A REVIEW ON EXCIPIENTS USED IN ORAL LIQUID DOSAGE FORMS

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Received on 19-01-2017 Accepted on: 20-03-2017

Abstract:

Excipients play an important role in formulating a dosage form. These are the ingredients which along with Active Pharmaceutical Ingredients make up the dosage forms. In most of the formulations these are present in a greater proportion with regards to active pharmaceutical ingredient, as it forms about the bulk of the formulation, it is necessary to select an excipient which satisfies the ideal properties for a particular excipient. Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are include in the manufacturing process or are contained in a finished pharmaceutical product dosage form. Excipients act as protective agents, bulking agents and can also be used to improve bioavailability of drugs in some instances. Excipients as like other active pharmaceutical ingredients need to be stabilized and standardized. Excipient quality plays a vital role in assuring safety, quality and efficacy of dosage forms.

Keywords: Excipients, Wetting agent, Surfactants, Buffering agents, Preservatives, Antioxidants.

Introduction:

Compared to conventional tablets and capsules, oral liquid dosage forms including solutions, syrups, suspensions, elixirs, and concentrates offer unique advantages to many patients. The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing¹-² Orally disintegrating tablets are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphagia³ For example, liquids may provide better patient compliance for those with swallowing difficulties and better dosage control versus a fixed tablet dose. However, there are also a number of “challenges” surrounding the formulation and development of these forms. Hence, liquid dosage forms are generally
formulated for use in geriatric and pediatric patients. But, this section of patients have been regarded as a small fraction of the overall population, pharmaceutical companies often develop oral liquid formulations out of necessity rather than responding to a patient need. However, there are potential advantages of oral liquid dosage forms, such as no dissolution time and rapid absorption from the stomach/intestines compared to tablets, which may be an important factor for pain-relieving drugs. Inherent in this benefit is the risk of reaching peak plasma levels too fast, which could be harmful. Finally, as the excipient technology advances, a controlled release profile in liquid dosage forms will likely become readily available.\textsuperscript{[4-8]}

**Formulation of liquids**

Oral liquids are formulated as solutions, suspensions and emulsions depending on the nature of the active ingredient particularly solubility and stability. They are also designed as ready to use liquids and powders for reconstitution into liquid orals like syrups, solutions, suspensions and emulsions\textsuperscript{[9]}. Liquid formulation needs various excipients including vehicle, solubilizer, stabilizer and viscosity builder, preservative and off course sweeteners, colour and flavour. The selection of these excipients is of major concern to design stable, effective and palatable oral liquid formulation.

**Selection of Excipients**

Characteristics of active drug are of major concern in developing an oral liquid dosage formulation. The major challenges in developing oral liquid dosage forms are (i) The stability of a drug in solution (ii) The solubility of a drug at the required level and (iii) An acceptable taste. It is the effective use of excipients, which allows formulators overcome these challenges. Additionally, an excipient’s compatibility with a drug in the solid state cannot infer the same compatibility in solution. However, if the mechanism of degradation of the drug is understood, the process of selecting suitable excipients to use in a solution will be much easier. Finally, some knowledge of the drug’s physical and chemical characteristics such as the solubility, pH stability, and pKa value (s) of reactive functional groups is essential in order to choose the proper excipients, effectively.

Ideally, the pH at which the drug is most stable would also be close enough to the solubility for delivering the desired dose in a tea spoon (approximately 5 mL). Requiring patients to take more than two tea spoon full at a time may not be advisable because of lower patient compliance. In such conditions, a simple oral solution or syrup formulation may be developed\textsuperscript{[10]}. However, if the pH at which the drug is most stable is not one at which there is enough solubility,
suspension formulation may be required. A quick means to identify whether or not a drug may be more suitable for solution or suspension is to overlap the pH-stability profile with the pH-solubility profile. This overlap creates a window, which may suggest which dosage form might be most desirable and subsequently the type of excipients needed.

**Excipients for Oral Liquid Formulations:**

Oral liquid formulation needs a meticulous blend of ingredients to perform various functions like wetting and solubilisation, stabilization and to impart suitable colour, taste and viscosity. The blend should be compatible, non-reactive and stable\[11\]. The common excipients generally required for any liquid formulation are vehicles (base), viscosity builders, stabilizers, preservatives, colours and flavours. In addition, solubilizers are required in case of clear liquids, suspending agents are needed for suspensions and emulsifying agents for emulsions.

**Wetting Agents and Surfactants**

Wetting agents are routinely used in pharmaceutical formulations, especially in liquid dosage forms to create a homogeneous dispersion of solid particles in a liquid vehicle. This process can be challenging due to a layer of adsorbed air on the particle’s surface\[12\]. Hence, even particles with a high density may float on the surface of the liquid until the air phase is displaced completely. The use of a wetting agent allows removal of adsorbed air and easy penetration of the liquid vehicle into pores of the particle in a short period of time. For an aqueous vehicle, alcohol, glycerin, and PG are frequently used to facilitate the removal of adsorbed air from the surface of particles. Whereas for a non-aqueous liquid vehicle, mineral oil is commonly used as a wetting agent. Typically, hydrophobic API particles are not easily wetted even after the removal of adsorbed air. Hence, it is necessary to reduce the interfacial tension between the particles and the liquid vehicle by using a surface active agent. Structurally, wetting agents comprise branched hydrophobic chains with central hydrophilic groups or short hydrophobic chains with hydrophilic end groups. For example, sodium lauryl sulfate is one of the most commonly used surface-active agents. Such surfactants, when dissolved in water, lower the contact angle of water and aid in spreadability of water on the particles surface to displace the air layer at the surface and replace it with the liquid phase. Wetting agents have a hydrophilic-lipophilic balance (HLB) value between 7 and 9.

**pH Modifiers and Buffering Agents**

The pH of an oral liquid formulation is a key point in many regards. Control of the formulation pH, could prevent large changes during storage. Therefore, most formulations utilize a buffer to control potential changes in the solution pH. The
amount of buffer capacity needed is generally between 0.01 and 0.1 M and a concentration between 0.05 and 0.5 M is usually sufficient. The selection of a suitable buffer should be based on

(i) Whether the acid-base forms are listed for use in oral liquids,

(ii) The stability of the drug and excipients in the buffer, and

(iii) The compatibility between the buffer and container.

A combination of buffers can also be used to gain a wider range of pH compared to the individual buffer alone. However, not all buffers are suitable for use in oral liquids. For example, a boric acid buffer may be used for optical and IV delivery but not in oral liquids because of its toxicity. Stability of formulation containing non-ionizable API may also depend on pH. For example, a specific functional group or a particular resonance structure that is stabilized in a specific pH range may facilitate a reaction between the excipient and the drug. However, the buffer may negatively influence the solubility of the drug and other excipients.

The effect depends on a combination of the polarity of the solute and of the salt. Non-polar solutes are solubilized (salted in) by less polar organic salts and are desolubilized (salted out) by polar salts. Conversely, polar solutes are salted in by polar salts and salted out by organic salts. The stabilizing effect of buffers that have multiple charged species in solution could also determine the potential reaction between excipients and API. For example, buffers that use carbonates, citrate, tartrate, and various phosphate salts may precipitate with calcium ions by forming sparingly soluble salts. However, this precipitation is dependent upon the solution pH. The activity of phosphate ions may be lowered due to interactions with other solution components.\textsuperscript{[13]}

**Suspending Agents and Viscosity-modifying Agents**

One of the most crucial factors involved in formulating a pharmaceutical suspension is the selection of an appropriate suspending agent. Suspending agents impart viscosity, and thus retard particle sedimentation. Other factors considered in the selection of the appropriate agent include desired rheological property, suspending ability in the system, chemical compatibility with other excipients, pH stability, length of time to hydrate, batch-to-batch reproducibility and cost. Suspending agents can be classified into cellulose derivatives, clays, natural gums, and synthetic gums. In many cases, these excipients are used in combination. For each agent, the concentration of use and the respective property such as ionic charge, water dispersibility, pH range, rheological flow behavior was determined.\textsuperscript{[14]}
**Vehicles:** Vehicles, in pharmaceutical formulations, are the liquid bases that carry drugs and other excipients in dissolved or dispersed state. Pharmaceutical vehicles can be classified as under: Aqueous vehicles: Water, hydro-alcoholic, polyhydric alcohols and buffers. These may be thin liquids, thick syrupy liquids, mucilages or hydrocolloidal bases. Oily vehicles: Vegetable oils, mineral oils, organic oily bases or emulsified bases.

1. **Water**

Purified water is obtained by distillation, ion exchange treatment, reverse osmosis or other suitable process. Water is intended for use in preparation of aqueous dosage forms except those intended for parenteral administration. Natural water contains large number of dissolved and suspended impurities. The dissolved impurities include inorganic impurities like salts of sodium, potassium, calcium, magnesium and iron as chlorides, sulfates and bicarbonates. Organic impurities present in purified water are either in soluble or insoluble state. Micro-organisms are the other impurities and the load of micro-organism in natural substances including water is called as bio-burden. Drinking water, termed as potable water in many texts, contains less than 0.1% of total solid and in United States; they should meet the requirements of U.S. Public health services regulations with respect to bacteriologic purity (Bio-burden). In general, acceptable drinking water should be clear, odourless, colourless and neutral with slight deviation in pH (due to dissolved solids and gasses). However, drinking water is not usable in pharmaceutical formulation, obviously due to the possible incompatibility of formulation components with dissolved impurities in water. Purified water USP is allowed for usage as vehicle or as a component of vehicle for aqueous liquid formulations except for those intended for parenteral administration (injections). It is obtained by distillation, ion exchange treatment, reverse osmosis or any other suitable process from water complying with the Federal Environmental Protection Agency with respect to drinking water.

2. **Alcohol (Ethyl Alcohol)**

It is used as a primary solvent for many organic compounds. Alcohol has been well recognized as a solvent and excipient in the formulation of oral pharmaceutical products. Next to water, alcohol is the most useful solvent in pharmacy. It is invariably used as hydro-alcoholic mixture that dissolves both water soluble and alcohol soluble drugs and excipients. Diluted alcohol NF, prepared by mixing equal volumes of Alcohol USP and purified water USP is a useful solvent in various pharmaceutical processes and formulations.
3. Glycerol

Glycerol (or Glycerin) is a clear, colorless liquid, with thick, syrupy consistence, oily to the touch, odourless, very sweet and slightly warm to the taste. When exposed to the air, it slowly abstracts moisture\(^\text{[18]}\). It is miscible with both water and alcohol. As a solvent, it is comparable with alcohol but because of its viscosity, solutes are slowly soluble in it unless it is rendered less viscous by heating. Glycerol is obtained by the decomposition of vegetable or animal fats or fixed oils and containing not less than 95 percent of absolute Glycerin. It is soluble in all proportions, in Water or Alcohol; also soluble in a mixture of 3 parts of Alcohol and 1 part of Ether, but insoluble in Ether, Chloroform, Carbon Disulphide, Benzin, Benzol, and fixed or volatile oils. Glycerin is used as vehicle in various pharmaceutical products like Elixir of Phosphoric acid, Solution of Ferric Ammonium Acetate, Mucilage of Tragacanth, Glycerin of boric acid, Glycerin of tannic acid, and in many Extracts, Fluid Extracts, Syrups and Tinctures. As glycerin is an excellent solvent for numerous substances, such as iodine, bromine, alkalies, tannic acid, many neutral salts, alkaloids, salicin, etc., it is a good vehicle for applying these substances to the skin and to sores. It does not evaporate nor turn rancid, and is powerfully hygroscopic\(^\text{[19]}\). As glycerin is sweet, it is an excellent flavouring agent. It is demulcent, and is used as a vehicle for applying substances, such as tannic acid, to the throat. It is rarely given by the mouth for any medicinal virtue. It has been administered for dyspepsia, for diabetes, and as a nutritive agent, but in each case without any good result. In oral liquid formulations, glycerin is used as co-solvent to increase solubility of drugs that show low solubility in water. It is also used to improve viscosity, taste and flavor. In external applications it is used as humectants.

4. Propylene Glycol USP

Pharmaceutical grade of Propylene Glycol is monopropylene glycol (PG or MPG) with a specified purity greater than 99.8\%\(^\text{[20]}\). Propyleneglycol has become widely used as a solvent, extractant and preservative in a variety of parenteral and non parenteral pharmaceutical formulations\(^\text{[21]}\). PG is an important ingredient for a multitude of uses, including:

- Solvent for aromatics in the flavour-concentrate industry
- Wetting agent for natural gums
- Ingredient in the compounding of citrus and other emulsified flavours
- Solvent in elixirs and pharmaceutical preparations
- Solvent and coupling agent in the formulation lotion, shampoos, creams and other similar products
• Very effective humectants, preservative and stabilizer

Preservatives

Preservatives are substances added to various pharmaceutical dosage forms and cosmetic preparations to prevent or inhibit microbial growth. An ideal preservative would be effective at low concentrations against all possible microorganism, be non-toxic and compatible with other constituent of the preparation and be stable for the shelf-life of the preparation.

Microbiological contamination presents a significant health hazard in oral liquids. Therefore, the use of preservatives become inevitable to prevent the growth of microorganisms during the product’s manufacture and shelf life, although it may be most desirable to develop a “preservative-free” formulation to address the increasing concerns about the biological activity of these compounds. Most formulations require some kind of preservative to ensure no microbial growth\[22\]

The majorities of preservatives are bacteriostatic rather than bacteriocidal, and consists of both acid and nonacid types. Among the acidic types are phenol, chloro-cresol, 9-phenyl phenol, alkyl esters of para-hydroxybenzoic acid, benzoic acid, boric acid, and sorbic acid, and their respective salts\[23\]. Therefore, the pH of solution, and the pKa of the preservative need to be carefully evaluated prior to selecting a preservative for a formulation. Neutral preservatives include chlorobutanol, benzyl alcohol, and beta-phenylethyl alcohol. Under alkaline conditions, it is generally regarded that microbial growth is insignificant and at these pH values, the need for a preservative is not generally recommended\[24\]. Preservatives often contain reactive functional groups, which are responsible for their antimicrobial activity but lead to unwanted reactions. Therefore, in addition to the excipient’s antimicrobial activity, other parameters should be evaluated during the formulation development for its compatibility with the API, other excipients, and the container system.

Antioxidants

Antioxidants are currently used as efficient excipients that delay or inhibit the oxidation process of molecules. The oxidation of an API in an oral liquid formulation is difficult to control due to low activation energies (2-12kcal/mol) for oxidation and photolysis compared to solvolysis, dehydration, and polymorphic transformations (10-56kcal/mol). Trace amounts of impurities, which are invariably present in the API or excipient catalyses the oxidation reaction\[25\]. Most
drugs exist in a reduced form, show increased instability when the solution is consistently introduced into an atmosphere of 20% oxygen. The pH of the solution may affect the oxidation of phenolic and sulfhydryl group containing drugs because it is principally the ionized form of these drugs that participate in the oxidation. For example, epinephrine is only slowly oxidized at pH < 4 but rapidly degrades under alkaline pH conditions[25].

Antioxidants can be compounds that can reduce a drug that has been oxidized, or compounds that are more readily oxidized than the agents they are to protect (oxygen scavengers). Many of the lipid-soluble antioxidants act as scavengers[26]. Antioxidants can also act as chain terminators, reacting with free radicals in solution to stop the free-radical propagation cycle. Mixtures of chelating agents and antioxidants are often used because there appears to be a synergistic effect. This occurs because many of the agents act at differing steps in the oxidative process[27-29]

Flavouring agent

Flavour refers to a mixed sensation of taste, touch, smell, sight and sound, all of which involve a combination of physico-chemical and physiological actions that influence the perception of substances. With the expansion of technology in the flavour industry, many artificial or imitation flavours have been created. Flavours used in formulation must be non-toxic, soluble (if for a clear product like syrup elixir) and stable and compatible with the preparation. Masking of few flavours is very difficult due to their complexity like male fern extract which is initially sweet, then astringent and finally bitter. Also sweetening agents that raise the blood sugar or increase caloric intake cannot be included in formulations for diabetics or patients or reducing diet respectively [30-33]

Conclusion

Excipients plays vital role in pharmaceutical dosage forms, it must be evaluated for their safety and stability. The various excipient interactions like drug-excipient interactions, excipient-excipient interactions and package-excipient interactions may render the excipient harmful for use in formulation. In order to avoid the use of incompatible excipients and to assure that that the excipients are safe and stable for use in the designing of the formulation, various stability testing procedures are carried out where the excipients are subjected to extreme conditions of temperature, humidity etc. If the stability testing data is in favor of the use of excipient in formulation the excipients are further tested for assuring safety, which is the most important feature of any formulation intended to be used in humans or animals. It is also important to note that the physical and chemical stability of a drug does not necessarily equate with its efficacy and safety in patients
As new excipients emerge, it's important to recognize their potential use in various complex delivery systems. The safety assurance of excipients helps the formulator to design an effective and safe dosage form with the use of efficient and safe excipients. Thus for an excipient to be in a formulation it must be highly stable, safe and efficacious, and above all it must comply with the expected performance in the formulation.

References:


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