EFFECT OF SURFACTANT ON DISSOLUTION OF SIMVASTATIN TABLETS; COMPARISON WITH USP

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ABSTRACT
Dissolution of poor soluble drugs is carried out by using surfactant for quality control test and drug release, which closely mimics the gastrointestinal conditions. Lower concentrations of surfactant can be useful tool for dissolution in comparison with recommended value of surfactants USP. The objective of this study was to provide a comparative assessment of dissolution profile of various concentration of sodium lauryl sulphate (0.1-0.5%) in six different brands of Simvastatin by applying dissolution profile comparison approach to check the similarity among lowest concentration (0.1%) with recommended values (0.5%). Dissolution was carried out with six units of each brand using USP apparatus-II (Paddle) at 37 ± 0.5°C in 900 ml phosphate buffer medium pH 7.0 with SLS at 50 rpm. Samples were withdrawn from the dissolution medium at 5, 10, 15, 30, 45 and 60 min interval, and analyzed by spectrophotometer at 239nm. Various statistical methods such as Model-independent methods including difference f1 and similarity factor f2, t-test and ANOVA were used for the comparison of in vitro dissolution patron among 0.1% and 0.5% SLS concentration. Results revealed that 0.1% SLS medium is sufficient for drug release of Simvastatin from tablet dosage form, five brands showed Q value = 80% in 30 minutes that is similar with recommended value of USP. The results of the study concluded...
that the presence of 0.1% SLS in dissolution medium improves the solubility and release profile of drug. It can also be used as a tool of quality control test for Simvastatin tablets.

**Key words:** Simvastatin, SLS, drug release, Dissolution.

**INTRODUCTION**

Dissolution is a dynamic property that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. In 1897, Noyes and Whitney published a paper on "Rate of solution of solid substances in their own solution", that was considered as a first known reference to dissolution testing\[1\]. After that the formulation scientists started thinking over this test. So in 1967 under supervision of Rudolph Blythe, the USP-NF Joint Panel on Physiological Availability was set up\[2\]. In 1969 first time, USP adopted dissolution test (USP-18) as official test for the measurement of drug release from its dosage form and Various applications of dissolution test included in vitro quality control test, in vivo prediction, IVIVC, food effects on drug release and surrogate for in vivo\[3,4,5,6\].

Dissolution testing is a critical pre-formulation solubility analysis research tool in the process of drug discovery that entails measuring the stability of the investigational product, achieving uniformity in production lots and determining it in vivo availability. Thus this Dissolution testing is an essential requirement for the development, establishment of in vitro dissolution and in vivo performance (IVIVR), registration and quality control of different dosage forms \[7\]. In case of poor soluble drugs dissolution is rate limiting step and absorption depends on amount of drug released in gastrointestinal tract. In this regards, various approaches are used to improve drug solubility and its release including pH changes and addition of surfactants or their combinations\[6,8,9,10,11,12\].

Simvastatin is a lipid reducing agent broadly used worldwide for the treatment of hypercholesterolemia as well as for minimizing the severity of chronic heart disease that causes morbidity and mortality\[13\]. Simvastatin is a Class II (low soluble and high permeable) drug according to BCS \[11\] and widely used drug included in statins which are HMG CoA reductase inhibitors. They are used for the lowering of cholesterol levels (low-density
lipoprotein, or LDL) and triglycerides, while elevating levels of cholesterol (high-density lipoprotein, or HDL) in the blood \(^{[14]}\).

In conventional compendial methods, surfactant is added in dissolution medium such as SLS to enhance the drug release and improve solubility of poor soluble compounds. Surfactants reduce interface between poor soluble drug particles and liquid medium eventually facilitate wettability of particle and make it solubilized.

To achieve high solubility of poorly soluble drugs, the USP recommended the addition of low concentrations of surfactant for the determination of batch uniformity and evaluation of drug release behavior. For the quality control test of Simvastatin tablets, USP suggested pH 7.0 buffer having 0.5% w/v SLS as dissolution medium \([14]\). FDA has also developed the guidelines for immediate releasing dosage form that based on statistical analysis which are used for comparing dissolution profiles \([15]\).

The objective of the present study was to compare the percentage drug release of Simvastatin tablets (20mg) in the presence of low concentrations of surfactant and to compare it with USP recommended quantity of surfactant with the help of statistical analysis including model independent, t-test and ANOVA test.

**MATERIAL AND METHOD**

Simvastatin was kindly gifted by Barret Hodgson Pvt. Ltd, Karachi, Sodium dihydrogen phosphate, sodium hydroxide, Sodium lauryl sulphate (Sigma-Aldrich, Germany), distilled water freshly prepared.

**Dissolution medium**

Dissolution medium prepared with different concentration of SLS (% w/v). pH 7.0 buffer was prepared by dissolving 8.28 gm of sodium di hydrogen phosphate in 6000 ml of distilled water and pH was adjusted (Jenway) by 50% w/v solution of sodium hydroxide (USP 32 NF 27) and prepared 0.1, 0.2, 0.3 0.4 and 0.5% SLS in buffer medium separately.
**In-vitro dissolution test**

In the present study, six marketed brand of Simvasttin (20mg) coded as Brand1, Brand2, Brand3, Brand4, Brand5 and Brand 6 were studied for in-vitro dissolution, carried out on six units of each brand in aforementioned mediums at 37°C in 900 ml by using apparatus 2 paddle assembly (Erweka DT 600) at 50 rpm. 10 ml samples were withdraw at different time interval (5, 10, 15, 30, 45 and 60 minutes) and filtered, analyzed spectrophotometrically at $\lambda = 239$ nm and drug release was calculated. At each interval sample was replaced by fresh medium.

**Standard Sample preparation**

Accurately weigh 10 mg of active (Reference standard) and transfer in to 10 ml volumetric flask, diluted with ethanol up to the mark, shake unless dissolved. now transfer one ml of this stock to 50 ml volumetric flask and make up volume with dissolution mediums respectively. This dilution is equivalent to 20µg/ml concentration.

**Dissolution test Comparison**

First run dissolution of brand1 in medium having 0.5% SLS. The profile of this dissolution is taken as reference. Study the dissolution of six brands in a medium having 0.1, 0.2, 0.3, 0.4 and 0.5% SLS respectively. Various approaches are used to compare the drug release profile in respective mediums such as model independent and statistical analysis.

**Model independent approach** A simple model independent approach was used in the present investigation that was difference factor ($f_1$) and similarity factor ($f_2$). The $f_1$ values should be close to 15, and $f_2$ values should be close to 100 [15].

$$f_1 = \frac{\sum_{t=1}^{n} | R_t - T_t |}{\sum_{t=1}^{n} R_t} \times 100$$

$$f_2 = 50 \times \log \left( 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right) - 0.5 \times 100$$

**Statistics**

T-test and One way ANOVA applied to compare dissolution profile among various medium of SLS and brands with significance level of 0.05.
RESULTS

The aim of present study was to evaluate the effect of low concentrations of surfactant on the dissolution of poor soluble drug, Simvastatin tablets (20mg). Six brands were tested in different concentrations of SLS and percentage drug release were determined (Figure 1).

![Figure 1 Percentage Drug release of brands in 0.1% and 0.5% SLS](image)

Results clearly reflected that all brands except one passed the dissolution test in 0.1% w/v of SLS and achieved recommended Q value as illustrated in Table 1 and Figure 2.

![Figure 2 Comparison of % Drug Release at 30 minutes between 0.5% and 0.1% SLS](image)

Table 1 dissolution test of various brands in different concentrations of SLS

<table>
<thead>
<tr>
<th>Dissolution medium</th>
<th>Brand 1</th>
<th>Brand 2</th>
<th>Brand 3</th>
<th>Brand 4</th>
<th>Brand 5</th>
<th>Brand 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.0, 0.1% SLS</td>
<td>pass</td>
<td>pass</td>
<td>fail</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td>pH 7.0, 0.2% SLS</td>
<td>pass</td>
<td>pass</td>
<td>fail</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
</tr>
<tr>
<td>pH 7.0, 0.3% SLS</td>
<td>pass</td>
<td>pass</td>
<td>fail</td>
<td>pass</td>
<td>pass</td>
<td>pass</td>
</tr>
</tbody>
</table>
To evaluate the similarities of drug release between two mediums (0.1% and 0.5% SLS) model independent approach and statistical analysis were used (t-test and ANOVA).

Model independent approach revealed similarity among all brands, except one brand i.e. brand 3 (Table 2) illustrated $f_1$ and $f_2$ values. T test applied on dissolution profiles and evaluated $p>0.05$ no significant difference results except one brand significantly different ($p<0.05$) and One way ANOVA showed in table 3 ($p>0.05$) no significant difference in dissolution profiles (Microsoft excel 2007).

### Table 2 model independent approach

<table>
<thead>
<tr>
<th>Comparison</th>
<th>0.1%sls with 0.5% sls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$f_1$</td>
</tr>
<tr>
<td>brand1</td>
<td>3.58</td>
</tr>
<tr>
<td>brand2</td>
<td>9.86</td>
</tr>
<tr>
<td>brand3</td>
<td>35.76</td>
</tr>
<tr>
<td>brand4</td>
<td>4.92</td>
</tr>
<tr>
<td>brand5</td>
<td>10.99</td>
</tr>
<tr>
<td>brand6</td>
<td>8.14</td>
</tr>
</tbody>
</table>

### Table 3 One way ANOVA

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>6105.583</td>
<td>6</td>
<td>1017.597</td>
<td>2.363815</td>
<td>0.050658</td>
<td>2.371781</td>
</tr>
<tr>
<td>Within Groups</td>
<td>15067.13</td>
<td>35</td>
<td>430.4893</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21172.71</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

A dissolution test is a mean of identifying and proving the availability of active drug materials in their delivered form. A dissolution test simulates the availability of active substance and allows the prediction of the time for complete release of the material from the dosage form.
In the pharmaceutical industry, drug dissolution testing is routinely used to provide critical in vitro drug release information for both quality control purposes, to assess batch-to-batch consistency of solid oral dosage forms such as tablets, and drug development, to predict in vivo drug release profiles.\textsuperscript{7}

Simvastatin is a lipophilic compound with log p value 4.39 and its solubility is independent of pH of medium. For quality control dissolution test, an anionic surfactant such as SLS is recommended in a concentration of 0.5% in buffer (pH 7.0). As the concentration of surfactant increases it will increase the solubility of drug particle and can overestimate the drug release, CMC of SLS achieved at 0.0082 M solution. This approach is not useful for in-vivo estimation of drug availability. In present work it was observed that lower concentration of SLS (0.1%) was as effective as 0.5% for release of Simvastatin drug from its tablets (0.003M). usually the solubility of drugs depends on the dose size. Jamzad and Fassih (2006) studied fenofibrate (54 and 160 mg) and evaluated that as concentration of SLS was increased, it increased the solubility of drug.

For quality control of Simvatatin, USP recommended pH 7.0 buffer with 0.5% SLS as dissolution medium, Q+5% value should be not less than 80%. In present study all brands showed this value in pH 7.0 with 0.1 % SLS (Figure 2) except one brand which failed to release even in 0.5%. The reason might be due to formulation parameters such as compression forces, hardness etc. Single et al in 2009 concluded that 0.1% SLS act as discriminative biorelevant media for self emulsifying capsules higher concentration not closely relate the gastrointestinal solubility of drug.

Statistical methods are useful tool to compared dissolution data of different mediums as shown in table 2. It was concluded that there was similarity between the result of 0.1% and 0.5% SLS medium for five brands, as suggested by FDA. The values of $f_1$ and $f_2$ are in range. t-test was evaluated on basis of paired observation, all profiles were similar (p>0.05) and one way ANOVA in Table 3 showed no significant difference in results (p>0.05).
CONCLUSION

It was concluded that a lower concentration of SLS (0.1%) is as effective as higher 0.5%. so this low concentration can be used for the routine quality control analysis and for the prediction of in-vitro-in-vivo relation of the drug.

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