Formulation, *in vitro* and Bioavailability Assessments of Ranitidine Rectal Suppositories

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**Authors’ contributions**

This work was carried out in collaboration among all authors. Authors KS, AMS and AK designed the studies and performed the statistical analysis. Authors MFI, NKA and ME wrote the protocol and wrote the first draft of the manuscript. Author HMA managed the analyses of HPLC. Author ME managed the literature searches. All authors read and approved the final manuscript.

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**ABSTRACT**

The objective of the current work was to develop and evaluate suppository dosage form in order to improve ranitidine bioavailability as a substitute to the oral administration. Suppocire (different grades), Witepsol W25 and polyethylene glycol (PEG) were used as suppository bases and prepared by molding method. The prepared formulations were examined for hardness, disintegration time, melting point, content uniformity, drug release, stability and bioavailability. The hardness ranged from 3.82 to 12.53 kg and disintegration time from 13.32 to 28.22 min. The melting points of fatty bases had values from 33.94 to 36.82±0.36°C while PEG based suppositories melting points were directly proportional chain length. Higher content uniformity was
observed in PEG based suppositories due to easy incorporation of RT into water soluble base. Release was affected by hydroxyl value and molecular weight (in cases of fatty and PEG bases respectively). All formulations were relatively stable after 12 months. In vivo studies of all formulations exhibited double peak phenomena. PEG based formula (S8) showed significant higher Cmax (10.05±1 μg/ml) and AUC0-12 (58.313±3.9 μg.h/mL) than fatty bases and oral solution. In conclusion, rectal administration of S8 could be prepared as an alternative to the oral dosage form to improve bioavailability and overcome the first-pass metabolism.

Keywords: Ranitidine; rectal suppositories; bioavailability.

1. INTRODUCTION

Ranitidine hydrochloride (RT) is as a reversible histamine H₂-receptors blocker with a limited effect on H₁-receptors [1,2]. RT is indicated in peptic ulcer, gastroesophageal reflux disease (GERD) and pathological hypersecretory conditions (e.g., Zollinger–Ellison syndrome) [3]. According to Biopharmaceutical classification scheme (BCS), RT is categorized as class III drug of high solubility (aqueous solubility is nearly 660 mg/ml) and low permeability through biological membranes (log P ~ 0.2) meaning that it is permeation rate limited drug. As the molecular weight of RT is relatively small (350 gm/mol) [4,5], paracellular route represents the majority of the percentage absorbed. However, the biological half life is relatively short (2.5-3.5 h) and relative bioavailability is nearly 50% of administered dose [6] due to extensive first pass metabolism [3].

Oral route of administration is considered as the most common and preferable route owing to ease of administration, patient compliance and flexibility in formulation [7]. However, oral route becomes unsuitable in some cases such as nausea, vomiting or convulsion. In such cases, the rectal route may offer a suitable alternate. Rectal route is also preferred if the drug is extensively metabolized or deactivated by liver enzymes [8]. The superior hemorrhoidal veins were reported to drain the absorbed drugs into the portal vein and subsequently into the liver. On the other hand, the middle and inferior hemorrhoidal veins drain the lower part of the rectum and venous blood is returned to the inferior vena cava. Therefore, drug absorbed in the latter system will initiate its circulation throughout the body, bypassing the liver [9]. Lymphatic circulation also assists in the absorption of rectally administered drugs [10]. Rate and extent of drug absorption following rectal administration are governed by several factors. Depending on the physicochemical properties of the base used, a suppository will either dissolve in the rectal fluid (in case of water soluble base as polyethylene glycol; PEG) or melt on the mucous layer (in case of oleaginous base). The lipid–water partition coefficient of a drug can particularly determine the choice of the suppository base and in turn influence drug release from that base. Lipophilic drug which has high affinity to fatty suppository base escapes slower than hydrophilic substance from fatty bases. On the other hand, water soluble bases dissolve in the anorectal fluids and release both water-soluble and oil-soluble drugs [11].

So, the aim of the present work was to formulate RT in different suppository bases. The prepared formulations were examined for physicochemical characteristics and in vitro RT release. Selected formulations were subjected to accelerated and shelf stability studies. Depending upon the obtained results, selected formulations were tested for in vivo bioavailability and compared with RT oral solution.

2. MATERIALS AND METHODS

2.1 Materials

RT was kindly gifted by Egyptian Pharmaceutical Industries Company (EPICO). Witepsol W25 was supplied by Nobel Dynamitte, West Germany. Suppocire A, Suppocire AI, Suppocire AM, Suppocire AP and Suppocire BM, were supplied by Gattefossé, France. Polyethylene glycol (PEG) 400, PEG 1000, PEG 1540, PEG 4000 and PEG 6000 were supplied by Sigma Aldrich (Germany). All other chemicals are of analytical grade.

2.2 Formulation of RT Suppositories

Molding from a melt technique was used to prepare all formulations of medicated and non-medicated suppositories. We used 1-gm capacity molds. Briefly, the base was molten at suitable temperature then the drug was added using magnetic stirrer until a homogenous mixture was
obtained. The mixture was then poured into molds and left for cooling and solidification. The suppositories were removed from the molds and kept in opaque containers in a refrigerator for 24 h before testing. For PEG based suppositories, blend of different molecular weight PEG bases was used to attain the most suitable consistency and best characteristics. The composition of different formulations is outlined in Table 1.

2.3 Physicochemical Evaluation of RT Suppositories

2.3.1 Determination of displacement value

For preparing a convenient suppositories containing RT with the suggested bases, the displacement values (DV) for each base must be determined firstly. The DV of RT was determined by comparing the weight of plain suppository bases with that of the medicated suppositories. Suppositories were of one gram size and containing 150 mg of RT. To determine DV, the prepared suppositories were left at room temperature for 24 hours before testing. Each experiment for both non-medicated and medicated suppositories containing 150 mg RT was investigated in triplicates.

The displacement values were calculated by using the following equation [12]:

\[ DV = \frac{(100 \times (N - M))}{(M \times A)} + 1 \]

Where,

\[ N = \text{Weight of non-medicated (plain) suppositories} \]
\[ M = \text{Weight of medicated suppositories} \]
\[ M = \text{Medicament (RT) percentage} \]

2.3.2 Accuracy of the formulated RT suppositories

Accuracy of RT suppositories was done to calculate the production yield of the prepared suppositories and to compare the actual drug content with the theoretical drug content in each suppository. Production yield was calculated by dividing the actual suppository weight by the theoretical suppository weight and then transferred to a percent. This step was done to show the efficacy of the formulation technique.

2.3.3 Hardness test or fracture point

The force necessary to break the suppository was measured to determine the brittleness and fragility of suppositories. The test was performed using hardness tester (Erweka Apparatus GMBH, Germany).

2.3.4 Disintegration test

This test was carried out to determine the time necessary for the suppository to disintegrate completely inside the rectum to release its drug to the absorption medium. Five suppositories from each formula were placed in water bath at 37± 0.5°C. The time from the beginning of deformation of the tested suppository until complete melting or dissolving was recorded.

2.3.5 Melting point

The melting point range was tested for both fatty bases water soluble base of RT suppositories. The test was carried out using melting point apparatus (Galen Kamp, Germany) and capillary tube. Five suppositories from each formula were allowed to melt at the lower possible temperature. The capillary tubes were dipped in the melted samples in a manner so as to fill 1 cm length of each tube. The samples inside the tubes were allowed to solidify till the ends of the tubes were sealed. The tubes were stored in a refrigerator till using. To carry out the test, the temperature of the tester was elevated to 5°C below the expected melting point of the base, and then the capillary tubes were inserted into their place in the apparatus. The temperature was raised at a rate of 0.5 °C/min. The temperatures at which the suppositories started to melt (start of capillary tube dipping) and the temperatures at which complete melting took place (complete dipping of capillary tube) were recorded.

2.3.6 Content uniformity

Five suppositories were randomly chosen and each suppository was weighed and allowed to melt or dissolve in 200 ml distilled water in a suitable beaker with the aid of magnetic stirrer, and heated to about 50°C on hot plate. Sample of 2 ml was withdrawn, filtered, diluted to a suitable volume and assayed spectrophotometrically at 313 nm (Jenway 6305 UV/VIS spectrophotometer, England).

2.4 In vitro RT Release

The release of RT from different formulations was carried out using rotating basket method (Erweka DT6R, Heusenstamm, Germany). The dissolution medium was 900 ml of distilled water maintained at 37°C. Suppositories were held in a
rotating basket at speed of 50 rpm. A sample of 3 ml of the dissolution medium was removed at predetermined time intervals (0.25, 0.5, 1, 1.5, 2, 2.5 and 3h) and replaced with an equal volume of distilled water. The withdrawn samples were assayed spectrophotometrically at 313 nm.

2.5 Shelf-Storage Stability Testing

The formulated suppositories were packed in glass container, protected from light and stored for 12 months at refrigerator temperature (4°C). Enough samples were evaluated at the beginning of the storage and at time intervals of 1, 2, 3, 6, 9 and 12 months.

2.6 Pharmacokinetic Study

This study was performed in order to investigate the bioavailability selected formulations (S3, S6 and S10 basing upon acceptable physical characteristics and stability) when compared with RT oral administration in rats.

2.6.1 Animals

White male albino rabbits (weighing ~2 kg), provided from the animal house of the faculty of pharmacy, were used in this study. They were housed under conventional laboratory conditions throughout the period of experimentation. The animal handling procedure was performed in accordance by the Animal Care and Use Committee of Jouf University, College of Pharmacy. The animals were fed a standard rat pellet diet and allowed free access to water.

2.6.2 Pharmacokinetic study

The experiment was carried out with 24 rabbits (n=6) divided randomly into four groups with six rats each. Group I, II and III were rectally administered S3, S6 and S10 respectively. Group IV administered a single oral dose of RT solution. At predetermined time intervals (pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12), blood sample (0.75 milliliter) was taken from the retro-orbital plexus and put into heparinized tube. Samples were directly centrifuged at 5000 rpm for 15 min to separate plasma and stored at −40°C until analysis.

2.6.3 Chromatography

The plasma concentrations of RT were determined by a HPLC (LC10 Analytical System, Shimadzu, Japan). The stationary phase consisted of Nova-Pack C18 (60Å, 3.9×150 mm, 4 µm, Waters, USA). The mobile phase consisted of 45:1:54 methanol: 0.05 M phosphate buffer pH 9.3: water. The mobile phase was delivered into HPLC apparatus at a flow rate of 1.5 ml/min, using maximum wavelength of 313 nm at pH 9.3. Measurement of samples was carried out after construction of calibration curve. Calibration curve was constructed by spiking one ml blank (drug free) plasma with different concentrations of RT to provide concentrations from (0.05-10 µg/ml). One ml of plasma, 50 µl of internal standard (procainamide in methanol; 50mg/L) and 15 µl of 6N sodium hydroxide were added.

<table>
<thead>
<tr>
<th>Code</th>
<th>Added RT (mg)</th>
<th>Suppocire</th>
<th>Witepsol</th>
<th>Base</th>
<th>PEG %</th>
<th>Water %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>150</td>
<td>Suppocire AP</td>
<td>-------</td>
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</tr>
<tr>
<td>S2</td>
<td>150</td>
<td>Suppocire BM</td>
<td>-------</td>
<td>------</td>
<td>------</td>
<td>-------</td>
</tr>
<tr>
<td>S3</td>
<td>150</td>
<td>Suppocire A</td>
<td>-------</td>
<td>------</td>
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</tr>
<tr>
<td>S4</td>
<td>150</td>
<td>Suppocire AM</td>
<td>-------</td>
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</tr>
<tr>
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<td>150</td>
<td>Suppocire AT</td>
<td>-------</td>
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</tr>
<tr>
<td>S6</td>
<td>150</td>
<td>-------</td>
<td>Witepsol W25</td>
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</tr>
<tr>
<td>S7</td>
<td>150</td>
<td>-------</td>
<td>-------</td>
<td>75</td>
<td>25</td>
<td>-------</td>
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<tr>
<td>S8</td>
<td>150</td>
<td>-------</td>
<td>-------</td>
<td>90</td>
<td>10</td>
<td>-------</td>
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<tr>
<td>S9</td>
<td>150</td>
<td>-------</td>
<td>-------</td>
<td>33</td>
<td>57</td>
<td>10</td>
</tr>
<tr>
<td>S10</td>
<td>150</td>
<td>-------</td>
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<td>20</td>
<td>30</td>
<td>50</td>
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<tr>
<td>S11</td>
<td>150</td>
<td>-------</td>
<td>-------</td>
<td>40</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>S12</td>
<td>150</td>
<td>-------</td>
<td>-------</td>
<td>50</td>
<td>50</td>
<td>-------</td>
</tr>
</tbody>
</table>
3. RESULTS AND DISCUSSION

3.1 Physicochemical Evaluation of RT Suppositories

In this work we used two types of suppository bases to prepare RT suppository semisynthetic oleaginous bases (Suppocire and Witepsol) and water-soluble bases (PEG). Visual inspection verified good surface appearance, absence of fissuring, fat blooming and migration of active ingredients.

Physicochemical evaluations were performed on all prepared batches. The obtained results are outlined in Table 2. Displacement values with respect to drug were found to be in range 1 to 2.1. Higher values were recorded in Suppocire based suppositories while lower values were found in PEG based suppositories. Contradictory results were observed in production yield where higher values were in PEG based suppositories and lower values were in Suppocire based suppositories. This behavior might be attributed to difference in specific gravity between water soluble bases (as PEG) and semi-synthetic fatty bases (as Suppocire). The hardness ranged from 3.82 to 12.53 kg. According to B.P., proper hardness of suppositories is considered for values above 5.4 kg [13]. So, all formulations complied with standard specification except S2 and S10. Regarding disintegration time, prepared formulations ranged from 13.32 to 28.22 min. This wide range was expected to directly affect dissolution pattern. The melting points of fatty bases had values from 33.94 to 36.82±0.36°C. In case of PEG based suppositories melting point ranged from 39.94 to 43.83°C. It was reported that melting point of PEG is directly proportional chain length [14] which was also revealed by our results. Generally, PEG based suppositories do not melt in colon but they dissolve or disintegrate colonic aqueous media. So the temperature required for complete disintegration was determined. Considering RT content uniformity, the difference between the average of each formula and the theoretical loading was less than ±9% with standard deviations of less than 5%. Higher content uniformity was shown in PEG based suppositories which might be ascribed to the direct and easy incorporation of RT (water soluble drug) into water soluble base or rather than dispersion of the drug particles in fatty bases (differ in nature).

3.2 In vitro RT Release

In vitro release profile of different formulations was assessed by rotating basket method.

Fig. 1 (A and B) depicts the dissolution properties of suppositories. It is obvious that different suppository bases influence the in vitro release pattern of drugs [15]. Generally, chemical composition and nature of the base and solubility of RT in the base affect drug release. Even the bases belonging to the same category, variation in drug release was observed. The higher hydroxyl value, the higher hydrophilic characteristic of the base. This can influence both the release and the absorption rates of the drug. The melting point influences the rate of bringing the drug free in the dissolution medium. S1 (Suppocire AP containing formulation) is composed of saturated polyglycolyzed glycerides with high hydroxyl value (30-50) and relatively suitable melting range (30-35°C). So, it can
3.4 Bioavailability Studies

Based on aforementioned results, it was found that three RT suppository formulations S1 (Suppocire AP based), S6 (Witepsol W25 based) and S8 (PEG based) had higher in vitro drug release than many other corresponding formulations and demonstrated good self-life stability for 1 year. So, they were selected for in vivo studies. For more convenient work, study was designed to carry out relative bioavailability studies in comparison with oral RT solution. Average plasma concentrations (n=6) were plotted with time to obtain the figure shown in Fig. 3. However, all investigated formulations exhibited two or more distinct peaks in all the curves of the animals and distinct double peaks in the mean plasma concentration-time plot. This double peak phenomenon of RT was reported by many literatures [18,19,20]. The appearance of the second peak might be ascribed to bile flow [21], enterohapatic recycling [22] or sustained release behavior of formulation which in turn resulted in parallel absorption of RT from the proximal and more distal parts of the intestine [20]. It is obvious that there was great variation in the plasma concentration-time profile between Suppocire AP based formulation and other investigated formulations. The main pharmacokinetic parameters of RT from different investigated formulations are listed in Table 3. The experimental results showed that S8 was of the highest (P <.05) rate and extent of RT absorption where C_{max} of S1, S6, S8 and RT solution were 3.23±0.12, 3.90±0.05, 10.05±1 and 3.82±0.66 µg/mL respectively. Regarding first peak, results also showed faster RT absorption from S6 than other investigated formulations (1h required for appearance of first peak) while RT solution required 2.5h. This confirmed faster absorption from rectal route than oral route. Although fatty bases (S1 and S6) were expected to enhance colonic drug release and hence absorption as they had low affinity to RT (hydrophilic drug), the PEG (hydrophilic) based formula (S8) showed significant higher AUC_{0-12} (58.313±3.9 µg.h/mL) than fatty bases (Suppocire AP and Witepsol W25; 29.122±2.3 µg.h/mL and 27.314±1.9 µg.h/mL respectively). This behavior may be explained colonic metabolism of RT. It was reported that RT is metabolized by colonic bacteria [23]. Authors used batch culture fermentation system to simulate colonic conditions and concluded that RT was degraded by cleavage of an N-oxide bond using UV and mass spectrometry analysis. In our case, we suggest that RT could promptly release from fatty bases and then extensively degraded in colonic environment before efficient absorption. Regarding PEG based batch (S8), RT was partitioned between two favorable media; aqueous media of colon and PEG matrix of suppository and slowly releases. This could minimize colonic degradation of RT. This suggestion could be partly explained lower absorption rate constant (0.397±0.02h⁻¹) and higher absorption half life (1.745±0.03h) when compared to other investigated formulations. Moreover, PEG can improve permeability of

3.3 Stability Studies

Stability studies of different formulations were investigated by storage at 4°C for 12 months. RT concentration was determined at different time points as shown in Fig. 2 (A and B). All formulations were relatively stable regarding RT concentration as the percentages remaining after 12 months were more than 90%.

3.2 Bioavailability Studies

The experimental results showed that RT was of the highest (P <.05) rate and extent of RT absorption where C_{max} of S1, S6, S8 and RT solution were 3.23±0.12, 3.90±0.05, 10.05±1 and 3.82±0.66 µg/mL respectively. Regarding first peak, results also showed faster RT absorption from S6 than other investigated formulations (1h required for appearance of first peak) while RT solution required 2.5h. This confirmed faster absorption from rectal route than oral route. Although fatty bases (S1 and S6) were expected to enhance colonic drug release and hence absorption as they had low affinity to RT (hydrophilic drug), the PEG (hydrophilic) based formula (S8) showed significant higher AUC_{0-12} (58.313±3.9 µg.h/mL) than fatty bases (Suppocire AP and Witepsol W25; 29.122±2.3 µg.h/mL and 27.314±1.9 µg.h/mL respectively). This behavior may be explained colonic metabolism of RT. It was reported that RT is metabolized by colonic bacteria [23]. Authors used batch culture fermentation system to simulate colonic conditions and concluded that RT was degraded by cleavage of an N-oxide bond using UV and mass spectrometry analysis. In our case, we suggest that RT could promptly release from fatty bases and then extensively degraded in colonic environment before efficient absorption. Regarding PEG based batch (S8), RT was partitioned between two favorable media; aqueous media of colon and PEG matrix of suppository and slowly releases. This could minimize colonic degradation of RT. This suggestion could be partly explained lower absorption rate constant (0.397±0.02h⁻¹) and higher absorption half life (1.745±0.03h) when compared to other investigated formulations. Moreover, PEG can improve permeability of
drugs by both disorganization of intercellular spaces and hence paracellular absorption (major route of RT absorption) and interaction with membrane transporters [24] (RT is a substrate for efflux and influx membrane transporters). By this way we could interpret higher bioavailability of RT as class III drug (permeability rate limited) from PEG based suppositories. In addition, relative bioavailability of the investigated formulations were 109.57, 102.76 and 219.39 for S1, S6 and S8, respectively confirming the superiority of S8 formulation over other investigated formulations in improving RT bioavailability.

Table 2. Physicochemical characteristics of different batches of RT suppositories (n=3, S±D)

<table>
<thead>
<tr>
<th>Code</th>
<th>DV</th>
<th>Production yield (%)</th>
<th>Hardness (kg)</th>
<th>Disintegration time (min)</th>
<th>Melting point (ºC)</th>
<th>Content uniformity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>2.1±0.3</td>
<td>99.4±2.6</td>
<td>5.77±0.12</td>
<td>16.20±0.62</td>
<td>33.94±0.72</td>
<td>99.4±2.6</td>
</tr>
<tr>
<td>S2</td>
<td>1.7±0.2</td>
<td>98.9±3.5</td>
<td>3.82±0.16</td>
<td>28.22±0.73</td>
<td>36.82±0.36</td>
<td>98.9±3.5</td>
</tr>
<tr>
<td>S3</td>
<td>2.1±0.4</td>
<td>98.7±4.3</td>
<td>7.56±0.60</td>
<td>14.38±0.45</td>
<td>35.70±0.54</td>
<td>98.7±4.3</td>
</tr>
<tr>
<td>S4</td>
<td>1.7±0.1</td>
<td>101.2±3.7</td>
<td>5.75±1.2</td>
<td>23.01±0.25</td>
<td>35.80±0.61</td>
<td>101.2±3.7</td>
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<tr>
<td>S5</td>
<td>1.8±0.2</td>
<td>99.3±4.4</td>
<td>8.95±0.94</td>
<td>25.26±0.95</td>
<td>35.89±0.93</td>
<td>99.3±4.4</td>
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<tr>
<td>S6</td>
<td>1.5±0.1</td>
<td>98.5±3.4</td>
<td>7.63±1.10</td>
<td>13.32±0.74</td>
<td>34.42±0.48</td>
<td>98.5±3.4</td>
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<td>S7</td>
<td>1.1±0.1</td>
<td>100.6±4.8</td>
<td>5.95±1.10</td>
<td>23.25±0.38</td>
<td>39.94±0.18</td>
<td>100.6±4.8</td>
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<tr>
<td>S8</td>
<td>1.0±0.1</td>
<td>108.7±3.2</td>
<td>12.49±0.63</td>
<td>21.48±0.65</td>
<td>41.00±0.67</td>
<td>108.7±3.2</td>
</tr>
<tr>
<td>S9</td>
<td>1.3±0.3</td>
<td>106±2.5</td>
<td>10.88±1.30</td>
<td>18.94±0.94</td>
<td>41.82±0.27</td>
<td>106±2.5</td>
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<td>S10</td>
<td>1.0±0.07</td>
<td>108.5±4.1</td>
<td>4.87±0.21</td>
<td>16.29±0.15</td>
<td>42.00±0.90</td>
<td>108.5±4.1</td>
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<td>S11</td>
<td>1.2±0.09</td>
<td>103.9±1.7</td>
<td>6.31±2.00</td>
<td>20.30±0.35</td>
<td>41.82±0.44</td>
<td>103.9±1.7</td>
</tr>
<tr>
<td>S12</td>
<td>1.4±0.1</td>
<td>108.8±2.9</td>
<td>12.53±0.57</td>
<td>24.30±0.83</td>
<td>43.83±0.75</td>
<td>108.8±2.9</td>
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Fig. 1. *In vitro* release of RT from different suppository formulations; (A) Fatty bases and (B) PEG base
Fig. 2. Shelf stability study of RT loaded suppository formulations; (A) Fatty bases and (B) PEG base.

Fig. 3. Plasma level-time curve of S1, S6, S8 and RT oral solution.
4. CONCLUSION

We have successfully prepared and in vitro characterized Suppocire (different grades), Witepsol W25 and polyethylene glycol (PEG; different grade mixtures) based suppositories containing RT. The prepared batches showed acceptable physical properties in terms of hardness, melting time, and uniformity of drug content. Release was particularly affected by hydroxyl value (in case of fatty base) and molecular weight (in case of PEG base). Our present study clearly shows that the formulation containing 90% PEG 400 and 10% PEG 1540 can be used to improve the bioavailability of poorly permeable drug such as RT. Selected formulation could be prepared to be used as an alternative outweighing the oral dosage form in improving bioavailability for people with special circumstances.

CONSENT

As per international standard or university standard, patient’s written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


