*AAPS PharmSciTech, Vol. 16, No. 3, June 2015 (© 2014)*
DOI: 10.1208/s12249-014-0250-4

*Research Article*

# Pediatric Suppositories of Sulpiride Solid Dispersion for Treatment of Tourette Syndrome: *In Vitro* and *In Vivo* Investigations

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*Received 25 August 2014; accepted 25 November 2014; published online 11 December 2014*

***Abstract.*** Pharmaceutical development was adopted in the current study to propose a pediatric rectal formulation of sulpiride as a substitute to the available oral or parenteral formulations in the management of Tourette syndrome (TS). The goal was to formulate a product that is easy to use, stable, and highly bioavailable and to achieve a rapid clinical efficacy. Towards this aim, sulpiride solid dispersion (SD) with tartaric acid at a weight ratio of 1:0.25 was incorporated into different suppository bases, namely witepsol W25, witepsol H15, witepsol E75, suppocire NA, suppocire A, glycerogelatin, and polyethylene glycols. The formulae were evaluated *in vitro* using different pharmacotechnical methods such as visual, melting, weight and content uniformities, drug release, differential scanning calorimetry (DSC), Fourier transform infrared (FTIR), and X-ray diffraction (XRD) analyses. *In vivo* bioavailability was also assessed in rabbits to compare the bioavailability of either raw sulpiride-incorporated or its SD-incorporated witepsol H15-based suppositories to its oral suspension (reference). Sulpiride SD-incorporated witepsol H15 formulation showed acceptable *in vitro* characteristics with a bioavailability of 117% relative to oral dosing, which excel that in humans (27% after dosing of oral product). In addition, the proposed formula not only passed the 6-month stability study but also proposed a promising scale-up approach. Hence, it showed a great potential for pediatric product development to manage TS in rural areas.

**KEY WORDS:** bioavailability; pediatric rectal suppositories; solid dispersion; sulpiride; tartaric acid.

## INTRODUCTION

The fundamental features of Gilles de la Tourette syndrome (TS) are motor and vocal spasms that vary in severity (1). Motor tics commonly start from the age of 1 year up to 8 years, with brief periods of eye blinking or some other facial spasms. Phonic tics, such as repetitive attacks of sniffing then vomiting, typically start from the second year of age, but they usually follow motor tics by a couple of years (2). TS is typically treated by blocking dopamine receptors using antipsychotic drugs, among which is sulpiride, a selective dopamine $D_2$ antagonist, which is the most effective for pediatric formulation (3). Having this case, there is a lack of pediatric products of sulpiride that can fulfill the needs of the developing countries, where TS is mostly prevalent among children and juveniles (4). In particular, there is a formulation that can be administered by unqualified personnel who cannot administer oral products ("non-*per os*") to children. The desired target product profile constitutes the following:

a. A sulpiride formulation that can treat all the symptoms of TS;
b. The formulation should be suitable to be used in both uncomplicated and complicated cases when an oral route is not possible (a non-*per os* patient);
c. The formulation must have an equivalent or better bioavailability than the oral route;
d. The formulation must be safe;
e. The formulation must be easy to use by nonprofessional personnel and must be amenable to near-home use;
f. The formulation should be made of cheap ingredients using simple and robust manufacturing processes; and
g. The formulation must be stable at different temperature and humidity conditions.

Different options have been investigated for a pediatric rectal formulation of sulpiride. Considering that the rectal route is mostly acceptable in the developing countries (5–7), it is especially to be used by untrained mothers with their children in both uncomplicated and complicated cases. Besides, the rectal route avoids at least partially the first-pass metabolism, improves the stability of drugs in the acidic pH of the stomach, and allows the administration of medications with unpleasant taste or odor (8). Sulpiride was the drug candidate for this indication because of its effectiveness and

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pharmacokinetic properties. Following intravenous bolus dosing, sulpiride showed a distribution volume of 2.7 L/kg and a prolonged half-life of 11–14 h and was considered to be convenient for once-daily administration. Sulpiride showed slow and incomplete absorption from the gastrointestinal tract with a bioavailability not exceeding 27% (9). Moreover, it is worth noting that there are no rectal products of sulpiride in the market and scarce information exists on its rectal availability. The poor water solubility and dissolution in the gastrointestinal fluids of sulpiride limited its oral bioavailability (10). As an approach to overcome this problem of sulpiride oral administration, solid dispersions (SDs) were proposed to incorporate the drug into a hydrophilic matrix. The mechanisms by which SD would improve the solubility and/or the dissolution rate included the formation of solid solution or solid suspension of the hydrophobic drug in a hydrophilic matrix. The prevailed mechanism is determined by the nature and chemistry of both drug and carrier. Moreover, the proportion of the drug to the bulk matrix solid was also one of the critical parameters to critically affect the performance of SD (11). Other mechanisms might also exist to describe the performance of the carrier matrix in enhancing the dissolution of hydrophobic medications including conversion into less stable or distorted crystalline structure, amorphization, and attenuation of particle size to submicron or nano range and in improving the wettability of the drug by the dissolution medium (12). In this regard, the aim of our previously published study was to propose a solid dispersion formulation of sulpiride with an enhanced bioavailability after oral administration (10). Different matrix-forming carriers have been investigated, among which is tartaric acid that was the most successful to improve sulpiride bioavailability by 2.5-fold. At this end, the aim of the second part of this study was to identify a suitable rectal formulation of sulpiride that would produce adequate plasma levels, treat all the symptoms of TS, and be affordable and acceptable for use in developing countries. The current study described the pharmaceutical screening of seven sulpiride rectal suppository bases, five oleaginous bases (witepsol H15, witepsol W25, witepsol E75, suppocire A, and suppocire NA), and two water-soluble bases (glycerogelatin and polyethylene glycol) compared to rectal controls. In addition, sulpiride rectal formulation with the best characteristics was evaluated for their bioavailability in rabbits.

## MATERIALS AND METHODS

### Materials

Sulpiride was supplied from Delta Pharma Co., Tenth of Ramadan, Egypt. Polyethylene glycol (PEG) (PEG 400, PEG 4000, and PEG 6000) was purchased from Hoechest Chemikalien, Werk Gendort, Germany. Metoclopramide, witepsol W25, witepsol E75, and suppocire NA were kindly supplied by EIPICO, Tenth of Ramadan, Egypt. Witepsol H15 and suppocire A were supplied by Memphis Co., Cairo, Egypt. Acetonitrile, ethyl acetate, dichloromethane, methanol, gelatin, glycerol, and tartaric acid were purchased from Nasr Pharmaceuticals Chemicals Co., Cairo, Egypt. All other chemicals and solvents were of analytical grade.

### Preparation of Solid Dispersions and Physical Mixtures

Solid dispersion of sulpiride and tartaric acid as the investigated carrier was prepared using an oil-in-water solvent evaporation technique (13). Accurately weighed quantities of sulpiride and tartaric acid with a drug to carrier ratio of 1:0.25 (*w*/*w*) were transferred into a flask. A sufficient quantity of methanol was added to dissolve the ingredients. The solution was then stirred at room temperature, and the organic solvent was evaporated under vacuum at a maximum temperature of 40°C. Solid residue was dried in a vacuum oven for 24 h at room temperature and then pulverized and sieved (14). Physical mixtures (PMs) were prepared by triturating the corresponding amounts of sulpiride and tartaric acid using a mortar and pestle and then transferred to a vacuum desiccator until use (13). The powder fractions of SD and PM that passed through a 355-μm sieve and retained on a 150-μm sieve were stored in sealed glass containers for further investigations.

### Preparation of Suppositories

Pediatric suppositories equivalent to 50 mg sulpiride of raw drug or its SD formulations with tartaric acid were prepared using either oleaginous or water-soluble bases. Five oleaginous bases (witepsol H15, witepsol W25, witepsol E75, suppocire A, and suppocire NA) were screened for their entrapment to sulpiride SD. In this regard, 50 mg sulpiride or its equivalent SD was accurately weighed and incorporated into the melted bases on a hot water bath and then stirred gently until uniformly distributed through the base. After congealing the melted base, the dispersion was poured into a clean lubricated mold and allowed to cool until solidification occurred.

Regarding the water-soluble bases, two bases were investigated, namely glycerogelatin and PEG bases. Glycerogelatin base was prepared according to the method stated in USP35-NF30 which consists of gelatin, glycerin, and water in a weight ratio of 2:7:1 (15). In particular, 50 mg sulpiride or its equivalent SD was accurately weighed, dispersed in the aqueous phase, poured on gelatin, and allowed to stand for 15 min. Glycerin was then incorporated and warmed at a temperature of 40°C until gelatin was totally dissolved and a clear homogenous solution free from air bubbles was obtained. The solution was poured into a clean lubricated mold and allowed to congeal. The obtained suppositories were then stored in tight containers, preferably at a temperature below 35°C, for further investigations. As shown in Table I, polyethylene glycol water-soluble bases were prepared in three formulae according to the reported method by Kauss and coworkers with some modifications (16). Fifty milligrams of sulpiride or its equivalent SD was incorporated into the melted PEG base on a hot water bath and stirred gently until it is uniformly distributed through the base. When the melted base started to congeal, it was poured into a clean dry mold and allowed to cool until mass solidification occurred (Table II).

### *In Vitro* Pharmacotechnical Controls of Sulpiride Suppositories

The prepared suppositories were visually inspected as an intact unit by splitting longitudinally at each removal from the

**Table I.** Composition of Different PEG Suppositories

| Component (% *w*/*w*) | Formula A | Formula B | Formula C |
|---|---|---|---|
| PEG 400 | 60 | 40 | – |
| PEG 4000 | – | 60 | 33 |
| PEG 6000 | 40 | – | 47 |
| Water | – | – | 20 |

Each suppository formula was incorporating 50 mg sulpiride or its equivalent SD

mold and at different stability conditions for color, clarity, and consistency. The absence of fissuring, pitting, fat blooming, exudation, sedimentation, and migration of the dispersed drug was also assessed. The weight uniformity was assessed by weighing 20 suppositories from each formula, and the average weight with its standard deviation was determined. Not more than two of the individual suppository weights should deviate from the average weight by more than 5%, and none deviates by more than 10% (15).

Sulpiride content uniformity was assessed by dispersing ten suppositories from each formula individually in a 250-mL capacity conical flask containing 100 mL Sörensen's phosphate buffers (pH 7.4) followed by shaking (and heating for fatty suppositories). The filtered clear solutions (solutions were cooled before filtration for fatty suppository bases) were measured spectrophotometrically at 290 nm against those from blank suppositories processed similarly. According to the US Pharmacopeia, the requirements for dosage uniformity were met if the drug amount in each suppository lies within the range of 85.0% to 115.0% of the label claim (50 mg) and the relative standard deviation (RSD) is less than or equal to 6.0% (15). The influence of the prepared suppositories to change the pH of the rectum was also assessed. For this purpose, three suppositories were digested with warm distilled water with pH 7.5 and cooled (for fatty suppositories) and the pH of the solution was determined (17). Regarding the mechanical strength, the prepared suppositories were classified as brittle or elastic by evaluating the crushing strength. The suppository is positioned in an upright position in an Erweka hardness tester (Erweka Type SBT; Erweka GmbH, Heusenstamm, Germany), and increasing weights are placed on it until it loses its structure and collapses. A good result was determined at a pressure of not less than 1.8 kg.

Liquefaction testing was performed on fatty suppositories to provide information on their behavior when subjected to a maximum temperature of 37°C. The test was done by measuring the time required for a suppository to liquefy under pressures similar to those found in the rectum (approximately 30 g) in the presence of water at a temperature of 37°C. For this purpose, an apparatus consisted of a 1.6-cm-diameter glass tube with a length of 23.5 cm and a 0.6-cm-diameter reduction at the base was used. The one end was blocked with a small rubber stopper to facilitate cleaning after use. A thermostat graduated in tenths of a centigrade was used. The tube and thermometer were held in place by means of a large rubber to a water bath set at a temperature of 37°C (18). The *in vitro* release of sulpiride from the prepared suppositories was also performed by a modified diffusion testing ($n$=6 for each formula). For this purpose, a cellulose ester membrane (MWCO 50 kDa) was soaked in distilled water for 15 min and then stretched firmly over the end of a diffusion glass tube. A volume of 3 mL of Sörensen's phosphate buffers (pH 7.4) was poured inside the tube. The tube was then attached to the shaft of the Pharmacopoeia I apparatus (Erweka GmbH, Heusenstamm, Germany) and then introduced into bowls containing 250 mL Sörensen's phosphate buffers (pH 7.4) maintained at a temperature of 37°C and centrifuged at 50 rpm. Samples (1-mL aliquot replaced by an equal volume of fresh dissolution medium) were withdrawn at 15, 30, 45, 60, 90, 120, 150, and 180 min. The samples were assayed for their drug contents using a spectrophotometric analysis at 290 nm against those from blank suppositories processed similarly (16).

### Preliminary Stability Testing

The prepared suppositories (containing SD) were kept individually in either aluminum blisters or plastic molds and stored at a relative humidity of 60% and temperatures of 4°C, 25°C, and 37°C over a period of 6 months. The *in vitro* release characteristics of sulpiride from the suppositories stored under these conditions were then evaluated.

### Solid-State Analysis

The differential scanning calorimetry (DSC) thermograms were recorded using a Shimadzu DSC system (Shimadzu Co., Kyoto, Japan). For this purpose, the 1.5-mg samples were heated in hermetically sealed aluminum pans over the temperature range of 30°C–300°C at a constant rate of 10°C/min under a nitrogen purge (30 mL/min). X-ray diffraction (XRD) patterns were obtained using a powder diffractometer (Kristallofex D-5000 powder diffractometer; Siemens AG Co., Berlin, Germany) with CuKα radiation. Diffractograms were run at a scanning speed of 8°/min with a $2\theta$ range of 0°–80°. A generator tension of 30 and 40 kV and a current of 30 mA were used for the XRD analysis of the sulpiride samples. Fourier transform infrared (FTIR) spectra were obtained on a PerkinElmer FTIR spectrophotometer, 1600 series (Perkin-Elmer Corporation, Norwalk, USA) using a KBr disk method. The scanning range was 200–4000 $cm^{-1}$ and the resolution was 1 $cm^{-1}$.

### Animal Pharmacokinetic Study

The animal handling procedure was performed in accordance to the approved protocol for the use of experimental animals set by the Standing Committee on Animal Care of the Faculty of Pharmacy, Zagazig University, Egypt (August 2012). White male albino rabbits (weighing ~2 kg) were provided from the animal house of the faculty of pharmacy. All animals were acclimatized and kept under constant temperature (25°C±2°C). Animals were divided into three groups of six rabbits each which receive an equivalent of 20 mg sulpiride per kg body weight of rabbits. Group I (control group) was administered with oral sulpiride suspension in water using an oral gastric tube followed by 50 mL of water to ensure full-dose administration. Group II (test group II) was administered with raw sulpiride-incorporated witepsol H15-based rectal suppository. On the other hand, group III (test group III) was administered with witepsol H15-based rectal suppository

**Table II.** Preparation and *In Vitro* Characterization of Sulpiride SD-Incorporated Suppository Formulations with Tartaric Acid (1:0.25 *w*/*w*)

| | Witepsol W25 | Witepsol H15 | Witepsol E75 | Suppocire A | Suppocire NA | PEG formula A | PEG formula B | PEG formula C | Glycerogelatin |
|---|---|---|---|---|---|---|---|---|---|
| Raw fatty base characteristics | | | | | | | | | |
| Hydroxyl value (mg KOH/g) | 20–30 | 5–15 | 12–15 | – | – | – | – | – | – |
| Saponification value (mg KOH/g) | 232.5 | 237.5 | 225 | – | – | – | – | – | – |
| Manufacturing process | | | | | | | | | |
| Process | Co-melted | Co-melted | Co-melted | Co-melted | Co-melted | Solid solution | Solid solution | Solid solution | Solid solution |
| Process temperature (°C) | 60 | 60 | 60 | 60 | 60 | 80 | 80 | 80 | 65 |
| Process time (min) | 15 | 15 | 15 | 15 | 15 | 20 | 20 | 20 | 45 |
| *In vitro* characterization | | | | | | | | | |
| Suppository aspect | Smooth, whitish, and cloudy | Smooth, whitish, and cloudy | Smooth, whitish, and cloudy | Smooth, whitish, and cloudy | Smooth, whitish, and cloudy | White, translucent, and marbled | White, translucent, and marbled | White, translucent, and marbled | Smooth, yellow, and transparent |
| Melting point (°C) | 33.5–35.5 | 33.5–35.5 | 37–39 | 35–36.5 | 35.5–37.5 | 56 | 54 | 59 | 45 |
| Melted aspect | Cloudy | Cloudy | Cloudy | Cloudy | Cloudy | Crystal clear | Crystal clear | Crystal clear | Clear solution |
| Mean weight±RSD (g) | 1.024±0.003 | 1.068±0.064 | 1.048±0.015 | 1.064±0.003 | 1.088±0.061 | 1.072±0.014 | 0.98±0.003 | 1.036±0.058 | 0.984±0.014 |
| Weight uniformity±5% | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Drug content±RSD (% of theoretical) | 90.16±0.54 | 104.24±3.01 | 94.24±0.86 | 107.12±1.18 | 105.62±4.61 | 104.24±3.07 | 107.72±0.11 | 102.42±3.64 | 108.34±2.68 |
| Effect on pH of the medium | 4.42±0.21 | 4.53±0.08 | 4.46±0.03 | 4.48±0.03 | 4.51±0.03 | 3.85±0.01 | 3.86±0.01 | 4.26±0.01 | 4.74±0.01 |
| Crushing strength±RSD (kg) | 2.6±3 | 3.5±4 | 2.3±2.7 | 1±1.4 | 3.2±1.4 | 2.2±2.9 | 1.8±2.4 | 2±2.2 | – |
| Softening time (min) | 4.5–5 | 5.5–6 | 15–18 | 5.5–6 | 6.5–8 | – | – | – | – |
| Drug released after 3 h±RSD (%) | 27.52±2.4 | 38.56±2.61 | 1.36±0.43 | 10.39±1.83 | 22.02±2.34 | 35.23±3.89 | 33.06±3.25 | 31.66±2.21 | 38.64±1.67 |

incorporating SD of sulpiride with tartaric acid at a ratio of 1:0.25 (*w*/*w*). At 0.25, 0.5, 1, 2, 4, 6, 8, and 24-h time intervals, the 2-mL blood samples were withdrawn from the sinus orbital vein into EDTA tubes. The samples were centrifuged immediately at 3000 rpm for 5 min to separate the plasma and stored at a temperature of −20°C for further analysis. After thawing to room temperature, 1 mL of the plasma was spiked with 0.1 mL of an internal standard (1.5 μg/mL metoclopramide in methanol concentration) and 0.1 mL of a NaOH solution (1 N). After thorough vortex mixing for 5 s, the mixtures were extracted with 6 mL of ethylacetate/dichloromethane (5:1 *v*/*v*) and then vortex mixed for 5 min and centrifuged at 3000 rpm for another 10 min. Five milliliters of the supernatants were then transferred to another clean glass tube and evaporated under a stream of nitrogen at a temperature of 40°C until complete dryness. A volume of 0.6 mL of phosphate buffer (pH 3) was added to reconstitute the residue, and 20 μL was injected into the HPLC for quantitative analysis according to the method described by Nobilis *et al.* with some modifications (19).

An HPLC system (Agilent 1200 series; Agilent Technologies Inc., Santa Clara, CA, USA) composed of quaternary pump, degasser, autosampler, Phenomenex C18 RP column (5 μm packing, 4.6×150 mm), Phenomenex C18 RP guard column, and diode array detector was employed. The mobile phase was composed of a mixture of 0.01 M phosphate buffer (adjusted to pH 3 using phosphoric acid) and acetonitrile at two ratios as follows: solvent A (90:10 *v*/*v* buffer and acetonitrile) and solvent B (80:20 *v*/*v* buffer and acetonitrile). Each chromatographic run was started by an isocratic elution using solvent A up to 4 min and then by linear gradient ramping of solvent B to 100% up to 6 min. The elution was kept at 100% solvent B up to 10 min followed by ramping of solvent A to 100% at 11 min, and it was then kept at 100% solvent A up to 15 min. The flow rate was kept at 1 mL/min, and the UV detection was set at 212 nm.

The pharmacokinetic parameters were evaluated from the plasma-drug level data obtained from individual rabbits in each group and were presented as mean±S.D. The calculated pharmacokinetic parameters that included the maximum plasma concentration ($C_{max}$, ng/mL), the time required to reach maximum plasma concentration ($T_{max}$, h), the area under the plasma concentration-time curve from time 0 to 24 h ($AUC_{0-24}$, ng $mL^{-1}$ $h^{-1}$), the area under the plasma concentration-time curve from time 0 to ∞h ($AUC_{0-\infty}$, ng $mL^{-1}$ $h^{-1}$), the elimination rate constant ($K_{el}$, $h^{-1}$), and the elimination half-life ($t_{1/2}$, h) were calculated using EquivTest® pharmacokinetic software (Statcon, Witzenhausen, Germany). The relative bioavailability was calculated from the comparison of $AUC_{0-24}$ of each test group with that of the control group according to the following equation:

$$\text{Relative bioavailability} = \left(AUC_{0-24}\text{ for test} \Big/ AUC_{0-24}\text{ for control}\right) \times 100$$

## RESULTS AND DISCUSSION

### Development and Optimization of Sulpiride SD-Loaded Suppositories

Sulpiride is a class IV drug according to the biopharmaceutical classification system (20) which exhibits poor aqueous solubility and/or poor permeability. It remains uncertain whether the poor bioavailability is due to poor solubility and dissolution or also poor permeability. SD technique is usually employed to enhance the rectal absorption of poorly soluble drugs (21) by enhancing their wettability, solubility, and dissolution rate (16,22), which complied with the preset desired target product profile.

Through our previously published article to develop sulpiride SD formulation, its SD with tartaric acid as a water-soluble carrier provided the greatest oral $C_{max}$ and $AUC_{0-24}$h in rabbits (10); hence, it was selected for further development of sulpiride-containing rectal suppositories. The obtained results showed that the bioavailability after oral sulpiride SD administration was approximately 180% relative to the corresponding raw sulpiride suspension, an encouraging finding considering the reported 27–30% oral bioavailability after oral administration of sulpiride solution to humans (9,23). Tartaric acid as a hydrophilic carrier for SD development offers various advantages such as low toxicity, high compatibility, high water solubility, and low cost (24), which complied with the desired target product profile. As tartaric acid might be slightly irritating to the gastrointestinal mucosa (25), no other additives or stabilizers were added to SD formulation in order to avoid complications, rectal intolerability, or early expulsion of the form. Different bases were investigated for their performance to formulate sulpiride SD-loaded pediatric rectal suppositories with tartaric acid. These included five oleaginous bases, namely witepsol H15, witepsol W25, witepsol E75, suppocire A, and suppocire NA, and two water-soluble bases, namely glycerogelatin and mixed polyethylene glycols. Oleaginous suppositories offer greater stability of SD formulation of sparingly water-soluble drugs than water-soluble bases, particularly in the molten state (26). Hence, the physical characteristics of the oleaginous suppositories could be more desirable for practical use. To prepare PEG-based water-soluble suppositories, a mixture of two PEGs of low and high-chain lengths is usually employed for the development of rapid-release suppositories (16). Different ratios of PEG 400, PEG 4000, and PEG 6000 were tested: 60% PEG 400 plus 40% PEG 6000 (PEG formula A), 40% PEG 400 plus 60% PEG 4000 (PEG formula B), and 33% PEG 4000 plus 47% PEG 6000 (PEG formula C). All PEG formulae exhibited melting ranges more than 45°C as per the preset target product profile (Fig. 1). These results are in good agreement

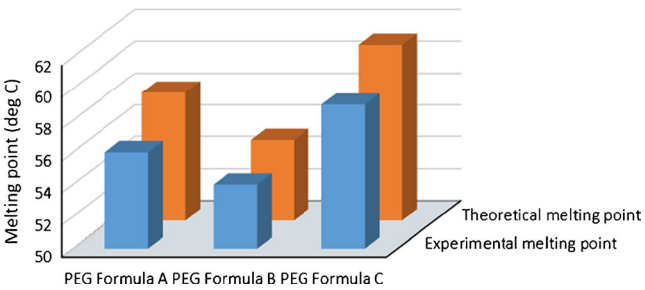


**Fig. 1.** Comparison of theoretical and differential scanning calorimetry (DSC)-measured melting point of various mixtures of PEG-based suppositories [60% PEG 400 plus 40% PEG 6000 (*PEG formula A*), 40% PEG 400 plus 60% PEG 4000 (*PEG formula B*), and 33% PEG 4000 plus 47% PEG 6000 (*PEG formula C*)]. The theoretical melting points were calculated from the individual melting points of PEGs in respect to their mixing proportions

with the reported data on PEG, showing that the melting point increases with its chain length (27).

Raw sulpiride-incorporated suppositories offer the advantage of simplicity of manufacturing due to the low water bath temperature, but they suffered from non-homogeneity and delayed drug release characteristics. Raw sulpiride powder did not dissolve in the melted mass of any of the investigated oleaginous bases or PEG bases at a temperature of 80°C. Hence, mixing raw sulpiride once melted with the molten base to form co-melted suppositories was the only available option. However, as the melting point of sulpiride is high (175°C) (10), it required a manufacturing temperature above 175°C (results not shown), in which an oven or an oily bath was employed. Moreover, the extended time at high temperature would affect the stability of the formulation and the color changed to darker color, indicating degradation and deterioration of the components. Using methanol as an intermediate solvent caused raw sulpiride to precipitate as soon as methanol started to evaporate from the molten bases. Moreover, the solubility of raw sulpiride in PEG 400 was still insufficient in PEG formulae A and B after 24 h of stirring. Consequently, the goal was to develop a formulation having homogenous and stable distribution of sulpiride as micronized domains with an enhanced drug release and a minimal precipitation. The option was to incorporate the solid dispersion of sulpiride with that of tartaric acid where the drug formed solid solution within the solid matrix. Solid solutions have been reported to enhance the drug dissolution rate and potentiate its release from the dosage form and are simple to manufacture (12,28). The optimal process temperature to prepare sulpiride SD-loaded suppositories was 80°C, which offer a better option regarding the final manufacturing time and temperature. Therefore, incorporating the SD into the investigated bases led to final forms with different characteristics. Table II describes all suppositories' formulations and hints on the manufacturing process and characterization.

### *In Vitro* Pharmacotechnical Controls of Sulpiride Suppositories

Table II describes the results of physical characterization of the nine formulations of sulpiride SD-loaded suppositories. The objective of this evaluation was to compare the performance of different suppository bases for the feasibility to prepare pediatric suppositories according to the desired target product profile. Regarding the visual observation, no color changes were observed between suppositories incorporating either raw sulpiride or its SD. In contrast to the corresponding sulpiride SD-loaded suppositories that were yellowish and transparent, the glycerogelatin-based suppositories with raw sulpiride were yellowish white and turbid due to dispersed insoluble drug particles. All sulpiride SD-containing oleaginous bases yielded suppositories that were smooth, whitish, and cloudy. On the other hand, the three formulae of PEG-based suppositories incorporating the SD were white, translucent, and marbled. When melted, oleaginous suppositories were cloudy with no drug crystals were observed. On the other hand, PEG-based suppositories were sulpiride-crystal clear where the different components were miscible at the liquid state. Similar observation was reported by Six *et al.* to describe the formation of solid solutions and eutectic mixtures on melting (29). Comparatively, sulpiride particles in suspension were clearly visible in the melt of suppositories incorporating raw drug.

Concerning the suppositories' weights and weight uniformity, all the prepared suppositories met the acceptable limits (not more than two of the individual weights should deviate from the average weight by more than 5%, and none deviates by more than 10% (15)). Considering the drug content uniformity testing for all formulae, the difference between the actual sulpiride loading and the theoretical loading was less than 9% with a variability of less than 5% (Table II). The acceptable content uniformity results might be due to the incorporation of sulpiride SD into the different bases as a solution completely mixed with the water-soluble bases or nanostructured within the fatty bases rather than as dispersed drug particles (30). The influence of the prepared suppositories to change the pH of the medium was also investigated. As shown in Table II, the suppositories containing sulpiride SDs decrease the pH of the medium from 7.5 to 3.85 due to the release of tartaric acid in the microdomains of solid solutions followed by its distribution throughout the medium (31). Considering the practical use of suppositories, the effects of either raw sulpiride or its SD on the base's crushing strength were examined. The bases' hardness values did not change significantly ($p<0.05$) by the incorporation of either the raw drug or its SD. This result would suggest that the low drug load to the bases did not deteriorate the mechanical strength of the suppository bases but, hence, maintain their clinical application. Table II shows that the hardness of sulpiride SD-containing suppositories complied with the previously mentioned specifications (not less than 1.8–2 kg), except suppocire A-based suppositories which exhibited a hardness value of ~1 kg. Hence, the prepared sulpiride SD-containing suppositories could be arranged according to the resultant hardness values as follows: witepsol H15>suppocire NA>witepsol W25> witepsol E75>PEG formula A>PEG formula B>PEG formula C>suppocire A.

Table II demonstrates the liquification time and the corresponding melting range of the oleaginous suppositories. All fatty suppositories complied with the pharmacopoeial requirements regarding the softening time (not more than 30 min). Moreover, a shorter softening time was accompanied with a lower melting range. The obtained data showed that sulpiride SD-incorporated witepsol E75-based suppositories exhibited the longest softening time (15–18 min) and the highest melting range (37°C–39°C). On the other hand, the witepsol W25-based suppositories possessed the shortest softening time (4.5–5 min) with a melting range of 33.5°C–35.5°C. It is worth mentioning that the compliance with pharmacopoeial specifications regarding the softening time does not guarantee the melting of oleaginous suppositories and subsequent drug release to meet the required release specifications. Further experiments should be performed to understand whether the oleaginous suppositories should melt, not only soften, at the temperature of dissolution and drug release.

*In vitro* drug release testing of suppositories is of critical importance not only to develop a formulation but also to test the consistency during manufacturing as a quality assurance tool. Different *in vitro* dissolution methods have been proposed in the literature such as the rotating basket method (32), the flow-through technique (33), and the dialysis tubing

method (34). The use of diffusion to exclude the boundary diffusion layer makes a fair discrimination among these methods. In the current study, a dialysis tube fitted to USP apparatus I has been employed as described by Janicki *et al.* after some modifications (33) because an acceptable correlation between the results of the *in vitro* drug release and its bioavailability in rabbits was reported. The apparatus was designed to simulate the small amount of water in the rectum and the drug distribution after release according to its portioning under a sink condition. Figure 2 shows the drug release from the prepared suppositories incorporating either raw sulpiride or its SD. Compared to the corresponding raw sulpiride-incorporated suppositories, Fig. 2 demonstrates that the incorporation of sulpiride as SD into the investigated bases resulted in a significant ($p<0.05$) enhancement of its release percentages. The permeation rate of sulpiride through the diffusion membrane into the outer phase was influenced by the solute concentration in the inner phase. This suggests that the driving force of drug permeation would be the concentration gradient of solute between the inner and outer phases. The dissolution rate of sulpiride was enhanced by its SD with tartaric acid; however, the amount dissolved at the plateau phase (after ~1 h) in the inner phase was about 70% of the incorporated drug amount. Hence, the low cumulative amount of dissolution could be explained by the duration of the supersaturated state inside the diffusion tubes.

The same performance of the investigated bases was observed for either raw sulpiride-incorporated or its SD-incorporated bases. Hence, the formulae can be arranged according to the percentage of sulpiride release after 3 h as follows: glycerogelatin>witepsol H15>PEG formula A>PEG formula B>PEG formula C>witepsol W25>suppocire NA> suppocire A>witepsol E75 (Fig. 2). The higher release of the drug from glycerogelatin base could be attributed to the rapid softening and solubilizing of the hydrophilic base. On the other hand, the higher release of sulpiride from PEG formulae A, B, and C could be explained by the osmotic action of PEG, the solubilizing effect of liquid PEG 400, and/or the hydrophilicity of PEG 4000 and PEG 6000 (35). It is worth noting that their diffusion tubes were filled with the dissolution medium during the release experiments. This phenomenon was not observed with witepsol H15-based suppositories despite that the percentage of sulpiride released was not significantly ($p<0.05$) different from that of the PEG formulae after 180 min (Table II). On the other hand, the sulpiride release from the oleaginous bases (except witepsol H15) was less than that from water-soluble bases. This was expected due to the higher affinity of hydrophobic raw sulpiride to the lipophilic bases. These observations are in good agreement with those obtained by other researchers to state a faster release of hydrophobic drugs from hydrophilic suppository bases than from hydrophobic ones, and *vice versa* (35,36). Comparing only the oleaginous suppositories, the highest release was obtained from witepsol H15 followed by witepsol W25, suppocire NA, suppocire A, and finally, witepsol E75 that showed a percentage of sulpiride release of 1% after 3 h. The highest saponification value and surfactant contents (Table II) of witepsol H15 compared to witepsol W25 and witepsol E75 could explain the result that the dispersion of the hydrophobic drug as micelles into the surrounding medium not only facilitates but also augments the dispersion action of tartaric acid to disperse the drug as a nanostructured solid solution (36,37). Another explanation of the variable release features from oleaginous bases could be correlated with the recorded melting range of each base (Table II). Using fatty bases with higher melting range (suppocire NA) resulted in significant ($p<0.05$) lower releases compared to the formulations with lower melting range (witepsol W25). However, the close relationship between the melting range of the fatty base and the percentage drug released as reported by Aoyagi *et al.* (38) was not applied here. The current study indicated that the surfactant content and the resultant hydroxyl value of the fatty base were more important for *in vitro* sulpiride release. Hence, it was affected more by the chemical composition than the melting range of the triglyceride base.

## Stability Study of Sulpiride-Loaded Suppositories

Stability of solid dispersion-based formulation is a critical factor during their development. The preliminary stability testing of sulpiride-loaded suppositories was performed before bioavailability assessment in experimental animals. Under each storage condition, namely a relative humidity (RH) of 60% and temperatures 4°C, 25°C, and 37°C for a

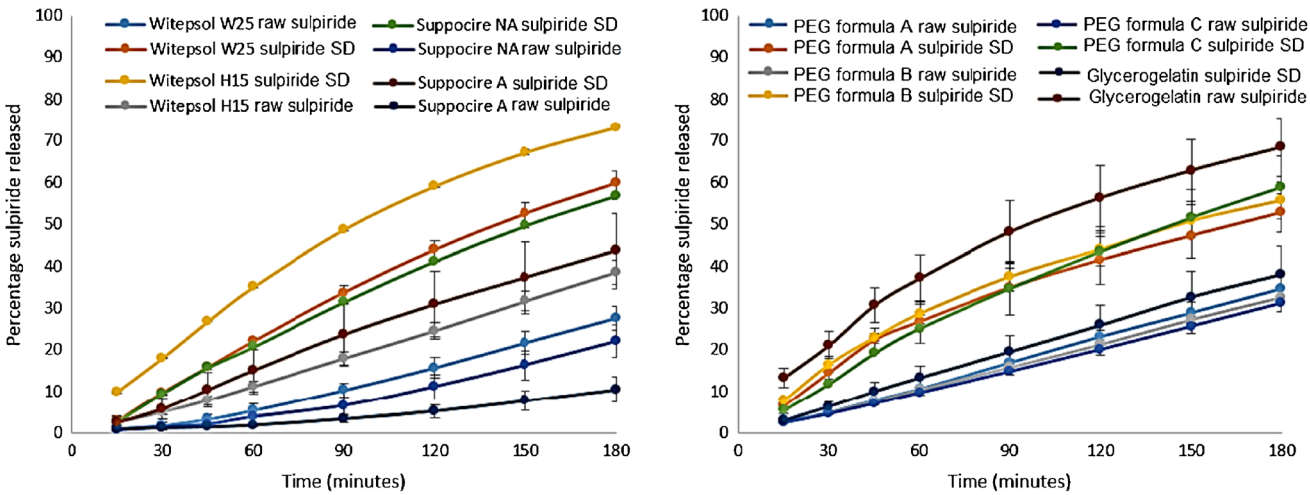


**Fig. 2.** *In vitro* sulpiride release from different suppository formulations incorporating either raw sulpiride or its SD with tartaric acid at a weight ratio of 1:0.25 using the modified diffusion method ($n=6$)

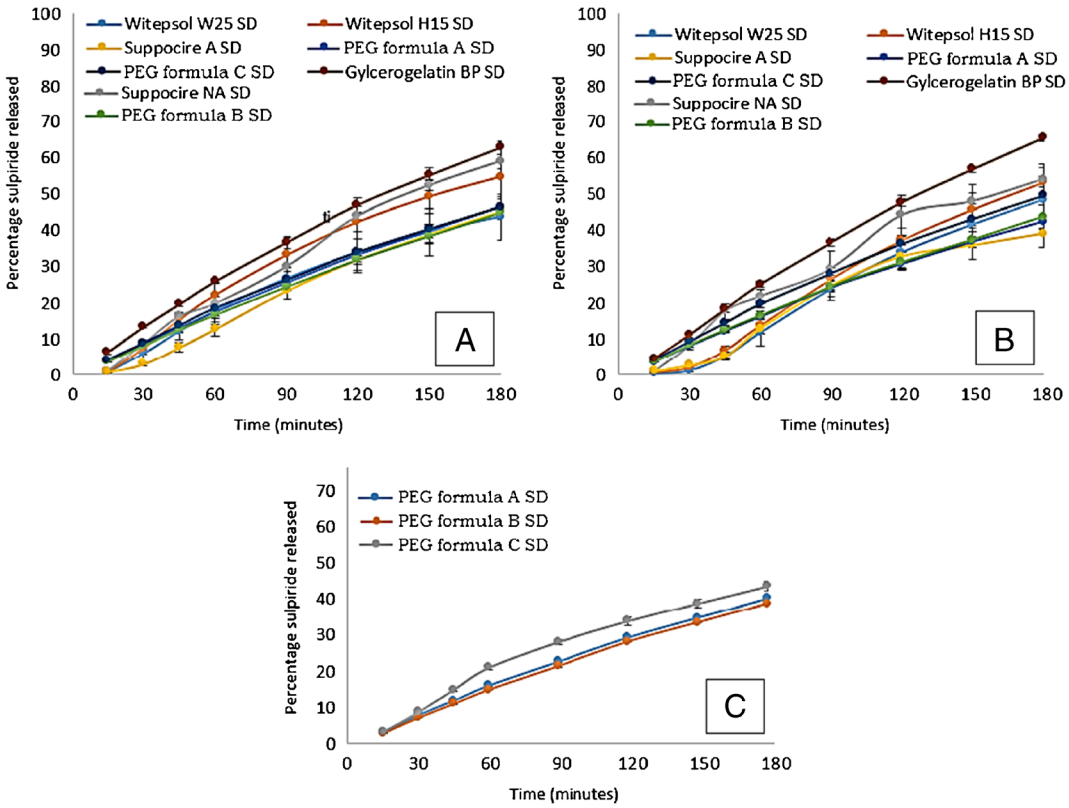


**Fig. 3.** *In vitro* sulpiride release from different suppository formulations incorporating sulpiride SD with tartaric acid at a weight ratio of 1:0.25 using the modified diffusion method ($n$=6) after storage for 6 months at **a** 4°C/60% RH, **b** 25°C/60% RH, and **c** 37°C/60% RH

period of 6 months, three primary conditions, sulpiride release, and physical characteristics were evaluated. No significant change in the appearance or melting was observed during the 6-month study for suppositories stored in aluminum blisters or plastic ones at temperatures 4°C and 25°C. However, for those kept in a plastic mold at 37°C/60% RH, the tails of both fatty and glycerogelatin-based suppositories became gradually pastier in 2 weeks, probably due to water captured. On the other hand, when kept under the same conditions, PEG-based suppositories became darker in color with a significant increase in hardness by approximately 20% after 2 months of storage.

The dissolution profiles of the fresh sulpiride SD-loaded suppositories and those after 6 months of storage were compared using the recommended difference factor f1 and similarity factor f2 (39). For sulpiride SD-loaded suppositories stored in aluminum blisters at the three stability conditions, the recorded profiles were similar, but different with f1=15.73 for those stored in a plastic mold at either 25°C/60% RH or 37°C/60% RH. In particular, Fig. 3a shows the sulpiride release from SD-incorporated suppositories stored at 4°C/60% RH. It is obvious that the drug release from suppocire NA, suppocire A, PEG formula A, and glycerogelatin-based suppositories was more or less similar to the fresh samples. On the

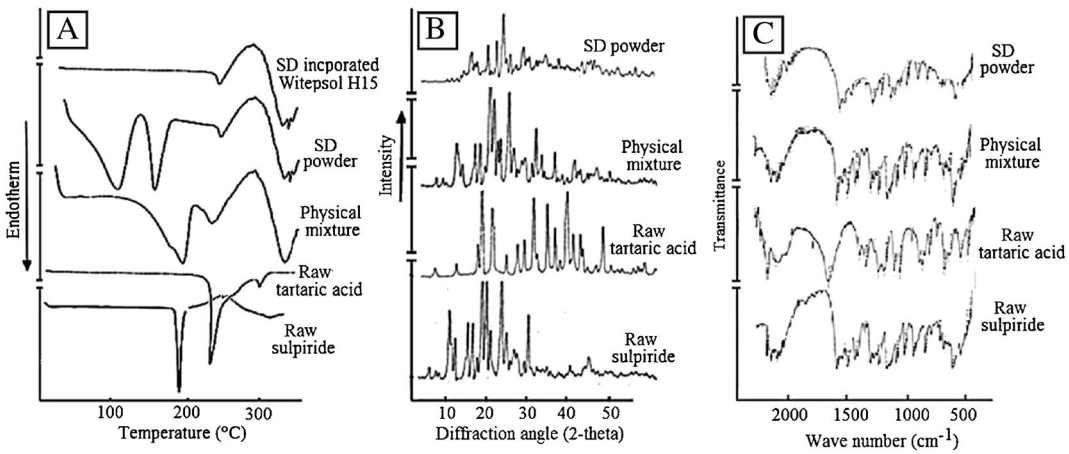


**Fig. 4.** Solid-state analysis (**a** DSC, **b** XRD, and **c** FTIR) of sulpiride SD with tartaric acid at a weight ratio of 1:0.25

**Table III.** Pharmacokinetics Parameters (Mean±RSD) After Administration of Oral Sulpiride Suspension and Either Raw Sulpiride or Sulpiride SD-Incorporated Witepsol H15-Based Rectal Suppositories to Rabbits

| Formulation | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $K_{el}$ ($h^{-1}$) | $t_{1/2}$ (h) | $AUC_{0-24}$ (ng $mL^{-1}$ $h^{-1}$) | $AUC_{0-\infty}$ (ng $mL^{-1}$ $h^{-1}$) | Relative bioavailability (%) |
|---|---|---|---|---|---|---|---|
| Oral sulpiride suspension | 532.06±135.13 | 0.83±0.29 | −0.15±0.04 | 4.7±1.19 | 1130.26±387.87 | 1156.58±394.72 | Control |
| Raw sulpiride-incorporated witepsol H15-based suppositories | 294.43±84.18 | 1.17±0.76 | −0.12±0.06 | 6.72±3.42 | 846.73±242.67 | 888.02±254.5 | 74.91 |
| Sulpiride SD[a]-incorporated witepsol H15-based suppositories | 918.57±274.36 | 0.25±0 | −0.15±0.01 | 4.75±0.24 | 1328.1±396.45 | 1373.37±407.87 | 117.50 |

[a] With tartaric acid at a ratio of 1:0.25 (*w*/*w*)

other hand, there was a nonsignificant reduction in release of the drug from witepsol W25, witepsol H15, and PEG formulae B and C. Sulpiride release from SD-incorporated suppositories stored at 25°C/60% RH is depicted in Fig. 3b. After 6 months, the significant highest reduction in drug release from about 73% to 53% within 3 h of dissolution was observed for witepsol H15-based suppositories. This result is in agreement with those reported by De-Blaey and coworker (40) for aging of aminophylline suppositories prepared with witepsol H15 during ambient storage. Figure 3c demonstrates the sulpiride release from PEG bases stored at 37°C/60% RH for 6 months. A significant reduction in drug release after 3 h by about 6%–11% was observed. This might be explained by the loss of moisture, hardening of the stored suppositories, and/or the degradation of bases at the storage temperature. In conclusion, the preliminary stability investigation highlighted the following points: (i) An acceptable stability of sulpiride SD-incorporated suppository was maintained when stored in an aluminum blister, (ii) it is important to avoid the higher temperatures and humidity, and (iii) witepsol H15-based suppositories would be recommended for further *in vivo* investigations.

## Solid-State Analysis

DSC was employed to determine different melting transitions and possible interactions between the drug and any of the investigated excipients. DSC studies were performed for the individual ingredients as well the prepared systems (Fig. 4a). Thermogram of raw sulpiride showed a sharp endotherm at a temperature of 175°C corresponding to its melting transition. Thermograms of sulpiride SD and physical mixture with tartaric acid demonstrate broadening of sulpiride melting transition due to the formation of a new distorted crystalline phase of sulpiride in the melt of tartaric acid. In addition, the thermogram of SD shows two new broad endotherms at temperatures around 100°C and 143°C to indicate the departure of crystalline water simultaneously when melting.

The thermogram of the SD-incorporated witepsol H15 base shows a disappearance of sulpiride melting peak with a diminished contribution from tartaric acid and the fatty base. Within the fatty matrix, sulpiride and tartaric acid PEG represented as a single entity with one weak transition at a temperature of 234°C that could be probably ascribed to the degradation event. The absence of the endothermic peak of sulpiride could illustrate that the drug would dissolve and distribute within the melted base and convert from a crystalline structure to a distorted amorphous structure (10). This distortion of the crystalline lattice of the drug would be the reason for the increased release and dissolution rate from its solid solution (22) and is confirmed by the drug release results. Furthermore, among the reported methods to prepare solid solutions, the proposed solvent evaporation followed by a fusion technique appeared to potentiate this distortion with acceptable stability. X-ray diffraction patterns performed on SD samples confirmed the crystallinity distortion of sulpiride (Fig. 4b). This finding was consistent with the results of FTIR analysis. The characteristic absorption peaks of sulpiride were detected at 3375 $cm^{-1}$ (N–H), 3205 $cm^{-1}$ ($NH_2$), 1632 $cm^{-1}$ (C=O), and 1322 $cm^{-1}$ ($SO_2$). In case of tartaric acid physical mixture, all the characteristic bands of sulpiride and tartaric acid were observed at the same positions, indicating weak to no interaction using the tumbling process to prepare their physical mixture. Different from raw sulpiride and tartaric acid spectra, disappearance and broader FTIR bands were observed for their SD, suggesting interactions between the two compounds (Fig. 4c). In view of the molecular conformation of sulpiride and the chemical structure of tartaric acid, hydrogen bonds between the free amino, carbonyl, and hydroxyl groups of the components were

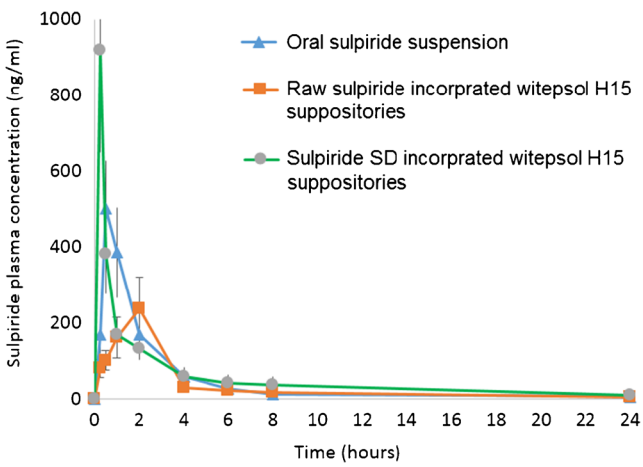


**Fig. 5.** Mean sulpiride plasma concentration (ng/mL) after administration of either oral sulpiride suspension or rectal witepsol H15-based suppositories incorporated with raw sulpiride or its SD with tartaric acid at a ratio of 1:0.25 (*w*/*w*) to rabbits

expected for SD. Indeed, the spectrum presented red shifting of the amino group-stretching bands (3375 and 3205 $cm^{-1}$ towards 3192 $cm^{-1}$) and blue shifting of the carbonyl-stretching bands (1632 $cm^{-1}$ towards 1756 $cm^{-1}$) associated with decreased peak intensity (Fig. 4). These results indicated that the hydrogen bond formed between the free amino groups of sulpiride and tartaric acid (red shifting). In conclusion, both the results of *in vitro* characterization and solid-state analysis indicated that the incorporation of sulpiride solid solution with tartaric acid within witepsol H15-based suppositories gave the fastest drug release with an acceptable physical stability of the formulation. Consequently, this formulation was further evaluated for the *in vivo* bioavailability in experimental animals.

### Bioavailability Studies

The developed bioanalytical method to quantitate sulpiride in the rabbit's plasma was precise, selective, robust, sensitive, and valid according to the FDA guidelines for industry on bioanalytical method validation (41) using metoclopramide as an internal standard. The obtained retention times of sulpiride and metoclopramide were 3.3 and 9.1 min, respectively. The drug concentration profiles obtained from the rabbits' plasma after administration of witepsol H15-based rectal suppository incorporating either raw sulpiride or its SD with tartaric acid at a weight ratio of 1:0.25 were compared to oral sulpiride suspension used as control (both administered at 20 mg/kg of the rabbit's body weight). The administered dose was calculated according to reported animal pharmacokinetic data (42).

The main pharmacokinetic parameters of sulpiride are presented in Table III and Fig. 5. Compared to either oral suspension or raw sulpiride-incorporated suppository, sulpiride SD-loaded suppositories gave an increased value of $C_{max}$ and $AUC_{0-24}h$ and a decreased $T_{max}$ value. The bioavailabilities of raw sulpiride-incorporated and sulpiride SD-loaded suppositories relative to its oral suspension were estimated as 75% and 117% after 24 h, respectively. The obtained bioavailabilities met the preset target product profile to exceed that after oral administration to humans (27%). Comparing the obtained results, the $AUC_{0-24}$ increased for sulpiride SD-loaded suppositories compared to raw sulpiride-incorporated suppository (1328.1 and 846.7 ng $mL^{-1}$ $h^{-1}$, respectively). Additionally, $T_{max}$ was faster for sulpiride SD compared to raw sulpiride-incorporated suppositories (0.25 and 1.17 h, respectively) and $C_{max}$ was 3.1-fold higher (Fig. 5, Table III). It is worth mentioning that sulpiride has low affinity to bind to red blood cells. This demonstrates that the plasma concentration of sulpiride directly correlates with its clinical efficacy. Regarding sulpiride metabolism, different reports have shown that unmetabolized sulpiride was most predominant in the blood. This indicates that its limited role in reducing the systemic availability of oral sulpiride can be attributed to the liver; however, the drug is mainly excreted unchanged in urine (43). Indeed, considering that sulpiride is a weak base existing in the ionized form at gastric pH, it is unsurprising that it is poorly absorbable. Moreover, its wide distribution and accumulation within the cellular compartments could explain the rapid decrease of its levels in the plasma during the distribution phase both for oral and rectal forms (44). In conclusion, sulpiride SD-loaded suppositories show an improved pharmacokinetic profile (higher $C_{max}$ and AUC and shorter $T_{max}$) that is important for an emergency pediatric treatment of TS.

However, considering the small number of experimental animals per each group, the obtained results are shown to be only indicative. The local intolerance along with advanced toxicology and toxicokinetic studies is still required to develop the proposed formulation in a large scale.

## CONCLUSION

Sulpiride SD-incorporated witepsol H15-based suppositories are a candidate formulation for further large-scale production. The optimization study to select the best formula among the ranges of suppository bases and SD carriers has made the optimized formulation to meet the required criteria for pharmacotechnical characteristics, stability, and bioavailability. A relative bioavailability of 117% was obtained for the selected formulation in rabbits with an acceptable stability at a temperature of 37°C for 6 months to indicate its tolerability in the tropical clime.

It is our hypothesis that the developed product will have both utility and potential interest in the market of pediatric medications. It could not only excel the oral form for the better control of complicated and uncomplicated TS but also benefit in cases were oral and parenteral routes cannot be accessed safely. Moreover, it is the formulation of choice to be administered by untrained personnel and would be suitable to near-home use.

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