Research Paper

Development and Evaluation of Enteric Coated Tablet Containing Diclofenac Sodium

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ABSTRACT: The influence of various polymers on the release rate of Diclofenac Sodium from enteric coated tablets was investigated in an attempt to formulate a delayed release solid dosage forms. Prepared the conventional diclofenac sodium tablets by wet granulation method (non-aqueous) using granulating fluid (isopropyl alcohol). Developed the aqueous coating formula using Shacryl and non-aqueous coating formula using HPMCP and optimized the best aqueous coating formula. Coating was performed in a mini coating pan at 107 rpm using low-pressure air atomized liquid spray techniques. Comparative dissolution, disintegration and antiulcer studies were performed on the best products and marketed products. The Comparative antiulcer studies were performed on wister albino rats using conventional, dummy and enteric-coated tablets.

KEYWORDS: Diclofenac Sodium, wet granulation method, Shacryl, HPMCP

Introduction

Drug substances are most frequently administered orally by means of solid dosage forms e.g. Tablets and capsules. Tablets are solid unit dosage forms containing a medicament and excipients compressed or molded into solid cylindrical shape having either flat or convex surfaces. Tablets may be round, oval, oblong, cylindrical or triangular.

A coating is applied to a tablet to modify the release pattern of the active ingredient from it. Many tablets are now coated because this can disguise or minimize the unpleasant taste of certain medicaments, protect the ingredients against decomposition and enhance the appearance. Some coating techniques permit even wider range of dosage regimens and can overcome inherent incompatibility. A coat can be applied which will be resistant to the gastric juices, but which is readily broken down in the lower G.I.T. These enteric coatings (Schroeter, LC et al., 1965), (Hasan MM et al., 1991), (Lecomte F et al., 2003) can protect medicaments against decomposition in the acid environment of the stomach and transport them to the area of G.I.T. from which they are absorbed.

This provides a further type of delayed release product (Rudnic EM et al., 1996).

Materials and Methods

Materials

Shacryl™ 30 D was a gift sample provided by Shausan Chemicals and Drugs Limited Chennai. Marketed tablets (Fenak-50) were purchased (manufactured by Medibos Lab. Ltd.) and all the chemicals were AR grade.

Methods

Tablets were prepared using 10%w/v of polyvinyl pyrrolidone (PVP) in isopropyl alcohol (IPA), (as granulating fluid) by non-aqueous wet granulation method. Three different formulas were selected on the basis of types and proportion of binder and diluent (M.C.C.). The drug, diluent, disintegrant and binder were mixed and powdered. Sufficient quantity of PVP in IPA was added to get a coherent mass and then the wet mass was passed through Sieve No. 16, granules were dried in hot air oven at 60°C for 15mins. Finally the manufacturing additives like talc and magnesium stearate were added and punched into tablets using rotary punching machine (11/32 inch punch size) (Table-1).
Table 1. Batches used for formulation of uncoated diclofenac sodium tablets.

<table>
<thead>
<tr>
<th>Batch</th>
<th>Drug (mg/tablet)</th>
<th>MCC (mg/tablet)</th>
<th>Lactose (mg/tablet)</th>
<th>Starch (mg/tablet)</th>
<th>Magnesium Stearate (mg/tablet)</th>
<th>Talc (mg/tablet)</th>
<th>Sodium CMC (mg/tablet)</th>
<th>PVA (mg/tablet)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch-1</td>
<td>50</td>
<td>120</td>
<td>45</td>
<td>35</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>260</td>
</tr>
<tr>
<td>Batch-2</td>
<td>50</td>
<td>90</td>
<td>45</td>
<td>35</td>
<td>5</td>
<td>5</td>
<td>30</td>
<td>-</td>
<td>260</td>
</tr>
<tr>
<td>Batch-3</td>
<td>50</td>
<td>80</td>
<td>45</td>
<td>35</td>
<td>5</td>
<td>5</td>
<td>- 40</td>
<td>-</td>
<td>260</td>
</tr>
</tbody>
</table>

Preparation of shacryl and HPMCP based coating tablets

The required quantity of shacryl, purified-water, diethyl phthalate (a plasticizer), titanium dioxide (opacifying agent) were mixed vigorously for half an hour. The coloring agent (Amaranth) was also added to the solution and filtered with a muslin cloth. 200 uncoated tablets were taken in a mini coating pan at 107 rpm (optimum) to develop three different batches. Coating solution was applied through spray gun system using low-pressure air atomized liquid spray techniques at 0.5ml per 2 seconds and dried at 60-70°C (Torres D et al., 1995). The coating materials deposit on the tablets and weight of tablets was increased by 8%, 15%, and 20% from its original weight (260mg ± 7.5%). Same procedure was followed in case of HPMCP coating sample and only shacryl was replaced with HPMCP (Hosny EA et al., 1998), (Parfitt K et al., 1999). Tablets were selected at random and checked for their weight before the coating and after application of specific number of coating and volumes of coatings until the desired weight gain was obtained.

Evaluation of formulated tablets

Weight variation test

USP weight variation test was run by weighing 20 tablets individually; calculated average weight was calculated and compared to the individual tablet weights as against the average.

Friability test

The laboratory friability tester (Roche Friabilator) subjects a number of tablets to determine the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25rpm, dropping the tablets at a distance of six inches with each revolution. Normally a pre-weighed tablet sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1% of their weight are generally considered acceptable.

% Friability = \( \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \)

Hardness test

Monsanto Tester was used to test tablet hardness. The optimum hardness regarded for uncoated tablet is 4-6 kg/cm².

Disintegration time (D.T) test

One tablet was placed in each tube of USP disintegration test apparatus and the basket was positioned in a 1 litre beaker of water, simulated gastric fluid or simulated intestinal fluid, at 37°C ± 2°C at 28 to 32 cycles per minute. Perforated plastic discs may also be used in the test.

Content-uniformity (drug content) test

10 tablets were weighed individually and powdered. Equivalent to 1 tablet (260mg) of theoretical drug content was weighed and dispersed in 100ml of pH 2.5-phosphate buffer. The UV absorbance after suitable dilution and filtration was measured at 276 nm against blank reagent. Test was performed in triplicate and drug content was calculated by using following formula.

\[
\text{Drug Content (mg)} = \left( \frac{\text{Absorbance} \times \text{Slope} \times \text{Intercept}}{\text{Dilution factor}} \right) \times \frac{1000}{\text{Dissolution Test}}
\]

In-vitro release rate of diclofenac sodium (Moffat AC et al., 1986), (Johnson PH et al., 2001), (Windholz M et al., 1983) was tested using USP dissolution test apparatus with a rotating basket at 100 rpm. A single tablet was placed in a small wire mesh basket and immersed in the dissolution medium contained in a 100ml flask. The flask was maintained at 37°C ± 0.5°C by a constant temperature bath. The samples were taken at 5, 10, and 20, up to 60 minutes in pH 2.5-phosphate buffer and then absorbance was measured by using UV-Visible spectrophotometer at λmax of 276nm (table-2).
### Table 2. Evaluation of three different batches of uncoated tablets

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameters</th>
<th>Batch – I</th>
<th>Batch – II</th>
<th>Batch – III</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Weight Variation test</td>
<td>Within the limits (+7.5%)</td>
<td>Within the limits (+7.5%)</td>
<td>Within the limits (+7.5%)</td>
</tr>
<tr>
<td>2.</td>
<td>Friability test</td>
<td>Within the limits (0.6%)</td>
<td>Within the limits (0.1%)</td>
<td>Within the limits (0.3%)</td>
</tr>
<tr>
<td>3.</td>
<td>Hardness test</td>
<td>3.5-4.5kg/cm²</td>
<td>5.8-6.0kg/cm²</td>
<td>6.0-6.2 kg/cm²</td>
</tr>
<tr>
<td>4.</td>
<td>Disintegration test (average time taken)</td>
<td>4 – 5 min</td>
<td>14 min</td>
<td>15 min</td>
</tr>
<tr>
<td>5.</td>
<td>Average Drug content</td>
<td>46.12mg</td>
<td>42.6mg</td>
<td>38.08mg</td>
</tr>
<tr>
<td>6.</td>
<td>Dissolution test</td>
<td>Mean cumulative % release within 45 minutes (96.5%)</td>
<td>Mean cumulative % release within 45 minutes (74.5%)</td>
<td>Mean cumulative % release within 45 minutes (68.4%)</td>
</tr>
</tbody>
</table>

**Evaluation of enteric-coated tablets**

(Carstensen JT et al., 1990)

**Disintegration Time (D.T)**

6 sharcyl coated and 6 HPMCP coated tablets were taken in separate basket racks, which were positioned in a 1 litre beaker of 0.1N HCl for 2 hr. (simulated gastric fluid) at 37°C ± 2°C without disks. Then same tablets were put in 1 litre beaker of pH 7.5 phosphate buffer with disks and operated for 2hr. and 15 minutes (Table-3).

**Content- uniformity test**

10 tablets were weighed individually and powdered; equivalent to 1 tablet (260mg) of theoretical drug content was weighed and dispersed in 100ml of pH 6.8-phosphate buffer. The UV absorbance after suitable dilution and filtration was measured at 276 nm against blank reagent (table-6). The Test was calculated by using following formula:

\[
\text{Drug Content (mg)} = \left( \frac{A_{\text{Absorbance}} \times \text{Slope} + \text{Intercept}}{\text{Dilation factor}} \right) \times 1000
\]

**Dissolution test**

Electrolab Dissolution Tester (TDT-08L) with a rotating paddle at 50 rpm was used. Three different products from sharcyl and HPMCP i.e. 8% weight gain, 15% weight gain and 20% weight gain and from each product, 6 tablets were selected at random and then subjected to in-vitro dissolution. 6-marketed tablets also subjected to dissolution studies.

The dissolution was started with 0.1N HCl for 2 hr and samples were withdrawn at 15 min intervals (figure-1, 3, 5). After 2 hours, the product was transferred to pH 6.8 phosphate buffer medium and the dissolution was carried out for 45minutes and the samples were withdrawn at 5 minutes intervals (figure-2, 4, 6). Bath volume was maintained at 1000 ml. The absorbance of each sample was observed in UV Visible spectrophotometer at 276nm against blank reagent.

**Comparative antiulcer studies using conventional diclofenac sodium tablets and enteric-coated tablets:**

Inbred male wistar albino rats (150-180gm) were fed with standard chow diet and water *ad libitum* and placed in cages with grating to avoid coprophagy. These were maintained at 25°C ± 2°C, 12hrs dark/light cycle and 60 ± 5% relative humidity. 18 animals were randomly distributed into 3 groups with six animals per group and fasted for 24hours with free access to water before the induction of ulcer. HCl-ethanol mixture (1.5ml of mixture containing 0.15N HCl in 70%v/v ethanol, p.o.) was used as ulcerogenic agent. The animals were grouped as follows:

- **Group – I** Dummy Tablets (10mg/kg)
- **Group – II** Conventional Diclofenac Sodium Tablets (10mg/kg)
- **Group – III** Enteric Coated Tablets (10mg/kg)

**Dose and Administration**

The drugs were administered twice daily at 9.30 A.M. and 17.30 P.M. at 8 hours interval for 5 days and were fasted for 24 hours in fasting cages. On 6th day, 1.5ml of HCl-ethanol mixture was administered orally. After 1hour of ulcer induction, animals were sacrificed by cervical dislocation and the stomachs were excised and inflated by injecting 2 ml of saline and fixed in 5% formalin for 30 minutes and opened along the greater curvature. Gastric damage visible to the naked eye was observed in the gastric mucosa as elongated black-red lines, parallel to the long axis of the stomach. Ulcer index in the animals was determined by measuring each lesion along its greatest length, five such lesions were taken as equivalent of a 1mm ulcer and summed. Ulcer index was expressed in mm. The percentage inhibition was determined as follows (Table-4)

\[
\% \text{Ulcer inhibition} = \left( \frac{\text{Control mean lesion index} - \text{test mean lesion index}}{\text{Control mean lesion index}} \right) \times 100
\]
Table 3. Disintegration test of enteric coated tablets in medium (0.1N HCL) and pH 7.5 phosphate buffer.

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Batch no.</th>
<th>Observation in 0.1N HCl</th>
<th>Observation in pH 7.5 Phosphate buffer</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC</td>
<td>H-1</td>
<td>Slight softening occurred after one hour</td>
<td>5 minutes ± 2</td>
</tr>
<tr>
<td></td>
<td>H-2</td>
<td>No signs of cracking or softening after one hour</td>
<td>9 minutes ± 1.6</td>
</tr>
<tr>
<td></td>
<td>H-3</td>
<td>No signs of cracking or softening after one hour</td>
<td>20 minutes ± 2</td>
</tr>
<tr>
<td>Shacryl</td>
<td>S-1</td>
<td>Slight cracking occurred after 45 minutes</td>
<td>8 minutes ± 1</td>
</tr>
<tr>
<td></td>
<td>S-2</td>
<td>No signs of cracking or softening after one hour</td>
<td>10 minutes ± 2.1</td>
</tr>
<tr>
<td></td>
<td>S-3</td>
<td>No signs of cracking or softening after one hour</td>
<td>15 minutes ± 1.2</td>
</tr>
</tbody>
</table>

N = 6

Table 4. Comparative anti-ulcer study in wistar albino rats using enteric – coated diclofenac sodium and conventional diclofenac sodium tablets on HCL ethanol induced gastric lesions in rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Dose (mg/kg) (p.o.)</th>
<th>Lesion Index (mm)</th>
<th>Percentage Inhibition of Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-1 (Dummy tablets)</td>
<td>10</td>
<td>38.8 ± 0.3</td>
<td>—</td>
</tr>
<tr>
<td>Group-2 (Conventional Doclofenac Sodium Tablets)</td>
<td>10</td>
<td>44.4 ± 0.6</td>
<td>– 15.92</td>
</tr>
<tr>
<td>Group-3 (Enteric Coated Diclofenac Sodium Tablets)</td>
<td>10</td>
<td>33.2 ± 0.2</td>
<td>+ 13.31</td>
</tr>
</tbody>
</table>

N = No. of Animals per group
All values were expressed in Mean ± SEM

![Fig. 1](image-url) Comparative graph showing the delayed release of the drug from the best aqueous coated product, non-aqueous coated product and marketed products (in 0.1 N HCl medium)
Fig. 2 Comparative graph showing the delayed release of the drug from the best aqueous coated product, non-aqueous coated product and marketed product (in pH 6.8 Phosphate Buffer).

Fig. 3 Stomach showing the Ulcer with different tablets.

Fig. 4 Stomach Showing the Ulcer with Conventional Diclofenac Sodium Tablets.
Result and Discussion

Evaluation of formulated tablets
10 tablets were selected from each batch randomly (except weight variation and friability test) and subjected to different tests for (hardness, disintegration, drug content and dissolution). After observation it was found that, the batch-1 was better than other batches (Table-2).

Evaluation of enteric coated tablets

Disintegration test
It was observed from the disintegration test of enteric coated tablets that the batches S-2 and H-2 with 15% weight gain by the coating process were found to be comparatively better than other batches like (S-1, S-3, H-1 and H-3) in terms of more stability in acidic medium and optimum rate of disintegration in pH7.5 phosphate buffer. (Table-2)

Drug content (uniformity) test
The drug content (uniformity) of selected batches S-2 and H-2 were 47.95 ± 0.25 mg and 50.7 ± 0.18 mg (96% and 101.4% of label claim) respectively. So, H-2 and S-2 batches were found to be within the limits of drug content (uniformity) test as per USP.

Dissolution test
It was found that the batches S-2 and H-2 with 15% weight gain by a coating process were found to be in compliance with acceptance limits with USP dissolution test for enteric-coated tablet. These batches were found to produce a comparatively higher drug release in intestinal pH 6.8 (figure-2).

Antiulcer Studies
It was found that, the Lesion Index of enteric-coated tablets was less than the dummy and conventional diclofenac sodium tablets (table-4). The percentage ulcer inhibition of enteric-coated tablets was found to be more than the dummy and conventional diclofenac sodium tablets (figure-3).

Conclusion
The selected new polymer (shacryl) was found to be compatible in entrapping the selected drug (diclofenac sodium). Among the three different formulas selected for the formulation of core tablet, batch-I was found to be comparatively better, since its physicochemical parameters were found to be within the USP limits. Coating of core tablets using shacryl for different weight gains like 8% weight gain, 15% weight gain and 20% weight gain produced the coated tablets with uniform thickness and elegance. Coating of core tablets using HPMCP to different weight gains like 8% weight gain and 15% weight gain produced the tablets of elegant appearance and uniform thickness. From the disintegration and dissolution tests of enteric-coated tablets, it has been observed that the batches S-2 and H-2 with 15% weight gain by the coating process were found to be comparatively better than the other batches (S-1, S-3, H-1 and H-3). The selected batches of S-2 and H-2 were found to be within the limits of drug content (uniformity) test as specified in USP.

The release profile of the drug, from the best batches of aqueous coated and non-aqueous coated products is comparable and equivalent to the release of the drug from the marketed product.
The formulated aqueous based enteric-coated diclofenac sodium tablets are found to have better ulcer protective effect than the conventional tablets in terms of higher percentage of ulcer inhibition and lower ulcer index. Thus the formulated, aqueous based enteric-coated tablet is found to be a better and cheaper alternative for conventional tablets and non-aqueous enteric-coated tablets in terms of better physicochemical properties and ulcer protective effects.

Abbreviations:

HPMCP : Hydroxy propyl methyl cellulose phthalate
MCC : Microcrystalline cellulose
D : Dextrorotatory isomer
rpm : revolutions per minutes
GIT : Gastrointestine
p.o. : Per oral
CMC : Carboxy methyl cellulose
PVA : Poly vinyl alcohol
S-1 : Shacryl coated tablets with 08% weight gain
S-2 : Shacryl coated tablets with 15% weight gain
S-3 : Shacryl coated tablets with 20% weight gain
H-1 : HPMCP coated tablets with 08% weight gain
H-2 : HPMCP coated tablets with 15% weight gain
H-3 : HPMCP coated tablets with 20% weight gain

References


