TOPOICAL DELIVERY OF SULFAMETHOXAZOLE: DESIGN, EVALUATION AND EFFECT OF PENETRATION ENHANCERS

Mukesh Sangra, Sandhya Jaiswal, G.D. Gupta
Department of Pharmacetics Research Div., ASBASJSM College of Pharmacy, Bela (Ropar), Punjab 140111 India.

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ABSTRACT
The present work investigates formulation development and evaluation of a topical gel of Sulfamethoxazole an antifungal drug. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. An antifungal medication is a pharmaceutical fungicide used to treat mycoses such as athlete’s foot, ringworm, candidacies. Antifungal drug works by exploiting differences between mammalian and fungal cells to kill the fungal organism without dangerous effect on host. The gels were formulated using gelling agent like Carbopol 940 and various penetration enhancers like Neem oil, Tulsi oil, and Eucalyptus oil and variation in their concentration was studied for their effect on the drug release profiles, permeation enhancement and flux values of the gels. Sulfamethoxazole topical gel formulation batches (G1 to G9) have been formulated using dispersion method. Fourier transform infrared spectroscopy (FTIR) study indicated no chemical or structural changes in Sulfamethoxazole during formulation studies. The gels were evaluated for pH, clarity, and viscosity, drug content, in vitro and ex vivo diffusion studies the maximum release obtained from Neem oil G1, G2, and G3 was 71.67%, 80.7% and 89.67 % respectively. The maximum release obtained from Tulsi oil G4, G5, and G6 was 71.8% and 81.9% 88.77% the maximum release obtained from Eucalyptus oil G7, G8 and G9 72.15% 80.5% and 89.22% it was found that release rate was increased with the increasing penetration enhancer concentration.

Corresponding author
Prof. (Dr). G.D. Gupta
Director-cum-Member Secretary
[Chairman: Board of studies, Pharmacy, PTU, JALANDHAR]
ASBASJSM College of Pharmacy,
BELA (Ropar)
+919417862160
drdgd@rediffmail.com


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INTRODUCTION:

Today many dosage forms are available; most of them are given by oral and parenteral routes. Oral route is widely used, but it follows GI-side effects, first-pass metabolism and results in an decrease in the bioavailability of the drug. In such cases, parenteral preparations are better than oral preparations as it avoid GI metabolism and first pass effect. Formulation of parenteral preparations requires well equipped laboratory with aseptic area. These make parenteral preparation costlier [1, 3]. Topical preparations avoid the GI-irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations give its action directly at the site of action. Skin is one of the most accessible organ of human body for topical administration and main route of topical drug delivery system. Fungal infections of skin are one of the common dermatological problems. Among the topical formulations a wide choice for the treatment from solid dosage to semisolids doses forms and to liquid dosage formulation the transparent gels have widely accepted in both cosmetics and pharmaceuticals. Topical drug administration is a localised drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical route [4].

Fungal infections usually occur as a result of decrease in the natural human defences due to either immunosuppressive diseases or immune suppressive agents and also in association with opportunistic heavy exposure to the fungus. When fungi infect the skin surface, they invade the stratum corneum to avoid being shed from the skin surface by desquamation, so the management of the superficial fungal infection begins with topical agent that can penetrate the stratum corneum cells. So the topical treatment is greatly valuable when there are no extensive lesions and is much favourable as it generates high local tissue levels. Sulfamethoxazole, a suitable drug candidate is an antifungal agent which inhibits the growth of bacteria. Sulfamethoxazole mainly affects the gastrointestinal tract including abdominal pain, diarrhoea, flatulence, nausea and vomiting. The half life of Sulfamethoxazole is 10 hr and with multiple dose 800 mg oral administrations. However, its use has been associated with a number of gastrointestinal disorders. These potential side effects may be overcome by the topical administration of the drug. Topical products for the treatment of dermatological diseases include a wide choice of vehicles ranging from solids to semisolids and liquid preparations including creams, gels, ointments, pastes, aerosols and solutions. Gel topical formulations offer better patient compliance. Gel is easily spreadable, easily removable, emollient, non-staining and compatible with several excipients. They are rheological referred to as pseudo plastic (shear thinning) systems. A number of polymers are used to provide the structural network that is the essence of a gel system. Gel formulations show variation with the variability of polymer type and concentration which affect drug release and hence the formula quality which must be optimized.

There are various medicated products that are applied to the skin. There are various hydrophilic polymers such as Carbopol 940, hydroxyl Propyl methyl cellulose (HPMC), Sodium alginate that are used in topical gel delivery system. Based on molecular fraction these polymers are used concentration between 1-5 % in topical formulation [5].

The present work aimed to formulate and evaluate topical Sulfamethoxazole gel formulations using polymer Carbopol 940 in order to avoid the drawbacks of the oral administration of Sulfamethoxazole and enhance the release of Sulfamethoxazole from the prepared gels. Selection of Carbopol 940 is the major key factor in deciding viscosity and in turn Sulfamethoxazole release from gel. Carbopol 940 can be preferred in extending drug release where reduced dose of drugs is favoured.

MATERIALS AND METHODS

Sulfamethoxazole was provided as a gift sample from ASOJ pharmaceutical limited, Ahmadabad, Gujarat, India. Carbopol 940 was obtained from Loba chemicals Mumbai. Dialysis membrane was procured from Hi media, Mumbai. All other chemicals used were of analytical grade.

Solubility of Sulfamethoxazole:

The solubility of Sulfamethoxazole was performed to validate experimental conditions. It was determined in phosphate buffer pH 7.4 (release medium), water and mixture of water and propylene glycol (80:20% w/w) (vehicle used in gel preparation). An excess amount of the drug was added to a flask containing 10 ml of each solvent. Then the mixtures were agitated at 100 rpm in a thermostatically controlled shaking water bath at 37± 0.5°C for 24 hours, filtered through filter disk 0.8μ (Sartorius), diluted and measured Spectrophotometrically at 256.9nm using an UV spectrophotometer against a blank similarly treated.

Preparation of gel:

The formulae used to prepare the Sulfamethoxazole gel formulation. The formulation was prepared by soaking Carbopol 940 in water for 24 hrs. The 2% drug was dissolved in ethanol and this solution was added to the above gel with continuous stirring. Triethanolamine (0.5%) was added to bring the pH neutral. Penetration enhancer Neem oil, Tulsi oil, Eucalyptus oil and propylene glycol were added with stirring. The final quantity was made up to 100 gm with distilled water. The prepared gel was kept for 24h for complete polymer dissolved [6, 7].

Drug characterization:

Sulfamethoxazole was characterized for its physical and chemical properties. FTIR spectra (Spectrum-RXI) was recorded and the spectral peaks were compared to that of Sulfamethoxazole. The absorbance maximum of the drug was determined by Ultra Violet spectroscopy (Perkin-Elmer, Lambda 25) and an accurate method for analysis was developed.

Drug excipients compatibility study:

Although considered pharmacologically inert, excipients can initiate, propagate or participate in chemical or physical interaction with drug compounds, which may compromise the effectiveness of a medication. Hence, to predict possible drug and
excipients interactions drug excipients compatibility study was carried out. The ratios of drug and excipients were selected, considering the required ratio of each excipient to the drug in final formulations. They were kept at a temperature of 50°C in order to facilitate chemical reactions if any. Compatibility was checked using FTIR. At the end of 15 days an FTIR spectra was recorded. The integrity of Sulfamethoxazole was checked by presence or absence of prominent peaks [8, 9].

![Figure 1: FTIR spectra of Sulfamethoxazole](image1.jpg)  ![Figure 2: FTIR spectra of Sulfamethoxazole and polymer](image2.jpg)

**EVALUATION OF GEL**

**Measurement of pH:**

The pH of various gel formulations was determined by using Digital pH meter. The measurement of pH of each formulation was done in triplicate and average values were calculated [10].

**Drug content:**

1 gm of the prepared gel was dissolved in 50 ml of methanol. 1 ml of this solution was further diluted to 100 ml. Then absorbance was measured at 256.5 nm. Drug content was calculated using the equation, which was obtained by linear regression analysis of calibration curve [11, 12].

**Viscosity study:**

Brookfield digital viscometer (model DV-I+, Brookfield Engineering Laboratory, INC., USA) was used to measure the viscosity (in cps) of the prepared gel formulation. The spindle (T-D) was rotated at 6 rpm. The viscosity of formulations was more correct which was near to 100% torque. Samples were measured at 30 ± 1°C. Reading was detected 30 sec after measurement was made, when the level was stabilized [13].

**Spreadability:**

Concentric circles of different radii were drawn on graph paper and a glass plate of 100±5 gm was placed gently on the gel and the spread diameter was recorded after 1 minute of each addition. Results were presented as the spreading area being a function of the applied mass [14].

**In vitro release studies:**

Drug release from selected gels was studied through a 0.45μm dialysis membrane. The membrane was mounted on Franz diffusion cells having a surface area of 3.14 cm² and receptor compartment with a capacity of 20 ml. The Receptor compartment was filled with Phosphate buffer solution (PBS) pH 7.4 as diffusion medium at 37±0.5°C. Reservoir solution was stirred continuously. 500 mg of gel was applied on membrane. Aliquots were withdrawn and were suitably diluted with isotonic PBS pH 7.4 and analyzed against a blank by UV spectrophotometer at 256.5 nm. The flux of the gels was calculated.

**Analysis of the release data:**

The release mechanisms of Sulfamethoxazole from the semisolid formulations were elucidated by fitting the release data to four kinetic models. Regression analysis was adopted to compute the constants and correlation of data (r²).

Zero order kinetics

\[ Q = k_0 t \]  

(1)

Where Q is the % of drug released at time t, \( k_0 \) is the zero order release constant and t is the time in hours.

First order kinetics

\[ \ln(100-Q) = \ln100 - k_1 t \]  

(2)

Where \( k_1 \) is the first order release constant.

Higuchi kinetics

\[ Q = K_H t^{1/2} \]  

(3)

Where Q is the amount of drug released at time t per unit area & \( K_H \) is the Higuchi release rate constant.

\[ KH = 2Co \left( \frac{D}{\pi} \right)^{1/2} \]  

(4)

Where \( Co \) is the initial drug concentration & D is the diffusion coefficient.

Korsmeyer peppas equation

\[ Mt/M_\infty = k_n \]  

(5)

Where \( Mt/M_\infty \) is the fraction of released drug at time t & n is the release exponent.
n value is indicative for the drug release mechanism, If n ≤ 0.5 it is a fickian diffusion mechanism, 0.5 < n < 1 it is non fickian mechanism (anomalous diffusion) and if n = 1, so release mechanism from the formulation follows a zero order mechanism (case-2 relaxation). In case of n > 1, it indicates a super case-2 transport. Anomalous diffusion or non-fickian diffusion refers to combination of both diffusion and erosion controlled release rate while case-2 relaxation and super case-2 transport refer to erosion of the polymeric chain.

Stability studies [18]

Physical stability:
The gel formulations were evaluated in terms of physical character like phase separation & change in colour, odour & rheological parameters.

Chemical stability:
The gel formulations were evaluated for drug content, separation of liquid exudates.

RESULT AND DISCUSSION

Gel consists of a small amount of inorganic particles or organic macromolecules, mainly entangled polymers, interpenetrated by relatively large volume of liquids. Typical three dimensional structures, characteristic of the gel, come from the links among the polymer chains. Topical delivery of a drug is used for producing a local action rather than systemic action which is produced by transdermal drug delivery. In present study topical gel of Sulfamethoxazole was formulated using Carbopol 940. This polymer possess excellent formulating properties and are easy to disperse and produce clear gel in concentrations of 1% w/w Sulphonamides are among the ty and permeation rates of gel formulations. Three Penetration enhancers are used for increasing the drug release.

The physical properties of the gels like colour, odour, grittiness, extrudability, pH, viscosity, spreadability, in vitro release, ex vivo and stability studies. All gel formulations were elegant in appearance. A thin and smooth film was formed on application to the skin and easily washable with the water. The in vitro diffusion of gel formulation was carried out with instruments Keshary-Chien. The maximum release obtained from Neem oil G1, G2, and G3 was 71.67%, 80.7% and 89.67% respectively. The maximum release obtained from Tulsi oil G4, G5, and G6 was 71.8% and 81.9% 88.77% the maximum release obtained from Eucalyptus oil G7, G8 and G9 72.15% 80 .5% and 89.22% it was found that release rate was increased with the increasing penetration enhancer concentration.

Table No 1: Formulation of Sulfamethoxazole with different polymer concentration.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>G6</th>
<th>G7</th>
<th>G8</th>
<th>G9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfamethoxazole</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Carbopol 940</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Propylene glycol</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<td>Propyl paraben</td>
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<td>0.2</td>
<td>0.2</td>
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<td>0.2</td>
<td>0.2</td>
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<tr>
<td>Neem oil</td>
<td>5%</td>
<td>7.5%</td>
<td>10%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tulsi oil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5%</td>
<td>7.5%</td>
<td>10%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eucalyptus oil</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5%</td>
<td>7.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Triethanolamine</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Purified water q. s</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: pH, drug content and viscosity of different formulations.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>pH</th>
<th>Drug content (%)</th>
<th>Viscosity (Cps)</th>
<th>Spreadability (g.cm/sec)</th>
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</thead>
<tbody>
<tr>
<td>G1</td>
<td>6.4±0.2</td>
<td>97.74±0.39</td>
<td>2193±2.15</td>
<td>16.66±0.55</td>
</tr>
<tr>
<td>G2</td>
<td>7.1±0.2</td>
<td>98.60±0.55</td>
<td>4688±3.08</td>
<td>12.27±0.28</td>
</tr>
<tr>
<td>G3</td>
<td>7.4±0.1</td>
<td>99.19±0.51</td>
<td>4892±3.28</td>
<td>11.53±0.26</td>
</tr>
<tr>
<td>G4</td>
<td>7.3±0.17</td>
<td>98.26±0.55</td>
<td>2895±4.88</td>
<td>11.11±0.41</td>
</tr>
<tr>
<td>G5</td>
<td>7.0±0.3</td>
<td>97.06±0.65</td>
<td>2348±4.76</td>
<td>11.53±1.41</td>
</tr>
<tr>
<td>G6</td>
<td>7.4±0.15</td>
<td>98.53±0.64</td>
<td>2799±8.90</td>
<td>11.11±0.51</td>
</tr>
<tr>
<td>G7</td>
<td>7.6±0.17</td>
<td>99.56±0.47</td>
<td>4382±7.23</td>
<td>10.71±0.61</td>
</tr>
<tr>
<td>G8</td>
<td>7.5±0.05</td>
<td>98.52±0.58</td>
<td>2854±6.87</td>
<td>10.34±0.38</td>
</tr>
<tr>
<td>G9</td>
<td>7.4±0.11</td>
<td>97.63±0.57</td>
<td>2760±5.15</td>
<td>10.00±0.58</td>
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</table>
Table 3: in vitro release study by zero order.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>G6</th>
<th>G7</th>
<th>G8</th>
<th>G9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.05</td>
<td>17.45</td>
<td>24.56</td>
<td>13.19</td>
<td>19.34</td>
<td>26.34</td>
<td>15.34</td>
<td>25.12</td>
<td>35.39</td>
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<tr>
<td>2</td>
<td>20.56</td>
<td>25.56</td>
<td>32.12</td>
<td>23.65</td>
<td>28.56</td>
<td>35.21</td>
<td>25.89</td>
<td>34.69</td>
<td>44.19</td>
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<td>3</td>
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<td>39.89</td>
<td>46.42</td>
<td>33.45</td>
<td>40.23</td>
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<td>36.72</td>
<td>45.6</td>
<td>56.19</td>
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<tr>
<td>4</td>
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<td>54.23</td>
<td>61.34</td>
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<td>73.45</td>
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<td>67.81</td>
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<td>7</td>
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<td>71.8</td>
<td>81.9</td>
<td>88.77</td>
<td>72.15</td>
<td>80.5</td>
<td>89.22</td>
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</table>

Figure 3: In-vitro release study profile of gel G1-G3  
Figure 4: In-vitro release study profile of gel G4-G6  
Figure 5: In-vitro release study profile of gel G7-G9

Table 4: In-vitro release studies by first order.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Time (hr)</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
<th>G6</th>
<th>G7</th>
<th>G8</th>
<th>G9</th>
<th>Log Cumulative % Drug retained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.949</td>
<td>1.917</td>
<td>1.878</td>
<td>1.938</td>
<td>1.907</td>
<td>1.867</td>
<td>1.928</td>
<td>1.874</td>
<td>1.810</td>
<td>1.874</td>
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<tr>
<td>3</td>
<td>2</td>
<td>1.900</td>
<td>1.917</td>
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<td>1.883</td>
<td>1.854</td>
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<td>8</td>
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<td>1.258</td>
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<td>1.445</td>
<td>1.290</td>
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Figure 6: *In-vitro* release study profile of gel G1-G3  
Figure 7: *In-vitro* release study profile of G4-G6.

Figure 8: *In-vitro* release study profile of gel G7-G9

Table 5: *In-vitro* release studies by Higuchi model.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Square root of time</th>
<th>Cumulative % Drug release</th>
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<tbody>
<tr>
<td></td>
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<td>G1</td>
</tr>
<tr>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>11.05</td>
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<tr>
<td>2</td>
<td>1.141</td>
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<td>7</td>
<td>2.645</td>
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</table>

Figure 9: *In-vitro* release study profile of gel G1-G3  
Figure 10: *In-vitro* release study profile of gel G4- G6

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The in vitro antibacterial activity of different concentrations of Sulfamethoxazole in phosphate buffer pH 7.4 (1%, 2%, 3% and 4% w/v) on staphylococcus aureus was evaluated by the measurement of the mean diameter of growth inhibition zones in millimetre. It was found that staphylococcus aureus is more susceptible in Sulfamethoxazole solution even at low concentrations. Figs. 5(a) and (b) show the growth inhibition zone of 1%, 3% Sulfamethoxazole solution in phosphate buffer against the bacteria. It was also found that the diameter of the growth inhibition zone increases with increasing the Sulfamethoxazole concentration. The solvent used phosphate buffer (pH 7.4) showed no antibacterial effect on the tested bacteria. The results of the selected Carbopol gel formulation that subjected to antibacterial activity 2% (c) are more satisfactory than 4% (d).

Fig. 5: The growth inhibition zone of 1% (a), 2% (c), 3% (b) and 4% (d) sulfamethoxazole solution in phosphate buffer

CONCLUSION
The present study concluded that the formulated gel possesses good physical characteristics and an acceptable release profile. 1% Carbopol 940 gel showed the highest in vitro drug release after 3 hours, high in vitro fungal inhibition and good stability at accelerated temperature 40°C after 3 months. So, it could be a promising topical alternative for the treatment of skin fungal infections and could be submitted for further clinical studies. The maximum release obtained from Eucalyptus oil formulation G7, G8 and G9 72.15%, 80.5% and 89.22% showed that release rate was increased with the increasing penetration enhancer concentration sulfamethoxazole inhibited the growth of clinical isolates of M. tuberculosis at achievable concentrations in plasma after oral administration. Susceptibility to sulfamethoxazole remained constant over a 12 year period. Although the current and prior studies demonstrate that sulfamethoxazole is active against M. tuberculosis the search needs to continue for more active, lipid-soluble sulphonamides that are better absorbed into tissues and have improved therapeutic efficacy.

REFERENCES