DOSAGE FORM FOCUS

Oral Solutions & Suspensions: The Art of Pharmacy

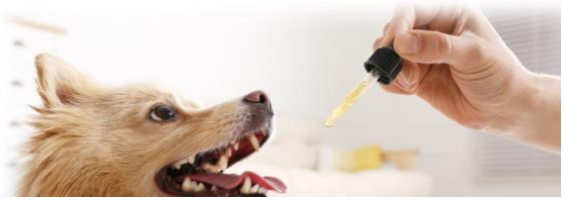
By Devan Patel, Senior Director, Project Management

In the dominant oral dosage delivery market, experts agree that liquid formulations are a viable and lucrative alternative to pills, tablets, and capsules that are difficult to take for some patient populations. Liquid formulations, such as solutions, suspensions, and emulsions offer dosing flexibility, a reduced risk of choking, and can be applied to geriatric, neonatal, and pediatric patients. Additionally, oral liquids assist with bioavailability because the drug is already in solution. Despite the advantages, there are challenges associated with liquid dosage, such as stability and palatability, parameters that need to be considered in the design. Formulating the right oral liquid dosage form in early-stage development depends on the art of pharmacy.

Solutions

Simply put, an oral solution is a medicine in liquid form. The oral solution is mixed with water and taken immediately. There are basically two types of solutions – syrups and elixirs – each presenting advantages as well as specific formulation challenges.

Syrups —
These are aqueous solutions containing sugar or sugar substitutes, with or without flavor agents. Sometimes they do not even contain a drug. Syrups provide a pleasant means of administrating a liquid from disagreeing tasting drugs. Think of them as a coating. The sweeter the syrup, the easier it is to trick the tongue into letting the drug through to the body. The sweetener, such as sucrose or high fructose corn syrup, has a built-in antimicrobial preservative, making the syrup more stable. Thickeners can be added to as well as a color agent. Formulators say to take note that the U.S. and Europe have different regulatory requirements for artificially sweetened syrups, which can create some development issues.



Elixirs —
Thinner than a syrup, elixirs are sweetened hydro-alcoholic (water and alcohol) liquids for oral use. Certain drugs, because of their solubility, require alcohol in the formulation. Typically, alcohol and water are used as solvents when the drug will not dissolve in water alone. Because an elixir can be 10 to 12 percent alcohol, they are self-preserving. In addition to active drug, elixirs usually contain flavoring and coloring agents to improve patient acceptance.

With all oral liquid solutions, dosing needs to be precise. An oral syringe, spoon or medicine cup should be provided to the patient to ensure accurate dosing. Additionally, flavoring liquids in early-stage development is a challenge because they cannot be tasted. In the art of pharmacy, some will turn to the artificial or electronic tongue, which perform electronic testing. Taste can be modified in the later stages of development to make the liquid more palatable.

Aqueous Suspensions

An aqueous suspension consisting of an active ingredient that is insoluble or sparingly soluble in water and a suspending agent. In a suspension, the medicine is mixed with a liquid, usually water, in which it cannot dissolve and, therefore, remains intact in the form of small particles. From a dosing perspective, one can give more drug with a suspension than a solution. Suspensions do require a lot of thickener to keep them from settling.

In general, suspensions can be more difficult to manufacture than a solution. One particular challenge is that the particle size has to be perfect; if the size is too fit, it will settle too quickly and if too small, they will eventually disappear. This is called Ostwald ripening. Again, this is where the art of pharmacy can be used to formulate a suspension using excipients that will prevent temperature from impacting particle size. Formulators will store the suspension at various temperatures to make a stabilized suspension.

The selection of an appropriate suspending agent is one of the most crucial factors in formulating an oral suspension. The factors considered in the selection of the appropriate suspending or viscosity enhancing agents include desired rheological property, suspending ability in the system, pH stability, chemical compatibility with drug substance and other excipients, reproducibility, and hydration time.[1]

Finally, it is important that a suspension formulated in early-stage development can be scalable during manufacturing. Pii, for example, can manufacture up to 300 gallons or 600 liters in formulation development.

Emulsions

Sometimes the only way to formulate a product is via emulsion. Emulsions are liquid preparation that can be either be an oil in water emulsion (O/W), water in oil emulsion (W/O) or multiple emulsions (water in oil in water (w/o/w) or oil in water in oil (o/w/o)). *Note: Ostwald ripening is often found in water-in-oil emulsions where oil molecules will diffuse through the aqueous phase and join larger oil droplets. Over time, this causes emulsion instability and eventually phase separation*.

Advantageous characteristics of an emulsion include[2]:

- Increased drug solubility: many drugs have limited aqueous solubility but have maximum solubility in oil phase of emulsion.
- Increased drug stability: many drugs are more stable when incorporated into an emulsion rather than in aqueous solution.
- Prolonged drug action: incorporation of a drug into an emulsion can prolong bioavailability.
- Improved taste: drugs with unpleasant taste are more palatable and thus more conveniently administered in emulsion form.

However, emulsions can be problematic to flavor as they have a propensity to denature or separate. This is because the flavor goes into the oil base and causes the emulsion to separate. As a result, only certain flavoring agents work with emulsions.

Summary

There are distinct advantages to using oral liquid medications. For older adults who have swallowing difficulties, oral solid dosage forms can be switched to suspensions or solutions. And for pediatric populations, oral liquid drugs offer flexible dosing and can be swallowed more easily. Palatability is improved via sweeteners, and smaller, more precise dosing can be better tolerated. An experienced contract development and manufacturing organization (CDMO) that understands the formulation challenges associated with oral solutions, suspensions, and elixirs can ensure that your product successfully reaches larger scale manufacturing. The key is starting in the early stages with the art of pharmacy.

References

1. Excipients Used in the Formulation of Pharmaceutical Suspensions, Pharmaceutical Technology, May 9, 2021.
2. Specialized Pharmaceutical Emulsions, Feb. 6, 2018.

ABOUT Pii

Pharmaceutics International, Inc. (Pii) is a US-based contract development and manufacturing organization (CDMO) located in Hunt Valley, Maryland. The experienced scientists, engineers, and staff at Pii pride themselves on adroitly employing a phase appropriate method of drug development for the prudent use of their client's resources as they solve challenging problems. In addition to offering end-to-end development services, Pii manufactures a variety of dosage forms to include complex parenteral drugs and has a wealth of analytical testing capabilities. Its Hunt Valley campus has four aseptic suites with lyophilization capabilities. Our talented professionals stand ready to help!

ABOUT THE AUTHOR

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Devan Patel joined Pii in 2012 as a member of the Project Management team.

Devan has held roles of increasing responsibility in Project Management leading key development and commercial programs for Pii for both the orals and injectables. With his leadership, Pii has built a world-class Project Management Organization (PMO) consistently characterized by superb customer experience. Over the years, Devan has used his knowledge and technical skills to play a vital role for the Operations team, managing key initiatives for the Parenteral/Sterile business unit, including managing the overall scheduling and planning of all Aseptic Operations. His collaborative style when working with cross-functional teams across Pii's business units and ability to anticipate problems before they occur as raised the role of project management to an artform. Devan delivers a positive, outcomes-focused experience for our client-partners, from initial contact through successful completion of each project.

Devan earned his Bachelors in Cell Biology and Molecular Genetics from the University of Maryland and a M.B.A. from Johns Hopkins University.

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