International Journal of Pharmaceutics 466 (2014) 109–121

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Polyoxylglycerides and glycerides: Effects of manufacturing parameters on API stability, excipient functionality and processing

Vincent Jannin [a,*], Jean-David Rodier [a], Jasmine Musakhanian [b]

[a] Gattefossé SAS, 36 chemin de Genas, Saint-Priest cedex 69804, France
[b] Gattefossé Corporation, Plaza I, 115 West Century Road Suite 340, Paramus, NJ 07652, USA

ARTICLE INFO

Article history:
Received 10 January 2014
Received in revised form 13 February 2014
Accepted 2 March 2014
Available online 05 March 2014

Keywords:
Lipid-based excipient
Polyethylene glycol ester
Critical quality attribute
Drug stability
Oxidation
Chemical reactivity

ABSTRACT

Lipid-based formulations are a viable option to address modern drug delivery challenges such as increasing the oral bioavailability of poorly water-soluble active pharmaceutical ingredients (APIs), or sustaining the drug release of molecules intended for chronic diseases. Esters of fatty acids and glycerol (glycerides) and polyethylene-glycols (polyoxylglycerides) are two main classes of lipid-based excipients used by oral, dermal, rectal, vaginal or parenteral routes. These lipid-based materials are more and more commonly used in pharmaceutical drug products but there is still a lack of understanding of how the manufacturing processes, processing aids, or additives can impact the chemical stability of APIs within the drug product.

In that regard, this review summarizes the key parameters to look at when formulating with lipid-based excipients in order to anticipate a possible impact on drug stability or variation of excipient functionality. The introduction presents the chemistry of natural lipids, fatty acids and their properties in relation to the extraction and refinement processes. Then, the key parameters during the manufacturing process influencing the quality of lipid-based excipients are provided. Finally, their critical characteristics are discussed in relation with their intended functionality and ability to interact with APIs and others excipients within the formulation.

Contents

* Corresponding author at: 36 chemin de Genas, Saint-Priest cedex 69804, France. Tel.: +33 472 229838; fax: +33 478 904567.
E-mail addresses: vjannin@gattefosse.com, vjannin69@gmail.com (V. Jannin).

http://dx.doi.org/10.1016/j.ijpharm.2014.03.007
0378-5173/

1. Introduction

Lipid excipients have a wide range of applications in pharmaceuticals, food and consumer products. Liquid glycerides are commonly used as solubilizers for lipophilic active pharmaceutical ingredients (API) whereas semi-solid and solid glycerides serve as matrix formers in sustained release tablets and capsules (Barthélémy et al., 1999; Jannin et al., 2006); as processing aids in the formation of dispersions or multi particulate systems (Jannin et al., 2003; N'Diaye et al., 2003); and as coatings for taste masking, prolonged release or lubrication (Jannin and Cuppok, 2013; Patil et al., 2011). Polyoxylglycerides on the other hand are utilized as solubility and bioavailability enhancers in self emulsifying systems (Chambin et al., 2009; Fernandez et al., 2009; Porter et al., 2007; Williams et al., 2013). These examples help demonstrate a physical-chemical versatility which is inherently linked to the nature of the lipid moieties which constitute these excipients.

Lipids (fats and oils) are generally defined by their polarity and ability to interact with aqueous media, properties conditioned by their composition. Fatty acids are the single common denominator in all lipids. The functionality of lipids is linked to their structural moieties, notably the type of fatty acids and their esters present. Fatty acids are abundant in nature, found notably in dietary lipids in the form of glycerides (fatty acid esters of glycerol). Glycerides and their fatty acid components serve as building blocks for the manufacture of lipid excipients. Depending on the intended characteristics of the final excipient, manufacturing may involve a complex series of processes such as fractionation, esterification, inter-esterification, alcoholysis, and multiple purification steps. The functionality of the end product in the pharmaceutical dosage form is therefore inherently linked to the source of the raw materials and the manufacturing processes. Precise control of composition and characteristics of lipid based excipient is essential for their subsequent use as a pharmaceutical excipient. However, these excipients can contain impurities that often contribute significantly to the degradation of API, as recently reviewed by Pr. V. Stella (Stella, 2013).

The purpose of the review is to explain the impact of the manufacturing processes of lipid-based excipients on the stability of pharmaceutical dosage forms manufactured. Variations of composition of these excipients deriving from natural products, the potential presence of process aids, additives, and/or stabilizers added during their extraction, refining, and processing can profoundly impact the stability of the API in dosage forms made using one or more of such excipients. In addition, different 'grades' of these lipid-based excipients have been introduced to provide enhanced product differentiation or functionality while at the same time being classified within the same general Pharmacopoeial monograph. Even if, lipid-based excipients are more and more routinely used there is still a lack of understanding of how excipient manufacturing processes – either directly or indirectly – can impact the drug product stability.

Hence, this review aims to elucidate the key parameters influencing two groups of lipid excipients: glycerides, being fatty acids esters of glycerol and polyoxylglycerides being fatty acid esters polyethylene glycol (PEG) and glycerol – presented in two separate sections. The first section starts by an introduction to the chemistry of natural lipids (fats and oils), fatty acids and their properties in relation to the extraction and refinement processes used. In addition, the critical characteristics of these excipients on their functionality and ability to interact with other materials and drug substances will be discussed.

2. Nature of lipids/excipients

2.1. Glycerides – definition

Glycerides are the primary components of dietary lipids (fats and oils). Lipids are fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds (Christie, 1987). Lipids are amphiphilic due to their dual molecular structure i.e. the lipophilic portion consisting of fatty acid(s) and the hydrophilic portion to which the fatty acid(s) are esterified (glycerol in the case of glycerides) (Jannin et al., 2008). They can be divided in two groups depending on their interaction with water (Larsson et al., 2006).

The first group relates to non-polar lipids that are non-miscible with water. Oils and fats are mainly composed of triacylglycerols (also known as triglycerides) and are the main components of this group. Triacylglycerols are composed of three fatty acids (acyl groups) esterified to glycerol (see Fig. 1). Their partial glycerides derivatives: diacylglycerols (diglycerides) are also non-polar. Diacylglycerols are composed of two fatty acids esterified to glycerol. Each diacylglycerol molecule exists as two different isomers: 1,2- and 1,3-position. The migration of fatty acid from one position to another is favored by temperature (even at room temperature for liquids) and the equilibrium mixture is reached.

The second group consists of polar lipids that can interact with water to form aqueous phases. Monoacylglycerols (monoglycerides) is one example of polar lipids. They can exist as two isomers as 1- (which is equivalent to the 3-) and 2-position. The 1-isomer is largely predominant in the equilibrium mixture reached after acyl migration.

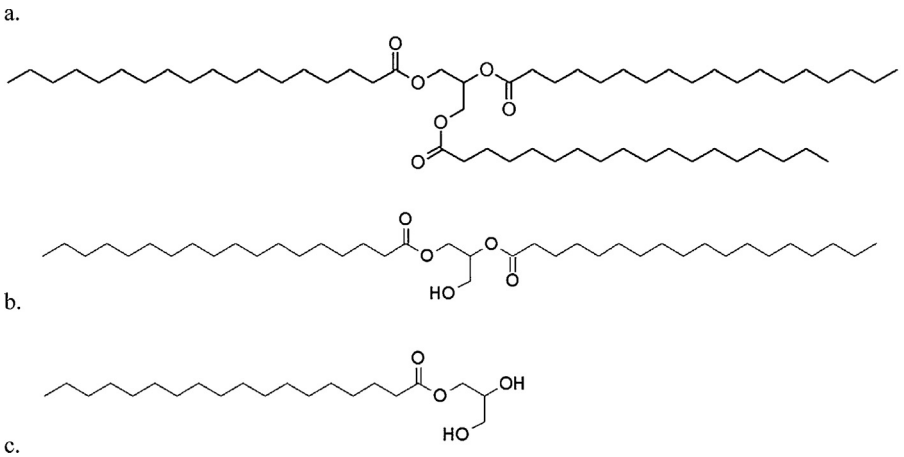

Fig. 1. Structures of acylglycerols: a. triacylglycerol; b. 1,2-diacylglycerol; c. 1-monoacylglycerol. The fatty acid used for this figure is stearic acid.