A Taste of Your Own Medicine

The bitter taste of active pharmaceutical ingredients creates a huge obstacle to dosage forms providing a user-friendly alternative to traditional, solid tablets. However, overcoming this can offer greater patient compliance and a source of new pharma revenue

Detlev Haack at Hermes Pharma

As far as challenges in healthcare go, increasing medical compliance is as serious as the discovery and development of new active pharmaceutical ingredients (APIs). Efforts to date have had minimal impact, with poor treatment adherence still relatively widespread – particularly for those with chronic conditions requiring frequent and long-term dosing (1,2). Age also appears to have a big part to play, with 50 per cent of those over 65 not administering their medicines as instructed, especially those requiring complex treatment regimens (3).

With the average age of the Western world population on the rise, the impact of medical adherence on patient wellbeing will continue to grow, leading to unnecessary disease progression, reduced functional ability and diminished quality of life. Fortunately, compliance can be improved by adjusting medical regimens to make them easier to adhere to – for example via increased patient education, the formulation of user-friendly medicines, and a reduction in the number and frequency of dosage.

User-Friendly Medicines

Oral administration has long been considered the simplest way to provide ongoing medication. However, oral dosage forms are not without their challenges. For example, solid tablets can be large, uncomfortable and even painful to swallow, while research has shown that factors including tablet size, shape and ease-of-swallowing can significantly affect treatment preference, adherence and, subsequently, effectiveness (4-6).

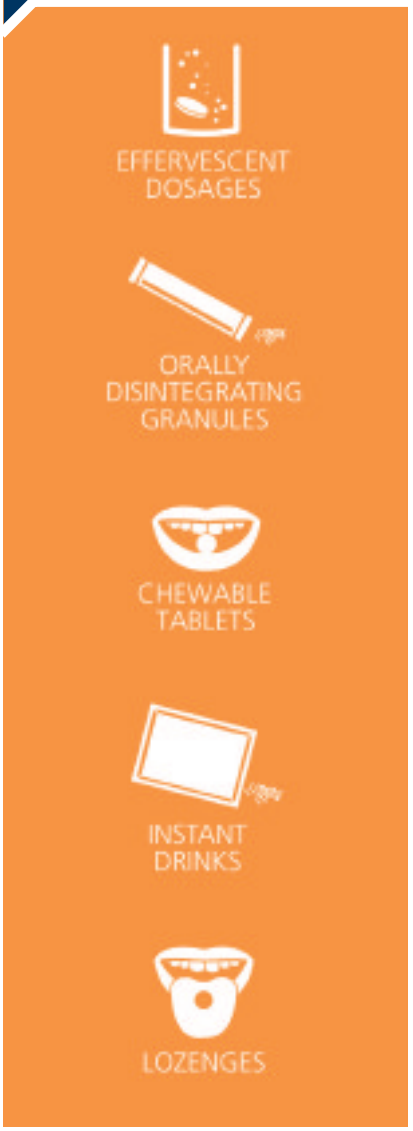
In some cases, solid tablets can be crushed and taken as a rough powder or dissolved/suspended in water, making them easier to swallow. However, most APIs have a very bitter taste, which is made most obvious when they are broken up for ingestion. This renders them unpleasant for patients to ingest and defeats the object of crushing or dissolving them in the first place. Furthermore, medicines that have been deliberately formulated as solid tablets may not exhibit the desired release and stability characteristics after they have been crushed, making this a potentially risky way to take medicines.

Given these factors, there is an unmet market need for making medicines more user-friendly. Dosage forms including effervescent tablets, instant drinks, orally disintegrating granules (ODGs), lozenges and chewable tablets have been specifically formulated to provide ease-of-use in combination with the desired medicinal, mechanical and taste properties (see Figure 1). Each can boost patient compliance by making it easier to follow a treatment regimen, improving outcomes and reducing healthcare costs. They also have a wider range of benefits, both for the pharmaceutical companies producing the medicines and the patients who require them.

Putting Patients First

User-friendly medicines are designed with the needs of the patient in mind, extending beyond their pure medical requirements to include convenience and provide choices. Solid tablets are constrained by one key factor – size. They must always be small enough to fit comfortably inside a patient's mouth, and then pass through the pharynx and oesophagus into the stomach. Because the amount of API incorporated in each

Figure 1: User-friendly dosage alternatives



tablet is limited, patients must often take multiple tablets, many times a day in order to achieve the desired dosing amount, release profile and therapeutic blood-levels.

In contrast, user-friendly medicines can be dissolved in water to create an enjoyable drink, sucked and chewed, or directly swallowed. Not only are they easier for patients to take, but if they are made available in different flavours, they can also satisfy individual preferences by providing a choice. As they are less limited by size, they can also include much higher amounts of API or combinations of APIs. This provides the opportunity to reduce dosing frequency and simplify treatment regimens, thereby further increasing patient compliance.

While this approach is likely to make it easier for all patient groups to take their medication, it is especially effective for those with swallowing difficulties, including the aged and infirm, young children and those with oesophageal sensitivity or injury. Due to their physical size, solid tablets can adhere to the oesophagus wall and cause irritation – a disadvantage avoided by user-friendly dosage forms.

Using cutting-edge drug delivery know-how and manufacturing technologies, user-friendly dosage forms can also be formulated to carefully control API release in the gastro-intestinal (GI) tract. In many cases, this can be achieved much faster than it can via traditional solid dosage forms. For example, drinkable and chewable medicines can start releasing the API as soon as they enter the patient's mouth, as is required for fast-acting medicines such as analgesics and antihistamines. Importantly, user-friendly dosage forms can also be formulated to delay the release of the API until it has passed further into the GI tract if this is necessary for effective treatment.

User-friendly dosage forms also offer other unique advantages. For example, effervescent tablets release carbon dioxide as they dissolve, which improves permeability in the GI tract and enhances API transport into cells, boosting bioavailability (7). They also move through the stomach more rapidly due to the pH-buffered solution created following the effervescent reaction, allowing the API to reach the small intestine faster and thereby leading to quicker absorption. The efficacy of drinkable medicines is more reliable and predictable than that of solid tablets, as the dissolved agents are evenly distributed in the liquid, preventing variability due to tablet disintegration and dissolution.

Brand and IP Advantages

The pharmaceutical industry faces significant challenges fuelled by patent protection issues, rising R&D costs and increasing competition from generic products. As well as offering a way to better meet the needs of patients, user-friendly dosage forms offer a powerful opportunity for pharmaceutical companies to prolong product lifecycles, increase market share and build brand equity.

The reformulation of established medicines of value into new dosage forms can be particularly useful for extending patent protection. This sort of lifecycle management makes it more difficult for rivals or developers of generics to create similar drugs, especially if new, patented technologies are required – for example to allow the fine-control of API release or to enable efficient taste-masking. This further safeguards the investments of pharmaceutical companies by providing stronger intellectual property protection. Such line extensions also lead to a more differentiated product range, meeting individual customer preferences. This results in greater brand value and better differentiation from competitors – factors which increase revenue and market share irrespective of patent status.

User-friendly dosage forms also allow pharmaceutical companies to develop new medicines optimised for specialised patient groups, such as children, the elderly, or people on long-term medication. As well as being tailored to meet their unique medical needs, these dosage forms can provide 'added value' by offering a choice of flavours and increased convenience with products that can be individually packaged, 'taken on the go', and easily integrated into daily routines. It is likely that patients who seek the benefits provided by these dosage forms will remain more loyal to the brand and may also be prepared to accept higher prices. Often, the new dosage forms also permit a more cost-effective treatment by reducing dosage frequency and complexity. This further improves the situation for every stakeholder – patients, reimbursers and pharmaceutical manufacturers.

Challenges of Developing and Manufacturing

User-friendly medicines have many benefits to offer to patients and the pharmaceutical industry, but their development and production is not without its challenges. Perhaps chief among these is the need to effectively mask the bitter taste of APIs, as user-friendly medicines spend a much longer time in the mouth than traditional solid dosage forms. This can be achieved by coating the API using one of a variety of techniques to make it more palatable. However, the choice of coating methodology can significantly influence the cost efficiency, speed and simplicity of formulation and manufacture; it is also important to adopt a coating process that can be adjusted to fine tune taste masking and API release parameters. Additionally, the selected coating excipients need to work effectively in combination with the API(s) of choice and must be reliably available for the duration of the product lifecycle in order to ensure success.

In many instances, the formulation of user-friendly medicines is further complicated by the fact that most APIs require optimisation on a case-by-case basis. It is also often necessary to use specialised coating and granulation techniques in order to generate medicines exhibiting the desired taste, stability and dissolution characteristics, for example hot melt coating in the case of ODGs and TOPO vacuum granulation technology for effervescent forms and chewable tablets

Figure 2: Laboratory scale fluid bed granulator used for hot melt coating to mask the unpleasant taste of APIs and other ingredients

(see box below, Figure 2 above and Figure 3 on page 38). This is especially true of sensitive forms like effervescent tablets, which must be produced and packaged under stringent conditions to prevent them from reacting with moisture in the air.

For these reasons, many pharmaceutical companies turn to outsourced service providers to develop and mass manufacture user-friendly dosage forms on their behalf. Specialised suppliers already have the knowledge and technical infrastructure in place to produce user-friendly medicines, extending to processes beyond manufacturing such as packaging, marketing and distribution. They will have invested significant time, resources and funds to research and develop new methods and technologies from drug design and formulation, to manufacturing and regulatory support, allowing them to produce these dosage forms in a cost- and time-efficient manner, often using processes unavailable through any other means.

Specialised Formulation Techniques

Hot Melt Coating
Traditional coating requires the dissolving of the API and excipients in a liquid, before spraying them onto a seed particle. However, when used, organic solvents can be expensive, toxic and flammable, while using water increases drying times and costs. Hot melt coating (HMC) removes the need for solvents while offering shorter processing times and lower production costs. During HMC, a molten, lipid-based mixture is sprayed onto the solid API particle at carefully controlled temperatures, which then solidifies to form a homogeneous coating.

TOPO
TOPO granulation is a single pot granulation technology which delivers highly stable and humidity-resistant granules needed for user-friendly dosage forms such as effervescent tablets and granules. It is a one-step vacuum system under fully instrumented in-process control. The process modifies the surface of the effervescent components and alters its binding mechanisms. Products arising from TOPO granulation dissolve quickly in water and are extremely moisture-resistant. They have a long shelf-life and can also be used in tropical regions.

TOPO technology requires only a very small quantity of liquid to start the effervescent reaction and granulation. In contrast to other techniques – those that require organic solvents, for example – TOPO uses only pure water for granulation. As a result, there are no solvent residues in the finished products.

Future Outlook

Medical compliance is still a serious problem, leading to ineffective and inefficient treatment. One way to overcome this challenge is the formulation of user-friendly medicines that better fit the lives of the modern populace. These dosage forms are fast, easy and pleasant for patients to ingest, as well as far simpler for carers to administer to the elderly and infirm. In addition to boosting compliance, they offer a host of other medical benefits for patients, potential savings for reimbursers and business advantages for pharmaceutical companies.

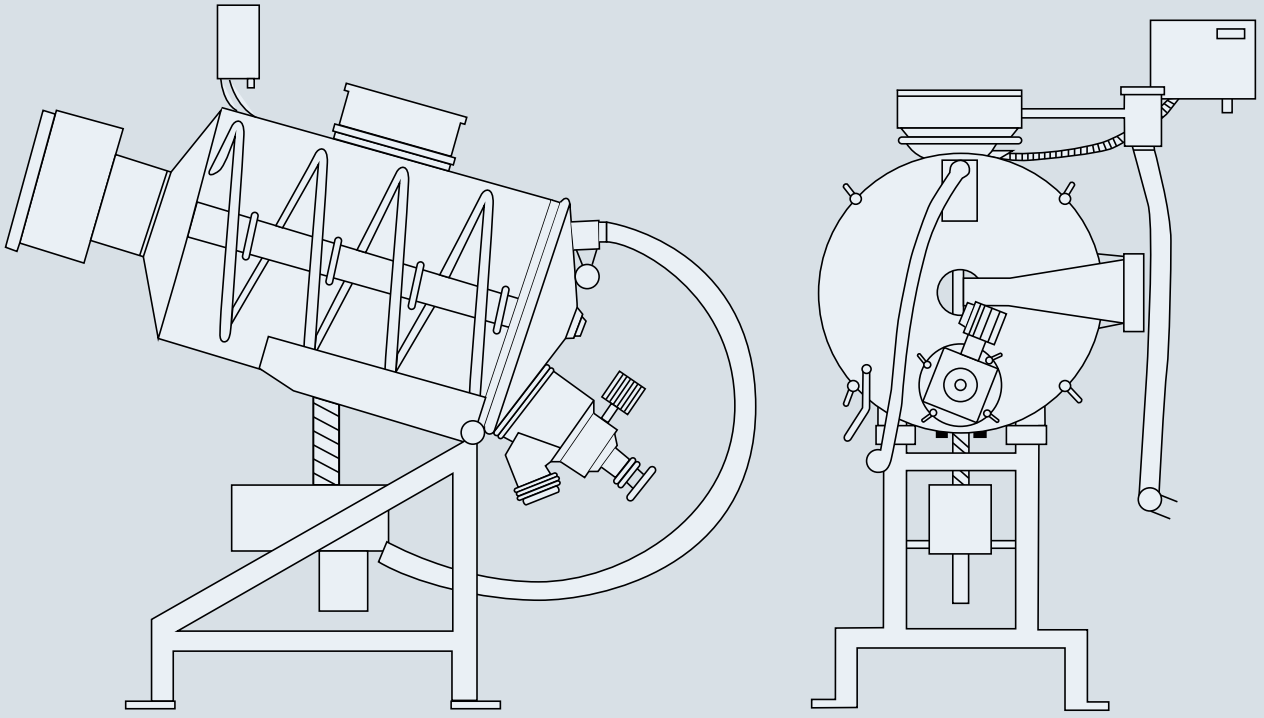


Figure 3: TOPO granulation technology illustration: in front is a suction hose where the raw materials are sucked into the vessel by the vacuum. At the front there is also a rotating sieve used to break up agglomerates at the end of the process. A spiraled stirrer, used to mix the granulate during the process, is located within the vessel. The vessel can be moved from a horizontal position into positions +/-20° from horizontal. The up and down movement helps to achieve intense blending of the contents when stirring occurs at the same time

We have embraced the concept of user-friendliness in household electronics and consumer goods for many years; now it is time to apply it to the pharma industry. While additional market research may be needed to further define the taste and dosage characteristics preferred by various patient groups, user-friendly dosage forms already represent a fast-growing and potentially highly lucrative market for pharmaceutical companies to explore, while generating effective medicines optimised to meet the medical and lifestyle needs of the modern patient.

Acknowledgement

We would like to thank Dr Martin Koeberle for his significant contribution to this article.

References

1. Boswell KA, Cook CL, Burch SP, Eaddy MT and Cantrell CR, Associating medication adherence with improved outcomes: a systematic literature review, *Am J Pharm Benefits* 4(4): e97-e108, 2012
2. Williams A, Manias E and Walker R, Interventions to improve medication adherence in people with multiple chronic conditions: a systematic review, *J Adv Nurs* 63(2): pp132-143, 2008
3. Royal Pharmaceutical Society of Great Britain, Merck S&D, *From Compliance to Concordance: Achieving Shared Goals in Medicine Taking*, RPSGB, London, 1997
4. Bhosle M, Benner JS, DeKoven M and Shelton J, Difficult to swallow: patient preferences for alternative valproate pharmaceutical formulations, *Patient Preference and Adherence* 3: pp161-171, 2009
5. Hussain MZ, Effect of shape of medication in treatment of anxiety states, *Br J Psychiatry* 120(558): pp507-509, 1972
6. Ogata I, Yamasaki K, Tsuruda A *et al*, Some problems for dosage form based on questionnaire surveying compliance in patients taking tamsulosin hydrochloride. *Yakugaku Zasshi* 128(2): pp291-297, 2008
7. Eichman JD and Robinson JR, Mechanistic studies on effervescent-induced permeability enhancement, *Pharm Res*, 15(6): pp925-930, 1998

About the author

Dr Detlev Haack, Director of R&D at Hermes Pharma, earned his PhD at the University of Hamburg on the subject of chemical and physical stability of Piroxicam in solid dispersion with PEG and PVP. In 1997, he received approbation as a pharmacist. From 2003-2007, Detlev was Manager of Sales and Business Development at Hermes Arzneimittel GmbH. He held the position of Associate Director of R&D there from 2007-2012 before becoming Director of R&D in 2013. His career includes a previous position as Head of Production at Altana Pharma Oranienburg GmbH.

Email: haack@hermes-pharma.com