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Preparation and characterization of Self-disintegrating fast dissolving valsartan tablets using novel hybridized polymer comprising Hydroxypropyl methylcellulose and Acacia gum.

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ABSTRACT

Background: Automation of pharmacotherapy is a recently emerging therapeutic approach that depends on advanced dosage form design engineered through carefully fabricated carriers from two or more excipients
The study seeks to develop and characterised in a solid dosage form, a novel, highly functional composite polymer using a hydrophilic natural (Acacia gum) and synthetic Hydroxypropyl methyl cellulose (HPMC) polymer via cross-linking
Methods: HPMC and Acacia gum (AG) ratio 4:0; 3:1; 2:2; 1:3 and 0:4 were cross linked using citric acid. The batches were characterised by FTIR, welling index, viscosity and pH. Five batches of powder blends were prepared using the hybridized HPMC-AG composite polymer 'F_1, F_2, F_3, F_4, and F_5 as binder in the valsartan (VAL) powder blends. The blends were evaluated for bulk density, angle of repose and compressibility index. Tablets were formulated by direct compression method using Cadmach rotary tableting machine, 12.5 mm die and compression pressure of 10 KN. The tablets parameters such as thickness, diameter, weight variation test, drug content, hardness, friability, and in vitro release studies in phosphate buffer solution (pH 6.8).
Results: The presence of the major functional groups of both polymers after cross-linking proved that there was no complex interaction after the reaction. The powder flow properties and tablets analysis for all batches F1 – F5, showed promising characteristics for an ideal tablet formulation, with average powder flow rate, tablet disintegration time, crushing strength and T90% as follow: F1 (0.10 gs-1, 16.00 min, 135 N, and 20.0 min.) respectively; F2 (0.254 gs-1, 8.48 min, 60 N, and 15.0 min.) respectively; F3 (0.269 gs-1, 10.30 mi, 85 N, and 12.0 min.) respectively; F4 (0.200 gs-1, 4.30 min, 65 N, and 8.0 min.) respectively; F5 (0.315 gs-1, 10.54 mi, 12 N, and 17.0 min.) respectively. The compact formulation 'F4'containing 80 mg VAL 50 mg HPMC, 150 mg AG and 120 mg cellactose have the best property for Self-Disintegrating Fast Dissolving VAL Tablet, better T90 % than the marked generic VAL tablets.
Conclusion: A new 2-component composite polymer highly hydrophilic was formed from citric acid cross-linked HPMC and AG. When used with cellactose to formulate VAL tablets it compressed directly and is suitable for formulation of a new Self-Disintegrating Fast Dissolving Oral Solid Dosage Form with improved bioavailability.

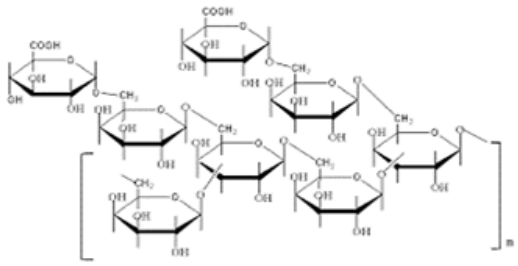
1. Introduction

Tablets are adjudged the most acceptable dosage form for drug delivery, since it is preferred by patients and the industry. Acacia gum (AG) is a prebiotic fibre that is soluble in water; it is used as pharmaceutical ingredient in medications because it acts as an emulsifier, texturizing, film-forming agent, dietary fibre and stabilizer [1].It is an exceptional binder as it forms very strong granules and tablets. Disintegration and dissolution however, are often impeded. Hydroxypropyl methyl cellulose (HPMC) as matrix-forming agents HPMC is low in cost and easy to manufacture, offers little risk of release of the total drug dose (dose dumping effect), provides appropriate release kinetics, and has been extensively studied [2]. Furthermore, pH independent drug release is preferable for oral controlled release formulations, so as not to be affected by intra- and inter-subject variations of both gastric pH and GI

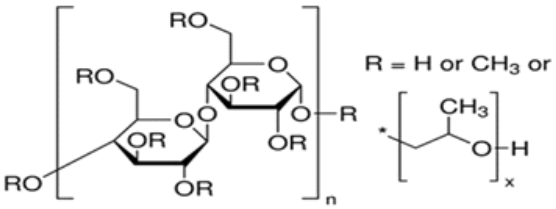
transit time. HPMC is a pH-independent material and the drug release rates from HPMC matrix formulations are generally independent of processing variables such as compaction pressure, drug particle size, and the incorporation of a lubricant [2] However, the mechanism that controls the release of these systems is the gelling of HPMC, which is not always ideal for controlling the release of highly soluble drugs. Often, large amounts of HPMC are required. Another problem is that HPMC is poorly compactable and has poor flow characteristics making it unsuitable for direct tableting while wet granulation can generate rigid particles [3]. Lactose is a soluble excipient and has been widely used in tablet dosage form [4,5,6,7]. Cellactose is one of the best excipients designed for direct compression [8]. Microcrystalline cellulose MCC is an ingredient in cellactose shown to increase dissolution rates and compressibility of tablets made by high shear granulation [9,10]. Valsartan (VAL) is a nonpeptide, orally active angiotensin II antagonist acting on the AT1 receptor subtype. It is classified as a class 3 compound according to the Biopharmaceutics Classification System. Thus having a good solubility but poor permeability, this leads to an overall poor bioavailability. VAL is slowly and partially absorbed from the gut. It is taken orally in the form of tablets of 40, 80, 160 and 320 mg. The absolute bioavailability of VAL is 10 – 30 %. Food decreases the exposure to VAL (as measured by area under the curve [AUC]) by about 40 % and peak plasma concentration (Cmax) 50 % [11].

Swelling Hydrogels are three-dimensional cross-linked polymer networks that are hydrophilic and swells without dissolution in a liquid medium. The absorbed liquid performs a selective filter role to permit free diffusion of some solute molecules, while the polymer network acts as a matrix to hold the liquid together [12]. When a dry hydrogel starts to soak water, the initial water molecules moving into the matrix will hydrate the most polar and hydrophilic groups. As the primary bound water polar groups are hydrated, the hydrogel linkage swells and exposes hydrophobic groups, which also intermingle with water molecules, resulting in hydrophobically bound water or secondary bound water. Primary and secondary bound water are often merged and solely referred to as total bound water [12].

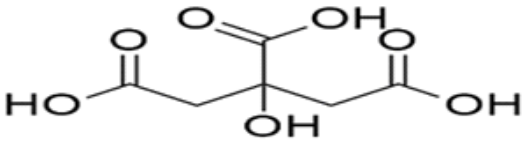
Below are the chemical structures of AG, HPMC, CA and VAL.

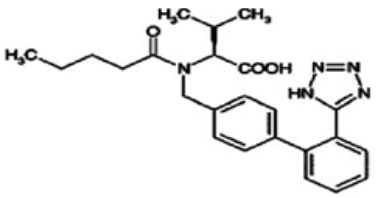


Acacia gum structure (source: Epharmacognosy)



HPMC structure (source:Bakerpedia)





Valsartan structure (source: ResearchGate)

1. Materials and Method

2.1 Materials

Valsartan Sodium (Zhucheng Haotian Pharma Co., Ltd), Cellactose (Molkerei MEGGLE Wasserburg GmbH & Co.KG), . HPMC (A4M, Methocel, Dow, USA), Acacia gum (sigma, Germany) Citric acid ((Biopac, CA, USA)), sodium hydroxide and potassium dihydrogen orthophosphate (Merck Specialties Pvt. Ltd), sorbitol (Meru Chem PVT. Indian)

2.2 Preparation of hydrogels forming solution of HPMC, AG and Citric Acid

A 1.5 g HPMC (A4M, Methocel, Dow, USA) were slowly dispersed in 50 mL of distilled water at 80 °C under constant stirring for 1 h. Sorbitol (S) was added to the plasticizer agent at 0.25% concentration. Afterwards, citric acid (Biopac, CA, USA) was added at 5 %w/v (p/pMC) concentrations as a cross-linker agent in the hydrogels forming solutions. Samples without citric acid were used as control. In all cases a total 100 mL volume was made up with cold distilled water. Hydrogels were prepared by casting and drying in an oven until reaching a constant weight and then stored at 20°C and 65% relative humidity (RH) in a controlled room. The above procedures were repeated for batches with combination of HPMC and Acacia gum (AG) ratio 3:1; 2:2; and1:3 (Table 1).

2.3 Physicochemical Characterization of the Hybridized PolymerMoisture Content Determination

Hydrogels moisture contents were determined by measuring their weight loss until constant weight. Moisture results were expressed as grams of water per 100 g of dried sample (ds).

2.3.1 Determination of swelling index

In a Petri dish, 500 mg of cross-linked was weighed, followed by adding 10 mL of distilled water. The mixture was shaken before being set aside for an hour. The remaining water in the Petri dish was removed after 1 hour, and the weight increase of the cross-linked methylcellulose was measured [13]. For methylcellulose, cross-linked acacia, and acacia, the same process was used.

Swelling Index % $(SI) = (W2 - W1/W1)\, x\, 100$ $Equation$ 1

Where W1 denote weight of compact at time '0' and W2 represent weight of compact at time't'

2.3.2 Fourier Transform Infrared Spectra of the Hydrogels with and without Citric Acid

The Fourier transform infrared (FT-IR) spectra of samples to characterize the presence of specific chemical groups were recorded in an IR spectrometer (Nicolet, iS10, Thermo Scientific, Madison, USA). Hydrogel, HPMC, VAL and AG were each obtained as 1–2 mm thick films and analyzed by FT-IR using Transmittance Mode. FT-IR spectra were obtained in the range of wavenumber from 4000– 400 cm^{-1} during 64 scans.. The FT-IR spectra were normalized and chemical groups were associated with major vibration bands.

2.4 Tablet compression

Formulation of valsartan tablets were prepared by direct compression method. Valsartan was mixed with the required quantities of the hybridised polymer (cross-linked HMPC) and cellactose were used for the preparation of matrix tablets (Table 1). The powders were blended thoroughly using a pestle and mortar. The powder blend was then lubricated with magnesium stearate and mixed for about 3 minutes. Finally the mixture was compressed on a 16-station rotary tablet machine (Cadmach, Ahmadabad, India). Tablets (405 mg) were compressed using a 12.5 mm Round-faced punch with the pressure load of 10 KN. The tablets were evaluated for friability, weight variation, hardness, in vitro disintegration time and in vitro release studies in phosphate buffer (pH 7.4) solution for 1 h.

Table 1: composition of each batch per tablet

Ingredients	F1	F2	F3	F4	F5
Valsartan (mg)	80	80	80	80	80
HPMC (mg)	200	150	100	50	0
Acacia (mg)	0	50	100	150	200
Cellactose (mg)	120	120	120	120	120
Talc (mg)	5	5	5	5	5

2.4.1 Physical evaluation of powder

2.4.1.1 Angle of Repose

Angle of repose which is the maximum angle possible between the surfaces of a pile of powder and horizontal plane can be measured using the equation:

$$tan\,\theta = h/r \qquad Equation\ 2$$

Where θ is the angle of repose, h is stands for the height of the pile, and r represents the radius of the base of the pile [14].

2.4.1.2 Bulk Density (Db) and Tapped Density (Dt)

A suitable amount of powder from each formulation was lightly shaken to break agglomerates and introduced into a 10 mL measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. Bulk density (Db) and tapped bulk density (Dt) were calculated using following formula [15,17]:

$$Db = Wp\ /Vb \qquad Equation\ 3$$

$$Dt = Wp\ /\ Vt = \qquad Equation\ 4$$

Where Wp, Vb, Vt, Db and Dt denote weight of powers, volume of bulk powder, volume of tapped powder, Loose Bulk Density (LBD) and Tapped Bulk Density.

2.4.1.3 Carr Index

The compressibility index of the powder blend was determined by Carr's compressibility index which is a simple test to evaluate the Db and Dt of a powder and the rate at which it packed down. The formula for Carr index is as below:

$$\text{Carr's index (\%)} = \frac{Db - Dt}{Db} \times 100 \quad \text{Equation 5}$$

2.4.1.4 Hausner's Ratio

It is determined by comparing the tapped density to the bulk density and it is expressed as:

- $\text{Hauser ratio (H)} = \frac{Dt}{Db}$ ..... Equation 6

Where Dt is tapped density of the powder and Db is bulk density of the powder.

2.4.2 Evaluation of Tablet Properties

2.4.2.1 Weight Variation

The test was performed according to specifications given in the USP. Randomly, 20 tablets were selected after compression and the average weight was determined. The percentage deviation from the mean was determined for each tablet [16].

2.4.2.2 Friability Test

This test was performed to determine the effects of friction and shock. Pre-weighed sample of 10 tablets was placed in the Erweka® friabilator and rotated at 25 rpm for about 4 minutes. The tablets were dedusted and reweighed, and the friability percentage was calculated using equation.

$$Friability\ (\%) = \left(\frac{[WI - WF]}{WI}\right) x\ 100 \quad \text{Equation 7}$$

Where, W_I is the initial weight of the 10 tablets and W_F is the final weight of the corresponding tablets.

Compressed tablets should not lose more than 1% of weight [17]. A maximum weight loss of 1.0% of weight of the tablets being tested is considered acceptable in most products.

2.4.2.3 Hardness Test

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The hardness of the tablets was determined by diametral compression using Erweka hardness tester and the results were expressed as a mean value of five determination

2.4.2.4 Thickness Test

The thickness was measured by placing tablet between two arms of the vernier calipers. Five tablets were taken and their thickness was measured .

2.4.2.5 Disintegration Time Test

A tablet was placed in each tube in the disintegration apparatus (Erweka ZTGermany) and the basket rack was positioned in a 1 L capacity beaker filled with distilled water to 600 ml mark at 37 °C. The time for the tablet to completely disintegrate and pass through the mesh at the lower end of each tube was recorded as the disintegration time. The results were expressed as mean of five determinations[15].

2.4.2.6 Content Uniformity

Ten tablets of each formulation were crushed and powder equivalent to 1 mg of VAL was suspended in approximately 50 mL of 0.1 N HCl and shaken for 15 minutes. Final volume was adjusted to 100 mL with 0.1 N HCl and filtered (Whatman No.1 filter paper). After serial dilution the absorbance of final solution was recorded at 250 nm using UV/Vis spectrophotometer against a reagent blank and the content was compared from a calibration curve prepared with standard VAL in 0.1 N HCl [12].

2.4.2.7 *In vitro* Dissolution Studies

Six tablets of each formulation were used in the dissolution experiments. The dissolution rates of valsartan were determined in USP 24 type II apparatus (paddle method, Erweka DT 6RGermany®) at 37 ºC in 900 mL phosphate buffer solution (pH 6.8) with the rotation speed of 50 rpm. At appropriate time intervals, 5 mL of sample was withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were analyzed spectrophotometrically at 250 nm. A linear correlation ($R^2 >$ 0.9976) was obtained over the range of 0.25–1.5µg/mL. The dissolution data obtained was plotted as per cent cumulative drug released versus time [16].

2.5 Data Analysis

Results were analysed using Graph Pad prism 7 (Graph Pad prism 6 software. Inc., USA), and the results were expressed as mean ± standard deviation. Differences of $P < 0.05$ was taken as statistically significant, others were

presented as %. Some presented in graphical form.

1. Results

Transparent and flexible hydrogels were obtained for all citric acid concentrations with the addition of citric acid in the plasticized HPMPC, AG and CA hydrogels (Figure 1).

Incorporation of 5% citric acid (AC) to HPMC+AG hydrogels plasticized with 0.25% sorbitol caused a significant decrease of swelling capacity with respect to hydrogels without citric acid. Citric acid was found to be a crosslinking agent for HPMC and AG hydrogels when used in low concentrations (5% w/w).

Table 2: Characterization of the cross linked 2-component composite polymers

Cross -linked HPMC + Acacia	Bulk volume (ml)	Tapped volume (ml)	Bulk density g/ml	Tapped density g/ml	Flow rate gs^{-1}	Angle of repose (0)	Car's index (%)	Hausner ratio
Ratio 3:1	8	6.9	0.636	0.738	0.909	31.75	13.82	1.16
Ratio 2:2	9.5	7.5	0.663	0.840	1.352	30.51	21.07	1.27
Ratio 1:3	9.7	7.6	0.732	0.934	0.985	37.07	21.63	1.28
HPMC	25	21	0.400	0.476	0.238	19.54	15.97	1.19
Acacia gum	14.5	11.5	0.697	0.878	2.530	27.41	20.76	1.26

From Table 2, the cross linked polymers (HPMC: AG) ratio 3:1, 2:2, 1:3, showed an impressive improvement in flow rate over HPMC but less than AG. They all showed higher level of compressibility index.

Table 3: Swelling Indices of cross-linked and normal polymers

Excipients Used	Before (g)	After (g)	Swelling Index (%)
HPMC + Acacia(3:1)	0.2	0.4	96
HPMC + Acacia(2:2)	0.2	1.0	400
HPMC + Acacia(1:3)	0.5	1.8	260
HPMC	0.5	4.8	866

3.1 Swelling index (SI)

The SI for cross-linked HPMC-AG ratio 3:1, 2:2, 1:3 are 96, 400, and 260 % respectively (Table 3). The SI for HPMC was determined as 866 %. The results indicate that cross HPMC with AG reduces the swelling index of HPMC

3.2 FT-IR Analysis

FT-IR spectra of AG showed bands at 3365 cm^{-1}, 2920 $cm^{-1,}$ 1729 cm^{-1}, 1609 cm^{-1} and 1426 cm^{-1} (Figure 1A), that of HPMC; 3483.91 cm^{-1}, 2926.65 cm^{-1}, 1637.99 cm^{-1}, 1052.25 cm-1. (Fig.1B). Valsartan FTIR : at 3455.41 cm^{-1}, 2961.48 cm^{-1}, 1729.82 cm^{-1}, 1603.71 cm^{-1}, 1106.07cm^{-1} (Fig. 1C), HPMC + Acacia :3464.91cm^{-1}, 2938.51cm^{-1}, 1732.98cm^{-1}, 1619cm-1, 1071.24cm^{-1} (fig. 1D), while that of HMPC+AA+Valsartan : 3531.40cm^{-1}, 3233.93cm^{-1}, 2939.31cm^{-1}, 1729.82cm^{-1}, 1600cm^{-1} (Fig 1E).

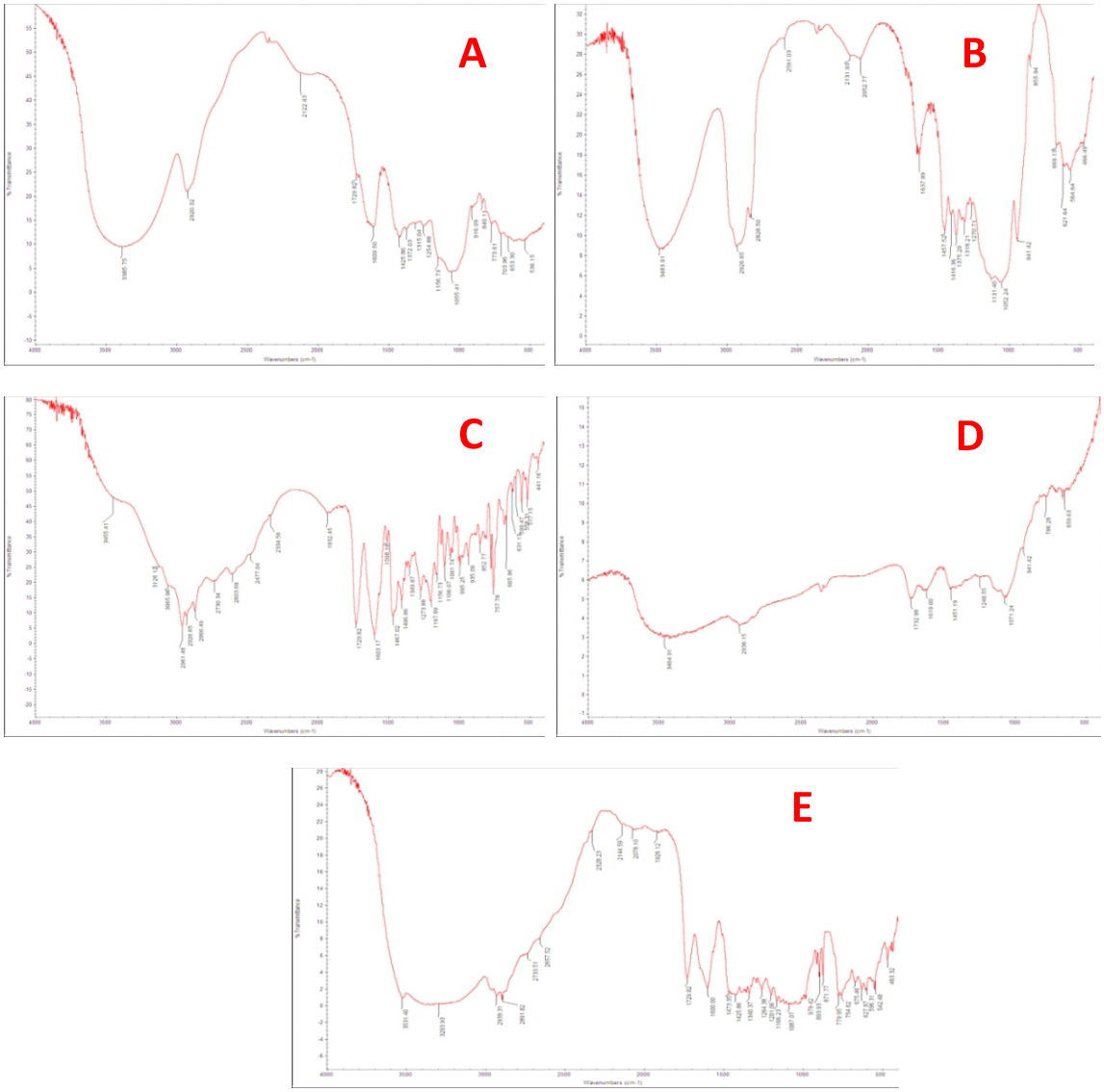


Fig. 1: FT-IR of Acacia gum (A); HPMC (B), Valsartan (C), HMPC2 + Acacia2 (D), HPMC + AA +Valsartan ©.

Table 4: Characterization of powder mixtures for direct compression

Crosslinked polymers plus excipients	Weight of powder (g)	Bulk volume (ml)	Tapped volume (ml)	Bulk density g/ml	Tapped density g/ml	Flow rate (gs^{-1})	Angle of repose (°)	Car's index (%)	Hausner ratio
F1	8.55	22	17.0	0.389	0.503	0.100	35.54	22.66	1.29
F2	8.69	17.5	14.0	0.497	0.621	0.254	37.04	19.97	1.25
F3	8.62	17.2	13.0	0.501	0.663	0.269	36.03	24.43	1.32
F4	8.68	17.0	14.0	0.511	0.620	0.200	37.04	17.51	1.21
F5	8.68	17.0	13.5	0.511	0.643	0.315	34.64	20.53	1.26

The blends of different proposed formulations (F1 to F5) were evaluated for Loss Bulk Density (LBD), Tapped Bulk Density (TBD), compressibility index and angle of repose (Table 4). The results of LBD and TBD ranged from 0.389 ± 0.001 to 0.511 ± 0.002 g/cm^3 and 0.503 ± 0.003 to 0.663 ± 0.004 g/cm^3, respectively. The results of compressibility index (%) ranged from 17.51 ± 0.02 to 24.43 ± 0.04 %. Generally, compressibility index values up to 30 % result in good flow properties. The results of angle of repose ranged from 34.64 to 37.04 °.

The results of angle of repose (36 - 40) indicate fairly good flow property, having static cohesive index 0.6 – 0.8.

Table 5: Compact properties of compressed tablets for batches F1to F5

Batch	Tab wt (g)	Tab. Diam - eter (mm)	Tab. Thick - ness (mm)	Tab. Crushing Strengh (kgf)	Disintegration (min)	Friability (%)	Drug content (%)
F1	0.410 ±0.002	12.50	2.50	13.5 ±0.3	16.00 ± 0.5	2.2	99.0 ±0.15
F2	0.405 ±0.001	12.80	2.80	6.0 ±0.1	8.48 ± 0.2	0.0	99.5 ±0.02
F3	0.405 ±0.002	12.85	2.75	8.5± 0.2	10.30 ± 0.4	0.0	99.0 ±0.05
F4	0.405 ±0.001	12.79	2.67	6.5± 0.3	4.30 ± 0.5	0.0	99.8 ±0.03
F5	0.410 ±0.003	12.74	2.58	12.0±0.2	10.54 ± 0.4	0.0	98.0 ±0.04

The thicknesses of tablets in all formulations were ranged from 2.50 ± 0.01 mm to 2.80 ± 0.03 mm. The weight of tablets in all formulations were ranged from 405 ± 0.15 % to 410 ± 0.31%.The hardness of all the formulations F1-F5 was found to be 60 ± 2 to 13.5 ± 1.0 N.

The disintegration ranged from 4.30 ± 0.5 to 16.0 ± 0.5 minute, friability of all the F1-F5 formulations was found to be 0.00 % to 2.2 % respectively. Drug content of all the formulations were ranged from 98.00 ± 0.15 % to 99.80 ± 0.02 %. All the values are given in (Table 5). The % swelling index of all the cross-linked polymers is given in (Table 3).

3.3 Beer's Concentration to confirm the linearity range

The drug was found to be soluble in 0.1 N sodium hydroxide. So, 0.1 N sodium hydroxide was selected for the analysis of valsartan by UV spectroscopy. Aliquots of standard solution of valsartan were suitably diluted to give varying concentrations ranging of 0.25- 1.50 µg/ml. The absorbance was measured at about 250 nm and values were presented (**Figure** 1)**.** The results of dissolution studies showed that $T_{90\%}$ for F1, F2, F3, F4, F5 and a marketed generic tablet (MGT) are 20, 15, 12, 17, and 20 min. respectively.

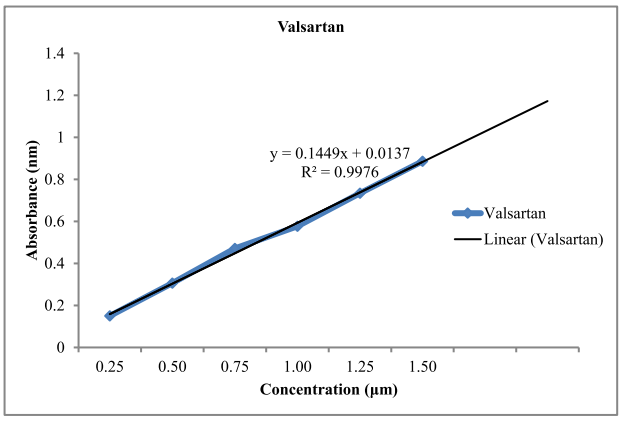


Figure 2 Calibration chart for Valsartan

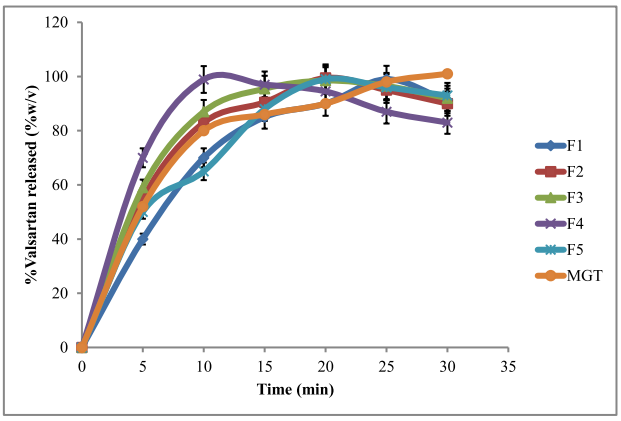


Figure 1: Percentage of valsartan released form the tablet batches A to D against time in minutes

4. Discussion

Citric acid cross-linking is reported to cause yellowing, when cured at high temperatures and/or long periods of time [18].

The interaction between citric acid, HPMC, AG and Valsartan was evaluated. Characterization of the resulting citric acid and hydrogels was carried out.

FT-IR spectra of GA showed characteristic bands at 3365 cm^{-1} for the OH group and 2920 cm^{-1} which represents the aliphatic groups (-CH_2, -CH_3). The band at 1729 cm^{-1} is due to asymmetric and symmetric stretching of the COO- group. The band at 1426 cm^{-1} is due to the bending of the -OH group away from the acid group. The maximum conformational and position variations of the -OH, -COO− groups at 3365 and 1609 cm^{-1}, respectively, were observed to contribute to the reduction. FTIR spectra of pure Valsartan displayed bands at 3455.41 cm - 1 due to N-H stretch, at 2961.48 cm^{-1} due to aliphatic groups, at 1729.82 cm^{-1} due to Carboxylate stretching. The spectra also showed bands at 1603.71 cm^{-1} due to C=N Bending, 1106.07cm^{-1} due to C-N bonding. The FTIR of HMPC displayed peaks corresponding to literature [19].

The most intense peak appeared at 1071.24 cm^{-1}, denoting the presence of the glucose ring appeared at 1037.07 cm^{-1} after cross-linking (Fig. 1D). The ratio of peak intensities at 1425.86 cm^{-1}, which represents –C-H absorptions is seen at 1473.33 cm^{-1} after cross-linking (Fig. 1D). The presence of the major functional groups of both polymers after cross-linking proved that there was no complex interaction after cross-linking. There was an extension of the absorption zone at 2000 -1500 cm-1 (Figure 1D) which was due to the interaction of the CA with the polymers. This band appearance shows the interaction between AC and polymers [20]. More so, the –OH stretch at 3365. cm^{-1} (Fig. 1A) and 3483.91 cm-1 appeared broader at 3233.93 cm^{-1} in Figure 1D.

The FTIR spectra of the cross-linked polymer and Valartan (Fig. 1E) showed the functional groups of Valsartan as: N-H stretching at 3531.40 cm^{-1}, carbonyl for carboxylate stretching appearing at 1729.82 cm^{-1}, while the aromatic ring appeared at 1600.00 cm^{-1}, and the C-N bonding is seen at 1166.23 cm-1. These results were comparable with those from other authors who observed the absorption band of citric acid crosslinked with different polymer matrices [21, 22, 23]. Xie et al.[24] proposed a mechanism explaining the crosslinking reaction of cellulose polymers with CA that when CA is heated, it is dehydrated to form a cyclic anhydride reacting with the polymer. According to Zhou et al.[25] the two main stages of the reaction of polyfunctional carboxylic acids with cellulose are due to fixation of carboxylic acids through esterification with a cellulose hydroxyl group and its subsequent reaction through esterification with another cellulose hydroxyl, which produces a cross-linking between the cellulose chains.

Hydrogels with added AC showed a lower swelling capacity with respect to hydrogels without citric acid as. It was observed that the cross-linked HPMC-Acacia gum hydrogel was highly hydrophilic rapidly dissolving in water giving a clear and transparent solution.

Formation of a more compact structure after crosslinking prevents swelling of the polymer [20]. Citric acid was found to be a crosslinking agent for Acacia gum and HPMC hydrogels when used in low concentrations (5% w / w). Cross-linking (esterification) took place between the carboxylic group of the citric acid and the hydroxyl groups of the HPMC.

The crosslinking decreased water permeability and swelling properties.

The FTIR spectrum of Valsartan self-disintegrating tablet exhibited characteristic bands consistent with the molecular structure of Valsartan which indicated that no chemical interaction occurred between the drug and the excipients used in the formulation (Fig. E).

Table 2, showed an improved flow rate for the cross linked polymers (HPMC: AG) ratio 3:1, 2:2, 1:3, over HPMC but less than AG. They all showed higher level of compressibility index.

The SI for cross-linked HPMC-AG ratio 3:1, 2:2, 1:3 were obtained as 96, 400, and 260 % respectively. They were found to be lower than the pure HPMC 866 % (Table 3). A possible explanation for lower SI values for the three cross-linked batches compared to the pure single individual polymer is likely due to the esterification between the carboxylic group of the citric acid and the hydroxyl groups of the HPMC during crosslinking leading to decreased swelling properties hence, reduced viscosity of complex polymers formed from hydrophilic HPMC and acacia gum (hybridized polymer). This new development will favour a rapid release of drug from tablets formulated with such hybridized complex polymer.

The blends of different proposed formulations (F1 to F5) were evaluated for Loss Bulk Density (LBD), Tapped Bulk Density (TBD), compressibility index and angle of repose. Table 4 showed acceptable physicochemical properties for all the powder mixtures.

The tablet thicknesses and weight variation test for all the

batches were within acceptable limit.

Formulations F1 to F5 were prepared from pure HPMC (F1), hybridized/cross-linked polymers (F2 to F4) and pure acacia gum (F5) respectively by direct compression method (Table 1). Formulations (F1) contained HPMC and cellactose, it exhibited very high crushing strength with physical problems such as surface cracking, and breakdown.. This batch disintegrated in 16 min. Formulations (F2-F4) prepared utilizing HPMC, acacia gum cross-linked and cellulose showed moderate hardness illustrated by crushing strength of 60, 85 and 65 N and disintegration time of 8.48 $\pm$ 0.2, 10.30 $\pm$ 0.4, and 4.30 $\pm$ 0.5 s, respectively (Table 5). These three batches possessed higher physical stability with 0.00 % friability. F5 comprising of acacia gum and cellactose, possessed higher crushing strength (12 N), higher physical stability with 0.00 % friability. The presence of acacia in varying concentration along with cellactose in formulations F4 to F5 modified the tablet hardness with 0.00 % friability. None of the tablets deviated from the average weight by more than ± 5 % [14].. However, tablets of batch F4 were prepared from combination of HPMC 50 mg, acacia gum 150 mg and cellactose 120 mg showed highest drug release property better than all other formulations with disintegration appearing as melting of tablets in average duration of 4 min. A marketed generic valsartan tablets (MGT) containing 80 mg active ingredient were purchased and the physicomechanical properties were compared with tablets of formulation F1 to F5. The MGT possessed T90 % of 20 min which is far higher than that of F2, F3, F4 and F5 (15, 12, 8, and 17 min. respectively.

5. Conclusion

The new trend in the field of pharmaceutical technology is automation of drug delivery system. This has placed a demand on establishment of new excipients engineered to have multiple functionalities. The new two component composite polymer obtained from cross-linking of HPMC and AG with CA is a novel excipient having a three in one functionality expressed as, high compressibility, self-disintegration and fast dissolution. This improved composite polymer highly hydrophilic yielded better valsartan release as measured by T90 % of 8.00 min. for the formulation F4 when compared with a marketed generic tablet with average T90 % of 20 min. Future generation of drug delivery systems could therefore be derived from engineering of polymers through cross-linking for both conventional and controlled release drug delivery systems.

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