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# Development of Misoprostol Suppositories for Postpartum Hemorrhage*

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## ABSTRACT

Misoprostol is a prostaglandin E1 analogue used to prevent and treat gastric ulcers. It has been commonly used in gynecology and obstetrics, especially for the management of postpartum hemorrhage (PPH). For this purpose, 1000 µg intrarectal (insertion of five 200 µg tablets) has been recommended as the third line after injectable oxytocin and methylergometrine. We proposed to manufacture a 1000 µg misoprostol suppository by determining formulation, release and stability. The administration facility was also evaluated. Several formulations of misoprostol suppositories were set up and evaluated. Misoprostol tablets and lipophilic bases (Hard fat—Adeps solidus Ph. Eur., Witepsol® H15 and Suppocire® AM and $AS_2X$) were used to obtain suppositories. Surfactants were also tested (polysorbates Tween® 20, Tween® 80 and sodium lauryl sulfate (SLS)). The formula was monitored by the misoprostol release curve with an *in vitro* test and dosed by a HPLC method. Stability was determined by evaluating the percentage of misoprostol content remaining over the time in suppositories stored at 4˚C and 25˚C. Facility of use versus tablets was evaluated by obstetricians of a Swiss regional hospital using a questionnaire. Misoprostol release was facilitated by adding surfactant to the lipophilic base. After 30 minutes, 59% ± 1.4% and 57% ± 8.2% of misoprostol was released with Adeps solidus + 1% SLS and Adeps solidus + 5% Tween 20 respectively. SLS was discarded to the final formula because of its irritating effect. After 7 months, suppositories still contained 94% ± 3.7% misoprostol with storage at 4˚C. The administration was considered easier and faster compared with intra rectal use of tablets. The formula, consisting of 5 crushed misoprostol tablets dispersed in a suppository base made of Adeps solidus + 5% Tween® 20, is stable for at least 7 months at 4˚C and facilitates the rectal administration of misoprostol in the treatment of PPH.

**Keywords:** Postpartum Hemorrhage; Misoprostol; Rectal

## 1. Introduction

Misoprostol is a synthetic prostaglandin E1 analogue, manufactured as an oral preparation available as 200 µg tablets used to prevent and treat gastroduodenal damage induced by nonsteroidal anti-inflammatory drugs [1]. The most common adverse effects of misoprostol are nausea, vomiting, diarrhea, abdominal pain, chills, shivering, and fever, all of which are dose-dependent [2]. Misoprostol taken by pregnant women increases uterine tone and contractions.

It has also become an important off-label drug in obstetrics and gynecology because of its uterotonic and cervical-ripening actions. It is an alternative to uterotonic drugs such as oxytocin, methylergometrine and prostaglandins, which are unstable at room temperature and require injection [3]. Misoprostol is only commercially available as 200 µg oral tablets in Switzerland. However the tablets are also effective when administered vaginally, rectally, buccally and sublingually. Misoprostol is useful for medical abortion, cervical ripening before surgical abortion, evacuation of the uterus in cases of embryonic or fetal death, and labor induction. The drug is also used in the third stage of labor to prevent and to treat postpartum hemorrhage (PPH). Misoprostol is considered as an "essential drug" by the World Health Organization (WHO) for the management of incomplete abortion and miscarriage, and for prevention of PPH when oxytocin is not available or cannot safely be used [4].

Any woman who gives birth can have PPH which may threaten her life. PPH is one of the leading causes of maternal mortality and an important cause of serious morbidity in the developing and developed world. Even the

*The authors declare that there are no conflicts of interest.

 

mild self-limiting cases have consequences for the patient's puerperium in the form of fatigue, tiredness, failure to breast-feed and possible need for haematinics or blood transfusion [5]. PPH is defined as a blood loss of greater than 500 mL for a vaginal delivery and greater than 1000 mL for a cesarean delivery. The predominant cause of PPH is uterine atony or failure of the uterus to adequately contract after delivery. The incidence of PPH is about 5% in Europe [6]. The majority of patients who develop PPH do so in the absence of well-known risk factors. The first step in reducing morbidity and mortality of PPH is therefore to improve methods of prevention [7]. Active management most commonly comprises uterine massage, controlled traction on the umbilical cord and the use of a medication to favor uterine contractions, e.g. intramuscular injection of oxytocin and/or ergot alkaloids (ergometrine) or misoprostol *per os*. The treatment consists of improving uterine tone and the exploration of the uterus for any evidence of retained placental tissues. The use of different molecules (oxytocin, sulprostone, misoprostol and/or ergometrine) is common in many countries.

Since 1987, misoprostol has been used to prevent or treat PPH in doses up to 600 µg in oral or sublingual administration [8-10] and up to 1000 µg rectally [11-16]. Misoprostol tablet can also be absorbed by both rectal and vaginal routes [17]. However, the rate of absorption varies considerably between these routes of administration. Rectal administration of misoprostol tablets is associated with a qualitatively similar absorption curve to that of the vaginal route but presents a lower bioavailability. The vaginal route could not be considered in this case because of the blood loss. Oral misoprostol reaches a high peak plasma concentration followed by a rapid fall [18]. Rectal misoprostol absorption in the third stage of labor avoids the first-pass effect and decreases the adverse effects. WHO does not recommend such practice for PPH [19] because its potential benefits and harms are currently unknown. However some organizations, e.g. the Swiss society of gynecology and obstetrics (SSGO), the international federation of gynecology and obstetrics (FIGO) and the international confederation of midwifes (ICM) [20] use it as third-line treatment.

The purpose of this study was to manufacture a 1000 µg misoprostol suppository using commercially available tablets and a suppository base and to determine the *in vitro* release, the stability and the facility of use.

## 2. Experimental

### 2.1. Materials

Hard fat-Adeps solidus Ph. Eur. and Witepsol®H15 were purchased from Hänseler (Herisau, CH). Suppocire® AM and Suppocire® $AS_2X$ were purchased from Gattefossé SAS (Saint Priest, France). Tween® 20, Tween® 80 and sodium laurylsulfate (SLS) were purchased from Hänseler (Herisau, CH). Cytotec® tablets 200 µg misoprostol were purchased from Pfizer (Zurich, CH). Benzophenone was purchase from Sigma Aldrich (Steinheim, Germany). Acetonitrile LC-MS Chromasolv, Fluka analytical was purchased from Sigma Aldrich (Steinheim, Germany). Pure misoprostol was purchased from Sigma Aldrich (Steinheim, Germany). HPCL-filtered water was obtained, in-house, from a Millipore model Synergy 185 (MA, USA)

### 2.2. Methods

**Suppository preparation:** Suppositories were manufactured according to the melting method by calculating the displacement value of the suppository bases. The 1000 µg misoprostol suppositories were prepared with different bases (Adeps solidus, Witepsol®H15, Suppocire® AM and Suppocire® $AS_2X$) and different surfactants (Tween® 20, Tween® 80 and sodium laurylsulfate (SLS)) at concentrations of 0.5%, 1%, 2%, 3% or 5%. Suppositories were prepared by crushing five 200 µg misoprostol tablets in a mortar, melting the suppository base with the surfactant in a water bath at 37˚C and adding the crushed misoprostol. The mixture was transferred in suppository molds of 3 g.

***In vitro* release:** A system was specially developed for the set-up of the *in vitro* release test. Three suppositories were put in a basket immersed in a 500 mL buffer bath at pH 7.2 containing SLS (from 0% to 5%) at 37˚C ± 1˚C with magnet agitation (100 rpm). A 900 µL volume was withdrawn from the medium at 2, 5, 10, 20 and 30 minutes and 100 µL of a 0.3 µg/mL solution of benzophenone (internal standard) was added. The solutions were analysed in triplicate by high-performance liquid chromatography (HPLC).

**Stability study:** Misoprostol stability in suppositories with the formula allowing the best release was assessed after conservation at 4˚C, 20˚C and 60˚C. Suppositories were tested immediately after preparation and at 7, 14, 30, 60, 90, 120, 150, 180 and 210 days. After the suppository was melted in a water bath at 37˚C ± 1˚C, 7.0 mL of acetonitrile was added and mixed for 2 min. with a Vortex-type mixer to extract the drug. The vortex mixer model SA7 was purchased from Stuard (UK). The mixture was centrifuged at 3000 rpm for 10 min. A 300 µL aliquot was mixed with 100 µL of a 30 µg/mL solution of benzophenone and 600 µL of acetonitrile. This solution was analysed in triplicate by HPLC.

**HPLC method:** Three HPLC methods were found in the literature for the analysis of misoprostol [21-23]. The method described by Hafirassou [23] was adapted and validated, following the ICH guidelines for the present study. The quantitative analyses were performed on an

 

HPLC pump Serie 1100 with a binair pump model F 1312 A (Agilent, USA). The separation was achieved on a Zorbax Eclipse XDB C18 column (4.6 × 150 mm, 5 µm (Agilent, USA), maintained at 23˚C. The equipment also consisted of an automatic injector model G 1367 A (Agilent, USA) with a 20 µL loop and an equipped with an UV detector model DAD SL G 1315 C (Agilent, USA) set at 202 nm. The mobile phase was prepared by mixing acetonitrile and filtered water in the ratio of 60:40 (v:v). The flow rate was set at 1 mL/min.

No interfering peaks were identified with the lipophilic bases, the surfactants or the degradation products of misoprostol. The retention times for misoprostol and benzophenone were 3.77 and 5.59 minutes, respectively (**Figure 1**).

**Standard solution and standard curve:** The linearity, trueness and accuracy of the analytical method were evaluated for both studies (release and stability). A standard solution of misoprostol was prepared by dissolving pure misoprostol in acetonitrile (100 µg/mL = S). This solution was kept at −20˚C. This solution was further diluted in acetonitrile (10 µg/mL=S1). The standard curve was built by plotting the ratio of misoprostol peak area to that of benzophenone according to misoprostol concentration and used for measuring drug concentrations in samples. Three replicate standards at three different days and two replicate injections were used for the standard curve.

Misoprostol standard solutions for the release study were prepared by diluting S1 with acetonitrile to concentrations of 0.3, 3 and 7.2 µg/mL. Each solution contains 0.3 µg/mL of benzophenone (internal standard) diluted in acetonitrile. The standard curve was linear over the concentration range of 0.3 - 7.2 µg/mL. A linear relationship was plotted over the concentration range of 0.3 - 7.2 µg/mL. The intercept was found to be not significantly different from 0 (Student t test, $\alpha = 0.05$). The intraday and interday relative standard deviations were found to be inferior to 6.2%.

Standard solutions for the stability study were prepared by diluting S solution to 3 different concentrations (28, 40 and 52 µg/mL) with benzophenone at 3 µg/mL in acetonitrile. This curve was also linear over the working range of 28 - 52 µg/mL. The plots intersected the origin at 0.08%. The intraday and interday coefficients of variation were ≤4.3% and 3.5%, respectively.

**Data analysis:** Misoprostol release was determined by calculating the percentage of misoprostol concentration liberated in the media according to time. Stability was determined by calculating the percentage of the initial concentration remaining after each time interval. Stability was defined as the retention of at least 90% from the initial concentration.

**Facility of use:** Because of this study the Swiss ethic committee was contacted, and it approved this project. The suppositories were proposed to the gynecology service of a regional hospital. They were used in 6 patients for the treatment of PPH as third-line treatment after oxytocin and methylergometrine instead of the 5 tablets of Cytotec® administrated rectally. The facility of use was evaluated through a questionnaire. These questionnaires were anonymously filled and sent to the pharmacy.

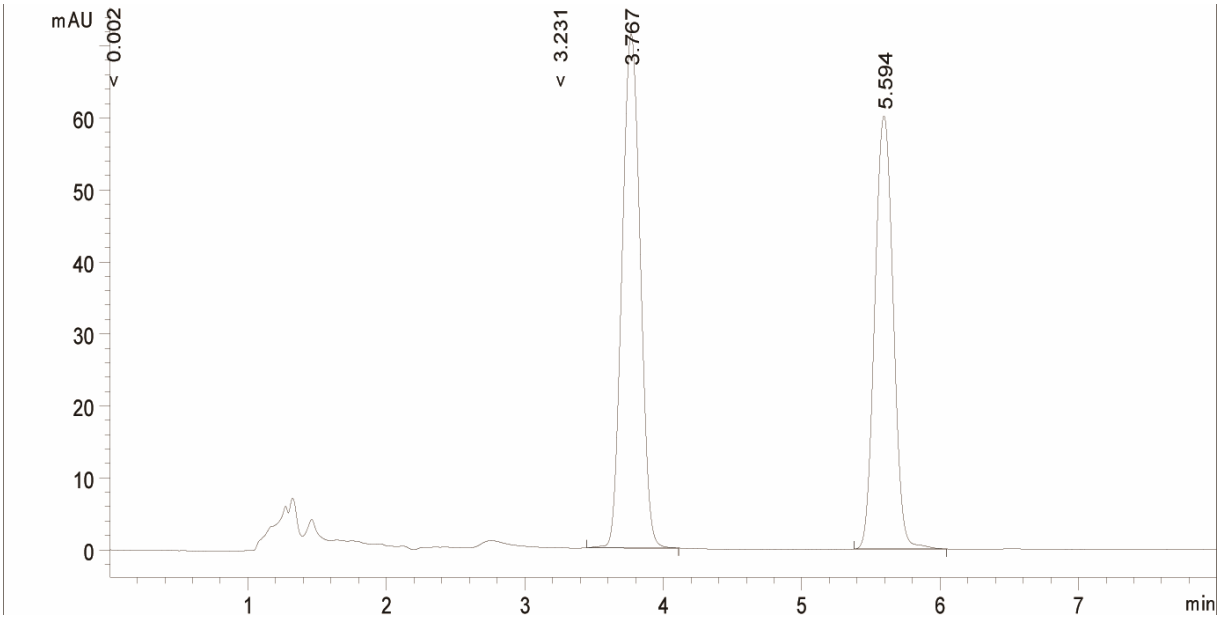


**Figure 1. Representative chromatogram of a 40 µg/mL misoprostol and a 3 µg/mL benzophenone solution in acetonitrile. Peak at 3.767 minutes = misoprostol, peak at 5.594 minutes = benzophenone (internal standard).**

 

## 3. Results and Discussion

The dosage of 1000 µg misoprostol suppository was chosen after discussion with the local gynecologists. Different surfactants were added to the suppository to improve the dispersion and absorption of the drug [24].

There is no standard method to determine the release of an active substance from a suppository and no medium simulating rectal fluid [25]. The European and American Pharmacopoeia propose a continue flow system to control drug dissolution for suppositories in water [26,27]. The Fédération internationale pharmaceutique (FIP) and the American Association of Pharmaceutical Scientists (AAPS) have proposed guidelines on suppository dissolution, using the continue flow system [28]. This system was not available for the present study. A specific system with a medium close to the rectal fluid (pH and temperature) was therefore developed. The addition of SLS (0% to 5%) in the medium is known to improve the dissolution of drug [29,30]. The optimal concentration of the SLS was obtained experimentally and fixed to 0.5%.

**Release:** Adeps solidus liberated the highest quantity of drug after 30 minutes (19% versus 16% for Witepsol®H15, 11% for Suppocire® AM and 6% for Suppocire® $AS_2X$, **Figure 2**). The adjunction of Tween® 80 to Adeps solidus and Witepsol® H15 presented a slight influence on misoprostol release from the suppository (data not shown). The adjunction of two others surfactants (SLS and Tween® 20) had more effects. Best results were obtained with the adjunction of 1% SLS (59% ± 1.4% after 30 minutes) and 5% Tween® 20 (57% ± 8.2%) to Adeps solidus (**Figure 3**). The use of SLS in the release medium enhances misoprostol solubility. SLS has however an irritant property for the mucous membrane [31]. This surfactant was discarded, even if exposure is limited to a single use. Thus, the formula retained contains 5 crushed tablets of Cytotec® in Adeps solidus with 5% Tween 20.

Release tests were conducted over 30 minutes. Indeed, a rapid effect is needed to treat PPH. The release test was performed in a 500 mL phosphate buffer media while the rectum is composed of about 2 mL fluid and the mucus action on the suppository can also influence the absorption. This test allowed us to compare different formula. Nevertheless, only an in vivo study with blood samples could accurately evaluate misoprostol release in the rectum and its bioavailability.

**Stability:** 1000 µg misoprostol suppositories contained more than 90% of the initial concentration after 210 days of storage at 4˚C (**Table 1**). At room temperature, the results were not homogeneous and content rapidly decreased at less than 90% (data not shown).

In the study from Hafirassou [23], the Suppocire® suppositories of misoprostol were not stable at more than 120 days at room temperature.

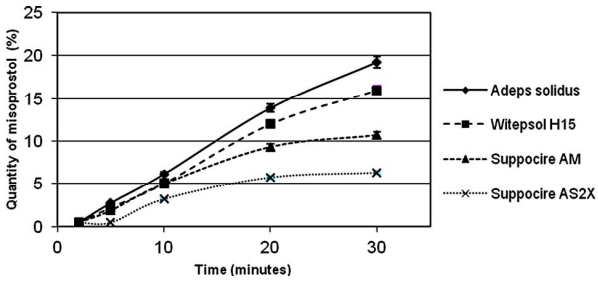


**Figure 2. Misoprostol release from different suppository bases.**

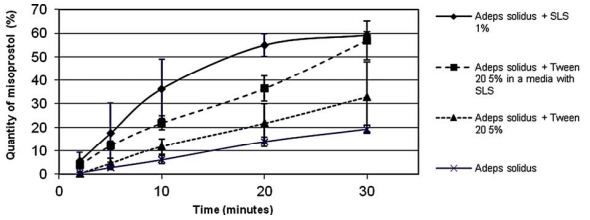


**Figure 3. Misoprostol release from Adeps solidus suppositories alone and with addition of 1% SLS and 5% Tween® 20 in a normal media and with 5% Tween® 20 in a medium containing 0.5% SLS (mean ± SD).**

**Table 1. Stability of 1000 µg misoprostol suppository conserved at 4˚C.**

| Day | % Initial concentration[a] | | |
|---|---|---|---|
| 7 | 96.9 | ± | 3.4 |
| 14 | 94.2 | ± | 0.9 |
| 30 | 96.2 | ± | 1.8 |
| 60 | 96.7 | ± | 1.4 |
| 90 | 93.5 | ± | 2.2 |
| 120 | 97.4 | ± | 2.2 |
| 180 | 97.5 | ± | 4.4 |
| 210 | 94.2 | ± | 6.2 |

[a]Mean ± S.D. of triplicate determinations for three samples (n = 3).

**Facility of use:** In a pilot study suppositories were used on a gynecology ward. Six questionnaires were filled and sent to the pharmacy. The six patients received oxytocine as prevention and a second dose of oxytocine added to methylergometrine before the use of a misoprostol suppository in case of a declared PPH. All doctors appreciate the facility of use (**Table 2**). PPH was stopped in 50% of the patients who received misoprostol suppository, which is in agreement with published studies [11-16,32]. The number of patients should be increased in a future study to evaluate to a larger extent the efficacy of this suppository versus tablet in the treatment of PPH.

 

**Table 2. Summary of survey after the use of misoprostol suppository.**

| Age (years) | Uterotonics used before misoprostol | Ease of use | PPH cessation | Time to stop PPH (minutes) | Additional treatment after misoprostol |
|---|---|---|---|---|---|
| 29 | Oxytocin 10 UI<br>Methylergometrine 0.2 mg im | easier | Yes | 25-30 | Oral methylergometrine |
| 40 | Oxytocin 20 UI<br>Methylergometrine 0.2 mg im | easier | Yes | 10 | - |
| 31 | Oxytocin 20 UI<br>Methylergometrine 0. 2 mg im<br>Dinoprostone rinsing of the uterine cavity | easier | Yes transitorily | - | Arterial embolization |
| 32 | Oxytocin 20 UI<br>Methylergometrine 0.2 mg im | easier | No | - | Hysterectomy |
| 37 | Oxytocin 10 UI<br>Methylergometrine 0.2 mg im | easier | Yes | 15 | - |
| 28 | Oxytocin 10 UI<br>Methylergometrine 0.2 mg im | easier | No | - | Arterial embolization |

## 4. Conclusion

A 1000 µg misoprostol suppository was elaborated with crushed tablets of misoprostol and hard fat (Adeps solidus Ph. Eur.) + 5% Tween® 20. The suppositories liberated *in vitro* 57% ± 8.2% of misoprostol after 30 minutes. The suppositories are stable for at least 7 months at 2˚C - 8˚C and facilitate the administration of misoprostol compared to tablets in the treatment of PPH.

## REFERENCES


[1] S. A. Pfizer, "Cytotec® (Misoprostol) Package Insert," Zurich, 2010.

[2] A. B. Goldberg, M. B. Greenberg and P. D. Darney, "Misoprostol and Pregnancy," *The New England Journal of Medicine*, Vol. 344, No. 1, 2001, pp. 38-47. doi:10.1056/NEJM200101043440107

[3] A. Elati and A. D. Weeks, "The Use of Misoprostol in Obstetrics and Gynaecology," *BJOG*: *An International Journal of Obstetrics and Gynaecology*, Vol. 116, Suppl. 1, 2009, pp. 61-69. doi:10.1111/j.1471-0528.2009.02329.x

[4] WHO, "WHO Model List of Essential Medicines," 17th Edition, WHO, Geneva, 2011.

[5] H. El-Refaey and C. Rodeck, "Post-Partum Haemorrhage: Definitions, Medical and Surgical Management. A Time for Change," *British Medical Bulletin*, Vol. 67, No. 1, 2003, pp. 205-217. doi:10.1093/bmb/ldg016

[6] O. Irion, S. Terraz, M. Boulvain, F. Boehlen and C. D. Becker, "Hémorragie de la Délivrance: Prévention, Embolisation Artérielle et Facteur VIIa Recombinant," *Revue Médicale Suisse*, Vol. 4, No. 176, 2008, pp. 2269- 2275.

[7] P. V. Rajan and D. A. Wing, "Postpartum Hemorrhage: Evidence-Based Medical Interventions for Prevention and Treatment," *Clinical Obstetrics and Gynecology*, Vol. 53, No. 1, 2010, pp. 165-181. doi:10.1097/GRF.0b013e3181ce0965

[8] N. F. Zuberi, J. Durocher, R. Sikander, N. Baber, J. Blum and G. Walraven, "Misoprostol in Addition to Routine Treatment of Postpartum Hemorrhage: A Hospital-Based Randomized-Controlled Trial in Karachi, Pakistan," *BMC Pregnancy and Childbirth*, Vol. 8, No. 40, 2008.

[9] G. Walraven, Y. Dampha, B. Bittaye, M. Sowe and J. Hofmeyr, "Misoprostol in the Treatment of Postpartum Haemorrhage in Addition to Routine Management: A Placebo Randomised Controlled Trial," *BJOG*: *An International Journal of Obstetrics and Gynaecology*, Vol. 111, No. 9, 2004, pp. 1014-1017. doi:10.1111/j.1471-0528.2004.00217.x

[10] G. J. Hofmeyr, S. Ferreira, V. C. Nikodem, L. Mangesi, M. Singata, Z. Jafta, *et al*., "Misoprostol for Treating Postpartum Haemorrhage: A Randomized Controlled Trial," *BMC Pregnancy and Childbirth*, Vol. 4, No. 16, 2004.

[11] M. Baruah and G. M. Cohn, "Efficacy of Rectal Misoprostol as Second-Line Therapy for the Treatment of Primary Postpartum Hemorrhage," *The Journal of Reproductive Medicine*, Vol. 53, No. 3, 2008, pp. 203-206.

[12] R. Shojai, R. Desbrière, S. Dhifallah, B. Courbière, D. Ortega, C. d'Ercole, *et al*., "Le Misoprostol par voie Rectale dans l'Hémorragie de la Délivrance," *Gynécologie Obstetrique & Fertilité*, Vol. 32, No. 9, 2004, pp. 703-707. doi:10.1016/j.gyobfe.2004.05.015

[13] A. U. Lokugamage, K. R. Sullivan, I. Niculescu, P. Tigere, F. Onyangunga, H. El Refaey, *et al*., "A Randomized Study Comparing Rectally Administered Misoprostol versus Syntometrine Combined with an Oxytocin Infusion for the Cessation of Primary Post Partum Hemorrhage," *Acta Obstetricia Gynecologica Scandinavica*, Vol. 80, No. 9, 2001, pp. 835-839. doi:10.1034/j.1600-0412.2001.080009835.x

[14] H. Abdel-Aleem, I. El-Nashar and A. Abdel-Aleem, "Management of Severe Postpartum Hemorrhage with


 

Misoprostol," *International Journal of Gynecology & Obstetrics*, Vol. 72, No. 1, 2001, pp. 75-76. doi:10.1016/S0020-7292(00)00321-0

[15] R. Shojai, L. Piéchon, C. d'Ercole, L. Boubli and J. E. Pontiès, "Le Misoprostol par Voie Rectale dans les Hémorragies de la Délivrance. Une étude Préliminaire," *Journal de Gynécologie Obstétrique et Biologie de la Reproduction*, Vol. 30, No. 6, 2001, pp. 572-575.

[16] P. O'Brien, H. El-Refaey, A. Gordon, M. Geary and C. H. Rodeck, "Rectally Administered Misoprostol for the Treatment of Postpartum Hemorrhage Unresponsive to Oxytocin and Ergometrine: A Descriptive Study," *Obstetrics and Gynecology*, Vol. 92, No. 2, 1998, pp. 212-214. doi:10.1016/S0029-7844(98)00161-6

[17] R. U. Khan, H. El-Refaey, S. Sharma, D. Sooranna and M. Stafford, "Oral, Rectal, and Vaginal Pharmacokinetics of Misoprostol," *Obstetrics and Gynecology*, Vol. 103, No. 5, 2004, pp. 866-870. doi:10.1097/01.AOG.0000124783.38974.53

[18] H. A. Mansouri and N. Alsahly, "Rectal versus Oral Misoprostol for Active Management of Third Stage of Labor: A Randomized Controlled Trial," *Archives of Gynecology and Obstetrics*, Vol. 283, No. 5, 2011, pp. 935-939. doi:10.1007/s00404-010-1466-5

[19] World Health Organization, "WHO Recommendations for the Prevention of Postpartum Haemorrhage," WHO Press, Geneva, 2007.

[20] International Confederation of Midwives/International Federation of Gynecology and Obstetrics. "Prevention and Treatment of Postpartum Haemorrhage: New Advances for Low Resource Settings," 2012. http://www.pphprevention.org/toolkit.php

[21] Pharmacopée Européenne. "Monographie du Misoprostol," Addendum 5.3, 2006, pp. 3764-3765.

[22] M. C. Williams, J. C. Tsibris, G. Davis, J. Baiano and W. F. O'Brien, "Dose Variation That Is Associated with Approximated One-Quarter Tablet Doses of Misoprostol," *American Journal of Obstetrics and Gynecology*, Vol. 187, No. 3, 2002, pp. 615-619. doi:10.1067/mob.2002.124959

[23] H. Hafirassou, F. Chiadmi, J. Schlatter, R. Ratiney and J. E. Fontan, "Stability of Misoprostol in Suppositories," *American Journal of Health-System and Pharmacy*: *Official Journal of the American Society of Health-System Pharmacists*, Vol. 62, 2005, pp. 1192-1194.

[24] N. Realdon, M. Dal Zotto, M. Morpurgo and E. Franceschinis, "Effects of Surfactant Characteristics on Drug Availability from Suppositories," *Die Pharmazie*, Vol. 63, No. 6, 2008, pp. 459-463.

[25] S. Azarmi, W. Roa and R. Löbenberg, "Current Perspectives in Dissolution Testing of Conventional and Novel Dosage Forms," *International Journal of Pharmaceutics*, Vol. 328, No. 1, 2007, pp. 12-21. doi:10.1016/j.ijpharm.2006.10.001

[26] R. Dunn, H. Reimers, L. Ward and J. Chapman, "Suppository Dissolution Utilizing USP Apparatus 4," *Dissolution Technologies*, Vol. 3, No. 1, 1996, pp. 18-19.

[27] B. Patel, R. C. Campos and A. I. Fernandes, "Formulation and *in Vitro* Evaluation of Chloral Hydrate Rectal Suppositories for Paediatric Use," 2*nd Congress of the Portuguese Society of Pharmaceutical Sciences and* 6*th Congress of the Portuguese-Spanish Chapter of the Controlled Release Society*, Lisbon, 2005.

[28] M. Siewert, J. Dressman, C. K. Brown and V. Shah, "FIP/AAPS Guidelines to Dissolution/*in Vitro* Release Testing of Novel/Special Dosage Forms," *AAPS PharmSciTech*, Vol. 4, No. 1, 2003, p. E7. doi:10.1208/pt040107

[29] V. P. Shah, J. J. Konecny, R. L. Everett, B. McCullough, A. C. Noorizadeh and J. Skelly, "*In Vitro* Dissolution Profile of Water-Insoluble Drug Dosage Forms in the Presence of Surfactants," *Pharmaceutical Research*, Vol. 6, No. 7, 1989, pp. 612-618. doi:10.1023/A:1015909716312

[30] L. Tang, S. U. Khan and N. A. Muhammad, "Evaluation and Selection of Bio-Relevant Dissolution Media for a Poorly Water-Soluble New Chemical Entity," *Pharmaceutical Development and Technology*, Vol. 6, No. 4, 2001, pp. 531-540. doi:10.1081/PDT-120000291

[31] R. A. Tupker, K. Vermeulen, V. Fidler and P. J. Coenraads, "Irritancy Testing of Sodium Laurate and Other Anionic Detergents Using an Open Exposure Model," *Skin Research and Technology*, Vol. 3, No. 2, 1997, pp. 133-136. doi:10.1111/j.1600-0846.1997.tb00175.x

[32] G. J. Hofmeyr, A. M. Gülmezoglu, N. Novikova, V. Linder, S. Ferreira and G. Piaggio, "Misoprostol to Prevent and treat Postpartum Haemorrhage: A Systematic Review and Meta-Analysis of Maternal Deaths and Dose-Related Effects," *Bulletin of the World Health Organization*, Vol. 87, No. 9, 2009, pp. 666-677. doi:10.2471/BLT.08.055715

 