catalyst being used in the synthesis. To ensure proper safety evaluation on the one hand and protection of intellectual property of the API or excipient manufacturer on the other, it should be possible in certain cases to disclose the sensitive information ONLY to the competent authority or preferably to the EDQM. Alternatively, generic statements identifying only the relevant class of metal and related limits could be issued.

Clarification is required from the regulators how the information about metal residues should be disclosed to authorities and drug manufacturers.

BREAKING NEWS

Global distribution of BASF pharma excipients in small pack sizes will be managed by Sigma Aldrich

University and development lab supplies now available from Sigma-Aldrich BASF SE and Sigma-Aldrich® have signed a global distribution agreement for a number of BASF's pharmaceutical excipients. Sigma-Aldrich will repackage the products into small pack sizes, making them available for academic-oriented research and development segments such as universities and laboratories.

The excipients portfolio offered comprises various grades of binders (Kollidons), coatings (Kollicoats) and solubilizers (Cremophors, Lutrols, Solutol). A complete list of products is available on the Sigma-Aldrich website at: www.sigmaaldrich.com

www.basf.com/group/ressrelease/P-11-161

Providing customers with rapid and well-presented information

Which pharmaceutical excipient ensures that tablets disintegrate instantly in the mouth even without drinking water? How do you get the most out of that excipient during production? What coloring agent colors tablets quickly and safely? Launched in February 2010, the new internet portal "Excipient Academy" provides background knowledge and news about chemical excipients and their uses. Pharmaceutical development employees from the pharmaceutical industry, universities and formulation labs can register here and sign on for seminars and workshops that share useful expertise and offer a platform for dialog. "Webinars", as these are called, teach these subjects online. Approximately 10 events are planned per year. The range of subjects extends from granulation to film coating to melt extrusion.

An information service to be expanded shortly offers documents and literature for download that tie in with the subjects on offer.

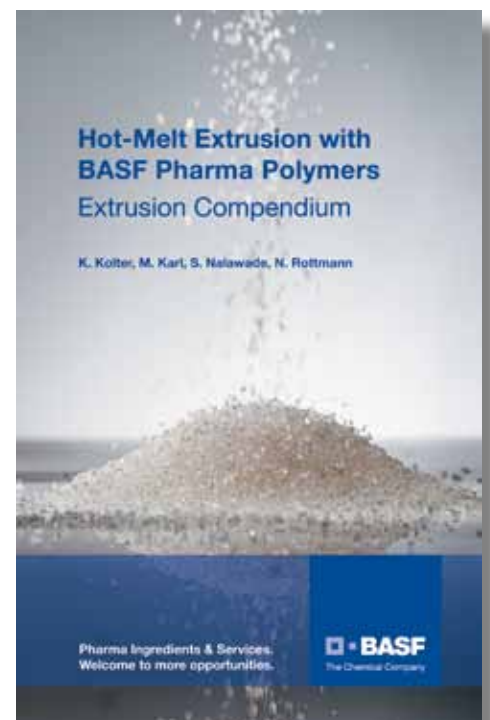
www.excipients-academy.basf.eu

Hot-melt extrusion with BASF pharma polymers – extrusion compendium

The first edition of the Hot-Melt Extrusion (HME) Compendium is now available. In this compendium, scientists at BASF present a range of polymers with both low and high glass transition temperatures for pharmaceutical technology. HME is currently generating significant interest in the pharma industry as the percentage of poorly soluble compounds continues to increase. HME makes it possible to increase these molecules' solubility and bioavailability. The compendium covers the chemistry of polymers and their applications in melt-extrusion and enables the desired release profiles and robust processing conditions to be achieved.

Please visit:

www.innovative-excipients.basf.com to download a copy of the HME Compendium. **You can read it and leave your comment on our website.**



BREAKING NEWS

CPhI Silver Innovation Award

Soluplus®, BASF's new excipient, was awarded the Silver Innovation Prize at CPhI in Paris, October 2010. Soluplus: The Solid Solution is unique because it enables new levels of solubility and bioavailability enhancement of poorly soluble drugs. Thus it is a promising solution to one of the greatest challenges of the pharmaceutical industry.

The Silver Innovation Award at CPhI is an outstanding achievement for this recent product launch of BASF. Dedicated to innovation, BASF has a long track record of new excipients which help its customers to be more successful.

Honor for Dr. Karl Kolter at AAPS

Dr. Karl Kolter, Head of BASF's Pharmaceutical Excipients Research and Development, was honored at the AAPS Annual Meeting and Exposition in New Orleans with the 2010 International Pharmaceutical Excipients Council Foundation (IPEC) Industry Research Achievement in Excipient Technology award. Dr. Kolter received the newly established award in honor of his outstanding history of research into novel pharmaceutical excipients. Dr. Kolter has been working for BASF since 1993. He has developed more than 22 new pharmaceutical excipients and has published over 120 research papers.

New Kollicoat® Smartseal 30 D brochure

Kollicoat® Smartseal 30D is the first aqueous dispersion of a protective polymer, combining a strong protective effect with efficient processing. It will help customers tackle challenges in formulating bitter or moisture-sensitive active ingredients.

Kollicoat Smartseal 30D offers superior protection for tablet, pellet and particle formulations – even in a very thin film. This helps pharmaceutical companies streamline and accelerate film coating.

To find out more about this innovative product, please download our brochure here:

www.kollicoat-smartseal.basf.com



EVENT

ExActCoat+ Experience your coating success

Kathrin Meyer-Böhm

BASF now opens up a new era of coating events: **ExActCoat+** is a comprehensive and interactive series of events designed to broaden knowledge of film coating and film coating equipment. For letting your coating success come true, **ExActCoat+** brings together practical experience on materials, processes and the fascinating theory behind them, all in an interactive way. **ExActCoat+** provides a platform for learning more about color determination, colored coating systems, instant and sustained release coating, protective coating and coating equipment. Coating experts from across the industry and from academia will be your partners for finding answers to your most difficult coating questions.

After a successful launch of **ExActCoat+** in 2010 in Hong Kong, Shanghai and Mumbai, the unique event series will be continued around the globe. Keep a look-out for your **ExActCoat+** event! **ExActCoat+** are planned for the US and Asia in the fall of 2011. If you have any questions, please contact your sales representatives; they will be glad to help.



FIGURE 1 Welcome to the practical sessions of **ExActCoat+** Hong Kong

Create your own colors: BASF and X-Rite break new ground in color coating of tablets

Kathrin Meyer-Böhm

BASF and X-Rite have teamed up to create an easy-to-handle on-site approach for color coatings of tablets by combining the latest tablet color determination device with BASF's Kollicoat IR Coating Systems. With ColorEye XTH, X-Rite offers a portable tool for color determination of tablets. The tablet color can then be easily transferred to the BASF Kollicoat IR Coating Systems recipe, perfectly producing the desired color shade.

This collaboration matches with the ongoing trend of immediate availability of results without any outsourcing activities and with minimal effort.

"This unique, systematic and easy-to-apply color matching approach draws on the expertise of both BASF and X-Rite, to provide a solution that responds specifically to the challenges that pharmaceutical formulators face today. This solution goes beyond what is offered today", says Dr. Kathrin Meyer-Böhm, Pharma Ingredients and Services, BASF SE. Within minutes the

color of a tablet can be determined by ColorEye XTH and transferred to a Kollicoat IR Coating Systems recipe that can be easily formulated on-site. This approach replaces complex logistic processes and ensures that in-house formulation knowledge remains confidential.

Please visit www.pharma-ingredients.basf.com and see the "News" section for more details.

CALENDAR

May 24-26, 2011

FCE Brasil
Sao Paulo

June 13-17, 2011

PharmSciFair
Prague

Jul 30 - Aug 3, 2011

CRS
National Harbor, ML

Aug 24-26, 2011

CPhI South America
Sao Paulo

Oct 23-27, 2011

AAPS
Washington, D.C.

Oct 25-27, 2011

CPhI Worldwide
Frankfurt

Nov 30-Dec 2, 2011

CPhI India
Mumbai

PREVIEW

Kollidon® grades: new packaging for even higher functionality

The latest innovation for the Kollidon product line is a new composition of packaging material which reduces any negative impact of the environment on the product quality.

This has led to a new standard for soluble povidone grades on the market: the new package of Kollidon allows BASF to supply products that meet compendial specifications even after many years of storage.

Find out more about the the reduced formation of peroxides in soluble povidones, resulting in a highly functional binder, in the next ExAct edition. You will see several advantages which can be transferred directly into real benefits for drug manufacturers.

CONTACT

What opportunities can we open up for you?

Would you like to discuss a particular challenge or product in detail? Or do you have any questions? Simply call or e-mail us. We will be glad to help.

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