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FORMULATION AND EVALUATION OF DICLOFENAC MATRIX TABLETS CONTAINING A HYDROPHILIC POLYMER, *SIDA ACUTA* GUM

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ABSTRACT

This study was carried out to formulate and evaluate hydrophilic matrix diclofenac tablet produced using *Sida acuta* gum (SAG) isolated from the powdered dried leaves of *Sida acuta*. Diclofenac matrix tablets containing 20-30% SAG, hydroxypropylmethylcellulose (HPMC) or SAG/HPMC, as matrix former were formulated using non-aqueous wet granulation method. The tablets were evaluated based on in vitro dissolution, swelling behavior, tablet hardness and friability, kinetics and mechanism of release. Tablet hardness ranged from 1.17 ± 0.29 to 6.22 ± 2.27 kgf. Tablet friability ranged from 0.17 to 0.95 %. Drug content ranged from 99.10 to 103.45 %. In vitro dissolution analysis showed that only formulations DS 1, DS 3 and DS 6 released < 50 % of diclofenac after 6 hr, while 100 % drug release was achieved in all the formulations from 7 h to > 12 h. The swelling index was in the order; HPMC > HPMC/SAG > SAG. SAG has swelling index that was approximately 25, 36, 50 and 70 % that of HPMC after 1, 3, 7 and 15 hr respectively. The order of release was first order except for DS6 and DS8 were zero order was predominant. The mechanism of release was by super case II transport except for DS 8 and DS 9 matrix tablets that was by anomalous (non – fickian) diffusion. There was no significant change in drug properties ($p \leq 0.05$) after 6 months of storage at ambient temperature. Diclofenac matrix tablet was formulated using SAG as the matrix former.

KEYWORDS: Diclofenac, *Sida acuta* gum, hydrophilic polymer, matrix tablet.

INTRODUCTION

Matrix tablet formulation is one of the easy ways of producing sustained release dosage forms through direct compression of blends of drug, retardant material, and other excipients to form a tablet in which drug is embedded in a matrix core of the retardant. Another method of having matrix tablets is to compress granules from a retardant – drug blends.[1]

There are three different classes of matrix tablets and this is determined by the nature of retardant used. They are insoluble inert or plastic matrix e.g polyethylene, insoluble erodible matrix e.g carnauba wax and the hydrophilic matrix such as carboxymethyl cellulose. Hydrophilic matrix formers, produce gel in situ when in contact with water. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion of the gelled layer. The type of polymer used and the drug: polymer ratio determines the extent to which diffusion or erosion controls release of the drug from the matrix tablet.

Sida acuta Burm. F is a shrub belonging to *Malvaceae* family and it is widely distributed in the subtropical regions where it is found in bushes, in farms and around habitations.[2] *Sida acuta* gum was isolated from the stem of the plant and used to produce sustained release metronidazole tablets.[3] Effects of *Sida acuta* and Corchurus olitorius mucilage on the physicochemical properties of maize and sorghum starches have been studied.[4] *Sida acuta* gum was isolated from the powdered dried leaves of *Sida acuta* plant. The gum produced had physicochemical properties that showed that it could be used as binder, suspending agent and hydrophilic matrix former in pharmaceuticals.[5]

This study was undertaken to formulate hydrophilic matrix tablets of diclofenac using *Sida acuta* gum derived from the leaves of the plant as the matrix former and to evaluate the effect varying the drug: polymer ratio had on the release of drug from the matrix.

MATERIALS AND METHODS

Materials

Isopropyl alcohol, acetone, (Guangxing Guanghua Chemical, China), Potassium dihydrogen orthophosphate, Dipotassium hydrogen phosphate (BDH Chemicals Ltd Poole England), Diclofenac, (Alpha Lab, Germany), hydroxylpropylmethylcellulose, polyvinyl pyrrolidone,

magnesium stearate, sodium hydroxide (Loba Chemie, Mumbia, India), were of analytical grades.

The leaves were collected from *Sida acuta* plants from bushes in the New G.R.A area of Trans – Ekulu, Enugu, Enugu state, Nigeria.

Isolation of *Sida acuta* gum

Sida acuta gum was isolated from the dried powdered leaves of *Sida acuta* following the method by previous researcher.[5]

Formulation of diclofenac matrix tablets

Diclofenac matrix tablets were prepared according to the formula on Table 1 using non – aqueous wet granulation method. Diclofenac powder was mixed thoroughly with the required quantity of *Sida acuta* gum, HPMC or mixture of *Sida acuta* gum and HPMC respectively according to the formula on Table 1. Lactose was added to the drug – polymer mix and it was blended properly. The required quantity of polyvinyl pyrrolidone (PVP) was weighed, dissolved in sufficient quantity of isopropyl alcohol and added to the powder –mix to form a damp mass. This was passed through 1.18 mm sieve. The granules formed were dried for 30 minutes at room temperature in open air and then in tray drier oven for 2 hrs at 40^0C. The dried granules were passed through 710 µm. Magnesium stearate and talc were added to the granules except for formulation DS7 and compressed into tablets with a predetermined force using a CJD 316 sixteen station rotary tablet press with 13 mm punch (Clit Jemkay Engs. Pvt, Ltd. Ahmedabad, India).

Table 1: Composition of diclofenac matrix tablets formulations DS 1 to DS 9

INGREDIENTS	DS 1	DS 2	DS 3	DS 4	DS 5	DS 6	DS 7	DS 8	DS 9
DICLOFENAC (mg)	100	100	100	100	100	100	100	100	100
SIDA ACUTA (mg)	100	100	150	50	75	100	100	0	0
HPMC (mg)	0	0	0	100	75	50	0	100	150
LACTOSE (mg)	260	260	210	210	210	210	260	260	210
TALC (mg)	10	10	10	10	10	10	0	10	10
MAGNESIUM SILICATE (mg)	5	5	5	5	5	5	0	5	5
PVP (mg)	0	25	25	25	25	25	25	25	25
IPA	QS	QS	QS	QS	QS	QS	QS	QS	QS
TOTAL (mg)	500	500	500	500	500	500	500	500	500

Key: HPMC – hydroxypropylmethylcellulose, PVP = polyvinyl pyrrolidone, IPA = isopropyl alcohol, QS – Sufficient quantity.

Evaluation of the Diclofenac Matrix Tablets

The compressed diclofenac matrix tablets were evaluated based on official and unofficial tests as discussed below.

Weight variation: Twenty tablets were selected randomly from respective formulations and weighed individually. The individual weights were compared with the average weight for weight variation.

Thickness: Ten tablets from each formulation were taken randomly and their thickness measured using a digital tablet thickness test apparatus (Veego tablet test apparatus, India).

Hardness: Five tablets were selected randomly from each formulation and hardness was determined using a digital tablet hardness test apparatus (Veego tablet test apparatus, India).

Friability: The friability of the prepared tablets was evaluated as the percentage weight loss of 10 tablets tumbled in a friabilator (Veego friability test apparatus, India) for 4 min at 24 rpm.

Drug content: Drug content of compressed tablets was determined by UV Spectrophotometric method. Ten tablets from each of the diclofenac matrix tablets formulations were accurately weighed and crushed in a mortar with pestle respectively. Quantity of powder that contained equivalent of 100 mg of diclofenac was weighed and dissolved in 100 ml of phosphate buffer pH 6.8. This was filtered through a 0.45-µm filter paper. The filtrate was diluted with phosphate buffer pH 6.8. The drug content was analyzed spectrophotometrically at 271.4 nm.using an UV – VIS spectrophotometer (UV - 1800, Shimadzu Japan). The absorbance value was compared with a reference standard curve of diclofenac.

In vitro dissolution studies of diclofenac matrix tablets: This was carried out using USP XX type 1 (Rotary basket) apparatus. One diclofenac matrix tablet was weighed and placed in the basket of a single unit Copley dissolution test apparatus (Erweka Apparatebau GMBH, Heusengtamm, Germany). The basket was inserted into the dissolution chamber that contained phosphate buffer pH 6.8 maintained at 37 ± 1^0C as the dissolution medium and rotated at a speed of 100 rpm. A 5 ml sample was withdrawn and replaced with 5 ml of fresh pre- heated dissolution medium after 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h. The sample was analysed using UV spectrophotometer 271.4 nm.

Swelling index (SI) of the diclofenac matrix tablets

The method used by previous researchers was used.[6, 7] Tablets were weighed individually along with the Petri dish (W_1), and then 10 ml of phosphate buffer (pH6.8) was added to each Petri dish. After 1 h, the excess amount of phosphate buffer was removed by using tissue paper. The swollen tablets were reweighed (W_2). The process was repeated after 3, 7 and 15 h respectively. Swelling index (S.I) was calculated using equation 3.

$$\text{Swelling index} = \frac{W2-W1}{W1} X\ 100 \quad \text{----------1}$$

Where W2 = final weight of tablet and W1 = initial weight of tablet.

In vitro drug mechanism and kinetics of release

The dissolution kinetics of diclofenac from formulations DS1-DS9 matrix tablets in phosphate buffer solution of pH 6.8 were determined by the application of the Zero Order [8, 9, 10] First Order[8, 9, 10] Higuchi[10, 11, 12] and Hixson – Crowell's Cuberoot Law[13] The mechanism of drug release was obtained by fitting the first 60% drug release data into the Korsmeyer – Peppas model[14, 15] as shown in equation 2 – 7.

Zero Order Model

$C = K_0 t$ …….....…….. (2)

C = % Release, K_0 = Zero Order rate constant expressed in units of concentration/time (t).

First Order Model

$\text{Log}C_r = \text{Log}C_0 - K_1 t/2.303$ ……..…….. (3)

C_r = % Remaining, C_0 = Initial concentration of drug, K_1 = First Order constant, t = Time

Higuchi's Square root Law Model

$Q = K_H t^{½}$ ……..…….... (4)

Q = % Released, K_H = Constant reflecting design variables of the system, t = Time

Hixson – Crowell's Cuberoot Law Model

$[(100 - f)/100]^{1/3} = 1 - K_{HC}t$……..... (5)

f = % Released, K_{HC} = Rate constant, t = Time

Korsmeyer – Peppas Model

$Mt/M\infty = Ktn$……..... (6)

Log Mt/M = log K +n log t …….(7)

Where, *Mt* / *M*∞ is the fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms for cylindrical shaped matrices[14, 15, 16 as given on Table 2.

Table 2: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

Stability Studies

Tablets from the optimized formulations, DS1was kept in airtight containers at room temperature for 6 months. Tablet samples were subjected to assay and *in vitro* dissolution test analysis after 3 and 6 months respectively.

Analysis of Data

Statistical analysis was done using Microsoft Excel and SPSS version 22.0. Data were analysed by one – way ANOVA. Differences between means were assessed by a two – tailed student's t – test. $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Evaluation of diclofenac granules from Formulations DS1 to DS9

Angle of Repose: The results on Table 3 showed that formulations DS1, DS3, DS6 and DS9 had angle of repose values between 25 and 30 which indicated good flow. Formulations DS2, DS4, DS7 and DS8 had values between 30 and 40 which indicated passable flow. Their flow properties can be improved upon by the addition of glidants.

Hausner's Ratio: Formulations DS2, DS3, DS4, DS7, DS8 have Hausner's ratio values below 1.2, which signified good flow. Formulations DS1, DS5, DS6 and DS9 had values between 1.25 and 1.5 which signified that their flow properties can be improved upon by the addition of glidant.

Carr's Compressibility Index: From Table 3, the Carr's Index values for formulations DS2, DS3, DS7 and DS8 were between 5 and 15 which indicated excellent flow for free flowing granules. Formulations DS1, DS4, DS5, DS6 and DS9 had Carr's index values between 15 and 21 which signified passable flow. Their flow can be improved by the addition of glidants.

Table 3: Micromeritics for diclofenac granules for formulations DS1 to DS9

F	ANGLE OF REPOSE ± S.D	BULK DENSITY ± S.D	TAPPED DENSITY ± S.D	HAUSNER RATIO ± S.D	CARR'S INDEX ± S.D
DS1	26.09 ± 1.39	0.41 ± 0.00	0.54 ± 0.01	1.29 ± 0.03	22.75 ± 1.83
DS2	33.82 ± 0.00	0.44 ± 0.02	0.49 ± 0.01	1.13 ± 0.03	11.54 ± 2.14
DS3	27.47 ± 0.00	0.43 ± 0.01	0.46 ± 0.01	1.07 ± 0.04	6.44 ± 3.63
DS4	33.82 ± 0.00	0.32 ± 0.00	0.39 ± 0.01	1.20 ± 0.03	16.75 ± 2.36
DS5	34.22 ± 0.00	0.34 ± 0.01	0.41 ± 0.01	1.21 ± 0.01	17.12 ± 0.99
DS6	29.68 ± 0.00	0.31 ± 0.01	0.38 ± 0.01	1.22 ± 0.03	17.79 ± 2.19
DS7	32.21 ± 0.00	0.48 ± 0.00	0.53 ± 0.00	1.11 ± 0.00	9.52 ± 0.00
DS8	37.6 ± 0.00	0.34 ± 0.01	0.40 ± 0.02	1.16 ± 0.01	13.65 ± 0.55
DS9	27.47 ± 0.00	0.33 ± 0.00	0.41 ± 0.00	1.27 ± 0.02	21.19 ± 1.46

***Key: F** = Formulations.*

Evaluation of diclofenac matrix tablets from Formulations DS1 to DS9

Thickness: The tablet thickness as shown on Table 4, ranged from 3.15 ± 0.05 to 3.71 ± 0.44, while the tablet diameter ranged from 13.00 ± 0.05 to 13.94 ± 0.04.

Hardness: This ranged from 1.17 ± 0.29 to 6.22 ± 2.27 kgf, as shown on Table 4. Hardness values of 4 kgf and above signifies tablets that will withstand the rigors of transportation and further handling. Formulations DS 1, DS 5, DS 6, DS 8 and DS 9 had hardness values that were less than 4 kgf, but because the tablets contained hydrophilic matrix, they swell and form viscous plug which allows the diffusion of drugs out of the matrix without its breakdown.

Friability: According to the results on Table 4, the friability for the matrix tablets formulations ranged from 0.17 to 0.95 %. All the formulations passed the test because they were below 1 %. The tablets will be able to withstand forces of abrasion during further handling and transportation.

Drug content: The percentage drug contents for the formulations ranged from 99.10 to 103.45 %, as shown on Table 4. This falls within the acceptable limits for diclofenac tablets.

Table 4: Tablet Evaluation of formulations DS 1 to DS 9.

F	DS 1	DS 2	DS 3	DS 4	DS 5	DS 6	DS 7	DS 8	DS 9
WEIGHT (g)	0.50 ± 0.01	0.51 ± 0.01	0.51 ± 0.00	0.50 ± 0.01	0.51 ± 0.01	0.50 ± 0.01	0.50 ± 0.00	0.50 ± 0.01	0.50 ± 0.01
HARDNESS (Kgf)	3.67 ± 0.29	4.13 ± 0.71	4.33 ± 0.58	6.22 ± 2.27	2.17 ± 0.29	3.67 ± 0.58	4.50 ± 1.32	1.17 ± 0.29	3.30 ± 0.63
THICKNESS (mm)	3.15 ± 0.05	3.70 ± 0.39	3.15 ± 0.14	3.59 ± 0.05	3.37 ± 0.08	3.21 ± 0.18	3.15 ± 0.18	3.33 ± 0.08	3.71 ± 0.44
DIAMETER (mm)	13.02 ± 0.08	13.43 ± 0.67	13.94 ± 0.04	13.03 ± 0.03	13.32 ± 0.08	13.10 ± 0.10	13.00 ± 0.05	13.05 ± 0.05	13.08 ± 0.13
FRIABILITY (%)	0.85	0.48	0.80	0.34	0.95	0.41	0.70	0.14	0.25
DRUG CONTENT	99.80	103.45	101.20	99.10	103.15	100.75	99.60	99.65	100.10

***Key: F** = Formulations.*

In vitro dissolution test: The in vitro dissolution test results as shown in Figure 1, indicated that the time for 50 % (t_{50}) of diclofenac to be released from the matrix tablets was 2 hr (DS 7, DS 8), 2 – 3 hr (DS 9), 3 hr (DS 4), 4 hr (DS 5), 4 – 5 hr (DS 2), 7 hr (DS 1), 8 hr (DS 3) and 9 – 10 hr (DS 6) respectively. T_{90} was 4 – 5 hr (DS 7), 6 – 7 hr (DS 9), 7 hr (DS 2, DS 4), 11 – 12 hr (DS 8), 12 hr (DS 5) and > 12 hr (DS 1, DS 3 and DS 6) respectively. T_{100} was 7 hr (DS 2), 9 hr (DS 9), 11 hr (DS 4), 12 hr (DS 7) and > 12 hr (DS 1, DS 3, DS 5 and DS 6) respectively.

This showed that only formulations DS 1, DS 3 and DS 6 still had up to 50 % of their drug content after more than 6 hr.

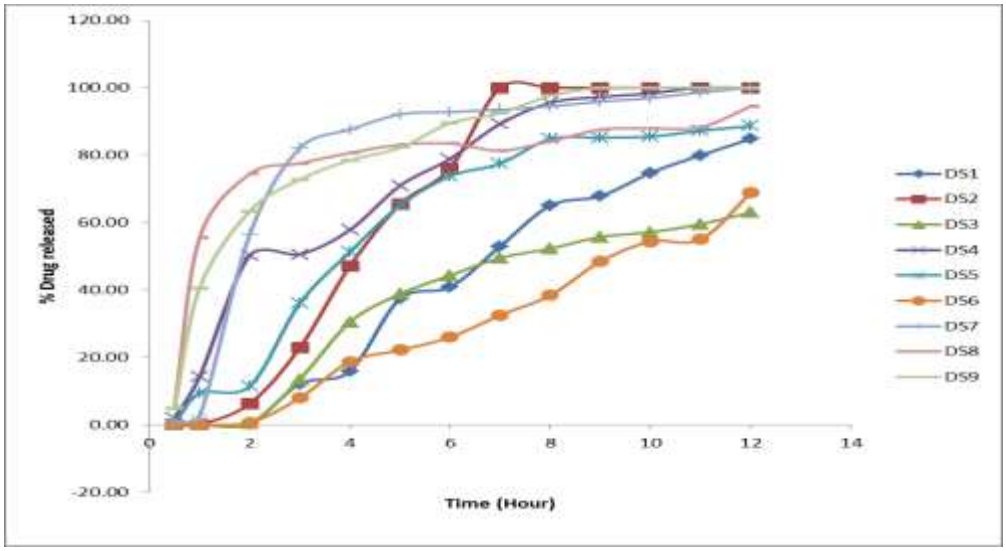

Fig. 1: In vitro % drug release profile of diclofenac from formulations DS 1 – DS 9 matrix tablets.

Key: DS1= SAG (20%), PVP (()%), DS2 = SAG (20%), DS3 = SAG (30%), DS4 = SAG (10%), HPMC (20%), DS5 = SAG (15%), HPMC (15%), DS6 = SAG (20%), HPMC (10%), DS7 (20%), Talc (0%), Mg. Stearate (0%), DS8 = HPMC (20%), DS9 = HPMC (30%).

Swelling index diclofenac matrix tablets

From Figure 2, it shows that Formulations DS1, DS2, DS3 and DS7 that contained only *Sida acuta* gum as polymer did not swell as fast as those that contained only HPMC or combination of HPMC and *Sida acuta* gum as polymers. After 1, 3, 7 and 15 hr, their rate of swelling were approximately 25, 36, 50 and 70 % that of HPMC. Formulations that contained combinations of *Sida acuta* gum and HPMC (DS4, DS5 and DS6), showed swelling rate that were better than that of *Sida acuta* gum alone but less than that of HPMC alone.

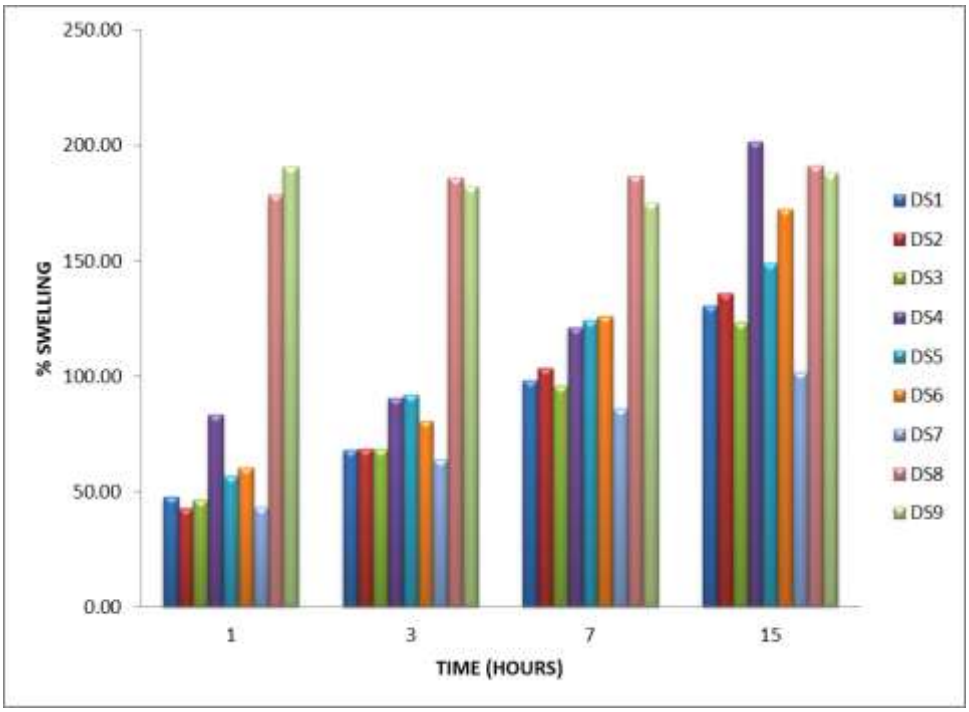

Fig. 2: Swelling behavior of diclofenac matrix tablets of for formulations DS1 to DS9.

Key: DS1= SAG (20%), PVP (()%), DS2 = SAG (20%), DS3 = SAG (30%), DS4 = SAG (10%), HPMC (20%), DS5 = SAG (15%), HPMC (15%), DS6 = SAG (20%), HPMC (10%), DS7 (20%), Talc (0%), Mg. Stearate (0%), DS8 = HPMC (20%), DS9 = HPMC (30%).

In vitro mechanism and kinetics of release

The first order release model was the predominant kinetics of release for formulations DS1, DS2, DS3, DS5, DS7 and DS9, though zero order and Hixson – Crowell model still contributed. Zero order was the predominant release model for formulations DS6 and DS8.

Hixson - Crowell model was the prevalent kinetics of release for formulation DS4 though first order and Higuchi also played some role.

The mechanism of release using the n – value from Korsmeyer – Peppas model was by super case II transport for formulations DS 1 to DS 7, while anomalous (non – fickian) diffusion was the mechanism of release of diclofenac from formulations DS 8 and DS 9 matrix tablets.

Table 5: Kinetics of release for the diclofenac matrix tablets formulations DS1 to DS9

KINETIC MODELS		DS1	DS2	DS3	DS4	DS5	DS6	DS7	DS8	DS9
ZERO ORDER	K	7.196	10.38	5.953	10.57	9.194	5.095	11.22	10.32	11.38
	R^2	0.951	0.878	0.915	0.738	0.841	0.952	0.368	0.85	0.223
FIRST ORDER	K_1	-0.17	-0.27	-0.09	-0.42	-0.21	-0.09	-0.36	-0.16	-0.43
	R^2	0.961	0.924	0.955	0.946	0.962	0.938	0.929	0.789	0.954
HIGUCHI SQUARE ROOT LAW	K_{HC}	19.87	29.51	16.84	30.94	26.54	13.99	33.31	31.48	33.55
	R^2	0.737	0.791	0.806	0.927	0.868	0.719	0.761	0.461	0.839
HIXSON - CROWELL CUBEROOT	K	-0.034	-0.095	-0.025	-0.079	-0.049	-0.021	-0.081	-0.059	-0.093
	R^2	0.925	0.842	0.945	0.967	0.936	0.91	0.845	0.114	0.946
KORSMEYER PEPPAS	K	0.003	0.005	0.005	0.110	0.030	0.004	0.058	0.281	0.224
	R^2	0.914	0.892	0.888	0.855	0.815	0.94	0.782	0.604	0.74
	N	2.561	2.507	2.491	1.047	1.691	2.397	1.414	0.611	0.731

Stability of diclofenac matrix tablets

Results of stability testing will be satisfactory if they show no change in physical properties like colour and appearance and the in vitro dissolution test and assay of tablets results are within the acceptable limits.[17]

As shown on Table 6, the result of analysis done on diclofenac matrix tablets from formulation D1 after 3 and 6 months did not show any significant difference ($p \leq 0.05$) from that done on the first day of analysis.

Table 6: Tablet evaluation for diclofenac tablets after storage for 6 months

FORMULATION	DICLOFENAC (DS1)		
TIME (MONTHS)	0	3	6
HARDNESS (kgf)	3.67 ± 0.29	3.85 ± 0.18	4.00 ± 0.42
FRIABILITY (%)	0.85	0.82	0.9
DRUG CONTENT (%)	99.8	99.7	99.7

CONCLUSION

Sida acuta gum was used as a hydrophilic matrix polymer in the formulation of diclofenac matrix tablets. It was better than hydroxypropylmethylcellulose as a hydrophilic polymer in the retardation of release of diclofenac from the matrix tablets.

Stability studies confirmed that the drug release profiles were not affected by storage.

REFERENCES

1. Lordi NG. Sustained release dosage forms. In: Lachman L and Lieberman HA (eds.). The Theory and Practice of Industrial Pharmacy, New Delhi; CBS Publishers & Distributors PVT. Ltd, 2009; 430-456.
2. Karou SD, Nadembega WMC, Ilboudo DP, Ouermi D, Gbeassor M, De Souza C, Simpore J. (Sida acuta Burm. f.: a medicinal plant with numerous Potencies. African). Journal of Biotechnology, 2007; 6(25): 2953-9.
3. Jackson C, Akpabio E, Agboke A. (Isolation, Characterization and Formulation Properties of a New Plant Gum obtained from Sida acuta). African Journal of Pharmaceutical Sciences and Pharmacy, 2011; 2(1): 48-57.
4. Oladipo FY, Nwokocha LM. (Effect of Sida acuta and Corchorus olitorius Mucilages on the Physicochemical Properties of Maize and Sorghum Starches). Asian Journal of Applied Sciences, 2011; 4(5): 514-25.
5. Okafo SE, Chukwu A. (Studies on *Sida acuta* Hydrogel I: Processing and Physicochemical Properties of the Derived Hydrogel Obtained From South East Nigeria). Int J Pharm Pharm Sci., 2017; 9(6): 5-11.
6. Pandey S, Shah RR, Gupta A, Arul B. (Design and Evaluation of Buccoadhesive Controlled Release Formulations of Prochlorperazine Maleate). Int J Pharm Pharm Sci., 2016; 8(1): 375-9.
7. Desai KG, Kumar TM.. (Preparation and evaluation of a novel buccal adhesive system). AAPS PharmSciTech, 2004; 5: 1-9.
8. Shoaib HM, Tazeen J, Merchant HA, Yousuf RI. (Evaluation of release kinetics from ibuprofen matrix tablets using HPMC). Pak. J. Pharm. Sci, 2006; 19(2): 119 –124.
9. Merchant HA, Shoaib HM, Tazeem J, Yousuf RI. (Once – daily tablet formulation and in vitro release evaluation of cefpodoxime using hydroxypropyl methylcellulose: a technical note). AAPS PharmSciTech, 2006; 7(3): Article 78.DOI: 10.1208/pt070378.

10. Abdelkader H, Abdalla OY, Salem H. (Formulation of controlled – release baclofen matrix tablets: influence of some hydrophilic polymers on the release rate and in vitro evaluation). AAPSPharmSciTech, 2007; 8(4): Article 100. DOI: 10.1208/pt0804100.
11. Higuchi T. (Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices). J. Pharm. Sci., 1963; 52: 1145–9.
12. Desai SJ, Singh P, Simonelli AP. Higuchi WI. (Investigation of factors influencing release of solid drug dispersed in wax matrices III. Quantitative studies involving polyethylene plastic matrix). J. Pharm. Sci., 1966; 55: 1230–4.
13. Hixson AW, Crowell JH. (Dependence of reaction velocity upon surface and agitation). Ind. Eng. Chem., 1931; 23: 923–31.
14. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA (Mechanisms of solute release from porous hydrophilic polymers). Int. J. Pharm, 1983; 15: 25-35.
15. Siepmann J, Peppas NA. (Modeling of drug release from delivery systems based on Hydroxypropylmethylcellulose (HPMC)). Adv. Drug Deliv. Rev., 2001; 48: 139–57.
16. Onyechi JO, Okafo SE. (Evaluation of carnauba wax in sustained release Diclofenac sodium tablet formulation). *J. Chem. Pharm. Res.*, 2016; 8(3): 714-21.
17. ICH Guidelines, Stability testing of new drug substances and products, Q1A(R2) Step 4 version, Available at: http://www.ich.org/cache/compo/363-272-1.