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HERMES PHARMA

Get the dose right™

HERMES PHARMA: USER-FRIENDLY DOSAGE FORMS, A WIN-WIN SITUATION FOR PATIENTS & PHARMA

Thomas Hein, PhD
Director, Sales & Business Development,
Hermes Pharma

"User-friendly oral dosage forms are particularly well-suited to patients with swallowing difficulties or those with chronic conditions requiring regular and prolonged dosing regimens. The elderly often suffer from both factors, with up to 50% of adults over 60 afflicted with dysphagia. This proportion increases up to as much as 75% for those in long-term care facilities."

Hermes Pharma is the expert in developing and manufacturing user-friendly solid oral dosage forms - including effervescent and chewable tablets, instant drinks, and orally disintegrating granules. For more than 40 years, the company has been working with pharmaceutical companies and producers of food and dietary supplements around the globe to expand their product lines and grow their brands. As a division of Hermes Arzneimittel, a leading German provider of branded high-quality medicines, Hermes Pharma offers customized solutions at every point along the pharmaceutical value chain, from new product development, to manufacturing and regulatory support. Drug Development & Delivery recently interviewed Dr. Thomas Hein, Director Sales & Business Development at Hermes Pharma, to discuss how user-friendly dosage forms help to put patients first, their advantages for patients and pharmaceutical companies, as well as the challenges associated with their development and production.

Q: What are user-friendly solid oral dosage forms, and why are they needed?

A: The easiest and simplest route of drug administration is oral ingestion. Traditionally, this has been achieved using solid tablets or capsules, which are swallowed whole and break down in the gastrointestinal tract of the patient to release their active pharmaceutical ingredients (APIs). However, swallowing large tablets is not always easy, and tablet shape, surface texture, and taste also lead many patients to dislike solid medicines. These factors combine to reduce patient compliance, subsequently impacting treatment effectiveness.

One way to circumvent these problems is to design oral dosage forms that are more user-friendly, such as effervescent and chewable tablets, orally disintegrating granules (ODGs), lozenges, and instant drinks. Consumers have embraced the

concept of user-friendliness in household electronics and consumer goods; now is the time to address the needs of the ill and those who care for them. By providing a wider range of alternative formulations, physicians, caregivers, and patients have more choice while preserving safety and efficacy. To effectively meet these needs, Hermes Pharma has been developing new ways of formulating and manufacturing dosage forms that are easy and pleasant to ingest, while offering the desired API-release characteristics, efficacy, and stability.

Q: What are the advantages of user-friendly solid oral dosage forms?

A: Advantages include ease-of-use and convenience for all patients, boosting compliance. User-friendly dosage forms can be taken with or without water to suit individual preferences and can be conveniently taken along to work, school, sports, or elsewhere. This makes it easier for patients to integrate medication into their daily lives, and reliably take medicines according to the intended and prescribed schedule. As user-friendly dosage forms are in solution when they enter the digestive tract, they do not cause esophagitis or other injuries, such as gastrointestinal lesions. As effervescent tablets and ODGs are absorbed quickly, they can also help provide rapid API release, such as is required for fast-acting drugs like analgesics. In other cases, the presence of carbon dioxide in effervescent formulations can improve bioavailability by boosting permeability through the intestinal epithelium. User-friendly solid oral dosage forms may also facilitate the incorporation of a wider range of dosage levels beyond what conventional tablets or capsule allow, enabling for example a larger amount of API to be taken in a single dose. This further simplifies administration, increasing patient compliance and making treatment more effective.

Q: Which patient groups benefit from user-friendly solid oral dosage forms?

A: User-friendly solid oral dosage forms are particularly well-suited to patients with swallowing difficulties (dysphagia), or those with chronic conditions requiring regular and prolonged dosing regimens. The elderly often suffer from both factors, with up to 50% of adults over 60 afflicted with dysphagia. This proportion increases up to as much as 75% for those in long-term care facilities. In this setting, current practice often involves crushing solid medicines for administration. However, this approach can cause API instability and unpredictable variation in dosing levels, while some medicines simply cannot be crushed and still remain effective, for example, those that have been formulated to provide slow API release. The bitter taste associated with crushed tablets also lowers patient compliance, further reducing the effectiveness of medication.

When treating chronic conditions, the impact of these factors is multiplied for every repeated dose, so it is essential that medicines are easy and convenient to administer and pleasant to take. This increases the chance that doses will not be missed and that the desired plasma concentration time profile will be achieved. For certain patients, mobility, motor, and cognitive function may also be an issue, so the simpler the treatment regimen, the more effectively it can be administered by the caregiver and followed by the patient. As those over 65 years old are already the largest users of medication in the developed world and form a growing proportion of the population, there is a great and pressing need to develop medicines that suit their requirements.

Children are another group to benefit from user-friendly dosage forms. Not only do they have smaller mouths, throats, and digestive systems than adults, thereby making swallowing adult-sized tablets difficult, their physiology is fundamentally different such that adult medicines may have unexpected effects on them. For example, gastric pH is thought to be consistently higher in younger children, impacting on the absorption of a given drug, while distribution rate is known to vary between adults and children due to relative proportions of body water, lean body mass, and fat. Currently, the predominant solution for treating children is to crush or fragment adult dosages, leading to poor palatability and bioavailability problems. This combination of factors was considered significant enough to trigger a directive from the World Health Organization (WHO) in 2007, which encouraged drug developers to "make medicines child size."

Q: Apart from boosting treatment effectiveness, what else do pharmaceutical companies gain from making medicines more user-friendly?

A: The pharmaceutical industry faces significant challenges fueled by patent protection issues, rising R&D costs, and increasing competition from generic products. User-friendly dosage forms can provide a welcome opportunity to expand existing product lines, prolong product life cycle, and revitalize brands. Such line extensions lead to increased customer awareness, greater brand value, and differentiation from competitors, factors that increase revenue and market share. For example, the Aspirin® brand owes much of its success not least to a product-line extension strategy that has resulted in the development of a multitude of dosage forms, such as effervescent products, chewable tablets, and ODGs.

As well as offering current medicines in a new form likely to boost compliance, there is the possibility to develop new drugs optimized for specialized groups of patients, such as children, the elderly, or people on long-term medication. These add extra value for patients, such as a choice of flavor and increased convenience through dosage forms that can be individually wrapped and "taken on the go." Patients and consumers who seek modern dosage forms are likely to remain more loyal to the brand and may also be prepared to accept higher prices. Often, the new dosage forms permit a more cost-effective treatment altogether, further improving the situation for patients, reimbursers, and pharmaceutical manufacturers.

Frequent regulatory changes also play an important role in the identification of appropriate patent expiration strategies. One such approach, confirmed by empirical research, is product-line extension involving the innovative modification of pharmaceutical drugs into new formulations, for example, user-friendly dosage forms. This sort of life-cycle management can also make it more difficult for rivals or developers of generics to create similar drugs, as the technical parameters are more difficult to replicate, and can often be protected by updated patents.

Q: What are the challenges associated with the development and production of user-friendly solid oral dosage forms?

A: As with all formulations, they must be physically and chemically stable enough to be manufactured, packaged, and transported without any loss of efficacy or usability, even after prolonged shelf storage. The excipients and API that will make up the final product need to be carefully selected and sourced to ensure they will work together correctly and will be reliably available from suppliers for the duration of the product life cycle. From a functional standpoint, the API itself must be released at the desired rate in the correct body location to achieve the desired therapeutic result. Successfully bringing an effective and user-friendly medicine to market also requires specific know-how across formulation and scale-up through to compounding, tableting, packaging, and marketing.

Perhaps the key issue surrounding formulation revolves around unpleasant taste, which is considered one of the main reasons for poor patient compliance. As user-friendly solid oral dosage forms spend more time in the mouth than traditional forms, the bitter taste associated with APIs must be effectively masked to render them palatable. Of particular relevance is the fact that effervescent forms are more sensitive to moisture, being deliberately designed to dissolve upon contact with water.

Therefore, effervescent tablets must be handled and manufactured in low humidity environments to ensure maximal stability. By keeping turnaround times as short as possible and packaging the final product in-line, degradation can be minimized. In addition to protecting the product, packaging itself requires specific expertise, as the final product may need to be both child-resistant and senior-friendly. Each of these elements must be considered early on and effectively balanced, identifying a process that will yield the desired result at an acceptable cost and within the required timeframe.

Given the potential complexities, it is not surprising that many pharmaceutical companies choose to outsource the process to dedicated providers. This avoids the need to invest time, money, and resources in developing the necessary expertise in-house, and negates the requirement to purchase any dedicated manufacturing equipment. However, when choosing a contract research and manufacture organization (CRMO), it is important to select a partner that truly understands the needs, limits, and stakeholders of the

organization, whether it be a small pharma company focused on a single product, or a large player looking to explore new options for a more extensive product portfolio. The partner should also be able to provide expert knowledge and service along the full length of the pharmaceutical value chain, integrating formulation and manufacture with the other parts of the development process to successfully bring a new product to market.

Q: How is Hermes Pharma meeting these challenges?

A: At Hermes Pharma, we optimize the development of user-friendly solid oral dosage forms from multiple perspectives, including investigating new methods of drug formulation, identifying reliable, well-characterized excipients and associated suppliers, preparing manufacturing workflows for scale-up, and experimenting with adequate product protection and packaging.

In terms of formulation, our teams have been testing new coating methods capable of producing stable, pleasant-tasting products that offer customizable dissolution profiles depending on the needs of each unique medicine. One such technique is Hot Melt Coating (HMC), which allows us to reproducibly encapsulate flavors, APIs, and other excipients without the need for potentially toxic and costly solvents, while simultaneously reducing manufacturing times and costs. As part of our ongoing research into optimizing the HMC process, we can formulate medicines with immediate- or sustained-release profiles depending on requirements. The new coatings not only have an agreeable taste, they also rank highly for other desirable traits, such as mouth feel, color, and texture, as well as offering the required physical and chemical protection for the API.

We also have experience in up-scaling the process for manufacture. This is especially valuable, as many of the excipients used for manufacturing user-friendly solid oral dosage forms bring their own unique challenges. For example, many of the lipids utilized for coating are soft and must be carefully stored and transported to maintain quality and process reproducibility. Traditional manufacturing processes requiring lubricants should also be carefully considered; for example, when producing effervescent tablets, lubricants can lead to a final product with an unpleasant soapy taste that forms a cloudy solution upon dissolution. This dosage form also requires specialized, low-humidity manufacturing conditions or sophisticated technologies - such as Topo Technology - that delivers granules that are less sensitive to humidity, but remain stable during storage while keeping a good solution profile needed for effervescent products.

Q: Why else should companies partner with Hermes Pharma?

A: Hermes Pharma has over 40 years of experience working with pharmaceutical companies and producers of food and dietary supplements around the globe to expand their product lines and grow their brands. We work with our clients in many different ways, from co-developing new products to licensing market-ready products based on our proprietary over-the-counter brands. Our integrated services cover the entire pharmaceutical value chain, including product design, formulation, analytical development, stability testing, manufacturing, QA, QC, and batch release, packaging, delivery, regulatory support, and life-cycle management. We use patented manufacturing technologies, and employ PAT and QbD principles when necessary to reliably deliver outstanding product quality and stability. With a dedicated focus on user-friendly dosage forms and unique expertise in taste-masking and flavoring, we have the experience and technology to see a project through to completion. We've proven this time and time again, building up a diverse and deep knowledge bank with which to effectively serve our customers. ◆

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