Quality by Design Coupled with Near Infrared in Formulation of Transdermal Glimepiride Liposomal Films

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ABSTRACT: This study is aimed at developing glimepiride (GMD) liposomal films using quality by design (QbD) and process analytical technology (PAT) principles. Risk analysis and Plackett–Burman design were utilized to evaluate formulation variables in two paths. Internal path included liposomal parameters (phosphatidylserine, cholesterol and drug concentrations, and pH of hydration medium). External path constituted films parameters, namely, polymer, plasticizer, and permeation enhancer percentages. As a PAT tool, near infrared (NIR)-based chemometric analysis was used in quantifying GMD contents. Liposomal formulations showed maximum GMD entrapment capacity of 41.9% with vesicular size of 0.51 μm at phospholipid to cholesterol to drug weight ratio of 2:1:0.8. Its transdermal films showed elongation ratio of 75%, folding endurance of 700-fold, 16.6% and 26.8% drug release after 1 and 12 h, respectively. Moreover, 3D response spaces for GMD entrapment and release characteristics were established. Regarding NIR analysis, partial-least-square regression model was accurate in quantifying drug content as indicated by the low root-mean-squared error of calibrations and prediction of 0.031 and 0.032, and bias values of 0.0015 and 0.0021, respectively. In conclusion, this study highlights the level of understanding that can be accomplished through a well-designed research based on QbD and PAT paradigms. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2062–2075, 2015

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INTRODUCTION

The frequent factors aiding for poor bioavailability after oral administration of drugs are attributed to their poor solubility, first-pass and presystemic metabolism, and low permeabilities. For drugs belonging to biopharmaceutical classification system (BCS) class II with low solubility and reasonable permeability, drug dissolution step is the rate-liming process of drug absorption and further bioavailability.[1] This can be addressed through alternating routes of administrations such as topical delivery of liposomes.[2] Transdermal drug delivery has outlaid its advantages over conventional oral drug delivery, especially for high-systemic acting drugs by circumventing the hepatic metabolism. This allowed for enhancing the bioavailability while minimizing the side effects of drugs with narrow therapeutic window.[3,4] Liposomes are high-deformable amphiphillic vesicles in bilayer conformation that can entrap both hydrophilic and hydrophobic drugs.[5] Apart from its high drug loading capability, they form depot enabling sustained release of the medicament.[6] The major component of liposome being phospholipids has a significant effect on drug permeation through stratum corneum of skin.[7] A better scope is expected for BCS class II drugs through liposomal topical delivery. Glimepiride (GMD) is long-acting third-generation sulfonylurea classified under antidiabetic drugs. The primary indication of GMD is the treatment of type-2 diabetes mellitus.[8] GMD acts by enhancing the production of intracellular glucose transporters by the pancreas, thereby reducing the systemic glucose levels.[9] It has a half-life of 5 h and 99.5% bound to plasma proteins.[10] Being classified as BCS II, GMD exhibits low water solubility (<0.5 μg/mL) with high permeability.[11] A therapeutic inefficiency would be resulted in because of the reduced dissolution rate to attain a peak plasma drug levels. For a better GMD bioavailability, it has been reported that increasing its oral dose results in severe adverse effects such as hypoglycemia (20%–30%), gastrointestinal tract irritation, and blood-related disorders.[12] To circumvent these major drawbacks of GMD, liposomes were proposed in the current study as a promising transdermal delivery approach for GMD. This approach would be attractive not only as a noninvasive procedure for GMD delivery, but also as a solution for its gastrointestinal complications.

Quality by design (QbD) paradigm aims to build up the product quality rather than to be tested.[13] This necessitates that quality-improving scientific methodologies to be

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implemented upstream starting from the early stages of product development and formulation design phases. QbD mines the critical therapeutic attributes followed by interpreting them into a group of critical quality attributes that the medicament should possess. Hence, a strategy of varying both critical formulation and critical process variables should be set up to constantly manufacture a medicament with the desired quality.[14] On the basis of QbD paradigm, the process of drug product development would comprise the following stages:

(a) Establishing a biologically relevant "target product quality profile" (TPQP).
(b) Establishing the development and large-scale manufacturing processes according to the preset TPQP.
(c) Mining both critical quality and critical process parameters followed by assessing the encountered risks (risk analysis and assessment).
(d) Employing a screening design of experiment approach to define the design space, and then classify the variables according to their influences on the critical quality parameters.
(e) Establishing an online control strategy to monitor the product quality throughout manufacturing for consistency, hence confirming that quality is built into the product.[15]

Near-infrared (NIR) spectroscopy can be employed as an alternative, rapid, and nondestructive analytical methodology with no special sample preparation or pretreatment. Moreover, this technique allows for data acquisition through transparent glass or plastic containers with acceptable accuracy. These features allow for online monitoring of considerable large number of samples during manufacturing without affecting the production yield. In this regard, NIR has been employed widely as an offline quality assessor and/or as a process analytical technology (PAT) tool during pharmaceutical manufacturing.[16] Multivariate data analysis and modeling methods such as principal component analysis (PCA) and multivariate curve resolution might be used to extract the latent variables among the NIR data in a description of its attribution to the samples characteristics.[17] On the contrary, modified algorithms such as principal component regression (PCR) and partial-least-squares regression (PLSR) are often employed to construct quantitative calibration models.[18] NIR spectroscopy along with chemometric modeling has been employed extensively for quantification of fatty acids and proteins in the food industry.[19,20] However, scarce information have been found to thoroughly evaluate the application of NIR and chemometric analysis for quantification of lipids in liposomes. The work presented in this paper is therefore a feasibility study to develop GMD in transdermal liposomal films through QbD paradigm. The TPQP was defined and risk assessment was conducted to mine the potential high-risk variables. Subsequently, a Plackett–Burman experimental design was employed to screen high-risk variables. An evaluation of the drug entrapment capacity (EC), vesicular size, and electrical parameters, and *in vitro* drug release from the prepared liposomes was conducted. In addition, the films were evaluated in terms of elongation ratio, folding endurance, and drug release. Furthermore, the possibility to quantitate drug and lipid content in liposome formulations by NIR transmission spectroscopy was attempted.

MATERIALS AND METHODS

Materials

Glimepiride was supplied by Medical Union Pharmaceuticals (MUP) (Abu Sultan, Ismailia, Egypt). Soybean phosphotidylserine (Alcolec® PS75P, soy lecithin containing 75% phosphatidylserine) was obtained from American Lecithin Company (Oxford, Connecticut). Cholesterol, propylene glycol (PG), and dimethyl sulfoxide (DMSO) were purchased from Sigma–Aldrich Corporate (St. Louis, Missouri). Hydroxypropyl methylcellulose (HPMC) of viscosity 4000 cp (2% solution) was procured from Acros Organics Company (Morris Plains, New Jersey). All other chemicals were of analytical grade and were used as received.

Preparation of GMD-Loaded Liposomes

Glimepiride liposomes were prepared by a phase evaporation/melting method as described by Belletti et al.[21] after some modifications followed by probe sonication. Briefly, specified amounts of the drug, phospholipid, and cholesterol according to Plackett–Burman screening design (Table 1) was weighed and dissolved in 3 mL of chloroform in 15 mL glass vials. The vials were shaken in a water bath at 60°C for complete solubilization of the components and a clear mixture is obtained. The organic feeds were slowly added dropwise with continuous stirring into the hydration media (30 mL phosphate buffer containing 0.01% sodium lauryl sulfate adjusted to different pH as specified in Table 1). The resulted dispersions were subjected to probe sonication (Sonics vibra cell; VCX 750, Newtown, Connecticut) at 40% amplitude for 1 min. The dispersions were then transferred into round bottom flasks of rotatory evaporator (BÜCHI Labortechnik, Flawil, Switzerland) for chloroform evaporation under vacuum at 40°C at 100 rpm for 45 min. The liposomal dispersions were then centrifuged (Eppendorf Centrifuge, Model 5415 C; Eppendorf-Netheler-Hinz GmbH 2000, Hamburg, Germany) at 65,000 rpm for 2 h. The resultant residue was reconstituted with 2 mL of distilled water followed by freezing in sealed glass vials at −2°C for further analysis.

Characterization of the Prepared Liposomes

Entrapment capacity was determined indirectly by determining the free (unentrapped) drug. After collecting the liposomal vesicles by centrifugation, the free GMD was assessed in the supernatant using an in-house developed and validated analytical chromatographic method. Hewlett Packard (HP) HPLC instrument (Agilent Technologies, California) equipped with HP 1200 UV detector was set at a wavelength of 228 nm. The chromatographic separation was accomplished by injecting 10 μL samples onto Luna (2) RP-18 (250 × 4.6 mm^2, 5 μm packing) reverse-phase analytical column (Phenomenex Inc., Torrance, California). The mobile phase was composed of acetonitrile–phosphate buffer (pH 3.5; 0.01 M) (45:55, v/v) with an isocratic flow rate of 1.0 mL/min. The detected number of moles of GMD loaded within the liposomal vesicles (i.e., actual loading) was compared with the number of moles of lipids (phospholipid plus cholesterol) in each sample. The vesicular capacity to encapsulate GMD was assessed using the following equation of weight