



Original Research Article

TABLETING PROPERTIES OF A DERIVATIVE OF CASHEW GUM DEVELOPED VIA CROSS-LINKING USING CITRIC ACID AND GLYCEROL

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 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 using the prescribed official tests. Tablets dissolution test was used to profile the drug release. CrosCCG used at concentrations of 10 %w/w or lower enhanced drug release while concentrations above 10 %w/w delayed drug release.

Keywords: Cashew gum, Derivative, Citric acid, Glycerol, tablet dissolution, drug release modification, Venlafaxine HCl

INTRODUCTION

In a preface to a book on Excipients development, Katdare and Chaubal;s opening sentence was “to facilitate the development of novel drug delivery systems and biotechnology derived drugs, the need for new excipients continues to increase” [1], strengthening the need for continued research into excipients development.

24 While the discovery or synthesis of novel therapeutic agents is taking the center stage in
25 most pharmaceutical companies, excipients development is the next most important area
26 worthy of being researched on. Excipients take the bulk of the floor in any research and
27 development (R & D) unit of any pharmaceutical company, underpinning their relevance
28 in drug delivery. An excellent therapeutic agent may be worthless if it cannot be
29 formulated into an appropriate dosage unit, by optimally harnessing the varied
30 functionalities of excipients or pharmaceutical aids required for its formulation.

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

44 Cashew gum (CG) has been cross-linking using two agents, citric acid (CTA) and
45 glycerol (GLY) in a work by same authors that is yet to be published, and this polymer
46 network (CrosCCG) is considered for use in this study, as drug release modifying agent



47 in Venlafaxine HCl (Ven. HCl) tablets. Increasing concentrations of CrosCCG were
 48 compared with a powerful binder/matrix former, hydroxypropyl methylcellulose
 49 (HPMC ER K100) used at 7.5 %w/w.

50

51 MATERIALS and METHODS

52 MATERIALS

- 53 • Sodium phosphate monobasic, (Caledon Laboratories Ltd, Canada)
- 54
- 55 • Venlafaxine HCl (Cadila Health Care Ltd., India)
- 56
- 57 • Hydroxypropyl methylcellulose - HPMC ER (K100) (Dow Chemicals, USA)
- 58
- 59 • Polyplasdone XL (Crospovidone NF) (ISP Technologies, USA)
- 60
- 61 • Croscamellose Sodium (FMC Biopolymer, USA)
- 62
- 63 • Lactose anhydrous (Kerry Bioscience, USA)
- 64
- 65 • Silicone Dioxide (Evonik Industries, USA)
- 66
- 67 • Magnesium stearate, (Tycol Healthcare, USA)
- 68
- 69 • Cashew gum and CrosCCG were as purified/synthesised in the laboratory
- 70 (IntelliPharmaceutics Inc., Canada)

71

72



73 METHODS

74 Extraction/Purification of CG

75 CG was extracted and purified using a method described by [16]. Dried exudates from
 76 cashew trees were collected, extraneous matter picked out manually and a weighed
 77 quantity was dispersed in deionised (DI) water. Acetone was used to precipitate/purify
 78 the gum.

79

80 Cross-linking CG using CTA and GLY

81 In a related study yet to be published, CG was cross-linked using two cross-linking
82 agents CTA and GLY and the resulting cross-linked polymer characterised.

83 A dispersion of appropriate quantities of CG, CTR, GLY and NaH_2PO_4 was made with
84 some DI water contained in a beaker. The homogenous mixture was transferred into a
85 culture dish and concentrated by heating at 40 °C for 18 h. The solid mass was heated at
86 140 or 170 °C for 30 min for the cross-linking process to take place, and thereafter DI
87 water was used to recover and purify the extracted gum (CrosCCG).

89 Formation of Granules

90 The wet granulation method was used to make granules as represented in Table 1. Ven.
91 HCl, Lactose DT and HPMC ER were used as active agent, diluent and binder
92 respectively. Increasing concentrations, 3, 10, 15 and 25 %w/w of CrosCCG were used to
93 make tablet batches represented by groups G2 to G5 respectively to demonstrate effect of
94 concentration on drug release. Croscarmellose and Crospovidone (G6 and G7)
95 respectively were used to grade level of enhancement of drug release by CrosCCG).
96 Modified drug release in this case is taken to be any deviation from the conventional
97 release profile of the binder used. The active agent and other excipients were accurately
98 weighed and dry mixed for 6 min using a low shear mixer (Kitchen aid, St. Joseph,
99 Michigan USA). DI water, as granulating liquid, was used to wet mass the powder mix
100 while being sheared to obtain optimum granulation. The damp granule mass was spread
101 on paper laid on a tray and dried in a forced air oven (Model 1370 F, VWR Scientific
102 Products, USA) for 3 h or when moisture content determined using moisture analyser



103 (Model LJ 16, Mettler Toledo, Switzerland) was lower than 2%. The dried granules were
 104 milled by passing through a mill (Quadro Comil, Model no. 197 R, Quadro Engineering
 105 Inc., Ontario Canada) fitted with a metal screen affixed to the granulator.

106 **Table 1:** Ven. HCl Tablet Batches Formulae Containing HPMC ER 7.5% as Binder
 107 and Some Polymers as Drug Release Modifiers
 108

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

109



110

111 **Tests on Granules**

112 **Density Measurements**

113 Densities of granules were measured using tap density tester USP (Electrolab, Model
 114 ETD-1020, Globepharm, 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:

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

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

$$\text{Hausner Ratio} = (V_o/V_f) \quad (3)$$

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

Where W is **weight** of sample, V_o is **Initial Volume** and V_f is the **Final Volume**

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 **(50)** g 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.

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.

137

138 **Determination of Powder Particle Size Distribution**

139 Ro-Tap (Model RX-29, W.S. Tyler, USA) was used for the  **determination**. Tarred sieves
 140 (W_1) with different sizes were arranged such that 600 μm was on top, followed by 425
 141 μm , then 250 μm , 150 μm , 106 μm , 53 μm and finally 0 μm (pan) at the bottom. Granule
 142 sample weighing 50 g was placed on the topmost sieve and the shaker  **operated** for 10
 143 min. The sieves with the retained granules were weighed (W_2). The weight of granule
 144 retained on each sieve was calculated using the following relationship

145
$$\text{Weight of powder retained} = W_2 - W_1 \quad (6)$$

146

147 **Addition of Extragranular Excipients**

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

152

153 **Compression of Granules**

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

158

159

Evaluation of Tablet Properties

Uniformity of Weight

Twenty  (20) tablets were randomly selected from each batch and individually weighed using AT 261 DeltaRange balance (Mettler Toledo, Switzerland). The mean weight and deviations from the mean were calculated.

Tablet Crushing Strength

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

Tablet Friability Test

FAB-2 Friability  tester (Logan Instruments Corp., USA)  was used to carry out the friability test. Twenty  (20) tablets from each batch were  taken and weighed and then 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, W_2 = final weight.

182 **Tablet Dissolution Test**

183 Dissolution test was carried out using the paddle method on D 800 Dissolution tester
 184 (Logan Instruments Corp., USA) as described in the USP [17]. The automated tester was
 185 set to analyze the amount of drug released after every 15 min of dissolution time. Paddle
 186 speed was 100 rpm as quantities amounting to 900 ml of DI water were used as
 187 dissolution medium, while the temperature was set at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Drug released was
 188 assessed at the Ven. HCl wavelength of 229 nm.

189

190 **Drug Release Data Model Fitting**

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

196 Drug release mechanism is commonly defined by the release exponent, n . When n is 0.45
 197 (Fickian diffusion); $0.45 < n < 0.89$ (Anomalous (non-Fickian) diffusion); 0.89 (Case II
 198 transport); $n > 1$ (Super case II transport) [18-20].

199

200 **Uniformity of dosage unit test**

201 The USP method [17] was used to determine the content uniformity using Hewlett
 202 Packard diode array spectrophotometer. Ten (10) tablets were weighed individually and
 203 the mean weight determined. The tablets were crushed and three samples of approximate
 204 weights to the mean tablet weight were assayed. The average of three values was taken as

205 the drug content. Ten  (10) tablets were weighed individually and the weights were used
206 to determine the uniformity of the dosage units proportionately according to the USP
207 method.

208

209 **Sub-Acute Toxicity Studies**

210 The method described by  (21) was adopted with some modifications. The experiment
211 was designed and the animals were treated in accordance with the Committee for the
212 Purpose of Control and Supervision on Experiments on Animals (CPCSEA) 1986 Animal
213 Guidelines. The animals (Wistar rats) were grouped into four with each group having 6
214 animals. Subgroups of 3 males and 3 females were made on each group. The animals
215 were conditioned as per the environment, mode of feeding and water supply.

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

The animals were fed the test material for 28 days and then sacrificed on the 29th day [22-24]. 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), aspartate transaminase (AST, SGOT), alanine transaminase (ALT, SGPT) were tested.

Statistical Analysis

All the results obtained that require statistical analysis were analyzed using GraphPad Prism software package. Results were expressed as mean $\pm$ SD and differences between means were considered significant at $P < 0.05$ using the analysis of variance (ANOVA) or student's t test.

RESULTS

Figure 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 °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 [25]. The objective is to quickly find those excipients that should be

249 avoided because of an obvious chemical incompatibility with a particular API [26].

250 Ideally if no interaction occurs, then the mixture should show equivalent transitions to

251 that of the individual components. If it does not, some interaction is indicated [25]. The

252 author, however, observed that issues arise because physical interactions occur that have

253 nothing to do with chemical interactions, which are the basic cause of concern. Presence

254 of impurities in a sample could cause decreases in melting temperatures or shortening of

255 peaks in a DSC curve commensurate to the level of impurity. CrosCCG in this case could

256 be identified as an “impurity” and so the decrease in both the intensity and measure of the

257 melting temperature may not be an indication of interaction. DSC may not give an all

258 conclusive indication of compatibility or otherwise of a given binary mixture and so

259 HPLC, MS are often further used to guide on drawing rational inferences on a drug-

260 polymer compatibility study. The insolubility of CrosCCG precluded the conduct of these

261 additional tests. Experienced analysts, however, have reported that useful information has

262 been obtained from DSC interaction studies and it should be noted that data indicating

263 non-interaction provide significant evidence that no interaction is occurring [25]. Drug

264 release data should be used to substantiate this claim.

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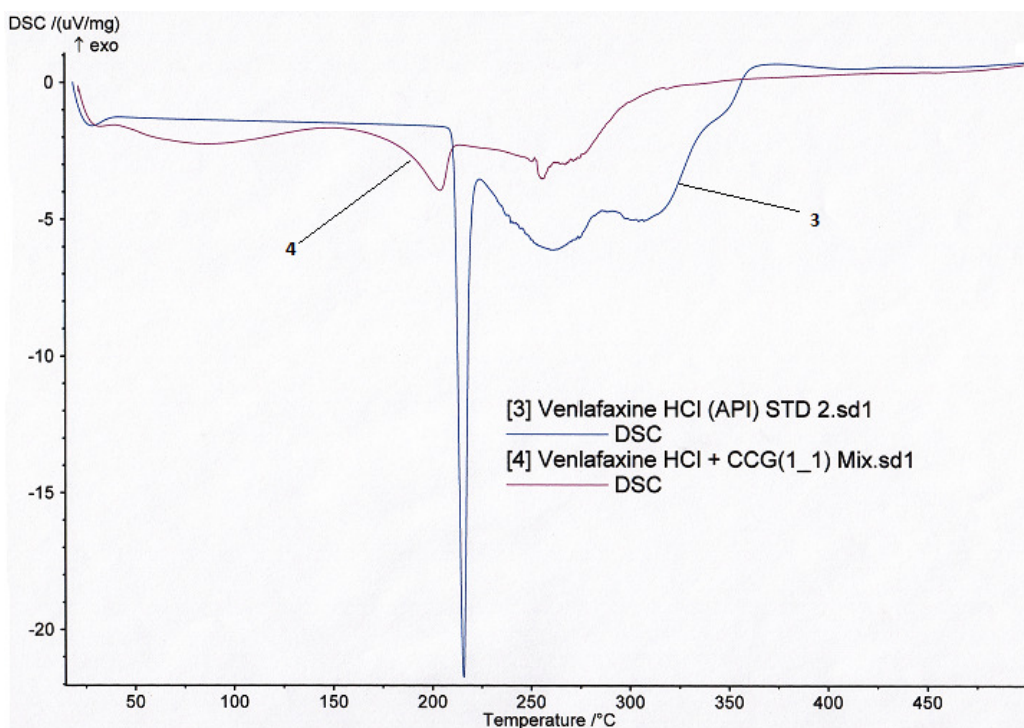


Figure 1: Overlay of DSC thermograms of Ven. HCl and its 50/50 binary mixture with CrosCCG

The properties of granules formed using HPMC ER at 7.5 %w/w as binder and some polymers at varying concentrations as drug release modifiers are shown in Table 2. G1 containing only HPMC ER as binder/matrix former was found to have highest values of Hausner ratio and compressibility index. Powders with % compressibility of 35 – 38 are said to have very poor flow, while those with 28 – 35 % compressibility are said to have poor flow [27]. The granules however failed to flow through the funnel in spite of having compressibility index in the range of flowable materials. Increase in concentration of CrosCCG (G2 to G5) was found to cause a decrease in compressibility index, Hausner ratio and angle of repose while the flow rate increase as the concentration of CrosCCG

281 increased. Inter-batch granule size distribution was found to be somewhat uniform and
282 skewed to the smaller size ranges as the granules were passed through a similar mill.

283 Batches G2, G6 and G7 differing from G1 only in having 3 % of a polymer added to
284 replace 3 % quantity of diluents also failed to flow. At 3 %w/w concentration, the
285 polymers, though free flowing, could not significantly influence the properties of the
286 formed granules.

287 
288 **Table 2:** Properties of Ven. HCl Granules Containing HPMC (ER) as **Binder** at 7.5
289 %w/w and Some Polymers as Release Modifiers
290

		Batches						
Parameter		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 (°)	B/L	-	-	34.19	33.84	33.26	-	-
	A/L	-	-	33.51	33.11	32.40	-	-

291 
292 **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)

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 to release 80 % of drug ($T_{80\%}$) of 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 Figures 3 & 4 show results of tablet properties. Intra and inter batch similarities in 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 dissolution *cum* drug release were however noticed between the batches.

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 Figure 3. Concentrations of CrosCCG at 10 %w/w or lower were found to significantly ($P=0.05$) enhance Ven. HCl while above 10 %w/w a significant ($P=0.05$) delay in drug release was noticed. The two varied results, classified as drug release enhancement and drug release retardation are hereby discussed in turn.

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

321 Release of Ven. HCl from tablets formulated using HPMC ER at 7.5 %w/w as **binder** was
 322 found to follow the Higuchi model. The dissolution data fitted into the various release
 323 models was found to fit the Higuchi model with a regression coefficient (R^2) of 0.996
 324 (Table 4). The value of n was found to be 0.45 indicating that the drug release was via
 325 Fickian diffusion [18-19]. Drug release from HPMC hydrogel tablets has been reported to
 326 be diffusion-controlled [28].

327

328

329 **Table 3:** Properties of Ven. HCl Tablets Containing HPMC ER as **Binder** and
 330 Some Polymers as Release Modifiers
 331

Parameter	Batches						
	T1	T2	T3	T4	T5	T6	T7
Weight variation (mg $\pm$ SD)	166.23 $\pm$ 1.97	166.67 $\pm$ 1.12	168. 10 $\pm$ 2.08	165.96 $\pm$ 1.74	167.03 $\pm$ 1.35	165.91 $\pm$ 2.40	167.21 $\pm$ 0.75
Crushing strength (KN $\pm$ SD)	5.63 $\pm$ 1.31	5.63 $\pm$ 0.55	5.12 $\pm$ 1.73	5.79 $\pm$ 2.21	5.44 $\pm$ 1.45	5.50 $\pm$ 0.52	5.47 $\pm$ 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

332

333 **Key:**

334 HPMC ER 7.5% alone (T1); + CrosCCG 3% (T2); +CrosCCG 10% (T3); CrosCCG
335 15% (T4); CrosCCG 25% (T5); +Crosccarmellose 3% (T6); + Crospovidone 3% (T7)

336

337

338 Inclusion of CrosCCG at 10 %w/w concentration increased ($P=.05$) the amount of drug
339 released even though T_{80%} still remained 90 min. At concentrations above 10 %w/w,
340 CrosCCG admixed with HPMC ER at 7.5 %w/w was found to further delay the drug
341 release. Dissolution of a soluble drug in high concentration from an insoluble matrix
342 follows the Higuchi square root equation wherein drug release is proportional to the
343 square root of time [29-30]. At 15 and 25 %w/w CrosCCG concentrations, T_{80%} became
344 120 min (Table 3) and the difference in drug release compared to HPMC ER alone was
345 statistically significant ($P=.05$) and still follows the Higuchi square root equation.

346 At 25 %w/w concentration of CrosCCG, a change in mechanism of drug release from
347 Fickian to anomalous (non-Fickian) diffusion with $n>5$ was observed. Extent of swelling
348 of CrosCCG may be a factor responsible for the observed deviation. A swelling-
349 controlled matrix used in drug delivery system must have satisfactory swelling properties
350 [31-32]. Swelling in polymers plays an important role in causing deviations from Fickian
351 diffusion usually as a consequence of the finite rates by which changes in polymer
352 structure occur. The process of sorption-desorption in a polymeric material exposed to

353 moisture leads to a flurry of events starting from swelling followed by stresses then
354 structural changes and relaxations [33-35].

355

356

357 **Table 4:** Mechanism and Kinetic of Drug-Release from Ven. HCl made with
358 HPMC ER 7.5% as Binder and Croscoll at 25 %w/w as Release Retardant

359

Mathematical model	HPMC ER K100		HPMC 7.5% + Croscoll 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

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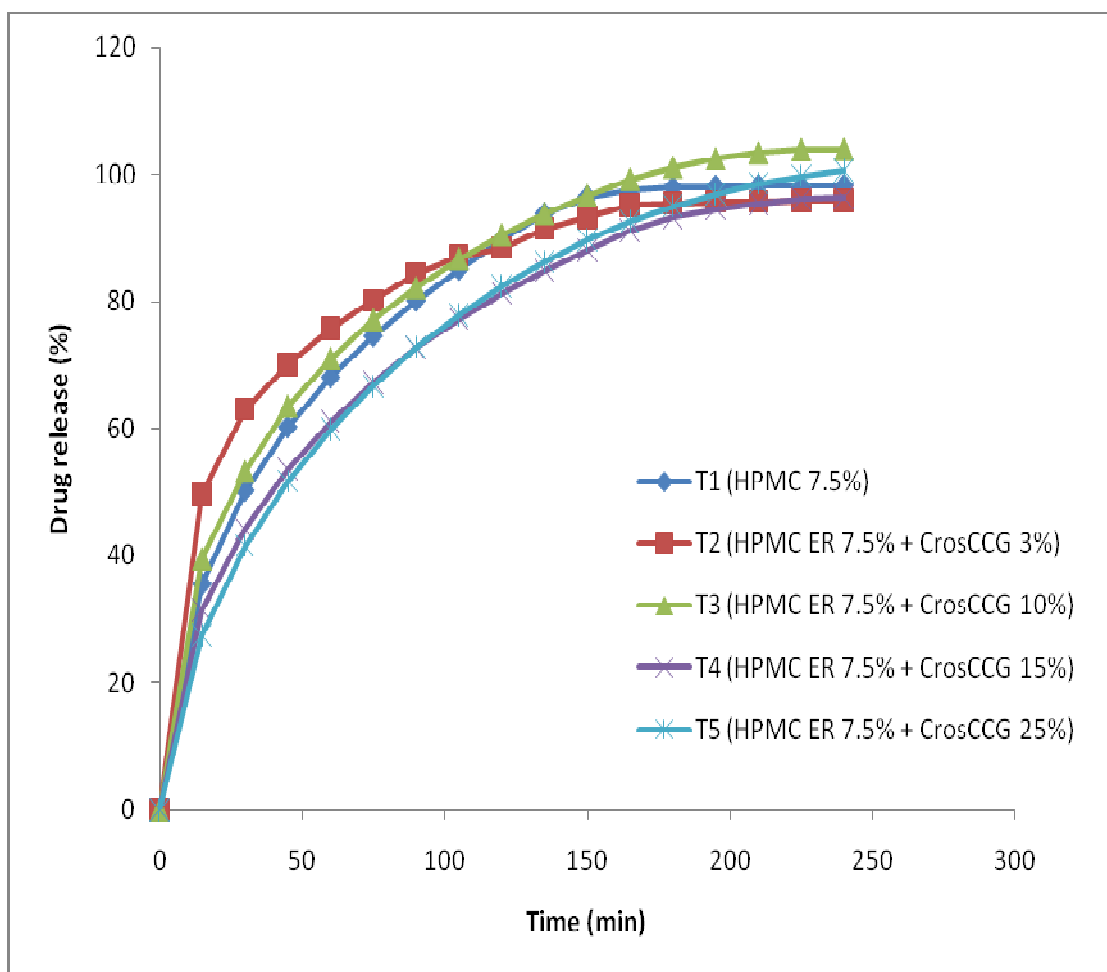


Figure 2: Effect of Concentration of CroscCG on Drug Release of Ven. HCl Containing HPMC ER as Binder at 7.5 %w/w

Figure 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 ($P=0.05$) when compared with drug-release from tablets containing HPMC ER alone or from one polymer to the other. Batches T2 containing

374 CrosCCG and T6 containing Croscarmellose had similar $T_{80\%}$ values of 75 %, a figure
 375 relatively lower than 90 % for the remaining polymers tested. At 15 min, Crospovidone
 376 caused greatest drug release amounting to 49.96 % followed by CrosCCG with 47.86 %
 377 and then Croscarmellose with drug release of 44.93 %. After 30 min of dissolution time,
 378 the drug release was 64.37 %, 62.01% and 59.42 % respectively for CrosCCG,
 379 Crospovidone and Croscarmellose.

380 At the 75th minute, drug release caused by CrosCCG almost equaled that of
 381 Croscarmellose. By the 90th minute and thereafter, however, Croscarmellose surpassed
 382 CrosCCG in drug release (Figure 4a). Interestingly, swelling ratio of CrosCCG and
 383 Croscarmellose showed similar trend. While CrosCCG showed superior swelling rates,
 384 Croscarmellose displayed greater swelling extent by similarly overtaking CrosCCG after
 385 about 80 min of swelling (Figure 4b). In trying to describe the rate of swelling of sodium
 386 starch glycollate and Croscarmellose, [36] concluded that rate, force and extent of
 387 swelling have an important role in disintegrants that work by swelling. Swelling was
 388 found to be the main mechanism of enhancing drug release exhibited by CrosCCG. A
 389 positive correlation exists between tablet disintegration time/cumulative percent of drug
 390 released and swelling [37] and also with water uptake [38]. This relationship was
 391 classically demonstrated when drug-release enhancement by CrosCCG and
 392 Croscarmellose each at 3 %w/w were plotted against time (Figure 4a). CrosCCG caused
 393 Ven. HCl release at a faster rate within the first 80 min of *in-vitro* dissolution time,
 394 beyond which however, Croscarmellose caused greater drug release. Interestingly, Figure
 395 4b showed how CrosCCG was superior to Croscarmellose in swelling rate but not in
 396 extent. The figure showed how the two curves intersected after about 80 min, where

397 swelling demonstrated by CrosCCG had seized and the curve had almost flattened out
398 while the Croscarmellose steadily swelled and eventually caused more drug release.

399 The type and amount of disintegrating agent employed in the formulation significantly
400 control the overall rate of dissolution of dosage form [39]. Cross-linked polymers have
401 been used to enhance drug-release from tablets [38, 40]. Crospovidone, a cross-linked
402 polymer, is a known superdisintegrant that causes tablet disintegration by wicking water
403 up into the tablet thereby causing the tablet to rupture [41-42]. In this study, it was found
404 to cause greater amount of drug to be released within the first 15 min of dissolution time.
405 Beyond 15 min of dissolution time, however, a change in events was noticed when
406 CrosCCG overtook Crospovidone in causing release of Ven. HCl. Of the polymers tested,
407 Crospovidone was the only one that acts via capillary (wicking) action, a “first step”
408 process that brings about the rapid penetration [42-44] of the tablet surfaces by water
409 causing instantaneous release especially of soluble drugs. This may possibly explain the
410 greater release rate within the first 15 min noted for Crospovidone.

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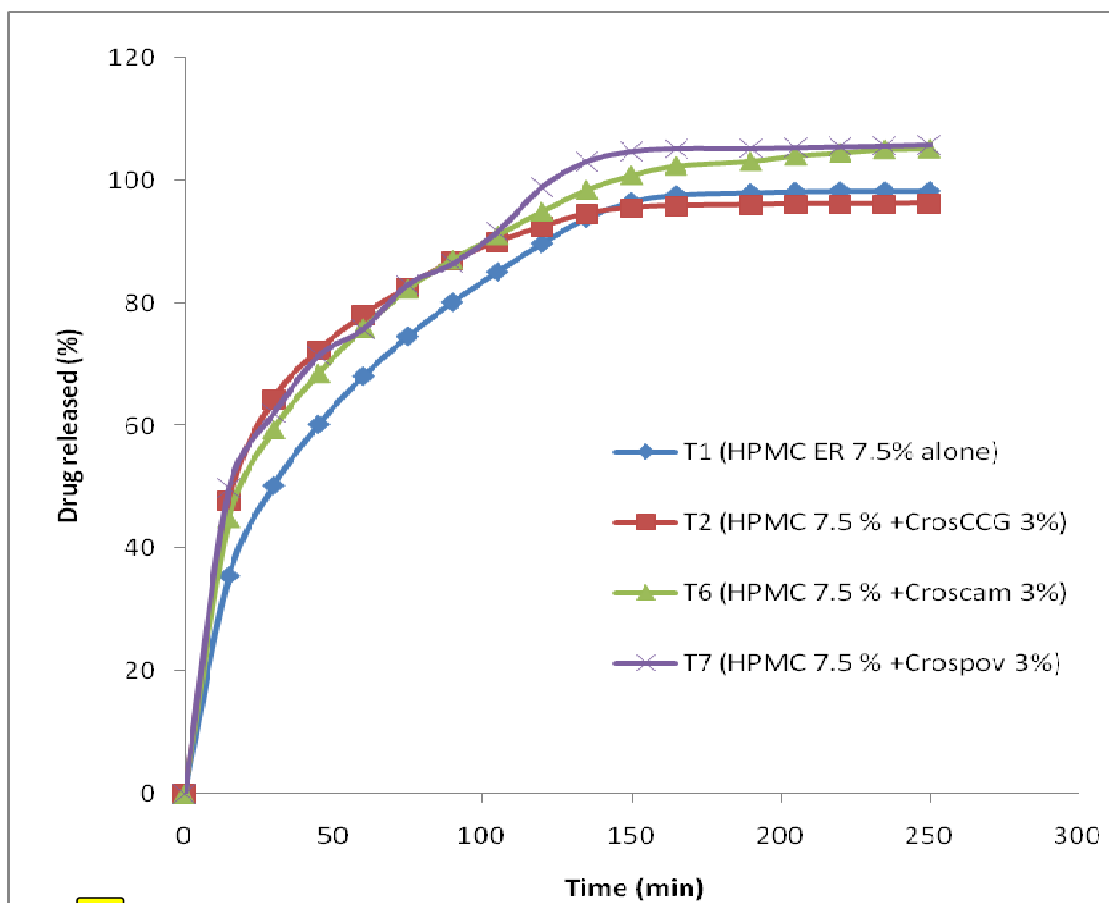


Figure 3: Effect of Various Polymers on Enhancing Van HCl Release from Tablets Formulated with HPMC R 7.5% as Binder

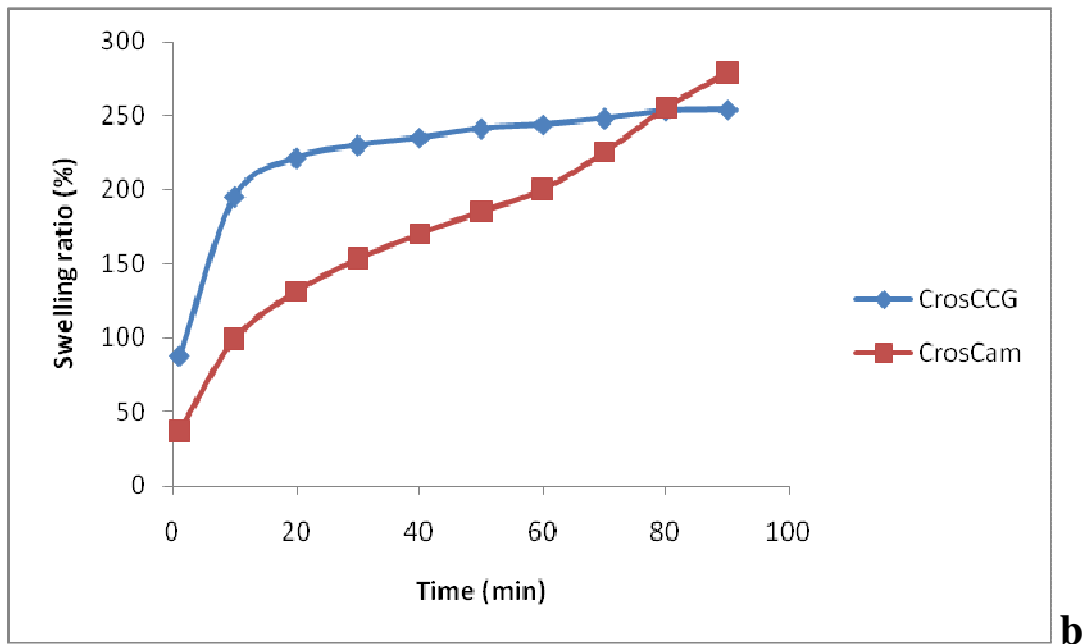
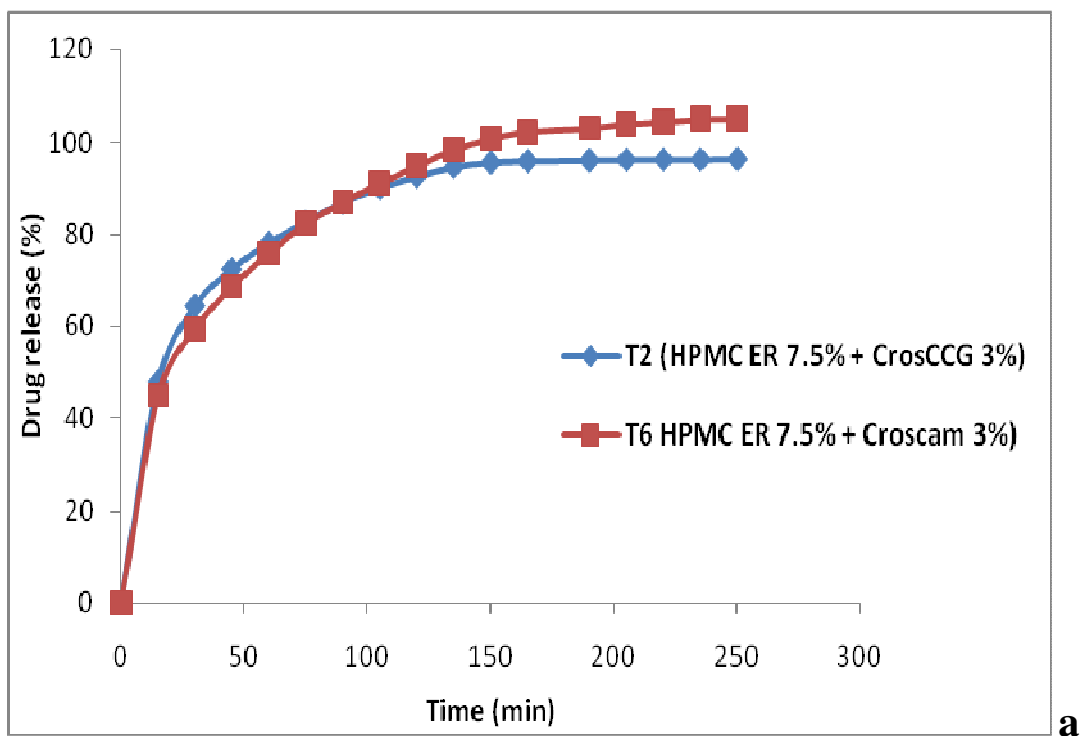


Figure 4: Relationship between CrosCCG and Croscarmellose (a) drug release and (b) Swelling ratio

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437



438 **Table** 5 shows the results of hematological studies carried out on Wistar rats fed with

439 CrosCCG at the selected concentrations. Comparisons between the control group fed with



440 **feed** not containing CrosCCG and test groups fed with increasing concentrations of the

441 material showed no significant differences ($P=.05$). The biochemical test results (Table 6)



442 also shows no **differences** ($P=.05$) between the control group and the test groups when



443 tested for **levels** of the biochemical parameters.

444 Acute toxicity studies conducted on CG has shown the gum to be non-toxic [45].

445 However, insolubility of the cross-linked polymer precluded acute toxicity testing in the

446 present study.



447 **Sub acute** toxicity studies on the animals revealed no apparent changes in the observable

448 behaviours of the animals, associated with possible toxic effect of the material, over the

449 28 day study period. The monitored animals' **feeding** and drinking habits were not



450 altered. None died, appeared dehydrated or **emaciated** either as a result of poor feeding,

451 drinking or toxic effect of the test material. Both treated and concurrent control group

452 displayed no clinical manifestations or signs of toxicity [21-22].

453 Table 5 showed the mean values of hematological parameters tested. Blood parameters

454 were used in assessing the effects of the material on the blood and eventually on the

455 body. The results obtained showed no differences ($P=.05$) between the control group and

456 the test groups. CrosCCG can be considered safe as it did not precipitate any untoward

457 changes in the hematological parameters tested [22, 46-47].

458 The results of the effect of CrosCCG on the biochemical parameters tested are as shown
 459 in Table 6. Intra- and inter- group statistical analysis of the alkaline phosphatase (ALP),
 460 serum glutamic pyruvate transaminase (SGPT, ALT), urea and platelets results using the
 461 one way Analysis of Variance (ANOVA) and treated with the Turkey's multiple
 462 comparison test showed no significant differences ($P= .05$) between the groups. Results
 463 on serum glutamic oxaloacetate transaminase levels (SGOT, AST) showed some
 464 difference ($P= .05$) when plasma enzyme levels in group AA1 females were compared
 465 with the group fed with the lowest dose, AA2 males, but other groups including AA4 that
 466 were fed with the highest dose showed no significant difference ($P= .05$). This is taken to
 467 be an anomaly, possibly a result of physiological variations and not treatment related.
 468 Since increase in concentration of plasma enzymes (AST, ALT, LDH etc) is taken as
 469 characterizing liver cell damage [22], it can be concluded that CrosCCG has no
 470 deleterious effect on liver cells.

471 **Table 5:** Hematological Parameters in Wistar Rats Fed with CrosCCG Over a 28 Day
 472 Period
 473

Experimental Group	BLOOD PARAMETER MEAN VALUE (SD)									
	PCV (%)	Hemoglobin (g/dL)	Total protein (g/dL)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Band (%)	TWBC ($\times 10^9/L$)
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

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= Aspartate transaminase; ALT= Alanine transaminase; Values in parenthesis represent SD

490

491 CONCLUSION

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

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