



**DRUG RELEASE MODIFICATION BY A CITRIC ACID AND GLYCEROL CROSS-
LINKED DERIVATIVE OF CASHEW (ANACARDIUM OCCIDENTALE L.) GUM**

ABSTRACT *Anacardium occidentale*

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.

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

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

25 pharmaceutical company, underpinning their relevance in drug delivery. An excellent
26 therapeutic agent may be worthless if it cannot be formulated into an appropriate dosage
27 unit, by optimally harnessing the varied functionalities of excipients or pharmaceutical
28 aids required for its formulation.

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

41 A derivative of Cashew gum (tagged CrosCCG) has been developed by cross-linking the
42 gum using two agents, citric acid (CTA) and glycerol (GLY), in a work by same authors
43 (16). In the present study, the polymer network (CrosCCG) is considered for use as a
44 drug release-modifying agent to formulate Venlafaxine HCl (Ven. HCl) tablets. Ven. HCl
45 is a highly water soluble, orally active serotonin and noradrenalin reuptake inhibitor used
46 in the treatment of major depressive disorders. Increasing concentrations of CrosCCG

were compared with a powerful binder/matrix former, hydroxypropyl methylcellulose (HPMC ER K100) used at 7.5 %w/w.

MATERIALS and METHODS

MATERIALS

- Sodium phosphate monobasic, (Caledon Laboratories Ltd, Canada)
- Venlafaxine HCl (Cadila Health Care Ltd., India)
- Hydroxypropyl methylcellulose - HPMC ER (K100) (Dow Chemicals, USA)
- Polyplasdone XL (Croscovidone 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)

METHODS

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.

Cross-linking CG using CTA and GLY

In a related study yet to be published, 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 40°C for 18 h. The solid mass was heated at 140 or 170°C 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).

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 500°C at a scan rate of $10^\circ\text{C}/\text{min}$ using nitrogen as purge gas. The Thermograms obtained were used to determine the compatibility or otherwise of Ven. HCl with the polymers as excipients.

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) was 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.

Table 1: Ven. HCl Tablet Batches Formulae Containing HPMC ER 7.5% as 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

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119 **Tests on Granules**

120 **Density Measurements**

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

124 Densities were determined using the following relationships:

125

$$126 \quad \text{Initial Density} = \frac{W}{V_o} \quad (1)$$

$$127 \quad \text{Tapped Density} = \frac{W}{V_f} \quad (2)$$

$$128 \quad \text{Hausner Ratio} = \frac{V_o}{V_f} \quad (3)$$

$$129 \quad \text{Compressibility Index} = \left[\frac{V_o - V_f}{V_o} \right] \times 100 \quad (4)$$

130 Where W is the weight of sample, V_o is the initial Volume and V_f is the final Volume

131

132 **Granule Flow Rate**

133 Glass funnel held by a retort stand with the tip 10 cm from the surface of the table top,
134 was used to measure the flow rate of the granules. Fifty-gram sample was poured into the
135 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.

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

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

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.

Compression of Granules

Betapress Manesty Machine (No. 74182, Manesty Machines Ltd., England) was used to compress the granules (Tables 1) using 0.2756 inch (7mm) 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.

Evaluation of Tablet Properties

Uniformity of Weight

Twenty 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 randomly 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 tablets from each batch were taken, 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 and W_2 = final weight.

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 $37^\circ\text{C} \pm 0.5^\circ\text{C}$. Drug released was assessed at the Ven. HCl wavelength of 229 nm.

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].

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.

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 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 intraperitoneal (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 of CrosCCG per 1 Kg feed over a 28 day period, respectively. 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), aspartate transaminase (AST, SGOT) and 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 the differences between means were considered significant at $P < 0.05$ using the analysis of variance (ANOVA) or student's t test.

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249 **RESULTS**

250 **Drug-Excipient Compatibility Studies Using DSC**

251 Figure 1 shows the DSC measurement curve demonstrating the compatibility or
252 otherwise of Ven. HCl (test drug) with CrosCCG (test polymer). The figure displays the
253 DSC thermograms overlay of 50/50 binary mixture of Ven. HCl and CrosCCG on that of
254 the pure drug. The melting temperature of the drug in its pure form that commonly ranges
255 between 215 to 217 °C appeared shifted to a lower value in the binary mixture. It is
256 important that the drug does not interact with any of the excipients in a way that is likely
257 to reduce its efficacy; therefore, excipients compatibility is important when considering
258 drug stability [26]. The objective is to quickly find those excipients that should be
259 avoided because of an obvious chemical incompatibility with a particular API [27].
260 Ideally if no interaction occurs, then the mixture should show equivalent transitions to
261 that of the individual components. If it does not, some interaction is indicated [26]. It was
262 observed that issues arise because physical interactions occur that have nothing to do
263 with chemical interactions, which are the basic cause of concern. Presence of impurities
264 in a sample could cause decreases in melting temperatures or shortening of peaks in a
265 DSC curve commensurate to the level of impurity. CrosCCG in this case could be
266 identified as an “impurity” and so the decrease in both the intensity and measure of the
267 melting temperature may not be an indication of interaction. DSC may not give an all
268 conclusive indication of compatibility or otherwise of a given binary mixture and so
269 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.

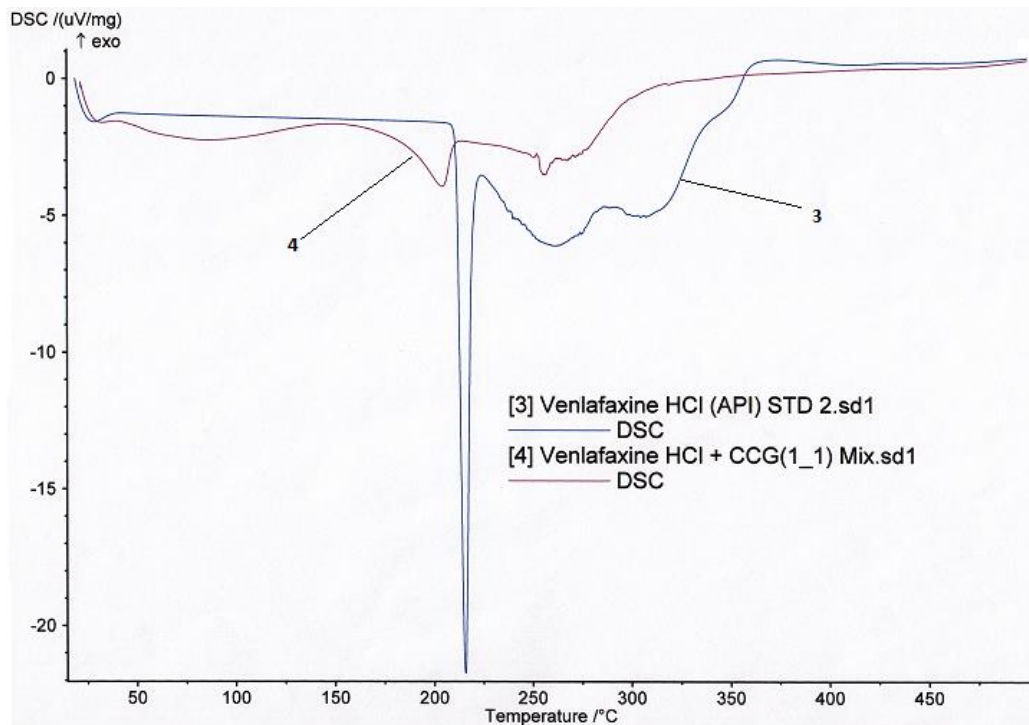


Figure 1: Overlay of DSC thermograms of Ven. HCl and its 50/50 binary mixture with CrosCCG

Granules Properties

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

297
 298 **Table 2:** Properties of Ven. HCl Granules Containing HPMC (ER) as a Binder at 7.5
 299 %w/w and Some Polymers as Release Modifiers
 300

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 (°)	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

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 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 cumulative 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 ($P=.05$) 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].

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 $\pm$ 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 $\pm$ SD)	7.040 $\pm$ 0.007	7.040 $\pm$ 0.006	7.040 $\pm$ 0.005	7.040 $\pm$ 0.005	7.040 $\pm$ 0.006	7.040 $\pm$ 0.006	7.040 $\pm$ 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)

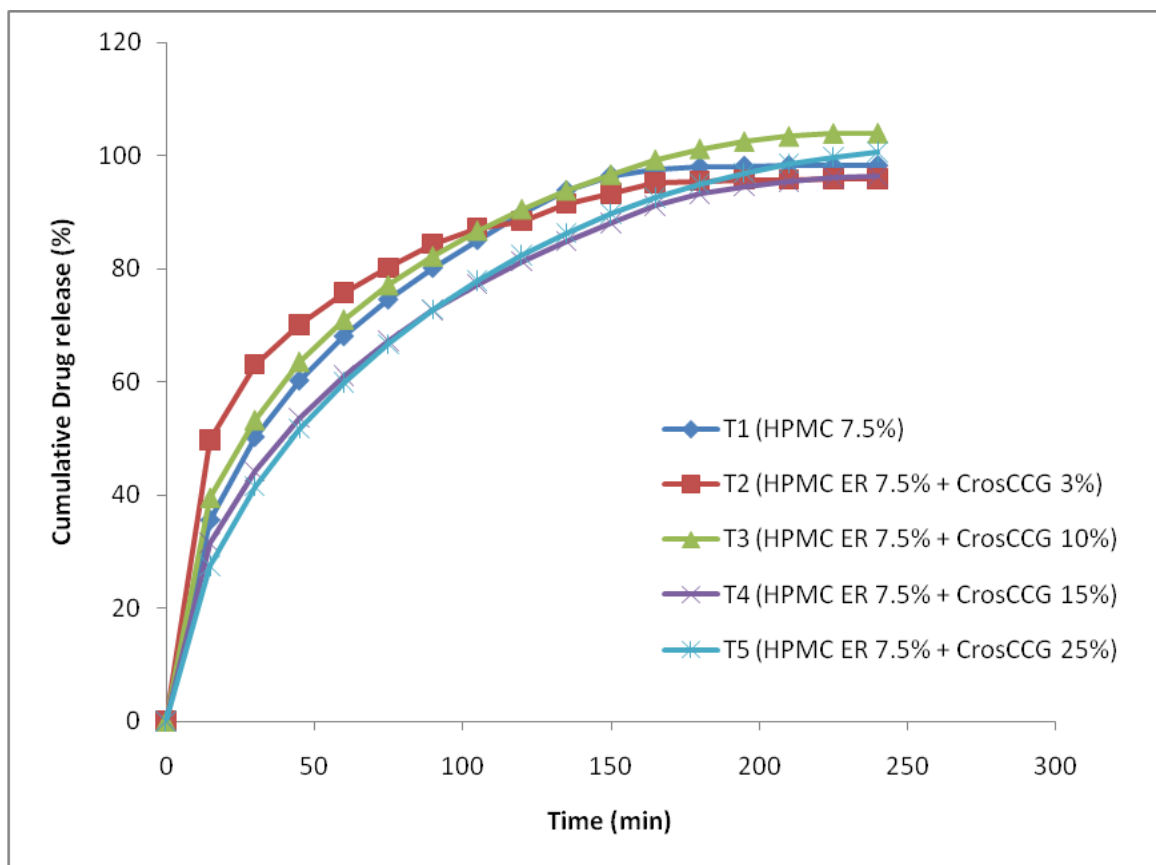
Inclusion of CrosCCG at 10 %w/w concentration increased ($P=.05$) the amount of drug released even though T_{80%} still remained 90 min. At concentrations above 10 %w/w, CrosCCG admixed with HPMC ER (7.5 %w/w) was found to further delay the drug release. Release of a soluble drug in high concentration 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 and 25 %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].

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

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374 **Figure 2:** Effect of Concentration of CroscCG on Drug Release of Ven. HCl
 375 Containing HPMC ER as a Binder at 7.5 %w/w
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379 Figure 3 show the dissolution profile of tablets containing CroscCG at 3 %w/w (T2)
 380 compared to two known super disintegrants, Croscarmellose (T6) and Crospovidone (T7)
 381 also at 3 % concentrations. The tablet batches showed similar physicochemical properties
 382 (Table 3) except $T_{80\%}$. All the polymers tested were found to enhance drug release with
 383 statistically significant effect ($P=0.05$) when compared with drug-release from tablets
 384 containing HPMC ER alone or from one polymer to the other. Batches T2 containing

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

391 At the 75th minute, drug release caused by CrosCCG almost equaled that of
392 Croscarmellose. By the 90th minute and thereafter, however, Croscarmellose surpassed
393 CrosCCG in drug release (Figure 4a). Interestingly, swelling ratio of CrosCCG and
394 Croscarmellose showed similar trend. While CrosCCG showed superior swelling rates,
395 Croscarmellose displayed greater swelling extent by similarly overtaking CrosCCG after
396 about 80 min of swelling (Figure 4b). In trying to describe the rate of swelling of sodium
397 starch glycollate and Croscarmellose, it was concluded that rate, force and extent of
398 swelling have an important role in disintegrants that work by swelling [37]. Swelling was
399 found to be the main mechanism of enhancing drug release exhibited by CrosCCG. A
400 positive correlation exists between tablet disintegration time/cumulative percent of drug
401 released and swelling [38] and also with water uptake [39]. This relationship was
402 classically demonstrated when drug-release enhancement by CrosCCG and
403 Croscarmellose each at 3 %w/w were plotted against time (Figure 4a). CrosCCG caused
404 Ven. HCl release at a faster rate within the first 80 min of *in-vitro* dissolution time,
405 beyond which however, Croscarmellose caused greater drug release. Interestingly, Figure
406 4b showed how CrosCCG was superior to Croscarmellose in swelling rate but not in
407 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 superdisintegrant 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.

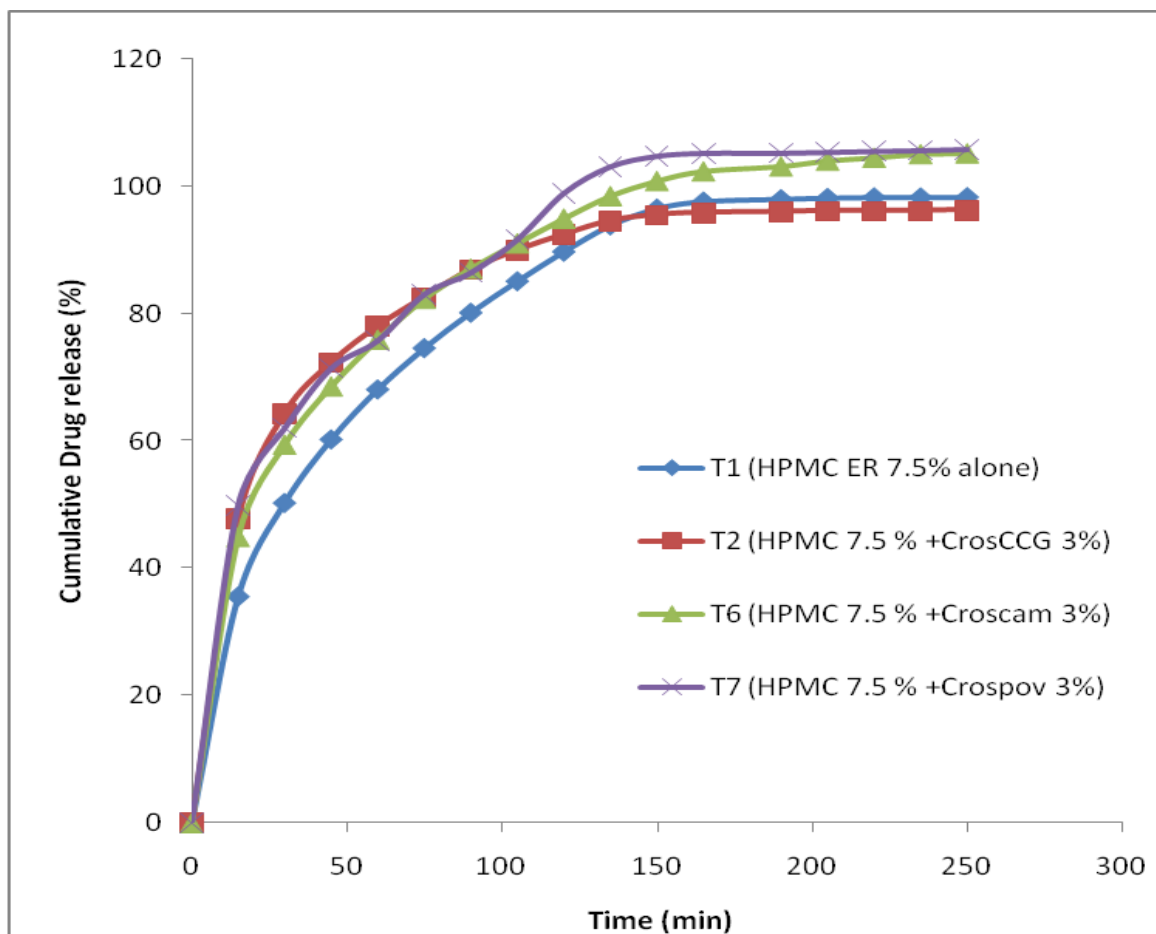
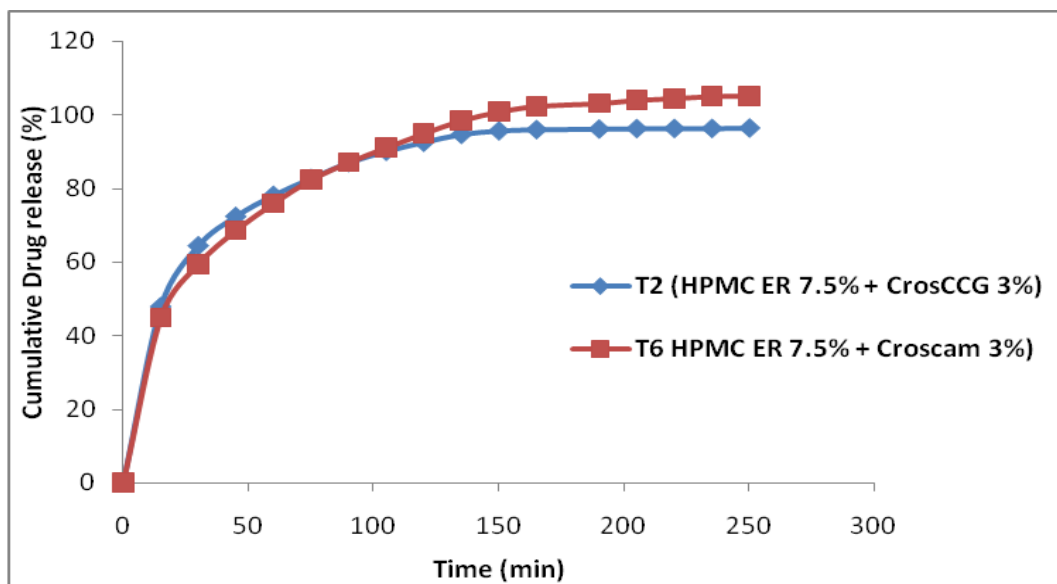
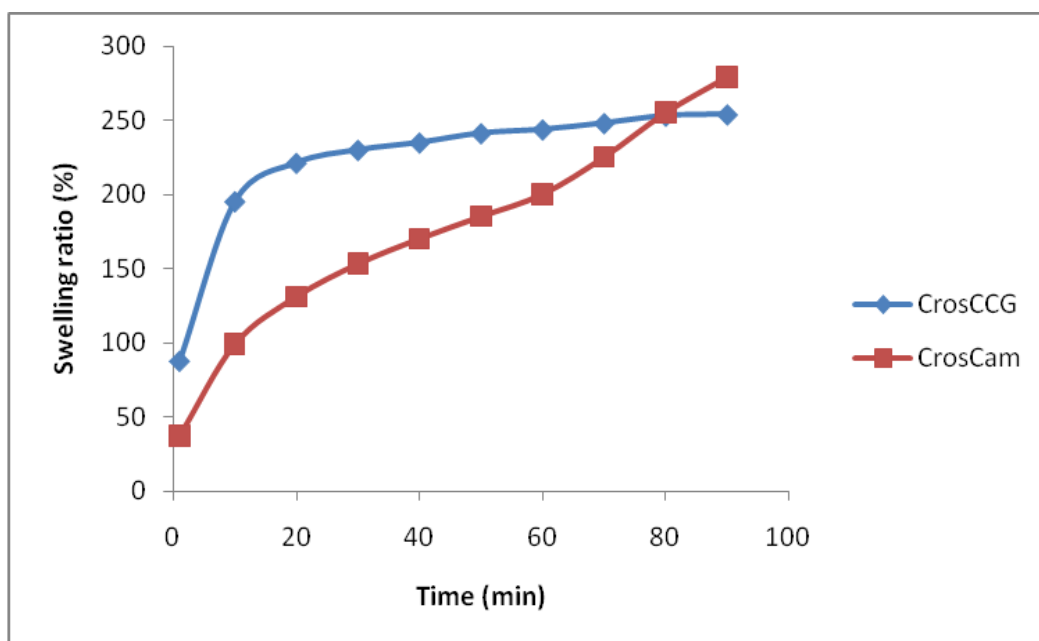


Figure 3: Effect of Various Polymers on Enhancing Ven. HCl Release from Tablets Formulated with HPMC R 7.5% as a Binder



a



b

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

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 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.

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 ($\times 10^9/L$)
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

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 found to be safe and has potentials to be used as a pharmaceutical adjunct in tablet formulations.

REFERENCES

1. Katdare, A. and Chaubal, M.V. (2006). Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems. *NeuroMolecular Pharmaceuticals, Inc.* Pp iii -v
2. Omidian, H. and Park, K. (2008). Swelling agents and devices in oral drug delivery. *J. Drug Del. Sci. Tech.*, **18** (2) 83-93.
3. Silva, D.A., Feitosa, J.P.A., Maciel, J.S., Paula, H.C.B. and de Paula, R.C.M. (2006). Characterisation of Crosslinked Cashew Gum Derivatives. *Carbohydrate Polymers*, **66** 16-26.
4. DeVane, C.L. (2003). Immediate release versus controlled-release formulations: Pharmacokinetics of newer antidepressants in relation to nausea. *J. Clin Psychiatry*, **64** (18) 14-19.
5. Pathak, N., Kumar, A., Meshkar, V., Pant, P. and Rao, R.T. (2012). Formulation and optimization of immediate release tablet of an antialcoholic drug by dry granulation method. *International Journal of Comprehensive Pharmacy*, **2** (3) 1-4.

- 535
536 6. Govedarica, B., Injac, R., Dreu, R. and Drcic, S. (2011). Formulation and
537 evaluation of immediate release tablets with different types of paracetamol
538 powders prepared by direct compression. *African Journal of Pharmacy and*
539 *Pharmacology*, **5** (1) 31-41.
540
541 7. Shukla, D., Chakraborty, S., Singh, S. and Mishra, B. (2009). Mouth dissolving
542 tablets I: An overview of formulation technology. *Scientia Pharmaceutica*, **76**
543 309-326.
544
545 8. Rao, K.M., Gnanaprakash, K., Sridhar, N., Ramkanth, S., Srinivasulu, M., and
546 Chety, C.M (2010a). Design and characterization of mouth dissolving tablets of
547 Zidovudine by using superdisintegrant and solubilizing agent. *Journal of*
548 *Pharmacy Research*, **3** (8) 1764-1768.
549
550 9. Rudnic, E.M. and Schwatz, J.B. (2005). Oral solid dosage forms. In: *Remington,*
551 *The science and practice of pharmacy*. Ed. Troy, D.B. Lippincott Williams and
552 Wilkins Pp 889-928.
553
554 10. Heinig, R., Ahr, G., Hayauchi, Y. and Kuhimann, J. (1997). Pharmacokinetics of
555 the controlled-release nisoldipine coat-core tablet formulation. *Int J Clin*
556 *Pharmacol*, **35** (8) 341-351.
557
558 11. Allen, L.V., Popovich, N.G., Ansel, H.C. (2005). Solid oral modified-release
559 dosage forms and drug delivery systems. In: *Ansel's Pharmaceutical Dosage*
560 *Forms and Drug Delivery Systems*, Lippincott William & Wilkins Pp 260-275.
561
562 12. York, P. (2005). The design of dosage form. In: *Pharmaceutics The Science of*
563 *DosageForm Design* Ed. Aulton M.E. Churchill Livingston Pp 1-13.
564
565 13. Ding, X., Alani, A.W.G. and Robinson, J.R. (2005). Extended-release and
566 targeted drug delivery systems. In: *Remington The Science and Practice of*
567 *Pharmacy*. Ed. Troy, D.B. Lippincott Williams & Wilkins Philadelphia. pp 939-
568 964
569
570 14. Shargel, L., Wu-Pong, S. and Yu, A.B.C. (2005). Multiple-dosage regimens. In:
571 *Applied Biopharmaceutics & Pharmacokinetics*, Published by Mc Graw Hill, Pp
572 185-217.
573
574 15. Collett, J.H. and Moreton, R.C. (2007). Modified-release peroral dosage form. In:
575 *Aulton's Pharmaceutics, the Design and Manufacture of Medicines*, Ed. Aulton,
576 M.E., Churchill Livingston Pp 483-499.
577

16. Abdulsamad A., Oyi, A.R., Isah, A.B. and Odidi, I. (2015). Derivatisation of cashew gum by esterification using citric acid and glycerol. *British Journal of Pharmaceutical Research* (In Press)
17. Abdulsamad A., Oyi, A.R., Isah, A.B. and Odidi, I. (2012). Characterisation and studies on binding properties of Cashew Gum and its Mixtures with Microcrystalline Cellulose in Venlafaxine Hydrochloride Tablet Formulations. *Nigerian Journal of Pharmaceutical Sciences*, **2** (2) 9-20
18. United States Pharmacopoeia (USP) 34 NF 29 (2011). Adipic acid NF Monograph, Pp 1425.
19. Talukdar, M.M., Michoel, A., Rombaut, P. and Kinge, R. (1996). Comparative study on zanthan gum for controlled-release drug delivery 1. Compaction and *in vitro* drug release behavior. *International Journal of Pharmaceutics* **129** 233-241.
20. Shoaib, M., Tazeen, J., Merchant, H.A. and Yousuf, R.I. (2006). Evaluation of drug release kinetics from Ibuprofen matrix tablets using HPMC. *Pak. J. Pharm. Sci.*, **19** (2) 119-124.
21. Dash, S., Murthy, P.N., Nath, L. and Chowdhuri, P. (2010). Kinetic modeling on drug release from controlled drug delivery systems. *Act Poloniae Pharmaceutica-Drug Research*, **67** (3) 217-223.
22. Tamta, A. Chaudhary, M. and Sehgal, R. (2009). A 28-days sub-acute toxicity study in swiss albino mice to evaluate toxicity profile of Neurotol Plus (Mannitol and Glycerol Combination). *International Journal of Biomedical Science* **5** (4) 428-433.
23. Aniagu, S.O., Nwinyi, F.C., Akumka, D.D., Ajoku, G.A., Dzarma, S., Izebe, K.S., Ditse, M., Nwaneri, P.E.C., Wambebe, C. and Gamaniel, K. (2005). Toxicity studies in rats fed nature cure bitters. *African Journal of Biotechnology*, **4** (1) 72-78.
24. Joshi, C.S., Priya, E.S. and Venkataraman, S. (2007). Acute and sub-acute toxicity studies on the polyherbal antidiabetic formulation Diakyur in experimental animal models *Journal of Health Science*, **53** (2) 245-249.
25. Biswas, M., Karan, T.K., Bhattacharya, S., Kumar, R.B.S., Ghosh, K. and Haldar, P.K. (2012). Acute and sub-chronic toxicity study of *Terminalia arjuna* leaf in swiss albino mice. *Pharmacologyonline* **1** 366-371.

26. Saunders, M. (2008). Thermal analysis of Pharmaceuticals. In: *Principles and Applications of Thermal Analysis*, Ed. Gabbott, G., Blackwell Publishing Pp 286-327.
27. Moreton, R.C. (2006). Excipient Interactions. In: *Excipient development for Pharmaceutical, Biotechnology, and Drug Delivery Systems* Eds. Katdare, A. and Chaubal, M.V., Published by Taylor and Francis Group LLC. Pp 93-108.
28. Staniforth, J.N. and Aulton, M.E. (2007). Powder flow. In: *Aulton's Pharmaceuticals, The Design and Manufacture of Medicines*. Churchill Livingstone, Edinburgh Pp 168- 179.
29. Lin, C. and Metters, A.T. (2006). Hydrogels in controlled release formulations: Network Design and mathematical modeling. *Advanced Drug Delivery Reviews*, **58** 1379-1408.
30. Fesssi, H., Marty, J.P., Puisieux, F. and Carstensen, J.T. (2002). The Higuchi square root equation applied to matrices with high content of soluble drug substance. *International Journal of Pharmaceutics*, **1** (5) 265-274.
31. Gupta, P., Vermani, K. and Garg, S. (2002). Hydrogels: from controlled release to pH-responsive drug delivery. *Drug Discovery Today*, **7** (10) 569-579.
32. Caykara, T., Bozkaya, U. and Kantoglu, O. (2003). Network structure and swelling behavior of poly(acrylamide/crotonic acid) hydrogels in aqueous salt solutions. *Journal of Polymer Science: Part B: Polymer Physics*, **41** 1656-1664.
33. Ganji, F., Vasheghani-Farahani, S. and Vasheghani-Farahani, E. (2010). Theoretical description of hydrogel swelling: A review. *Iranian Polymer Journal*, **19** (5) 375-398.
34. Edwards, D.A. (1996). Non-Fickian diffusion in thin polymer films. *Journal of Polymer Science: Part B: Polymer Physics*, **34** 981-997.
35. Kee, D.D., Liu, Q. and Hinestroza, J. (2005). Viscoelastic (non-Fickian) diffusion. *The Canadian Journal of Chemical Engineering* **83** 913-929.
36. Mazumder, S., Bruining, J. and Wolf, K.H. (2006). Swelling and anomalous diffusion mechanism of CO₂ in coal. International Coalbed Methane Symposium, No. 0601, The Netherlands
37. Saharan, V.A., Kukkar, V., Kataria, M., Gera, M. and Choudhury, P.K. (2009). Dissolution enhancement of drugs. Part I: Technologies and effects of carriers. *International Journal of Health Research*, **2** (2) 107-124.

38. Zhao, N. and Augsburger, L. (2005a). The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of Hydrochlorothiazide from directly compressed tablets. *AAPA PharmSciTech* **6** (1) Article 19.
39. Zhao, N. and Augsburger, L. (2005b). Functionality comparison of 3 classes of superdisintegrants in promoting Aspirin tablet disintegration and dissolution. *AAPA PharmSciTech* **6** (4) Article 79.
40. Kumar, V. and Tewari, D. (2005). Dissolution. In: *Remington, the Science and Practice of Pharmacy*, Ed.Troy, D.B., Lippincott Williams and Wilkins, Pp 672-688.
41. Fu, Y., Yang, S., Jeong, S.H., Kimura, S. and Park, K. (2004). Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies. *Critical ReviewTM in Therapeutic Drug Carrier Systems*, **21** (6) 433-475.
42. Davies, P. (2009). Oral Solid Dosage Forms. In: *Pharmaceutical Preformulation and Formulation*, Second Edition. Ed Mark Gibson. Informa Healthcare New York Pp 267-430.
43. Deshmukh, H., Chandrashekhara, S., Nagesh, C., Murade, A. and Usgaunkar, S. (2012). Superdisintegrants: A recent investigation and current approach. *Asian J. Pharm. Tech.* **2** (1) 19-25.
44. Pahwa, R., Piplani, M., Sharma, P.C., Kaushik, D. and Nanda, S. (2010). Orally disintegrating tablets- friendly to pediatrics and geriatrics. *Archives of Applied Science Research*, **2** (2) 35-48.
45. Bhowmik, D., Chiranjib, B., Yadav, J., Chandira, R.M. and Sampath Kumar, K.P. (2010). Emerging trends of disintegrants used in formulations of solid dosage forms. *Der Pharmacia Lettre*, **2** (1) 495-504.
46. Abdulsamad, A., Bhatia, P.G. and Ojile, J.E. (2006). Phytochemical, toxicological and rheological properties of cashew gum and its dispersions. *Nigerian Journal of Pharmaceutical Research*, **5** (1) 85-90.
47. Ramesh, B. K., Raghavendra, H.L., Kantikar, S.M. and Yogesh, H.S. (2010). Toxicological evaluation and histopathological analysis of *TERMINALIA PANICULATA* ROTH. *International Journal of Pharmaceutical Sciences*, **2** (2) 537-543.
48. Kengkoom, K., Chaimongkolnukul, K., Chedyu, S., Inpukaew, R. and Ampawong, S. (2012). Acute and sub-chronic oral toxicity studies of the extracts

709 from herbs in Phikud Navakot. *African Journal of Biotechnology*, **11** (48) 10903-
710 10911.
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726