Formulation and evaluation of controlled release colon targeted micro sponge of Aceclofenac

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Abstract
Aim - Continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. Microsponges are porous, polymeric nanostructures that are mostly used for prolonged action. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. This system can work efficiently for systemic as well as local effect.

Experimental work - In present study, Aceclofenac microsponge formulation was prepared by Quasi emulsion solvent diffusion technique using Ethyl cellulose, Eudragit RS100, Eudragit S100 and Eudragit RL100 in different conc. Prepared microsponge were evaluated for % Practical yield, % Loading efficiency, particle size. Drug- excipients compatibility studies were performed by FTIR. Optimized batch of Aceclofenac microsponge was further formulated as tablet formulation for colon delivery. Prepared tablet formulations were evaluated for physical parameters like Pre & Post compression evaluation. The drug release data of optimized Batch were fitted into different kinetic models which show that the drug release from tablet formulations follows zero order release.

Result - Various batches were formulated using different drug polymer ratio and optimized batches were selected and further formulated as tablet and various parameters were being examined and batch MS 6 II was selected as the best batch which showed 97.55% of release in 24 hrs and studied for the various kinetic models which show that the drug release from tablet formulations followed zero order release with r² value of 0.99 and n value for korssmayr pepas shows n value 0.942 shows that it is non-fickian diffusion of drug release.

Conclusion - Aceclofenac was successfully encapsulated into Microsponge by Quasi emulsion solvent diffusion technique using Eudragit RS100 as polymer for enhancement of solubility, flow properties and compression characteristics and controlling the release rate upto 24 hrs. After stability study there were no physical changes and same drug release with Aceclofenac was observed. Hence, the batch MS 6 II was stable.

Keywords: Aceclofenac, Microsponge, Loading efficiency, Quasi-Emulsion-solvent-diffusion technique.

1. Introduction [1-8]

Conventional drug products like tablets and capsules are formulated to release the active drug immediately to obtain rapid and complete absorption of drug. In recent years various modified drug products have been developed to release the active drug at a controlled rate. The modified dosage forms have been developed due to certain limitations of conventional drug products. A typically peak valley plasma concentration time profile is obtained which makes to difficulty in achieving steady state condition.

Poor patient compliance which increases the chances of missing the dose of a drug with a short half life for which frequent administration is necessary.

The unavoidable fluctuation in the drug concentration may leads to under medication or overmedication as the steady state concentration values falls or rise beyond the therapeutic range.

The fluctuation in drug levels may leads to precipitation of the adverse effect especially of a drug with a small therapeutic index (TI) when ever over medications occurs [1, 2].

Non site specificity.

Continuous intravenous administration at a programmed rate of infusion has been recognizes as the superior mode of drug delivery not only to bypass hepatic “first pass” elimination, but also to maintain a constant, prolonged and therapeutic effective drug level in the body. However, this method of drug delivery entails risks and therefore necessitates a close medical supervision of the drug therapy.
Recently, there has been a growing recognition that the benefits of intravenous drug infusion can be closely duplicated, without its inconvenience and hazards, by using the oral route as a part of drug administration to provide continuous drug delivery into the systemic circulation. The biological effects of drug are determined by many factors, which are strongly influenced by the chemistry of the drug compound. Some research work in drug development has shown that the chemical modification of the parent compounds can alter the physico-chemical properties of the drug and it will affect its absorption, distribution and excretion. This approach for the new drug delivery designs has been termed as latentiation. Most drug compounds are not inherently long-lasting in the biological system and require multiple daily dosing to achieve the desired therapeutic results. The effects of pharmaceutical ingredients and formulation designs on the biological activity of the drug have been reviewed extensively in various scientific studies. An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired therapeutic drug concentration at the site of action in a constant manner. This is possible through the oral administration of conventional dosage forms in particular dosing intervals throughout the drug therapy. To overcome the inconvenience of multiple dosing, the controlled release or sustained release drug delivery systems have been increasingly gaining popularity in the treatment of various diseases. Such drug formulation designs offer the advantage of conveniently delivering the drug to the systemic circulation and also maintain the desired level of drug into the blood for an extended period of time with a single oral dose. Controlled release dosage forms are not only capable of maintaining drug therapeutic levels with a narrow fluctuation range, but they make it possible to significantly reduce the frequency of drug administration.

Consider the single dosing of a hypothetical drug that follows a simple pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug, e.g., a solution, suspension, capsule, tablet, etc., probably will produce a drug blood level versus time profile similar to that shown in. It can be seen from this figure that administration of a drug by either intravenous injection or an extra-vascular route, e.g., orally or intramuscularly, does not maintain drug blood levels within the therapeutic range for extended periods of time. The short duration of action is due to the inability of conventional dosage forms to control temporal delivery.

2. Materials and Method

Aceclofenac was received as gift sample from Lupin Pharma, Mumbai, India. PVA and Dichloromethane, were used of S.D. Fine chemicals Mumbai. Directly compressible lactose, Magnesium stearate, talc were used from Qualikem Ltd. Vadodara, India and all other chemicals were used of analytical grade. Ratio fr drug: polymer was taken 1:1 1:3 1:5 1:7 1:9 1:11 respectively.

2.1 Method of Preparation

2.1.1 Quasi-emulsion solvent diffusion

The microsponges containing Aceclofenac were prepared by quasi emulsion solvent diffusion method using the different polymer amounts. To prepare the Inner Phase, Polymers were dissolved in dichloromethane. Then, Aceclofenac was added to solution and dissolved under ultrasonication at 35 °C. The inner phase was poured into the PVA in water (outer phase) contain 0.1% W/V solution. Following 60 min of stirring, the mixture was filtered to separate the microsponges. The microsponges were dried in an air-heated oven at 40 °C for 12 hrs and weighed to determine production yield (PY).

2.2 Drug and Excipients interaction study.

FT-IR

The possibility of any interaction between Drug and Excipient used in the formulation of Microsponge was assessed by carrying out the FT-IR. The FTIR Spectral measurements were taken as ambient temperature using Perkin Elmer (spectrum 100), Japan. The drug was dispersed in KBr powder and pellets were made by 6000 kg/cm². FT-IR spectra were...
obtained by powder diffuse reflectance method of FT-IR spectrophotometer.

2.3 Characterization of microsponge

2.3.1 Loading efficiency and production yield

The loading efficiency (%) of the microsponges was calculated according to the following equation:

\[
\text{Loading efficiency} = \frac{\text{Actual drug content in microsponge}}{\text{Theoretical drug content}} \times 100
\]

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponge obtained.

\[
\text{Production yield} = \frac{\text{Practical mass of microsponges}}{\text{Theoretical mass (polymer + drug)}} \times 100
\]

2.3.2 Particle size and shape

Particle size and shape analysis of microsponge formulation was performed by scanning electron microscopy and Trinocular microscopy.

2.3.3 In-vitro drug release study

In vitro release rate studies of microsponges were carried out by filling equivalent amount of microspone in capsules and as per basket method specified in USP. They were placed in 1.2 pH HCl for 2 hrs, 6.8 pH phosphate buffer for 6 hours and pH 7.4 phosphate buffer solutions for remaining hrs at 37 °C and rotated at 50 rpm. Aceclofenac amount in withdrawn samples was determined by spectrophotometrically at 275 nm.

2.4 Preparation of Microsponge Tablet

Microsponge tablet was prepared by taking equivalent amount of drug dose at the 3500 kpa pressure and evaluated for the various parameters.

Pre compression Evaluation

Post compression Evaluation

2.4.1 Hardness

Hardness of the 3 tablets from each batch was measured using Monsanto hardness tester.

2.4.2 Friability

Pre-weighed 6 tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

2.4.3 Weight variation

USP weight variation test was done by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average weight variation tolerance.

2.4.4 Content uniformity

Weigh accurately a quantity of the mixed contents of the 20 tablet equivalent to 200 mg of Aceclofenac, add 10 ml of water and allow standing for 10 min with occasional stirring. Then add Ethanol to produce 100 ml and filter. To 5 ml of the filtrate, mixtures of equal volume of Ethanol and phosphate buffer pH 7.4 to produce 100 ml measure the absorbance of resulting solution at maximum at about 275 nm.

2.4.5 Dissolution test

In vitro drug release studies were performed using USP dissolution test apparatus (Type II). The dissolution studies were performed at 100 rpm at 37±0.5 °C in pH 1.2 pH for first 2 hr, 6.8 pH for 8 hrs and pH 7.4 for rest of studies. Aliquots were withdrawn periodically and replaced with fresh medium & analysed at 275 nm.

2.4.6 Kinetic data analysis

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order describes the systems where drug release rate is independent of its concentration. The first order describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion. The following plots were made: cumulative % drug release vs. time (zero order kinetic models); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model) and log cumulative % drug release vs. log time (korsmeyer model).

2.4.7 Stability of the tablets

Formulation showing optimum release was selected for stability studies. According to ICH guidelines, selected formulation was stored at 40 °C temperature and 75% relative humidity (RH) for a period of 3 months. Formulation was evaluated at periodical intervals of one month for drug content; hardness and physical appearance.

2.5 Result and Discussion

Fig 1 shows drug excipient compatibility for pre-formulation study. The different ratio of drug: polymer 1:1 1:3 1:5 1:7 1:9 1:11 was taken respectively for various batch of MS 1 to MS 6 which was shown in table 1 along with Internal phase and external phase & results are shown in table 2 and drug release data are shown in figure 2 for all six batches of MS 1 to MS 6.

2.5.1 Pre-formulation study

FTIR of Aceclofenac + Eudragit RS 100

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Fig 2: FTIR of Aceclofenac + Eudragit RS 100
Formulation Table

Table 1: Microsponge Formulation

<table>
<thead>
<tr>
<th>Batch</th>
<th>MS 1</th>
<th>MS 2</th>
<th>MS 3</th>
<th>MS 4</th>
<th>MS 5</th>
<th>MS 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Internal Phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aceclofenac (mg)</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>EUDRIT RS 100 (mg)</td>
<td>200</td>
<td>600</td>
<td>1000</td>
<td>1400</td>
<td>1800</td>
<td>2200</td>
</tr>
<tr>
<td>DCM (ml)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>External Phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVA (mg)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Water (ml)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Result of microsponge formulation

<table>
<thead>
<tr>
<th>Batch</th>
<th>Drug : Polymer ratio</th>
<th>Mean Size (μm) ± SD&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Production Yield (%) ± SD&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Loading Efficiency (%) ± SD&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS1</td>
<td>1:1</td>
<td>78±10.22</td>
<td>&lt;30</td>
<td>57±2.98</td>
</tr>
<tr>
<td>MS2</td>
<td>1:3</td>
<td>99±8.89</td>
<td>68±1.83</td>
<td>71±1.38</td>
</tr>
<tr>
<td>MS3</td>
<td>1:5</td>
<td>108±7.44</td>
<td>72±2.29</td>
<td>79±2.44</td>
</tr>
<tr>
<td>MS4</td>
<td>1:7</td>
<td>138±15.81</td>
<td>75±0.87</td>
<td>84±2.67</td>
</tr>
<tr>
<td>MS5</td>
<td>1:9</td>
<td>168±5.04</td>
<td>84±3.81</td>
<td>92±0.98</td>
</tr>
<tr>
<td>MS6</td>
<td>1:11</td>
<td>202±11.07</td>
<td>89±2.34</td>
<td>97±0.67</td>
</tr>
</tbody>
</table>

Fig 3: Release Study of Batch MS 1 – MS 6

From the above result it was concluded that batch MS 5 and MS 6 showed 90% and 92% of drug release in 24 hrs and hence they were formulated further for the microsponge tablet formulation as Batch MS 5-I, MS-5 II, MS 6-I and MS 6-II with equivalent amount of drug loaded in microsponge by direct compression method & Pre- post compression evaluation in Table 3-4 and drug release study of Batch MS 5-I to MS 6-II Evaluated also for the SEM for the optimum batch.

Preparation of the microsponge tablet

Table 3: Preparation of microsponge tablet

<table>
<thead>
<tr>
<th>Batch</th>
<th>MS 5 I</th>
<th>MS 5 II</th>
<th>MS 6 I</th>
<th>MS 6 II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microsponge(mg)</td>
<td>215</td>
<td>215</td>
<td>210</td>
<td>210</td>
</tr>
<tr>
<td>Eq. to 200 mg of Aceclofenac</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starch(mg)</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>MCC(mg)</td>
<td>75</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Directly compressible Lactose(mg)</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Mg. Stearate(mg)</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Talc(mg)</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
Microspponge Tablet formulation data

Table 4: pre compression data

<table>
<thead>
<tr>
<th>Batch</th>
<th>Angle of Repose (θ)</th>
<th>Bulk Density (g/cc)</th>
<th>Tapped Density (g/cc)</th>
<th>Hausner Ratio</th>
<th>Compressibility %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS 5 I</td>
<td>19.39</td>
<td>0.73</td>
<td>0.74</td>
<td>1.09</td>
<td>8.29</td>
</tr>
<tr>
<td>MS 5 II</td>
<td>18.97</td>
<td>0.72</td>
<td>0.78</td>
<td>1.1</td>
<td>6.98</td>
</tr>
<tr>
<td>MS 6 I</td>
<td>19.55</td>
<td>0.72</td>
<td>0.77</td>
<td>1.07</td>
<td>7.43</td>
</tr>
<tr>
<td>MS 6 II</td>
<td>19.08</td>
<td>0.71</td>
<td>0.76</td>
<td>1.04</td>
<td>6.79</td>
</tr>
</tbody>
</table>

Post compression data

Table 5: Post compression data

<table>
<thead>
<tr>
<th>Batch</th>
<th>Hardness n=3(kg/cm²) ± SD</th>
<th>Friability % n=6 ± SD</th>
<th>Wt. Variation n=20 ± SD</th>
<th>Content Uniformity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS 5 I</td>
<td>5.6±0.18</td>
<td>0.17±0.05</td>
<td>427±0.52</td>
<td>98</td>
</tr>
<tr>
<td>MS 5 II</td>
<td>5.7±0.8</td>
<td>0.32±0.11</td>
<td>437±0.32</td>
<td>94</td>
</tr>
<tr>
<td>MS 6 I</td>
<td>5.6±0.14</td>
<td>0.25±0.09</td>
<td>421±0.19</td>
<td>97</td>
</tr>
<tr>
<td>MS 6 II</td>
<td>5.8±0.21</td>
<td>0.28±0.05</td>
<td>427±0.25</td>
<td>98</td>
</tr>
</tbody>
</table>

From the above data it was concluded that Batch MS 6-II showed optimum result for Pre and Post compression data with better drug release 97% compared to other with batches, hence evaluated for the SEM and for zero order kinetic model.

Table 3: SEM image result

<table>
<thead>
<tr>
<th>Sample Identification code</th>
<th>Mean particle size(μm) ± S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch MS 6 II</td>
<td>189±1.22</td>
</tr>
<tr>
<td>Batch MS 6 II</td>
<td>191±2.25</td>
</tr>
</tbody>
</table>

Fig 4: Release Study of Microspponge Tablet of Batch Ms 5 I – Ms 6 II

Fig 5: SEM Image of Ms 6 II
Result of Various Kinetic Models

**Zero Order Kinetic Release**

![Zero Order Kinetic Release](image)

**Fig 7:** Zero Order Kinetic Release

Batch MS 6 II was evaluated for the stability study for 3 months and there was no change in physical appearance and no change in release study and Batch MS 6-II was stable after 3 months which was shown in figure.

![Stability study after 3 months](image)

**Fig 8:** Stability study after 3 months

### 3. Summary and conclusions

#### 3.1 Summary

In the present study, Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also reduce side effects, and modify drug release profiles. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. Aceclofenac has very short half-life, poor flow properties and compression characteristics, and also very low aqueous solubility. Its concentration abruptly falls to lower level, so the frequency of administration also increases. By formulating microsponge CDDS, dosing frequency and toxicity level reduced. Its adverse effects can be overcome by encapsulation of the active ingredient. Encapsulation would both protect the gastrointestinal mucosa from direct exposure to Aceclofenac and lower plasma levels by retarding and controlling the release rate and also enhance the solubility of poorly water soluble drug Aceclofenac, and also Improved the flow properties and compression characteristics of the Aceclofenac. The different polymer were used to prepared microsponge Eudragit RS100. The prepared microsponges were evaluated for, % production yield, % Loading efficiency, and in vitro drug release study, Solubility study On the basis of this evaluation, Eudragit RS100 was optimized. Then stirring speed (law, medium, high) and volume of internal phase (20 ml) were optimized. On the basis of this evaluation with high stirring speed and 20 ml of internal volume was optimized. Further it was evaluated for molecular properties by SEM, FT-IR study. From the result of above evaluations it was concluded that the microsponge was successfully formed between drug and the polymer. The optimized microsponge then incorporated into the controlled release tablets. These tablets were evaluated for physical properties, drug content and in vitro dissolution study, and kinetic modeling. From the results of above evaluation studies, formulation MS 6 was optimized.

#### 3.2 Conclusions

The study conclusively demonstrated that Aceclofenac can successfully encapsulated into Microsponge by emulsion solvent diffusion technique using Eudragit RS100 as polymer for enhancement of solubility, flow properties and compression characteristics and controlling the release rate up to 24 hrs. The prepared optimized Microsponge formulation was then formulated into tablet to get controlled release of drug up to 24 hrs. Drug release kinetics of this formulation correspond best to zero order release model and drug release mechanism as per n value of Korsmeyer & Peppas was found to be 0.94 indicates Non- Fickian zero-order release. Batch MS 6 II shows best result with 97% of release in 24 hrs with particle size of 191 μm, 97% loading efficiency & 89% of production yield & here was the zero order release of batch MS 6 II with r² of 0.994.

### 4. References

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