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Rapid communication

# Milk as a medium for pediatric formulations: Experimental findings and regulatory aspects

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ABSTRACT

In the case of pediatric medicinal products the selection of an appropriate and palatable liquid dosage form can make the difference between treatment success and failure. Since the recent adoption of Pediatric Regulations in the U.S. and E.U., there is a greater demand for age-appropriate medicines for children. Extended research on the use of milk on drug administration in pediatric population has shown the multiple benefits of its use. Milk exhibits great solubilizing, gastroprotective and taste masking properties, which are very important characteristics in the case of insoluble, irritating and bitter-tasting active compounds. Milk-based formulations rely on a novel, simple and user-friendly approach for the delivery of ionized and unionized lipophilic drugs. In parallel they can provide critical nutritive elements and a wide range of biologically active peptides, very important elements especially for pediatric patients.

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## 1. Introduction

Oral administration is the major route of drug delivery for the treatment of many diseases. However, poor solubility of some lipophilic drugs limits their oral bioavailability and is one of the major problems encountered during formulation of orally administered drugs. Another important limitation of most drug substances is their bitter taste that affects their palatability and consequently the compliance of patients, especially in the pediatric population. Therefore, the improvement of the rate and extent of absorption as well as the enhanced palatability of the administered drugs is highly desirable.

One of the most popular approaches for improving oral bioavailability of sparingly water-soluble drugs has been through the use of lipid-based drug delivery systems. Milk is a natural, abundant and inexpensive emulsion that is a daily nutrient of children and can be used as a carrier with the desired characteristics for oral drug delivery. It exhibits great solubilizing, gastroprotective and taste masking properties, which are very important characteristics in the case of insoluble, irritating and bitter-tasting active compounds.

Numerous reports in the literature have demonstrated that the solubility of lipophilic drugs in milk is much higher than their aqueous solubility (Macheras and Reppas, 1986a,b; Macheras et al., 1991, 1990, 1989). Furthermore, an important number of *in vitro* and *in vivo* studies with milk formulations of different active substances have shown their superiority in terms of solubility, dissolution (Macheras and Reppas, 1986a,b; Topaloglou et al., 1999), and bioavailability when compared to conventional oral formulations of lipophilic drugs (Macheras and Reppas, 1986a,b; Macheras et al., 1991). Recent work by Bennett et al. (2012) has focused on improving the bitter taste and gastric irritation of ibuprofen, a non-steroidal anti-inflammatory agent, through its incorporation in milk products with varying fat content. Another study has also presented a novel nipple shield delivery system for antiretroviral drug administration to infants during breastfeeding (Gerrard et al., 2012).

## 2. Milk-based formulations

Our work focuses on the use of milk, a natural oil-in-water emulsion, as the basic component for what we call milk-based formulations. The main principle of this type of formulations is that the sparingly soluble active ingredient is presented in solubilized form *in vivo*, using milk as a dispersing carrier, avoiding in that way the dissolution process. This leads to improved absorption and bioavailability of the drug.

The primary steps of the manufacturing process of milk-based formulations include the dissolution of the drug in the appropriate solvent system (water–alcohol mixtures or alkaline buffer solutions) and the incorporation of the dissolved drug in a specific volume of milk, which may be either instantly administered or undergo further

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processing (freeze-drying and reconstitution with water) before administration. This approach can be considered universal for ionized lipophilic drugs as well as for unionized lipophilic drugs exhibiting adequate solubility in alcohol or water–alcohol mixtures.

Several drug molecules with different chemical and pharmacological properties have been already tested in animal models and human volunteers. These include over-the-counter (OTC) and widely prescribed drugs, like acetylsalicylic acid, non-steroidal anti-inflammatory drugs (meloxicam, tenoxicam, nimesulide, mefenamic acid, tolfenamic acid and ketoprofen), cyclosporine, danazol, sulfamethizole and dicumarol (Charkoftaki et al., 2010; Macheras and Reppas, 1986a,b; Macheras et al., 1991, 1990, 1989). Representative pharmacokinetic profiles following single oral administration of milk-based formulations containing meloxicam, cyclosporine and salicylic or acetylsalicylic acid in human volunteers can be found in previously published work by Charkoftaki et al. (2010). Other possible drug candidates also include antiretroviral combinations, as well as several antibiotics and anticancer agents, either for a more 'friendly' and palatable way of administration in pediatric population, or for the switching from the intravenous to oral therapy.

## 3. Regulatory aspects

Milk-based formulations (either classical or freeze-dried) rely on a novel, simple and physiologically friendly approach for the delivery of ionized and unionized lipophilic drugs. These formulations open a new avenue for the use of milk, a natural and abundant medium, as a dispersing agent and drug carrier. Milk as the basic component of the formulation constitutes a very important part of the final pharmaceutical product that cannot be considered as a simple, classical excipient.

In the case of pediatric medicinal products, the selection of appropriate and palatable excipients plays a major role in their pharmaceutical development. The European Medicines Agency (EMA) highlights some important aspects that have to be considered for the selection of suitable excipients in the formulation of pharmaceutical products intended for the pediatric population. The first and most important consideration is the safety profile of the excipient both in terms of single and long-term administration; a parameter that is directly associated with the expected duration of treatment and the severity of the condition to be treated. Furthermore, the function of the excipient, as well as any potential alternatives that increase the palatability and overall acceptability of the formulation is another important parameter that guides the selection of an excipient. Finally, the potential of sensitization or severe allergic reactions, which in some cases may be even life threatening, is a serious complication that also has to be considered.

From a regulatory aspect, milk has not been officially registered as an excipient. Nevertheless, it is considered as a basic food in many diets, with an established safety. Casein, the major milk protein is included in the list of Generally Recognized As Safe (GRAS) Substances.

## 4. Conclusions

It is well known that milk consists of ingredients that provide critical nutritive elements and a wide range of biologically active peptides to both neonates and adults (Séverin and Wenshui, 2005). The immunological protection of milk against various types of infections also contributes to its general beneficial profile (Goldman et al., 1994; Hanson, 1998).

Milk-based formulations rely on a novel, simple and physiologically friendly approach for the delivery of ionized and unionized lipophilic drugs. By incorporating milk in the formulation, the drug is in a dissolved form, resulting in enhanced pharmacokinetic properties. The gastroprotective and taste masking properties of milk also contribute to its favorable profile for its use as a drug carrier. Current work focuses on the incorporation of antiretroviral and anticancer agents in the milk-based formulation, whereas further *in vitro* studies are scheduled to be performed with lactose-free milk.

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