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Formulation and Evaluation of Enteric Coated Tablets of Sodium Diclofenac Utilizing a Polymeric System

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Abstract

Challenges in the formulation of modern enteric coatings have been more and more relying on polymers containing carboxylic acid groups as a functional moiety. The rise in pH level above the point of dissolution causes the ionization of the polymer and, subsequently the release of the drug. The selection of a pH-sensitive polymer with a suitable coating thickness and pH-dependent solubility is crucial. Diclofenac sodium, a non-steroidal anti-inflammatory drug used to treat mild to moderate pain, is also known to cause an increased risk of serious gastrointestinal (GI) adverse events, such as bleeding, ulceration, etc. Therefore, this study aims to develop a formulation utilizing a combined system of anionic copolymers for the formulation of enteric-coated tablets using diclofenac sodium as the prototype drug. In the presented work, Diclofenac sodium was formulated as delayed-release tablets using Opadry YS clear utilized at a 4% weight gain in combination with Acryl-EZE, an aqueous acrylic enteric system utilized at 3 different coating weight gains, 7%, 10%, and 15 %. The data supports the theory that a thicker enteric coat secures a better dissolution rate of Diclofenac sodium.

Keywords: formulation, enteric coated tablets, sodium diclofenac, polymeric system

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INTRODUCTION

The use of polymers in the formulation of drugs plays an important role in improving their bioavailability, providing altered drug releases in accordance with therapeutic requirements (1,2).

Current trends emphasize the use of enteric coatings with combined polymers to achieve drug release at a particular pH in the lower gastrointestinal tract (2,3). Because of their potential uses as surface-modifying agents as well as drug transporters, these polymer combinations are of great interest. Additionally, they exhibit synergistically enhanced bioavailability and a more effective drug release profile (3). Due to a number of benefits, including local drug release, avoidance of drug degradation in the upper gastrointestinal tract, and improved bioavailability and efficacy, there has been a recent surge in interest in oral medications with modified release and a specific therapeutic effect in the large intestine. Most of the polymers used for enteric coatings function by presenting a surface that is stable at the acidic pH of the stomach (pH ~ 3) but rapidly disintegrates at a relatively more basic pH (pH above 5.5) (4,5). Polymers commonly used for enteric coating can be derived from cellulose such as: cellulose acetate phthalate (C-A-P), cellulose acetate succinate (C-A-S), hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose (HPMC) (6,7). Other, non-cellulosic polymers used as enteric coatings include copolymers of methacrylic acid and methyl methacrylate or ethyl acrylate, terpolymers of methacrylic acid, methacrylate, and ethyl acrylate, and polyvinyl acetate phthalate (PVAP) (6,7). Methacrylic acid-ethyl acrylate anionic copolymers contain carboxylic groups in their structure that make the copolymer insoluble in acidic media but soluble in neutral and alkaline media, making it ideal for use as a coating agent for film enteric (8).

Diclofenac sodium is a non-steroidal anti-inflammatory drug used to treat rheumatoid arthritis, osteoarthritis, periarticular disorders such as bursitis and tendinitis, conditions such as renal colic, acute gout, and inflammatory bowel disease (9). The immediate release of the drug from the tablet makes it immediately available for absorption in the upper gastrointestinal (GI) tract, resulting in side effects such as bleeding, ulceration, intestinal wall perforation, and local toxicity (10,11). It has been reported that local toxicity is not only caused by inhibition of prostaglandin synthesis but is probably also due to direct contact of the drug with the mucosa (9-11). These side effects can be avoided by coating the drug with an enteric polymeric combination that does not allow its exposure to the stomach's acidic environment, but digestion in the intestinal medium, where it provides therapeutic action.

Despite the growing interest in this direction, in our country there is a very limited use of the system of polymeric combinations in the industrial development of drugs with modified release. Therefore, this study aims to develop a formulation utilizing a combined system of anionic copolymers for the formulation of

enteric-coated tablets using diclofenac sodium as the prototype drug.

METHODS

All materials used in this study were commercial samples. Diclofenac sodium (ALL PRO CORPORATION CO, LTD – China), Microcrystalline cellulose (JRS Pharma - Germany), Pregelatinized starch (COLORCON LIMITED), Sodium starch glycolate (JRS Pharma - Germany), Magnesium Stearate (Transmare Chemie NV – Netherland), Opadry YS clear (COLORCON LIMITED), Acryl Eze (COLORCON LIMITED). All other chemicals were of analytical reagent grades.

1.1. Formulation of 50 mg Diclofenac Sodium core tablets

Core diclofenac sodium tablets were prepared by direct compression method according to the formula given in Table 1.

Manufacturing process: Diclofenac Sodium, Microcrystalline Cellulose, and Pregelatinized starch, were passed through a sieving system using a 1.2 mm screen at an impeller speed of 2500 rpm. The mixture was further blended for 5 minutes. Sodium starch glycolate was added into the blender and the mixing process continued for 15 minutes. Finally, magnesium stearate (previously passed through a 60-mesh/250-micron screen) was added to the powder mixture and blended for an additional 3 minutes. The blended mixture is compressed at Ronchi AR 23 tablet compression machine using 8 mm flat surface punches. The compression force was adjusted to give a tablet thickness of 4.3 mm and hardness in the range of ≥ 60 N.

Compression parameters of 50 mg Diclofenac Sodium core tablets are presented in Table 2.

Table 1. Formulation of 50 mg Diclofenac Sodium Tablets

Ingredients	**Source**	**%**	**Function**
Diclofenac Sodium	ALL PRO CORPORATION CO, LTD – China	21.74	Active ingredient
Microcrystalline Cellulose (Microcell 102)	JRS Pharma - Germany	45.16	Diluent
Pregelatinized starch	COLORCON LIMITED	30.1	Diluent/Binder
Sodium starch glycolate	JRS Pharma - Germany	2	Disintegrant
Magnesium stearate	Transmare Chemie NV – Netherland	1	Lubricant
Total		**100**	

Table 2. Compression parameters of 50 mg Diclofenac Sodium core tablets

Parameters	Specification
Description	Round tablets
Average weight	230 mg ± 7.5 %
Diameter	8 mm
Thickness	4.3 mm
Hardness	≥ 60 N

solids in purified water to 3 different coating weight gains, 7%, 10%, and 15 % using an unperforated coating pan (CGS-France) coating system (20 L pan).

Sub-coating and coating parameters of 50 mg Diclofenac Sodium tablets are presented in Table 3.

Table 3. Sub-coating and coating parameters of 50 mg Diclofenac Sodium Tablets

Coating Process Parameters	Unit	Sub-Coating (CGS)	Enteric-Coating (CGS)
Tablet Charge	kg	18	18.7
Inlet Air Temperature	° C	65	60
Product Bed	° C	45	40
Exhaust Temperature	° C	40	45
Fluid Delivery Rate	ml/min	50	40
Pan Speed	rpm	7	7
Air Volume	m^3/hr	260	280
Pattern Air Pressure	psi/bar	1.4	1.1

Tablets Coating

Sub-Coating

Diclofenac tablets were sub-coated with a 4% weight gain with Opadry YS clear (reconstituted at 10% solids in purified water) using an unperforated coating pan system (CGS-France) (13).

Enteric Coating

Sub-coated diclofenac tablets were subsequently coated using Acryl Eze reconstituted at 10%

1.2. Post-compression evaluation

Weight variation

Ten tablets from the formulated batch were randomly selected and individually weighed. The average weight of the selected tablets was calculated by using a precision balance (Mettler Toledo, XP404S). The USP limit for the percentage deviation for tablets with an average weight between 80 mg and 250 mg, should not exceed 7.5%.

Hardness

The hardness of a tablet indicates the tensile strength and is measured in terms of load/pressure required to crush a tablet when placed on its edge. Hardness influences the disintegration and dissolution times. Erweka Type TBH30 hardness tester is used to measure the hardness of the formulated tablets.

Friability

During the production, packaging, and transportation processes, tablets are continuously exposed to mechanical shocks and aberration. Therefore, tablets should be formulated to resist this kind of stress. Friability refers to the loss in weight of tablets in the containers due to the removal of fine particles from their surfaces. The friability of a sample of 10 tablets is measured using Erweka Type TA100 friability tester (25 rpm for 4 minutes). Tablets were re-weighed after the removal of fines (de-dusted), and the percentage of weight loss was calculated. It is expressed in (%). Friability below 1% is acceptable.

Drug content

Assay was determined in accordance with the USP monograph for Diclofenac sodium delayed-release tablets (12). The USP specification indicates that the tablets should contain not less than 90.0% and not more than 110.0% of the labeled amount of diclofenac sodium.

Uniformity of Dosage Units

A sample of 10 tablets was analyzed individually for the drug content, and the results were used to calculate the arithmetic mean, and relative standard deviation (RSD).

Assessment of Liquid Uptake

Diclofenac tablets (n=6) of each of the enteric coating weight gains were individually weighed and reciprocated for 2 hours in the test media, HCl 0.1 N and pH 4.5 acetate buffer solution in a USP disintegration apparatus ("Erweka" – SOTAX DT3) at 37 ± 2°C. At the end of this time interval, the tablets were removed and inspected for any defects (bloating or swelling).

Any excess surface moisture was gently blotted dry using a paper towel, and the tablets were reweighed individually. The percent liquid uptake was calculated according to Equation 1.

Less than 10% liquid uptake has been shown to correlate to acceptable enteric protection for tablets.

$$\mathbf{LU}\ (\%) = [(\mathbf{Tf} - \mathbf{Ti})/\mathbf{Ti}]\ \mathbf{x}\ \mathbf{100} \quad \textbf{Equation 1}$$

LU (%): Percent liquid uptake

Tf: Final tablet weight (mg)

Ti: Initial tablet weight (mg)

In vitro drug release study

This study is performed to evaluate the ability of the coating layer to remain intact and prevent drug release in the physiological environment of the stomach and small intestine. In vitro drug release studies were carried out in accordance with the USP monograph for Diclofenac sodium delayed-release tablets (12), and 900 mL medium was maintained at 37 °C. Tablets were tested in pH 1.2 HCl buffer for 2 h and then the dissolution medium was replaced with pH 6.8 phosphate

buffer. Drug release was determined using a USP-compliant automated dissolution bath, apparatus 2 (paddles method) at 50 rpm. At various time intervals (10, 20, 30, 40, 50, and 60 minutes), samples of 5 ml were withdrawn, and the amount of Diclofenac sodium released was estimated for acid and phosphate buffer, respectively. Drug concentration was calculated and expressed as a cumulative percent of the drug released. The USP specification for the acid phase is not more than 10% diclofenac sodium released in the medium, while for the phosphate buffer phase, it is not less than 80% drug released in the medium after 45 minutes (12).

Stability test

Stability testing was carried out to provide evidence of how the quality of the manufactured tablets may change with time under the influence of environmental factors such as temperature and humidity. The stability study was carried out in a climatic chamber at 25±2°C/60±5% relative humidity for 9 months and 40±2°C/75±5% relative humidity for 6 months. The drug content and dissolution behaviors from diclofenac tablets of enteric coating with 15% weight gain were tested in three-month intervals according to the USP monograph for Diclofenac Sodium delayed-release tablets (12).

RESULTS AND DISCUSSION

In the present work, Diclofenac sodium was formulated as delayed-release tablets using Opadry YS clear utilized at a 4% weight gain in combination with Acryl-EZE, an aqueous acrylic enteric system utilized at 3 different coating weight gains, 7%, 10%, and 15 %.

Weight variation, hardness and friability

The compressed core tablets were characterized, and their properties are summarized in Table 4.

All tablets from each formulation passed the weight variation test, as the % weight variation was within the pharmacopeia limits. The average hardness was maintained at 61.7 N, and no variation in the hardness was found which clearly indicates that the blending was uniform.

The average friability of the formulations was found to be 0.34 % and was within the official requirement (less than 1%).

Table 4. Characteristics of core tablets

Tests	Results
Avg. Weight (mg) (n=20)	231
Min. Weight (mg)	224.5
Max. Weight (mg)	231.3
RSD (%)	*0.37*
Hardness (N) (n=20)	61.7
Thickness (mm) (n=20)	4.1
Friability (%) (n=10)	0.34%

Drug content and Uniformity of Dosage Units

Assay of diclofenac sodium core tablets was done using the HPLC method (12) and the drug content was estimated. The average assay results were within the range of 90% to 110% of the label claim (LC), and the RSD was less than 2% as shown in Table 5.

Table 5. Assay results of diclofenac enteric-coated tablets

Test	Results
Avg. Assay (% of LC)	102.3
RSD (%)	1.6
Uniformity of dosage (%)	105.2 -109

In vitro drug release study

Enteric-coated diclofenac sodium tablets at all coating weight gains passed the acid stage of the dissolution test, with no release from tablets subjected to 2 hours in the acid phase. Greater than 80% (Q+5%) of Diclofenac was released in the pH 6.8 buffer phase, as shown in Table 6 and Figure 1.

Table 6. Dissolution of Enteric Coated Diclofenac tablets in HCl 0.1N and pH 6.8 buffer phase

Test Medium		**HCl 0.1 N**	
Coating Weight Gain (%)	7	10	15
Acid uptake (%)	165.88	166.7	8.27
Release in HCl 0.1N (%)	NA	NA	NA
Release in pH 6.8 buffer phase (%)	69	79	102

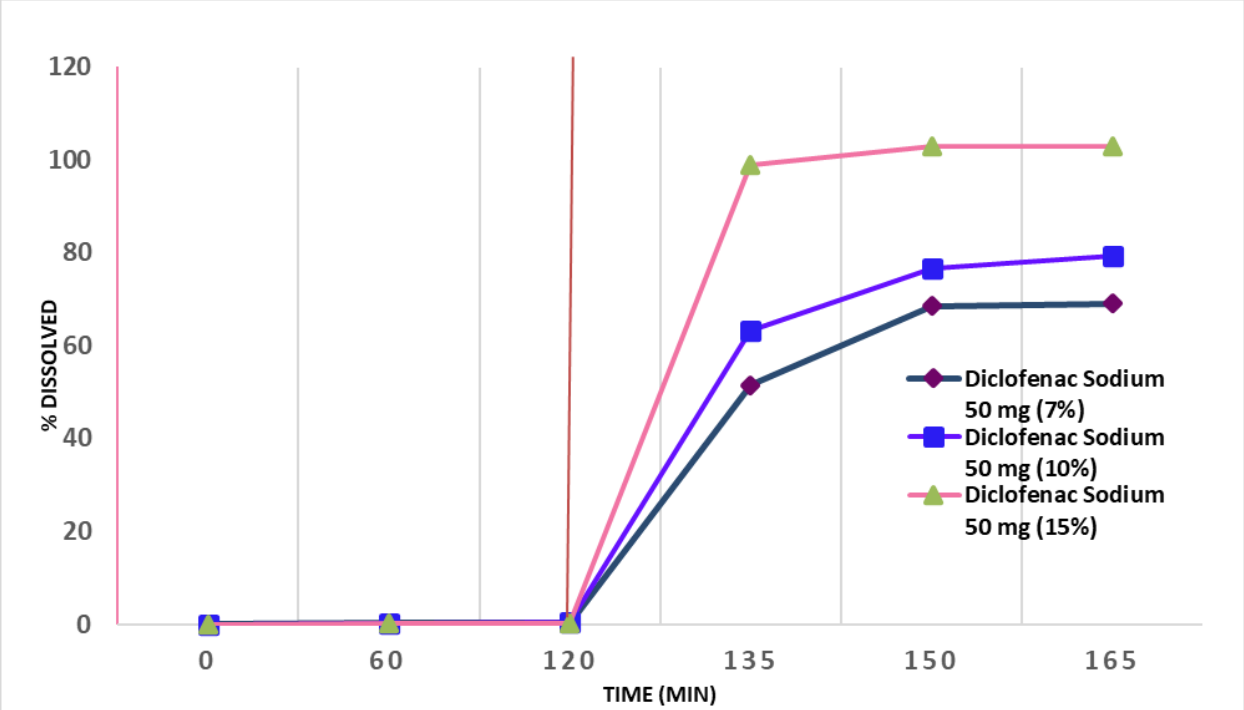

Figure 1. Dissolution of Enteric Coated Diclofenac tablets in HCl 0.1N and pH 6.8 buffer phase

Stability Study

For stability studies, the 15% coating tablets were chosen. The drug content and dissolution behaviors from diclofenac tablets of enteric coating with 15% weight gain were tested in three-month intervals according to the USP monograph for Diclofenac Sodium delayed-release tablets (12). In the lower-percentage coating of Akryl Eze, the proportion of dissolution decreases as a result of the formation of the solvated layer. The results of the stability study are presented in Table 7.

CONCLUSIONS

A delayed-release diclofenac tablet formulation was developed using Opadry YS clear in combination with Acryl-EZE. From early studies results there was a direct correlation between the thickness of the enteric coat and the dissolution data for the release of Diclofenac sodium. The data supports the theory that a thicker enteric coat secures a better dissolution rate of Diclofenac sodium. It is believed that there is a correlation between the acid uptake results and the low-release dissolution data for 7% and 10% enteric-

Table 7. Stability study of Enteric Coated Diclofenac tablets

25±2°C/60±5% RH				
Evaluations made	**At initial (0 month)**	**At the end of 3 months**	**At the end of 6 months**	**At the end of 9 months**
Percentage Drug Content (%)	107.221	107.543	108.365	108.51
In-vitro dissolution study	103.124	102.851	104.627	105.00
40±2°C/75±5% RH				
Percentage Drug Content (%)	107.221	105.237	104.776	
In-vitro dissolution study	103.124	100.478	95.13	

coated Diclofenac sodium, as they show higher acid uptake percentages. Enteric coated Diclofenac tablets coated with 4% sub-coat and 15% enteric coat, meet the USP diclofenac sodium assay criteria.

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