EFFECT OF FORMULATION AND PROCESS VARIABLES ON DRUG CONTENT AND ENTRAPMENT EFFICIENCY OF ACECLOFENAC NANOSUSPENSION

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ABSTRACT

The present investigation was undertaken to study the effect of polymer and surfactant concentration (formulation variables) and sonication time / agitation speed (process variables) on drug content and entrapment efficiency of nanosuspension of a water insoluble drug aceclofenac. To perform this task, nanosuspension of aceclofenac for oral route were prepared by o/w emulsion method using eudragit L100 as polymer and tween 80 as surfactant in different concentrations at various sonication time and agitation speed. The prepared nanosuspensions of aceclofenac were analyzed for the drug content, entrapment efficiency and other evaluation parameters. The observed results strongly indicated that the effect of formulation and process variables were found to have significant effect on drug content and entrapment efficiency of aceclofenac nanosuspension. From the results of all 27 trials the formulations F-14BYM, F-15BYH, F-23CYM and F-24CYH exhibited optimum characteristics.

Key words: Aceclofenac, Nanosuspension, Drug content, Entrapment efficiency, Eudragit L100, Tween 80

INTRODUCTION

Oral route has been the commonly adopted and most convenient route for the drug delivery. Oral drug delivery system has received more attention in the pharmaceutical field, because of its more flexibility in designing the dosage form than other drug delivery systems1. In recent years novel drug delivery systems like nanosuspension draws a considerable attention in the search for adverse drug reactions and improved patient compliance2.

Aceclofenac is a NSAID used in treatment of pain and inflammation in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and low back pain3. It has adverse effects like, gastritis, diarrhea, abdominal pain, dyspepsia, anemia, thrombocytopenia, granulocytopenia, edema etc4,5,6. Half-life of 4-4.3hrs suggests that the drug to be made as controlled release. Further the less bioavailability suggests that the drug should be delivered in a proper bioavailability enhancement device. Nanosuspension fulfills the objective. By preparing aceclofenac as nanosuspension may prolong the therapeutic concentration of drug in blood and will improve the efficacy and patient compliance by reducing the dose and dosing frequency.

As a nanosuspension it should possess optimum drug content and high entrapment efficiency. Drug content is the amount of drug which is available for release in the drug delivery system. The amount of drug entrapped in the polymeric carrier is termed as entrapment efficiency7. Entrapment efficiency affects the release of the drug from the delivery system. Various factors like type of polymer used, drug polymer ratio, sonication time, agitation speed, surfactant concentration, solubility of drug and polymer may also affect the drug release and entrapment efficiency8.

In this present work the effect of polymer (eudragit L100), surfactant (tween 80) concentration and sonication time/agitation speed on drug content and entrapment efficiency were studied.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as a gift sample from Tablets India Ltd. Eudragit L100 and tween 80 were purchased from Himedia. The other ingredients used in this formulation were of analytical grade.

Methods

Formulation of Aceclofenac nanosuspension9,10

Aceclofenac nanosuspensions were prepared by o/w emulsion method using eudragit L100 as polymeric carrier and tween 80 as surfactant. The eudragit L100 and aceclofenac were dissolved in methanol and transferred to 5ml of methylene chloride by constant stirring. This solution was then gradually added into water containing tween 80 and was kept at a low temperature using an ice water bath. During addition, the mixture was vigorously mixed using magnetic stirrer. The resulting emulsion obtained was sonicated in a probe sonicator, and further stirring was continued for 60 minutes. Solvent residues were allowed to evaporate under a slow magnetic stirring of the NS at room temperature (20°-23°C) for 8–12 hours. The following parameters were optimized for obtaining a desired formulation.

1) Drug polymer ratio
   a) 1:1 – F-1AXL to F-9AZH
   b) 1:2 – F-10BXL to F-18BZH
   c) 1:3 – F-19CXL to F-27CZH

2) Surfactant concentration
   a) 0.01% - F-1AXL to F-3AXH, F-10BXL to F-12BZX, F-19CXL to F-21CXX
   b) 0.02% - F-1AYL to F-3AYH, F-10BYL to F-12BYH, F-19CYL to F-21CYH
   c) 0.03% - F-1AZL to F-3AZH, F-10BZL to F-12BZH, F-19CZL to F-21CZH
3) Sonication time and agitation speed
   a) 2 min/2000rpm
      F-1AXL, F-4AYL, F-7AZL, F-10BXL, F-13BYL, F-16BZL, F-19CXL, F-22CYL, F-25CZL
   b) 4 min/4000rpm
      F-2AXM, F-5AYM, F-8AZM, F-11BXM, F-14BYM, F-17BZM, F-20CXM, F-23CYM, F-26CZM
   c) 6 min/6000rpm
      F-3AXH, F-6AYH, F-9AZH, F-12BXH, F-15BYH, F-18BZH, F-21CXH, F-24CYH, F-27CZHH

Optimization of formulation
The formulations were optimized by multifactorial design. The parameters aceclofenac/eudragit L100 ratio, tween 80 concentration and agitation speed/sonication time were considered. By using these parameters 27 trials were optimized by considered the drug content and entrapment efficiency. The results were categorized as: positive effect (+1), no effect(0) and negative effect(-1).

Characterization of Nanosuspension
The prepared aceclofenac nanosuspensions were evaluated for tests including drug content and entrapment efficiency.

Drug content
Aceclofenac content was analysed by taking a specified volume of nanosuspension formulations and ultra-centrifuged at 25000g and the amount of drug in the supernatant was assessed by UV-Visible spectrophotometer at 275 nm. The formula used to calculate drug content was given below:

\[
\text{Drug content} = \frac{\text{Weight of drug in nanoparticles}}{\text{Weight of nanoparticles}} \times 100
\]

Determination of Drug Entrapment Efficiency
Entrapment efficiency of various nanosuspension formulations prepared were calculated. The formula used to calculate the percentage drug entrapment was:

\[
\text{Drug entrapment} = \frac{\text{Mass of drug in nanoparticles}}{\text{Mass of drug used in formulation}} \times 100
\]

RESULTS AND DISCUSSION
Preparation of Nanosuspension
Aceclofenac nanosuspensions were prepared by o/w emulsion method. The prepared nanosuspensions were found to be turbid and stable. No visible sedimentation was noticed atleast for a period of 7 days.

Drug Content
The drug content was analyzed for 27 trials and the results were noted in table 1, 2 and 3. Formulation F-1AXL exhibited minimum drug content of 16%±1.6 and F-14BYM exhibited maximum drug content of 82±1.1.

Entrapment efficiency
The entrapment efficiencies of 27 formulations were calculated and the results were noted in table 1, 2 and 3. Formulation F-1AXL exhibited minimum entrapment efficiency of 22.2±0.6% and F-14BYM exhibited maximum entrapment efficiency of 89.6±0.9%.

Optimization of formulation
From the results of 27 trials the formulations F-14BYM, F-15BYH, F-23CYM and F-24CYH were considered as ideal and selected for further studies. The drug content of F-14BYM, F-15BYH, F-23CYM and F-24CYH formulations were found to be 82±1.1, 79±2.3, 81±1.6 and 80±1.1 respectively. The entrapment efficiencies of F-14BYM, F-15BYH, F-23CYM and F-24CYH formulations were found to be 89.6±0.9% 86.2±1.6%, 88.9±1.3% and 88.6±1.5% respectively.

Effect of formulation and process variables on Drug Content
The drug content of formulations varied from minimum of 16±1.6% (F-1AXL) to maximum of 82%±1.1% (F-14BYM). The optimization studies suggested that the increase in the amount of eudragit L100 indicated increase in the drug content, except in formulations F-8AZM, F-15BYH, F-18BZH, F-24CYH and F-27CZH. The drug content was not increased in formulation beyond a level because of the saturation of the adsorption of drug molecules on the polymeric matrices. This further indicated that the drug is physically adsorbed on to the polymer and it correlates with results of the IR spectroscopic and DSC studies. Increase in sonication time/agitation speed produced increase in drug content. But the drug content remains same in F-7AZL and F-8AZM, F-17BZM and F-18BZH. Drug content decreased in increase in polymer concentration of 1:3.

Effect of Polymer/surfactant concentration on entrapment efficiency
From the reports it has been indicated that entrapment efficiency increased with increase in eudragit L100 concentration. It is well evident that the concentration of tween 80 also played a predominant role in achieving the nanosuspensions with more entrapment efficiency. The increase in tween 80 concentration, from 0.01% to 0.02% there is an increase in entrapment efficiency. But the increase in the concentration of tween 80 from 0.02 to 0.03% entrapment efficiency decreased. This may be due to increase in concentration of the surfactant beyond the critical micellar concentration, reduces the effectiveness in reducing the surface tension with a consequent increase in particle size and reduced entrapment efficiency. But this occurs only when the drug polymer ratios were 1:1 and 1:2. For drug: polymer ratio 1:3 at 0.03% of tween 80, there is reduction in entrapment efficiency which might be due to the formation of aggregates.

Effect of sonication time/agitation speed on entrapment efficiency
Increase in sonication time/agitation speed showed an increase in entrapment efficiency. But increase in sonication time/agitation speed for drug:polymer ratio of 1:2, the entrapment efficiency is reduced for 0.02% from 4min/4000 to 6 min/6000. This may be due to particle aggregation due to over speed. Similar sonication time/agitation speed was applied to drug:polymer ratio of 1:3, but the entrapment efficiency was reduced. The increase in polymer concentration indicated a direct impact on entrapment efficiency. The entrapment efficiencies of formulations vary from minimum of 22.2±0.6% and maximum of 89.6±0.9%. F-1AXL showed minimum of 22.2±0.6% and F-14BYM exhibited maximum of 89±0.9%. From the results of all 27 trials the formulations F-14BYM, F-15BYH, F-23CYM and F-24CYH were considered as ideal and selected for further studies. They have an entrapment efficiency of 89.6±0.9%, 86.2±1.6%, 88.9±1.3% and 88.6±1.5% respectively. considered as ideal and selected for further studies. They have an entrapment efficiency of 89.6, 86.2, 88.9 and 88.6, respectively.
The formulations F-14BYM, F-15BYH, F-23CYM and F-24CYH were identified as the optimized formulations with respect to drug content, entrapment efficiency and particle size, these formulations were selected for the other studies. The optimization results were given in table 4.5 and 6.

CONCLUSION

In the present study an attempt has been made to develop a nanosuspension of Aceclofenac using different concentrations eudragit L100 as polymer and tween 80 as surfactant. The polymer concentration and surfactant concentration played an impact on the drug content and entrapment efficiency. Further sonication time and agitation speed also affected the drug content and entrapment efficiency. These studies concluded that polymer and surfactant concentration with desired sonication time and agitation speed have significant effect on drug content and entrapment efficiency. From the results formulations F-14BYM, F-15BYH, F-23CYM and F-24CYH were considered as optimal and carried over for further studies.

REFERENCES


<p>| Table 1. Drug content and Entrapment efficiency of aceclofenac nanosuspension |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Batches of nanosuspension containing Aceclofenac</th>
</tr>
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<tbody>
<tr>
<td>F1AXL</td>
<td>F2AXM</td>
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<tr>
<td><strong>Drug content (%)</strong></td>
<td>16±1.6</td>
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<tr>
<td><strong>Entrapment efficiency (%)</strong></td>
<td>22.2±0.6</td>
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</table>

<p>| Table 2. Drug content and Entrapment efficiency of aceclofenac nanosuspension |</p>
<table>
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<th>Parameter</th>
<th>Batches of nanosuspension containing Aceclofenac</th>
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<tr>
<td>F10BXL</td>
<td>F11BXM</td>
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<tr>
<td><strong>Drug content (%)</strong></td>
<td>45±1.6</td>
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<tr>
<td><strong>Entrapment efficiency (%)</strong></td>
<td>56.6±1.1</td>
</tr>
</tbody>
</table>

<p>| Table 3. Drug content and Entrapment efficiency of aceclofenac nanosuspension |</p>
<table>
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<th>Parameter</th>
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<tr>
<td>F19CXL</td>
<td>F20CXM</td>
</tr>
<tr>
<td><strong>Drug content (%)</strong></td>
<td>59±1.0</td>
</tr>
<tr>
<td><strong>Entrapment efficiency (%)</strong></td>
<td>65.6±0.9</td>
</tr>
</tbody>
</table>

Values expressed as ±S.D in percentage
### Table 4 Optimization of Aceclofenac Nanosuspension

<table>
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<th>Parameter</th>
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<tbody>
<tr>
<td></td>
<td>F1AXL</td>
</tr>
<tr>
<td>E.E</td>
<td>-1</td>
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<tr>
<td>Drug content</td>
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### Table 5 Optimization of Aceclofenac Nanosuspension

<table>
<thead>
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<th>Parameter</th>
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<tbody>
<tr>
<td></td>
<td>F10BXL</td>
</tr>
<tr>
<td>E.E</td>
<td>0</td>
</tr>
<tr>
<td>Drug content</td>
<td>-1</td>
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### Table 6 Optimization of Aceclofenac Nanosuspension

<table>
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</thead>
<tbody>
<tr>
<td></td>
<td>F19CXL</td>
</tr>
<tr>
<td>E.E</td>
<td>+1</td>
</tr>
<tr>
<td>Drug content</td>
<td>+1</td>
</tr>
</tbody>
</table>

+1 = Positive effect, 0 = No effect, -1 = Negative effect

**PERCENTAGE DRUG CONTENT OF ACECLOFENAC NANOSUSPENSION FORMULATIONS**

**PERCENTAGE ENTRAPMENT EFFICIENCY OF ACECLOFENAC NANOSUSPENSION FORMULATIONS**

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