Development of Diclofenac Sodium Delayed Release Tablets USP Opadry® Enteric (94 Series)

The objective of this study was to develop diclofenac sodium delayed release tablets USP using an Opadry® Enteric (94 Series), acrylic-based coating system. Opadry Enteric (94 Series) is a fully formulated delayed release coating system from Colorcon suitable for application by organic or hydro-alcoholic processing techniques. The Opadry Enteric (94 Series) is based on methacrylic acid copolymer (methacrylic acid-methyl methacrylate 1:1 copolymer) with polymer dissolution starting at pH 6.0.[1]

MATERIALS AND METHODS

Core Tablet Manufacture

Tablet Formulation

Diclofenac sodium and all other ingredients listed in Table 1, except sodium starch glycolate and magnesium stearate, were passed through a Quadro Comil U-5 using a 1.2 mm grater screen at an impeller speed of 2500 rpm. The mixture was then blended in a P-K Twin Shell blender for 5 minutes. Next, sodium starch glycolate was added and blending continued for 15 minutes. Finally, magnesium stearate (passed through a 60-mesh/250 micron screen) was introduced to the powder mixture and blended for an additional 3 minutes.

Table 1 – Formulation of 50 mg Diclofenac Sodium Tablets

Ingredients [Manufacturer]	Formula	
	Percent	mg / Tablet
Microcrystalline Cellulose NF [Microcel 102, Blanver]	**45.16**	**103.86**
Co-processed mix of Corn Starch/Pregelatinized Starch [StarCap 1500®, Colorcon]	**30.10**	**69.24**
Diclofenac Sodium USP [Medilom & Co]	**21.74**	**50.00**
Sodium Starch Glycolate NF [Explosol , Blanver]	**2.00**	**4.60**
Magnesium stearate NF [Hyqual, Mallinckrodt]	**1.00**	**2.30**
Total	**100.00**	**230.00**

Tablet Compression

Diclofenac tablets were compressed to a target tablet weight of 230 mg on an instrumented (SMI) Piccola (Riva) 10-station rotary tablet press equipped with 8mm standard, round, concave punch tooling and operated at 30 rpm.

Tablet Coating

Seal-Coating

Diclofenac tablets were seal-coated to a 4% weight gain with Opadry 03K19229 clear (reconstituted at 10% solids in purified water) using a side-vented 15" coating pan (Compulab, Thomas Engineering, USA). The coating process parameters employed in the coating operation are listed in Table 2.

Enteric Coating

Seal-coated diclofenac tablets were coated using Opadry Enteric 94O580000 reconstituted at 10% solids in a hydro-alcoholic solvent system, (88:12, isopropanol: water) to 5, 10, and 15% weight gains. Coating was performed in a Vector LDCS fully-perforated pan coating system (0.5 L pan). The dispersion preparation procedure employed was as outlined in the 'Preparation and Use Guidelines' for Opadry Enteric 94 series.[2] Process parameters employed in the coating operation are listed in Table 2.

Table 2- Coating Process Parameters

Coating Process Parameters		**Seal-Coating (15" Thomas Compu-Lab)**	**Enteric-Coating (0.5 L Vector)**
Tablet Charge	g	1600	600
Inlet Air Temperature	°C	65	40
Product Bed Temperature	°C	45	30
Exhaust Temperature	°C	50	27
Fluid Delivery Rate	g/min	20	14
Pan Speed	rpm	15	25
Air Volume	cfm	170	30
	m^3/hr	289	51
Pattern Air Pressure	psi/bar	25/1.7	10/0.7
Atomization Air Pressure	psi/bar	20/1.4	8/0.6

Tablet Testing

Tablet Physical Properties Testing

The physical properties of the core tablets including thickness, weight, and crushing strength were measured on an Erweka Multicheck Tablet Tester. Tablet friability was determined using a Vankel Vanderkamp Friabilator.

Assay

Drug assay was determined in accordance with the USP monograph for diclofenac sodium delayed release tablets.[3] The USP specification states that the tablets contain not less than 90.0% and not more than 110.0% of the labeled amount of diclofenac sodium.

Uniformity of Dosage Units

Uniformity of dosage units for diclofenac core tablets was carried out in accordance with the USP General Chapter: <905> Uniformity of Dosage Units. A sample of 10 tablets was assayed individually and the assay results were used to calculate the arithmetic mean, relative standard deviation (RSD) and acceptance value (AV). The USP 32 acceptance criteria are met if AV is less than 15.

Drug Release Testing

Dissolution testing was carried out in accordance with the USP monograph for diclofenac sodium delayed release tablets. Drug release was determined using a USP compliant automated dissolution bath, Apparatus 2 (paddles) at 50 rpm. At the end of the acid stage, (2 hours in 900 mL 0.1 N hydrochloric acid), an aliquot was withdrawn and tested for the amount of diclofenac sodium released. Drug release was also determined in a modified test medium (pH 4.5 acetate buffer).[4] The specification for the acid phase is not more than 10% diclofenac sodium released. The acid (0.1 N HCl/ pH 4.5 acetate buffer) was then drained from the vessel, and replaced with pH 6.8 phosphate buffer. Sample aliquots were withdrawn from the phosphate buffer phase at 10, 20, 30, 40, 50, and 60 minutes and analyzed for amount of diclofenac released. The USP specification for the buffer phase is not less than 80% drug released after 45 minutes.

Chromatographic Purity

The test was carried out in accordance with the USP monograph for diclofenac sodium delayed release tablets. The USP specifies a limit of not more than 1.0% of any individual impurity and not more than 1.5% of total impurities found.

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, 0.1 N HCl and pH 4.5 acetate buffer solution in a USP disintegration apparatus at 37 ± 2°C. At the end of this time interval, the tablets were removed from the disintegration bath and inspected for any defects (bloating or swelling). Any excess surface moisture was gently blotted dry using a paper towel, and the tablets reweighed individually. The percent liquid uptake for a tablet was calculated according to Equation 1. Historically, less than 10% liquid uptake has shown to correlate to acceptable enteric protection for tablets.

$$LU\ (\%) = [(T_f - T_i)/T_i] \times 100 \quad \text{..... Equation 1}$$

LU (%): Percent liquid uptake
T_f: Final tablet weight (mg)
T_i: Initial tablet weight (mg)

Disintegration Testing

Diclofenac tablets that were observed to be physically intact following the liquid uptake test in 0.1 N HCl were then reciprocated in the disintegration apparatus using pH 6.8 phosphate buffer maintained at 37 ± 2°C as the immersion liquid. The time taken for all of the tablets to disintegrate completely was noted.

Stability Testing

Enteric coated diclofenac tablets were packaged in 100cc HDPE bottles (Drug Plastics, USA), with and without desiccant, and stored for 6 months at accelerated conditions of 30°C/65%RH and 40°C/75%RH. Stability was monitored via drug release, assay, chromatographic impurities, liquid uptake and disintegration time of enteric coated tablets.

RESULTS AND DISCUSSION

Physical Characterization

The compressed core tablets were characterized and their properties summarized in Table 3.

Table 3- Physical Properties of Diclofenac Core Tablets

Test	Results
Avg. Weight (mg) (n=20)	243.1
Min. Weight (mg)	240.5
Max. Weight (mg)	245.3
RSD (%)	0.57
Crushing Strength (kp) (n=20)	9.6
Tensile Strength (MPa)	1.94
Thickness (mm) (n=20)	4.42
Ejection Force (N)	143.61
Avg. Compression Force (kN)	17.77
Friability (%)	0.30

Assay and Uniformity of Dosage Units

The average assay results of diclofenac core tablets were within the range of 90% to 110% of the label claim (LC), and the RSD was less than 6%. The acceptance value (AV) obtained for core tablets was 11.4 (Table 4a). The assay results of diclofenac enteric coated tablets (Table 4b) were within the range of 90% to 110% of the label claim.

Table 4a- Assay and Uniformity of Dosage Units (Diclofenac Core Tablets)

Test	Results
Avg. Assay (% of LC)	106.6
RSD (%)	2.7
AV	11.4

LC: Label Claim, AV: Acceptance Value

Table 4b: Assay and Uniformity of Dosage Units (Coated Tablets)

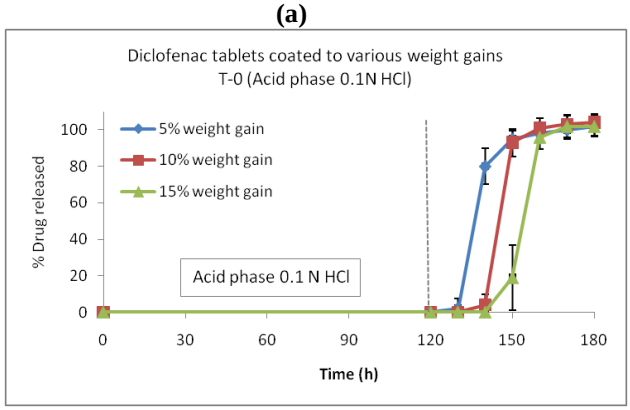
Coating Weight Gain (%)	5	10	15
Assay	107.7	107.5	107.8

Drug Release Testing

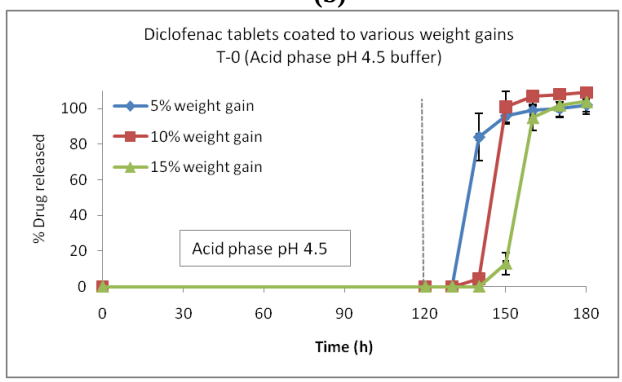
Enteric coated diclofenac tablets at all coating weight gains passed the acid stage of the dissolution test, with no release from tablets subjected to 2 hours in 0.1N HCl or pH 4.5 acetate buffer. Greater than 80% (Q+5%) diclofenac was released in the pH 6.8 buffer phase within 45 minutes (Figure 1). Drug release rates in the buffer phase became slower with the increase in enteric coating weight gain.

Fig. 1: Diclofenac released from enteric coated tablets at 5, 10 and 15% weight gain acid phase (a) 0.1 N HCl (b) pH 4.5 acetate buffer. Buffer phase in both cases is pH 6.8 phosphate buffer. (Vertical line represents a change in dissolution media.)

(a)



(b)



Chromatographic Purity

The total impurity (Table 5) for enteric coated diclofenac tablets (all weight gains) was determined to be 0.06%.

Table 5: Total Chromatographic Impurities of Enteric Coated Diclofenac Tablets

Coating Weight Gain (%)	5	10	15
Total Impurities	0.06	0.06	0.06

Assessment of Liquid Uptake (LU)

At all the coating levels evaluated, tablets demonstrated very low liquid uptake (i.e., less than 5%) both in 0.1 N HCl and pH 4.5 acetate buffer (Table 6).

Table 6: Assessment of Liquid Uptake (LU) in 0.1 N HCl

Test Medium	0.1 N HCl			pH 4.5 acetate buffer		
Coating Weight Gain (%)	5	10	15	5	10	15
LU ± std dev (%)	4.5 ± 0.4	4.4 ± 1.0	3.4 ± 0.4	2.5 ± 0.4	3.3 ± 0.3	2.7 ± 0.1

Disintegration Time

Diclofenac core tablets disintegrated in pH 6.8 phosphate buffer media within 2-8 minutes. Results (Table 7) indicate that diclofenac tablets, enteric coated at higher coating weight gains, had longer disintegration times than those coated at lower levels. The longer disintegration times are attributed to the greater amount of polymer that must be dissolved at higher coating weight gains.

Table 7: Disintegration Time (DT)

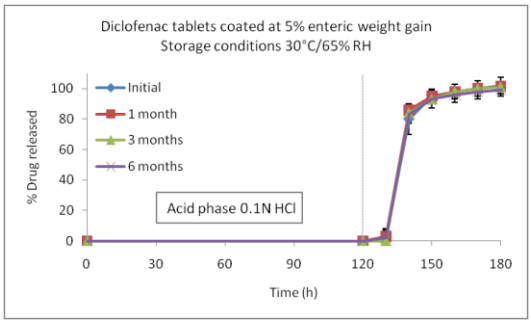
Test Medium	pH 6.8 Phosphate Buffer		
Coating Weight Gain (%)	5	10	15
DT (min)	21- 32	48- 55	58- 60

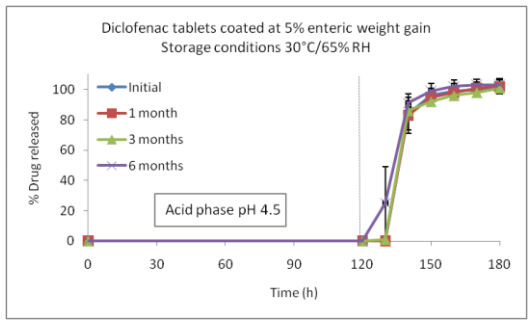
Stability Testing

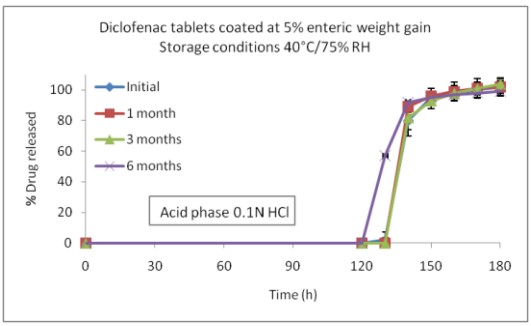
Drug release testing (Figure 2) indicates that the enteric coating (5% wg) continued to provide good protection in acid phase and greater than 80% release in 45 minutes when stored at 6 months 30°C/65%RH or 40°C/75%RH, with or without desiccant. Similar results were obtained for the enteric coated tablets at 10% and 15% weight gain when stored for 6 months at 30°C/65%RH or 40°C/75%RH, with or without desiccant (data not shown).

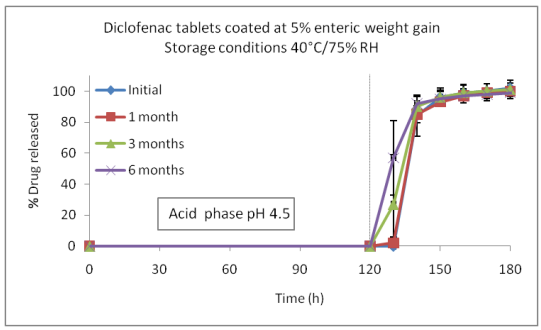
Fig. 2 – Diclofenac Release from Enteric Coated Tablets (5% coating weight gain)

(a) Packaged Without Desiccant

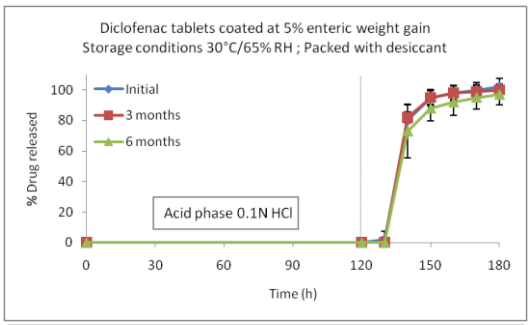


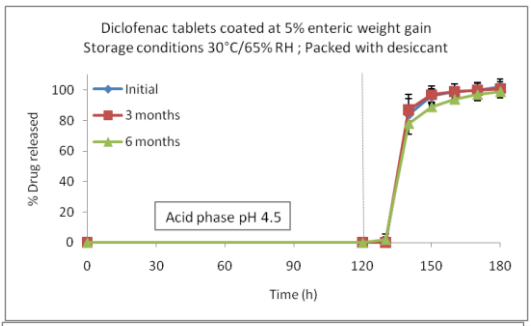


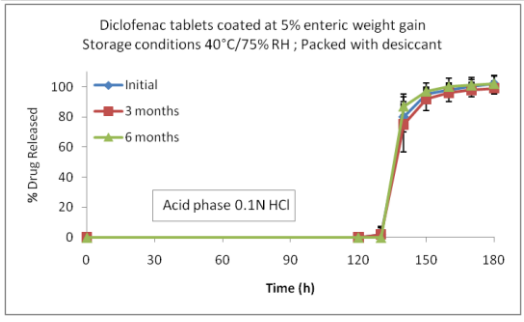


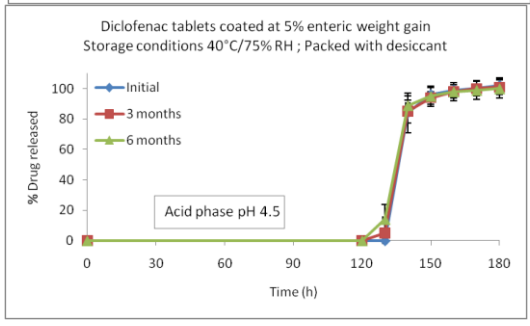


(b) Packaged With Desiccant









Assay of coated tablets stored at 6 months 30°C/65%RH or 40°C/75%RH (Tables 8a and 8b) met the USP requirements (90- 110% of the labeled amount of diclofenac tablets).

Table 8a: Assay of Coated Tablets on Storage for 6M at 30°C/65%RH

Storage Condition		30°C/65%RH					
Packaging		100 cc HDPE Container Without Desiccant			100 cc HDPE Container With Desiccant		
% Weight Gain		5	10	15	5	10	15
Assay							
Stability time point	Initial	107.7	107.5	107.8	107.7	107.5	107.8
	1 month	107.9	108.5	109.6	NA	NA	NA
	2 months	NA	NA	NA	NA	NA	NA
	3 months	107.0	108.1	108.1	107.8	108.1	109.1
	6 months	106.2	105.9	106.7	106.9	106.9	106.5

Table 8b: Assay of Coated Tablets on Storage for 6M 40°C/75%RH

Storage Condition		40°C/75%RH					
Packaging		100 cc HDPE Container Without Desiccant			100 cc HDPE Container With Desiccant		
% Weight Gain		5	10	15	5	10	15
Assay							
Stability time point	Initial	107.7	107.5	107.8	107.7	107.5	107.8
	1 month	108.3	107.3	106.7	NA	NA	NA
	2 months	106.5	106.0	105.6	NA	NA	NA
	3 months	106.3	107.6	106.5	107.1	107.2	105.9
	6 months	105.4	107.1	105.8	107.1	107.3	105.9

Chromatographic impurities (Tables 9a and 9b) were within USP specified limits through 6 months of storage at 30°C/65%RH or 40°C/75%RH.

Table 9a: Total Chromatographic Impurities of Coated Tablets on Storage for 6M at 30°C/65%RH

Storage Condition		30°C/65%RH					
Packaging		100 cc HDPE Container Without Desiccant			100 cc HDPE Container With Desiccant		
% Weight Gain		5	10	15	5	10	15
Total Impurities							
Stability time point	Initial	0.06	0.06	0.06	0.06	0.06	0.06
	1 month	0.18	0.25	0.20	NA	NA	NA
	2 months	NA	NA	NA	NA	NA	NA
	3 months	0.14	0.36	0.62	0.06	0.11	0.12
	6 months	0.20	0.50	0.72	0.53	0.13	0.16

Table 9b: Total Chromatographic Impurities of Coated Tablets on Storage for 6M at 40°C/75%RH

Storage Condition		40°C/75%RH					
Packaging		100 cc HDPE Container Without Desiccant			100 cc HDPE Container With Desiccant		
% Weight Gain		5	10	15	5	10	15
Total Impurities							
Stability time point	Initial	0.06	0.06	0.06	0.06	0.06	0.06
	1 month	0.64	0.62	0.83	NA	NA	NA
	2 months	0.25	0.60	0.73	NA	NA	NA
	3 months	0.25	0.71	0.81	0.11	0.14	0.25
	6 months	0.30	0.91	0.88	0.11	0.18	0.24

The liquid uptake (Tables 10a and 10b), both in 0.1 N HCl and pH 4.5 acetate buffer was lower than 10% through 6 months of storage at 30°C/65%RH or 40°C/75%RH.

Table 10a: Assessment of Liquid Uptake (LU) in 0.1 N HCl

Test Medium		**0.1 N HCl**					
Storage Condition		30°C/65%RH			40°C/75%RH		
% Weight Gain		5	10	15	5	10	15
LU ± std dev (%)							
Stability time point	Initial	4.5 ± 0.4	3.3 ± 0.3	2.7 ± 0.1	4.5 ± 0.4	3.3 ± 0.3	2.7 ± 0.1
	1 month	4.1 ± 0.2	2.8 ± 0.2	2.4 ± 0.5	4.6 ± 0.6	3.0 ± 0.4	2.7 ± 0.4
	2 months	NA	NA	NA	4.8 ± 0.7	2.8 ± 0.3	1.7 ± 0.3
	3 months	5.2 ± 1.3	3.5 ± 1.3	3.3 ± 1.0	4.1 ± 0.5	3.3 ± 0.3	2.2 ± 0.4
	6 months	4.7± 0.5	3.3 ± 0.4	2.8 ± 0.1	4.5 ± 0.4	2.9 ± 0.2	2.4 ± 0.4

Table 10b: Assessment of Liquid Uptake (LU) in pH 4.5 acetate buffer

Test Medium		**pH 4.5 Acetate Buffer**					
Storage Condition		30°C/65%RH			40°C/75%RH		
% Weight Gain		5	10	15	5	10	15
LU ± std dev (%)							
Stability time point	Initial	4.4 ± 1.0	3.4 ± 0.4	2.5 ± 0.4	4.4 ± 1.0	3.4 ± 0.4	2.5 ± 0.4
	1 month	4.9 ± 0.2	3.0 ± 0.2	2.7 ± 0.2	4.7 ± 0.4	3.3 ± 0.5	3.1 ± 0.3
	2 months	NA	NA	NA	5.5 ± 0.6	3.2 ± 0.5	2.5 ± 0.3
	3 months	5.1 ± 0.4	3.9 ± 1.1	2.9 ± 0.3	5.3 ± 0.5	3.4 ± 0.2	2.6 ± 0.1
	6 months	6.0 ± 0.3	5.6 ± 4.5	3.4 ± 0.2	9.3 ± 5.8	4.2 ± 0.4	3.3 ± 0.2

Disintegration times of diclofenac tablets stored at 6 months 30°C/65%RH or 40°C/75%RH are recorded in Table 11.

Table 11: Disintegration Time (DT)

Test medium		**pH 6.8 Phosphate Buffer**					
Storage Condition		30°C/65%RH			40°C/75%RH		
% Weight Gain		5	10	15	5	10	15
DT (minutes)							
Stability time point	Initial	21- 32	48- 55	58- 60	21- 32	48- 55	58- 60
	1 month	13- 22	25- 32	33- 45	15- 19	18- 25	28- 31
	2 months	NA	NA	NA	15- 18	19- 23	28- 31
	3 months	18- 22	30- 32	36- 42	18- 21	34- 37	40- 43
	6 months	17- 19	29- 35	39- 41	17- 20	35- 36	44- 46

CONCLUSIONS

A delayed release diclofenac tablet formulation was developed using Opadry Enteric. Enteric coated tablets met all requirements of the USP monograph for diclofenac sodium delayed release tablets. Enteric coated tablets met the USP specification through 6 months storage at accelerated storage conditions.

REFERENCES

1. Opadry Enteric -Product Information Sheet, Colorcon Technical Literature. http://www.colorcon.com/literature/marketing/mr/Delayed%20Release/Opadry%20Enteric/Chinese/Opadry%20Enteric%20-%20Prod.Info.Sheet-revised.pdf
2. Opadry Enteric -94 Series, Preparation and Use Guidelines, Colorcon Technical Literature. http://www.colorcon.com/literature/marketing/mr/Delayed%20Release/Opadry%20Enteric/Chinese/73AEADAAD4421F01E044001B7878E7B0
3. United States Pharmacopeia 32/National Formulary 27 Online, 2010. http://www.uspnf.com/uspnf/login
4. Miner, P., Katz, P., Chen, Y., Sostek, M., American Journal of Gastroenterology, 98 (12), 2616-2620 (2003).

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