Power to the Patients

Treatment adherence and brand loyalty can be boosted by medicines that are easy to use and appeal to a broad range of patients, providing a unique commercial opportunity for pharma companies to increase market share and differentiate themselves from competitors

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Modern patients enjoy access to a wealth of information via the internet, leading them to request specific treatments from their healthcare practitioners. Many patients now also pay for their own healthcare and are more involved in the treatment purchase decision. For these reasons, medicines that appeal to a wide range of patient preferences – from treatment needs through to lifestyle requirements – are more likely to enjoy greater medical and commercial success.

These changes also come at a time when poor treatment adherence is still a significant problem, with more than 25 per cent of patients complaining of difficulties when swallowing medication (1). A number of region-, culture- and age-related considerations also contribute to the issue, with different groups of patients preferring medicines with certain tastes and appearances. The pharmaceutical industry could help reverse this trend through the development of new, user-friendly medicines specifically designed to simultaneously meet the medical, lifestyle and personal preferences of patients.

Patient Benefits

The simple, effective and safe delivery of an active pharmaceutical ingredient (API) is one of the most important factors that influence treatment efficacy, tolerability and patient compliance. The oral route is considered the most effective way to administer medication, with most medications traditionally formulated as either solid tablets or capsules. However, evidence from several studies has suggested that the size and shape of tablets can significantly influence treatment adherence, preference and effectiveness (2-4).

The development of user-friendly dosage forms is becoming an increasingly popular means to combat these issues and increase patient compliance. By circumventing the need to swallow solid tablets, user-friendly dosage forms are especially well-suited to children, the elderly and those suffering from esophagitis. However, as they are much easier to administer and – in the case of chewable tablets, lozenges and orally disintegrating granules (ODGs) – can be taken without the need for water, anywhere and at any time, they are likely to boost compliance and treatment effectiveness for all patients.

By effectively sidestepping the physical limits of solid tablets, user-friendly dosage forms allow greater amounts of APIs to be delivered in a single dose, while different combinations of APIs can also be delivered together in the same formulation. This approach can help to simplify treatment regimens for patients on a number of medications, as well as those usually requiring frequent doses throughout the day.

Commercial Advantages

As well as providing benefits for patients, the formulation of new and existing medicines into user-friendly dosage forms can offer significant advantages to pharmaceutical manufacturers. From a brand standpoint, companies that develop medicines with patient preference in mind will be perceived as caring about the full range of patient needs, breeding brand loyalty through a diverse range of dosage options and flavours. In the same way, new dosage forms can provide a means of re-energising current offerings and prolonging product lifecycles, while helping to increase market share.

Medicines reformulated in user-friendly dosage forms can also offer a means of strengthening a company's intellectual property (IP) protection. By providing additional benefits over the original medicine, the new form is likely to be granted an extended patent by regulatory bodies. The formulation of user-friendly dosage forms requires specific expertise – for example, in taste masking, flavouring and understanding patient preferences – as well as patented production processes, all of which prevent other manufacturers from easily creating generic copies.

Figure 1:
A wide range of user-friendly dosage forms are available

Flavour Challenges

User-friendly dosage forms can be produced in a variety of different types and flavours, optimised to meet the needs of different patient groups. Solid dosage forms include effervescent tablets, instant drinks, ODGs, lozenges and chewable tablets (see Figure 1). All of these forms are tasted more thoroughly than traditional solid medicines, as they dissolve either before ingestion or in the mouth and tend to spend more time in the mouth before being swallowed. As most APIs have a very bitter taste, the main challenge faced during their development revolves around taste masking, usually achieved using flavourings and/or coatings.

Choosing a flavouring is not always a simple task. Firstly, it must be stable and chemically inert over a long period of time, as any reaction between the dosage constituents could lead to degradation of the API. Furthermore, most flavourings are initially sourced in liquid form, so they must be converted into a solid for use, for example via encapsulation. Flavours are often included as part of a coating, which is administered to both protect API stability and mask taste, with the exact coating method employed varying for each dosage form.

Drinkable Medicines

Easier for patients to swallow than solid tablets, drinkable medicines can take several forms. Instant drinks are made up of powders or granules that are stirred into a fluid before administration. Alternatively, medicines can be formulated as solid effervescent tablets that dissolve upon contact with liquid, creating a drink via the release of carbon dioxide.

Drinkable medicines render tablet size and shape irrelevant, making them much easier to ingest and enabling larger doses of multiple APIs to be included within the same formulation. As the medicine is already completely dissolved when it enters the body, there is no need for tablet breakdown in the gastrointestinal tract, which can lead to faster onset of action and increased bioavailability. This also means that controlling API distribution is easier, preventing the variability sometimes caused by incomplete or delayed tablet breakdown in the stomach. Lastly, in the case of hot instant drinks, the higher temperatures involved can increase API solubility, further improving bioavailability.

The development of drinkable medicines requires specific expertise and dedicated manufacturing conditions. For example, APIs formulated as effervescent tablets or instant drinks are especially susceptible to moisture, so environmental humidity must be carefully controlled at all times. In order to provide the bioavailability benefits described above, it is also important that they dissolve immediately and completely upon contact with water, without leaving unpleasant residues or foam on the surface that could impact on taste or mouth-feel. As drinkable medicines are ingested in solution, patients are also much more exposed to the bitter taste of APIs than is the case for solid tablets. Finally, instant drinks often use hot water, making smell an issue to be considered. For these reasons, effective API taste masking and/or flavouring is essential for ensuring a pleasant experience.

To ensure high quality, most drinkable formulations start out in granular form. In the case of effervescent tablets, the granulate containing an API can be directly compressed to form a solid tablet, a process requiring the use of sugar alcohol binders.

These binders are important for rendering the tablets stable enough to handle, but can cause the generation of an unpleasant film or foam upon dissolution. The same problem is observed if dry granulation is used for formulation, as the lubricants involved can also cause the production of a filmy residue. Fluid bed granulation can avoid some of these problems, but requires the use of potentially costly and toxic organic solvents in order to prevent the effervescent reaction from accidentally triggering. Finally, due to the natural instability of these dosage forms, they cannot be stored as bulk materials and must be packaged immediately after production instead. As a result, production facilities may need integrated (inline) processes to ensure products can be packaged as soon as possible after formulation.

One option that circumvents many of these problems is the use of TOPO technology (see box). TOPO uses an oscillating vacuum approach combined with iterative surface passivation to form a solid tablet without the need for binders. The process minimises the instability risks posed by moisture in the air and can be used to formulate an extremely stable product.

Chewable Tablets and Lozenges

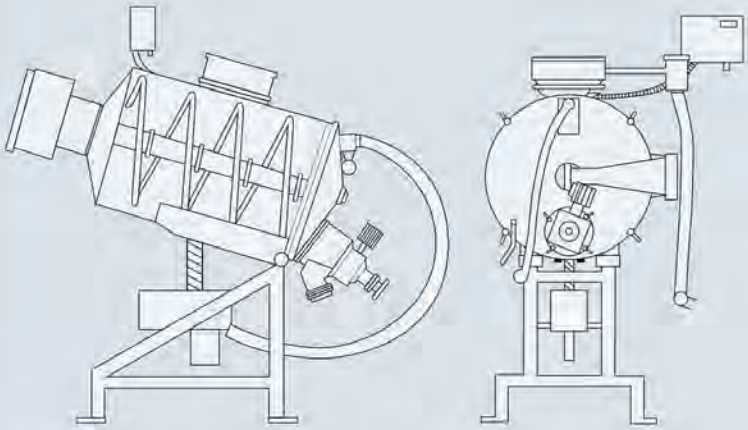
Dosage forms that can be taken without water are likely to fit much better into the busy lives of patients, as they can be taken 'on the go' – whether at work, school, while travelling or when playing sport. To meet this requirement, chewable tablets are designed to rapidly dissolve in the mouth, minimising the need for disintegration in the stomach and thereby boosting speed of onset while reducing dose variability. By using specific manufacturing techniques, they can also be formulated to create a slight 'fizzy' effect in a patient's mouth, stimulating the release of saliva and making the experience more enjoyable.

In contrast to chewable tablets, lozenges are solid preparations that are slowly sucked to promote dissolution in the mouth. They are particularly effective for young children and the elderly, as they are easy to administer and require no chewing – a significant benefit for patients with few or no teeth.

As well as being easier to swallow, chewable tablets and lozenges spend longer in the mouth. This enables rapid API take-up via buccal absorption and reduces the impact of the first-pass effect, leading to faster onset and improved bioavailability. This is especially true in the case of lozenges, which can also be used to deliver APIs locally to the tongue, gums, throat, teeth and other areas of the mouth.

As with other user-friendly dosage forms, chewable tablets and lozenges are tasted more thoroughly than conventional solid medicines, so the bitter taste of APIs must be masked, for example

The TOPO Process



TOPO technology is a patented, single pot granulation technology that 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 (climatic zones IV).

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

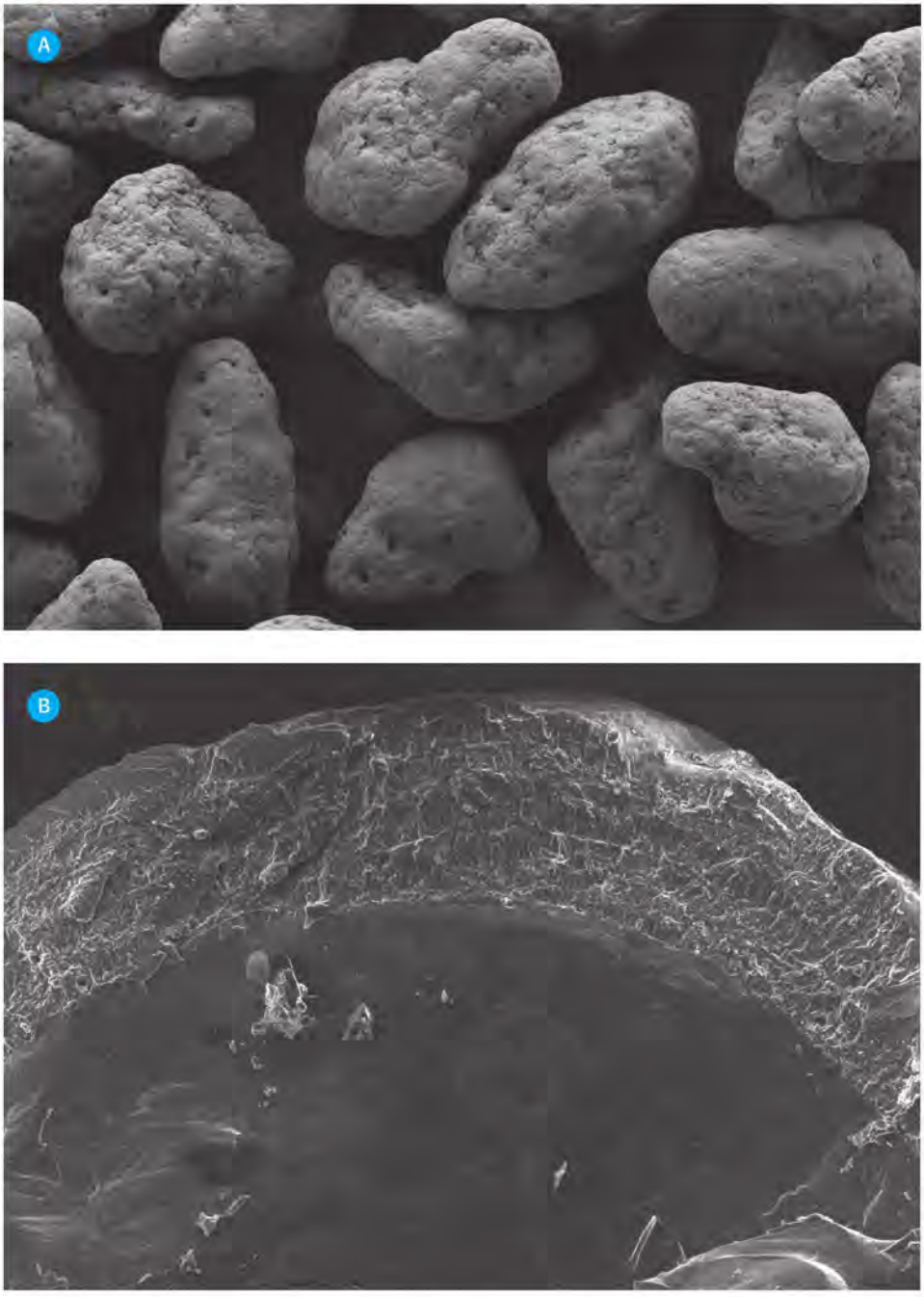


Figure 2:
HMC can be used to create ODGs with a homogenous coating. A) Scanning electron microscope image of ODGs coated with lipids using the HMC process. B) Cross-section image of a single ODG, illustrating the homogenous nature of the coating

using coatings and/or flavours. In addition, they are inherently hard, especially after prolonged storage. This can make them difficult to chew, particularly for young children or the elderly, so storage conditions and shelf-life must be carefully considered during the development of the formulation. Mouth-feel is also important, especially when minerals need to be processed, as this can lead to an unpleasant 'gritty' feeling in the mouth.

Orally Disintegrating Granules

ODGs consist of small granules that dissolve directly in the mouth without the need for external liquid, providing many of the same benefits offered by chewable tablets and lozenges. The main difference is that ODGs are packaged as a granulated powder rather than a compacted solid. This means that they dissolve more rapidly in the mouth, leading to even faster onset of action. However, they can also be prone to some of the stability challenges associated with formulating and manufacturing effervescent tablets and instant drinks.

As with most user-friendly dosage forms, masking the bitter taste of APIs is very important when formulating ODGs. In this case, the coating must also rapidly break down upon contact with saliva, while content uniformity within the dosage form is also necessary for effective use. The particle sizes of the API and excipients need to match in order to avoid segregation during formulation, as this can lead to unwanted dosing variability. Finding just the right size and chemical balance is also essential for maintaining the stability of the API, flavours and other excipients, as well as for modulating the release profile of the dosage form.

Given the complexity of coating ODGs, manufacturers have been developing solvent-free approaches to generate products with the required dissolution and stability profiles. Hot melt coating (HMC) is gaining popularity as it provides an effective way of coating ODGs that is faster and more economical than many traditional solvent-based methods. The process involves covering a solid core particle with a molten coating material, which immediately solidifies to form a homogenous coating (see Figure 2). HMC has already been used to produce ODGs with delayed or sustained release profiles, but until recently it had proven more difficult to formulate rapid release medications. Fortunately, recent research efforts have shown that the process can be successfully adapted to produce ODGs with rapid dissolution characteristics (see Figure 3).

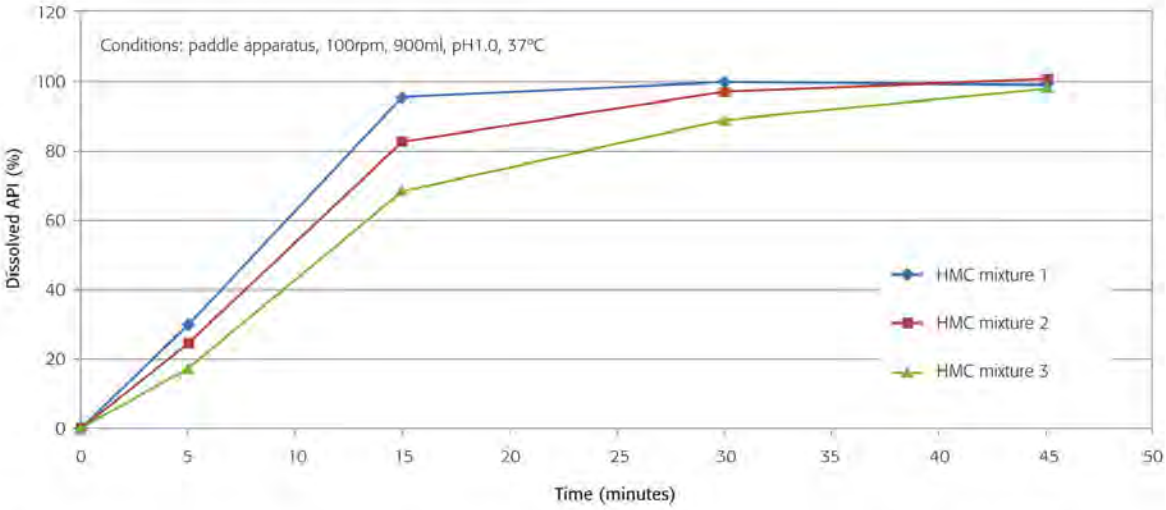


Figure 3: Dissolution profiles of a crystalline water-soluble API coated with different mixtures using HMC

It is worth noting that HMC parameters often need to be optimised for each individual API-excipient combination. While this can make development more complex, it also offers an excellent opportunity to defend product lines from competition by generic and other pharmaceutical manufacturers. In some cases, the new formulation can also be patented, further strengthening IP protection. It is this unique blend of low cost, processing speed and replication difficulty that will likely see HMC become the go-to solution for producing ODGs in the future.

Conclusion

With patient adherence still a major challenge and patients more involved in the selection of their own medicines than ever before, a unique opportunity has arisen to better meet their needs and increase treatment compliance through the development of user-friendly dosage forms. Commercially, these new dosage forms offer a way for pharmaceutical companies to access new markets, increase market share and differentiate their products from competitors'.

However, the development and manufacture of user-friendly dosage forms can be challenging, as taste masking and release parameters must usually be optimised on a case-by-case basis and the conditions necessarily vary considerably. As a result, many pharmaceutical companies outsource product design and manufacture to expert service providers, which actively invest in new technologies and expertise specifically optimised for developing and manufacturing these new dosage forms.

By utilising the benefits of user-friendly dosage forms, value is created for every stakeholder. Patients are provided with more choice and easy-to-use medicines. This boosts compliance and medical effectiveness, reducing the cost of failed treatments to healthcare providers. The new medicines also enable pharmaceutical companies to increase customer loyalty and diversify product portfolios, increasing revenues and market share by more effectively meeting the needs of patients.

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