International Journal of Pharmaceutics 496 (2015) 766–779

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Optimization, physicochemical characterization and *in vivo* assessment of spray dried emulsion: A step toward bioavailability augmentation and gastric toxicity minimization

Mohammed M. Mehanna[a,b,*], Jana K. Alwattar[a], Hoda A. Elmaradny[a]

[a] Department of Pharmaceutical Technology, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon
[b] Department of Industrial Pharmacy, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt

ARTICLE INFO

Article history:
Received 17 September 2015
Received in revised form 2 November 2015
Accepted 4 November 2015
Available online 10 November 2015

Keywords:
Dry emulsion
Factorial design
Spray drying
Class II
Bioavailability
Dissolution

ABSTRACT

The limited solubility of BCS class II drugs diminishes their dissolution and thus reduces their bioavailability. Our aim in this study was to develop and optimize a spray dried emulsion containing indomethacin as a model for Class II drugs, Labrasol®/Transuctol® mixture as the oily phase, and maltodextrin as a solid carrier. The optimization was carried out using a 2^3 full factorial design based on two independent variables, the percentage of carrier and concentration of Poloxamer® 188. The effect of the studied parameters on the spray dried yield, loading efficiency and *in vitro* release were thoroughly investigated. Furthermore, physicochemical characterization of the optimized formulation was performed. *In vivo* bioavailability, ulcerogenic capability and histopathological features were assessed. The results obtained pointed out that poloxamer 188 concentration in the formulation was the predominant factor affecting the dissolution release, whereas the drug loading was driven by the carrier concentration added. Moreover, the yield demonstrated a drawback by increasing both independent variables studied. The optimized formulation presented a complete release within two minutes thus suggesting an immediate release pattern as well, the formulation revealed to be uniform spherical particles with an average size of 7.5 μm entrapping the drug in its molecular state as demonstrated by the DSC and FTIR studies. The *in vivo* evaluation, demonstrated a 10-fold enhancement in bioavailability of the optimized formulation, with absence of ulcerogenic side effect compared to the marketed product. The results provided an evidence for the significance of spray dried emulsion as a leading strategy for improving the solubility and enhancing the bioavailability of class II drugs.

1. Introduction

The implementation of novel screening technologies generated a wave of new active pharmaceutical ingredients (API) with a limited aqueous solubility (Hansen et al., 2004), which in turn affect the dissolution and thus decreases its absorption and bioavailability (Dollo et al., 2004). The improvement of the solubility and dissolution of poorly soluble drug, especially of class II is required in order to augment its therapeutic efficacy. Various strategies were followed to overcome this problem, such as complexation (Hiral et al., 2012), nano-crystallization (Bajaj et al., 2012), particle size reduction (Rawat et al., 2011), solid dispersions (Saquib and Nayak, 2012), and incorporation in lipid formulation (Pedersen et al., 1998). One of many systems of later proposed lipid incorporation is the preparation of emulsion for enhancing the dissolution and bioavailability through the inclusion of the drug in the oily lipid phase. Although liquid emulsions were able to improve the bioavailability of drugs with limited aqueous solubility, yet the prepared formulation exert less stability than other oral formulations (Christensen et al., 2001). The emulsion has many reported instabilities and limitations including coalescence, phase separation, flocculation, and creaming (Dixit and Nagarsenker, 2007).

The above stated limitations believed to be overcame via the design of a dry emulsion, where the final product is a solid dry powder containing lipid droplets (Hansen et al., 2004). The dry emulsion is a solid-state dosage form composed of an o/w or w/o emulsion containing either soluble or insoluble carrier dissolved/dispersed in the aqueous phase. The removal of the aqueous phase will lead to incorporation and encapsulation of the lipid phase within the solid carrier. For the removal of the aqueous phase, a drying step of the emulsion was performed. Various methods were

* Corresponding author.
E-mail addresses: dr_mehanna@yahoo.com, mmhanna@bau.edu.lb (M.M. Mehanna).

http://dx.doi.org/10.1016/j.ijpharm.2015.11.009
0378-5173/

used namely: drying under vacuum by rotary evaporation (Shively, 1993), spray drying (Christensen et al., 2001; Takeuchi et al., 1992), and lyophilization (Molina, 1995). Studies have shown an increased interest in the preparation of a dry emulsion for enhancing the solubility of many drugs belonging to BCS class II drugs (Baek et al., 2014; Dixit and Nagarsenker, 2007; Yin et al., 2009), further commercial techniques such as wet film evaporator may be used (Zeboudj et al.,2005).

Carriers are a vital component in dry emulsion formulation as they are the matrix for the preparation, that are either water soluble such as maltodextrin (Corveleyn and Remon, 1998) or insoluble such as colloidal silica (Seo et al., 2013) in the formulation. Most carriers employed in dry emulsions for the enhancement of poorly aqueous solubility active ingredients are hydrophilic in nature. These carriers can enhance solubility during *in vitro* dissolution and after oral administration (Gupta et al., 2013). Different criteria arise for the selection of carriers, such as the process yield, stability, and solubility parameters of the drug and polymer (Dhirendra et al., 2009).

Indomethacin (IND), a class II BCS drug, is a non-steroidal anti-inflammatory API used to treat gout, headache, arthritis, and brursitis (Mendieta et al., 2012). Being a class II member, IND is characterized with high permeability and low aqueous solubility, thus exhibiting a low dissolution rate with poor bioavailability. Over the years many attempts have been performed to enhance its aqueous solubility which in turn improves its dissolution rate and bioavailability. These methods include the introduction of a surfactant (Krasowska, 1980), using adsorbants (Alsaidan et al., 1998), formulation of coprecipitate (Gong et al., 2005), hydrotropes and cosolvent techniques (Etman and Nada, 1999), solid dispersion (Wang et al., 2007), complexation with cyclodextrins (Jambhekar et al., 2004), liquisolid compact formulations (El-Badry et al., 2009).

In the light of the above facts, the main objective of the current study is to improve the solubility and dissolution rate of IND as a model drug for BCS class II through preparation of a dry emulsion formulation. The development of an optimized formulation is a tedious, expensive and time consuming process were different factors influence the preparation. Therefore, the application of a factorial experimental design methodology provides an efficient method to evaluate the factors and understand their effect on the formulation process. Furthermore, physicochemical characterization of the optimized formulation was performed using scanning electron microscope, differential scanning calorimetry and Fourier transform infrared. *In vivo* bioavailability, ulcerogenic side effect and histopathological features of the stomach were evaluated.

2. Materials and methods

2.1. Materials

Indomethacin purchased from Ningbo Hi-Tech Zone Yefeng New Materials Technology Co., Ltd., Labrafac® (Capric triglyceride (USA FDA II G)), Labrafil® M 1944 (Oleoyl macrogol-6 glycerides EP), Labrasol® (Caprylocaproyl macrogol-8 glycerides EP), Transuctol® (Highly purified diethylene glycol monoethyl ether EP/NF), Caproyl® 90 (Propylene glycol monocaprylate (type II) NF), Lauroglycol® (Propylene glycol monolaurate (type II) EP/NF) were received as generous gifts from Gattefosse Co. (St. Priest, France). Glucidex® 19 IT (maltodextrin) was a gift from Roquette Freres (Lestrem, France), corn oil, canula oil, sunflower oil, poloxamer 188 (P188), gelatin, and Tween® 80 (polyethylene glycol sorbitan monooleate) were purchased from Sigma Co. (Sigma–Aldrich, Steinheim, Switzerland). All other solvents and materials used were of analytical grade.

2.2. Solubility studies of indomethacin in various vehicles

The solubility of IND was determined in various vehicles according to the method followed by Mehanna et al. (2015) using a shaking water-bath (FALC,WB-MF24, Treviglio—Italy). An excess quantity of indomethacin was added into a capped glass vial containing 2 ml of each vehicle. The mixture was shaken at 100 rpm at 25 °C for 24 h then left to equilibrate. Using a 0.22 μm Millipore filter, clarification was performed. The filtrate obtained was suitably diluted and drug content was determined at λ_{max} 320 nm using a spectrophotometer (Optima, SP-3000PLUS, Tokyo, Japan).

2.3. Preparation of emulsion

To assess the effect of different factors for the preparation of a stable emulsion with optimum physical characteristics for construction of a dry emulsion formulation, different oil in water ratios, emulsifier's type, oil phase and emulsification process were studied. The selection of oil phase and emulsifiers were determined based on solubility studies (Baek et al., 2014), with the selection of ultrasonication based on the final volume of the preparation, with a ratio 1:10 oil to water to maximize flowability of the final preparation. Indomethacin was dissolved into the oil mixture Labrasol®: Transuctol® (1:1 ratio mixture), while 5% Tween® 80 was added to the aqueous phase in the presence of various concentrations of carrier and solid surfactant. The two phases were emulsified using ultrasonicator (Langford Sonomatic, SO575H) for 30 min at room temperature.

2.4. Preparation of dry emulsion

Spray drying of the prepared emulsion was performed using a mini spray drier (Lab Plant, SD-O6AG, Fiely, North yorkshive, England). The fluid nozzle utilized was 0.5 mm operating at 4 bar for the atomization of the emulsion at 5 ml/min flow rate, with 135 °C inlet temperature, fan speed of 35 and outlet air temperature at 80 °C. The powder from the outlet air was collected from the cyclone and collecting chamber. The flow rate chosen was based on the effect of the different flow rate on the final products yield and loading efficacy (Hansen et al., 2004).

2.5. Experimental design

Factorial design system is a statistical method used to establish a valid objective and conclusion from the analysis of the data provided, which is classified into variables with different levels and responses obtained from such inputs. The purpose of the factorial design is to understand the implications of different factors with various levels on the experimental models and the prediction of the responses from the model within the domain obtained. The experimental design is a two factor, three levels design (2^3 factorial design) that requires a total of nine runs. Table 1 elaborates the studied factors and their corresponding levels. The two factors examined were the percentage of solid carrier and the percentage of poloxamer 188. Each factor is conveyed in three levels which are

Table 1
Independent factors and their respective levels utilized for the construction of 2^3 factorial design experiments.

Independent variables	Level used, actual (coded)		
	Low (−1)	Medium (0)	High (1)
X_1 = % w/v carrier (maltodextrin)	20	25	30
X_2 = % w/v solid surfactant (poloxamer 188)	0	2.5	5