DEVELOPMENT AND CHARACTERIZATION OF SALICYLIC ACID EMULGEL FOR TOPICAL DELIVERY BY USING DIFFERENT GELLING AGENTS

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KEYWORDS:
Emulgels, Salicylic acid, Topical drug delivery, Gelling agents.

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ABSTRACT
Salicylic acid is 2-hydroxy benzoic acid, the simplest aromatic carboxylic acid. It is a compound obtained from the bark of the white willow and wintergreen leaves, and also prepared synthetically. It has bacteriostatic, fungicidal, and keratolytic actions. Its salts, the salicylates, are used as analgesics. Salicylic acid emulgel formulations were prepared using three different types of gelling agents: Carbopol 934, Carbopol 940 and HPMC K4M. The main objective behind the formulation of salicylic acid emulgel is to increase the topical delivery of hydrophobic drug (salicylic acid) and to determine the influence of the type of the gelling agent (carbopol 934, carbopol 940 and HPMC K4M) on the drug release from the prepared emulgel. Oleic acid is used as permeation enhancer. The prepared emulgel were evaluated for their physical appearance, pH determination, viscosity, spreadability, in vitro drug release, and stability studies. All gels showed acceptable physical properties concerning color, homogeneity, consistency, spreadability and pH value. Among all the emulgel formulations, the best formulations were F1 and F4. The in vitro release rate of Emulgel was evaluated using Diffusion cell containing dialysis membrane with phosphate buffer pH 7.2 as the receptor medium. The release rate of the F1 Formulation was found to follow Higuchi model. The gelling agent i.e. carbopol 934 showed superior drug release than followed by Carbopol 940 and HPMC K4M. It was observed that the drug release decreased with increase in polymer concentration. The emulgel was found to be stable with respect to physical appearance, pH, rheological properties and drug content at all temperature and conditions for two month at ambient conditions.
INTRODUCTION:
Salicylic acid is 2-hydroxy benzoic acid, the simplest aromatic carboxylic acid\(^1\). It is a compound obtained from the bark of the white willow and wintergreen leaves, and also prepared synthetically. It has bacteriostatic, fungicidal, and keratolytic actions. Its salts, the salicylates, are used as analgesics. It can be divided under various categories according to its different properties such as, Keratolytic (exfoliation of skin cells), Moisturizing, Skin & hair conditioning effects, Acidulant (acidifying effect), Anti-acneic, Anti-dandruff effects, Anti-fungal Anti-inflammatory, Anti-pruritic (anti-itching) effect etc. Salicylic acid is a key ingredient in many skin-care products for the treatment of acne, psoriasis, calluses, corns, keratosis pilaris, and warts. It works by causing the cells of the epidermis to slough off more readily, preventing pores from clogging up, and allowing room for new cell growth.

Salicylic acid is also used as an active ingredient in gels which remove verrucas (plantar warts). Salicylic acid inhibits the oxidation of uridine-5-diphosphoglucose (UDPG) competitively with nicotinamide adenosine dinucleotide (NAD) and noncompetitively with UDPG. It also competitively inhibits the transferring of glucuronyl group of uridine-5-phosphoglucuronic acid (UDPGA) to the phenolic acceptor. The wound-healing retardation action of salicylates is probably due mainly to its inhibitory action on mucopolysaccharide synthesis.

Approved indications
- Acne, Acne scarring
- Pores, Seborrheic dermatitis
- Xeroderma, Ichthyosis
- Warts, Plantar Warts

In addition to its analgesic and antipyretic properties, salicylic acid possesses keratinolytic properties and fungicidal properties.

Topical drug delivery is an attractive route for local and systemic treatment\(^2\). In comparison to conventional routes topical drug delivery offers several advantages such as –
- It avoids the first-pass metabolism and the gastrointestinal tract.
- Topical delivery has the potential for sustained and controlled drug release.
- It is a non-invasive mode of drug delivery with no trauma or risk of infection\(^3\).
The common types of dosage forms for topical use include solutions, suspensions, emulsions, semisolids (e.g., foams, ointments, pastes, creams, and gels), solids (e.g., powders and aerosols), and sprays. The use of transparent gels has expanded now-a-days both in cosmetics and in pharmaceutical preparations. Gels offer many advantages as topical drug delivery but there is a major limitation is in the delivery of hydrophobic drugs. So to overcome this drawback an emulsion based approach called as EMULGEL is used. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent & pleasing appearance.

In the present study, the objective was to develop topical Emulgel formulations of Salicylic acid using three different types of gelling agents: carbopol 934, carbopol 940 and HPMC K4M in varying concentrations. Oleic acid is used as penetration enhancer. The emulgels were evaluated for physical appearance, rheological behavior, drug release and stability.

**MATERIALS AND METHODS**

**Materials**

Salicylic acid was procured from Ankur pharma Pvt. Ltd., Carbopol 934 and Carbopol 940 was obtained from Ipca drug laboratories. HPMC K4M was obtained from Central drug house, Mumbai. All other chemicals were used of analytical grade and without any further chemical modification.

**Equipment**

Digital balance (Shimadzu Corporation, Japan), UV-Visible spectrophotometer (Elico sl 210, India), pH meter (Elico ph meter), Magnetic stirrer, (Hicon grover enterprises), IR spectrophotometer (Perkin elmer spectrum two, India), Brookfield Viscometer (Brookfield Engineering Laboratories, Inc. USA).

**Preparation of Emulgel**

Different formulations were prepared using varying amount of gelling agent and penetration enhancer. The method only differed in the process of making gel in different formulations. The preparation of emulsion was same in all the formulations. The gel bases were prepared by
dispersing Carbopol 940 and Carbopol 934 in distilled water separately with constant stirring at a moderate speed using mechanical shaker. Formulations F1, F2 and F3 were prepared by Carbopol 934 and F4, F5 and F6 by Carbopol 940 as gelling agent. In formulations F7, F8 and F9 the gel were prepared by dispersing HPMC in heated distilled water (75°C) and the dispersion was cooled and left overnight. The pH of all the formulations was adjusted to 5.5 to 6.5 using tri ethanol amine (TEA). The oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl and propyl paraben were dissolved in propylene glycol and mixed with aqueous phase. Salicylic acid, being hydrophobic was dissolved in oil phase. Oleic acid was also mixed in oil phase. Both the oily and aqueous phases were separately heated to 70° to 80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the Emulgel. The composition of different formulations has been discussed in Table no.1.

**Table: 1 Compositions of Salicylic acid Emulgel Formulations (% w/w)**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carbopol 934</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Carbopol 940</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
<td>_</td>
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<tr>
<td>HPMC K4M</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>_</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td>Light liquid paraffin</td>
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<td>4</td>
<td>4</td>
<td>4</td>
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<td>Tween 80</td>
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<tr>
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<td>0.5</td>
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<td>0.5</td>
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<tr>
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<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Acetone</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<td>0.03</td>
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<td>0.03</td>
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<tr>
<td>Propyl paraben</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
<td>q.s</td>
</tr>
</tbody>
</table>

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CHARACTERIZATION OF EMULGELS

Organoleptic properties

The prepared Emulgel formulations were inspected visually for their pH, colour, homogeneity, consistency, grittiness and phase separation \[^{10}\].

**Measurement of pH**

The pH of Emulgel formulations was determined by using digital pH meter. One gram of gel was dissolved in 100 ml of distilled water and it was placed for two hours. The measurement of pH of each formulation was done in triplicate and average values were calculated \[^{11}\].

**Rheological Study**

The viscosity of the formulated batches was determined using a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, USA) with spindle 07. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25±1°C) before the measurement was taken. Spindle was lowered perpendicular in to the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted \[^{12}\].

**Spreading Coefficient**

Spreading coefficient was determined by apparatus suggested by Mutimer et al (1956). It consists of a wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of ‘Slip’ and ‘Drag’ characteristics of emulgel. A ground glass slide was fixed on the wooden block. An excess of emulgel (about 2 gm) under study was placed on this ground slide. The emulgel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook. Weight of 1 gm was placed on the top of the two slides for 5 min to expel air and to provide a uniform film of the emulgel between the two slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time (in sec) required by the top slide to separate from ground slide was noted \[^{13, 14}\]. A shorter interval indicates better Spreading coefficient.

It is calculated by using the formula: \( S = \frac{M \cdot L}{T} \)

**Where,**

\( M \) = weight tied to upper slide
\( L \) = length of glass slides
\( T \) = time taken to separate the slides
Drug content determination\textsuperscript{15,16}

Weigh accurately 1 gm of Emulgel and it was dissolved in 100 ml of Methanol. The volumetric flask was kept for 2 hours and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. The absorbance was measured spectrophotometrically at 231.6 nm after appropriate dilution against corresponding Emulgel concentration as blank. The drug content was determined using following formula.

\textbf{Drug Content} = (\textbf{Concentration} \times \textbf{Dilution Factor} \times \textbf{Volume taken}) \times \textbf{Conversion Factor}.

\textit{In Vitro Drug Release Study}\textsuperscript{17,18}

The \textit{in vitro} drug release studies were carried out using a modified Franz diffusion (FD) cell. The formulation was applied on dialysis membrane which was placed between donor and receptor compartment. PB pH 7.2 was used as a dissolution media. The temperature of the cell was maintained at 37°C by circulating water jacket. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. A similar blank set was run simultaneously as a control. Sample (5 ml) was withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 231.6 nm and the cumulative % drug release was calculated. The difference between the readings of drug release and control was used as the actual reading in each case. The cumulative % drug release profile of all the formulation batches has been shown in Table no.3.

\textbf{Release kinetics of selected formulation (F1 and F4)}

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing.

\begin{itemize}
  \item Zero order (cumulative % drug release \textit{v/s.} time).
  \item First order (log cumulative % drug retained \textit{v/s.} time).
  \item Higuchi model (cumulative % drug retained \textit{v/s.} Square root of time).
  \item Peppas model (log cumulative % drug release \textit{v/s.} log time).
\end{itemize}

\textbf{Stability Studies}

The prepared emulgels were packed in aluminium collapsible tubes (5 gm) and subjected to stability studies at 5°C, 25°C/ 60% RH, 30°C/65% RH, and 40°C/75% RH for a period of 3 months. Samples were withdrawn at 15-day time intervals and evaluated for physical appearance, pH, rheological properties and drug content\textsuperscript{19}. 

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Results and discussion

Physical Examination

Emulgel formulations were white viscous creamy preparation with a smooth homogeneous texture and glossy appearance. Results have been discussed in Table no.2.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Colour</th>
<th>Homogeneity</th>
<th>Consistency</th>
<th>Phase separation</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>White</td>
<td>Excellent</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>F2</td>
<td>White</td>
<td>Excellent</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>F3</td>
<td>White</td>
<td>Excellent</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>F4</td>
<td>White</td>
<td>Excellent</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>F5</td>
<td>White</td>
<td>Excellent</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>F6</td>
<td>White</td>
<td>Excellent</td>
<td>Excellent</td>
<td>None</td>
</tr>
<tr>
<td>F7</td>
<td>Transparent</td>
<td>Fair</td>
<td>Fair</td>
<td>None</td>
</tr>
<tr>
<td>F8</td>
<td>Transparent</td>
<td>Fair</td>
<td>Fair</td>
<td>None</td>
</tr>
<tr>
<td>F9</td>
<td>Transparent</td>
<td>Good</td>
<td>Fair</td>
<td>None</td>
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</tbody>
</table>

Measurement of pH

The pH of Emulgel formulations was determined by using digital pH meter. The pH of the Emulgel formulations was in the range of 6.1±0.1 to 5.6±0.01, which lies in the normal pH range of the skin and would not produce any skin irritation. There was no significant change in pH values as a function of time for all formulations. The data is shown below in figure no.1.

![Figure 1: pH of different Formulations F1- F9](image-url)
Rheological Study

The emulgel was rotated at 50 rpm for 10 min with spindle 07. The corresponding reading was noted. The viscosity of the emulgel was obtained (Fig. 2). The viscosity of the formulations increases as concentration of polymer increases.

![Viscosity vs Formulation](image)

**Figure 2: Viscosity of different Formulations F1- F9**

5.2.1. Spreadability test

Spreadability test was carried out for all the formulations. The spreadability indicates that the Emulgel is easily spreadable by small amount of shear. Spreadability of the Emulgel decreases with the increase in the concentration of the polymer. The spreadability is very much important as it shows the behaviour of Emulgel when it comes out from the tube. Given in figure no.3.

![Spreadability Coefficient vs Formulation](image)

**Figure 3: Spreading Coefficient of Different Formulations F1-F9**
Drug content determination
The drug content of the formulated emulgel was estimated by spectrophotometrically at 231.6 nm. The results were within the official limits as shown in Fig 4.

![Drug content graph](image)

**Figure 4: Drug content of Different Formulations F1-F9**

In Vitro Drug Release Study
The release of salicylic acid from the emulgel was varied according to concentration of polymer. The release of the drugs from its emulsified gel formulation can be ranked in the following descending order: F1 > F4 > F5 > F2 > F3 > F6 > F7 > F8 > F9 Where the amounts of the drug released after 8 hours were 74.74%, 71.04%, 70.03%, 69.01%, 68.51%, 66.68%, 66.20%, 63.08%, 57.26% respectively. The progressive increase in the amount of drug diffusion through membrane from formulation attributed to gradual decrease in the concentration of polymer. It has been concluded that, if we increase the concentration of polymer, the diffusion of drug through the membrane also decreases. The cumulative % drug release profile of all the formulation batches has been shown in Table no.3 and graph is plotted between cumulative % drug releases versus time as shown in figure no.5.
### Table no 3: In-vitro release data of formulation F1-F9

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>2</td>
<td>27.45</td>
<td>27.61</td>
<td>23.73</td>
<td>14.4</td>
<td>22.55</td>
<td>19.60</td>
<td>14.4</td>
<td>15.35</td>
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<tr>
<td>3</td>
<td>36.39</td>
<td>35.46</td>
<td>28.8</td>
<td>19.06</td>
<td>24.60</td>
<td>26.21</td>
<td>22.05</td>
<td>19.88</td>
<td>18.92</td>
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<tr>
<td>4</td>
<td>42.58</td>
<td>40.66</td>
<td>34.11</td>
<td>29.05</td>
<td>26.74</td>
<td>29.67</td>
<td>26.60</td>
<td>24.60</td>
<td>22.30</td>
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<tr>
<td>5</td>
<td>51.24</td>
<td>43.87</td>
<td>40.49</td>
<td>35.04</td>
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<td>31.95</td>
<td>29.05</td>
<td>27.08</td>
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<td>6</td>
<td>56.39</td>
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<td>66.68</td>
<td>66.20</td>
<td>63.08</td>
<td>57.26</td>
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</table>

**Figure 5**: *In Vitro* Cumulative % Drug Release Profile of Formulations F1 – F9
Ex vivo Release Study
This study was carried out only on two best optimized formulations. The study showed the release of the drugs from its emulsified gel formulation F1 and F4 were 75.74% and 71.04% respectively in 8 hours. The results are show in figure no.6.

Figure 6: Ex vivo Cumulative % Drug Release Profile of Formulations F1 – F4

KINETICS OF DRUG RELEASE
The results obtained in in vitro release studies were plotted in different kinetic models. Regression coefficient (R^2) values of different kinetic models are shown in Table 8. This indicated that the release data of best formulation (F1) follows Higuchi model kinetics and F4 follows zero order kinetics because the value of R^2 is greater in this model. The mechanism of drug release is determined by Korsmeyer Peppas where ‘n’ is the release exponent hence the mechanism of drug release is case II transport for both F1 and F4 formulations given in table no.5

Table 4: Model fitting release profile of formulation F1 to F4

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi plot</th>
<th>Korsmayer Peppas plot</th>
<th>‘n’ value</th>
<th>Best fit model</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.917</td>
<td>0.987</td>
<td>0.993</td>
<td>0.634</td>
<td>1.072</td>
<td>Higuchi plot</td>
</tr>
<tr>
<td>F4</td>
<td>0.992</td>
<td>0.985</td>
<td>0.947</td>
<td>0.829</td>
<td>1.256</td>
<td>Zero order</td>
</tr>
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CONCLUSION
From above results, we can conclude that salicylic acid gel formulations prepared with different gelling agents: carbopol 934, carbopol 940 and, HPMC K4M, showed acceptable physical properties concerning color, homogeneity, consistency, spreadability and pH value. Among all gel formulations, carbopol 934 gels shows superior drug release after that carbopol 940, and then
HPMC K4M shows decreasing order of drug release. In carbopol gel formulations, the drug release was decrease with increase in carbopol concentration because polymer concentration increases, viscosity increases. Stability studies in all gel formulations showed that, the physical appearance, drug content, pH, rheological properties, and drug release in all gel formulations remain unchanged upon storage for two months.

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**REFERENCES:**

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