

Toward application of microsponges in transdermal drug delivery system

Abstract

Transdermal drug delivery system (TDDS) is a dosage form designed to deliver drug through skin by topical route of administration to the systemic circulation or for local treatment. As a new type of dosage form, TDDS has a number of special merits, but inevitably at the same time it possess some distinct disadvantages, such as low permeability and the drug mostly enter the systemic vascular. Microsponges are a kind of micro-sized and polyporous particles which can entrap effective constituents, and are biologically safe. And Microsponges also exhibit distinctive advantage at the aspect of drug release. The TDDS can enhance drug stability, decrease side effects, improve bioavailability and so forth, which has been used mostly through topical and oral administration, and applied broadly in medical and cosmetic field. This review presents application of microsponges in TDDS including its preparation, properties and drug-released studies in the recent advancements.

Keywords: bioavailability, microsphere, transdermal drug delivery system, preparation, characterization, drug-released studies

Volume 1 Issue 1 - 2015

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Received: April 30, 2015 | Published: June 03, 2015

Abbreviations: TDDS, transdermal drug delivery system; FDA, food and drug administration; EC, ethyl cellulose; BPO, benzoyl peroxide; SEM, scanning electron microscopy; AUC, area under the curve; EE, entrapment efficiency; DSC, differential scanning calorimetry; MED, minimal erythema dose; SPF, sun protection factor

Introduction

Compared with drug dosage forms for oral and parenteral administration, Transdermal drug delivery system (TDDS) can minimize and avoid some restrictions relating to dosage forms effectively. Due to the conventional delivery systems suffering from certain restrictions like Peak and Valley phenomenon i.e., they show fluctuations in plasma drug concentration and cannot render sustained effect.¹ However, the TDDS can meet the requirement to keep relatively stable plasma drug concentration and prolong delivery of drug, in a steady-state profile and minimizes the peak-associated side effects, which thus ensures the level of the drug is effective for treatment on the minimal therapeutic concentration. In general, Transdermal drug delivery system, as a controlled drug delivery system, is exceedingly humanized, commodious and prolong the period of time of release of drug, if need arises (e.g. systemic toxicity) with less pain sensation while administrating drug candidates.² Additionally, TDDS permits the permeation of drugs across the skin and into the systemic circulation which avoids the hepatic first-pass effect observed in the course of oral administration and inconvenience of frequent parenteral administration.³

As a new drug carrier of TDDS, Microsponges are mostly used for topical⁴⁻¹⁰ and oral administration.¹¹⁻¹⁵ For other topical delivery systems, the traditional delivery systems are required of frequent dosing to keep relatively stable local concentrations of effective constituent for therapeutic effectiveness because of low effectiveness.

Thus to avoid this defect it is indispensable to design a new drug delivery system to prolong the residual time of drug in the epidermis or the dermis, while reduce its penetration into the body.⁷

For this reason, as a porous polymeric microsphere, Microsponges can fulfill such aims uniquely.⁴ Microsponges are porous, polymeric microspheres (Figure 1) which are invariably used for topical delivery system,^{4-5,7-10} its inside are full of lacunas and its particle size is 5~300µm in diameter.

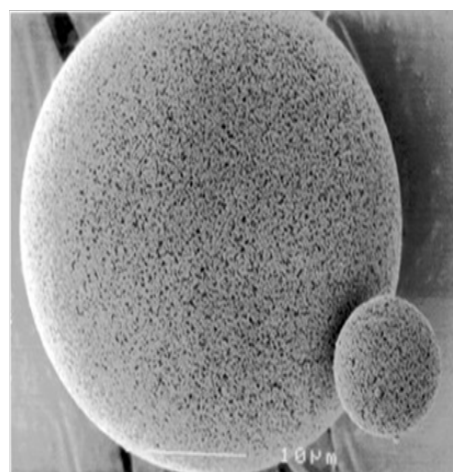


Figure 1 Scanning electron micrograph of microsponges.

As a drug carrier for skin-target delivery, microsponges have several advantages:

- (a) High bioavailability of drugs, especially for some poorly soluble drugs. By comparing drug release property of emulgel containing mupirocin-loaded microsponges (MS emulgel) and mupirocin

ointment (MP ointment), mupirocin emulgel (MP emulgel) through *in vitro* drug release studies, the study found that permeability coefficient of MS emulgel was $(2.49 \pm 0.06) \times (10^{-3} \text{ cm} \cdot \text{h}^{-1})$, lower than MP ointment $(7.57 \pm 0.20) \times (10^{-3} \text{ cm} \cdot \text{h}^{-1})$ and MP emulgel $(4.24 \pm 0.08) \times (10^{-3} \text{ cm} \cdot \text{h}^{-1})$, which showed that MS emulgel enhanced drug retention within the epidermis, and improved topical bioavailability.⁷

- (b) Non-irritation. The precious study carried out skin stimulant experiment using the New Zealand white rabbit, and the result showed no abnormality on the unbroken and damaged rabbit skin. The primary irritation index was calculated to be 0. Thus, the result indicated that microsponges are non-irritational to the rabbit skin.^{5,7}
- (c) Prolonged the duration of action of drug. *In vitro* drug release studies indicated that drug action duration of MP ointment (4-10h) and MP Emulgel (4-10h) are both shorter than that of MS emulgel (24h).⁷
- (d) Stability. Within 3 months, microsponges had no change in their physical appearance, pH, and drug content.^{7,13-16}

Initial discoveries

At the beginning, microsponges were used in oral drug delivery system. For example, as early as 1989, Kawashima¹⁷ had prepared the ibuprofen microsponges by using quasi-emulsion solvent diffusion method, and since then, this kind of method for preparation of microsphere was commonly used.¹⁸⁻²¹ And subsequently, the advantages of microsponges were found and revealed by researches gradually.

In the early time, the microsponges used in Transdermal drug delivery system was benzyl peroxide microsponges in 1991.^{5,22} And later, the Retin-A microsponges (0.1% or 0.04% tretinoin) and Carnac microsponges (0.5% 5-fluorouracil) for acne and actinic keratoses respectively were approved by Food and Drug Administration (FDA). Afterward, microsponges for topical skin-target drug delivery are widely developed and utilized in topical drug delivery system, such as mupirocin microsphere, hydroxyzine hydrochloride microsphere, paeonol microsphere and so on.

Preparation and application

Usually, microsponges were prepared mainly by two methods. One is a quasi-emulsion solvent-diffusion method,^{7,8,23} and another is free-radical suspension polymerization. But, irradiation, high temperature, or catalysis to activate the monomer is indispensable reaction condition¹⁶ when microsponges were prepared by free-radical suspension polymerization, and the manufacturing processes are complex and reproducibility is poor. Compared with this way, the quasi-emulsion solvent-diffusion method is not only easily performed in the laboratory, but also has the potential to prepare microsponges readily in the factory.^{7,24}

In the process of preparation, in order to optimize the preparation process of microsponges^{7-9,25,26} and improve release of drug,²⁷⁻²⁸ the factors including drug/polymer ratio, disperse phase solvent amount, stirring time, speed and stirrer type on the preparation of microsponges always need to be investigated. Afterwards, the thermal behavior, surface morphology, particle size and pore structure of microsponges should be examined. Eventually, for the purpose of evaluating the effect of microsponges, we always carry out *in vitro*²⁴ and *in vivo* drug release studies.^{7,8,10}

In 2006, Jelvehgari et al.²⁴ produced ethyl cellulose (EC) micro particles containing benzoyl peroxide (BPO). BPO micro particles were prepared by an emulsion solvent diffusion method. In the process of preparation (Figure 2), the researcher investigated such factors: drug /polymer ratio, stirring rate, volume of disperse phase, and found that those factors influenced the particle size, drug content and drug release behavior of microsponges.²⁹⁻³¹

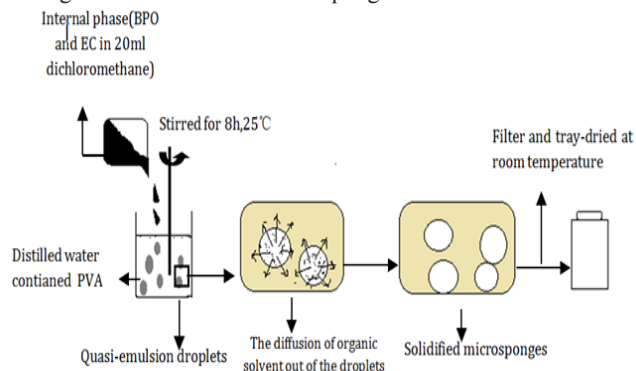


Figure 2 Preparation of BPO microsponges by quasi-emulsion solvent diffusion method

In addition, the release dynamic characteristic of BPO from microsponges was discussed. The author conducted the release studies using Franz diffusion cells (ERWEKA, Germany), and the result showed that the kinetics of the release of BPO from microsponges corresponds to zero-order dynamic model. Afterwards, samples were withdrawn at different time points and was analyzed using HPLC. Each test was carried out in triplicate and the mean of three observations was reported. The data of drug release indicated that the rate of initial hour was higher than that of the second hour. Then, within the next 7h, the flux remained constant, which showed the entrapped drug released from microsponges.

Later, in 2011, Hydroxyzine Hydrochloride¹⁰ as a drug model, which was used to produce a novel drug-loaded dosage form-microsponges that could control the release of drug into the skin. The method of preparation of Hydroxyzine HCl microsponges was a little different from the method of preparation of BPO microsponges.

When microsponges were prepared by the said method (Figure 3), the following factors could be used to optimize the preparation of drug microsphere:

- a. Drug/polymer ratio
- b. The percent of magnesium stearate
- c. Polymer/solvent ratio in the presence and absence of Span 80
- d. Pore inducers.

The researcher evaluates preparation of Hydroxyzine HCl microsponges by the entrapment efficiency calculated through the following formula: (Practical drug loading/Theoretical drug loading) $\times 100$.

Unlike previous mentioned *in vitro* release studies, this article used cellulose nitrate membrane instead of animal skin to perform the study of drug release. In addition, the research assayed the drug content of microsponges with spectrophotometer at $\lambda_{\text{max}} = 231 \text{ nm}$ ³²⁻³³ rather than HPLC.

The procedure of drug diffusion was divided into two parts. Firstly, the aqueous solution was diffused to the matrix and drug was

dissolved; secondly, the drug from the pores spread to the dissolution medium. Thus, the release curve (Figure 4) of Hydroxyzine HCl from the microsphere indicated that the process has two obvious phases. In the first three hours, the rate of release of drug increases gradually and approaches closely to the highest rate, then followed by a placid release phase. In the *in vivo* studies, the author detected

pharmacodynamic activity of antihistamines by percutaneous injection of histamine in skin of subjects, and the skin was treated by this microsphere, which was able to restrain wheal and flare response induced by histamine. There are two groups ($n=4/\text{group}$) used in this study, Group I (dealt with blank microsponges) and Group II (dealt with medicated products)

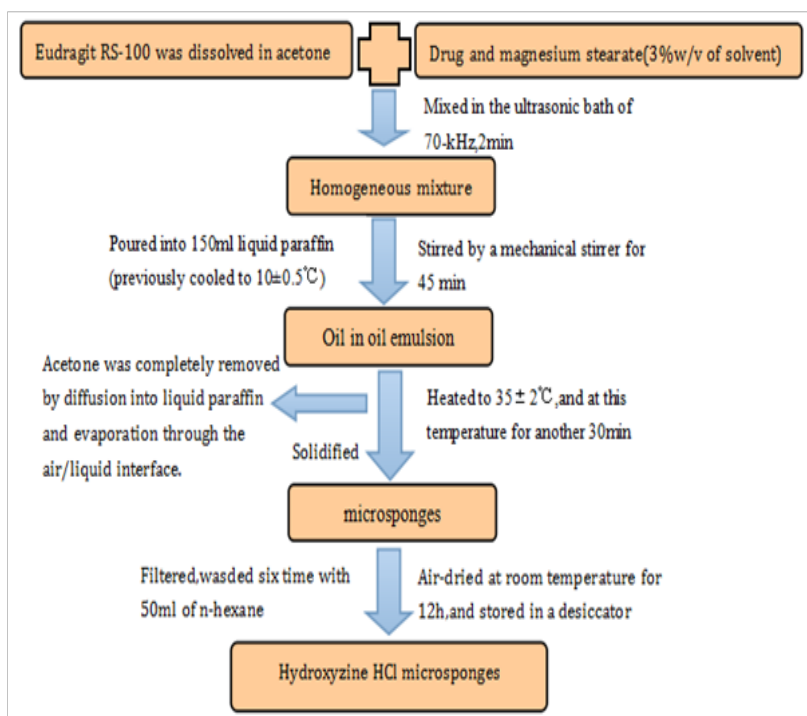


Figure 3 Preparation of Hydroxyzine HCl microsponges by oil in oil emulsion solvent diffusion method.

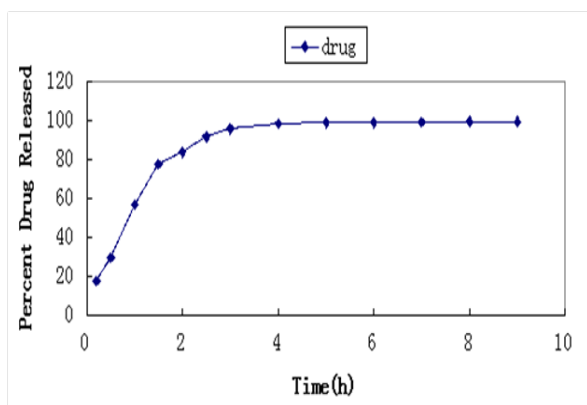


Figure 4 The *in vitro* release profile of HYD-HCl from microsponges.¹⁰

Compared with the innovative wheal areas, the rabbit of Group I cannot be cured, but another group can be cured after 4h (Figure 5). It showed that wheal and flare can be cured by the medicated microsphere. In 2013, the group of Liu et al.⁸ firstly put forward a new skin-target drug delivery system containing Paeonol which was extracted from the root of *Paeonia suffruticosa*, a kind of traditional Chinese medicine. The preparation of Paeonol microsponges is the same as flurbiprofen microsponges,¹⁵ using the quasi-emulsion solvent-diffusion method (Figure 6).

In this paper, the researcher evaluated the feature of the paeonol microsponges from the followed factors: scanning electron

microscopy (SEM), yield, entrapment efficiency, and particle size, and then prepared paeonol microsponges into a cream to analyze and research on release of paeonol *in vitro* and *in vivo*.

The Franz diffusion cells were used to carry out the release studies *in vitro*, and the content of drug samples withdrawn at different time points were analyzed by HPLC.

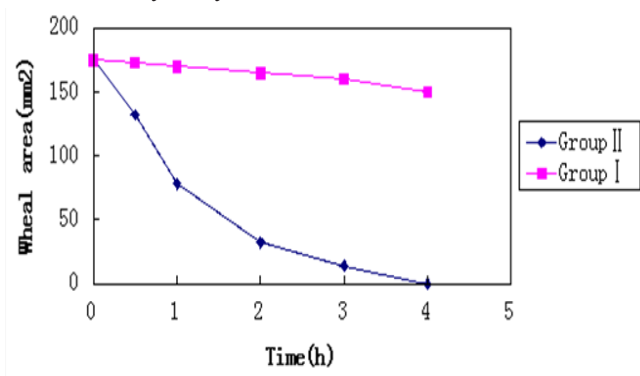


Figure 5 Wheal and flare response induced by histamine¹⁰

In contrast, the flux (J_{ss}) of Paeonol microsphere cream was $(21.17 \pm 0.284) \text{ mg/cm}^2/\text{h}$, higher than Paeonol cream $(17.29 \pm 0.312) \text{ mg/cm}^2/\text{h}$ and saturated aqueous solution of paeonol $(3.46 \pm 0.091) \text{ mg/cm}^2/\text{h}$ (Figure 7). The zero order ($R^2=0.997$) of Paeonol microsphere cream was the highest among three different formulations, and the zero order was higher than first order and Higuchi. Thus, the result

proved that the kinetics of *in vitro* release curve of paeonol from microsphere cream satisfied the zero order kinetics.

In *ex vivo* drug-residues studies, the amount of paeonol from paeonol microsphere cream stored in the skin was almost one and a half times than the paeonol cream at 24h (1.3627 ± 0.0699 mg/cm² vs. 0.9988 ± 0.0801 mg/cm²). The result showed that microsphere delayed the release of drug into the skin.

In this article, the intra-dermal micro dialysis was used in the *in vivo* release studies among different formulations of paeonol.

The mean $t_{1/2}$ for the paeonol microsphere cream was 935.1 min, while was 548.6 min for the paeonol cream, indicating that the microsphere form has a good distribution into the skin. In addition, the drug content of paeonol microsphere cream was extremely steady compared with paeonol cream Figure 8, helping the drug to be released in specific area. It is useful for treating dermatosis because the drug was reserved as much as possible in the treated areas. The area under the curve (AUC) measured by micro dialysis showed that the paeonol microsphere could deliver a mass of paeonol to the skin, and thus improved its bioavailability. Microsponges may be a promising skin-target drug delivery system for treating dermatosis.

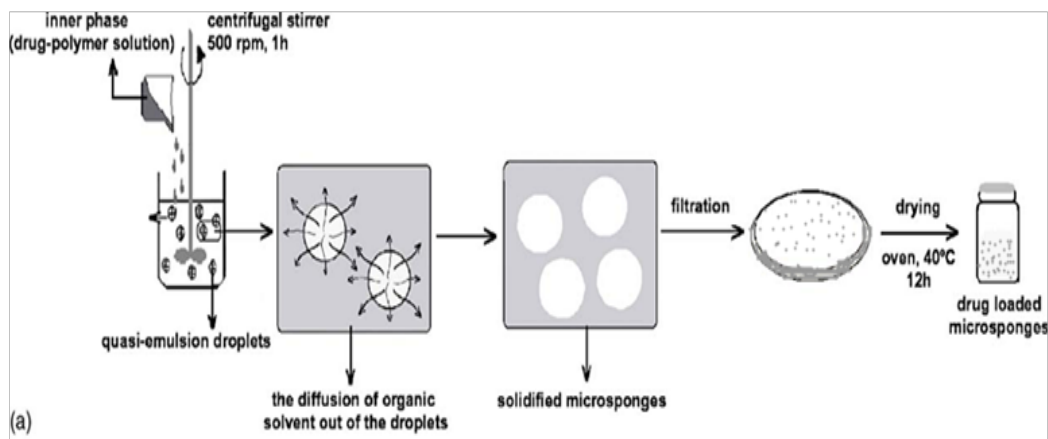


Figure 6 Preparation of Paeonol microsponges by quasi-emulsion solvent diffusion method

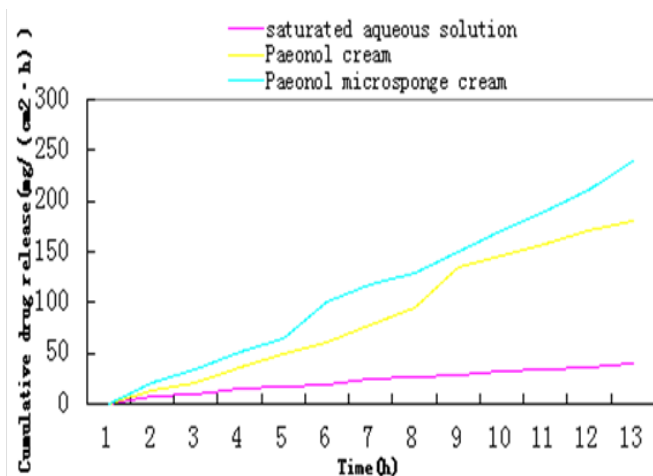


Figure 7 In vitro drug-release studies of 50mg/g paeonol cream, 50mg/g paeonol microsphere cream and 505.52mg/ml saturated aqueous solution. All data are shown as means \pm SD (n=3).⁸

Oxybenzone is a broad-spectrum sun-screening agent generally used in the formulation of cream, gel and lotion. In 2014, Pawar and coworker⁹ formulated Oxybenzone loaded microsphere gel to improve the efficacy of sun protection, and reduce toxicity. The preparation of Oxybenzone microsphere was similar to BPO microsphere, and the method was the quasi-emulsion solvent-diffusion method Figure 9.

In order to evaluate the optimized formulation, researcher investigated the following variables: physiochemical characterization, yield, particle size, percent entrapment efficiency (%EE), drug release, surface topography, and differential scanning calorimetry (DSC). Next, the study also examined rheological characterization,

skin irritation, minimal erythema dose (MED), and sun protection factor (SPF) determination to evaluate the prepared gel.

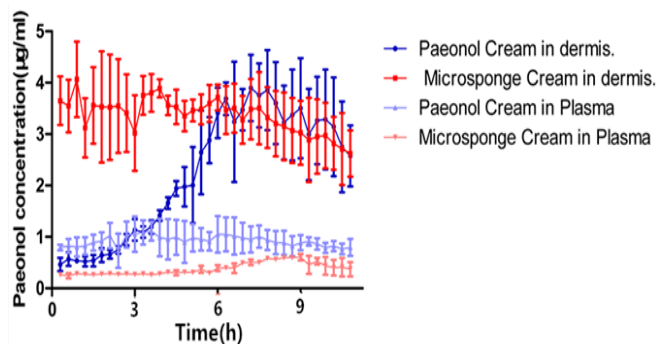


Figure 8 Paeonol concentration in intradermal liquid and plasma by in vivo microdialysis for paeonol cream and paeonol microsphere cream. All data are shown as means \pm SD (n=3).

By USP dissolution test apparatus, researcher detected the rate and extent of drug release from Oxybenzone loaded microsphere. The percentage of drug released at different time intervals was calculated and plotted against time.

The optimization of Oxybenzone loaded microsphere gel showed that the preparation was successful and enhanced sun-screening efficiency. Additionally, the creep recovery of blank microsphere was 65.11%, while drug loaded microsphere gel was 74.05% (Figure 10). As we known, the high creep recovery was helpful for promising gelling with higher elasticity. Meanwhile, SPF was increased and topical retention of drug was also enhanced in drug loaded microsphere gel, indicating the microsphere gel is remarkable in the *in vitro* and *ex vivo* evaluation study.

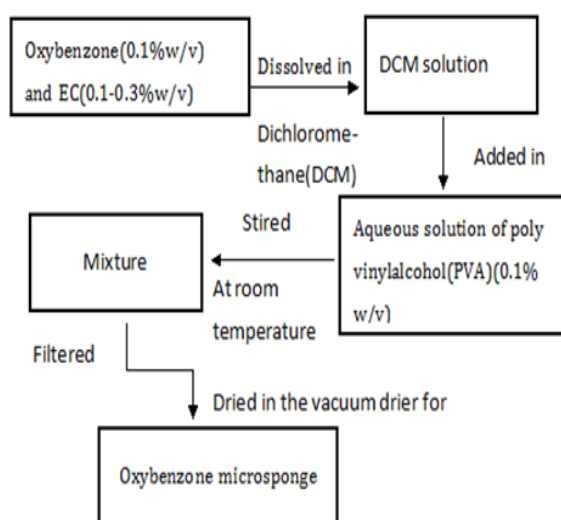


Figure 9 Preparation of Oxybenzone microsponges by quasi-emulsion solvent diffusion method.

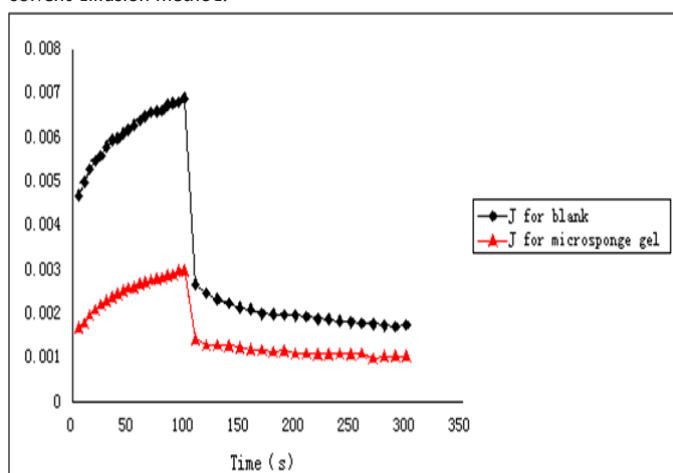


Figure 10 Creep recovery of blank and drug loaded microsphere gel.⁹

Summary and outlook

Microsponges are increasingly drawing attention from researchers all over the world due to the advantages of extending the residual time of drug in the epidermis or the dermis, while reducing its penetration into the body. In addition, microsponges can reduce skin irritation and other side effects and frequency of drug application, and improve efficacy and patient compliance. We believe that microsphere-based emulgel formulations would play a crucial role in the treatment of skin disease and at the aspect of development and progress of traditional Chinese medicine, and it will be a potential area to attract more and more pharmaceutical researchers to engage in TDDS study in the future.

Acknowledgements

We sincerely thank the Natural Science Foundation of China (81373975), Guangdong College Chinese Cosmetics Engineering Centre Construction (GCZX-A1007), Guangdong Natural Science Foundation (2014A03010342) and the Youth Training Program of Southern Medical University (PY2013N009) for financial support.

Conflict of interest

The author declares no conflict of interest.

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