FORMULATING SUPERIOR ORAL SUSPENSIONS FOR BETTER PATIENT COMPLIANCE

In this article, Rina Chokshi, PhD, Global Commercial Marketing Manager, and Dago Caceres, Global Strategy Director, both of IFF Pharma Solutions, discuss how leveraging key ingredients in oral suspensions can enhance stability and sensory attributes, as well as encourage patient compliance.

For many drug formulators and manufacturers, patient compliance remains a key area of focus. With around half of treatment failures attributed to low patient compliance, better drug design and improved delivery options could increase the likelihood that patients will take their medications as prescribed, potentially improving outcomes and reducing healthcare expenditure.

Chewable tablets, orally disintegrating tablets and liquid formulations may all lead to higher rates of patient compliance – particularly in populations that have difficulty swallowing, such as paediatrics, geriatrics and patients with dysphagia. These patients often require alternative drug formats to traditional tablets and capsules, and frequently show the greatest preference for oral liquid formulations.

Research has identified oral suspensions as one of the top delivery formats in the liquid formulations space. The key advantage of an oral suspension is its ability to preserve the structure of the APIs within it without any dissolution, while also providing the patient with an easy-to-swallow liquid format. The fact that the API is not completely dissolved allows the suspension to deliver a higher drug concentration than an equivalent volume of liquid solution.

Demand for suspensions has grown, largely due to their increased bioavailability and ability to contain high doses of APIs. Suspensions also enable easier customisation, allowing for appropriate dosing for all patients, regardless of age or weight. Additionally, suspensions are easy to taste-mask; formulators can overcome any unpleasant tastes from the active ingredient by limiting the amount of drug in solution and by adding flavourings to the liquid vehicle. After all, sensory enhancement of the drug experience goes hand in hand with achieving better rates of patient compliance.

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CONSIDERATIONS FOR OPTIMAL SUSPENSION FORMULATIONS

Suspensions are finely divided, undissolved drugs that are dispersed in liquid vehicles. They appear in two forms, ready-to-use liquid suspensions and dry powder reconstitutable suspensions, which are dispersed into water by the patient, caregiver or pharmacist before use. They are not to be confused with solutions, which are liquid preparations in which the drug and the various excipients are dissolved in a suitable solvent or aqueous system.

Oral suspensions require a careful balance of ingredients to ensure both drug efficacy and a positive sensory experience. In a suspension formulation, alongside the API, there are multiple excipients included to ensure a stable, uniform drug product with pleasant taste and mouthfeel. A suspending agent, protective colloid and viscosifier are commonly applied as critical functional excipients.

As with any drug format, formulators must overcome a number of challenges when creating suspensions. While it is necessary to source consistently safe, high-quality ingredients, manufacturers must also consider how ingredients may contribute to viscosity, pourability and pleasant sensory attributes. There is also often a need to overcome turbidity, clumping and concerns around the API settling. Suppliers experienced with suspensions can offer both product solutions and expertise in navigating the complex regulatory landscape.

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UNDERSTANDING KEY INGREDIENTS

Suspending agents create a gel-like network, allowing for uniform dispersion of API while remaining stable over extended periods of storage. Often, suspending agents are not used alone, as each has its own unique strengths and weaknesses. For example, colloidal microcrystalline cellulose (cMCC) is a well-established and versatile excipient comprised of co-processed microcrystalline cellulose and sodium carboxymethyl cellulose (NaCMC). It offers several key properties and functionalities that make it an ideal suspending agent, including its thixotropic behaviour for stabilising suspensions and its ability to stabilise reconstitutable dry suspension formulations. cMCC forms a gel-like network and remains stable over a broad range of pH and temperatures.

Despite these strengths, there can be challenges when it comes to activating cMCC. Once dispersed in an aqueous medium, cMCC must be activated so that individual particles deagglomerate and provide optimal suspension properties. To activate it, producers may use water during the milling stage or use high shear agitation. Once activated, cMCC is stable under a wide range of temperature conditions.

Xanthan gum is another common stabilising agent – it is efficient, readily soluble and provides the necessary rheological properties and formulation homogeneity at very low use levels. Xanthan gum is most typically used in formulating reconstitutable dry powder suspensions, although it can also serve as a viscosifier in liquid formulations, typically in combination with cMCC to further aid formulation stability. Furthermore, the desired viscosities and textures can often be provided with only a low level of xanthan gum. At the same time, its pronounced shear-thinning behaviour enables handling of even highly viscous solutions.

Frequently, producers may choose food-ingredient suppliers that are able to generate a pharmaceutical-grade xanthan gum as a supplier. However, this may compromise quality. Manufacturers should preferentially obtain pharmaceutical-grade xanthan gum from a trusted supplier with expertise in pharmaceutical drug formulation.

Lastly, highly purified NaCMC forms clear solutions in water at all temperatures and has exceptional water-binding properties, with the benefit of being available in a wide range of viscosity grades. It can function as a thickener, stabiliser, binder or protective agent in suspension formulations.

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While cMCC can act as a standalone suspending agent, it can also be synergistically incorporated with xanthan gum or NaCMC to allow for a wide range of functionalities. When used properly, these ingredients work together to enhance the sensory experience of the drug product. Appropriate use of functional ingredients, excipients and polymers can help ensure an effective and appealing suspension drug product.

ACHIEVING FORMULATION STABILITY

Formulation stability is critical for an efficacious drug product. When not paired with the right thickening and suspending agents, APIs can agglomerate, resulting in unstable formulations that do not perform as intended. Formulation stability can be affected by several factors, such as pH level, salt content or various ions.

In a suspension formulation, all ingredients must disperse uniformly to function fully and allow accurate dosing. Achieving this outcome depends on the stability of the suspension formulation. Formulation stability largely depends on selecting the right suspending agent.

For formulation stability, it is often recommended that formulators turn to cMCC as an effective suspending agent. Its activated aqueous dispersion forms a strong, gel-like network and functions as a structured vehicle to effectively suspend the active pharmaceutical ingredient in the formulation. Xanthan gum can also be considered, specifically for facilitating reconstitutable suspension formulations, as it remains stable across a wide pH range, when heated and in the presence of salts or acids. Xanthan gum also contributes to the stability of undissolved APIs in the suspension and can be used to fine-tune the rheological features of a formulation.

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In one study, liquid model suspensions were prepared with these excipients, and their rheological properties and stability were evaluated.[1] The findings indicated that cMCC formulations are very stable during four-week storage at room temperature, while xanthan gum formulations are relatively stable to begin with but show slight phase separation in week four. NaCMC formulations are the least stable, with the API settling within one week. This research confirms that cMCC provides optimal stability for oral suspensions, although formulators can consider pairing it with xanthan gum, as needed.

MAINTAINING VISCOSITY AND POURABILITY

For liquid oral suspensions, formulators must consider viscosity and pourability. The viscosity of a suspension at rest and when being poured is critical to the efficacy of the drug. Liquid suspensions at rest will need higher viscosity to help stabilise the API within the suspension to prevent sedimentation and aggregation of the particles. However, during administration, the liquid suspension must become less viscous upon shear for pourability, while retaining pleasant sensory attributes. The right combination of polymers is critical to ensure that viscosity and thickness meet the most stringent standards, while also appealing to patients.

Xanthan gum is efficient and robust as a singular suspending agent at low use levels. At the same time, its pronounced shear-thinning behaviour enables handling of even highly viscous solutions. It can also be used as a secondary ingredient to another suspending agent, such as cMCC, especially as a viscosifier, while also aiding with the stability of oral liquid formulations.

Formulators can boost viscosity with a combination of xanthan gum and NaCMC.[1] The research shows that, at about pH 3.5, suspensions containing only cMCC are not stable, showing phase separation in week four. However, the addition of NaCMC stabilises the suspension, showing a strong synergistic effect.

SENSORY ENHANCEMENT OF THE DRUG EXPERIENCE

Oral liquid suspensions tend to achieve greater patient compliance due to their ability to enhance the sensory attributes of the drug product. Taste, smell, texture and appearance must all appeal to patients, or manufacturers run the risk of poor compliance.

Oftentimes, ingredients in a suspension work against each other to create an end product that can be too gritty or result in a chalky mouthfeel. Formulators can overcome these challenges by selecting the right functional excipients and taste-masking agents at varying levels. Low use levels of xanthan gum can effectively provide desirable textures to improve mouthfeel. Most often, the use levels (in liquids) are 0.05–0.5%. NaCMC can also modify the texture of suspensions for a more appealing mouthfeel. Additionally, carrageenan can offer a natural solution for gelling and thickening.

The appearance of a drug can also impact patient compliance, especially with paediatrics. To achieve the desired visual appeal for suspension formulations, selecting an excipient that has little-to-no colouring is ideal. NaCMC provides a clear suspension vehicle, while xanthan gum offers a translucent or turbid suspension vehicle. On the other hand, cMCC allows for an opaque suspension vehicle.

To help mask unpleasant tastes, formulators may use selective hydrophobic polymers that may also contribute to coating capabilities, such as moisture protection and sustained release. Adding sweeteners can enhance palatability and contribute to viscosity. However, in suspensions intended for paediatric use, the sweetening agent must be less than 5 mg/kg of patient body weight. While taste-masking agents can overcome unpleasant tastes in suspensions, xanthan and NaCMC are flavourless and odourless, making them virtually impossible to detect on their own.

Formulators have a myriad of possible ingredient combinations to choose from that can contribute to specific sensory characteristics, such as texture and taste. Prioritising sensory enhancement, alongside stability and viscosity, can help ensure patient compliance and, in so doing, a drug's effectiveness.

SUPERIOR SUSPENSIONS REQUIRE REGULATORY EXPERTISE

Superior suspensions require manufacturers to consider the regulatory aspect of each ingredient in the formulation. This includes standard excipients, flavouring agents and colourants. It becomes even trickier when taking the global, often unharmonised, regulatory environment into consideration, such as when catering to the growing demand for oral suspensions in China, due to its ever-growing geriatric population.

While there are several high-quality suppliers of any given pharmaceutical excipient, it is not guaranteed that they understand the complex regulatory environment and intricacies of oral suspension formulations. From the complexities of the US FDA's Inactive Ingredient Database to the intricacies of excipient regulations in countries like China, partnering with an ingredient supplier with extensive experience in the field can help formulators navigate these markets and overcome regulatory challenges.

It is anticipated that demand for suspensions will continue to rise in the coming years, specifically for liquid oral formulations. This demand will likely be especially pronounced in countries with large paediatric and geriatric populations, such as the US and China. It is also expected that demand for suspensions will be driven by over-the-counter medications, such as ibuprofen, and antibiotics, such as amoxicillin. A solid supply partner with expertise in the field can help manufacturers navigate common formulation challenges to achieve superior suspensions that will appeal to patients and increase compliance rates in low-compliance populations.

ABOUT THE COMPANY

IFF Pharma Solutions is a global leader in food, beverage, health, biosciences and sensorial experiences. For more than 130 years, the company has been focused on finding the most innovative solutions to help bring "better for you" products to market. While it has grown over the years, IFF remains agile in its approach and puts its customers' needs at the forefront of the company's thinking. IFF's product portfolio includes the taste, texture, scent, nutrition, enzyme, culture, soy protein and probiotic categories.

REFERENCE

1. *Zhang Y et al, "Comparison of Commonly Used Pharmaceutical Suspending Agents". AAPS National Biotechnology Conference, Oct 2021, Poster.*

ABOUT THE AUTHORS

Rina Chokshi is the Global Commercial Marketing Manager for IFF Pharma Solutions. In this role, she is responsible for developing and implementing the global and regional marketing strategies for IFF Pharma's product portfolio. Dr Chokshi has over 18 years of experience in the pharmaceutical industry and extensive knowledge in oral solid dosage form development. She led a team of R&D and technical service scientists for the development and launch of new products, such as Avicel SMCC (DuPont, DE, US) and Aquateric N100 (DuPont, DE, US). Dr Chokshi earned her bachelor's degree in Pharmaceutics from the University of Mumbai (India) and her master's and PhD in Applied Pharmaceutical Sciences from the University of Rhode Island (US).

Dago Caceres is the Global Strategy Director for IFF Pharma Solutions. In this role, he leads the creation of strategies and strategic plans to ensure alignment of a business's vision with its activity, to achieve sustainable, long-term growth. Throughout his career, Mr Caceres has taken on many roles in developing market-driven strategies that have cultivated an extensive expertise in product, field and strategic marketing, as well as in commercial and business development. Mr Caceres has a degree in chemical engineering from the National University of Colombia (Bogotá, Colombia) and an International MBA from the Darla Moore School of Business at the University of South Carolina (US).