Formulation and Evaluation of Naproxen Tablets Produced using a Natural Binder

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ABSTRACT

Sida acuta gum (SAG) is derived from the powdered dried leaves of the plant, *Sida acuta* burm. F (fam: Malvaceae).This study was conducted to evaluate naproxen tablets formulated using SAG as binder.SAG was isolated by maceration of the powdered dried leaves of *Sida acuta* and the subsequent precipitation of the formed mucilage with isopropyl alcohol. The precipitated gum was dried in an oven at 40 ^{0}C and stored in an airtight container. Tablets of naproxen were prepared by wet granulation method using 0.5, 1.0, 1.5, 2.0%of SAG (N1, N2, N3, N4 respectively), 1.5, 20% of acacia (N5,N6) and 1.5, 2.0% of sodium carboxymethylcellulose(N7, N8) as binders. Formulation N9 did not contain any binder. The tablets were evaluated for hardness, friability, disintegration time, *in vitro* dissolution and drug content. Tablet hardness ranged from 0.5 ± 0.00 (N9) to 4.00 ± 0.30 kgf (N3). Friability ranged from 0.13 (N7) to 2.19 % (N9). Disintegration time ranged from 0.17 ± 0.04 (N5) to 96 67 ± 5.77 min (N4). The percentage drug released after 45 min, from all the formulations was 100 % except for N3 (21.59 %), N4 (20.20 %), N7 (23.04 %) and N8 (19.57 %). Naproxen tablets were successfully formulated using SAG as binder.Tablet disintegration time increased with increased binder concentration for all the formulations.

Keywords: *Sida acuta* gum, Naproxen, Binder, Tablets, Disintegration time

INTRODUCTION

Gums are amorphous translucent substances that are insoluble in alcohol and most organic solvents but soluble in water to give a viscous, sticky solution, while some form a jelly – like mass (Choudhary and Pawar, 2014). Gums are divided into natural, semi - synthetic and synthetic gums. Natural gums are obtained from plants (e.g. starch, acacia, and cashew gum), animals (e.g. gelatin, chitosan), marine algae and sea weeds (e.g. alginic acid) and microorganisms (e.g. xanthan gum) (Evans, 2004).Natural gums have the advantages of being safe, biocompatible, biodegradable, affordable and locally available (Girish et al, 2009; Deogade et al, 2012; Reddy and Manjunath, 2013).Natural gums are used as binders in tablet formulations. They are also used as disintegrants, suspending agents and matrix polymer. Binders are excipients used to glue or hold powders together to form granules. They **e**nsure that granules and tablets are formed with the required mechanical strength. There are many natural binders and they include starch mucilage (Musa et al, 2008; Chalapathi et al, 2010; Bayor et al, 2013), gelatin solution, acacia, tragacanth gum, *Albizia zygia*gum (Odeku, 2005),Grewia gum (Okafor and Chukwu, 2003), *Mangifera indica* gum (Sivakumar et al, 2010) *Ocimum tenuiflorum* Linn. seed mucilage (Kamble, 2012) and okro gum (Hussain et al, 2017**),** Linseed mucilage **(**Alaa and Elnazeer, 2019). Some natural gums such as starch are modified by gelatinization, acetylation and acid modification and used as binders (Oluyemisi and Abioye, 2017). Binders are incorporated either as dry powder or as solution during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets. As dry powder, they are mixed with other ingredient(s) before wet granulation or in dry granulation (roller compaction, slugging).Solution binders are dissolved or dispersed in the granulating fluid and then incorporated as a solution or dispersion. Water is the most common granulating fluid, but sometimes it is used in a co-solvent system with, e.g. ethanol. Naproxen is a non-steroidal anti-inflammatory drug (NSAID). It is used in the treatment of inflammation and pain associated with arthritis. It is absorbed very fast from the gastrointestinal tract following oral administration. It has a half life of about 12 h and an average oral bioavailability of 95% from tablet relative to oral solution (Reddy et al, 2012).

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Sida acuta gum is produced by the precipitation of the filtrate that results from the maceration of powdered dried leaves of *Sida acuta* in distilled water using isopropyl alcohol (Okafo and Chukwu, 2017a). *Sida acuta* gum has been used as hydrophilic polymer matrix for sustained release, mucoadhesive and floating tablet formulations (Okafo and Chukwu, 2017b; Okafo et al, 2017; Okafo et al, 2019).

This study was conducted to evaluate the use of *Sida acuta* gum as binder in the formulation of naproxen tablets.

MATERIAL AND METHODS

Materials

Isopropyl alcohol, acetone (Guangxing Guanghua Chemical, China), Potassium dihydrogen orthophosphate, Dipotassium hydrogen phosphate (BDH Chemicals Ltd Poole England), naproxen (Divi's Laboratories Limited, India) was received as a gift from Swiss Pharma Nigeria Limited, Lagos, acacia (T. Baker, U.S.A), sodium carboxymethylcellulose (Titan Laboratories, India), magnesium stearate, sodium hydroxide (Loba Chemie, Mumbia, India) and other laboratory reagents were of analytical grades.

Sida acuta leaves were collected from plants in New G.R.A, Trans – Ekulu, Enugu, Enugu state, Nigeria.

Preparation of naproxen tablets using *Sida acuta* gum, acacia or NaCMC as binder

Tablets of naproxen were prepared using wet granulation method according to the formula on Table 1. *Sida acuta* gum, acacia or sodium carboxymethylcellulose were used as binders in concentrations of 0.5, 1, 1.5 and 2 % w/v to produce granules for formulations N1 to N9. Naproxen powder, lactose and corn starch were mixed thoroughly. The respective binder powder was converted to binder solution by the addition of little water, was added to the powder – mix and blended thoroughly to form a wet mass. The wet mass was passed through 1.18 mm sieve, and the wet granules formed were dried in the oven at 50 ^{0}C for 2 h. The dried granules were passed through 710 µm sieve. Magnesium stearate and talc were mixed the dried granules and compressed into the respective tablets at the predetermined force using a CJD 316 sixteen station rotary tablet press with 13 mm punches (Clit Jemkay Engs. Pvt, Ltd. Ahmedabad, India).

Table 1: Composition of naproxen tablets formulated with different concentrations of *Sida acuta* gum, acacia or NaCMC as binder

Ingredients	N 1	N 2	N 3	N 4	N 5	N 6	N 7	N 8	N 9
Naproxen (mg)	250.00	250.00	250.00	250.00	250.00	250.00	250.00	250.00	250.00
Sida acuta (mg)	2.50	5.00	7.50	10.00	-	-	-	-	-
Acacia(mg)	-	-	-	-	7.50	10.00	-	-	-
NaCMC (mg)	-	-	-	-	-	-	7.5.0	10.00	-
Corn starch (mg)	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00
Lactose (mg)	216.25	213.75	211.25	208.75	211.25	208.75	211.25	208.75	218.75
Talc (mg)	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Mgst (mg)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Total (Mg)	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00	500.00

Key: NaCMC = sodium carboxymethylcellulose, MgSt = Magnesium stearate

Evaluation of Granules

The Hausner's ratio, Carr's index and angle of repose values of granules were determined.

Evaluation of Tablets

The compressed tablets were evaluated for weight variation, hardness, friability, disintegration time, drug content and *in vitro* dissolution.

Tablets weight variation

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

Tablet hardness

Tablet hardness was determined by inserting individually five tablets selected at random from each of the naproxen tablet formulations into a model VDIGITAB HI, Veego digital tablets hardness test apparatus (Veego Instruments Corporation, Mumbai, India).The hardness value displayed for each of the tablets was recorded.

Tablet friability

Ten tablets were weighed and tumbled in a friabilator (Veego friability test apparatus, India) for 4 min at 25 rpm, after which they were de-dusted and re-weighed. Friability was determined using equation

$$Friability = \frac{(Initial\ weight - final\ weight)}{Initial\ weight}\ X\ 100\% \text{ ----------.1}$$

Tablet disintegration time

Six tablets selected at random from each of the naproxen tablet formulations were used for disintegration test. The mean disintegration value obtained for the six tablets was recorded.

Drug content of tablets

Ten tablets from each formulation were accurately weighed and crushed in a mortar with pestle respectively. An equivalent of 100 mg of naproxen was weighed from the ground tablets and dissolved in 100 ml of phosphate buffer (pH 7.4). A 0.45-µm filter paper was used to filter it; the filtrate was diluted with phosphate buffer (pH 7.4) and analyzed using a UV – VIS spectrophotometer (UV - 1800, Shimadzu Japan) at 230.4 nm wavelength. The naproxen content of each tablet formulation was determined by matching the obtained absorbance value with a reference standard curve of naproxen.

***In vitro* dissolution studies**

A tablet from each of the naproxen formulations was weighed and inserted in the basket of a single unit Copley dissolution test apparatus (Erweka Apparatebau GMBH, Heusengtamm, Germany) which was rotated at a speed of 100 rpm. The dissolution medium used was phosphate buffer (pH 7.4) and it was maintained at 37 ± 1^0C. A 5 ml sample was withdrawn and replaced with 5 ml of fresh pre- heated dissolution medium after 10, 20, 30, 45 and 60 min. A UV spectrophotometer set at 230.4nm wavelength, was used to determine absorbance for the samples. This test was repeated twice for all the tablet formulations.

Analysis of Data

Data were analyzed statistically using Microsoft Excel and SPSS version 21.0 (IBM Corp., Armonk, New York, 2012). They were analyzed by one – way ANOVA. The 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 naproxen granules formulated using *Sida acuta* gum, acacia or NaCMC as binder. The result on Table 2 shows that granules from all the formulations produced using *Sida acuta* gum, acacia or NaCMC as binder had angles of repose that indicated passable to relatively good flow. Those with passable flow may be improved by the addition of glidant such as talc. The Hausner ratio value for granules from the different formulations was less than 1.25 and that showed good flow. Also, the Carr's index value was less than 15 for granules from all the formulations and this signified excellent flow property.

Table 2: Powder Characterizations for naproxen granules produced using *Sida acuta* gum, acacia or NaCMC as binder

Formulation	Angle of Repose	Bulk Density	Tapped Density	Hausner Ratio	Carr's Index
N1	25.63 ± 0.93	0.43 ± 0.03	0.48 ± 0.02	1.12 ± 0.07	10.50 ± 5.35
N2	29.68 ± 0.74	0.43 ± 0.01	0.46 ± 0.02	1.08 ± 0.03	7.28 ± 2.50
N3	30.96 ± 0.00	0.41 ± 0.02	0.44 ± 0.02	1.07 ± 0.00	6.17 ± 0.26
N4	30.96 ± 0.00	0.42 ± 0.02	0.44 ±0.01	1.05 ± 0.03	4.83 ± 2.97
N5	28.65 ± 1.11	0.44 ± 0.01	0.49 ± 0.01	1.11 ± 0.03	10.25 ± 2.18
N6	29.95 ± 1.76	0.43 ± 0.03	0.46 ±0.02	1.07 ± 0.02	6.31 ± 1.73
N7	27.92 ± 0.00	0.44 ± 0.02	0.47 ± 0.01	1.06 ± 0.02	5.81 ± 2.19
N8	31.79 ± 0.83	0.47 ± 0.01	0.49 ± 0.00	1.03 ± 0.01	3.14 ± 1.31
N9	32.73 ± 1.68	0.43 ± 0.00	0.49 ± 0.01	1.13 ± 0.03	11.59 ± 2.51

Key: SAG = *Sida acuta* gum
N1 = SAG (0.5%), N2 = SAG (1.0%), N3 = (1.5%), N4 = (2.0%), N5 = acacia (1.5%), N6 = acacia (2.0%), N7 = NaCMC (1.5%), N8 = NaCMC (2.0%), N9 = 0% binder

Evaluation of naproxen tablets formulated using *Sida acuta* gum acacia or NaCMC as binder

Hardness

The hardness of naproxen tablets formulated using *Sida acuta* gum, acacia or NaCMC as binder is shown on Table 3. This showed that naproxen tablets formulated with *Sida acuta* gum (0.5% w/w), acacia (1.5 and 2.0 % w/w) or NaCMC (1.5%w/w) failed the hardness test (< 4 kgf). Naproxen tablets formulated using *Sida acuta* gum (1.0 to 2.0%w/w)

or NaCMC (2.0%w/w) as binder passed the hardness test (≥ 4 kgf). These tablets should be able to withstand the stress of further processing, handling and transportation. The result shows that *Sida acuta* gum and NaCMC have higher binding capacity than acacia at equivalent binder concentration. Formulation N9, which did not contain any binder, had the least hardness value (0.5 kgf). It showed that there was very little cohesive force between the particles. The hardness values of the tablets were significantly affected by the type and concentration of binder used during formulation ($p < 0.05$).

Tablet Friability

The friability of naproxen tablets formulated using different concentrations of *Sida acuta* gum, acacia or NaCMC as binder (N1 to N9) is shown on Table 3. The friability of the naproxen tablets from all the formulations were below 1 % except formulation N9 tablets that contained no binder. This indicates that tablets from all the formulations except N9 could withstand abrasion during further handling and transportation. The absence of binder in formulation N9 may have resulted in low cohesive force between their particles which may explain their high friability value. As the binder concentration increases, the friability was found to decrease for all the formulations.

Weight variation

As shown on Table 3, the % weight deviation for Formulations N1 to N9 tablets ranged from 0.00 to 4.08. They all showed a deviation of less than 5 % and were within the accepted limit. Variation in tablet weight could result from poor flow of granules, difference in granules size arising from improper sieving, presence of very fine granules, improper setting of machine and improper flow rate.

Disintegration time

The result on Table 3 shows that the disintegration time for tablets formulated with different concentrations of *Sida acuta* gum increased (0.85± 0.06 to 96.67 ± 5.77 min) as the concentration of the binder (0.5 to 2 %) increased. When used at the same binder concentration (e.g. 2 %), the disintegration time for tablets formulated with *Sida acuta* as binder (96.67 ± 5.77 min) was more than that formulated with NaCMC (36.33 ± 1.15 min) and acacia (1.21 ± 0.69 min). The disintegration time of the tablet formulations was significantly affected by the type and concentration of binder used during formulation ($p < 0.05$). The binders when ranked according to the increasing order of disintegration time will be acacia <NaCMC<*Sida acuta* gum. This shows that to achieve a given disintegration time, lesser quantity of *Sida acuta* gum would be used compared to the other binders.

Drug content

The drug content of the naproxen tablets formulated with different concentrations of *Sida acuta* gum, acacia or NaCMC as binder (N1to N9) ranged from 98.3 to 103.7 %. This is an indication of proper powder mixing and good powder or granule flow from the hopper to the die of the tableting machine.

Tablet thickness

The thickness of naproxen tablets from the various formulations ranged from 3.31 to 3.83 mm. They were found to be within limit of deviation from average value (not more than 5%).

Table 3: Evaluation of naproxen tablets formulated using different concentrations of *Sida acuta* gum, acacia or NaCMC as binder

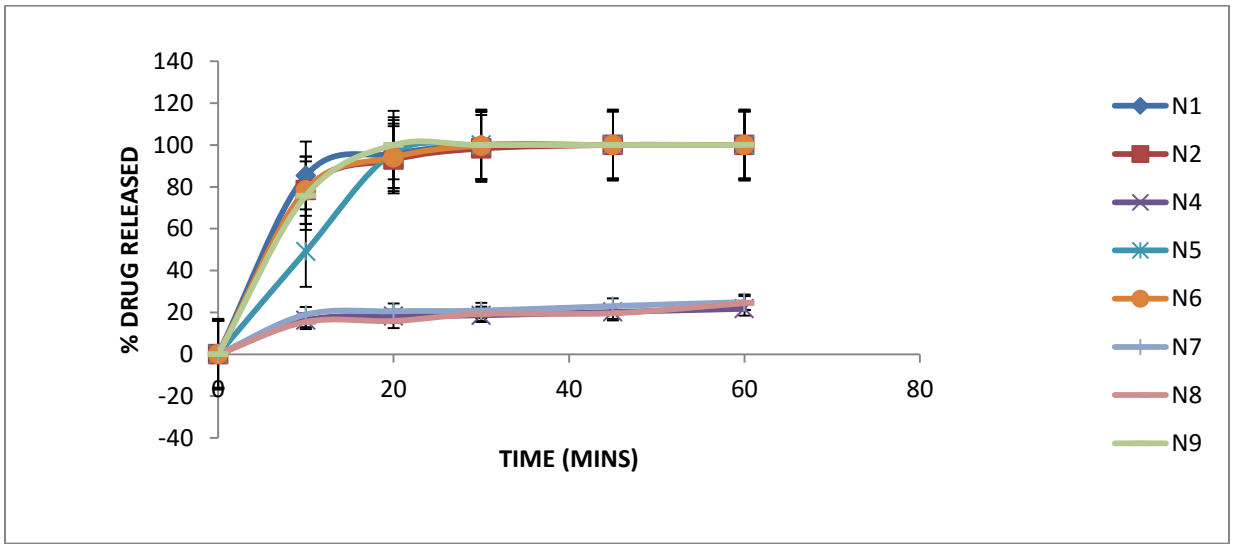
F	N 1	N2	N 3	N 4	N 5	N 6	N 7	N 8	N 9
Weight (g)	0.48 ± 0.01	0.49 ± 0.01	0.50 ± 0.01	0.50 ± 0.01	0.51 ± 0.03	0.49 ± 0.01	0.50 ± 0.02	0.48 ± 0.01	0.49 ± 0.01
Hardness (Kgf)	3.0 ± 0.50	4.0 ± 0.20	4.0 ± 0.30	4.0 ± 0.00	3.0 ± 0.80	3.0 ± 0.00	3.0 ± 0.00	4.0 ± 0.00	0.5 ± 0.00
Thickness (mm)	3.52 ± 0.09	3.41 ± 0.16	3.31 ± 0.16	3.83 ± 0.72	3.47 ± 0.08	3.49 ± 0.15	3.40 ± 0.17	3.47 ± 0.09	3.58 ± 0.08
Diameter (mm)	13.25 ± 0.13	13.28 ± 0.05	13.07 ± 0.10	13.17 ± 0.07	13.08 ± 0.02	13.13 ± 0.04	13.30 ± 0.05	13.03 ± 0.04	13.07 ± 0.09
Friability (%)	0.30	0.29	0.24	0.17	0.53	0.35	0.18	0.13	2.19
DT (min)	0.85 ± 0.06	8.78 ± 3.02	65.00 ± 5.00	96.67 ± 5.77	0.17 ± 0.04	1.21 ± 0.69	30.00 ± 2.00	36.33 ± 1.15	1.12 ± 0.25
DC (%)	98.30	100.50	99.20	103.70	101.40	99.75	99.45	98.80	100.30

Key: F = formulations, DT = disintegration time, DC = drug content, SAG = *Sida acuta* gum
N1 = SAG (0.5%), N2 = SAG (1.0%), N3 = (1.5%), N4 = (2.0%), N5 = acacia (1.5%), N6 = acacia (2.0%), N7 = NaCMC (1.5%), N8 = NaCMC (2.0%), N9 = 0% binder

In vitro drug release from naproxen tablets formulated using _Sida acuta_ gum acacia or NaCMC as binder

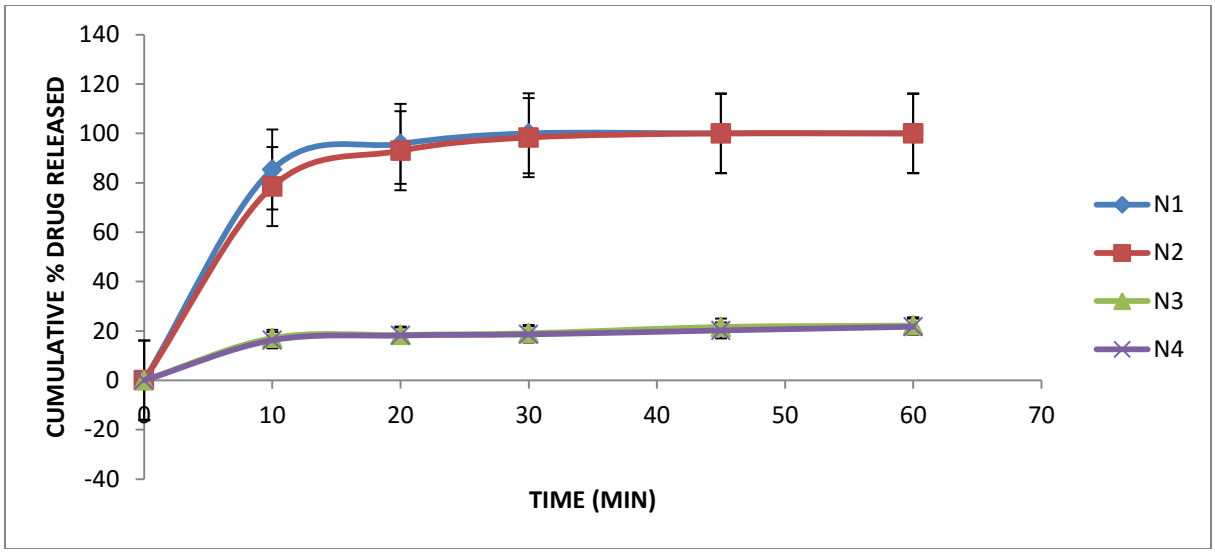
From Figures 1 to 4, it was shown that after 45 min, naproxen released from all the formulated tablets was 100 % except for tablets formulated using 1.5 and 2.0% of *Sida acuta* gum (N3 and N4) and NaCMC (N7 and N8). Therefore, all but for formulations N3, N4, N7 and N8 passed the dissolution test.

Figures 1 and 2 showed that as the binder concentration in the formulation increased, N1 (0.5 %), N2 (1%), N3 (1.5 %) and N4 (2 %), the percentage drug released after 10 min decreased (85.37, 78.42,17.10 and 16.24 % respectively). As shown in Figures 3 and 4, at equal binder concentration (e.g. 2 %), the percentage drug released after 60 minutes was highest for acacia (100 %), followed by sodium carboxymethylcellulose (24.42 %) and least for *Sida acuta* (21.70 %). The percentage drug released after 60 minutes from formulation N9 which contained zero binder was the same (100 %) as that of formulations N1, N2, N5 and N6.



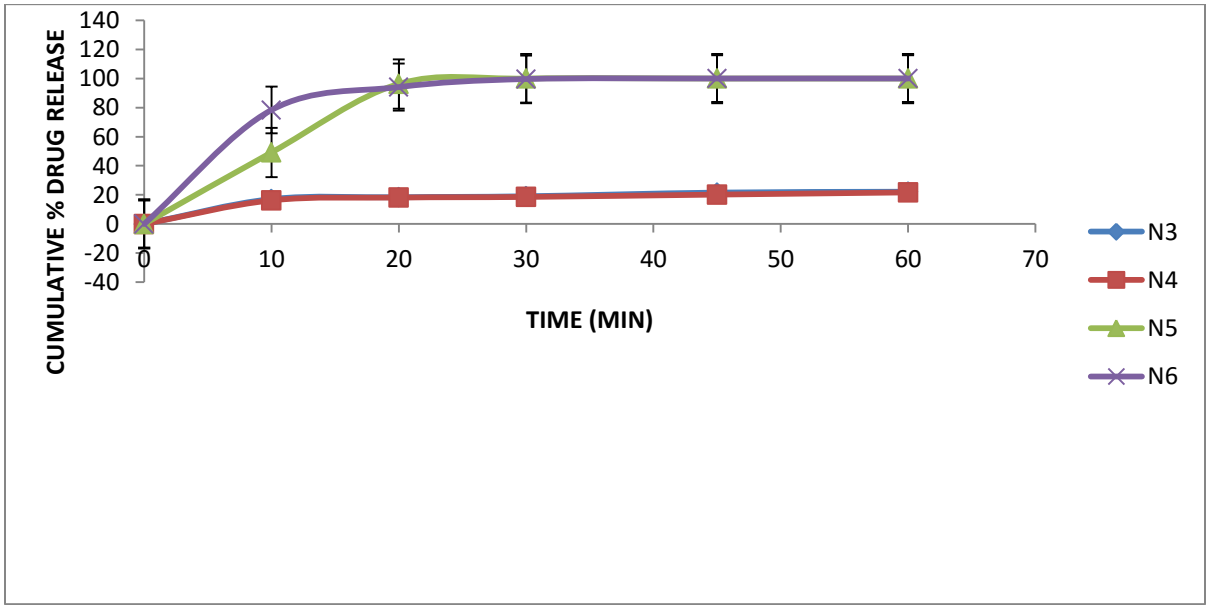
Key: SAG = *Sida acuta* gum, NaCMC = sodium carboxymethylcellulose, N1 = SAG (0.5%), N2 = SAG (1%), N3 = SAG (1.5%), N4 = SAG (2%), N5 = Acacia (1.5%), N6 = Acacia (2%), N7 = NaCMC (1.5%), N8 = NaCMC (2%), N9 = No binder

Fig. 1: _In vitro_ % drug release profile of naproxen from tablets formulated using _Sida acuta_ gum, acacia or NaCMC as binder (N1 – N9)



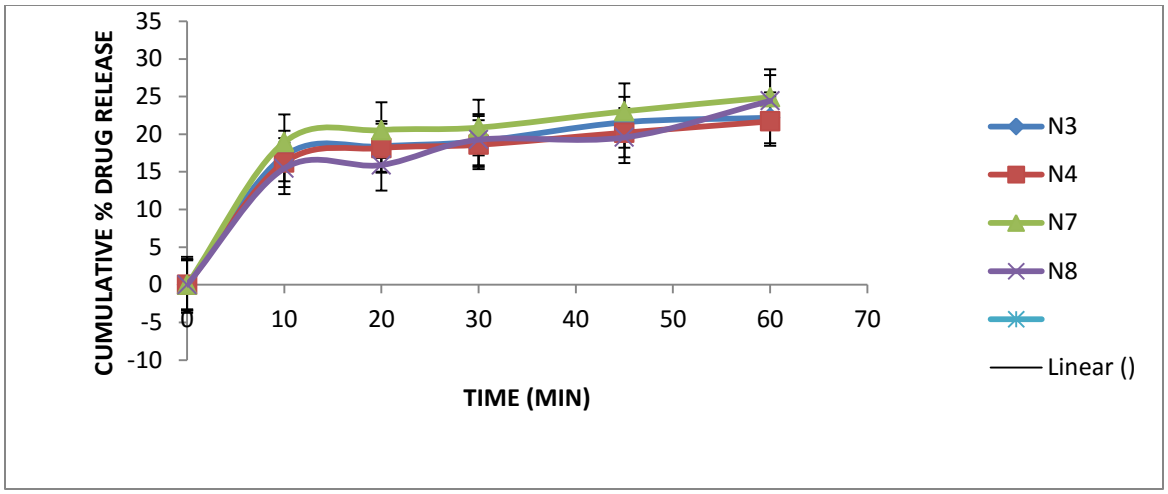
Key: SAG = *Sida acuta* gum, N1 = SAG (0.5%), N2 = SAG (1%), N3 = SAG (1.5%), N4 = SAG (2%),

Fig. 2: *In vitro* % drug release profile of naproxen from tablets formulated using *Sida acuta* gum as binder (N1 – N4)



Key: SAG = *Sida acuta* gum, N3 = SAG (1.5%), N4 = SAG (2%), N5 = Acacia (1.5%), N6 = Acacia (2%),

Fig. 3: *In vitro* % drug release profile of naproxen from tablets formulated using *Sida acuta* gum or acacia as binder (N3, N4, N5 and N6)



Key: SAG = *Sida acuta* gum, NaCMC = sodium carboxymethylcellulose, N3 = SAG (1.5%), N4 = SAG (2%), N7 = NaCMC (1.5%), N8 = NaCMC (2%),

Fig. 4: *In vitro* % drug release profile of naproxen from tablets formulated using *Sida acuta* gum or NaCMC as binder (N3, N4, N7 and N8)

CONCLUSION

Sida acuta gum was successfully used as binder in the formulation of naproxen tablets at low concentrations (0.5 -2 % w/w).*Sida acuta* gum was as good as sodium carboxymethylcellulose and better than acacia when used as binder in naproxen tablets. It will be more economical to use *Sida acuta* gum as binder when compared to the standard binders used in this study because smaller quantity of *Sida acuta* gum will be used. Also the *Sida acuta* plant being freely available in nature will make its procurement less expensive.

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