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Optimizing Dosage Forms for Improved Therapeutic Compliance

Swallowing difficulties continue to transcend all age groups

The oral route of administering medicines remains the most common for many reasons including cost, convenience and public familiarity. Of the oral dosage forms available, tablets and capsules are often the most well known and therefore the default choice for pharmaceutical and healthcare companies. However, swallowing is a complex process and data from a recent market study has shown that more than half of the population experiences difficulties swallowing tablets and capsules, a factor that can seriously impact on compliance. While alternative routes that exploit developments in drug delivery technology have become increasingly popular over the last two decades, including the transdermal and inhalation routes, the cost of these is significantly higher than oral medicines, where a wide range of low-cost generic alternatives is also available. Here we review how the swallowing process works, the challenges this poses for patients and pharmaceutical companies, and how these can be overcome by developing oral dosage forms that are cost-efficient and more user-friendly.

HOW SWALLOWING WORKS

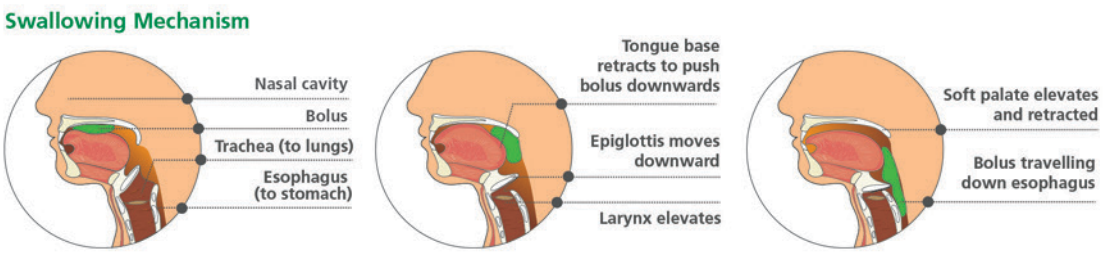
Tablets and capsules—both soft gelatin and hard gelatin—are among the most familiar oral medicines that most people encounter. To be effective, they need to be swallowed whole. The active pharmaceutical ingredient (API) is then absorbed via the gastrointestinal (GI) tract in order to exert the desired pharmaceutical effect. Despite being an almost automatic physiological process, swallowing can still prove difficult for many people. It is widely recognized that swallowing requires the co-ordination of muscle actions and the presence of saliva as a lubricant. Typically, the swallowing process can be divided into the following stages[1]:

1. Oral preparation stage: the mouth starts to chew the food and mix it with saliva.
2. Oral stage and pharyngeal stage: the bolus is pushed backwards by the tongue into the pharynx. Then several swallowing reflex motions occur, including a series of complex throat neuromuscular reactions, which push the bolus into the esophagus.
3. Esophagus stage: the bolus is pushed into the stomach through the esophagus.

During the oral phase of swallowing medicines, the dose form is usually moistened by the action of the tongue against the palate in combination with water, which is usually imbibed to support swallowing. It is then propelled by the tongue towards the oropharynx, facilitated by closing of the nasopharynx via upward movement of the soft palate.[2] Scintigraphy data shows that swallowing a bolus of water takes just 1.5s, while tablets generally take a little longer at around at 4-7s.[3] Any tablets that take longer than 20s to clear from the esophagus are classified as adherent.[4] As one might expect, uncoated tablets show a longer residence time than coated tablets, and a prolonged adhesion to the esophageal mucosa is common.[5] These factors all contribute to how pleasant/unpleasant the experience is for the patient.

As previously described, saliva plays an essential role in swallowing and its production is stimulated by chewing. A child will generally produce saliva at a rate between 0.4 ml/min (unstimulated) and 0.9 ml/min when chewing. In adults, this rate can rise to 1.5 ml/min when chewing but may be as low as 0.2 ml/min in the elderly.[6] This saliva adds to the resting pool of 3-5 ml, sitting below the tongue and in the cheek-gum boundary. Most tablets and capsules are not designed to be chewed, as the API they contain usually has a very bitter and unpleasant taste plus the action of chewing or breaking up such dosage forms can actually impede their pharmaceutical effectiveness. As such, tablets and capsules are much harder to swallow than foodstuffs and the addition of water is usually required.

Figure 1. Swallowing mechanism



HARD TO SWALLOW

Dysphagia is a condition that occurs when a person cannot smoothly swallow food from the mouth to the stomach. It is believed to affect around 1 in 25 adults in the U.S. Although the problem is relatively widespread, a minority of people actually seek medical care for their swallowing problem, even though the subjective impact and associated workdays lost with the swallowing problem can be significant.[7]

It is interesting to note that, while the process of swallowing is an almost automatic physiological maneuver in the young, adaptive cerebral changes in the co-ordination of the swallowing reflex are observed in the elderly, suggesting that the brain cortical region increases the time for pharyngeal triggering,[8] resulting in swallowing smaller volumes, the accumulation of residue and a higher rate of laryngeal penetration.[9] This results in an increased rate of dysphagia among the elderly.

So what are the implications of swallowing for the pharmaceutical industry and, more specifically, the common tablet or capsule? In addition to those people with dysphagia, there are many others who experience difficulties when swallowing tablets and capsules, and for whom food is no issue. In fact, a recent market survey of 1,000 U.S. adults showed that more than 50% report difficulties swallowing tablets and capsules[10] (*Figure 2, p.104*).

Of the people experiencing difficulties swallowing tablets, around a quarter reported the issue as serious and 70% as uncomfortable. Only 4% considered these difficulties to not be a problem. Importantly, the overwhelming majority of people having difficulties swallowing tablets did not report any similar problems with foodstuff or fluids, suggesting that this trend is specifically linked to tablets/capsules.

While difficulties swallowing tablets may have been predicted among those aged over 65, the survey showed that this is actually a problem that affects all adult age groups and that it is most commonly reported among those aged 16-24 years. One possible reason for this trend might be today's modern world of convenience and choice, with younger people growing up to expect every product they encounter to offer a positive and stress-free experience, including medicines. This conclusion is somewhat supported by the fact that young people were more likely to report issues with factors such as taste than older survey participants (*Figure 3, p.106*).

A WORRYING TREND

Many people with difficulties swallowing tablets reported simply drinking lots of water or other fluids to wash it down (*Figure 4, p.106*). However, a worrying number report resorting to breaking tablets before swallowing (23%) or crushing them up and dissolving them in water (14%), both of which can affect API release profile, bioavailability and medical efficacy. The same issue would affect the 10% of participants who reported having chewed tablets/cap-

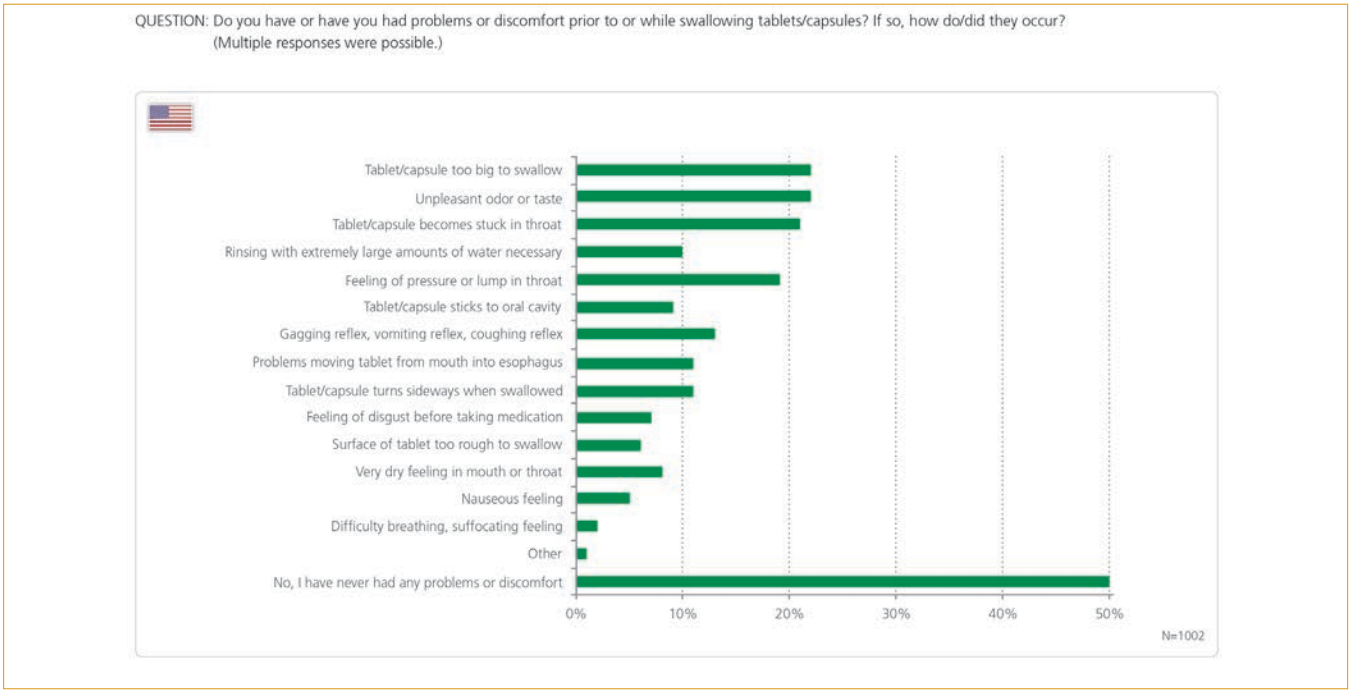


Figure 2. Shows the problems/discomfort experienced by US survey participants prior to or while swallowing tablets/capsules. Multiple responses were possible.

sules before swallowing them. Perhaps most worryingly of all, 10% of people had resorted to not taking their medication at all in the face of swallowing difficulties.

Non-compliance not only risks affecting the individual's health but also impacts on the healthcare system as a whole. The consistent use of medications, for example, completing a prescribed treatment in full, can lead to a reduced reliance on hospital and other medical services.[11] In the U.S., non-compliance is thought to cost the healthcare system as much as $289 billion a year.[12]

SAME ROUTE – DIFFERENT VEHICLE

An alternative approach that can benefit patients, healthcare providers, reimbursers and pharmaceutical companies is the formulation of user-friendly dosage forms, rather than traditional solid tablets or capsules. These may include effervescent tablets, orally disintegrating granules (ODGs), chewable tablets, lozenges and instant drinks. In Germany, Austria and Switzerland, effervescent dosage forms are widespread and offer another welcome alternative to swallowing tablets. User-friendly dosage forms also have a number of other advantages beyond the swallowing aspect, as outlined in *Table 1 (p.107)*. In general, all such dosage forms are easier to swallow. In addition, when developed by companies with the necessary technical expertise, they have a better taste than traditional tablets and capsules, and can even offer the opportunity to create medicines with modified API release profiles and bioavailability.

From a practical point of view, ODGs and other user-friendly dosage forms are better suited for use on-the-go than conventional forms and may be individually packaged in stick packs and foil strips. User-friendly dosage forms such as effervescent tablets can incorporate large amounts of API that, therapy permitting, could be consumed all at once as a daily dose rather than in multiple tablets over the course of the day, which also offers benefits to patients.

Improved adherence associated with new dosage forms has been widely reported by studies concerning the treatment of patients with, for example, human immunodeficiency virus (HIV), osteoporosis, diabetes, hypertension, the need for contraception and overactive bladder.[13,14,15,16,17]

MAXIMIZE THE INNOVATIVE VALUE OF PHARMA PRODUCTS

The goal of the pharmaceutical industry is to develop new therapies that improve patient lives. However, companies must also be profitable in order to invest the large sums required to discover and develop new medicines, and bring pharmaceutical products to market that can be manufactured at a reasonable price. Consequently, pharmaceutical companies are increasingly committed to the development of integrated life cycle management strategies to achieve maximum revenues from each product in their portfolio.

Frequent regulatory changes also play an important role in these processes, especially the identification of appropriate patent expiration strategies. One strategy, confirmed by empirical research, is product-line extensions involving the innovative modification of pharmaceutical medicines into user-friendly dosage forms.[18] The potential benefits are many, ranging from enhanced product lifecycle management and extended IP protection through to convenient dosing for patients with specific needs who would benefit from greater accessibility to a therapeutic agent, including those patients who experience difficulties swallowing conventional tablets and capsules.

Another useful patent expiration strategy is the development of a successor product, such as the development of single-pill-combinations containing several APIs. The pairing of two or more components in one fixed combination product can provide convenience, increased patient compliance and,

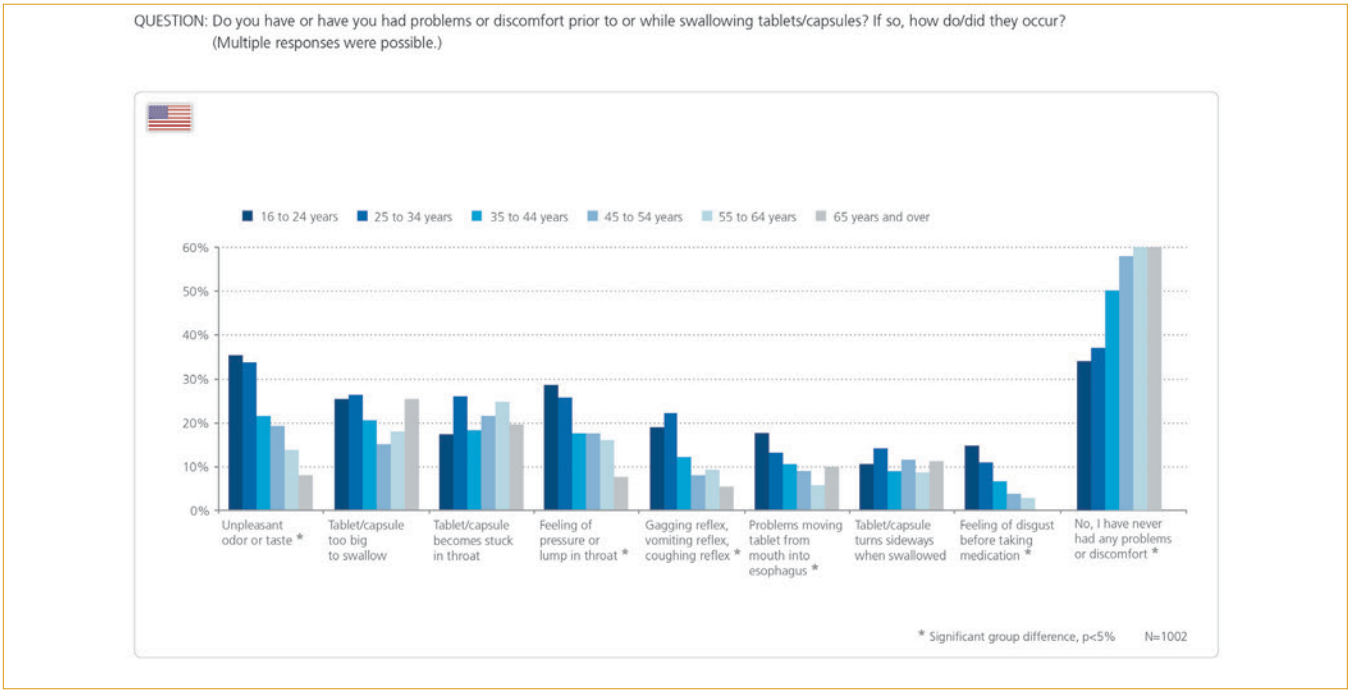


Figure 3. Shows the problems/discomfort experienced by survey respondents while swallowing tablets/capsules. Multiple responses were possible. Results were analyzed based on the age of the participant.

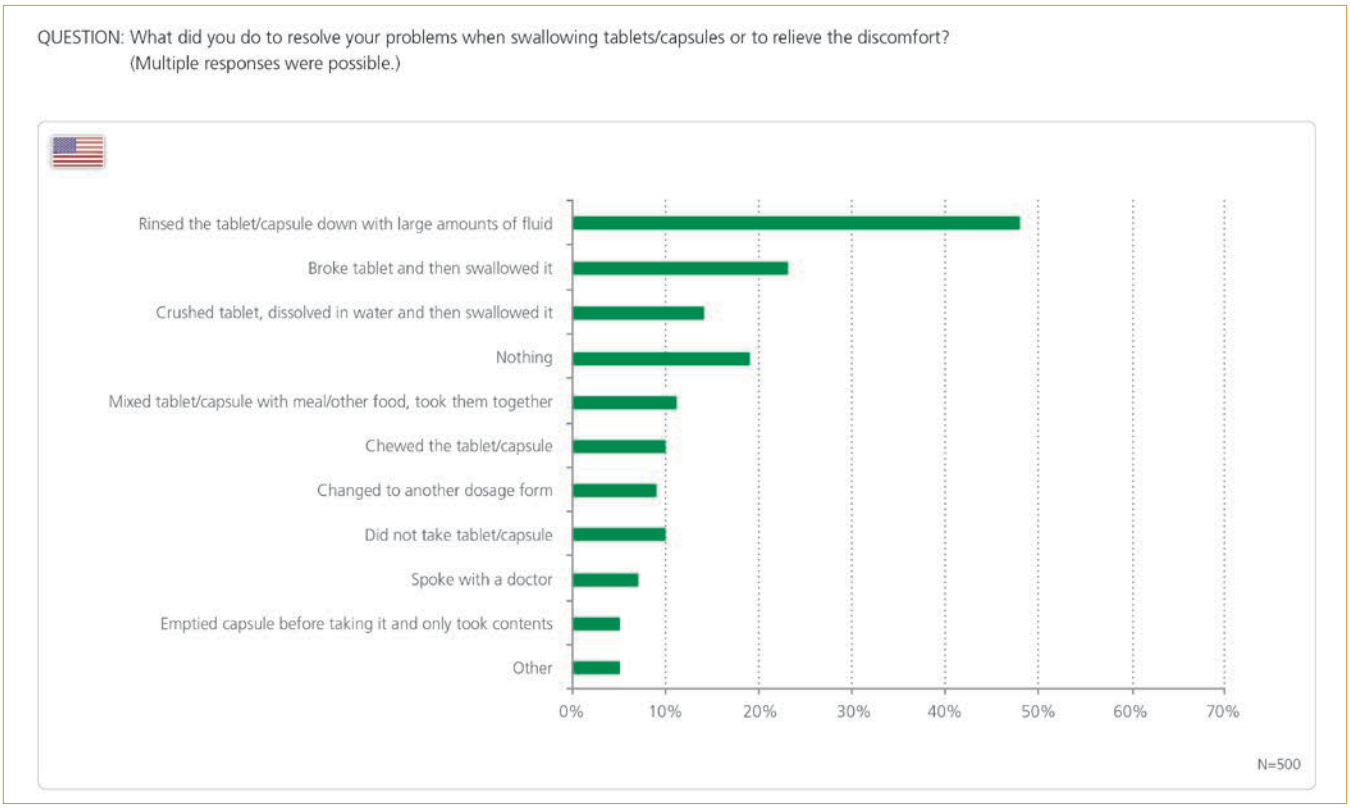


Figure 4. Shows the different solutions adopted by survey respondents in order to overcome difficulties swallowing tablets (multiple choice survey, multiple selections allowed).

TABLE 1

User friendly dosage forms	Benefits
Effervescent tablets	• Excellent bioavailability and rapid release of API • Minimization of gastric irritation • Offer rehydration benefit by increasing liquid intake
Orally disintegrating granules	• Dissolve in the mouth in seconds • Convenient, take anywhere without water • Can also be designed for extended release
Chewable tablets	• Convenient, take anywhere without water • Can be used for poorly soluble APIs • Reduces the risk of medicine-induced esophagitis (when a tablet is caught in the esophagus and dissolves while remaining in contact with the sensitive esophagus lining)
Lozenges	• Can provide a local as well as a systemic effect • Can be made with a fizzy effect that stimulates saliva production
Instant drinks	• Offer rehydration benefit by increasing liquid intake • Can be either hot or cold depending on intended use • No residues or foam

from a therapeutic standpoint, better overall disease management. Moreover, combination products can provide a synergistic effect by targeting one or multiple diseases. Due to their many potential benefits, pharmaceutical companies are currently developing double or triple combination products to match changing therapy needs.[19] Many user-friendly dosage forms are not restricted by size in the same way as traditional solid tablets and capsules might be, making it easier to increase the amount of API(s) present in a single dose.

ENLISTING EXPERT SUPPORT

The case and need for innovation are both strong. Thinking about a product in terms of 'user-friendliness' helps identify new target groups among the population and allows pharmaceutical and healthcare companies to tailor products to those with swallowing difficulties, which our survey suggests is as much as 50% of consumers. In this light, user-friendly oral dosage forms represent an ideal basis for product line extensions targeted at all age groups and patient populations in order to ease the intake of medicines and uphold a treatment regimen, provided that the properties of the API are suitable to the respective dosage formulation.

However, the fact that different age groups report subtle differences when defining why they experience swallowing problems might also provide an early indicator that products could be customized to meet the needs of specific demographics. What's more, the flexibility to offer a range of dosage forms in different flavors would allow consumers to seek out their favorites. A 'customer-centric' product strategy such as this is likely to create brand advocates and breed brand loyalty, something that might prove especially important in areas such as the over-the-counter (OTC) market.

So how can pharmaceutical companies formulate existing and new medicines as innovative new dosage forms such as effervescent tablets, ODGs, lozenges, instant drinks and chewable tablets? Firstly, working with these dosage forms requires significant technical expertise and can involve the use of specific machinery not usually found in traditional pharmaceutical manufacturing plants. As an example, different APIs have unique physical characteristics, which must be understood and catered for when reformulating into alternative dosage forms. These include particle size, particle size distribution and shape, all of which can affect the flowing properties of solid matter during formulation and therefore have a direct impact on the performance characteristics of a product. Once such performance characteristic is the medicine's mouth feel, for example, large particles feel gritty and unpleasant in the mouth. If particles are too small they tend to fully absorb the saliva available.

When developing new dosage forms, working with third party companies allows Pharma to tap into external sources of innovation and expertise. These partners have had the chance to develop suitable strategies and technologies to overcome the challenges of working with these new dosage forms, making the process of developing them more efficient and cost-effective. Specialist providers can advise on factors such as the most suitable dosage form or excipient for a given product, which might range from filling materials such as sugar alcohols, to flavors, sweeteners, colorants, product appeal enhancements and various coatings. Many suppliers also have the regulatory and marketing experience to assist with taking a new product through the regulatory approval process and then to market.

CONCLUSION

Swallowing is a complex, semi-automatic process, and difficulties swallowing tablets are widespread. While many expect this among the elderly, it is clear from the data shown that such difficulties transcend all age groups. User-friendly dosage forms can not only offer improved patient convenience and acceptability, but also offer pharmaceutical companies the opportunity to extend product lines, survive patent expiration and build better brand loyalty. Challenges such as masking the bitter taste of APIs, avoiding unpleasant aftertastes, and disguising unfavorable organoleptic properties associated with granules, powders and solutions, can be overcome by working with specialist third party experts.

In the future, it is likely that consumers will continue to demand products with improved usability and convenience throughout the full spectrum of their daily lives—the data in our survey suggests that the area of solid oral dosage forms will be no different. Pharmaceutical companies that appreciate and act on this trend are the most likely to meet the needs of modern patients, boosting patient compliance, treatment effectiveness and, ultimately, the bottom line of their balance sheets. **CP**

References

For the full list please visit the online version of this article at ContractPharma.com.

DR. THOMAS HEIN is Senior Vice President Commercial and Regulatory Affairs at HERMES PHARMA. Having earned his PhD in pharmaceutical technology at the University of Regensburg in Germany, Dr. Hein has made significant entrepreneurial contributions to HERMES PHARMA. Since 2001 he has been responsible for the division's commercial operations, worldwide portfolio management and marketing.