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Development of nanostructured lipid carriers containing salicyclic acid for dermal use based on the Quality by Design method

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ABSTRACT

The aim of our present work was to evaluate the applicability of the Quality by Design (QbD) methodology in the development and optimalization of nanostructured lipid carriers containing salicyclic acid (NLC SA). Within the Quality by Design methology, special emphasis is layed on the adaptation of the initial risk assessment step in order to properly identify the critical material attributes and critical process parameters in formulation development.

NLC SA products were formulated by the ultrasonication method using Compritol 888 ATO as solid lipid, Miglyol 812 as liquid lipid and Cremophor RH 60® as surfactant. LeanQbD Software and StatSoft. Inc. Statistica for Windows 11 were employed to indentify the risks.

Three highly critical quality attributes (CQAs) for NLC SA were identified, namely particle size, particle size distribution and aggregation. Five attributes of medium influence were identified, including dissolution rate, dissolution efficiency, pH, lipid solubility of the active pharmaceutical ingredient (API) and entrapment efficiency.

Three critical material attributes (CMA) and critical process parameters (CPP) were identified: surfactant concentration, solid lipid/liquid lipid ratio and ultrasonication time. The CMAs and CPPs are considered as independent variables and the CQAs are defined as dependent variables. The 2^3 factorial design was used to evaluate the role of the independent and dependent variables. Based on our experiments, an optimal formulation can be obtained when the surfactant concentration is set to 5%, the solid lipid/liquid lipid ratio is 7:3 and ultrasonication time is 20 min. The optimal NLC SA showed narrow size distribution (0.857 ± 0.014) with a mean particle size of 114 ± 2.64 nm. The NLC SA product showed a significantly higher in vitro drug release compared to the micro-particle reference preparation containing salicylic acid (MP SA).

1. Introduction

Application of the „quality by design" methodology according to the ICH Q8 guideline is a fairly new approach in the development process of new pharmaceutical products. The QbD approach is usefull in the daily pharmaceutical industrial practice (ICH Q8, 2009). It is a systematic approach that begins with predefined objectives, and emphasizes product and process understanding, as well as process control, based on sound science and quality risk management. The process starts with the determination of the quality target product profile (QTPP) and the critical quality attributes (CQAs). Critical material attributes (CMAs) and critical process parameters (CPPs) are identified, as well as risk assessment is carried out (ICH Q9, 2006) in order to identify the material attributes and process parameters which potentially affect product CQAs.

Therefore, the QbD approach is more proactive and refers to a systematic process compared to the mainly empirical methodologies used earlier (Beg et al., 2015; Shah et al., 2015; Xu et al., 2011; Xu et al., 2012; Kan et al., 2014; Wang et al., 2015; Kovacs et al., 2016). Risk assessment and the design of experiments (DoE) techniques within the risk assessment process are key elements of QbD methodology (Fig. 1). Risk assessment includes the identification of potential hazards plus the analysis and evaluation of the risks associated with the exposure to these hazards (Beg et al., 2015). The ICH Q9 guideline lists several quality management tools (e.g. Ishikawa diagram, Pareto analysis, risk estimate matrix etc.) and favors the design of experiments (DoE)

Abbreviations: API, active pharmaceutical ingredient; CMAs, critical material attributes; CCS, critical control strategy; CPPs, critical process parameters; CQAs, critical quality attributes; DoE, design of experiments; DS, design space; ICH, International Council for Harmonisation; LD, laser diffraction; MP-SA, micro-sized lipid particle containing salicyclic acid; NLC SA, nanostructured lipid carriers containing salicyclic acid; NSAID, non-steroidal anti-inflammatory drug; PAT, process analytical technology; QbD, Quality by Design; QRM, quality risk management; QTPP, quality target product profile; REM, risk estimate matrix; SA, salicyclic acid.

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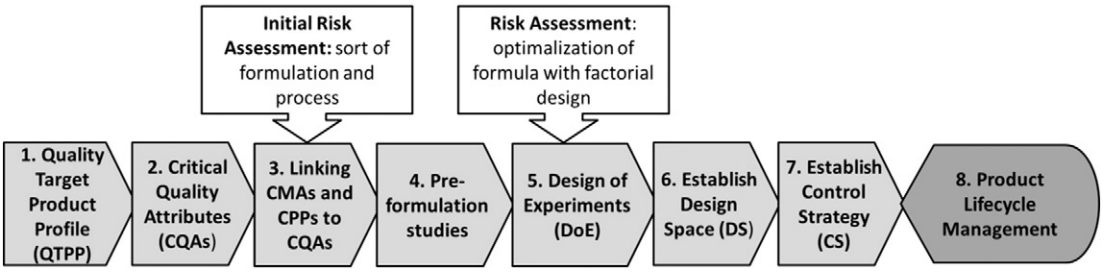

Fig. 1. Flow chart of Quality by Design approach in formulation development.

techniques (e.g. screening techniques, interaction effect techniques etc.) (Singh et al., 2011).

Our hypothesis that the adaptation of the QbD based dosage form development in the early research phase leads to a more systematic R&D approach, and consequently gives a greater potential to the final product to reach the market earlier, has already been proved for newly developed nasal formulas (Pallagi et al., 2015).

Now the QbD approach is applied to the development of a complex dosage form, namely for Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLCs), which are potent drug delivery systems for e.g. dermal use. These systems are derived from o/w emulsions by replacing the lipophilic liquid phase with solid lipid(s), which are dispersed in an external aqueous phase with suitable emulsifier(s) (Baroli, 2010). The active substance is present in a dissolved or dispersed form, and is characterized by a size range of 40 to 1000 nm (Müller et al., 2002; Pardeike et al., 2009; Subedi et al., 2009). Nanostructured Lipid Carriers (NLCs) is the term used for second generation solid lipid nanoparticles that contain a lipid matrix of mixed solid and liquid lipids.

The main advantages of these systems include the following: (1) they are ideal carriers to incorporate low water-soluble active substances and to stabilize oxidation-/photo-sensitive materials (Müller et al., 2002; Pardeike et al., 2009); (2) as dermally applied systems (McGrath and Uitto, 2010; Prow et al., 2011; Cevc and Vierl, 2010) they ensure close contact with the lipid bilayer of the stratum corneum, resulting in a more efficient and deeper drug penetration into the skin layers (Yang et al., 2013). Their occlusive properties resulting from film formation were also reported for NLC formulations (Wissing and Müller, 2002a, 2002b), as well as their protective capacity against environmental effects such as UV radiation (also called physical UV filter function) (Müller et al., 2014; Lacatusu et al., 2011).

Salicylic acid (SA) as an NSAID drug with antifungal, anti-infective and keratolytic properties was used as model drug because of its wide therapeutic use (e.g. for the treatment of acne, psoriasis, callouses, corns, keratosis pilaris and warts), its physicochemical properties (molecular weight < 400 Da, log $P = 2–3.8$), and also because SA is poorly water soluble, thereby it is a good candidate for our studies. Incorporating salicylic acid into NLC nanoparticles may protect against the irritating side effects and may enhance skin penetration, thereby it is possible to achieve the same effect with less amount of active substance compared to conventional pharmaceutical dosage forms (Casanova and Santos, 2016).

The first aim of our present work was to adapt the QbD approach in the optimalization and development of stable salicyclic acid loaded nanostructured lipid carriers for dermal use. As the first step of this process, the QTPP and CQAs were determined, then an initial risk assessment was carried out to optimalize the material attributes (CMAs) and process parameters (CPPs) affecting the critical quality attributes (CQAs) of SA-containg NLC systems. Our further aim was the practical implementation of the 2^3 factorial design method as a risk assessment tool in order to determine the optimal composition for the formulation. Thirdly, methods of monitoring selected critical parameters as "in-process" and as final product quality control measures were also adopted and recommended for the NLCs.

2. Materials and methods

2.1. Materials

Salicylic acid was purchased from Sigma-Aldrich (USA), Compritol 888 ATO (glyceryl behenate/dibehenate) was supplied by Azelis Hungary Ltd. (Hungary), Miglyol 812 (caprylic/capric triglyceride) was provided by Sasol GmbH (Germany) and Cremophor RH 60 (PEG-60 hydrogenated castor oil; HLB value:15–17) was kindly supplied by BASF SE Chemtrade GmbH (Germany). Bidistilled water was used throughout the experimental work. All other chemicals were of analytical grade unless otherwise stated.

2.2. Methods

2.2.1. Definition of the QTPP

The initial step of the QbD based development is to define the target product profile (TPP) and the selected QTPP based on requirements of stakeholders (patient expectations, industrial and regulatory aspects). TPP includes the defintion of the route of administration, the dosage form, maximum and minimum doses, appearance etc. QTPPs are quality, safety and efficiency features of a product, such as stability, drug release profile, pharmacokinetical attributes, purity, bioavailability etc.

Table 1
(A) Values of the examined independent variables (X_1, X_2 and X_3) and types of dependent variables (Y_1, Y_2). (B) Summarizes the compounds of the prepared formulations.

A

Type of variables	Levels	
Independent variables	Low (−1)	High (+1)
X_1: surfactant concentration (w/w%)	1	5
X_2: solid/liquid lipid ration	7:3	9:1
X_3: ultrasonication time (min)	10	20
Dependent variables		
Y_1: particle size		
Y_2: particle size distribution		

B

Cremophor RH 60 (w/w%)	NLC 1 1	NLC 2 1	NLC 3 5	NLC 4 5	NLC 5 1	NLC 6 1	NLC 7 5	NLC 8 5
Lipid ratio	9:1	7:3	9:1	7:3	9:1	7:3	9:1	7:3
Ultrasonication time (min)	10	10	10	10	20	20	20	20