The TOPO Granulation Technology Used in the Manufacture of Effervescent Tablets

New, user-friendly dosage forms enable product line extensions

Dr. Detlev Haack • Hermes Arzneimittel GmbH – Division Hermes Pharma, Grosshesselohe (Germany)
Irmgard Gergely • Dr. Gergely & Co., Vienna (Austria)
Christian Metz • bene-Arzneimittel GmbH, Munich (Germany)

Correspondence: Dr. Detlev Haack, Hermes Arzneimittel GmbH – Division Hermes Pharma, Georg-Kalb-Str. 5-8, 82049 Grosshesselohe (Germany)

Summary

The effervescent tablet has proven to be a very user-friendly dosage form for the intake of pharmaceuticals. For the pharmaceutical industry, effervescent tablets represent a means to expand product lines, prolong product life cycles and thus expand market share.
bene-Arzneimittel is a mid-sized, internationally-operating family business focusing on high-quality pharmaceutical products. The company decided to market a 1000 mg peppermint-flavored effervescent tablet as a line extension for its well-known paracetamol brand "ben-u-ron®". Hermes Pharma, a division of Hermes Arzneimittel GmbH, was contracted to develop, manufacture and comply with all regulatory requirements up to market launch. Paracetamol, however, is poorly soluble in water and needs special processing to dissolve completely in water. For this purpose, Hermes Pharma utilized its unique TOPO vacuum granulation technology in which the company has specialized.
This paper describes the benefits of an effervescent paracetamol tablet in contrast to perorally administrated paracetamol tablets and compares the TOPO vacuum granulation technique to conventional manufacturing procedures. The TOPO granulation is based on a surface modification of the citric acid, a so-called "passivation" of the citric acid which is applied to the effervescent mixture during the process. The granulation process can be controlled by repeatedly applying a vacuum during the procedure, thus producing an effervescent tablet which is quickly and completely soluble and at the same time extremely resistant to humidity. In addition, the patented flavor-manufacturing process which produces tailor-made flavors is described as well as subsequent manufacturing steps.

1. Introduction

Effervescent tablets have become a preferred dosage form for applying active pharmaceutical ingredients (APIs), especially for pain relief. Convenient intake, quick onset of action and good tolerance favor this dosage form. The possibilities of providing pharmaceuticals with a specific flavor and API taste masking are important criteria. Because patients take the API in a dissolved form, an unpleasant taste can be immediately detected.

The development of effervescent tablets requires extensive technical expertise on the part of the manufacturer. Specific experience, not only with regard to formulation development, but also regarding taste masking and subsequent manufacturing, is required.

bene-Arzneimittel was looking for a way to differentiate its portfolio with user-friendly medicines and opted for an effervescent tablet as a line extension to its existing paracetamol products established in 1959. Under the brand name ben-u-ron®, the company markets paracetamol in the form of tablets, capsules, oral liquids and suppositories. A ben-u-ron® tablet with 1000 mg of API has

been available since 2007. For its line extension, the company sought a partner with the relevant expertise in product development, registration, manufacturing and quality management, all of which to be provided externally. Hermes Pharma is a specialist in this field. The company is a full-service provider along the entire pharmaceutical value chain delivering solutions for its own branded products as well as for other companies: pharmaceutical development including formulation and analytical services, stability testing, scaling-up, process validation, manufacture, packaging and regulatory services.

A critical success factor included identifying the appropriate manufacturing procedure to completely dissolve the bitter and poorly water-soluble paracetamol and at the same time generate a pleasant taste for the tablet. Hermes Pharma's TOPO vacuum granulation technology proved to be the ideal solution.

2. Benefits of paracetamol effervescent tablets

Paracetamol is a widely-used pain relief drug characterized by a favorable side effects profile. Each year some 65 billion doses of paracetamol are taken worldwide. An effervescent tablet as an extension for the paracetamol product line provides the following benefits for bene-Arzneimittel:

- Effervescent tablets allow the administration of large quantities of API in a single dose. Due to its pleasant taste and easy intake in dissolved form, they are preferred by patients who need medication in large doses over a prolonged period.
- In contrast to conventional formulations, active ingredients in effervescent tablets are more quickly resorbed. The resorption of paracetamol is significantly quicker in an effervescent tablet compared to a conventional tablet. The maximum paracetamol plasma concentration is reached 18 minutes earlier with an effervescent tablet [1].
- As a rule, pH-neutral solutions remain 10 to 20 minutes within the stomach before they arrive at the small intestine [2]. With effervescent tablets the passage through the stomach is accelerated by the buffered solution and the API reaches the small intestine earlier and thus is absorbed earlier [3].
- In addition, irritations caused by tablets which can adhere to the esophagus wall can be avoided by taking effervescent tablets and hence with paracetamol effervescent tablets as well. This is particularly critical for elderly or bedridden patients [2].
- The carbon dioxide released in the solution of the effervescent tablets creates a permeability improvement of the cell membranes and enhances the transport of the API into the cell [4].
- All ingredients in a dissolved paracetamol effervescent tablet are evenly distributed, preventing local concentration peaks.

Based on these benefits, in 2008, bene-Arzneimittel decided to commission the development and manufacture of a 1000 mg paracetamol effervescent tablet which was then successfully launched at the end of 2011.

3. TOPO vacuum granulation versus conventional manufacturing techniques of effervescent tablets

For the production of effervescent tablets various manufacturing methods are in use:

3.1 Conventional manufacturing of effervescent tablets

The most important aspect in the conventional manufacturing of effervescent tablets is the exact control of the relative humidity during the process. If the relative humidity at a temperature of ca. 21 °C stays below 20 percent, various manufacturing procedures for perorally administered tablets are in principle applicable. In this case, direct compression, dry granulation and granulation with, e.g., fluid bed granulators are possible [5].

3.1.1 Direct compression

Direct compression is the best option for low price products. Especially with food supplements, direct compression is the most common procedure. Binders such as dextrose, sorbite and others need to be added in quantities of at least 200 mg per tablet. However, large quantities of sugar alcohols can have adverse effects, e.g., cause diarrhea. Spray drying of acid salts (e.g., monosodium citrate) is an alternative method of direct compression. Effervescent tablets manufactured with this process, however, have low mechanical stability.

For the above mentioned reasons, it is advisable to granulate the components before tabletting and thus produce a stable, high quality product.

3.1.2 Dry granulation

Dry granulation requires the internal addition of water soluble lubricants. The acidic and alkaline components can be processed either together or separately. Dry granulation is generally acceptable for moisture sensitive substances and cost-effective due to high throughput rates. In the manufacture of effervescent tablets this method is used rarely, as effervescent tablets manufactured this way possess low mechanical and chemical stability in comparison to those produced by the granulation procedures described below.

3.1.3 Fluid bed granulation

With fluid bed granulation, the acidic and alkaline components can be granulated together or separately. When granulated separately, the addition of organic solvents is not necessary. However, when granulated together, organic solvents such as isopropanol or ethanol are required to prevent the effervescent reaction

TechnoPharm 2, Nr. 3, 186–191 (2012)

from starting immediately and uncontrolled. Small quantities of water can be added as the granulation and the drying process take place in one step. It is important that only small water quantities are added to be able to control the reaction. The addition of organic solvents entails higher safety requirements in manufacturing and added environmental impact. This leads to higher costs, not to mention the enormous energy expenditure involved in the air conditioning required for this process.

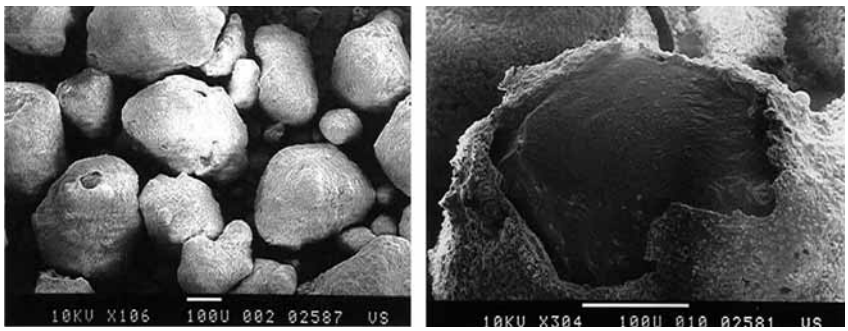

Fig. 1: Scanning electron microscope images of citric acid crystals whose surfaces are coated with a white layer of sodium citrate. On the right is a magnification of the layer development on the crystal.

3.2. The TOPO vacuum granulation

Hermes Pharma was a pioneer in applying TOPO vacuum granulation. This procedure comprises a synthetic granulation to enlarge the particles and increase their stability resulting in a granulate which is easy to tabletize and extremely moisture resistant. By granulating in a vacuum, an uncontrolled chain reaction is prevented. This patented procedure is the basis for all effervescent tablets produced by Hermes Pharma.

3.2.1 TOPO granulation procedure

The TOPO granulation is a process utilized for the manufacture of effervescent granulate containing at least one organic acid (e.g., citric acid) and at least one alkaline carbonate (e.g., sodium hydrogen carbonate). By adding water, the acid dissolves on the surface, the sodium hydrogen carbonate starts a reaction, is fixed, and a granulate forms.

The TOPO technology is based on a surface modification of the citric acid applied in the effervescent mixture. The reactive citric acid is coated with an alkaline carbonate during the process and passivated. Sodium citrate develops on the acid surface (Fig. 1). Depending on the duration of the granulation, about 20 to 30 percent of the citric acid converts into citrates during the reaction, so that the citric acid is coated with layers of citrates a few micrometers in thickness. The proportion of the converted citric acid transformed into citrate can be identified via infrared analytics, titration of the citric acid or semi quantitative determination of the carbon dioxide content after acidification [6].

Only a small amount of water which is needed for granulation is added during the TOPO process. Additional water develops during the chain reaction from the conversion of citric acid with bi-carbonates or carbonates activated through moistening. To control and manage this chain reaction, a vacuum is applied repeatedly for certain periods of time during the granulation process to eliminate the reaction water. During this process step, the vacuum oscillates within the TOPO granulator between a maximum and a minimum value. The number of oscillating movements defines the reaction and the thickness of the moisture resistant surfaces (Fig. 2). This so-called "oscillating vacuum" ("Pendelvakuum") is patented (EP165113 B1).

3.2.2. Benefits of TOPO granulation

TOPO granulation has a number of benefits compared to conventional procedures:

- The product arising from TOPO granulation dissolves quickly in water, as the release of carbon dioxide in water starts immediately. At the same time it is extremely moisture resistant which enables a long shelf life of the fin-

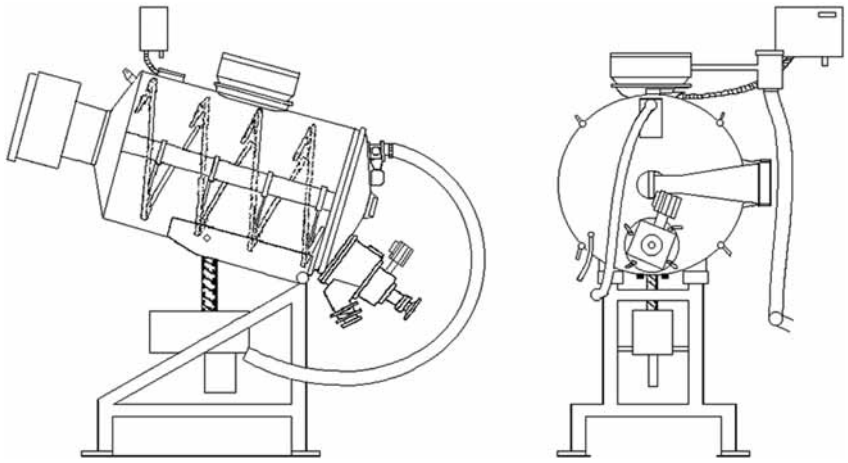

Fig. 2: Schematic illustration of the TOPO granulator: In front is a suction hose where the raw material is sucked into the vessel by the vacuum. At the front is also a rotating sieve used to break up agglomerates at the end of the process. A spiral stirrer used to mix the granulate during the process is located within the vessel. The granulation vessel can be moved from a horizontal position into positions +/- 20° from horizontal. The up and down movement ("swinging") helps to achieve intense blending of the contents when stirring at the same time.

Table 1

API distribution and mass variance of a 1000 mg paracetamol effervescent tablet

			Content uniformity		Mass uniformity	
Batch	Disintegration time (s) at release	Disintegration time (s) after 36 months storage at 25°c	Mean of 10 single tablets (%)	Relative standard deviation (%)	Mean of 10 single tablets (%)	Relative standard deviation (%)
1	136	140	100.6	1.5	100.6	0.4
2	131	127	98.8	0.6	99.2	0.7
3	161	158	99.6	0.9	99.4	0.3

The content uniformity of the paracetamol distribution in an active pharmaceutical ingredient (API) concentration of ca. 23 % (1000 mg API in a tablet with 4.4 g mass) is very homogenous. Relative standard deviations of the content uniformity are below 2 % in all batches and the relative standard deviations of mass uniformity are below 1 %. This was achieved by a narrow distribution of particle sizes with good flow properties within the granulate. Disintegration time is just above 2 minutes and does not change during storage.

ished product and its use also in tropical regions; products for even countries in climatic zones IV+ can be supplied without difficulty.

- The citrate coating facilitates increased stability against acid-sensitive agents. As also alkaline agents can be coated, this benefit is equally effective for agents sensitive to alkali.
- Manufacturing can take place at a relative humidity of 30 percent within the room.
- The atmospheric pressure lowered by the vacuum leads to reduced drying temperatures and shorter drying times. Fill capacities of about 500 kg granulate can generally be dried within 15 minutes.
- TOPO granulation provides a transparent solution of the paracetamol effervescent tablet with very homogenous distribution of the API. As the flow characteristics improve due to enlarged particles and thus also the dosage accuracy, a homogenous distribution of the agent is achieved without additional blending (Table 1), enabling more efficient manufacture.
- The effervescent tablets disintegrate quickly, even if stored over a long period. The quick and transparent dissolution of the paracetamol is achieved by the addition of surface-active agents, as well as the above described granulation of the paracetamol with the effervescent components.
- Due to its excellent thermal stability, the paracetamol can be granulated directly with the other components, without risking chemical degradation of the API. Only small quantities of water are added and no organic solvent so that the procedure is not hazardous to the environment.

4. Flavoring

The taste of an effervescent tablet is of particular importance for compliance. As a result, bene-Arzneimittel chose the flavor peppermint, which is associated with freshness and pleasant relief of headache-related distress.

For developing and manufacturing custom flavors in effervescent tablets a patented procedure is used:

Sugar alcohols like mannitol and sorbitol are introduced into a double jacketed vessel; a melting process is initiated while stirring constantly at 150 to 160 °C. Glucono-delta-lactone (GDL) is added and while blending, the melting process continues until a homogenous melt develops. Subsequently, the liquid flavoring components are blended with a high pressure blender so that micro droplets are formed. The melt is then deposited onto a conveyor belt and solidifies into an amorphous structure. After cooling, the non-crystalline melt is milled into particles of the desired particle size (Fig. 3).

When adding water, the matrix of the sugar alcohols and the GDL is dissolved and fine aroma droplets are released, suspended in water (Fig. 4).

Flavors produced according to this procedure have the following benefits:

- They remain stable over many years, as the aromatic oil droplets are hermetically sealed. Oxidation and other negative impacts can be excluded.
- During the manufacturing process, optimal pH conditions prevail (a small portion of the gluconic acid develops during the process). Thus, a slightly acidic pH value exists within the amorphous melt, so that the liquid components do not degrade by saponification.
- In contrast to preparations without GDL, the procedure does not need inert gas.
- Anti-oxidants, e. g., vitamin E acetate, may be added to extremely sensitive flavors.

Fig. 3: Photo of particles of the non-crystalline, solidified aroma taken with a light microscope.

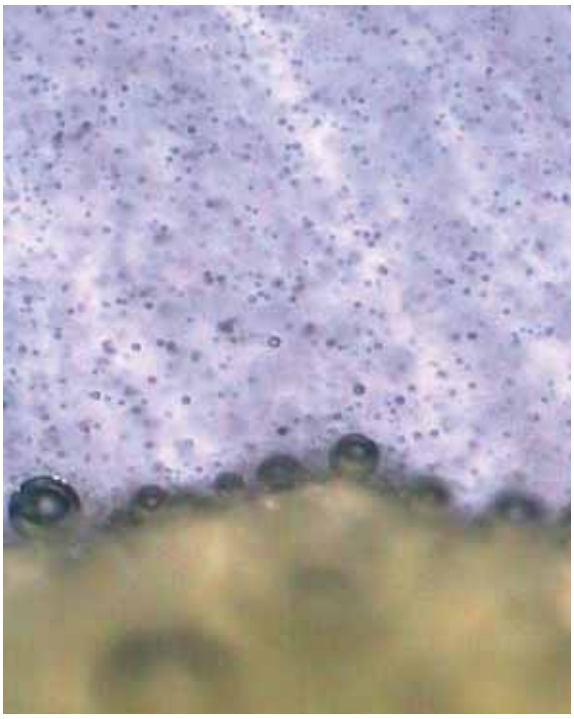

Fig. 4: Photo of the aroma suspended in water taken with a light microscope. The lower part shows the dissolving particle; within the solution (upper part) small suspending aroma droplets are visible.

5. Blending and tabletting

The next manufacturing step involves combining the milled flavorings with the granulate in a tumble blender. This mixture is then processed into effervescent tablets in an automated tablet press and packaged online. For tabletting, magnesium stearate or water soluble lubricants can be added to the granulate. At Hermes Pharma, however, lubricants are added externally, so that only traces of the lubricant adhere onto the tablet's surface. This avoids the development of a film when dissolving the effervescent tablet.

6. Packaging

bene-Arzneimittel markets its effervescent paracetamol tablets in foil strips, a very efficient way of packaging. A modern packaging machine can produce up to 70,000 foil strips per hour. The four-sided sealed foil strips provide the benefit of packing each tablet separately, so that single tablets can be taken along as a daily dose. Foil strips are also ideal for packaging particularly sensitive products, as they seal off air and moisture tightly.

By passivating the citric acid with the TOPO vacuum technology even effervescent tablets with moisture sensitive APIs can be packed in polypropylene tubes. Effervescent tablets in tubes remain stable up to three years after opening (in-use stability) – another advantage of TOPO technology compared to conventional procedures.

Literature

[1] Rygnestad, T., Zahlesn, K. and Samdal FA, Absorption of effervescent paracetamol tablets relative to ordinary paracetamol tablets in healthy volunteers. Eur. J. Clin. Pharmacol., 56 (May, 2000) (21); 141-143.

[2] Weitschies, W., Arzneiformen: Eine Reise durch den Verdauungstrakt. *Pharm. Ztg.* 146 (2001); 10-16.

[3] Nürnberger, B. and Brune, K., Buffering the stomach content enhances the absorption of diflunisal in man. Biopharmaceutics & Drug Disposition, 10 (1989); 377-387.

[4] Eichmann, J.D. and Robinson, J.R., Mechanistic studies on effervescent-induced permeability enhancement. Pharmaceutical Research, 15 (1998) (6); 925-930.

[5] Schmidt, P.C. und Christin, L., Brausetabletten – Eine fast vergessene Arzneiform. Pharmazie 45 (1990): 89-101

[6] Bartsch, H., Die Topogranulation, Pharm. Ind. 41 (1979): 696-698.

Editor-in-chief: Claudius Arndt. Managing editor: Kerstin Jarosch. Publisher: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Gemany). Phone: +49 (0) 8191-98578 12, Fax: +49 (0) 8191-98578 19. e-mail: redaktion-tp@ecv.de. http://www.ecv.de. Typesetting: Rombach Druck- und Verlagshaus GmbH & Co. KG (Germany) / Printed by Holzmann Druck GmbH & Co. KG, Bad Wörishofen (Germany).