TABLETING →
DIRECT COMPRESSION →
CO-PROCESSED LACTOSE

Technical brochure
RetaLac®

MEGGLE
EXCIPIENTS & TECHNOLOGY

MEGGLE's co-processed hypromellose lactose excipient (4000 mPa·s) for direct compression: RetaLac®

General information

Modified release applications continue to be a development strategy for the global pharmaceutical industry. Products nearing patent expiration are candidates for product life-cycle management using this approach; however, other benefits such as improved efficacy through more structured active pharmaceutical ingredient (API) release profiles, cost effective product manufacture, and improved patient compliance exist. With various options available for API modified release delivery, hypromellose (hydroxypropyl methylcellulose or HPMC) has historically been the excipient of choice to form hydrophilic matrices [1]. The basic structure of the commonly known methyl and hydroxypropyl mixed ether of cellulose is illustrated in **figure 1**.

In the hypromellose chemical structure diagram (shown below), the substituent "R" may represent a hydrogen atom, or the methoxy or hydroxypropyl functional groups, which when substituted onto the cellulose backbone, form the hypromellose structure. The degree of substitution as well as the molecular weight affect the physiochemical properties. To define the level of methoxy or hydroxypropyl degree of substitution, the major global pharmacopoeias (Ph. Eur., USP-NF, and JP) differ with four defined hypromellose species (1828, 2208, 2906, 2910), classified according to their relative degree of substitution: the first two digits indicate the percentage of methoxy groups, while the subsequent two digits represent the percentage of hydroxypropyl groups. Exacting limits for the degree of substitution have been established. In addition, there is a method to determine average chain length by evaluation of apparent viscosity. Hypromellose grade 2208, with a nominal viscosity of roughly 4000 mPa·s (2% solution, 20 °C), may be regarded as a very frequently used grade in modified release formulation development and manufacture.

Although hypromellose offers broad flexibility in tailoring API release due to differing substitution levels and molecular weights, processability is generally limited to traditional labour, time, and energy intensive wet granulation manufacturing methods.

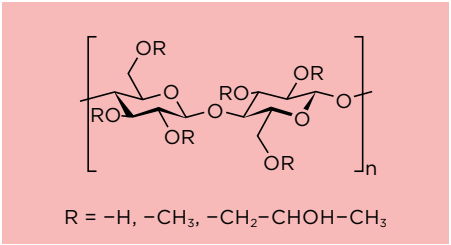


Figure 1: *Basic chemical structure of hypromellose. The substituent R represents either a hydrogen atom, a methyl, or a hydroxypropyl group. The corresponding physicochemical properties are strongly affected by content and distribution of substitution, as well as the molecular weight (n).*

Direct compression (DC) is the prominent method in the pharmaceutical industry. DC offers many benefits, including, but not limited to, enhanced chemical stability and cost containment [2]. With requirements for increased functional performance (such as improved powder flow and content uniformity) growing steadily, new excipients are needed. Given the physical characteristics that fine, fibered cellulose derivatives possess, it is not surprising that hypromellose does not satisfy every development or production need. Although hypromellose manufacturers have introduced improvements such as agglomeration, the material still exhibits insufficient performance overall. Issues such as segregation, low densities, poor powder flow, and reduced compactability limit its elegant use in DC applications.

Recently, through a proprietary agglomeration process, a co-processed composition comprising hypromellose and lactose, offering suitable alternatives to overcome these limitations, was developed. Possessing enhanced functional performance, the new excipient offers characteristics desired in formulation development and manufacture and may be of significant interest to innovator and generic pharmaceutical companies.

Product description

RetaLac® is the first hypromellose/lactose-based, co-processed excipient specifically designed for DC and dry granulation of modified release formulations.

While a binary composition, RetaLac® is monoparticulate in structure, having hypromellose and lactose in each particle. It is characterized by superior functional performance such as improved flow and blendability. Additionally, due to its monoparticulate structure, RetaLac® possesses both plastic and brittle fracture deformation characteristics, enhancing compactability in DC compared to traditional wet granulated and physical admixtures of the parent ingredients.

API release is controlled predominately by diffusion through the hydrophilic matrix, and is most robust in the range of pH 1.0 to 7.4. To minimize development time, API dissolution prediction as a function of tablet geometry is possible. This is aided by RetaLac®'s dramatic improvement in wettability compared to HPMC alone or in traditional wet granulations and simple admixtures.

Regulatory & quality information

The raw materials used to produce RetaLac® 80, alpha-lactose monohydrate and hypromellose, comply with Ph. Eur., USP-NF, and JP monograph requirements. Since no chemical modifications result during co-processing and individual chemical identities are maintained, RetaLac® can be considered as a physical blend of alpha-lactose monohydrate and hypromellose [3].

A RetaLac® drug master file (DMF) is available during FDA (Food and Drug Administration) drug product submission review and approval. Specifications and regulatory documents can be downloaded from www.meggle-pharma.com.

Our pharma-dedicated production facility in Wasserburg, Germany is certified according to DIN ISO 9001:2015 and has implemented GMP according to the Joint IPEC-PQG (Good Manufacturing Practices Guide for Pharmaceutical Excipients) and USP-NF General Chapter <1078> GOOD MANUFACTURING PRACTICES FOR BULK PHARMACEUTICAL EXCIPIENTS. MEGGLE has been an EXCiPACT™-certified excipient manufacturer and supplier since 2014.

The Wasserburg facility demonstrates MEGGLE's complete lactose production capability range, including sieving, milling, agglomeration, spray-drying, and co-processing. Additionally MEGGLE is a member of IPEC (International Pharmaceutical Excipients Council).

MEGGLE invests considerably in the sustainability of raw material sourcing, production standards, and efficiency. We are actively engaged in environmental protection. In order to guarantee the quality of our products, our commitment and adherence to established pharmaceutical standards remains is our highest priority.

Application

Co-processed excipients are innovative, superior products exhibiting unique functional characteristics not achieved through simple blending. The following chart provides recommended areas of application.

international excipients certification

Areas of application					
Co-processed lactose					
	Capsules	Tablets (modified release application)		Others	
	Capsule filling	Direct compression (suitable for multi-layer and mini tablets as well)	Dry granulation	Preparation of aqueous HPMC formulations	Extrusion, spheronization
RetaLac®	+	+	+	+	+
+ = Highly suitable					

BENEFITS

RetaLac®

- Direct compression of modified release formulations
- Superior processability compared to corresponding wet granulated and physical admixture of parent ingredients
- Dissolution can be quantitatively predicted as a function of tablet geometry
- Drug release from hydrophilc matrix is governed by diffusion and is very robust within a pH range of 1.0–7.4
- RetaLac®, exhibiting monoparticulate structure, provides plastic deformation behavior and brittle fracture as well, which leads to overall improved compactibility
- Dramatic improvement in wettability compared to pure hypromellose

Particle size distribution (PSD)

Figure 2 shows typical laser diffraction particle size distribution analysis for RetaLac®, MEGGLE's co-processed hypromellose/ lactose excipient. Results show a typical x_{10}, x_{50} and x_{90} of 55, 150 and 260 µm, respectively.

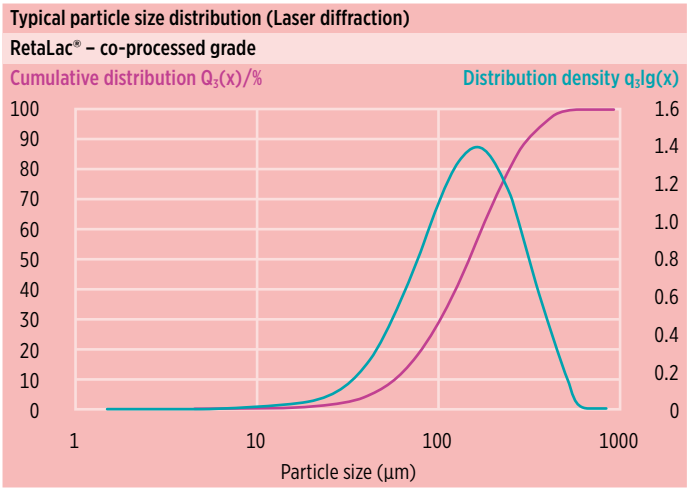


Figure 2: *Typical cumulative PSD and distribution density of MEGGLE's co-processed excipient, RetaLac®, with a typical x_{10}, x_{50} and x_{90} of 55, 150 and 260 µm, respectively. Analyzed by Sympatec®/ Helos & Rodos particle size analyzer.*

Isotherms

Due to the hypromellose content, RetaLac® shows a tendency to absorb moisture at elevated relative humidity, as shown by dynamic vapor sorption **(figure 3)**. Interrestingly, the equivalent physical admixture maintains a largely similar behaviour to RetaLac® (not shown).

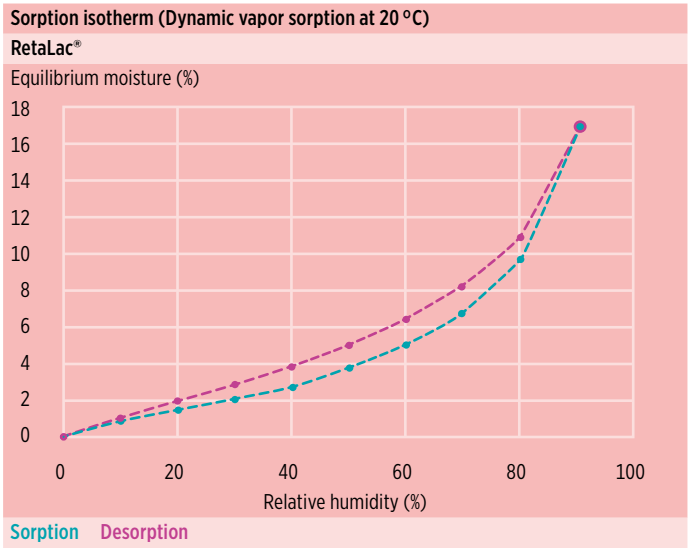


Figure 3: *Water-absorption-desorption isotherm (20 °C) of RetaLac®. Water-uptake is mainly driven by hypromellose and proportional to the moisture of the surrounding atmosphere. Co-processed RetaLac® and its corresponding physical admixture show a similar behavior. Analysis performed by SPSx-1µ moisture sorption test system.*

Batch-to-batch consistency

Batch-to-batch consistency for all lactose products can be attributed to MEGGLE's long history and experience in lactose manufacture, and broad technical expertise. Constant in-process and final product testing ensures consistency and quality.

Scanning electron micrograph (SEM)

MEGGLE's co-processed excipient, RetaLac®, appears as a white, or almost white, odorless powder, which is freely flowing and partially soluble in cold water. It comprises equal parts of hypromellose (type 2208, a.k.a. K-type) with a nominal viscosity of 4000 mPa·s, together with a milled alpha-lactose monohydrate grade, both of compendial quality. A specialized spray-agglomeration process generates textured, highly structured particles, binary in composition, and monoparticulate in nature with x_{50} in the range of many directly compressable excipients, 100 µm to 200 µm.

SEM image of RetaLac® demonstrates agglomeration of crystalline alpha-lactose monohydrate and fibrous hypromellose into porous, spheroidal particles, desired for formulation development and manufacture. The individual components, lactose and hypromellose, cannot be separated by physical means. Flow and compaction properties of co-processed RetaLac® outperform the simple physical admixture.

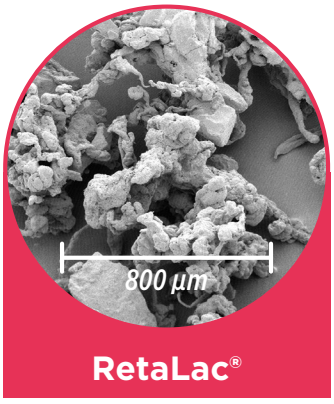


Figure 4: *SEM image of RetaLac® particles exhibits morphological properties desired for formulation development and manufacture. Hypromellose is agglomerated with crystalline alpha-lactose monohydrate resulting into a porous, spheroidal particle having excellent flow and compaction properties, Zeiss Ultra 55 FESEM (U = 5 kV; Au/Pd sputtered).*

Functional related characteristics

Powder flow

Flow is an important consideration in many preparations as it may impact critical formulation attributes like tablet weight uniformity as well as tablet production rates. Various methods are commonly used for quantification: angle of repose, density derived factors, volume or/and mass flow, or flowability index using a FlowRatex® [4]. For data see **figures 5 and 6**.

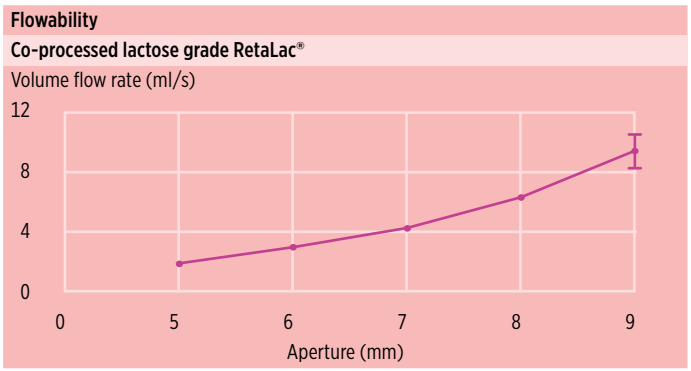


Figure 5: *Volume flow rate (ml/s) as a function of aperture size (mm diameter) for MEGGLE's co-processed RetaLac® analyzed by a FlowRatex®.*

Specific surface

While RetaLac® exhibits a rough, highly textured structure, it exhibits a relatively low BET surface value **(figure 6)**. Co-processing the parent ingredients reduces specific surface values in comparison to the corresponding physical admixture within a factor of 0.5.

Flowability

Co-processed lactose

	Angle of repose (°)	Density bulk (g/l)	Density tapped (g/l)	Hausner ratio	Carr's index (%)	BET surface (m^2/g)
RetaLac®	36	340	460	1.35	26.09	0.27

Figure 6: *Typical powder functional values for co-processed RetaLac®. All methods were performed according to compendial standards. BET surface area and pore volume measurements were performed by an instrumented Quantachrome Autosorb®-3 (adsorbent Kr_2, outgas time and temperature: 7 hrs at 50 °C, in vacuo).*

Drug release kinetics

The overall drug release mechanism of hypromellose-based pharmaceutical formulations strongly depends on composition, API solubility, excipient(s) and polymer(s) used, as well as tablet geometry [5]. Release profiles of three model APIs having different solubilities were evaluated at varying initial drug loads (0–60 % theophylline, paracetamol and diprophylline) upon dissolution testing in two media, 0.1 M HCl and a phosphate buffer system **(figure 7)**. Impact of initial drug content on absolute drug release is shown for theophylline. A monotonic increase of absolute amounts of drug is observed, independent of the dissolution medium **(figure 8a)**.

Composition

Drug release kinetics

Drug content (%)	5	10	20	30	40*	50*	60*
Drug (g)	5.0	10.0	20.0	30.0	40.0	50.0	60.0
RetaLac® (g)	94.5	89.5	79.5	69.5	58.5	48.5	38.5
Mg stearate (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5

* Addition of 1 % fumed silica

Figure 7: *Composition of investigated systems comprised of MEGGLE's co-processed lactose excipient RetaLac® and the following drugs: theophylline, paracetamol and diprophylline. Tablet preparation (single-station tablet press Korsch; Berlin, using flat-faced punches) was performed by DC at comparable hardness (60–70 N), constant diameter (11.3 mm) and tablet height (2.4 mm). Drug release was analyzed using USP 35 dissolution apparatus (paddle method, 80 rpm, 37 °C; Sotax®, Basel, Switzerland) in 900 ml 0.1 M HCl or phosphate buffer, pH 7.4. All experiments were conducted in triplicate.*

Drug release profile

Impact of initial drug content

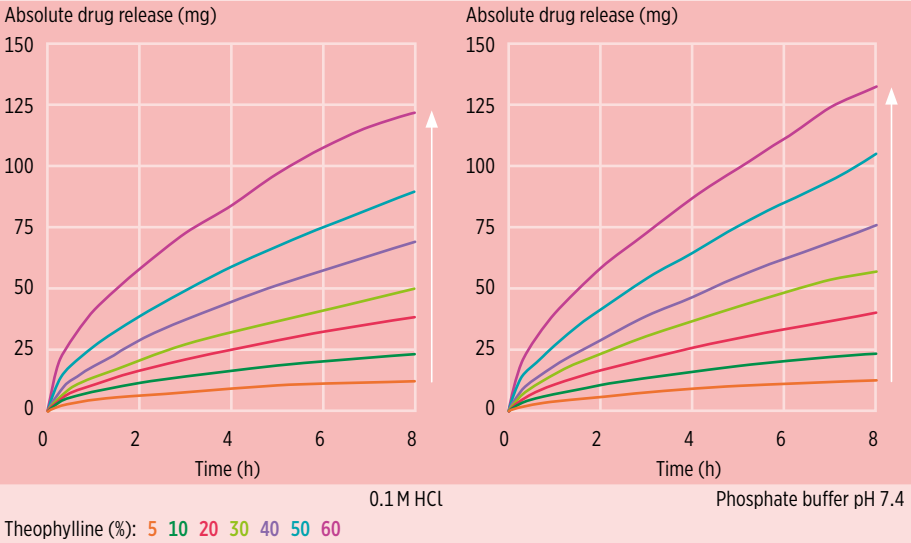


Figure 8a: *Effects of the initial theophylline content (as indicated in the diagrams) on the* ***absolute*** *drug release from RetaLac®-based tablets upon exposure to buffer systems 0.1 M HCl and phosphate buffer, pH 7.4 (Initial tablet height 2.4 mm and diameter 11.3 mm).*

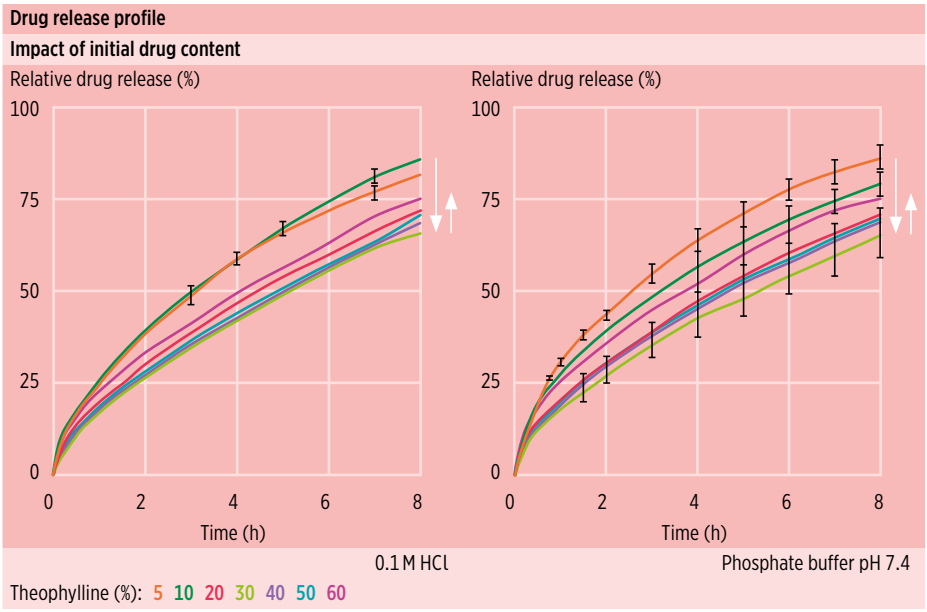


Figure 8b: *Effects of the initial theophylline content on the* ***relative*** *drug release from RetaLac®-based tablets upon exposure to buffer system 0.1 M HCl and phosphate buffer, pH 7.4 (Initial tablet height 2.4 mm and diameter 11.3 mm).*

However, the impact of the initial drug content on **relative** drug release provides an insight into phenomena during drug dissolution. Relative drug release decreases first and starts to increase again at drug loads of greater than 40 % theophylline. A possible explanation for this observed decrease could be that for poorly water-soluble drugs, the amount within the tablet could exceed the amount of dissolved drug, thus not being available for diffusion. On the contrary, at higher drug loads (> 40 % theophylline) porosity of the matrix increases, leading to increased absolute drug transfers **(figure 8b)**.

This effect is significantly less pronounced for paracetamol and diprophylline. A representative overview of absolute and relative release kinetics at various initial drug contents is depicted in **figures 9a and 9b**.

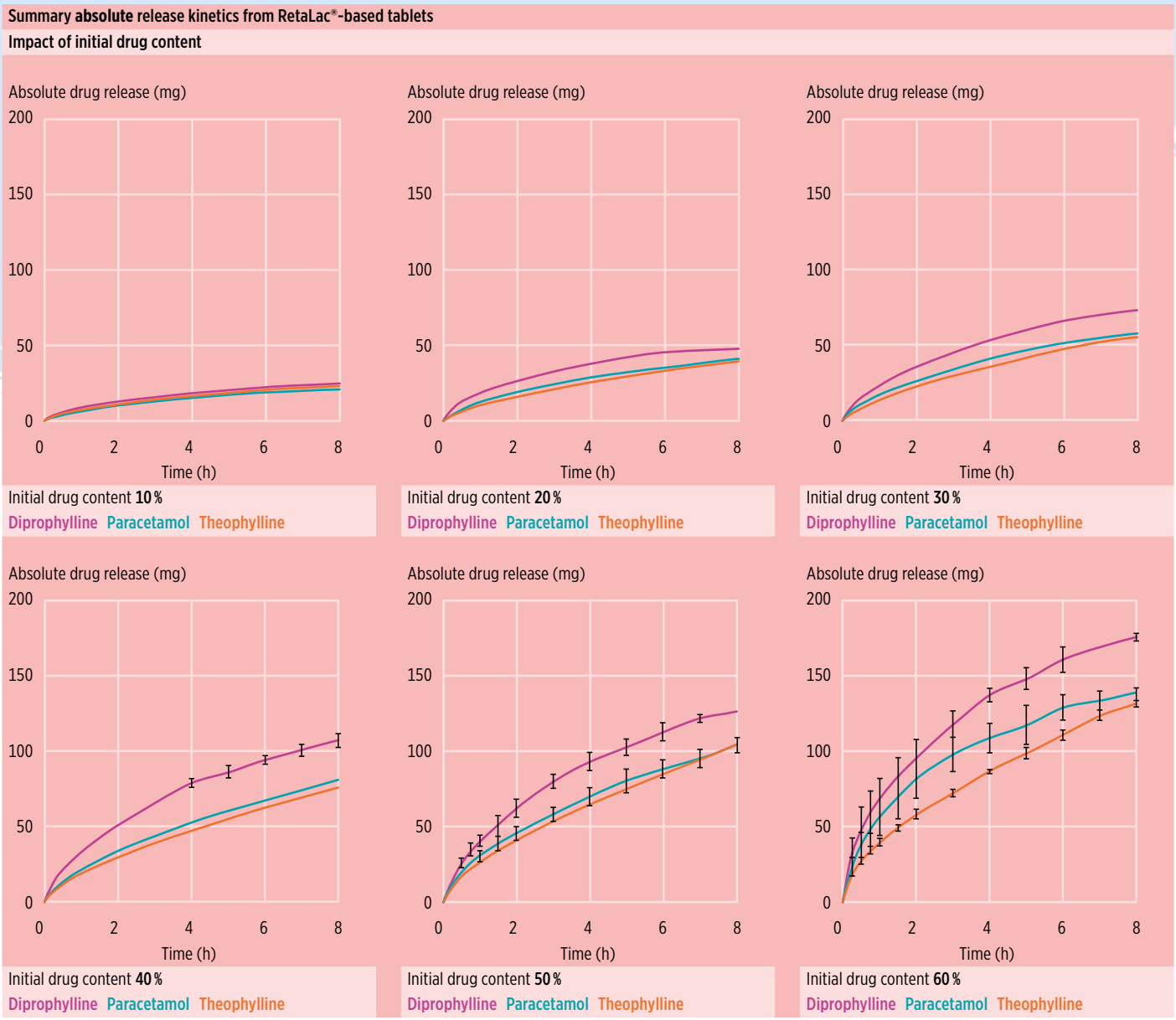


Figure 9a: *Effects of the type of drug (theophylline, paracetamol and diprophylline) on the* ***absolute*** *release kinetics from RetaLac®-based tablets with different initial drug content upon exposure to 0.1 M HCl buffer system, pH 7.4 (Initial tablet height: 2.4 mm and diameter 11.3 mm). In not all cases error bars are visible.*

Since the introduction of modified release formulations, sustainable attempts have been made to theoretically predict drug release profiles [6]. The basic intent is to support rational development and minimize excessive experimentation in practical formulation development efforts, and thus help reduce cost. For RetaLac®-based tablets, various approaches of varying complexity have been applied: (i) Fick's second law of diffusion of a cylindrical device was used as a predictive model, assuming uniform drug distribution, radial and axial mass transport and perfect sink conditions. (ii) A complex numerical analysis taking additionally limited drug solubility into account, and (iii) an overly simplified early-time approximation. There was a positive correlation of theory and experimental data in all cases, allowing significant simplifications in predicting drug release design of RetaLac®, exclusively [7, 8]. For the first time, a very simple approximation may be used for quantitative prediction of design of hypromellose/lactose tablets on the release of drugs exhibiting very different water solubility. The reason for this unexpected short cut may lie in the dramatic increase of wettability of hypromellose due to co-processing with lactose. High water content (primordial for drug mobility) is achieved within a relatively short period of time and remains "about constant," independent of drug load. This may be reflected in constant diffusivities. From a practical point of view, very simple equations may be used for product optimization and reduction in development time **(figure 10)**.

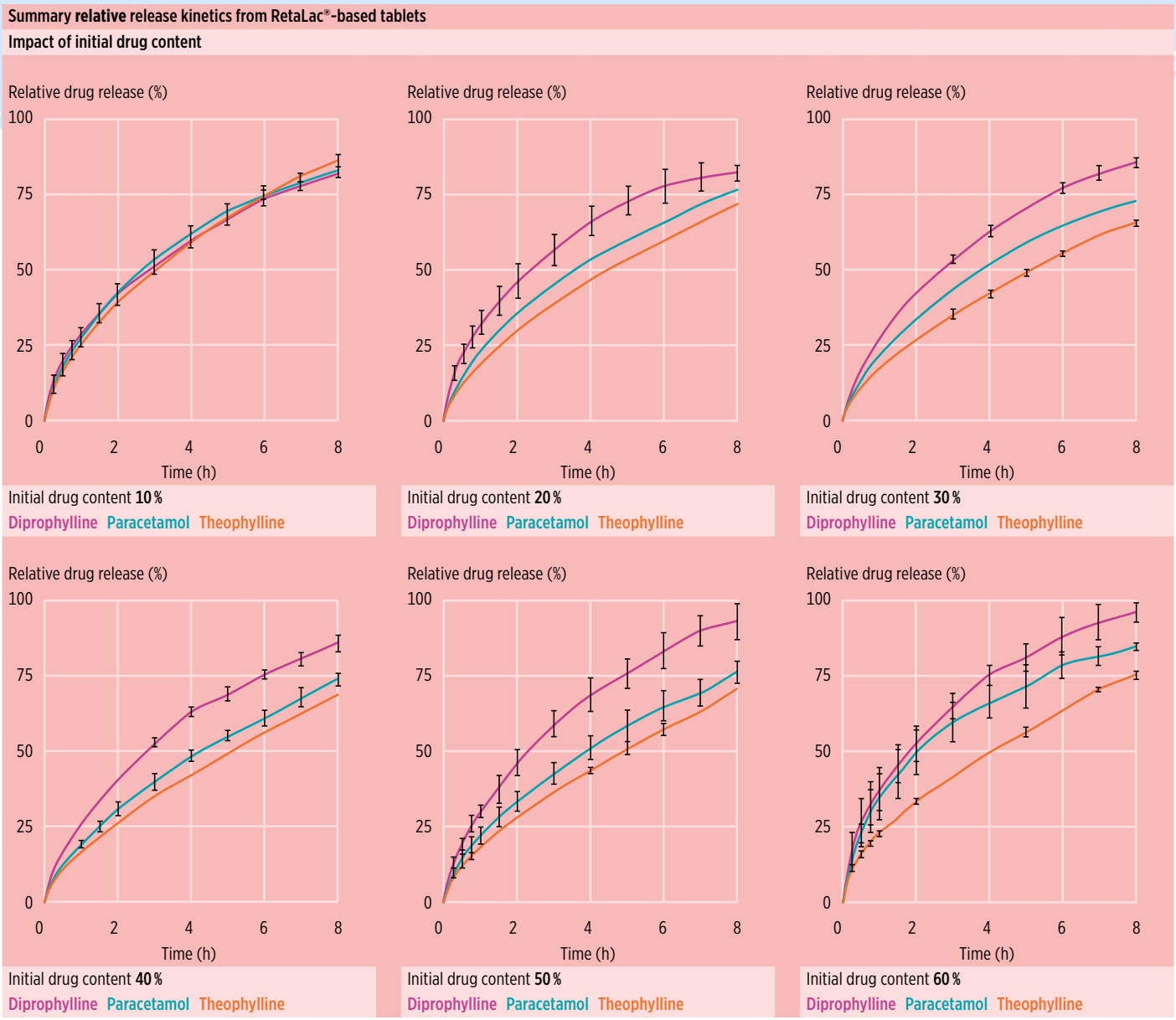


Figure 9b: *Effects of the type of drug (theophylline, paracetamol and diprophylline) on the* ***relative*** *release kinetics from RetaLac®-based tablets with different initial drug content upon exposure to 0.1 M HCl buffer system, pH 7.4 (Initial tablet height: 2.4 mm and diameter 11.3 mm). In not all cases error bars are visible.*

$$\frac{M_t}{M_\infty} = 4\sqrt{\frac{Dt}{\pi R^2}} - \frac{Dt}{R^2}$$

Figure 10: *A simple approximation may be used to predict drug release of RetaLac®-based formulations assuming cylindrical devices, where M_t stands for absolute cumulative amounts of drug released at time t and M_∞ for absolute cumulative amounts of drug released at infinity. D denotes the diffusivity and R stands for the radius of the cylindrical tablet. Only radial diffusion is considered [7, 8].*

Compendial requirements

RetaLac® has been designed to enable DC of hypromellose-based matrix formulations. However, various pharmacopoeias make specific demands on basic tablet properties, such as drug content uniformity, mass uniformity, or friability.

RetaLac®-based formulations easily fulfill the criteria of Ph. Eur. with regard to drug content and tablet mass, independent from drug load. According to method of analysis "uniformity of content of single-dose preparations (2.9.6.)", individual drug contents of ten tablets with an overall weight >250 mg should be between 85 % and 115 % of the average content.

Results for RetaLac®-based formulations with different initial theophylline loads are shown in **figure 11** and had been found in full conformity to compendial requirements. None of the samples showed an individual content outside of the 85–115 % requirement, while relative standard deviation (RSD) did not exceed 6.54 %.

Likewise, the test on "uniformity of mass of single-dose preparations" had been determined according to Ph. Eur. (2.9.5.) and should not exceed ± 5 % of the mean tablet mass. The results of initial drug loads between 10 % and 60 % theophylline content indicated conformity and no single drug load exceeded a RSD of 3 % (not shown).

Finally, friability of tablets should not exceed 1%. A gravimetric test showed maximum values not exceeding 0.5 % at maximum drug load of 60 % theophylline.

Compendial requirements						
Uniformity of content of single-dose preparations						
Initial drug loading (%)	10	20	30	40	50	60
Tablet Drug content (mg)						
#1	27.00	55.96	86.52	109.97	147.74	176.97
#2	27.73	55.05	86.86	110.17	147.67	171.89
#3	27.17	55.41	86.66	110.07	149.72	176.60
#4	30.21	54.95	74.55	100.41	128.55	162.58
#5	30.04	53.77	72.61	107.31	127.2	165.43
#6	29.27	54.29	82.23	100.37	138.48	160.98
#7	28.18	52.83	88.46	117.17	149.25	179.65
#8	26.66	54.52	79.68	111.09	147.06	165.29
#9	27.34	57.73	79.01	118.69	142.83	172.55
#10	28.52	57.90	77.32	118.35	147.56	169.85
mean	**28.21**	**55.24**	**81.39**	**110.36**	**142.61**	**170.18**
sd	1.20	1.53	5.33	6.23	8.02	6.12
RSD (%)	4.25	2.76	6.54	5.64	5.62	3.59
min	26.66	52.83	72.61	100.37	127.20	160.98
max	30.21	57.90	88.46	118.69	149.72	179.65
85 % mean	23.98	46.95	69.18	93.81	121.22	144.65
115 % mean	31.05	63.53	93.60	126.91	164.00	195.71
number of tablets not conform	0.00	0.00	0.00	0.00	0.00	0.00
	↓	↓	↓	↓	↓	↓
	conform					

Figure 11: *Individual results of the test "uniformity of content of single-dose preparations, Ph. Eur. (2.9.6.)". None of the samples with initial drug load between 10 % and 60 % theophylline showed an individual value outside the 85–115 % drug content uniformity requirement. RSD did not exceed 6.54 %.*

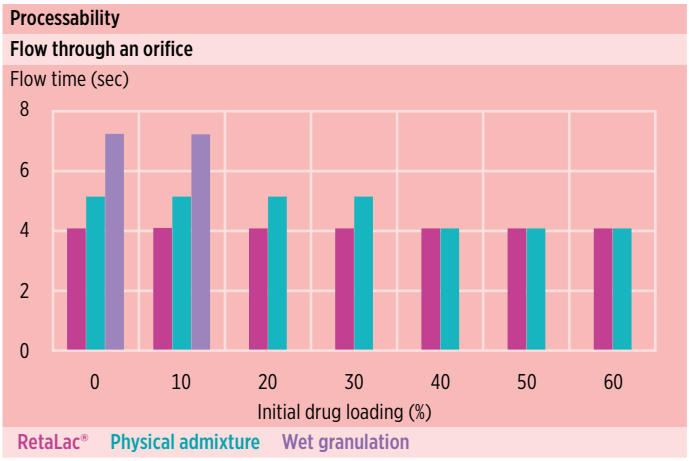


Figure 12: *Effect of preparation method on the propanalol HCl powder/granules flow time. The wet granulated form (only possible up to 10 % drug load) demonstrated slowest flow times, followed by the physical admixture and RetaLac®. Flow time was measured using a standardized funnel.*

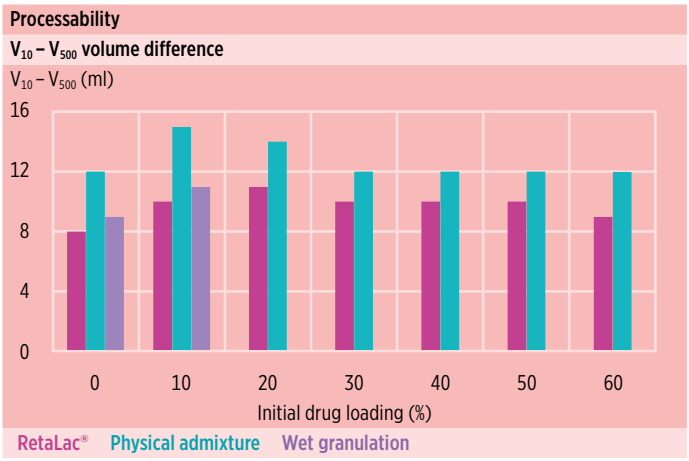


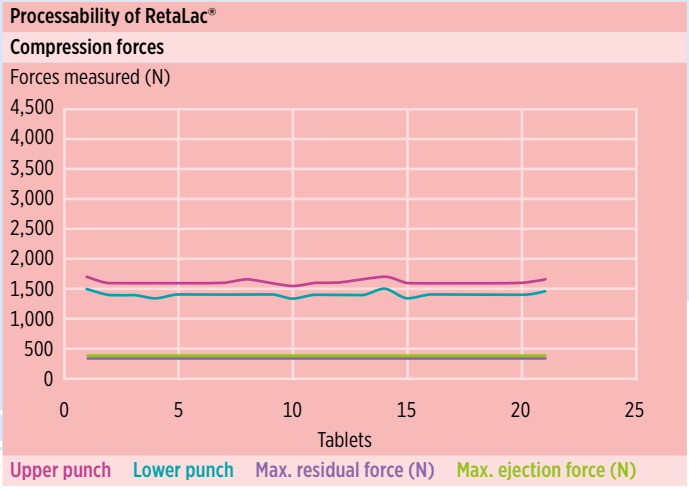
Figure 13: *Effect of preparation method on the $V_{10} - V_{500}$ volume difference of the powder/granules. Compressability was measured with a tap volumeter. The apparent volumes were recorded after 10 and 500 taps ($V_{10} - V_{500}$). RetaLac®-based powder blends showed lowest $V_{10} - V_{500}$ values.*

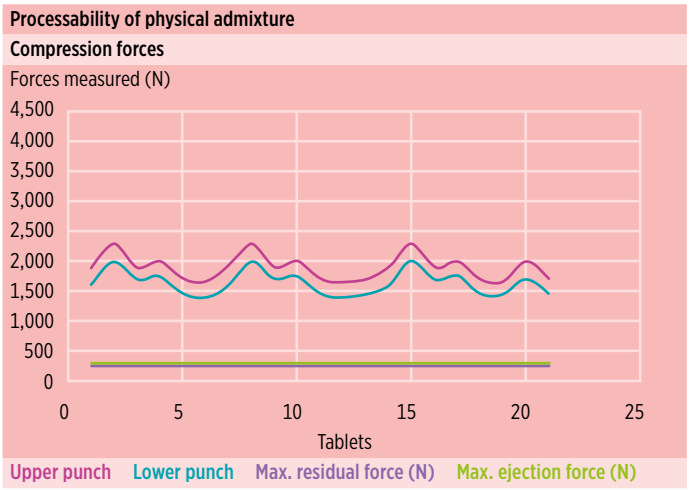
Processability

Excipients produced via co-processing are supposed to show better functionality compared to the physical mixture with the same components. This could be shown for RetaLac®. In a model formulation employing Propranolol HCl as active pharmaceutical ingredient, RetaLac® was compared against a physical blend of a special, agglomerate hypromellose and agglomerated lactose and against a formulation prepared via traditional wet granulation using ethanol.

RetaLac® shows superior performance to physical admixture and wet granulated formulation. Co-processed excipients should exhibit superior performance in comparison to the corresponding physical admixture. In a model formulation containing propranolol HCl, RetaLac® was compared to a physical admixture comprised of a special, agglomerated DC-grade of hypromellose and a traditional ethanol-based wet granulation process. As powder flow is a primary function in DC, flow time was evaluated using a standardized funnel at various initial drug loadings. RetaLac®-based blends show the shortest flow times, followed by blends comprising a physical admixture. Interestingly, it was not possible to supply wet-granulated preparations of drug loads higher than 10 % due to coarse granules exhibiting high weight and hardness variation. Flow time of RetaLac®-based blends was not affected by increasing drug loads **(figure 12)**.

To evaluate the impact of compactability and/or segregation on bulk pharmaceutical powder blends, a tap volumeter is often used. Powder blend volumes are measured after 10 and 500 taps (V_{10} and V_{500}), respectively. A low $V_{10} - V_{500}$ value may indicate less fluctuation in die filling and thus, more uniform tablet weight and hardness. Difference in volume is recommended to be below 20 ml. Physical admixture comprising hypromellose and lactose and the wet granulated form clearly outvalue RetaLac® in its $V_{10} - V_{500}$ magnitudes, independent of the initial drug load. Granules from wet granulation were found in between, showing slightly higher results than RetaLac® **(figure 13)**.





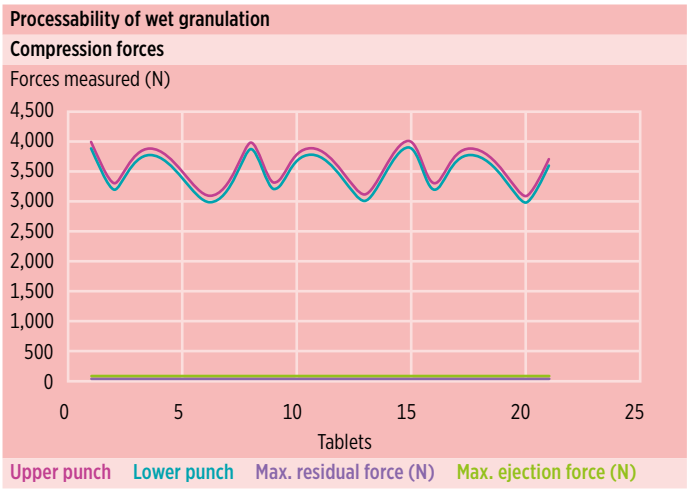


Figure 14: *Maximum compression force measured by upper (purple), lower (mint green) punch and maximum residual (violet) and ejection (grass green) forces for tablets containing 10 % propranolol HCl prepared by three different methods. RetaLac®-based tablets and physical admixture showed overall lowest values in force measurement compared to the wet granulated form. However, co-processed RetaLac® performs most consistently. Cylindrical tablets were prepared by a single-punch tablet press (Korsch EK 0; Berlin) using flat-faced punches.*

To ensure proper and predictable powder compaction, maximum compression forces, as measured by upper and lower punch, as well as residual and ejection force, are routinely monitored. In general, constant forces, within certain limits are preferred during production operations [9]. If a formulation containing 10 % propranolol HCl is prepared by three different methods (RetaLac®-based, physical admixture and wet granulation) resulting powder blends show diverging performance on the tablet press. For RetaLac® and physical admixture, compaction forces are significantly lower compared to wet granulation. Wet granulation and physical admixture show an excessive fluctuation over time. However, co-processed RetaLac® performs consistently **(figure 14)**.

Irrespective of the method of preparation and drug load, all tablets exhibited friability values below 1%. All tablets produced at 10 % initial drug load exhibited similar results. Beyond 10 % drug loading, RetaLac® exhibits superior performance compared to the physical admixture **(figure 15)**.

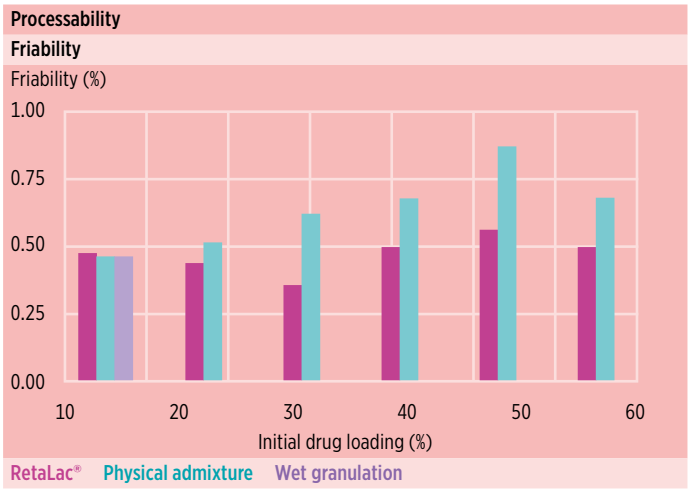


Figure 15: *Effect of preparation method on the friability of tablets based on lactose, hypromellose and propranolol HCl at different initial drug loading.*

Example formulation

Vitamin C in a sustained release formulation

With RetaLac®, it is possible to achieve a simplified sustained release of Vitamin C in excess of 80 % after 8 hours using DC. Flow and density of the powder appeared very good. Compaction force of 200 MPa resulted in a tablet hardness of approximately 100 N with a corresponding friability of 0.5 %. Compaction was performed on an eccentric tablet press using round, flat punches with 11.3 mm in diameter **(figures 16 and 17)**.

Example formulation		
Composition		
Content	**(%)**	**(mg)**
Ascorbic acid 97 %	51.54	257.7
RetaLac®	47.96	239.8
Mg stearate	0.50	2.5
Total	100	500

Figure 16: *Composition of an example application comprising MEGGLE's co-processed hypromellose and lactose excipient RetaLac® and Vitamin C. Tablet preparation was performed by DC (single-punch press Korsch EK 0; Berlin, using flat-faced punches with a diameter of 11.3 mm).*

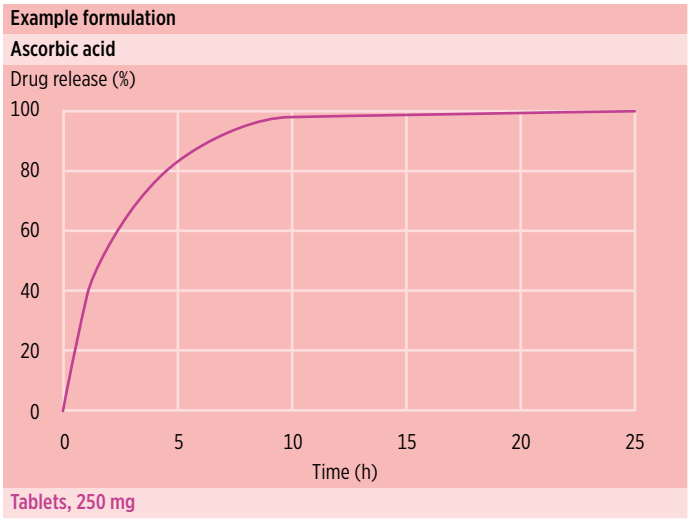


Figure 17: *Relative drug release of Vitamin C from a RetaLac®-based tablet in aqueous medium according to the monograph "Ascorbic acid tablets" (USP-NF). Tablet preparation was performed by DC, all trials were performed sixfold.*

Packaging and shelf life

Packaging material complies with Regulation (EC) No. 1935/2004 and 21 CFR 174, 175, 176, 177 and 178. Stability tests have been performed according to ICH guidelines and an ongoing stability program is implemented. **Figure 18** provides an overview about packaging size and material, and product shelf life.

Packaging and shelf life			
RetaLac®			
	Size	**Material**	**Shelf life**
RetaLac®	12 kg	Plastic drum with PE-EVOH-PE inliner	24 Months

Figure 18: *Packaging and shelf life of MEGGLE's RetaLac®.*

Literature

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Submitted by

MEGGLE Group Wasserburg
BG Excipients & Technology
Megglestrasse 6 –12
83512 Wasserburg
Germany

Phone +49 8071 73 476
Fax +49 8071 73 320
service.pharma@meggle.de
www.meggle-pharma.com

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