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Review Article

REVIEW ON ORAL SUSPENSIONS FOR PAEDIATRIC PATIENT

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Abstract
Majority of the conventional dosage form are unacceptable for paediatric patients, since have different developmental needs and dosing requirements than other segments of the population. The prerequisites for a quantifiable dosage form to provide depending on bodyweight and also flavour profile are two of the obstacles specific to paediatric oral formulations, making them quite scientifically difficult to design. The biopharmaceutical and physicochemical properties of the active pharmaceutical ingredient such as physical or chemical stability, solubility are determine which formulation is suitable. More regulatory incentives have recently led to an increase in the development of paediatric formulations. The aim of this review is to provide the information about the recent approaches to oral suspensions, its various limitations and advantages, the rationale on formulation of oral suspension, different excipient used in formulation, some marketed formulations.

INTRODUCTION

Paediatrics is the specialty of medicine that deals with treating new-borns, kids, teenagers, and young adults. As paediatric patients have different developmental needs and dose requirements than other segments of the population, the majority of traditional drug delivery systems are not appropriate for them. Suspensions can be described as preparations with finely divided drug particles dispersed almost uniformly throughout a vehicle, with or without stabilisers and other additives, and when the drug demonstrates a minimal level of solubility[1]. Pharmacies may have difficulties when preparing liquid oral dose forms for paediatric patients. Oral paediatric formulations might be single-use, multiple-use, or involve manipulation. The best showing for preservative-free paediatric formulations has led to less multiuse solutions or suspensions in favour of single-use oral dosage forms, which has been the most important advancement.

Numerous recent improvements in paediatric formulations were initially sparked by appropriate government regulation incentives that promoted the creation of paediatric formulations. Now that the novel chemical entity is in phase 2 clinical trials, it is standard procedure to begin developing paediatric formulations. Although the licensed medicinal products manufactured by licensed pharmaceutical companies are often inappropriate for safety of paediatric patients. Applications for marketing-authorization of investigational medicines must include a Paediatric investigative plan (PIP) since the Paediatric Regulation took effect in 2007. It should be noted that this only applies to medications with new active pharmaceutical ingredients (API) and has occasionally been accomplished effectively. Since so many years, oral drug administration has become the most extensively used method for systemic drug delivery among all the pharmaceutical goods on the market. The advantages of the oral dosage form are ease of administration, patient compliance, and formulation stability which led to its high level of acceptability.

The antibacterial oral suspensions contains preparations of antibiotics (e.g, erythromycin derivatives), Sulfonamides (e.g, sulphamethoxazole), other anti-infective agents (e.g, methenamine mandelate) or combination of these agents (e.g, sulphamethoxazole-trimethoprim). Infants, children, and adult patients who prefer liquid over solid preparations can easily intake the antibiotic oral solution, such as those prepared by reconstitution.

Despite the fact that studies have shown that a oral solution that has been dissolved in a liquid is stable for 24 hours after preparation, though when kept in refrigeration for the specified amount of time (often 7 to 14 days, depending on the preparation), reconstituted solution stays stable. This time period is enough to complete a prescription schedule of a patient, however if the

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medication remains after the prescribed course, then it should be discarded as it would be unsafe for use. Because the supplied dose is dependent on the patients' weight and age, the fixed single doses are a significant limitation of these dosage forms. Some propose mini-tablets in that case as they improve the flexibility of dosing. But for paediatric patients, oral suspensions forms are the gold standard because they enable accurate dosing by taking out the right amount from a multi - dose container[2].

Advantages of oral suspensions[3]

- Therapeutic drugs with limited solubility can be delivered using suspensions, which is a helpful drug delivery technique.
- Pharmaceutical suspensions may be used as an alternative method of drug administration for patients who have trouble swallowing solid dosage forms, such as children, geriatric patients, and older adults.
- The bioavailability of drugs in suspension is higher than that of other dose forms. Solution > Suspension > Capsule > Compressed Tablet > Coated Tablet are in order of decreasing bioavailability.
- Physical variables including temperature, sedimentation rate, and liquid flow characteristics have little effect on drug dosage.
- Controlling the duration and onset of activity, for example, using Protamine Zinc-Insulin suspension can be done and also when certain medications are made as suspensions, their chemical stability can be increased, for example with Procaine Penicillin G.

Disadvantages of oral suspensions[3][4]

- The physical parameters that affect drug dosage vary from such the storage temperature, the formulation's rate of sedimentation, the viscosity and pourability of the liquid, content homogeneity, flocculation, and redispersion.
- Because it's a bulk formulation, there's a potential that a single dose won't be accurate.
- As pharmaceutical suspensions are inherently unstable, it takes competence in formulation to guarantee that the formulation's physical stability is maintained throughout the shelf-life.
- During storage, breakage and caking take place.

Reasons for formulation of oral suspensions[3]

- The drug's lacklustre chemical stability in an aqueous medium is the most frequent justification for the manufacture of suspensions for reconstitution.
- To produce sustained and controlled medication release.
- to cover off the drug's unpleasant aftertaste.
- Avoiding the physical stability issues that are frequently present in conventional suspensions is another factor in the formulation of suspensions.
- Drugs which are in the suspensions form a resistance towards degradation effects like oxidation and reduction

Global Standards and Guidelines for the Development of Paediatric Drugs

Global regulatory organisations, including the USFDA, the European Medicines Evaluation Agency (EMEA), and the Central Drugs Standard Control Organization (CDSCO), have passed legislation requiring the evaluation of the efficacy and safety of new medications and off-patent medications in paediatric populations.

The CDSCO and Drug Control General of India are responsible for enforcing Schedule Y of the Drugs and Cosmetics Act 1940 and Rules 1945, which provides criteria for performing clinical investigations in paediatric patients (DCGI). In order to encourage and support the development of better and safe paediatric medication products, the European Paediatric Formulation Initiative (EPFI) was established in 2007.

In order to raise awareness about the enhanced accessibility and availability of child-specific medications, WHO established the "make medicines child size" programme in 2007[5]. The FDA Safety and Innovation Act (FDASIA) was passed in 2012, and one of its provisions mandates that sponsors who intend to submit an application for a medication subject to PREA do so as soon as possible in the development process by submitting an initial paediatric study plan (iPSP).

The European Medicines Agency (EMA) published a guideline on pharmaceutical development of medications for paediatric use in 2013. It covers a number of formulation development considerations, including drug properties, excipient selection and frequency of dosing, formulations with modified release, tolerability, container closure systems, dose-measuring devices, administration devices, and packaging of medications for children.
According to FDASIA, USFDA released draught guidance on the format and procedure for filing an iPSP in March 2016. In a document titled "Points to Consider" in the Development of Paediatric Drugs, the World Health Organization (WHO) outlines various aspects of drug development, including desirable characteristics of paediatric drugs, flexible dosage forms, formula design, excipient safety, taste masking, dosage forms pertinent to oral, rectal, parenteral, dermal, and inhalation route of administration, packaging, and labelling [6].

ICH guidelines for oral suspension[3][7]

Generally, more than one test is done for powders and liquids used for reconstitution as oral liquid.

a) Uniformity of dosage form

This statement refers to both the dosage form's mass and the amount of the active ingredient it contains. Either one of them should generally be included in the specification. When applying weight variation for new drug products that surpass the threshold value to permit testing consistency by uniformity of weight, candidates should ensure that the uniformity of the product is sufficient during drug development. Tests may be carried out during development, if necessary, but the specification should contain the acceptance criteria

b) pH

The intended range along with the acceptance criteria is provided for wheather it is applicable or not.

c) Dissolution

Along with the qualities mentioned above, it would be useful to add dissolving testing and acceptance standards for oral suspensions and dry powder formulations for resuspending. Testing for dissolution should take place before release. Ordinarily, immediate-release dose forms are seen to be acceptable for single-point measurements. Modified release dose forms should be sampled at many points at suitable intervals.

d) Rheological Properties

Rheological parameters (viscosity/specific gravity) may be appropriate to include in the specification for somewhat viscous mixtures or suspensions.

e) Water content & Alcohol content

When suitable, a water content test and acceptability criteria for oral products that need reconstitution should be recommended. Loss on drying is typically regarded as satisfactory if the impact of absorbed moisture vs. water of hydration has been sufficiently characterised throughout the product's development. The alcohol amount should be stated if it is indicated quantitatively on the labelling in conformity with applicable laws. It could be measured or computed.

Drug Properties

Drug ingredients come in a variety of forms, including acidic, basic, ampholytic, zwitterionic, and salt forms. When creating flexible formulations, it's crucial to take into account drug features such molecular weight, dissociation constant (pKa), polymorphism, particle size, solubility, permeability (logP), stability, and flavour. The dry mixture, or composition, must be a consistent mixture of the right amount of each ingredient during manufacturing. It must not separate into an uneven mixture because this could lead to dosing problems. The powder mixture must promptly and thoroughly disperse in the aqueous medium during reconstitution. To provide a precise and consistent dose, the patient must be able to redisperse and pour the reconstituted suspension with ease[8].

Excipients used

Excipients are chosen based on their suitability for reconstitution as well as the desired physical form of powder mixture. The number of excipients in a formulation should be kept to a minimum because the more excipients there are, the higher the risk of issues. Upon reconstitution, all excipients should diffuse quickly. This standard rule out a number of suspending agents. Numerous preservatives are also inappropriate[3].

Suspending agents

Suspending agents also known as thickening agent used in the oral formulations when active ingredients in oral liquids have low water solubility, two-phase systems (liquid with solid particles scattered in it) frequently occur. The aqueous solution becomes viscous due to the presence of thickening agents, which also slow down caking and the rapid sedimentation of suspended particles. Suspending agent also help with the stability of the formulation for their surfactant activity. During reconstitution, rapid hand shaking should be able to quickly disperse any suspending agents. This eliminates a number of popular suspending agents since they need to be hydrated, heated, or mixed with high shear to achieve optimal dispersion. Natural polysaccharides like tragacanth and xanthan gum as well as semi-synthetic polysaccharides like hydroxyethyl cellulose are well-known thickening agents. Besides that, acacia, carboxymethylcellulose sodium, lota carrageenan, microcrystalline cellulose with carboxymethylcellulose sodium, Povidone, propylene glycol alginate, silicon dioxide, Sodium starch glycolate are being used as thickening agent. Some other commercially used suspending agent combinations are Avicel RC 591, Avicel RC 581 and Avicel CL 611[1]. A typical suspending agent is a mixture of sodium carboxymethylcellulose and microcrystalline cellulose. Considering sodium carboxy methyl cellulose and microcrystalline cellulose are anionic substances, they cannot be used with many cationic excipients[7].

Wetting agents

Many medications in oral suspension are hydrophobic, meaning they defy moisture and are difficult to wet. For optimal drug dispersion at the lowest possible effective concentrations, the formulator must use the proper wetting agent. Extra wetting agent has the tendency to froth and taste bad. Surfactants like Polysorbate 80, Hydrophilic

colloid like acacia, guar gum, Solvents like glycerine, polyethylene gycol and polypropylene glycol are mainly used as wetting agents [8].

Sweeteners

Sweeteners are used to increase the patient acceptency. The suspending agents in drugs, especially clays, are typically unpleasant and have a bland flavour. Sweeteners help cover up the unpleasant flavour. A flavouring agent is also used alongside with sweeteners in case sweetening agents are not capable of complete taste masking. Sucrose, Mannitol, Aspartame, Sodium Saccharin, and Dextrose are the sweeteners that are widely used. In the colon, sucrose is hydrolyzed to the monosaccharide's glucose and fructose, that should be avoided by paediatric patients with fructose intolerance. In contrast, an optimal frequent consumption for artificial sweeteners such sodium saccharin, sodium cyclamate, or aspartame must be taken into consideration. Sorbitol and Sorbitol solution are contraindicated for these people and may produce osmotic diarrhoea. The addition of saccharin or its salts is prohibited in paediatric preparations [2].

Preservatives

Preservatives used in liquid oral dosage forms include sodium benzoate, potassium sorbate, methyl-4-hydroxybenzoate, propyl-4-hydroxybenzoate, and propylene glycol. The creation of suspensions for the unique needs of paediatric patients remains a crucial task in pharmacies, despite new rules and the emergence of promising new dose forms. There aren't many clinical studies examining the chemicals' toxicity. The European Medicines Agency has some suggestions about the use of preservatives in children. Allergic responses may be brought on by methyl-4-hydroxybenzoate and propyl-4-hydroxybenzoate. However, because they work well in the pH range of 1 to 8.5, hydroxybenzoates are frequently utilised. In oral preparations, propylene glycol is occasionally employed as a preservative. When comparing the benefits and hazards of these preservatives, potassium sorbate exhibits the highest risk-benefit relationship; nevertheless, its use is only beneficial in the pH range of 3.5 to 5.5 [9].

Colouring agents

Colours can be obtained naturally or from synthetic sources. Natural colouring age preferred over synthetic colours. Colour helps to identify the product and the colour should be accepted by particular country. Titanium dioxide(white), Brilliant blue(Blue), Indigo carmine(Blue to yellow), Amaranth(Red), Tartarazine(Yellow), Annatto seeds(Yellow to Orange) are some widely used colouring agents[10].

Packaging & storage[3]

1. The packaging of dry powders for reintroduction should have inadequately wide mouth containers with enough air space above the liquid to allow for easy flow of the contents.
2. To guarantee consistent dispersion of solid materials and to provide uniform and accurate dosage, the label should include the instruction: "Shake well before Use."
3. The powder should be stored at room temperature.
4. They are given orally in 5 ml increments. Multiple doses are delivered orally, one dose at a time, using a proper measurement tool that is typically included in the container.
5. The dry powders need to be kept in a container that is tightly sealed and shielded from moisture, freezing, extreme heat, and light.

Marketed Oral Suspensions

- Zovirax®(Acyclovir) oral suspension from GlaxoSmithKline is used to treat Herpes with a dose of <40 kg; 20mg/kg q.i.d. and >40 kg; 800mg(20 ml) q.i.d. . Formulation contains Methylparaben, Propylparaben, Carboxymethylcellulose sodium, Banana flavour, Glycerin, Microcrystalline cellulose, Sorbitol, Water[5].
- Tegretol®(Carbamazepine) is formulated by Novartis is an antiseizure and specific analgesic for trigeminal neuralgia with a dose of <6 years 10-20 up to 35 mg/kg/day, q.i.d. 6-12 years; 50mg (2.5ml) q.i.d. up to 1000mg daily. Formulation contains Citric acid, Dyes, Flavors, Potassium sorbate, Propylene glycol, Sorbitol, Sucrose, Xanthan gum, Water[9][11].
- Delsym® Over-the-counter(Dextromethorphan Polistirex) is a suspension formulated by Celltech is used as cough antitussive with a dose of 12-13 months; 1.25ml, 2-5 years; 2.5ml, 6-12 years; 5ml, >12 years; 10ml. The formulation contains Citric acid, Dye, EDTA, Ethanol (0.26%), Ethylcellulose, Flavors, High-fructose corn syrup, Methylparaben, Polyethylene glycol 3350, Polysorbate 80, Propylene glycol, Propylparaben, Sucrose, Tragacanth, Vegetable oil, Water, Xanthan gum[12].
- Trileptal®(Oxcarbazepine) is a oral suspension formulated by Novartis. Trileptal is used as antiseizure with a dose of initially, 8-10 mg/kg b.i.d. upto 1200mg per day, 20-29kg; 900mg/day, 29-39kg; 1200mg/day, >39kg; 1800mg/day. The suspension containing Ascorbic acid, dispersible cellulose, ethanol,

macrogol stearate, methylparaben, propylene glycol, propylparaben, sodium saccharin, sorbic acid, sorbitol, yellow-plum-lemon aroma, water[2][8].

- Viravan®-DM (Phenylephrine Tannate, Pyrilamine Tannate, Dextromethorphan Tannate) is formulated by PediaMed Pharmaceuticals used as antihistamine, antitussive, nasal decongestant with a dose of 2-6 years; 2.5ml, >12 years; 5-10ml, 6-12 years; 5ml. The formulation contains Citric acid, Glycerin, Grape flavour, magnesium aluminium silicate, methyl paraben, sucralose, sodium benzoate, sodium citrate, ammonium glycyrrhizinate, Sucrose, Xanthan gum, Water [5].
- Mintezol®(Thiabendazole) is formulated by Merck, which is used to treat anthel-mintic or we can see the suspension expels intestinal worms with a dose of 14kg; 250mg b.i.d. The formulation contains Acacia, Calcium phosphate, Flavors, Lactose, Magnesium stearate, Mannitol, Methylcellulose, Sodium saccharin[5][2].
- Banzel®(rufinamide) oral suspension from Eisai was approved in 2015 for the treatment of seizures only with LGS at a dose of 5-22.5 mg/kg up to 1600 mg twice daily using a dose volume of 0.125-0.56 mL/kg up to 40 mL of a formulation containing 40 mg/mL of the following ingredients: microcrystalline cellulose, carboxymethylcellulose sodium, hydroxyethyl cellulose, citric acid, simethicone emulsion[8][13].

Development of alternative compounded suspension vehicle

A committed team must work hard to overcome the drawbacks of the formulation. However, suspension vehicle, which is customizable by each in a collaborative effort with other organisations, Deutscher Arzneimittel-Codex/Neues RezepturFormularium (DAC/NRF) created a ready-to-use vehicle that could be purchased from a drugstore or a pharmaceutical company. It can also be prepared easily by the pharmacists. At the moment, stability tests of this suspension vehicle are carried out using the 10 most popular APIs for paediatric patients[1][11].

CONCLUSION

The physiology of children has a direct impact on the pharmacokinetic properties of drugs that are consumed. Drug absorption, distribution, metabolism, and excretion vary between developing youngsters and fully developed adults. The physiology of children has a direct impact on the pharmacokinetic properties of drugs that are consumed. There are at least 17 different paediatric oral formulations on the market. The development of paediatric formulations can be technically difficult, and the physicochemical characteristics and flavour of the active ingredient, as well as the required dose, frequently determine which formulation type should be used. The clinical development of paediatric formulations has received more attention over the last ten years. Large pharmaceutical corporations have invested in developing drugs for children, but because the paediatric market is less than that for adult medications, it is not given top priority. So, there is a need of specialization.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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