

Instantly Dissolving Powders for Producing Standardized Biorelevant Dissolution Media for Quality Control of Poorly Water Soluble Drugs

J. Quinton¹ D. Streich¹ R. Geissbuehler¹ H. Schwebel¹ P. van Hoogevest^{1,2} A. Basit³ M. Leigh¹ J. Grunkemeyer^{1*}

¹ Phares Drug Delivery AG, Muttenz, Switzerland ² Adjunct Professor, Department of Pharmacy, University of Basel, Basel, Switzerland ³ Department of Pharmaceutics, School of Pharmacy, London, UK

* Corresponding author Tel: +41 (61) 317 9040 Fax: +41 (61) 317 9050 E-mail: info@phares.biz

Introduction & Objectives

One of the standard tools for the quality control of lipophilic drugs and their oral dosage forms is the testing of inter and intra batch reproducibility of the dissolution characteristics. Since the dissolution rate and extent of the lipophilic drug *in-vivo* determines its degree of oral absorption, it is of paramount importance to use biorelevant dissolution media. Moreover, the dissolution media must have reproducible compositions and should be, convenient to prepare in view of the large volumes required for routine QC testing. To date, standard media like FaSSIF (Fasted State Simulated Intestinal Fluid) and FeSSIF (Fed State Simulated Intestinal Fluid), propagated by the USP (1), require elaborate techniques, chlorinated solvents for preparation and have a limited shelf life. Furthermore, they do not take into consideration the fact that pancreatic phospholipase A₂ hydrolyses lecithin (di-acyl lecithin) to lysolecithin (mono-acyl lecithin) in the duodenal fluid (2).

The objective of the current study is to present easy-to-use powders which can be simply added to aqueous buffers to produce standardized biorelevant intestinal fluid for testing of lipophilic drugs.

Methods

Test drugs and dosage forms, taurocholate salt, soy bean lysolecithin and soy bean lecithin were purchased from reputed suppliers operating under cGMP conditions. All other chemicals used were at least of analytical grade.

As a benchmark, the dissolution media FaSSIF and FeSSIF containing di-acyl lecithin were prepared using the dichloromethane (DCM) emulsion method (1) on a lab scale. The use of dichloromethane in the processing of these fluids is disadvantageous due to its chlorinated nature. An alternative (commercial) method involving co-dissolving the cholate salt and lecithin at 4: 1 w/w in a non-chlorinated liquid phase followed by drying to yield a free flowing powder under cGMP conditions was developed. FaSSIF and FeSSIF with mono-acyl lecithin were prepared by replacing the di-acylphospholipid (DAP) with the same molar amount of mono-acyl lecithin (MAP) using this non-chlorinated solvent approach. The resulting powders had excellent powder flow properties, irrespective of the lipid employed. The powders produced were checked for taurocholate, (mono-acyl) lecithin, water, solvent content and dissolution properties in water. Dissolution media were prepared by simply dissolving an aliquot of the powder in water or buffer with the desired pH and ionic strength, corresponding to the FaSSIF or FeSSIF media compositions. Dissolution rates of model drugs in the various media were determined in triplicate at 37 °C using USP apparatus/methods and drug-specific HPLC methods.

Results & Discussion

The modification to obtain a more biorelevant and standardized medium is achieved by the use of a reproducible quality of mono-acyl lecithin at cost-effective prices. The interbatch reproducibility of the quality of the mono-acyl lecithin is provided in Table I.

Table I: Interbatch reproducibility of MAP for standardized dissolution media

	Specifications	Batch 899163-1	Batch 899212-1
Mono-acyl lecithin content	n.l.t. 80 %	85.7 %	80.2 %
Di-acyl lecithin content	n.m.t. 20 %	14.2 %	15.0 %
Peroxide value	Max. 10	1.5	3.2
Water	Max. 2 %	1.1 %	0.5 %
Ethanol	Max 0.5 %	0.3 %	0.4 %
Heavy metals	n.m.t. 10 ppm	complies	complies

Customized dissolution media powder could be manufactured at taurocholate to DAP or MAP weight ratios of 4 to 1. The powders dissolved immediately in phosphate or acetate buffer of the prescribed pH value. In this way, the elaborate method to prepare the FaSSIF and FeSSIF media by using dichloromethane (1) can be avoided. Furthermore, the short shelf-life of aqueous concentrates (3) can be overcome by using an instantly dissolving powder that can easily be prepared when the media is required. The particle size of the mixed micelles as determined by Photon Correlation Spectroscopy (PCS) showed no difference in size after dissolving the powder in buffer or using the dichloromethane method. In Figure 1, the dissolution rates at 37 °C of the lipophilic model drugs ketoconazole and phenytoin are depicted in FaSSIF and FeSSIF, with either DAP or MAP, prepared by the dichloromethane method or the new convenient powder dissolution medium method. The presence of the phospholipid did not interfere with the HPLC determination of the drugs.

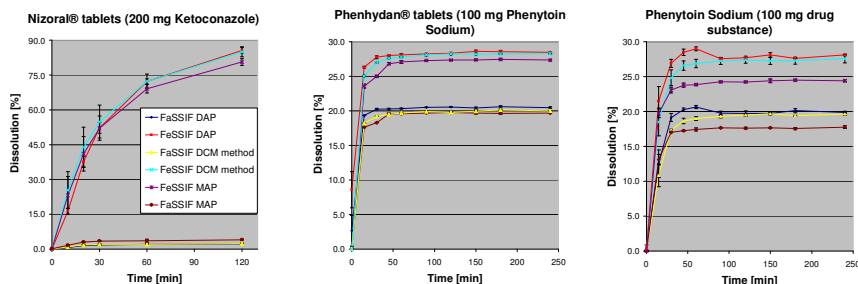


Fig. 1: Influence of drug substance, dosage form and composition of dissolution medium and preparation thereof on the *in-vitro* dissolution

The drug dissolution characteristics of the FeSSIF or FaSSIF containing DAP were the same for the studied drugs irrespective of the preparation method used to produce the dissolution media. Dissolution characteristics of the improved FaSSIF and FeSSIF media prepared from powders in which the DAP were replaced by an equimolar amount of MAP shows the same pattern in the case of ketoconazole and phenytoin tablets. However, in case of phenytoin drug substance significant differences could be observed in the % dissolution after 30 min.

Conclusions

- The instantly dissolving powders, prepared under cGMP, are convenient for QC departments in need of preparing simulated intestinal fluids reproducibly and at large daily bulk volumes
- FaSSIF and FeSSIF media prepared by the DCM emulsion method can be replaced by media prepared from powdered cholate-lecithin complexes
- The powder approach enables the easy preparation of simulated intestinal fluids and gives the user the freedom to choose their own buffer system
- Media incorporating mono-acyl lecithin are more biorelevant compared to media containing di-acyl lecithin and should have a higher degree of prediction of *in-vivo* dissolution of poorly water soluble drugs

Literature

- (1) Marques M., Dissolution Technologies (2004) 16.
- (2) Kossena G.A et al., J. Pharm Sci (2004) 93 (2), 332-348.
- (3) Ilardia-Arana D. et al., J. Pharm Sci (2006) 95 (29), 248-255.

