



## ADVANCED APPROACHES FOR DELAYED-RELEASE FORMULATIONS

There is growing awareness of the potential for delayed-release formulations to improve patient compliance and increase therapeutic effect. Maria Montero Mirabet, PhD, Senior Project Manager, Drug Delivery Services, and Brigitte Skalsky, PhD, Senior Director, Scientific Communication, both of Evonik Health Care, review advances in delayed-release technology including advances in enteric-coating applications and the use of pulsatile technology to provide tailored lag times.

Delayed-release formulations continue to be a highly relevant formulation approach. Traditionally, the main focuses have been to protect acid-sensitive drugs against gastric fluid and to safeguard gastric mucosa against aggressive actives. In the future, however, targeted drug delivery will be the major motivator for formulating drugs with delayed-release characteristics.

The potential of delayed-release formulations to improve therapeutic effects is reflected in the number of market authorisations in this area, as listed by the US FDA. Although immediate-release (IR) dosage forms strongly dominate the pharmaceutical market, manufacturers increasingly select modified-release approaches to improve their products. New modified-release products, either as extended or delayed release, can lead to better patient compliance or to improved treatment of diseases with specific therapeutic needs.

As an example, rheumatic arthritis (RA) is associated with high cytokines levels, especially in the early morning.<sup>1</sup> Patients with RA can be treated with the glucocorticoid prednisone. This therapy is highly efficient if the drug plasma concentration matches the circadian rhythm of RA patients.<sup>2</sup>

The first commercial product of prednisone was launched several decades

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ago as an IR tablet. Although the drug itself is powerful, when administered in the evening, the IR tablet does not achieve therapeutic plasma concentration to treat the high level of pro-inflammatory cytokine excretion in the early morning. Several scientific communications reported the efficacy of a delayed-release prednisone formulation, targeting the circadian pattern of inflammatory mediators and thus relieving the morning stiffness of rheumatic patients.<sup>3</sup>

However, not until 2012 did the first commercial prednisone delayed-released product gain approval by the FDA (RAYOS® Delayed-Release Tablets; Horizon Pharma, Dublin, Ireland). According to packaging information, RAYOS® releases the active approximately four hours after intake. Administration in the evening therefore leads to an optimal therapeutic plasma level in the early morning hours. As a result, both patient compliance and therapeutic effect have been improved.



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## ENTERIC COATING TECHNOLOGY

Delayed drug release is commonly achieved by the application of an enteric coating on dosage forms such as tablets, capsules and multiparticulates. The main function of an enteric coating is to confer protection. It might be needed to avoid gastric mucosa irritation when exposed to certain drugs, such as non-steroidal, anti-inflammatory drugs (NSAIDs), or to avoid the degradation of acid-sensitive actives, such as enzymes, peptides or proton pump inhibitors (PPIs) in gastric juice. Protection can be easily provided with the application of polymeric coatings, which build films that are insoluble at acidic pH values. For more than 60 years EUDRAGIT® L 30 D-55, a fully synthetic (meth)acrylic copolymer that is soluble above pH 5.5, has been a widely used coating to confer gastric resistance. The reliable functionality of these coatings is reflected by the huge number of marketed drugs formulated with this EUDRAGIT® polymer. Other than cellulosic ethers, EUDRAGIT® polymers are entirely synthetic and thus provide stable product characteristics in narrow specification ranges, reliable processing and defined dissolution characteristics – thereby supporting the QbD approach.

## ENHANCED DRUG RELEASE AFTER STOMACH TRANSIT

In addition to their protective function, enteric coatings are also applied for the local treatment of intestinal diseases. As an example, duodenal peptic ulcers need to be treated locally against *Helicobacter pylori* with antibiotics like clarithromycin and amoxicillin in combination with acid blockers such as cimetidine or ranitidine. Pharmaceuticals for inflammatory bowel diseases, e.g. budesonide, or gastro-intestinal (GI) lavage, e.g. bisacodyl, also use delayed-release coatings implementing EUDRAGIT® L 30 D-55 to target the small intestine.

Focusing on the right absorption site and overcoming drug dissolution or solubility limitations are crucial for the therapeutic effect of certain drugs. Besides that, variations on GI transit times, ionic composition, viscosity and pH of intestinal fluids can have an influence on the *in vivo* performance of drug products.<sup>4</sup> Such variations in gut physiology are not necessarily mimicked by the compendial *in vitro* dissolution test methods.

Still, for most drugs a release within 30 minutes in buffer medium should be fast enough to ensure therapeutic plasma concentrations. However, there are other active pharmaceutical ingredients (APIs) where potential disintegration prolongations of the dosage form *in vivo* may cause discrepancies to the *in vitro* results and consequently an unforeseen reduced response of the medication.<sup>5</sup>

Especially challenging are poorly permeable drugs (BCS III & IV), such as hydroxychloroquine sulphate, atenolol, metforminhydrochloride or furosemide,<sup>6</sup> and poorly water soluble actives (BCS II), such as the NSAIDs ketoprofen, ibuprofen and oxaprozin. Carvedilol (non-cardioselective beta blocker), ketoconazole (antifungal) or fenofibrate (hypercholesterolemia) actives can also be considered in this context.<sup>7</sup>

The solubility of BCS II drugs can vary with the pH range of the small intestine and according to its buffer capacity. As examples, carvedilol and ketoconazole are weak basic drugs ( $pK_a \geq 6$ ) that show a higher solubility at pH values in the duodenum and proximal jejunum. In particular, carvedilol is reported to be mainly absorbed at the duodenum with an important decrease of the amount of drug absorbed from the jejunum.<sup>7</sup> Thus a rapid dissolution in the proximal small intestine can improve its absorption, and hence its bioavailability.

Besides drug properties, gut physiology and its enzymatic activity can influence the stability of certain drugs. The drug efflux transporter p-glycoprotein (P-gp) plays a significant role in limiting cellular uptake.<sup>8</sup> Drugs used in chemotherapy, immunosuppression, hypertension, allergy,

infection and inflammation are substrates of this transporter which goes along with reduced absorption and permeation of the drugs. Examples reported are aldosterone, cortisol, doxorubicin and verapamil.<sup>9</sup> Furthermore, it is reported that the expression of P-gp progressively increases from the proximal to distal region of the intestine.<sup>10</sup> Hence, targeting such drugs to the upper intestine with a rapid onset of action can avoid the exposure to high levels of P-gp and thus enhance bioavailability.

In collaboration with University College London (London, UK), Evonik has developed a novel double-layer technology marketed under the brand name DuoCoat® (Figure 1a). The system can be applied to both monolithic dosage forms and multiparticulates. It consists of two anionic EUDRAGIT® coating layers. The outer layer is a regular EUDRAGIT® L 30 D-55 enteric coating that protects the formulation during gastric transit and starts to dissolve at pH 5.5 by salt formation of the carboxylic acid groups. The inner layer is another enteric EUDRAGIT® L 30 D-55 coating which has been neutralised by the addition of sodium hydroxide. The degree of neutralisation determines the dissolution speed of the coating. The buffer capacity of the neutralised inner layer and thus drug release can be optimised by the addition of organic acids.<sup>5</sup>

When the DuoCoat® formulation enters the duodenum, the environmental pH value increases and at pH 5.5 the outer EUDRAGIT® coating starts to swell and dissolve. Subsequently, intestinal fluid penetrates into the system and reaches the neutralised inner coating layer.

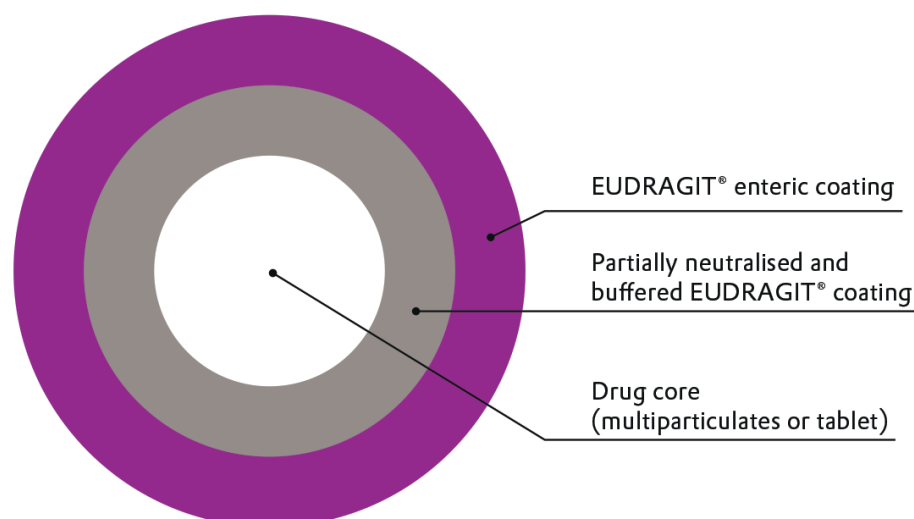


Figure 1a: DuoCoat® formulation design.

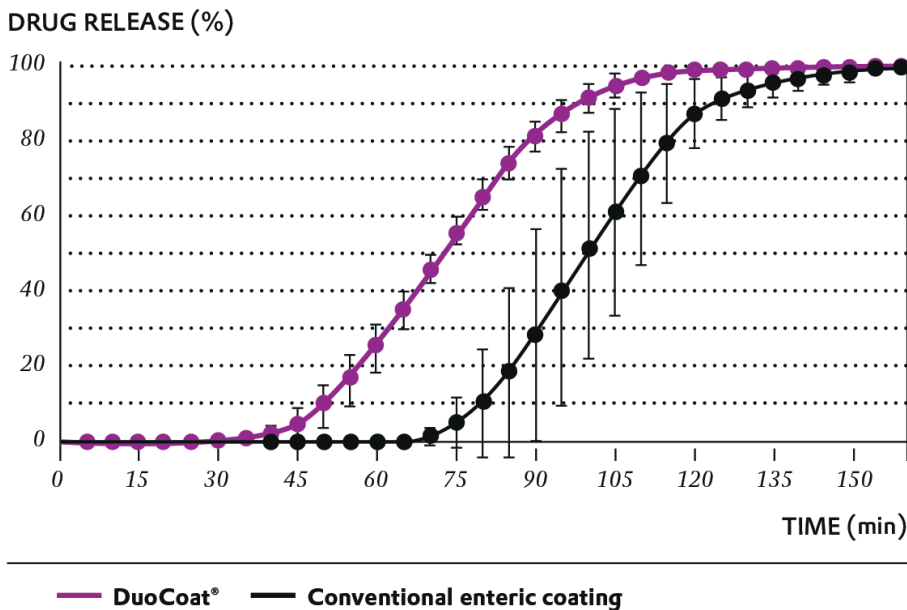


Figure 1b: *In vitro* dissolution profiles (USP II paddle, Hank’s buffer pH 5.6), after two hours in 0.1 N HCl (not shown).

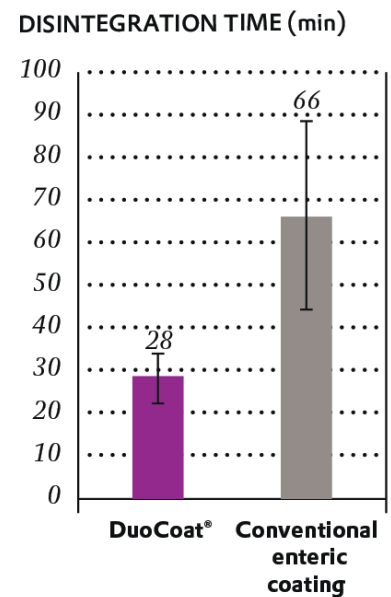


Figure 1c: *In vivo* mean disintegration times of radiolabelled prednisolone formulations (P<0.05).

The inner layer then rapidly dissolves and thus boosts drug release. The accelerated drug release of prednisolone DuoCoat® tablets in comparison with the standard enteric-coated tablets was proven *in vitro* in bio-relevant media<sup>11</sup> (Hank’s buffer pH 5.6) which followed a two-hour incubation period in acidic medium (Figure 1b).

The almost three-times faster disintegration time was confirmed in an *in vivo* study in man (Figure 1c). On average, DuoCoat® tablets disintegrated after 20-35 minutes in the proximal small intestine, and thus were significantly faster than the conventional enteric tablets.<sup>12</sup> By varying the EUDRAGIT® polymer type, specific areas of the GI tract can be targeted with rapid action onset by leveraging the specific dissolution pH values of the polymer used.

### PULSATILE RELEASE WITH TAILORED LAG TIMES

The risk or symptom levels of certain diseases are influenced by the circadian rhythm. Examples are ischaemic heart disease, allergic asthma or arthritis. Medication compliance is often low for such diseases, as night dosing would be required to reduce nocturnal and morning symptoms.

EUDRATEC® MOD, a multiparticulate formulation technology by Evonik, enables high drug plasma levels in the early morning hours while dosing the medication the evening before. Built as a modular system with four different steering tools, pulsatile drug release patterns can be

“The reduction to once-daily dosing confers a major therapeutic benefit for patients who would otherwise need to take medication during the night.”

generated with lag time and slope of the release pattern both tailored to specific therapeutic needs. An inert core is layered with a combination of the API and an organic salt or acid respectively, and then coated with an insoluble but permeable EUDRAGIT® RS/RL layer.

After administration of the formulation and its exposure to GI fluids the permeability of the film coating allows

intestinal fluids to penetrate through the coating and dissolve the organic salt or acid. The resulting anions interact with the cationic polymers and thus increase the permeability of the coating which leads to the intended pulse effect. The thickness and composition of the outer layer control the lag time, whereas the type of organic salt has an impact on the dissolution rate of the drug (Figure 2a).

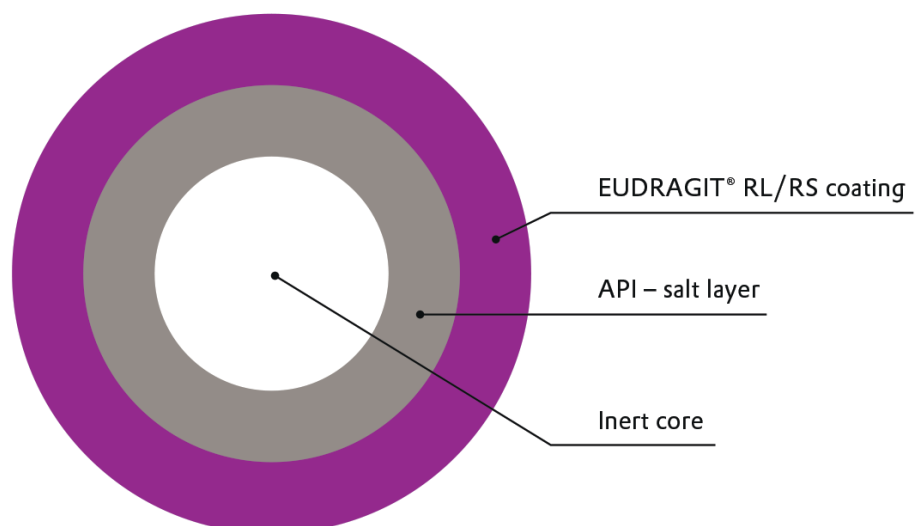


Figure 2a: EUDRATEC® MOD formulation design.

A commercialised example using Evonik's pulsatile technology is Dilzem® (diltiazem hydrochloride prolonged-release hard capsules). Diltiazem hydrochloride is administered to patients who suffer from hypertension and ischaemic heart disease. These patients need a strict medication schedule to reduce morning symptoms and avoid severe health issues. As diltiazem hydrochloride reaches a maximum plasma concentration three to four hours after administration and the risk for severe health issues is highest in the early morning, at least one intake during the night would be required using conventional formulations. Dilzem®, with its pulsatile drug release is able to achieve the highest plasma concentration ( $C_{max}$ ) about 10 hours after dosing (4 hours lag time and 5-6 hours drug release, as shown in Figure 2b) and thus easily provides the therapeutic effect while the patient sleeps. The reduction to once-daily dosing confers a major therapeutic benefit for patients who would otherwise need to take medication during the night.

### ENTERIC FORMULATIONS RESISTANT TO ALCOHOL

Certain patient populations, especially those suffering from strong chronic pain or depression, may tend to consume alcoholic beverages in combination with their medication as a way to cope, contrary to the medical instructions. However, the presence of a hydro-alcoholic solution in the stomach can trigger the dissolution of the delayed-release coating and thus result in "alcohol-induced dose dumping" (ADD). Different from extended-release formulations where ADD might result in high plasma concentrations and thus generate severe side or even lethal effects, with delayed-release formulations ADD consequences are not expected to be as serious. However, loss of the drug effect and hence therapeutic failure, as well as unintended gastric irritation or damage, must be avoided to ensure compliance and successful therapy.

After the Palladone® case received public attention in 2005, the EU EMA and US FDA have provided guidance to avoid alcohol-induced dose dumping of pharmaceuticals. Whereas the EMA regulation is focused on all kinds of modified-release formulations, the FDA has selected individual actives

### MEAN PLASMA CONCENTRATION (ng/mL)

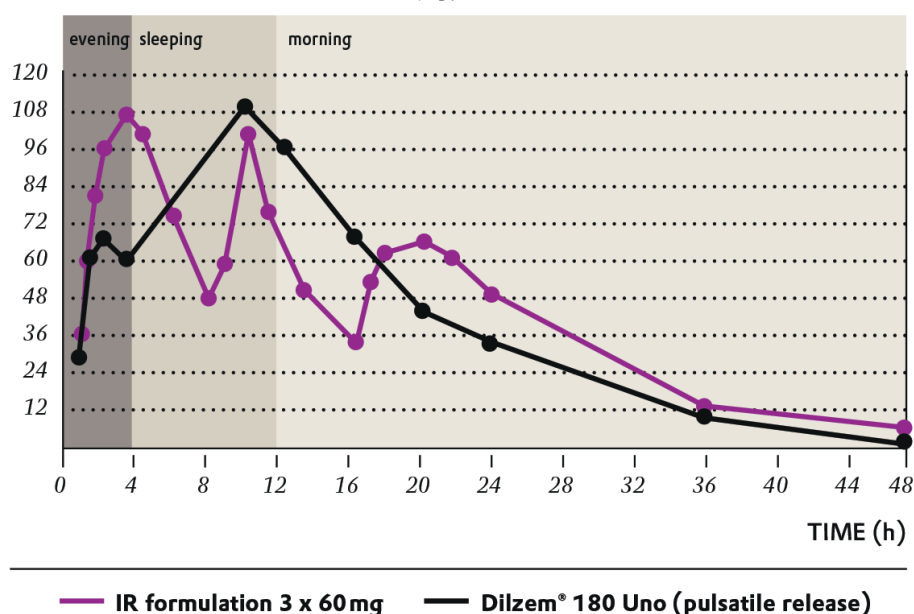


Figure 2b: *In vivo* plasma profiles for Dilzem® 180mg/240mg Uno, product information (Pfizer, 2007).

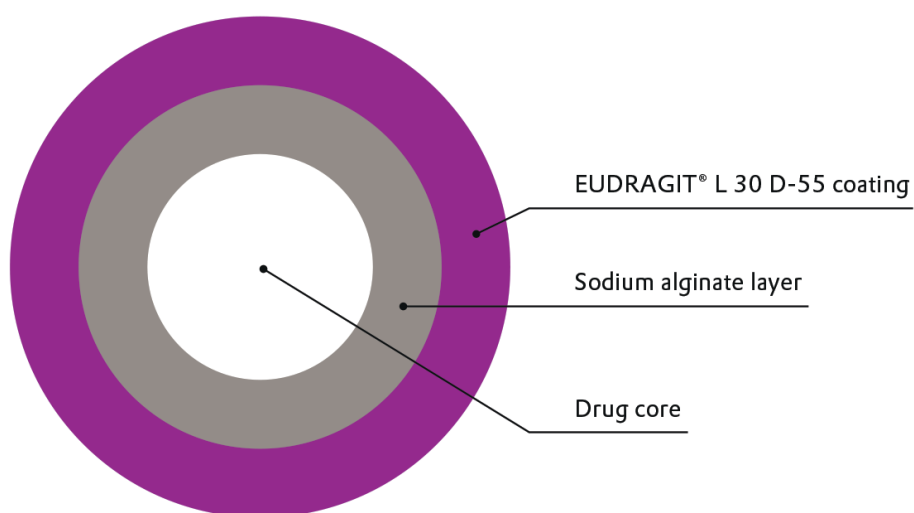


Figure 3a: EUDRATEC® ADD formulation design.

that can become harmful under the ADD effect. Most of these actives are opioids, normally administered as extended-release dosage forms. However, delayed-release products of duloxetine (antidepressive) or dexlansoprazole (PPI) are also required by the FDA to be alcohol deterrent.

EUDRATEC® ADD, a double coating formulation technology, meets the requirements of the FDA regarding ADD. It is capable of generating monolithic and multiparticulate formulations that are resistant to hydro-alcoholic media for over two hours with alcohol concentrations of up to 40%. Multiparticulates are

especially sensitive to ADD because of their higher surface area. EUDRATEC® ADD technology starts from an API core which is coated with a sodium alginate layer, followed by an enteric coating based on EUDRAGIT® L 30 D-55 (Figure 3a). Sodium alginate is a hydrocolloid isolated from marine algae which is soluble in water but insoluble in alcohol. By combining the enteric EUDRAGIT® film with an alginate subcoat the different solubility behaviours of these polymers prevent premature drug release independent from the alcohol concentration (Figure 3b, next page).

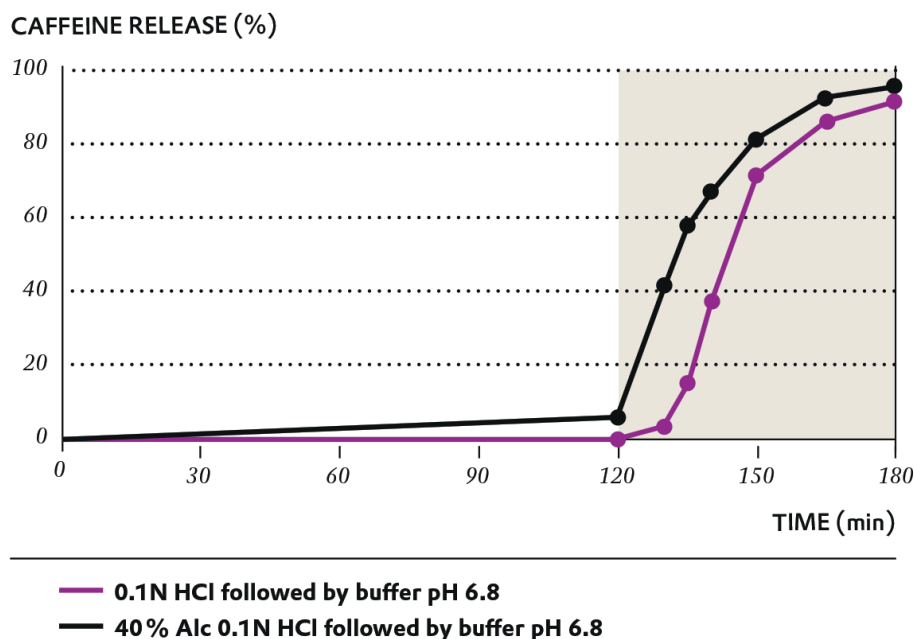


Figure 3b: EUDRATEC® ADD dissolution profiles shown with caffeine pellets.

“Experts can help choose the right excipients for the final application, and professional development services can shorten the way to commercialisation and earlier market launch.”

## CONCLUSION

Overall, the goal and mission of pharmaceutical manufacturers is to produce medicines that offer improved quality of life, fewer hospitalisations and fewer side effects. However, the path to commercialisation is long and challenging. On average it takes at least ten years

from initial discovery to market launch, with average development costs of about \$2.6 billion (£2 billion).<sup>13</sup> Drugs that target the intestinal tract especially need a deeper evaluation of their site-specific bioavailability, stability and safety.

Besides drug properties, unique therapeutic needs such as chronotherapies, or special regulatory requirements need to be considered during development. Hence, intelligent selection of drug delivery approaches become increasingly important. Experts can help choose the right excipients for the final application, and professional development services can shorten the way to commercialisation and earlier market launch.

Evonik, with more than 60 years of experience in the functional applications of EUDRAGIT® polymers, offers its knowledge to support developers and manufacturers and guide them with

formulation development and commercial manufacturing. A partnership with Evonik, either for new developments or for the application of EUDRATEC® technologies can speed up and optimise the road to the market.

## ABOUT THE COMPANY

Evonik, the creative industrial group from Germany, is one of the world leaders in specialty chemicals. Profitable growth and a sustained increase in the value of the company form the heart of Evonik's corporate strategy. Evonik benefits specifically from its innovative prowess and integrated technology platforms. Evonik is active in over 100 countries with more than 34,000 employees. In fiscal 2016 the enterprise generated sales of around €12.7 billion and an operating profit (adjusted EBITDA) of about €2.165 billion. The Nutrition & Care segment is led by Evonik Nutrition & Care GmbH and contributes to fulfilling basic human needs. That includes applications for everyday consumer goods as well as animal nutrition and healthcare. This segment employed about 7,500 employees, and generated sales of around €4.3 billion in 2016.

Evonik's Health Care Business Line serves as a best-in-class strategic partner to the pharmaceutical, medical device and food ingredients industry. The broad product portfolio, deep technical know-how and advanced global capabilities create value by helping our customers reduce risk, enhance quality, improve efficiencies and differentiate their brands. The product and service portfolio includes API contract manufacturing, pharmaceutical excipients, advanced food ingredients, amino acids, cell culture ingredients as well as oral and parenteral drug delivery technologies.

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