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Drug Release Modification by Using Citric Acid and Glycerol Cross-linked Derivatives of Cashew (*Anacardium occidentale* L.) Gum

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Authors' contributions

This work was carried out in collaboration between all authors. Author ARO designed the study and wrote the protocol. Author ABI managed the literature searches, analyses of the study performed the spectroscopy analysis. Author AA managed the experimental process and wrote the first draft of the manuscript and author IO provided the lab, research materials and participated in the experimental process. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

A derivative of cashew gum (CrosCCG) developed by cross-linking the gum with two cross-linking agents, citric acid and glycerol, has been used to modify drug release in Venlafaxine Hydrochloride tablets. Wet granulation method was used to formulate the tablets using hydroxypropyl methylcellulose (HPMC ER K100) as a binder at 7.5%w/w. Increasing concentrations of the derivative was used to modify the drug release. The granules and the tablets formed were assessed by being subjected to the prescribed official tests. CrosCCG used at concentrations of 10 %w/w or lower enhanced drug release while concentrations above 10%w/w delayed drug release.

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Keywords: Cashew gum; derivative; citric acid; glycerol; tablet dissolution; drug release modification; venlafaxine HCl.

1. INTRODUCTION

To facilitate the development of novel drug delivery systems and biotechnology-derived drugs, the need for new excipients increases [1]. While the discovery or synthesis of novel therapeutic agents is taking the center stage in most pharmaceutical companies, excipients development is the next most important area worthy of being researched on. Excipients take the bulk of the floor in any research and development (R & D) unit of any pharmaceutical company, underpinning their relevance in drug delivery. An excellent therapeutic agent may be worthless if it cannot be formulated into an appropriate dosage unit, by optimally harnessing the varied functionalities of excipients or pharmaceutical aids required for its formulation.

Cross-linked polymer networks have found relevance in pharmaceutical drug delivery courtesy of their ability to swell and had been principally used as swellable devices or as disintegrants [2]. Even dispersible polymers like gums when appropriately cross-linked, are rendered insoluble, absorb water and swell [3]. These properties had permitted the development of tablets with release profiles that classically differ from the conventional immediate release tablets (that are expected to dissolve within 30 min) [4-6]. One class includes those tablets designed to dissolve within seconds of contact with a liquid medium like the saliva in the mouth e.g. the orally dissolving tablets [7,8]. This feat is achieved commonly by using super disintegrants in the concentration range of 2-4%w/w to produce rapid disintegration of tablets [9]. The second class include those tablets whose rate of drug release has been modified to be usually over an elongated period of time e.g. the extended release, enteric coated formulations etc [10-15].

A derivative of Cashew gum (tagged CrosCCG) has been developed by cross-linking the gum using two agents, citric acid (CTA) and glycerol (GLY), in a work by same authors [16]. In the present study, the polymer network (CrosCCG) is considered for use as a drug release-modifying agent to formulate Venlafaxine HCl (Ven. HCl) tablets. Ven. HCl is a highly water soluble, orally active serotonin and noradrenalin reuptake inhibitor used in the treatment of major depressive disorders. Increasing concentrations of CrosCCG were compared with a powerful binder/matrix former, hydroxyprophyl methylcellulose (HPMC ER K100) used at 7.5%w/w.

2. MATERIALS AND METHODS

2.1 Materials

- Sodium phosphate monobasic, (Caledon Laboratories Ltd, Canada)
- Venlafaxine HCl (Cadila Health Care Ltd., India)
- Hydroxypropyl methycellulose - HPMC ER (K100) (Dow Chemicals, USA)
- Polyplasdone XL (Crospovidone NF) (ISP Technologies, USA)
- Croscamellose Sodium (FMC Biopolymer, USA)
- Lactose anhydrous (Kerry Bioscience, USA)
- Silicone Dioxide (Evonik Industries, USA)
- Magnesium stearate, (Tycol Healthcare, USA)
- Cashew gum and CrosCCG were as purified/synthesised in the laboratory (IntelliPharmaceutics Inc., Canada)

2.2 Methods

2.2.1 Extraction/purification of CG

Cashew gum (CG) was extracted and purified using a method described by [17]. Dried exudates from cashew trees were collected, extraneous matter picked out manually and a weighed quantity was dispersed in deionised (DI) water. Acetone was used to precipitate/purify the gum.

2.2.2 Cross-linking CG using CTA and GLY

In a related study by same authors [16], CG was cross-linked using two cross-linking agents CTA and GLY and the resulting cross-linked polymer was characterised.

A dispersion of appropriate quantities of CG, CTR, GLY and NaH_2PO_4 was made with some DI water contained in a beaker. The homogenous mixture was transferred into a culture dish and concentrated by heating at 40ºC for 18 h. The solid mass was heated at 140 or

170ºC for 30 min for the cross-linking process to take place, and thereafter DI water was used to recover and purify the extracted gum (CrosCCG).

2.2.3 Drug excipient compatibility studies using DSC

Compatibility of CrosCCG and Ven. HCl as active pharmaceutical ingredient (API) was assessed by the following procedure. About 10 mg samples of Ven. HCl and a thoroughly triturated 50/50 physical mixture of powders of CrosCCG and Ven. HCl were respectively encapsulated in aluminium disposable pans. DSC scans were run to measure the energy changes associated with heating the samples to 500ºC at a scan rate of 10ºC/min using nitrogen as purge gas. The Thermograms obtained were used to determine the compatibility or otherwise of Ven. HCl with the polymers as excipients.

2.2.4 Formation of granules

The wet granulation method was used to make granules as represented in Table 1. Ven. HCl, Lactose DT and HPMC ER were used as an active agent, diluent and binder respectively. Increased concentrations; 3, 10, 15 and 25%w/w of CrosCCG were used to formulate tablet batches represented by groups G2 to G5 respectively to demonstrate the effect of increasing concentrations of CrosCCG on drug release. Croscarmellose and Crospovidone (G6 and G7) respectively were used to grade level of enhancement of drug release by CrosCCG. Modified drug release in this case is taken to be any deviation from the conventional release profile of the binder used. The active agent and other excipients were accurately weighed and dry mixed for 6 min using a low shear mixer (Kitchen aid, St. Joseph, Michigan USA). DI water, as granulating liquid, was used to wet the powder mix while being sheared to obtain optimum granulation. The damp granule mass was spread on paper laid on a tray and dried in a forced air oven (Model 1370 F, VWR Scientific Products, USA) for 3 h, or when moisture content determined using moisture analyser (Model LJ 16, Mettler Toledo, Switzerland) became lower than 2%. The dried granules were milled by passing through a mill (Quadro Comil, Model no. 197 R, Quadro Engineering Inc., Ontario Canada) fitted with a metal screen affixed to the granulator.

2.2.5 Tests on granules

2.2.5.1 Density measurements

Densities of granules were measured using tap density tester USP (Electrolab, Model ETD-1020, Globepharma, U.S.A.), where the bulk and tapped densities as well as compressibility index and Hausner ratio were determined using the USP 1 method. Densities were determined using the following relationships:

$$\text{Initial Density} = (W/Vo) \quad (1)$$

$$\text{Tapped Density} = (W/Vf) \quad (2)$$

$$\text{Hausner Ratio} = (Vo/Vf) \quad (3)$$

$$\text{Compressibility Index} = [(Vo-Vf)/Vo] \times 100 \quad (4)$$

Where W is the weight of sample, Vo is the initial Volume and Vf is the final Volume

2.2.5.2 Granule flow rate

Glass funnel held by a retort stand with the tip 10 cm from the surface of the table top, was used to measure the flow rate of the granules. Fifty-gram sample was poured into the funnel with the opening blocked. Using a timer, the time taken for the material to pass through the opening, upon removal of the block, was determined. Average of three readings was used to calculate the flow rate.

2.2.5.3 Angle of repose

The height (h) and the diameter (d) formed by the granules heap in earlier flow measurement were measured and used to calculate the angle of repose (θ) of the granules using the following equation.

$$\text{Angle of repose, } \tan\theta = h/r \quad (5)$$

Where h is the height of the heap, r is the radius of the base of the heap.

2.2.5.4 Determination of powder particle size distribution

Ro-Tap (Model RX-29, W.S. Tyler, USA) was used for the determination of particle size distribution. Tarred sieves (W_1) with different sizes were arranged such that 600 µm was on top, followed by 425 µm, then 250 µm, 150 µm, 106 µm, 53 µm and finally 0 µm (pan) at the

bottom. Granule sample weighing 50 g was placed on the topmost sieve and the shaker was operated for 10 min. The sieves with the retained granules were weighed (W_2). The weight of granule retained on each sieve was calculated using the following relationship

$$\text{Weight of powder retained} = W_2 - W_1 \quad (6)$$

2.2.5.5 Addition of extragranular excipients

Weighed quantities of silicone dioxide and magnesium stearate (Table 1) were added to the granules and blended using shear mixer and afterwards thoroughly shaken in cellophane bag. Granule flow rate and angle of repose were determined as earlier described.

2.2.5.6 Compression of granules

Betapress Manesty Machine (No. 74182, Manesty Machines Ltd., England) was used to compress the granules (Table 1) using 0.2756 inch (7 mm) punch and die setting, and compression pressure of 4.5 metric tonnes to produce a batch of 1,000 tablets with a target weight of 167 mg.

2.2.6 Evaluation of tablet properties

2.2.6.1 Uniformity of weight

Twenty tablets were randomly selected from each batch and individually weighed using AT 261 Delta Range balance (Mettler Toledo, Switzerland). The mean weight and deviations from the mean were calculated.

2.2.6.2 Tablet crushing strength

The crushing strength (KgF) of 10 tablets selected randomly from each batch was determined using VK 200 Tablet Hardness Tester (Vankel, USA). The mean and standard deviations were calculated.

2.2.6.3 Tablet friability test

FAB-2 Friability Tester (Logan Instruments Corp., USA) was used to carry out the friability test. Twenty tablets from each batch were taken, weighed and placed on the friabilator, which was then operated for four (4) min at 25 rpm (100 revolutions). The tablets were de-dusted, reweighed and the difference in weight was determined using the following relationship:

$$\% \text{ Friability} = (W_1 - W_2 / W_1)\, 100 \quad (7)$$

Where W_1 = original weight and W_2 = final weight.

2.2.6.4 Tablet dissolution test

Dissolution test was carried out using the paddle method on D 800 Dissolution tester (Logan Instruments Corp., USA) as described in the USP [18]. The automated tester was set to analyze the amount of drug released after every 15 min of dissolution time. Paddle speed was 100 rpm and 900 ml of DI water were used as dissolution medium, while the temperature was set at 37ºC±0.5ºC. Drug released was assessed at the Ven. HCl wavelength of 229 nm.

2.2.6.5 Drug release data model fitting

The drug release data was fitted into various drug release kinetic models. Zero order, first order, Hixon Crowell and Higuchi kinetic models were employed in describing the drug-release kinetics while Korsmeyer-Peppas equation provided valuable information on the drug-release mechanism. The model that best fits the data was taken as the model describing the drug-release mechanism for the preparation.

Drug release mechanism is commonly defined by the release exponent, n. When n is 0.45 (Fickian diffusion); $0.45 < n < 0.89$ (Anomalous (non-Fickian) diffusion); 0.89 (Case II transport); $n > 1$ (Super case II transport) [19-21].

2.2.6.6 Uniformity of dosage unit test

The USP method [18] was used to determine the content uniformity using Hewlett Packard diode array spectrophotometer (Minnesota, USA). Ten tablets were weighed individually and the mean weight was determined. The tablets were crushed and three samples of approximate weights to the mean tablet weight were assayed. The average of three values was taken as the drug content. Ten tablets were weighed individually and the weights were used to determine the uniformity of the dosage units proportionately according to the USP method.

2.2.6.7 Sub-acute toxicity studies

The method described by Tamta et al. [22] was adopted with some modifications. The experiment was designed and the animals were treated in accordance with the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) 1986 Animal Guidelines. The animals (Wistar rats) were grouped into four with each group having 6

Table 1. Ven. HCl tablet batches formulae containing HPMC ER 7.5% as a binder and some polymers as drug release modifiers

Ingredients	Batch number/QUANTITY (%)						
	G1	G2	G3	G4	G5	G6	G7
Venlafaxine HCl	30	30	30	30	30	30	30
Lactose DT	61.5	58.5	51.5	46.5	36.5	58.5	58.5
HPMC ER	7.5	7.5	7.5	7.5	7.5	7.5	7.5
CrosCCG	-	3	10	15	25	-	-
Croscarmellose	-	-	-	-	-	3	-
Crospovidone	-	-	-	-	-	-	3
Silicon dioxide	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	100	100	100	100	100	100	100

animals. Subgroups of 3 males and 3 females were made on each group. The animals were conditioned as per the environment, mode of feeding and water supply.

CrosCCG was not soluble and so could not be made into solutions for oral or intraperitonial (IP) administrations and this precludes the conduction of acute toxicity studies. Sub-acute toxicity studies were thus carried out to ascertain the safety or otherwise of the cross-linked polymer. Group 1 was made to serve as control while groups 2, 3 and 4 were fed 2.5, 5.0 and 10.0 grams respectively, of CrosCCG per 1 Kg feed over a 28 day period. The polymer was added in its solid state into the feed mix prior to being molded. The same mold formula as per respective groups was used to feed the animals throughout the 28 day period of treatment. Continuous water supply was ensured, *ad libitum*, using clean drinkers. Deaths, loss of weight, inability to eat or drink during the study period were observed.

The animals were fed the test material for 28 days and then sacrificed on the 29th day [23-25]. Blood samples for the tests were collected via jugular vein puncture following administration of anesthesia. Hematological parameters including packed cell volume (PCV), hemoglobin count, neutrophils, lymphocytes, monocytes, eosinophils levels were also determined. Biochemical parameters including alkaline phosphatase (ALP), aspertate transaminase (AST, SGOT) and alanine transaminase (ALT, SGPT) were tested.

2.2.7 Statistical analysis

All the results obtained that require statistical analysis were analyzed using GraphPad Prism software package. Results were expressed as mean ± SD and the differences between means were considered significant at P=.05 using the analysis of variance (ANOVA) or student's t test.

3. RESULTS

3.1 Drug-excipient Compatibility Studies Using DSC

Fig. 1 shows the DSC measurement curve demonstrating the compatibility or otherwise of Ven. HCl (test drug) with CrosCCG (test polymer). The figure displays the DSC thermograms overlay of 50/50 binary mixture of Ven. HCl and CrosCCG on that of the pure drug. The melting temperature of the drug in its pure form that commonly ranges between 215 to 217 ^{o}C appeared shifted to a lower value in the binary mixture. It is important that the drug does not interact with any of the excipients in a way that is likely to reduce its efficacy; therefore, excipients compatibility is important when considering drug stability [26]. The objective is to quickly find those excipients that should be avoided because of an obvious chemical incompatibility with a particular API [27]. Ideally if no interaction occurs, then the mixture should show equivalent transitions to that of the individual components. If it does not, some interaction is indicated [26]. It was observed that issues arise because physical interactions occur that have nothing to do with chemical interactions, which are the basic cause of concern. Presence of impurities in a sample could cause decreases in melting temperatures or shortening of peaks in a DSC curve commensurate to the level of impurity. CrosCCG in this case could be identified as an "impurity" and so the decrease in both the intensity and measure of the melting temperature may not be an indication of interaction. DSC may not give an all conclusive indication of compatibility or

otherwise of a given binary mixture and so HPLC, MS are often further used to guide on drawing rational inferences on a drug-polymer compatibility study. The insolubility of CrosCCG precluded the conduct of these additional tests. Experienced analysts, however, have reported that useful information has been obtained from DSC that provides significant evidence that no interaction is occurring [26]. Drug release data should be used to substantiate this claim.

3.2 Granules Properties

The properties of granules formed using HPMC ER at 7.5%w/w as a binder and some polymers at varying concentrations as drug release modifiers are shown in Table 2. G1 containing only HPMC ER as a binder/matrix former and G2, G6 and G7 containing 3% release enhancing agents were found to have Hausner ratios above 25% and a compressibility index of 1.35 or higher, and powders/granules with such values have poor flowability [18,28]. These granules failed to flow through the funnel and so could not give any angle of repose further demonstrating their poor flowability. The inability of the granules to flow, however, did not forestall the formulation of quality tablets after compression. Increasing the concentration of CrosCCG (G2 to G5) was found to cause a proportionate decrease in compressibility index, Hausner ratio and angle of repose with a corresponding increase in flow rate. The flowability of granules with compressibility index of 21 -25% and Hausner ratio of 1.26 -1.34 are said to be passable [18]. Inter-batch granule size distribution was found to be somewhat uniform and skewed to the smaller size ranges as the granules were passed through a similar mill.

3.3 Tablet Properties

Preliminary studies showed that use of CrosCCG alone as tablet binder/matrix former even at 25 %w/w did not produce tablets with delayed drug release. Instead, relatively softer tablets that break highest at 4.0 KN, with a friability of 0.58% and time required to release 80% of drug ($T_{80\%}$) was 15 min. This result therefore showed that CrosCCG cannot be solely used as binder or matrix former to delay drug release even at 25 %w/w concentration. Concomitant use with another binder/matrix former, HPMC ER, was thereafter investigated and effects of increased concentration of CrosCCG on a fixed HPMC concentration were observed.

Table 3 and Figs. 3 & 4 show results of tablet properties. Intra and inter batch values for tablet weights, crushing strength, friability, content of active ingredient and diameter were observed not to significantly differ as shown by the values or standard deviations obtained. Significant variations in cumulative drug release were however noticed between the batches.

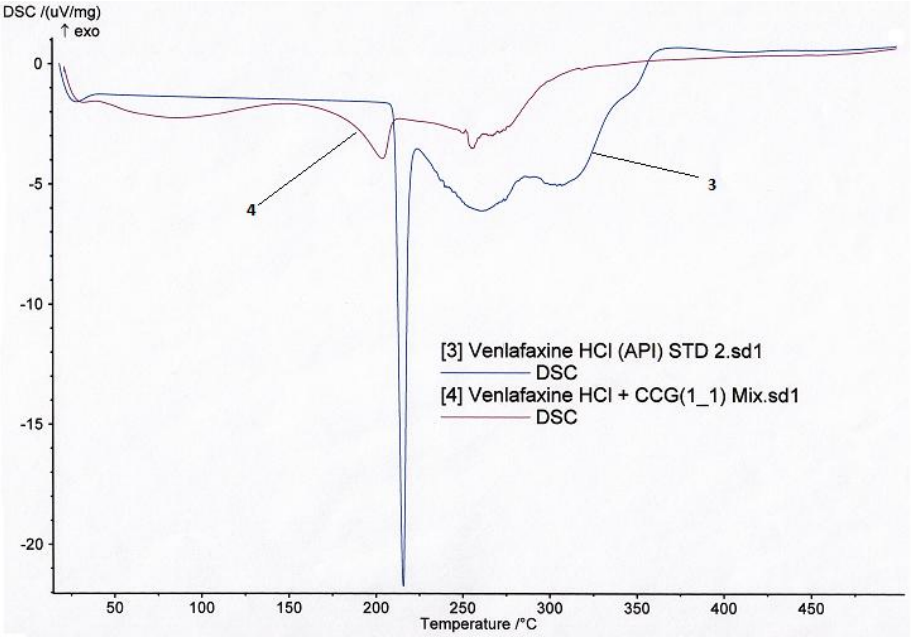


Fig. 1. Overlay of DSC thermograms of Ven. HCl and its 50/50 binary mixture with CrosCCG

Table 2. Properties of Ven. HCl granules containing HPMC (ER) as a binder at 7.5 %w/w and some polymers as release modifiers

Parameter		Batches						
		G1	G2	G3	G4	G5	G6	G7
Bulk density (g/ml)		0.613	0.523	0.619	0.645	0.682	0.623	0.613
Tap density (g/ml)		0.846	0.708	0.829	0.849	0.871	0.843	0.841
Compressibility index (%)		26.50	25.00	24.20	22.90	20.60	25.00	26.00
Hausner ratio		01.38	1.35	01.34	01.31	01.27	1.35	1.37
Flow rate (g/s)	B/L	NF	NF	1.87	2.12	2.42	NF	NF
	A/L	NF	NF	2.03	2.38	2.83	NF	NF
Angle of repose (º)	B/L	-	-	34.19	33.84	33.26	-	-
	A/L	-	-	33.51	33.11	32.40	-	-

Key: HPMC ER 7.5% alone (G1); +CrosCCG 3% (G2); +CrosCCG 10% (G3); +CrosCCG 15% (G4); +CrosCCG 20% (G5); +Croscarmellose 3% (G6); Crospovidone 3% (G7); B/L =before lubrication; A/L =after lubrication; NF =no flow

Joint use of HPMC and increasing concentrations (3, 10, 15 and 25%w/w) of CrosCCG revealed an interesting concentration dependent drug release property as shown in Fig. 2. Concentrations of CrosCCG at 10%w/w or lower were found to significantly (P=.05) enhance Ven. HCl release while above 10%w/w a significant (P=.05) delay in drug release was noticed. The two varied results, classified as drug release enhancement and drug release retardation are hereby discussed in turn.

A significant (P=.05) retardation in drug release was noticed as the concentration of CrosCCG was increased from 10%w/w (T3) to 15 %w/w (T4) with a ($T_{80\%}$) of 90 min and 120 min respectively (Table 3). Increasing the concentration to 25%w/w (T5) was however not found to produce significant difference (*P*=.05) in drug release compared to T4.

Release of Ven. HCl from tablets formulated using HPMC ER at 7.5%w/w as a binder was found to follow the Higuchi model. The dissolution data fitted into the various release models was found to fit the Higuchi model with a regression coefficient (R^2) of 0.996 (Table 4). The value of n was found to be 0.45 indicating that the drug release was via Fickian diffusion [19,20]. Drug release from HPMC hydrogel tablets has been reported to be diffusion-controlled [29].

Inclusion of CrosCCG at 10%w/w concentration increased (*P*=.05) the amount of drug released even though $T_{80\%}$ still remained 90 min. At concentrations above 10%w/w, CrosCCG admixed with HPMC ER (7.5%w/w) was found to further delay the drug release. Release of a soluble drug in high concentration from an insoluble matrix follows the Higuchi square root equation wherein drug release is proportional to the square root of time [30,31]. At 15 %w/w CrosCCG concentrations, $T_{80\%}$ became 120 min (Table 3) and the difference in drug release compared to HPMC ER alone was statistically significant (*P*=.05) and still follows the Higuchi square root equation.

At 25%w/w concentration of CrosCCG, a change in mechanism of drug release from Fickian to anomalous (non-Fickian) diffusion with n>0.5 was observed. Extent of swelling of CrosCCG may be a factor responsible for the observed deviation. A swelling-controlled matrix used in drug delivery system must have satisfactory swelling properties [32,33]. Swelling in polymers plays an important role in causing deviations from Fickian diffusion usually as a consequence of the finite rates by which changes in polymer structure occur. The process of sorption-desorption in a polymeric material exposed to moisture leads to a flurry of events starting from swelling followed by stresses then structural changes and relaxations [34-36].

Fig. 3 show the dissolution profile of tablets containing CrosCCG at 3%w/w (T2) compared to two known super disintegrants, Croscarmellose (T6) and Crospovidone (T7) also at 3% concentrations. The tablet batches showed similar physicochemical properties (Table 3) except $T_{80\%}$. All the polymers tested were found to enhance drug release with statistically significant effect (*P*=.05) when compared with drug-release from tablets containing HPMC ER alone or from one polymer to the other. Batches T2 containing CrosCCG and T6 containing Croscarmellose had similar $T_{80\%}$ values of 75%, a figure relatively lower than 90% for the remaining polymers tested. At 15 min, Crospovidone

caused greatest drug release amounting to 49.96% followed by CrosCCG with 47.86% and then Croscarmellose with drug release of 44.93%. After 30 min of dissolution time, the drug release was 64.37%, 62.01% and 59.42% respectively for CrosCCG, Crospovidone and Croscarmellose.

At the 75th minute, drug release caused by CrosCCG almost equaled that of Croscarmellose. By the 90th minute and thereafter, however, Croscarmellose surpassed CrosCCG in drug release (Fig. 4a). Interestingly, swelling ratio of CrosCCG and Croscarmellose showed similar trend. While CrosCCG showed superior swelling rates, Croscarmellose displayed greater swelling extent by similarly overtaking CrosCCG after about 80 min of swelling (Fig. 4b). In trying to describe the rate of swelling of sodium starch glycollate and Croscarmellose, it was concluded that rate, force and extent of swelling have an important role in disintegrants that work by swelling [37]. Swelling was found to be the main mechanism of enhancing drug release exhibited by CrosCCG. A positive correlation exists between tablet disintegration time/cumulative percent of drug released and swelling [38] and also with water uptake [39]. This relationship was classically demonstrated when drug-release enhancement by CrosCCG and Croscarmellose each at 3%w/w were plotted against time (Fig. 4a). CrosCCG caused Ven. HCl release at a faster rate within the first 80 min of *in-vitro* dissolution time, beyond which however, Croscarmellose caused greater drug release. Interestingly, Fig. 4b showed how CrosCCG was superior to Croscarmellose in swelling rate but not in extent. The figure showed how the two curves intersected after about 80 min, where swelling demonstrated by CrosCCG had seized and the curve had almost flattened out while the Croscarmellose steadily swelled and eventually caused more drug release.

The type and amount of disintegrating agent employed in the formulation significantly control the overall rate of dissolution of the dosage form [40]. Cross-linked polymers have been used to enhance drug-release from tablets [39,41]. Crospovidone, a cross-linked polymer, is a known super disintegrant that causes tablet disintegration by wicking water up into the tablet thereby causing the tablet to rupture [42,43]. In this study, it was found to cause greater amount of drug to be released within the first 15 min of dissolution time. Beyond 15 min of dissolution time, however, a change in events was noticed when CrosCCG overtook Crospovidone in causing release of Ven. HCl. Among the polymers tested, Crospovidone was the only one that acts via capillary (wicking) action, a "first step" process that brings about the rapid penetration [43-45] of the tablet surfaces by water causing instantaneous release especially of soluble drugs. This may possibly explain the greater release rate within the first 15 min noted for Crospovidone.

3.4 Sub-Acute Toxicity Studies of CrosCCG

Table 5 shows the results of hematological studies carried out on Wistar rats fed with CrosCCG at the selected concentrations. Comparisons between the control group fed with a feed not containing CrosCCG and test groups fed with increasing concentrations of the material showed no significant differences (P=.05). The biochemical test results (Table 6) also shows no significant differences (P=.05) between the control group and the test groups when tested for the levels of the biochemical parameters.

Acute toxicity studies conducted on CG has shown the gum to be non-toxic [46]. However, insolubility of the cross-linked polymer precluded acute toxicity testing in the present study.

Sub-acute toxicity studies on the animals revealed no apparent changes in the observable behaviours of the animals, associated with possible toxic effect of the material, over the 28 day study period. The monitored animals' feeding and drinking habits were not altered. None of the animals died, appeared dehydrated or emaciated either as a result of poor feeding, drinking or toxic effect of the test material. Both treated and concurrent control group displayed no clinical manifestations or signs of toxicity [22,23].

Table 5 showed the mean values of hematological parameters tested. Blood parameters were used in assessing the effects of the material on the blood and eventually on the body. The results obtained showed no statistically significant differences (P=.05) between the control group and the test groups. CrosCCG can be considered safe as it did not precipitate any untoward changes in the hematological parameters tested [23,47,48].

The results of the effect of CrosCCG on the biochemical parameters tested are as shown in Table 6. Intra- and inter- group statistical analysis of alkaline phosphatase (ALP), serum glutamic

pyruvate transaminase (SGPT, ALT), urea and platelets results using one way Analysis of Variance (ANOVA) and treated with the Turkey's multiple comparison test showed no significant differences (*P*= .05) between the groups. Results on serum glutamic oxaloacetate transaminase levels (SGOT, AST) showed some difference (*P*= .05) when plasma enzyme levels in group AA1 females were compared with the group fed with the lowest dose, AA2 males, but other groups including AA4 that were fed with the highest dose showed no significant difference (*P*= .05). This is taken to be an anomaly, possibly a result of physiological variations and not treatment related. Since increase in concentration of plasma enzymes (AST, ALT, LDH etc) is taken as characterizing liver cell damage [23], it can be concluded that CrosCCG has no deleterious effect on liver cells.

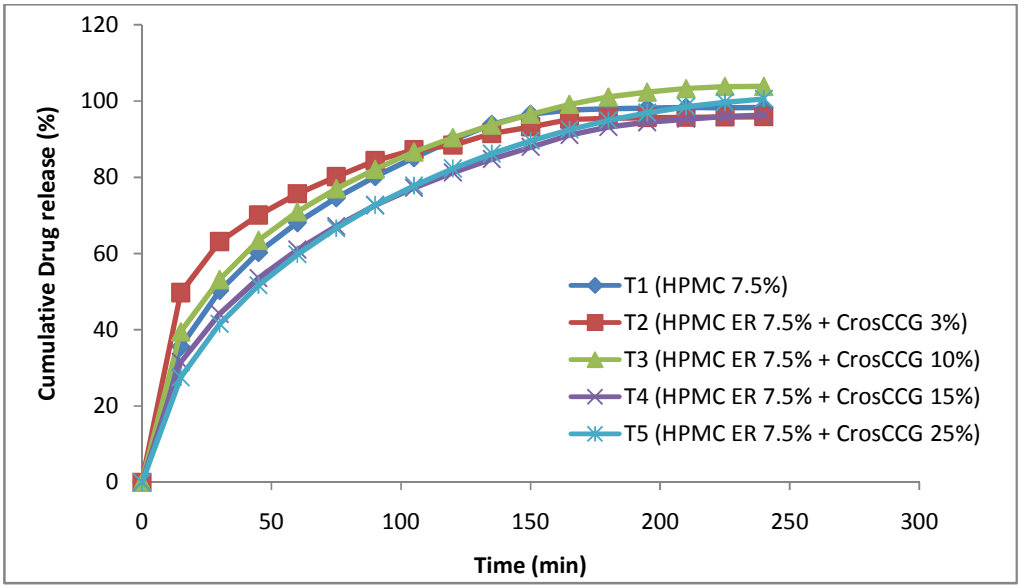


Fig. 2. Effect of concentration of CrosCCG on drug release of Ven. HCl containing HPMC ER as a binder at 7.5%w/w

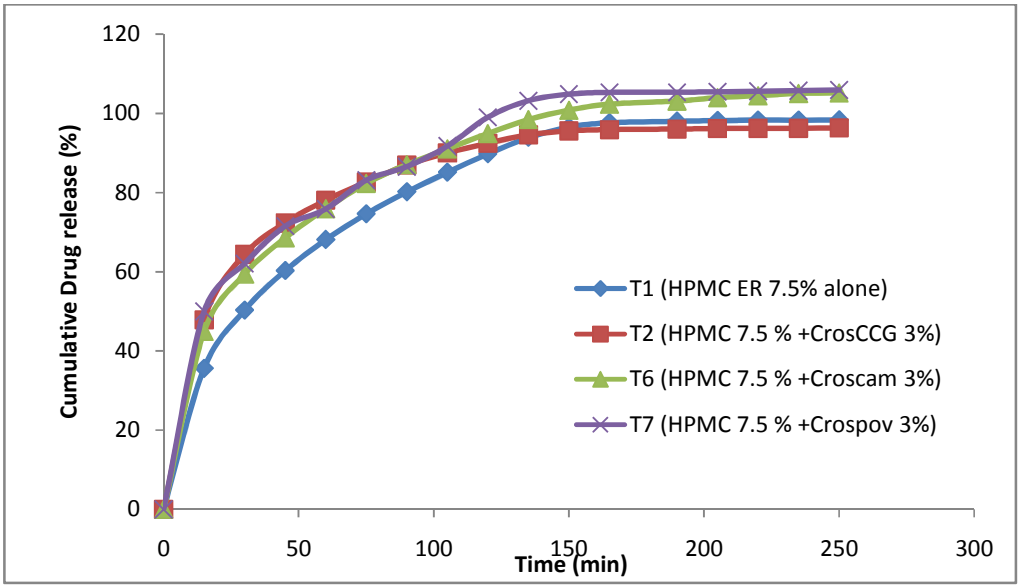


Fig. 3. Effect of various polymers on enhancing Ven. HCl release from tablets formulated with HPMC R 7.5% as a binder

Table 3. Properties of Ven. HCl tablets containing HPMC ER as a binder and some polymers as release modifiers

Parameter	Batches						
	T1	T2	T3	T4	T5	T6	T7
Weight variation (mg±SD)	166.23±1.97	166.67±1.12	168.10±2.08	165.96±1.74	167.03±1.35	165.91±2.40	167.21±0.75
Crushing strength (KN±SD)	5.63±1.31	5.63±0.55	5.12±1.73	5.79±2.21	5.44±1.45	5.50±0.52	5.47±0.79
Friability (%)	0.12	0.19	0.43	0.39	0.57	0.03	0.17
Content of active ingredient (%)	101.56	98.39	100.81	94.23	99.08	99.21	96.87
$T_{80\%}$ (min)	90	75	90	120	120	75	90
Diameter (mm ± SD)	7.040±0.007	7.040±0.006	7.040±0.005	7.040±0.005	7.040±0.006	7.040±0.006	7.040±0.004

Key: HPMC ER 7.5% alone (T1); + CrosCCG 3% (T2); +CrosCCG 10% (T3); CrosCCG 15% (T4); CrosCCG 25% (T5); +Croscarmellose 3% (T6); + Crospovidone 3% (T7)

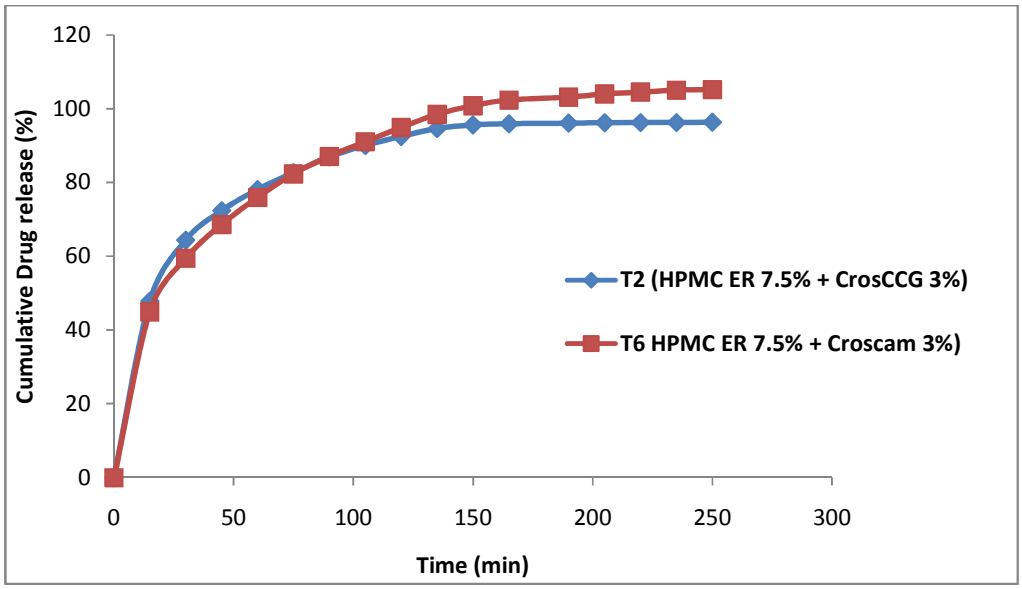
Table 4. Mechanism and Kinetics of drug-release from Ven. HCl made with HPMC ER 7.5% as a binder and CrosCCG at 25 %w/w as a release retardant

Mathematical model	HPMC ER K100		HPMC 7.5% + CrosCCG 25%	
	Regression coefficient (R^2)	n	Regression coefficient (R^2)	n
Zero Order	0.967		0.965	
First Order	0.908		0.882	
Hixson-Crowell	0.933		0.917	
Higuchi	0.996		0.997	
Korsmeyer-Peppas	0.997	0.45	0.997	0.53

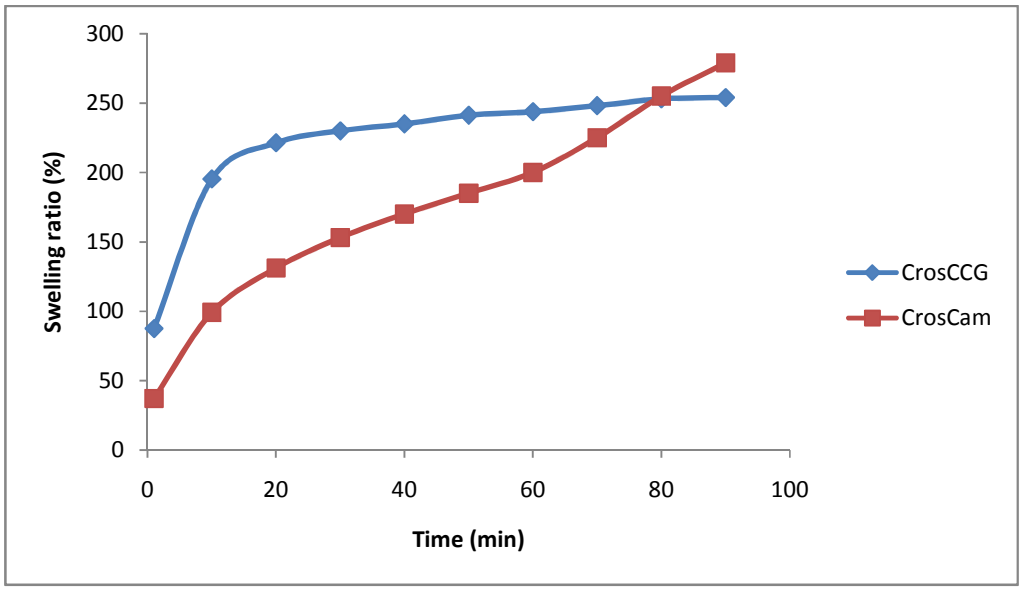
Table 5. Hematological parameters in wistar rats fed with CrosCCG over a 28 day period

Experimental group	Blood parameter mean value (SD)									
	PCV (%)	Hemoglobin (g/dL)	Total protein(g/dL)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Band (%)	TWBC ($x10^9$/L)
AA1 (Cgrp)	44.0(2.5)	14.6(0.8)	6.6(0.5)	15.8(5.3)	81.0(5.3)	1.8(1.5)	-	-	1.3(1.2)	11.2(2.5)
AA2	44.2(2.9)	14.6(1.1)	6.7(0.6)	16.2(5.0)	79.5(6.8)	1.7(1.9)	0.3(0.5)	1.0(2.5)	0.8(1.2)	8.1(3.8)
AA3	44.5(1.9)	14.6(0.8)	6.6(0.7)	16.0(6.6)	79.5(6.6)	2.0 (1.8)	1.7(3.2)	-	0.5(0.8)	9.8(2.0)
AA4	46.0(2.9)	15.3(1.0)	6.7(0.7)	20.8(9.5)	74.7(7.8)	2.7 (2.8)	0.3 (0.8)	0.3 (0.8)	1.2(1.2)	8.2(2.7)

Key: Cgrp = Control group; PCV = Packed cell volume; TWBC = Total white blood; cells; Values in parenthesis represent SD



a



b

Fig. 4. Relationship between CrosCCG and Croscarmellose (a) drug release and (b) Swelling ratio

Table 6. Biochemical parameters in wistar rats fed with CrosCCG over a 28 day period

Expt. group	ALP	AST/SGOT	ALT/SGPT	Platelets	Urea
AA1 (Cgrp)	57.0 (23.7)	14.5 (10.1)	12.3 (16.1)	436.8 (120.3)	6.4 (2.9)
AA2	44.3 (21.7)	8.5 (6.7)	7.5 (2.9)	341.7 (151.5)	6.4 (0.7)
AA3	44.5 (17.4)	8.0 (1.5)	5.7 (2.0)	358.3 (152.1)	6.3 (1.9)
AA4	36.5 (14.3)	15.3 (6.9)	4.5 (2.3)	567.5 (171.0)	6.1 (2.6)

Key: ALP= Alkaline phosphatase; AST= Aspertate transaminase; ALT= Alanine transaminase; Values in parenthesis represent SD

4. CONCLUSION

The cashew gum derivative (CrosCCG) developed by cross-linking with two safe and environmental friendly cross-linking agents; citric acid and glycerol, when used alone even at 25 %w/w concentration was not found to sustain the release of Venlafaxine HCl. However when jointly used with HPMC ER as a matrix former, it was found to display a concentration dependent effect on the release of the drug. At low concentrations, it exhibits a drug release enhancing property while at high concentrations it delayed drug release. This derivative was found to be safe and has potentials to be used as a pharmaceutical adjunct in tablet formulations.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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