

Characterization of Simulated Biorelevant Media (FeSSIF and FaSSIF) Produced from a Standardized Instantly Dissolving Powder



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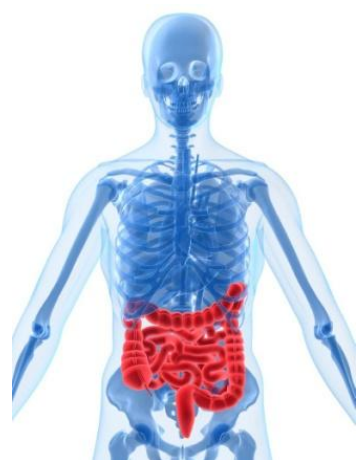
Introduction

The biorelevant media FeSSIF and FaSSIF simulate the two kinds of fluid found in the human small intestine (1):

FeSSIF – Fed State Simulated Intestinal Fluid (after food)

FaSSIF - Fasted State Simulated Intestinal Fluid (before food)

These biorelevant media help you to understand the solubility of drugs in the upper part of the gut where absorption of most drugs takes place. Biorelevant FeSSIF and FaSSIF contain mixed micelles comprising of bile salts (taurocholate) and phospholipids (lecithin) in a molar ratio of 4 to 1, along with buffers and osmotic adjusters.



Previous preparation methods of FeSSIF and FaSSIF are time consuming and do not allow the production of standardized, reproducible media which are the main requirements for industrial use. Biorelevant media like FeSSIF and FaSSIF contain natural components which can be variable and are susceptible to chemical and physical instability. Therefore, to overcome these weaknesses, Phares SIF® Powder (2), an instantly dissolving powder combined with a Standard Operating Procedure (SOP (3)) describing preparation and use, has been developed to prepare reproducible FeSSIF and FaSSIF easily.

Purpose

To evaluate the physicochemical properties of biorelevant media produced from different batches of Phares SIF® Powder using an SOP.

Methods

An SOP was developed and used to prepare reproducible biorelevant FeSSIF and FaSSIF media from an instantly dissolving powder.

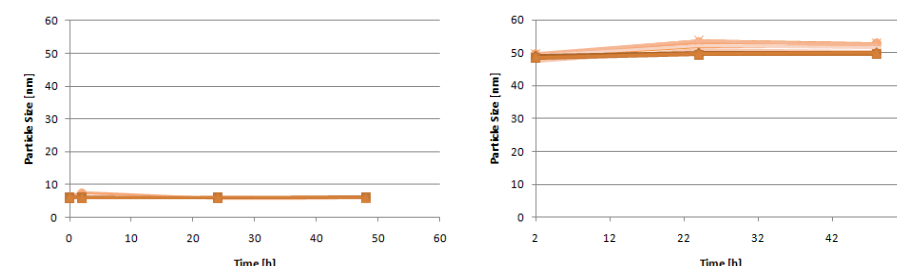
PCS and turbidimetry were used to measure the particle size of FeSSIF and FaSSIF, cryo transmission electron microscopy (TEM) to observe the appearance of the particles, ³¹P-NMR to check the lysolecithin content and malondialdehyde assay and UV spectrophotometry to monitor oxidation.

Results

Physical Characterization

The inter and intra batch reproducibility of the Z_{av} particle size of FeSSIF and FaSSIF measured by PCS are demonstrated in Figure 1.

Figure 1 Particle Sizes for 3 Batches in Triplicate for FeSSIF (left) and FaSSIF (right)



The results of the particle size analysis demonstrate that reproducible FeSSIF and FaSSIF can be produced from an instantly dissolving powder combined with an SOP. Turbidimetry was found to be insensitive because the particle size of the media was too small.

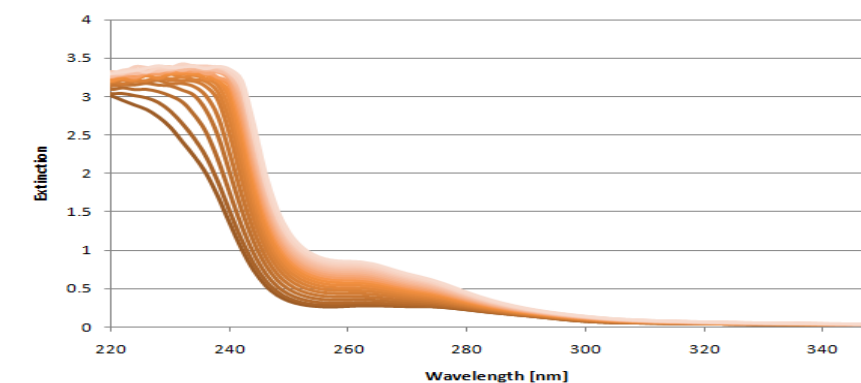
The cryo-TEM supported the particle size results. The FeSSIF appeared to contain micellar structures below 10 nm. In contrast, FaSSIF appeared to contain micelles, disc-like micelles and possibly vesicles (liposomes) with an average size of around 50 nm (4).

Chemical Characterization

³¹P-NMR showed that the lecithin in FeSSIF and FaSSIF media did not hydrolyze within 48 hours at 37 °C. No increase in MDA indicative for significant oxidation of the unsaturated fatty acids in lecithin was detected. However, the UV spectroscopic measurements on FeSSIF and FaSSIF showed a very small increase of oxidized lecithin (≤ 0.01 % Mole after 24 hours). This causes a large extinction at wavelengths less than 300 nm because of the extremely high molar extinction coefficient of $27'000$ (M⁻¹cm⁻¹) as shown in Figure 2.



Figure 2 Increase of the Extinction in FeSSIF Media



To avoid interference with UV measurement of drug content, HPLC or specialist UV equipment are recommended as an analytical method for accurate quantitative drug analysis in the presence of FeSSIF and FaSSIF.

Conclusions

Biorelevant FeSSIF and FaSSIF can be reproducibly prepared when using a combination of an instantly dissolving powder and an SOP describing preparation and use with respect to:

- Particle size
- Hydrolysis
- Dissolution rate

Although oxidation is very low we recommend that you use HPLC as your analytical method.

References

- (1) Galia E., Nicolaidis E., Horter D., Lobenberg R., Reppas C., Dressman J.B.. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. *Pharmaceutical Research*. **1998**, 15 698-705.
- (2) International Patent No.: WO2007054342 (A1)
- (3) Phares SIF® Powder Preparation Protocol V 09_10_06
- (4) To see the micrographs visit booth 438.