EFFECT OF pH AND ORGANIC HYDROXYLATED ADDITIVES ON N-DESMETHYLDIAZEPAM SOLUBILIZATION BY NON-IONIC SURFACTANTS

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ABSTRACT

N-desmethyldiazepam, was solubilized in different non-ionic surfactant solutions including members of polysorbates, Myrj5, Eumulgin C and Brij 35 at 25 and 35°C.

Polysorbate 80 was more efficient in solubilizing the drug than polysorbate 20 and Brij 35 was more efficient than Brij 58. On the other hand, Eumulgin C1000 was found to be more efficient than Eumulgin C1500 and Myrj 52 was found to be more efficient than Myrj 53 and Myrj 59 respectively.

Always raising the temperature of the investigated solutions caused a positive temperature effect and a decrease in Km values.

Adjusting the pH of Eumulgin and Brij solutions caused a gradual decrease in the quantity of the drug solubilized by raising the pH from pH 4.0 to 7.4.

Theoretical treatment to quantify the role of both the core and the capsular regions of the micelle in N-desmethyldiazepam solubilization showed that the core of the micelle plays the most important role in solubilizing the drug.

The drug was solubilized in Eumulgin and Brij series containing 5 and 10% w/v of propylene glycol, glycerol, polyethylene glycol 400 (PEG 400)
and polyethylene glycol 4000 (PEG 4000). The incorporation of propylene glycol, glycerol and PEG 400 or 4000 increased the solubilizing efficiencies of the surfactants toward the drug at 25 C.

Incorporation of 5% w/v of these additives in the tested Eumulgin and Brij solutions caused an increase in the Km values of the drug and the reverse is true for 10% w/v of these additives.

INTRODUCTION

The interaction between drugs and non-ionic surfactants is both of profound theoretical interest and considerable practical importance in pharmaceutical formulations. The prime aim in pharmaceutical formulations is to solubilize practically water-insoluble drugs to bring them in solution for their further formulations in liquid dosage forms. Another aim is the investigation of the solubilized systems concerning factors affecting solubilization, mode of incorporation of the drugs in the solubilized systems, stability of drugs in solubilized systems and pharmacological availability of drugs from solubilized systems.

Adjusting the pH of the non-ionic surfactant solutions was found to have a role in drug solubilization.

The effect of certain hydroxylated additives on the solubilization process is well demonstrated. When these additives were incorporated in certain non-ionic surfactant solutions they increased the solubilizing efficiencies toward certain drugs and reduced the concentration of such solubilizers needed to attain the therapeutic doses of such water-insoluble drugs. This process is termed co-solubilization. The solubilizing efficiencies of certain non-ionic surfactant solutions
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toward chloramphenicol were found to increase depending upon the nature of the additives used$^{12,13}$.

The effect of different additives on the micellar solubilization of methotrimeprazine$^{14}$ and carbamazepine$^{15}$ was also reported.

Since N-desmethyldiazepam is practically water-insoluble and is presented only in solid dosage forms of 2-5 mg, the aim of the present work is to study:
1- Solubilization of the drug in series of different non-ionic surfactant solutions.
2- Effect of adjusting the pH of the tested Eumulgin and Brij solutions to pH 4.0, 6.0 and 7.4 on the drug solubilization.
3- Role of the core and the capsule of Myrij micelles on the drug solubilization.
4- Effect of certain organic hydroxylated additives including propylene glycol, glycerol, PEG 400 and PEG 4000 on the process of N-desmethyldiazepam solubilization.

EXPERIMENTAL

Materials:

N-desmethyldiazepam (Hoffman-La Roche Co. Ltd, Basle, Switzerland).

Polysorbates:

(Atlas Chemical Industries, Inc. Willimington Delaware, (USA) were polysorbate 20 and polysorbate 80.

Eumulgins:

(Henkel International, Dusseldrof, Fedral Rebuplic of Germany) were Eumulgin C1000 and Eumulgin C1500.
Myris:

(Atlas Chemical Industries, Inc. Wilmington Delaware, USA) were: Myrij 52, Myrij 53 and Myrij 59.

Brij:

(Atlas Chemical Industries) were Brij 35 and Brij 58.

Buffer Components:

(BDH, Poole, England) were: sodium dibasic phosphate and citric acid (McIlvian buffer).

The additives: were propylene glycol (Prolabo, Pelee Paris, France), glycerol (BDH, Poole, England), PEG 400 and PEG 4000 (Sigma Chemical Company).

Apparatus:

Thermostatically controlled shaker (Seity Company, Cairo, Egypt). UV-self-recording spectrophotometer (Pye-Unicam, SP-1025, England).


Centrifuge (Prolabo, Pelee, Paris, France).

Methods:

1-Solubilization of N-desmethyldiazepam in non-ionic surfactant solutions:

Excess of the drug was equilibrated with 10 ml of different concentrations (2.5, 5, 7.5 and 10% w/v) of the non-ionic surfactant solution in 15 ml screw-capped tubes. The tubes were shaken top-to-bottom in a constant temperature waterbath of 25 and 35°C. After equilibration for four days, the tubes were centrifuged to sediment excess solid drug. The tubes were then re-equilibrated without shaking for further 24 hours period at the same investigated temperatures. Samples were withdrawn from the supernatant liquid in the tubes and their drug content was determined spectrophotometrically.
at 231 nm after appropriate dilution with distilled water. The drug concentrations were determined from Beer's plot which is linear over the determined concentrations. It was found that the presence of the non-ionic surfactant solutions in the dilution range used, neither interfered in the spectrophotometric assay of the drug nor produced any shift of its maximum absorbance$^{14,15}$.

2-Solubilization of N-desmethyldiazepam in certain non-ionic surfactant solutions of controlled pH values:

The pH of the Eumulgin and Brij solutions was adjusted to pH 4.0, 6.0 and 7.4 using McIlvian buffer. The solubilizing efficiencies of those solutions of the previously mentioned pH values toward the drug were carried out as mentioned before.

3-Solubilization of N-desmethyldiazepam in different non-ionic surfactant solutions containing 5 and 10% w/v of the investigated additives:

The non-ionic surfactant solutions investigated containing 5 and 10% w/v of the used additives were evaluated regarding their solubilizing efficiencies. The additives used were propylene glycol, glycerol, PEG 400 and PEG 4000. The solubilizing efficiencies of those solutions containing the additives toward the drug were carried out as mentioned before. It was found that the presence of the surfactant solutions and the additives investigated, in the dilution range used, neither interfered in the spectrophotometric assay of the drug nor made any shift of its maximum absorbance$^{14,15}$.

RESULTS AND DISCUSSION

The solubility of N-desmethyldiazepam in the investigated non-ionic surfactant solutions increases linearly by increasing the surfactant concentrations, Fig.1. The systems investigated
were always one liquid plus solid which represents true micellar solubilization of this drug.

Cloudiness was not observed in the solubilized systems because of the relatively high content of the ethylene oxide moieties in the surfactants investigated, which gives rise to surfactants with relatively high cloud points. Furthermore, N-desmethyldiazepam did not depress the cloud points of these surfactants even at the highest temperature investigated.

The solubilities of N-desmethyldiazepam in the investigated non-ionic surfactant solutions (mg/g) at different temperatures investigated is shown in Table 1. It is evident from Table 1 and Fig. 1 that polysorbate 80 with longer hydrocarbon chain is more efficient as a solubilizer for the drug than polysorbate 20. Thus, surfactants with longer hydrocarbon chain in a homologous series are more efficient as solubilizers indicating that the drug is solubilized mainly in the micellar core.

Extending the polyoxyethylene chain length in a homologous series of surfactants leads to a decrease in the amount of the drug solubilized, as shown in Table 1 and Figs. 1 and 2. That is why Eumulgin C1500 is less efficient as a solubilizer for the drug than Eumulgin C1000. Also, Myrij 59 is less efficient for solubilizing the drug than Myrij 53 which is in turn less efficient than Myrij 52. The last finding proved that the polyoxyethylene chain; the capsular region; the mantle of the micelle, plays a little part in N-desmethyldiazepam solubilization, while the hydrocarbon chain; the core of the micelle; plays the major part in this aspect. Thus, by extending the polyoxyethylene chain of the micelle, the relative volume of the core will be decreased compared to the total micellar volume. These results agree with the results obtained on the solubilization of benzoic acid and salicylamide by pure series of non-ionic surfactant solutions, and other solutes by Myrij series.
Brij 35, although shorter in the hydrocarbon chain and longer in ethylene oxide moiety than Brij 58, was found to be more effi-
cient as a solubilizer for N-desmethyl diazepam, Table 1 and Fig. 2. This could be interpreted on the basis of the unlinked ethylene
oxide chains which form mixed micelles and also some impurities
present in these solutions.

The solubilizing capacities of the investigated non-ionic surfactant solutions in distilled water expressed as mg medic-
ment per gm surfactant are shown in Table 1. These solubilizing
capacities are the slopes of the solubility isotherms of N-desme-
thyldiazepam in the investigated solutions, Figs. 1 and 2. The
non-ionic surfactant solutions used for solubilizing N-desmethyl-
diazepam at 25 C could be arranged according to their solubili-
zing efficiencies as follows: Brij 35 > Eumulgin C1000 > Brij 58 >
polysorbate 80 > Eumulgin C1500 > Myrij 52 > Myrij 53 > polysorbate 20 >
myrij 59.

The solubility of N-desmethyl diazepam in different non-ionic surfactant solutions of 35 C is illustrated in Table 1. On com-
paring the solubility of the drug at 25 C with that of 35 C, a
positive temperature effect was observed. The solubilizing ef-
ciciencies of the non-ionic solutions investigated toward the drug
drug at 35 C could be arranged as follows Brij 35 > Eumulgin C
1000 > polysorbate 80 > Eumulgin C1500 > polysorbate 20 > Brij 58 >
Myrij 53 > Myrij 59.

The distribution coefficient is defined as Km which equals
Cm/Cw, where Cm is the concentration of the drug in the micellar
phase (weight and Cw is the concentration of the drug in the aque-
ous phase (w/w). It was found that the Km values vary according
to the variation in the surfactant molecular structure, as seen
from Table 2. The higher the value of the Km, the higher the
amount of the drug incorporated within the micelle, assuming
that the drug is solubilized by partition between the micellar and aqueous phases. On raising the temperature from 25 to 35°C, the calculated Km values between the micellar phases fall. This may be attributed to the consideration that both the micellar and aqueous phases solubilities are changed by raising the temperature but not by the same ratio. If the effect of temperature is even on both phases, no change in the Km value would be expected, but in fact this is not the case.

For investigating the effect of pH on N-desmethyldiazepam solubilization, Eumulgins and Brijs were chosen for conducting such a study; as they possess atherial linkage, and are stable than polysorbates and Myrj which possess ester linkage. Furthermore, Brijs and Eumulgins are more efficient as solubilizers for the drug. Thus, non-ionic surfactant solution of pH 4.0, 6.0 and 7.4 were used and the process of solubilization was conducted at 25 and 35°C. As seen from Table 1 and Fig. 3 and by comparing the solubilizing efficiencies of the non-ionic surfactant solutions of pH 4.0, 6.0 and 7.4 and those prepared in distilled water, it is obvious that the solubility of the drug decreases as the pH of the non-ionic surfactant was increased. As the pH increases, the amount of citric acid in the buffer solution decreases and the amount of sodium dibasic phosphate increases. Citric acid probably acts as a co-solubilizer and assists in drug solubilization in the non-ionic surfactant solutions investigated, while sodium dibasic phosphate, as an electrolyte, has a salting effect on the non-ionic surfactant monomers, leading to a decrease in their solubilizing efficiencies. That is why non-ionic surfactant solutions of pH 4.0 (having higher concentration of citric acid and lower concentration of sodium dibasic phosphate) are the most efficient solubilizers. Another explanation for the observed increase in the drug solubility by lowering the pH values of the investigated non-ionic surfactant
solutions involves that the $pK_a$ of the drug is equal to 3.3 which suggests that the drug is in the non-ionized undissociated form which favours its micellar solubilization.

Among the non-ionic surfactant solutions of pH 6, Eumulgin C1000 was the best solubilizer for the drug at both temperatures investigated, while Brij 35 was the least. The same findings were observed for the non-ionic surfactant solutions of pH 7.4 at 35°C.

The theoretical treatment proposed by Mukerjee $^{5,18,19}$ and by Goodhart and Martin $^{20}$ has been adopted to quantify the role of both the core and the capsular region of the micelle in solubilizing the drug.

Assuming that the solubilize will be distributed between the micellar core composed of the stearyl groups (R) and the micellar capsule, consisting of the ethylene oxide groups (Eo), Goodhart and Martin $^{20}$ expressed the micellar solubility as equivalents of solubilize per equivalent of (Eo) groups. The amount solubilized in equivalent per liter of solution S, will be given by the equation:

$$ S = a \frac{C_{Eo}}{C_{Eo}} + b \frac{C_{R}}{C_{Eo}} $$

Where $C_{Eo}$ and $C_{R}$ are the concentrations of the solubilize in equivalent per liter of (Eo) and (R) groups respectively, (a) and (b) are the proportionality constants. On dividing by $C_{Eo}$ one obtain:

$$ S/C_{Eo} = a + b \frac{C_{R}}{C_{Eo}} $$

So that if $S/C_{Eo}$ in equivalent per equivalent is plotted against $C_{R}/C_{Eo}$, Table 3, a linear relationship should be obtained with the intercept (a) representing the solubilization in the capsule (equivalent of solubilize per equivalent of Eo groups). The slope (b) represents the solubilization in the core (equivalent of solubilize per equivalent of R groups).
Fig. 4 shows the plot of the data obtained on solubilizing the drug using Myrj series (Myrj 52, 53 and 59), according to Mukerjee treatment at 25 and 35 C. These data are also represented in Table 3. The values of (a) and (b) are shown in Table 4.

It could be noticed that N-desmethyldiazepam was solubilized mainly in the core of the micelles. Furthermore, the amount of the drug solubilized in the capsule decreased by extending the polyoxyethylene chain from 40 (Myrj 53) to 50 (Myrj 53) to 100 (Myrj 59) at the two temperatures investigated.

Table 3 also shows that the ratio between the amount of the drug solubilized in the core and the capsule was constant at the two temperatures investigated for each Myrj member.

The solubilizing efficiencies of Eumulgin and Brij aqueous solutions containing 5% w/v propylene glycol at 25° are shown in Table 5 and Fig. 5. It is clear that propylene glycol produced an increase in the solubilizing efficiencies of the respective surfactants. This increase could be attributed to the suppressive effect of propylene glycol on the liquid crystal formation in the non-ionic surfactant solutions.16

Table 5 and Fig. 6 illustrate the solubilizing efficiencies of Eumulgin and Brij solutions containing 10% w/v propylene glycol at 25 C. It is obvious that this high concentration of propylene glycol caused a decrease in the solubilizing efficiencies of the investigated solutions. The observed decrease may be attributed to the increased hydrophilicity of the non-ionic surfactant micelles, by incorporating this higher concentration of propylene glycol in the capsular region of the micelles.11 Furthermore, the expanded capsular region caused relative decrease in the core volume, which is mainly responsible for the drug solubilization, to the whole micellar volume.
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On raising the temperature of the investigated solutions containing propylene glycol from 25 to 35 C, solutions containing 5% w/v showed a negative temperature effect, except for Brij 35, while the non-ionic surfactant solutions containing 10% w/v of this additive showed a positive temperature effect, Table 5.

Table 5 and Fig. 7 demonstrate the effect of 5% w/v glycerol on the solubilizing efficiencies of Eumulgin and Brij solutions toward N-desmethyl diazepam at 25 C. On comparing the efficiencies of the investigated non-ionic surfactant solutions alone to those containing this concentration of glycerol, it is clear that the incorporation of a such concentration caused a marked increase in the efficiencies of the latter. This increase could be attributed to the effect of glycerol as a co-solubilizer for this drug, consequently the solubility could be increased.

The effect of 10% w/v of glycerol is also shown in Table 5. The investigated solutions containing this concentration of glycerol showed a pronounced increase in case of Brij 58 than Brij 35 and Eumulgin C1000 than Eumulgin C1500, especially if compared with the non-ionic surfactant solutions alone at 25 C. Glycerol, incorporated in the capsular region of the micelle made a relative decrease in the core volume to the totally expanded micelle containing glycerol, resulting in a decrease in the micellar solubilizing capacities. Raising the temperature caused a negative temperature effect to those solutions containing 5% w/v glycerol and the reverse was found for those solutions containing 10% w/v of this additive.

Fig. 8 and Table 5 illustrate the effect of 5% w/v PEG 400 on the solubilizing efficiencies of Eumulgin and Brijs at 25 C.
Comparing the efficiencies in absence and in presence of this
crconcentration of PEG 400 at 25 C it is clear that itus presence caused a slight increase in the efficiencies of Eumulgin
C1500 and Brij 58. Table 5 illustrate also the effect of 10%
w/v PEG 400 on the solubilizing efficiencies of the investiga-
ted Eumulgin and Brij solutions at 25 C. Higher concentrations
of PEG 400 caused an increase in the solubilizing efficiencies
of the investigated solutions compared to 5% w/v of the same
additive except for Eumulgin C1500 solution. The decrease obse-
ved in the solubilizing efficiency of Eumulgin C1500 contain-
ing 10% w/v PEG 400 may be attributed to the incorporation of
this higher concentration of PEG 400 in the relatively longer
polyoxyethylene chain of Eumulgin C1500 (50 ethylene oxide units)
leading to a relative decrease in the micellar core volume. The
observed increase in the rest of the non-ionic surfactant solu-
tions containing 10% w/v may be due to the effect of this addi-
tive at this concentration on the process of solubilization.

The presence of this long chained alcohol in this concentration
may induce the aggregation of monomers into micelles, conse-
quently the cmc values decreased and the solubilizing efficiencies
was increased. Low molecular weight alcohols may act also as
a co-solubilizer for this drug.22

Raising the temperature for the investigated solutions con-
taining PEG 400, from 25 to 35 C, caused a negative effect in
case of 5% w/v except for Brij 35 and a positive effect was ob-
erved in case of 10% w/v.

The effect of 5% w/v PEG 4000 on the solubilizing efficien-
cies of the investigated non-ionic surfactant solutions at 25C is
shown in Table 5, comparing these efficiencies in absence and in
presence of this concentration of PEG 4000, implies that its
presence caused an increase in the solubilizing efficiencies
of the investigated solutions, even more than the same concen-
tration of PEG 400 at the same temperature. This may support the assumption that these additives affect the micellar volume to different extents, depending upon the hydrophilic and the hydrophobic characteristics of both the surfactant and the additive molecules.

10% w/v PEG 4000 incorporated in the investigated non-ionic surfactant solutions generally caused a decrease in their solubilizing efficiencies compared to 5% w/v, which could be attributed to the increased hydrophilicity of the medium by increasing the concentration of PEG 4000 at both temperatures.

Raising the temperature for the investigated non-ionic surfactant solutions containing 5 and 10% w/v of PEG 4000 generally caused a positive temperature effect except Brij 58 containing 5% and Eumulgin C1500 containing 10%.

Table 6 gives an idea about the distribution of N-desmethyldiazepam between the micellar pseudophase and the aqueous phase, i.e. the Km values \(^{11,21}\) of the drug in the different investigated solutions. The effect of temperature and different included additives on the Km values was also investigated. The effect of the additives on the solubility of the drug in the micellar and the aqueous phases caused the Km values to decrease or increase \(^{11,21}\) according to the effect of the additive and whether it promotes aqueous or micellar solubilization. This indicates that when the Km value was increased (compared to its value in the surfactant alone) the additive induced more solubilization of N-desmethyldiazepam in the micellar pseudophase than in the aqueous phase, and the reverse is true when the Km value was decreased. It is noticed that the Km values was generally decreased on raising the temperature from 25 to 35°C indicating that more solubilization of the drug in the continuous aqueous phase was induced at higher temperature.
The $K_m$ values of the drug were generally increased in presence of 5% w/v of: propylene glycol, glycerol, PEG 400 and PEG 4000 at both temperatures investigated, and the reverse was true for 10% w/v of the last mentioned additives. This could be attributed to the increased aqueous solubilities of the drug in the presence of 10% w/v of those additives.
### Table 1: Effect of Different Non-Tonic Surfactant Solutions of Different PH Values

<table>
<thead>
<tr>
<th>PH</th>
<th>Water</th>
<th><em>PAF</em> 55</th>
<th><em>PAF</em> 35</th>
<th><em>MWL</em> 55</th>
<th><em>MWL</em> 53</th>
<th><em>MWL</em> 65</th>
<th><em>EPA</em> C150</th>
<th><em>EPA</em> C170</th>
<th><em>POLYSORBATE 80</em></th>
<th><em>POLYSORBATE 20</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3</td>
<td>12.06</td>
<td>14.33</td>
<td>13.35</td>
<td>10.58</td>
<td>12.89</td>
<td>4.28</td>
<td>5.46</td>
<td>7.39</td>
<td>16.79</td>
<td>14.59</td>
</tr>
<tr>
<td>5.5</td>
<td>6.79</td>
<td>9.54</td>
<td>8.02</td>
<td>7.44</td>
<td>6.75</td>
<td>2.22</td>
<td>9.65</td>
<td>0.93</td>
<td>14.97</td>
<td>14.44</td>
</tr>
<tr>
<td>7.4</td>
<td>8.37</td>
<td>7.34</td>
<td>6.97</td>
<td>6.56</td>
<td>11.65</td>
<td>15.67</td>
<td>10.97</td>
<td>16.56</td>
<td>12.07</td>
<td>15.66</td>
</tr>
<tr>
<td>7.7</td>
<td>9.80</td>
<td>9.61</td>
<td>12.77</td>
<td>12.07</td>
<td>10.66</td>
<td>15.67</td>
<td>12.79</td>
<td>16.79</td>
<td>15.97</td>
<td>16.74</td>
</tr>
<tr>
<td>9.5</td>
<td>11.65</td>
<td>15.67</td>
<td>10.97</td>
<td>14.97</td>
<td>15.66</td>
<td>16.79</td>
<td>14.97</td>
<td>16.79</td>
<td>15.97</td>
<td>16.74</td>
</tr>
</tbody>
</table>

*Note: Inorganic C1500 C1700 Sulfonation on N-deethylated Topiramate Me/6 surfactant = Surfactant Solubility of N-deethylated Topiramate at 25 and 35 C.*

*The table shows the solubility of N-deethylated Topiramate me/6 surfactant in different pH conditions and solutions.*
Table 2: Distribution Coefficient (Km) of N-Desmethyldiazepam between the Micellar and Aqueous Phases at 25 and 35 C.

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Distribution coefficient (Km)</th>
<th>25 C</th>
<th>35 C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysorbate 20</td>
<td>504</td>
<td></td>
<td>410</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>856</td>
<td></td>
<td>487</td>
</tr>
<tr>
<td>Eumulgin C1000</td>
<td>1004</td>
<td></td>
<td>549</td>
</tr>
<tr>
<td>Eumulgin C1500</td>
<td>737</td>
<td></td>
<td>457</td>
</tr>
<tr>
<td>Myrij 52</td>
<td>536</td>
<td></td>
<td>356</td>
</tr>
<tr>
<td>Myrij 53</td>
<td>433</td>
<td></td>
<td>295</td>
</tr>
<tr>
<td>Myrij 59</td>
<td>295</td>
<td></td>
<td>146</td>
</tr>
<tr>
<td>Brij 35</td>
<td>1131</td>
<td></td>
<td>645</td>
</tr>
<tr>
<td>Brij 58</td>
<td>835</td>
<td></td>
<td>444</td>
</tr>
</tbody>
</table>
Effect of Ph and Organic Hydroxylated Additives on N-Demethyl Diazepam Solubilization by Non-ionic Surfactants.

### Table 3: Distribution of N-Demethyl Diazepam between the Cores and Capsules of Myristylsilica

<table>
<thead>
<tr>
<th>Myristylsilica</th>
<th>C17 E100</th>
<th>C17 E50</th>
<th>C17 E40</th>
</tr>
</thead>
<tbody>
<tr>
<td>C25</td>
<td>0.0075</td>
<td>0.010</td>
<td>0.028</td>
</tr>
<tr>
<td>C32</td>
<td>0.0082</td>
<td>0.015</td>
<td>0.022</td>
</tr>
<tr>
<td>C35</td>
<td>0.0085</td>
<td>0.020</td>
<td>0.030</td>
</tr>
</tbody>
</table>

*Calculated by Muerjee's method, 5'-18, 3-94*

<table>
<thead>
<tr>
<th>Surfactant C25</th>
<th>25</th>
<th>35</th>
</tr>
</thead>
</table>
| Part oxide    | 5 | 7 | C/C0 | capsule and core
| Part oxide    | 5 | 7 | C/C0 | capsule and core

Ratio of the amount of N-demethyl Diazepam in the core and capsule at 25 and 35 C.
Table 4: Amount of N-methylidiazepam incorporated in Capsule (a) eq./eq. and core (b) eq./eq. for the Myrj series calculated by Mukerjee's method, at 25 and 35°C.

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>25°C (a)</th>
<th>25°C (b)</th>
<th>35°C (a)</th>
<th>35°C (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myrj 52</td>
<td>1.66</td>
<td>7.2</td>
<td>1.99</td>
<td>8.69</td>
</tr>
<tr>
<td>Myrj 53</td>
<td>1.35</td>
<td>6.05</td>
<td>1.45</td>
<td>6.51</td>
</tr>
<tr>
<td>Myrj 59</td>
<td>0.75</td>
<td>3.59</td>
<td>0.82</td>
<td>3.96</td>
</tr>
</tbody>
</table>
### Table 5: Solubility of N-Deethylchlorpromazine E/4 by Non-ionic Surfactants in Presence of Various Additives at 25 and 30°C

<table>
<thead>
<tr>
<th>Additives</th>
<th>25°C</th>
<th>30°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertaconazol</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Sertaconazol + Surfactant</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Sertaconazol + Propylene Glycol</td>
<td>1.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

**Effect of pH and Organic Hydrolyzed Additives on N-Deethylchlorpromazine E/4 Solution Solubilization**
<table>
<thead>
<tr>
<th>P.E.G. 4000</th>
<th>Surfactant</th>
<th>Cyrcrol</th>
<th>Propylene Surtactant +</th>
<th>Surtactant +</th>
</tr>
</thead>
</table>

Table 6: Effect of different additives on the distribution coefficient (kD) of N-deuterioaldehydes between micellar and aqueous phases at 25°C and 30°C.
Effect of pH and Organo Hydroxylated Additives on N-Desmethyl diazepam Solubilization by Non-Ionic Surfactants.

Fig. (1): Solubility of N-Desmethyl diazepam in Different Non-Ionic Surfactant Solutions at 25°C.
Key: △ Eumulgic 1000, □ Eumulgic 1500, ○ Polysorbate 20, ● Polysorbate 80.

Fig. (2): Solubility of N-Desmethyl diazepam in Different Non-Ionic Surfactant Solutions at 25°C.
Key: ○ Brij 35, ■ Brij 58, ○ Myrij 52, △ Myrij 53, ● Myrij 59.

Fig. (3): Solubility of N-Desmethyl diazepam in Different Non-Ionic Surfactant Solutions of pH 4 at 25°C.
Key: The Same as Fig. 1 & 2

Fig. (4): Micellar Solubilisation of N-Desmethyl diazepam in Polyoxymethylene-Steareate Solutions at 25 and 35°C.
The Number of Equivalent Solubilised by Equivalent Ethylene Oxide Group (S/C 30) is Plotted Against the Molar Ratio of Alkyl Ethylene Oxide (Cn/C30) for the Surfactants.
Key: The Same as Fig. 1 & 2
Fig. (5): Solubility of N-Demethyldiazepam in Different Non-Ionic Surfactant Solutions Containing Propylene Glycol 5% W/V at 25°C.

Key: The same as Fig. 142.

Fig. (6): Solubility of N-Demethyldiazepam in Different Non-Ionic Surfactant Solutions Containing Propylene Glycol 10% W/V at 25°C.

Key: The same as Fig. 142.

Fig. (7): Solubility of N-Demethyldiazepam in Different Non-Ionic Surfactant Solutions Containing Glycerol 5% W/V at 25°C.

Key: The same as Fig. 142.

Fig. (8): Solubility of N-Demethyldiazepam in Different Non-Ionic Surfactant Solutions Containing P.E.O. 400 5% W/V at 25°C.

Key: The same as Fig. 142.
Effect of pH and Organic Hydroxylated Additives on N-Desmethyl diazepam Solubilization by Non-ionic Surfactants.

REFERENCES


9) A.E. Aboutaleb, M.S. Mesiba and Aly A. Abdel Rahman, Pharmazie, 6 (1982).


19) P. Mukerjee, ibid, 60, 1531 (1971).


تأثير ضبط الأس الآيدروجيني وكذلك بعض الاضافات العفوية الآيدروكسيليائية على تدريب ن - ديميثيل ديازيبام بواسطة منشطات السطح غير المثاينة

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ن - ديميثيل ديازيبام - الدواء، النفس المعروف والذي لا يذوب في الماء.آذيب بواسطة سلام من منشطات السطح غير المثاينة لها نفس السلسلة الهيدروكربونية، وهي عديد السويبرات 1، عديد السويبرات 2، عديد السويبرات 49، ومواد كيميائية أخرى كثيرة. ولقد وجد أن عديد السويبرات 20 له كفاءة ذوبانية لهذا العقار أكبر من عديد السويبرات 20.

ولقد وجد أن الآلية سلسلة عديد أوكس ايثيلين في مجموعة مماثلة يقلل من المقدرة الإدراكونية لهذه المجموعة ووجد أن ارتفاع درجة الحرارة يؤدي إلى زيادة الكفاءة الإدراكونية لمنشطات السطح غير المثاينة مواد البخت.

ولقد ضبطت الأس الآيدروجينية لكل من محاليل الاميلجينات وبرم في أنسس مقدارها 2.7. وفقذلك لدراسة تأثير ضبط الرقم الآيدروجيني على المقدرة الإدراكونية للكفاءة السطحية.

وبصفة عامة وجد أن ارتفاع الأس الآيدروجيني لهذه المنشطات قلل تدريجيا من المقدرة الإدراكونية الخاصة بها.

ولقد أتيت بخلاصة جاب خطة لدراسة دور كل من القلب والبشرة للشباك المجموعة المجرف في تدريب N - ديميثيل ديازيبام كمهما. ولقد وجد أن قلب الشباك هو الذي يقوم بالدور الرئيسي في تدريب العقار بينما تقوم البشرة بدور ثانوي في هذا المجال.

ولقد أذب العقار في مجموعتين الاميلجين والبشرة المعتهبة على 50 وزرتن/جم من بعض الاضافات الآيدروكسيليائية. ولقد وجد أن وجود البروبيلين جليكول والجلسرول في تركيز 5 وزن/جم أثر في المقدرة الإدراكونية لمنشطات السطح غير المثاينة على درجة حرارة 25 درجة، وأيضًا، وجد أن منشطات السطح غير المتياينة المعتهبة على 10 وزن/جم من كل عديد أيثيلين 490. عدد أيثيلين جليكول 490 أكثر كفاءة في دضاعة العقار من ماليتها التي لا تحتوي على هذه الاضافات.

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