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RELEASE PROPERTIES OF PARACETAMOL GRANULATIONS FORMULATED WITH GUM FROM THE FRESH FRUITS OF *THEOBROMA CACAO*

***U. E. Osonwa and A. Chukwu**
Department of Pharmaceutical Technology and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka.
Email: udumaosonwa@yahoo.com; mobile: +2348038733305

Abstract
Theobroma cacao gum, TCG was derived as a dry powder from fresh fruits of *Theobroma cacao.* Various granulations of paracetamol were prepared with TCG at the concentrations of 0.5 – 4% w/w. Similar formulations were prepared using sodium carboxymethyl cellulose, SCMC and acacia gums as standards. In each case the release properties of the drug were studied in both 0.1 N HCl and 0.1 N NaOH. Generally, drug release showed TCG < SCMC< acacia. For example, the T_{20} - values in 0.1 N HCl at 4 % adhesive concentration were as follows: acacia, 17 min, SCMC, 20 min, TCG, 43 min. A change in dissolution medium from 0.1 N HCl to 0.1 N NaOH markedly increased drug release. Release in 0.1 N NaOH was in the order TCG < SCMC< acacia.

Keywords: *Theobroma cacao* polysaccharide, paracetamol, granulations, drug release, dissolution media

INTRODUCTION

Brooks and Guard (1952) reported the presence of lysigenous cavities filled with mucilaginous substances in roots, stems, flowers, and leaves of the cocoa plant. Polysaccharides of cacao were first characterized by Whistler *et al* (1956), who found differences in hot-water-soluble polysaccharides between seed and pod husks which are by-products of cocoa processing. The husk polysaccharide has been found to contain pectins (Blakemore *et al.*, 1966; Adomako, 1972; Figueira *et al.*, 1992, 1993). Previous studies (Chukwu and Osonwa, 2009a) had shown the yield of the gum from the fresh fruits to be high and that it has high bulk. Also, the mucilage may not retain its adhesive property when used in operations involving much heating. Because of the low charring temperature of 85 ± 1^{o}C, sterilization of the polysaccharide by dry heat may not be possible. A 1 % aqueous dispersion has a pH of 6.55 ± 0.01. It has a high ash value. It does not contain alkaloids, tannins and flavonoids, reducing/deoxy sugars. However, saponins and starch are present in trace amounts. It contains the following heavy metals in safe amounts- Fe, Zn, Mn, Pb, Ni, Cr, Cu, As, Cd and V. The acute toxicity testing in mice further showed that TCG is safe for all practical uses as the animals did not die at very high doses. Another previous work (Chukwu and Osonwa, 2009b) showed that granulations of paracetamol formulated with the polysaccharide were more friable than those

*Corresponding author
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formulated with either SCMC or acacia.

Paracetamol is an odourless, white, crystalline powder with a bitter taste. It has analgesic and antipyretic actions similar to, but weaker than, those of aspirin; it has no anti-inflammatory properties. It is indicated for the treatment of mild to moderate pain, and pyrexia (The Pharmaceutical Codex, 1979; Emdex 2007; The British National Formulary, 2009).

EXPERIMENTAL

Harvesting and processing of *Theobroma cacao* gum (TCG)

Immature young fruits of *Theobroma cacao* were harvested during the rainy season in the month of April from Uyo suburbs, Akwa Ibom State of Nigeria. Extraction of the gum was carried out by crushing the entire biomass and precipitating with 7 parts of acetone (BDH), washing the precipitate with another 7 parts of acetone and washing twice with Alcohol (BDH). Drying was done in a desiccator for 24 h.

Materials

The materials used are: paracetamol (MERCK) and gums- acacia and sodium carboxymethyl cellulose (SCMC) (BDH).

Granulation

Granule batches of paracetamol were prepared with TCG at the following concentrations: 0.5%, 1%, 3% and 4% w/w (500 mg drug/dose). Similar formulations were prepared using SCMC and acacia gum, respectively. The moist granulation method (Rawlins, 2004) was adopted. A volume of purified water just enough to moisten the entire mass was used for each batch. The damp mass was forced through 1.7 mm sieve (Shital, England). The granules were exposed to air at ambient temperature of 29 ± 0.5 ^{o}C and at a relative humidity of 56±1 % until dry. Periods of 12 hours each were allowed for the drying. The dry granules in each case were sieved through sieve 1.00 mm, 0.50 mm and 0.25 mm. The granules were labeled as: size 1.00 mm/0.50 mm – A; 0.50 mm/ 0.25 mm –B; 0.25 mm/0.00 mm - C.

Drug content, uniformity of content and dissolution studies

Beer's calibration curve

To get the Beer's curve for paracetamol in 0.1 N HCl, 100 mg of paracetamol was dissolved in 100 ml of 0.1 N HCl to get 100 mg% solution. This stock solution was then appropriately diluted to get 0.1, 0.2, 0.3, 0.4, 0.5, and 1 mg% solutions of paracetamol. The absorbance of each solution was read of in the spectrophotometer at a wavelength of 245 nm. Absorbance values were then plotted against concentration and the Beer's calibration constant was calculated.

Likewise, to get the Beer's curve for paracetamol in 0.1 N NaOH, 100 mg of paracetamol was dissolved in 100 ml of 0.1 N NaOH to get 100 mg% solution. This stock solution was then appropriately diluted to get 0.01, 0.02, 0.03, 0.04, 0.06, 0.08 and 0.1 mg% solutions of paracetamol. The absorbance of each solution was read off in the spectrophotometer at a wavelength of 257 nm. Absorbance values were then plotted against concentration and the Beer's calibration constant was calculated.

Granule drug content determinations

Granules were randomly picked 10 times from different parts of the granules batch such that the granule quantity picked each time was supposed to contain the target dose of 500 mg of paracetamol. They were then crushed together, mixed, and then an aliquot equivalent to 500 mg of paracetamol was weighed out. The

aliquot was then dispersed in 100 ml of 0.1 N HCl and analyzed spectrophotometrically to determine the absorbance and hence concentration, from which the drug content was calculated according to the Beer-Lambert's relationship

Absorbance (a) = a constant (K) x concentration (C)
……..…(5)

From this, we get

$C = a / K$ ……(6)

K is obtained as the slope of the graph when absorbance is plotted against concentration in the Beer- Lambert's relationship. The drug content was then calculated as

Drug content = C x volume …….(7)

The percentage deviation from the label dose was calculated as

% deviation = 100 (500mg -drug content)/ 500 mg
…….(8)

Granule uniformity of content determinations

Here 10 aliquots of granules as in the Drug Content Assay were randomly picked from different parts of each granule batch. Each was then crushed, dispersed in 100 ml of 0.1 N HCl and analyzed spectrophotometrically to determine the absorbance and hence concentration, from which the drug content was calculated according to the Beer-Lambert's relationship. The mean and standard deviation of the drug content for each granule batch was calculated using the Microsoft Excel®. The Relative Standard Deviation (RSD) was calculated as

$RSD = 100 S / X_{mean}$ .....(9)

where S = sample standard deviation defined by

and $S = [\sum (X_i - X_{mean})^2 / (n-1)]^{1/2}$
……..(10)

S is the sample standard deviation; X_{mean} is the mean of the values obtained from the units tested expressed as a percentage of the label claim; n is the number of units tested; X_1, X_2, X_3, …. X_n are the individual values (X_i) of the units tested expressed as a percentage of the label claim.

Dissolution testing of granulations

A modified BP flow- through method was used to test the release of each drug by leaching. It uses the BP dissolution apparatus basket as mesh enclosed in a fine cloth mesh. The quantity of granules equivalent to 500 mg paracetamol dose was introduced into the funnel. Dissolution medium at an ambient temperature of 29 ± 1^{o}C was allowed to fall under gravity unto the granules at a rate of 60 ± 1 drop/ minute. Dissolution media were 0.1 N HCl or 0.1 N NaOH. Sampling was done at 5, 10, 15, 20, 30, 40 and 60 min and analyzed spectrophotometrically.

The granules used were sizes 1.00 mm/ 0.50 mm and size 1.70 mm / 1.00 mm. Percentage drug release at each sampling time was calculated as

Percentage release = 100 x quantity released/ drug content ……(11)

RESULTS AND DISCUSSION

Drug content and uniformity of content

The results of the drug content tests are shown in Table 1. The United States Pharmacopoeia (2005) states that the paracetamol content should not be less than 90.0 % of the label claim, and should not be more than 110.0 %. This translates to a deviation of not less than -10 % and not more than 10 % of the label claim of 500 mg/dose. From table 2a, the least deviation was -0.12 % and the highest was 0.81 %. These values are within the tolerable limits of drug content. Thus, all the

granulation of paracetamol conformed to the acceptable limits.

Table 1: Results of Drug Content Test for Granulations of Paracetamol

ADHESIVE	Concentration (% w/w)	Mean Drug Content (mg)	SD
	0.5%	**501.73**	**0.35**
TCG	**1%**	**499.42**	**-0.12**
	3%	**504.05**	**0.81**
	4%	**501.73**	**0.35**
SCMC	**0.5%**	**499.42**	**-0.12**
	1%	**499.42**	**-0.12**
	3%	**504.05**	**0.81**
	4%	**499.42**	**-0.12**
	0.5%	**501.73**	**0.35**
Acacia	**1%**	**497.11**	**-0.58**
	3%	**499.42**	**-0.12**
	4%	**499.42**	**-0.12**

In the test for uniformity of content, The United States Pharmacopoeia (2005) states that, unless otherwise specified in the individual monograph, the requirements of dosage uniformity are met if the amount of the active ingredient in not less than 9 of the 10 dosage units as determined from the Content Uniformity method lies within the range 85.0 % to 115.0 %, and no unit is outside the range 75.0 % to 125.0 % of the label claim or if the Relative standard deviation of 10 dosage units is less than or equal to 6.0 %. If 2 or 3 units are outside the range of 85.0 % to 115.0 % of the label claim but not outside the range of 75.0 % to 125.0 % of the label claim, or if the Relative standard deviation is greater than 6.0 % or both conditions prevail, 20 additional units should be tested. The requirement is met if not more than 3 units of the 30 are outside the range of 85.0-125.0% of label claim, and the Relative standard deviation of the dosage units does not exceed 7.8 %. No batch had a Relative standard deviation of drug content of more than 6 % (Table 2b). Thus, they all conformed to acceptable limits.

Table 2: Results of Uniformity of Content Test for Granulations of Paracetamol

ADHESIVE	Concentration (% w/w)	RSD (%)
	0.5%	**1.56**
	1%	**1.61**
TCG	**3%**	**1.55**
	4%	**2.23**
	0.5%	**2.12**
	1%	**2.12**
SCMC	**3%**	**2.48**
	4%	**2.02**
	0.5%	**1.71**
	1%	**2.62**
Acacia	**3%**	**1.82**
	4%	**1.90**

Drug release

Earlier report by Chukwu and Osonwa (2009b) showed that within 0.5 -4 % adhesive concentration, the friabilities were in the order TCG> acacia> SCMC. However, drug release in 0.1N HCl at 4 % w/w concentration showed the trend TCG < SCMC < acacia throughout the dissolution period (Figure 1). These results show that TCG has a tendency to retard release of paracetamol in solid dosage forms in 0.1 N HCl more than either SCMC or acacia gum showing that TCG may be more beneficial as a sustained-release excipient in these formulations than either acacia or SCMC at these concentrations. This effect might be due to high gelling.

At 1 % adhesive concentration (Figure 2), paracetamol release in 0.1 N HCl was higher with granules formulated with acacia gum than with

either SCMC or TCG. Drug release with granules formulated with SCMC had similar release profile with those formulated with TCG till 10 min after which drug release from granules formulated with SCMC continuously superseded that of granules formulated with TCG throughout the experiment. By 60 min, drug release was in the order acacia > SCMC> TCG. This correlates with the trend observed with adhesives at 4 % concentration (Figure 1). These results further indicate that paracetamol release from granules formulated with TCG in 0.1 N HCl will have release rate less than those containing either acacia or SCMC.

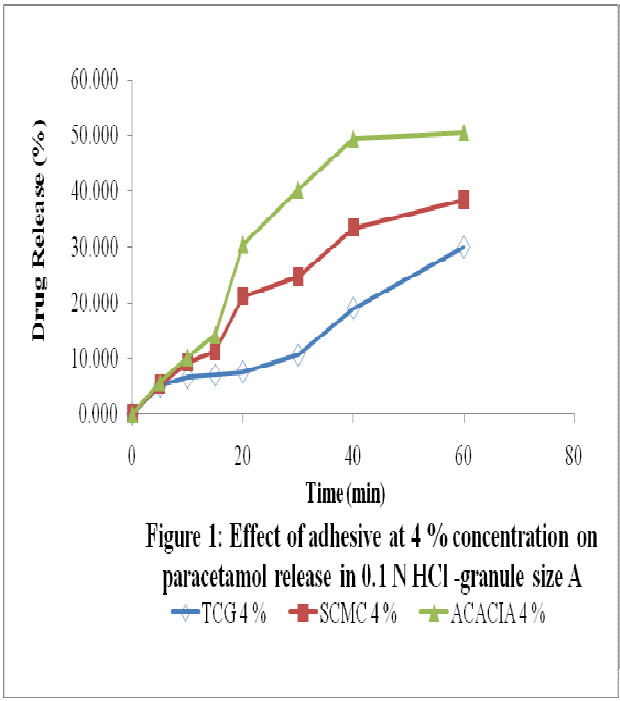

Figure 1: Effect of adhesive at 4 % concentration on paracetamol release in 0.1 N HCl -granule size A

The effect of particle size on drug release from granules formulated with TCG, in 0.1 N HCl are shown in Figures 3and 4. At 4 % concentration (Figure 3) granules of particle size 1.70 mm / 1.00 mm showed consistently greater release than granules of size 1.00 mm / 0.50 mm. At 5 minutes, the bigger -sized granules had released less than 1 % while the smaller sized granules had already released up to 5 %. This time lag for release is likely as a result of the longer time it took for the larger sized granules to hydrate. At 4 % concentration (Figure 3), similar trend was obtained with paracetamol granules formulated with TCG at 1 % concentration (Figure 4) even though the release was much faster for both granule sizes than for the granules formulated with adhesives.

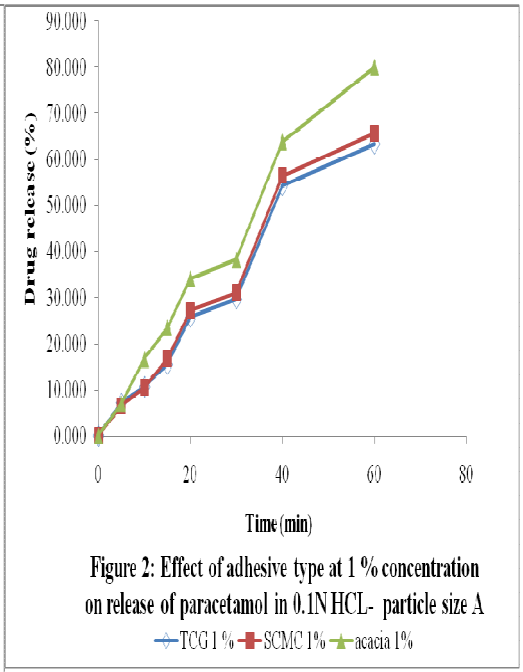

Figure 2: Effect of adhesive type at 1 % concentration on release of paracetamol in 0.1N HCL- particle size A

For both granule sizes, paracetamol release in 0.1 N HCl (Figures 5 and 6), rose consistently with time in the order of decreasing adhesive concentration. For the granules of particle size 1.70 mm/ 1.00 mm (Figure 5), paracetamol release rose sharply for all the adhesive concentrations after the 20th minute and this rise was consistent till the 60th minute. There was also concentration –dependent paracetamol release for the granules of size 1.70 mm/ 1.00 mm (Figure 6). Significant differences in drug release became apparent by the 10th minute and the drug release profiles of the different adhesive concentrations became so pronounced by the 20th minute and this difference was maintained up till the 60th minute. These results agree with earlier published works with results that the greater the adhesive concentration the

less the drug release (Armstrong, 1999).

Figure 7 shows the release profiles of paracetamol granules formulated with TCG at concentrations of 1, 3 and 4 % in 0.1 N NaOH, respectively. Drug release was in the order- 1% TCG concentration > 3 % TCG concentration > 4 % TCG concentration, throughout the 60 min of assessment. By 30min, granules formulated with 1 % TCG had already released up to 98 % of the drug; granules formulated with TCG at 3 % concentration had released 70.49 % of paracetamol; while granules formulated with TCG at 4 % concentration had released 52.94 % of the drug. These results further strengthen the fact that increase in TCG concentration from 1-4% greatly delays paracetamol release. Hence, using the higher concentration will favor a more sustained or delayed release of paracetamol in the alkaline environment of the small intestine

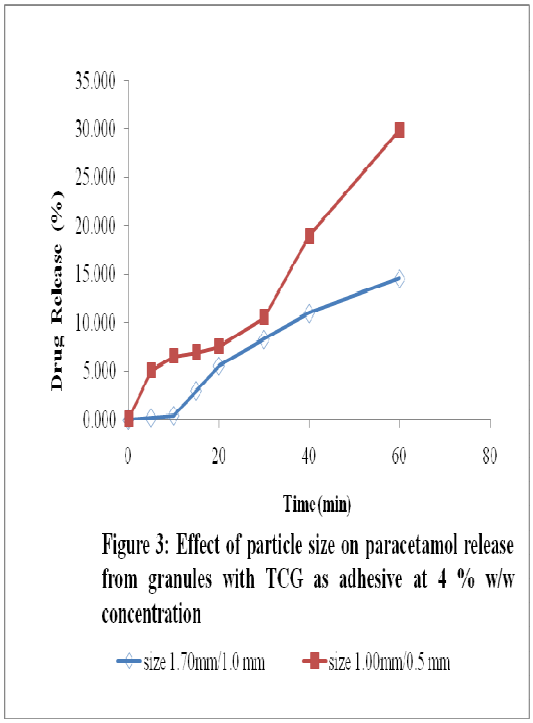

Figure 3: Effect of particle size on paracetamol release from granules with TCG as adhesive at 4 % w/w concentration

(Aulton, 1999).

Release of paracetamol from

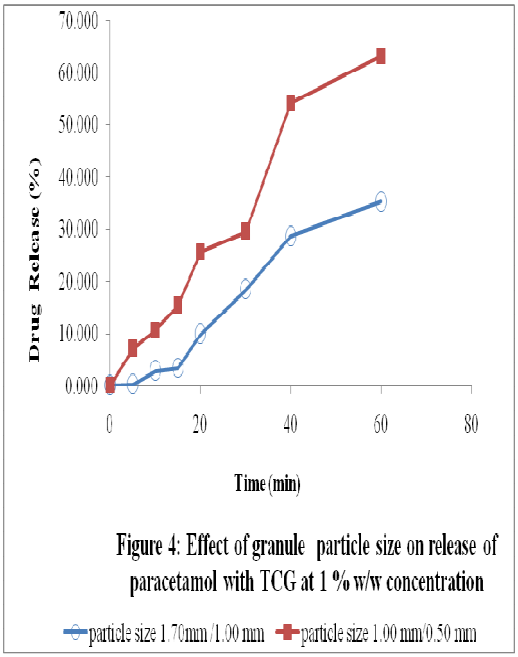

Figure 4: Effect of granule particle size on release of paracetamol with TCG at 1 % w/w concentration

granules formulated with the adhesives at 4 % concentration in 0.1 N NaOH was gradual with variable release orders (Figure 8). However, by the 60th minute granules formulated with acacia gum had released the entire drug while those formulated with TCG or SCMC had released 58.65 % and 75.49 % of the drug, respectively. These results indicate that an enteric coated formulation of paracetamol formulated with TCG would have a more sustained release rate in the alkaline environment of the small intestines, than granules formulated with either SCMC or acacia gum as adhesives.

With a change in dissolution medium from 0.1 N HCl to 0.1 N NaOH, there was a greatly marked increase in paracetamol release for the granules with TCG at 4 % concentration (Figure 9). At 30 min, release in 0.1 N HCl was only 10%, whereas release in 0.1 N NaOH was 52.94 %. Paracetamol in solution

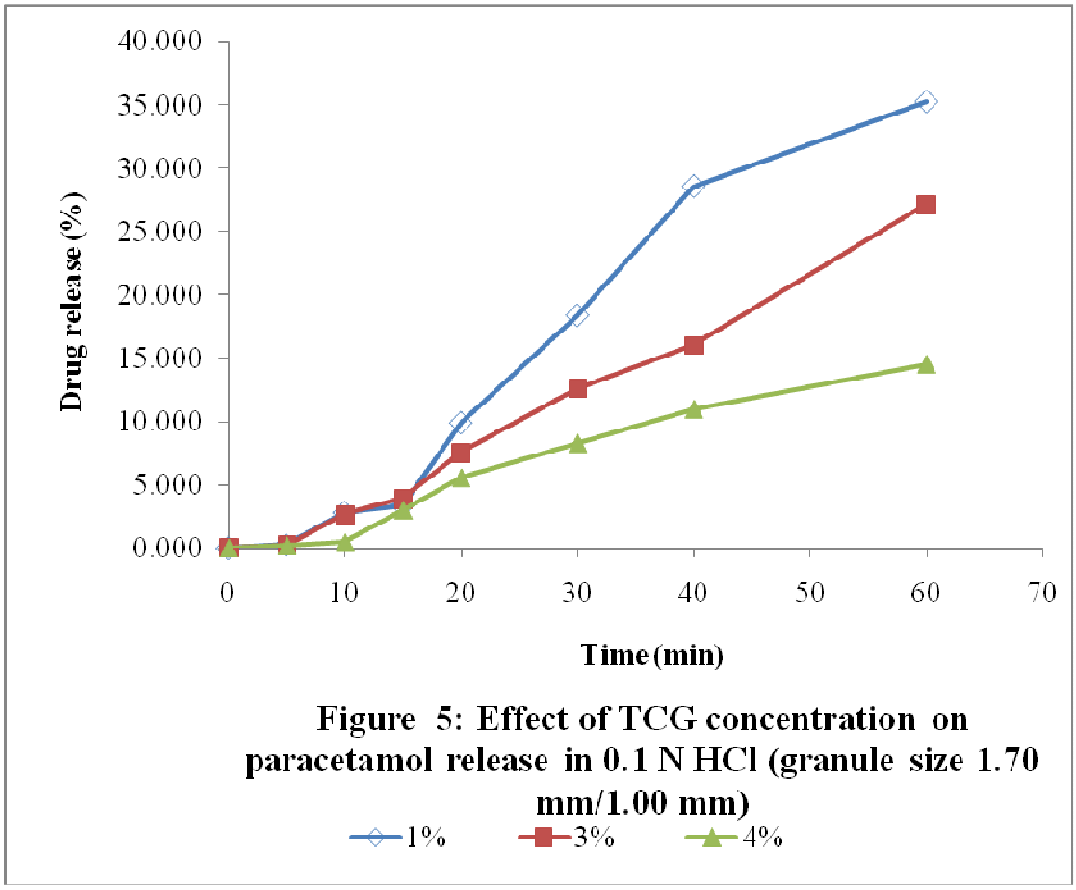

Figure 5: Effect of TCG concentration on paracetamol release in 0.1 N HCl (granule size 1.70 mm/1.00 mm)

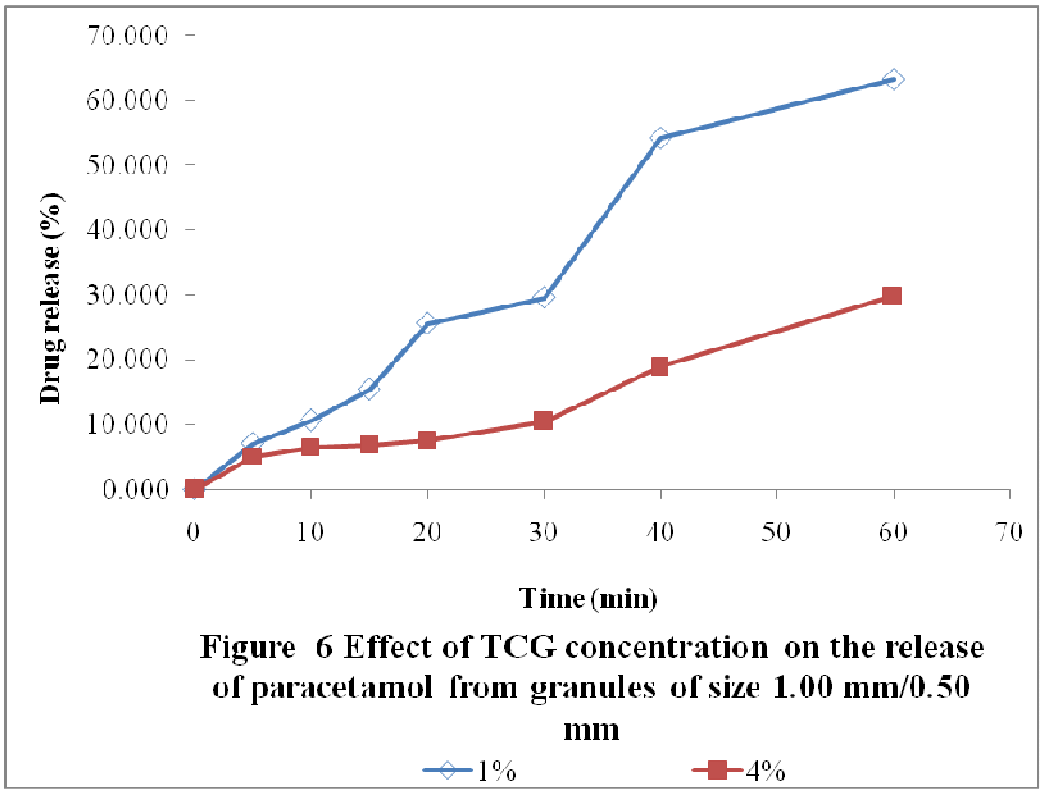

Figure 6 Effect of TCG concentration on the release of paracetamol from granules of size 1.00 mm/0.50 mm

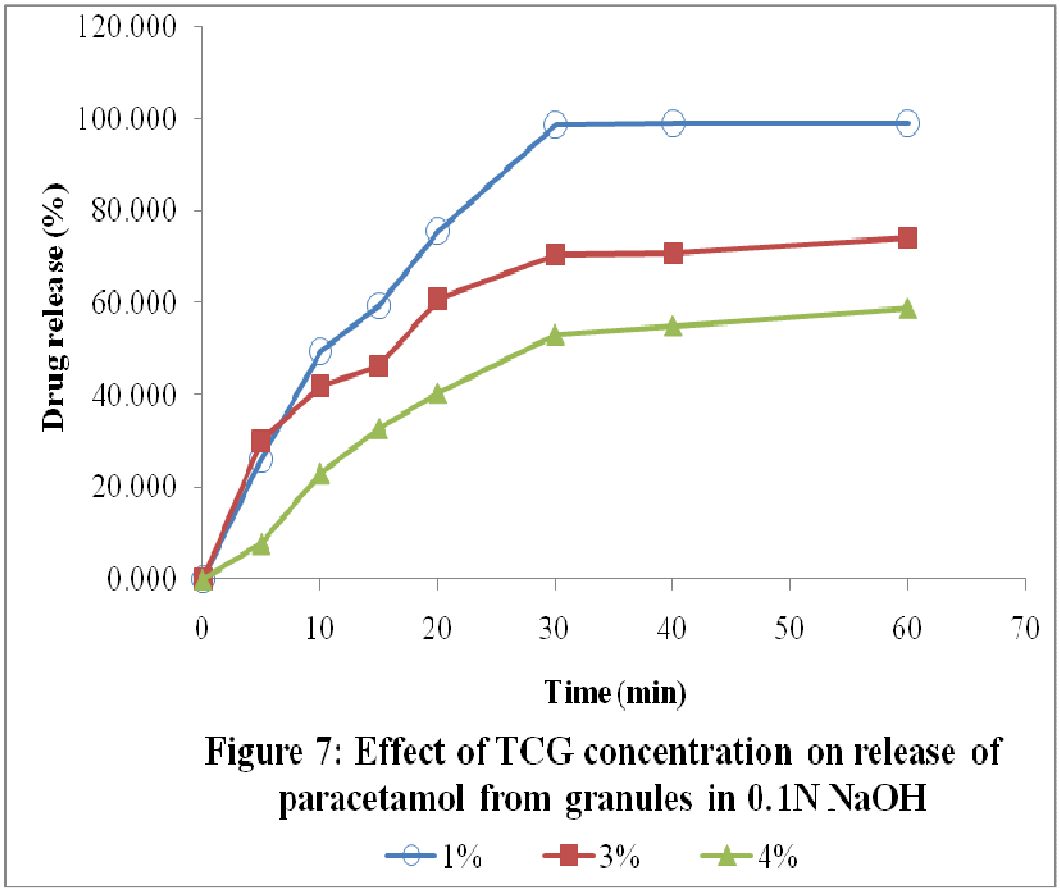

Figure 7: Effect of TCG concentration on release of paracetamol from granules in 0.1N NaOH

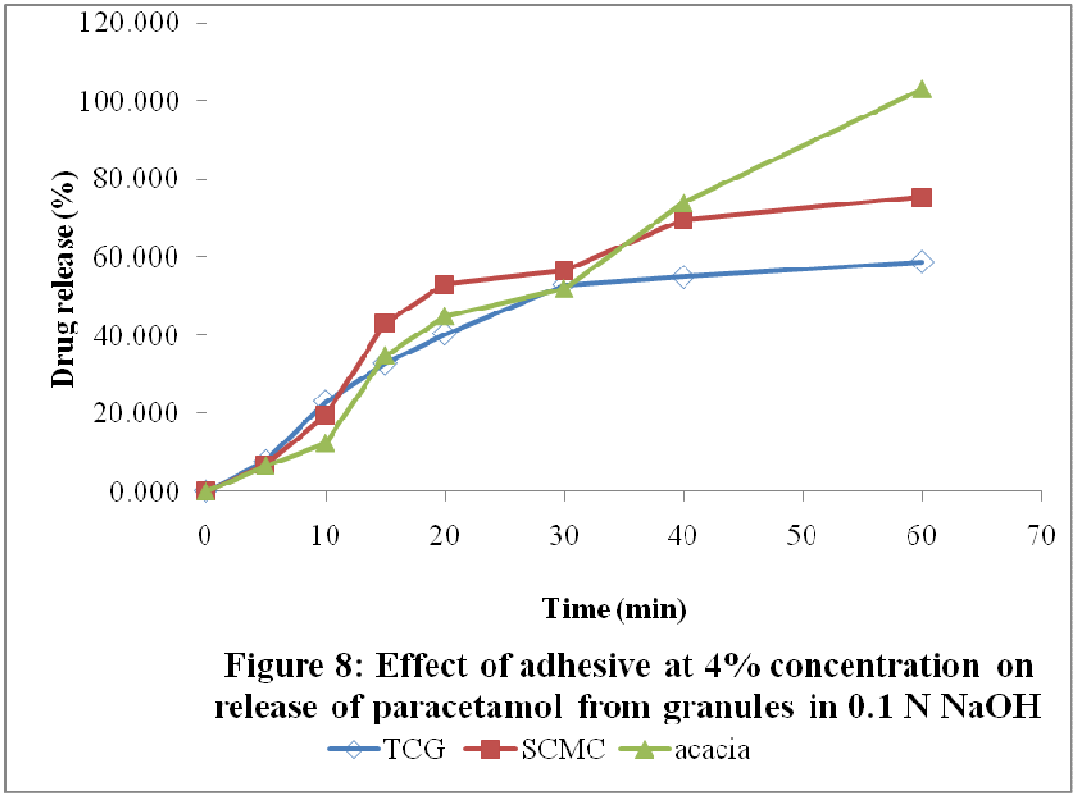

Figure 8: Effect of adhesive at 4% concentration on release of paracetamol from granules in 0.1 N NaOH

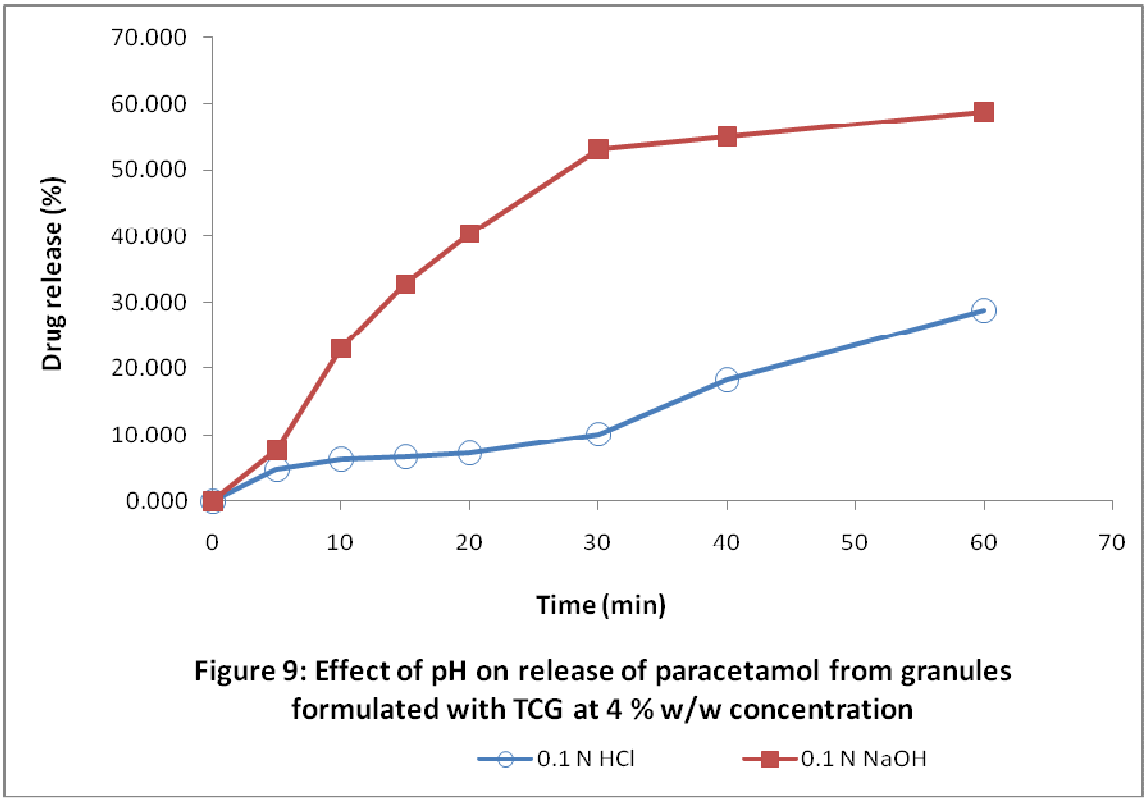

Figure 9: Effect of pH on release of paracetamol from granules formulated with TCG at 4 % w/w concentration

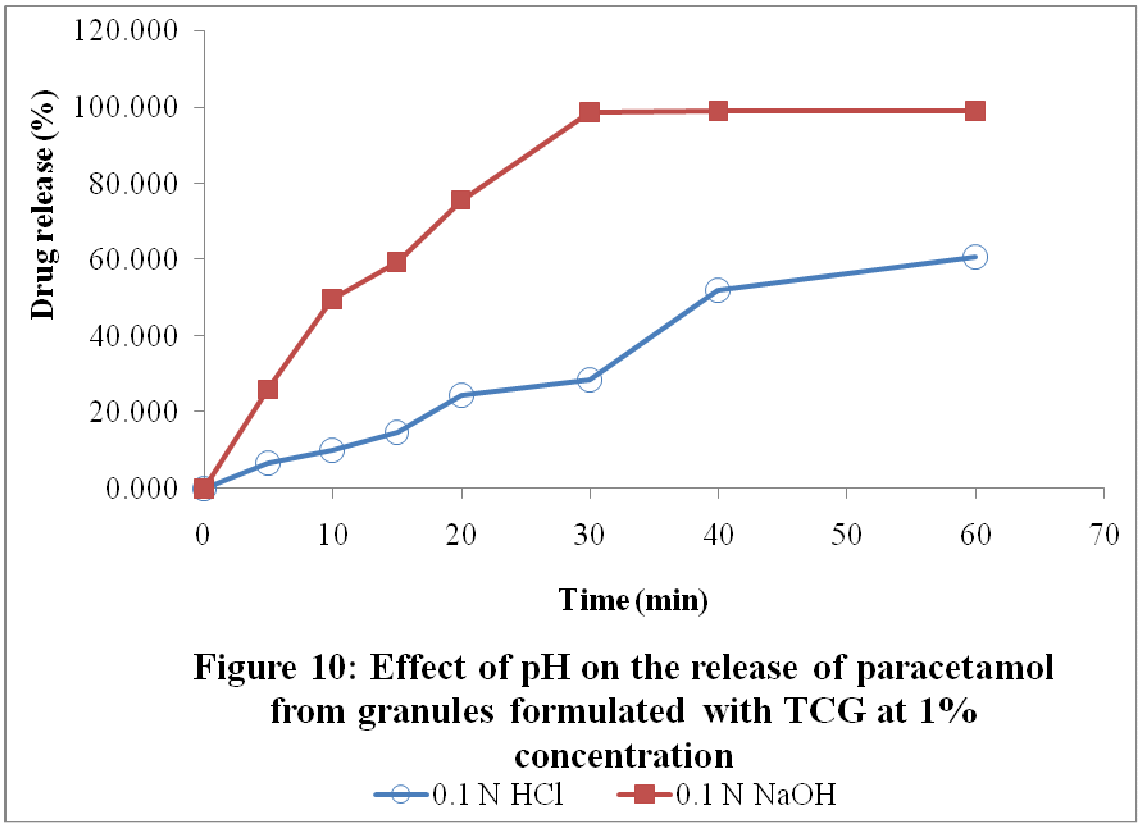

Figure 10: Effect of pH on the release of paracetamol from granules formulated with TCG at 1% concentration

gives a slightly alkaline pH and so drug release in the alkaline medium would have been expected to be retarded. Hence, this sudden pronounced paracetamol release can only be attributed to events surrounding the adhesive. This indicates that TCG tends to lose its structure in a strongly alkaline environment which might be due to chemical reactions. Hence, TCG at higher concentrations might be used to produce an immediate or prompt release formulation in the alkaline environment of the small intestine.

At 1% TCG concentration, paracetamol release was faster in the alkaline medium than in acid (Figure 10). At 30 min, release in 0.1 N HCl was only 28.40 %, whereas there was total release in 0.1 N NaOH. This further suggests a loosening up of the TCG molecules or a chemical reaction that has affected its structure. These results indicate that with paracetamol tablets or granules, drug release may be faster in the small intestine than in the gastric acidic environment.

CONCLUSION

Drug release in 0.1 N HCl reduced with increase in adhesive concentration and at equivalent concentrations was in the order - TCG < SCMC < acacia showing that release is slower with TCG than with either SCMC or acacia. Reduction in particle size appreciably increased paracetamol release rate. Increase in pH increases release of paracetamol from granules when TCG is the adhesive, but this release is still slower than with either SCMC or acacia gum.

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