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Characterization and evaluation of *Terminalia randii* gum as a binder in carvedilol tablet formulation

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Abstract

The gum exudates obtained from the incised trunk of *Terminalia randii* (Family Combretaceae) have been evaluated as binding agent in carvedilol tablet formulations in comparison with standard binders - polyvinylpyrrolidone (PVP) and corn starch. The physicochemical properties of the gum was characterized by scanning electron microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR), X-ray powder diffraction (XRPD), particle size analysis, pH and viscosity determinations. The mechanical properties of the tablets were assessed using the crushing strength and friability tests while drug release properties were assessed using the disintegration and dissolution times. The crushing strength of the tablets increased while the friability decreased with increase in the concentration of the binding agents. The ranking of the crushing strength of the tablet was formulations containing PVP > Terminalia gum > corn starch while the ranking for friability was the reverse. The disintegration and dissolution times of the tablets also increased with increase in the concentration of the binders. The ranking of the disintegration time was PVP > Terminalia gum > corn starch while the ranking of dissolution time was Terminalia gum > PVP > corn starch. The results indicate that the binding properties of Terminalia gum compared favorably with those of the standard binders and could also find application in controlled release tablet formulations.

Keywords: Terminalia gum, binding agent, polyvinylpyrrolidone, carvedilol, corn starch

Introduction

Binders are one of the most widely used pharmaceutical excipients in tablet formulation. They impact cohesion to pharmaceutical powders and improve the compaction and flow properties of the granules (Banker and Anderson 1986, Odeku 2005). Binders impact strength to tablets and provides resistance to capping and chipping during processing, handling and transportation. A wide array of plant polymers have been employed as emulsifying agents (Odeku et al. 1997, Nasipuri et al. 1999), suspending agents (Verma and Razda 2003, Femi-Oyewo et al. 2004), matrices for sustained drug release (Deshmukh et al. 2009, Emeje et al. 2009) and binders in tablet formulations (Odeku and Itiola 1998, Panda et al. 2008). These polymers have been found to be very useful and in some cases, they have shown superior properties to existing polymers. The fact that these polymers are inexpensive, widely available, non toxic and biodegradable has fostered interest in them.

Terminalia randii Bak.f. (Family Combretaceae) is a small deciduous tree about 10-15m high. The branches

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are arranged horizontally in tiers or as an inverted cone, and the leaves set at the end of the branches are clustered in groups of 3-6 at the end of the branches. The bark is smooth with beige to grey brown colour, with yellowish or beige slash while the stem is pubescent. The plant is native to Madagascar but it is widely distributed from Senegal to Cameroon as far as Uganda, Eastern and Southern Africa. Extracts of the stem and bark of *Terminalia randii* are used in the treatment of dysentery, diarrhea, hemorrhoids and wounds. The root extracts are used as tonic, astringent, diuretic, aphrodisiac and in the treatment of body weakness, depression, cough, jaundice, urinary infection, colic, tooth decay. Extracts of the leaves are used for the treatment of tuberculosis, fever, skin diseases, impetigo and leprosy.

Terminalia gum is exudates obtained from the incised trunk of the tree *Terminalia randii*. A literature search has revealed that so far, no work has been done to characterize this naturally available and non-toxic gum and to investigate its use in pharmaceutical formulations. Thus in the present work, Terminalia gum has been characterized using Fourier Transform Infrared Spectroscopy, X-ray powder diffraction, scanning electron micrograph, pH and viscosity measurements. The binding properties of Terminalia gum has been evaluated in a carvedilol tablet formulation and compared with those of commonly used binding agents - polyvinylpyrrolidone and corn starch using the mechanical and drug release properties as assessment parameters.

Materials and Method

Materials

The materials used were carvedilol.(Ranbaxy Pharmaceuticals, New Delhi, India), corn starch (S.D Fine Chemicals Ltd, Mumbai, India), polyvinylpyrrolidone Molecular weight 58,000 (ISP Technologies Inc, Wayne, USA), lactose monohydrate (Ind-Swift Labs Ltd, Parwanoo, India) magnesium stearate and talc (Loba Chemie PVT Ltd, Mumbai, India). Terminalia gum obtained from the incised trunk of *Terminalia randii*, was collected from Olabisi Onabanjo University, Ago-Iwoye, Nigeria. The plant was authenticated by Mr O.S. Shasanya of the Forest Research Institute of Nigeria (FRIN) with a Voucher number of FHL NO 107917. All other materials used are analytical grade.

Collection and extraction of Terminalia gum

The trunk of the tree *Terminalia randii* was incised and the gum exudates were allowed to dry and then hand picked from the trees. The dried gum was washed and dried in hot air oven at 40°C for 48 h. The gum was then crushed to break up the gum and then hydrated in double strength chloroform water for 5days with intermittent stirring. The mucilage obtained was strained through a clean calico cloth and the gum was precipitated with 95% w/v ethanol. The precipitated gum was filtered, washed with diethyl ether and then dried in hot air oven. The dried gum was pulverized and passed through sieve size No 60 (250 μm).

Characterization of Terminalia gum

The viscosities of aqueous dispersions containing different concentrations (1%w/v, 2%w/v, 5%w/v and 7.5%w/v) of Terminalia gum were determined at room temperature using a Brookfield's viscometer (Brookfield Engineering Lab Inc., Middleboro, MA, USA).

The pH of a 1%w/v of the gum was determined with a microprocessor based pH Meter (Model 1012, Esico, Mumbai, India).

The particle size and the particle size distribution of Terminalia gum powder were determined by using the Malvern Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, UK).

The powdered gum was mounted on an aluminium stub and coated with gold in a fine coat ion sputter JFC-1100 (JOEL, Tokyo, Japan). The SEM photograph of the powdered gum was taken with a JSM 6100 scanning microscope (JOEL, Tokyo, Japan) at a voltage of 15KV.

The FTIR spectrum of the powdered gum was recorded with a Perkin Elmer RXI spectrophotometer (Connecticut, USA). The dry powder was mixed with KBr and pressed into pellets. The spectrum was obtained by scanning between 4000 and 500/cm.

An X-ray diffraction pattern of the powdered gum was obtained with XPERT-PRO diffractometer (PAN Analytical, Almelo, Netherlands). The X-ray diffraction pattern was obtained at room temperature using Cu as anode material, operated at a voltage of 45KV and current 40mA. The sample was analyzed in the diffraction angle (2θ) range of 5° to 50°.

Preparation of granules

Batches of granules with a basic formulation containing 6.25% w/w carvedilol (drug), 80.75% w/w lactose (filler) and 5% w/w corn starch (disintegrant) were prepared using wet granulation method. The binders - Terminalia gum, corn starch, and polyvinylpyrrolidone were used at concentrations of 7.5% w/w and 10% w/w. The materials were accurately weighed and thoroughly mixed and then moistened with appropriate quantity of mucilage the binding agent until a coherent mass was formed. The mass was passed through a No 16 (1180 μm) mesh sieve and the granules obtained were dried in a tray dryer (Narang Scientific Works, New Delhi, India) at 50°C for 2 h. The dried granules were passed through No 20 (850 μm) mesh sieve and then mixed with 1% w/w magnesium stearate and 2% w/w talc.

Granule properties

The angle of repose of granules was determined by the fixed funnel method Panda et al. (2008). The bulk and tapped densities were determined by weighing 2 g (W) of granule a 10 mL measuring cylinder. After the initial volume (V_O) was measured and the cylinder was tapped on a hard surface until no further change in volume was observed. The tapped volume (V_T) was noted. Bulk density (BD) and tapped density (TD) were calculated using the following formula:

$$BD = W / V_O$$

$$TD = W / V_T$$

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = \frac{TD - BD}{TD} \times 100$$

Hausner ratio was calculated from the ratio of the tapped density to the bulk density. The granule size and size distribution of each batch of granule were determined by using the Malvern Mastersizer 2000 (Malvern instruments Ltd, Worcestershire, UK).

Preparation of tablets

Granules (100mg) were compressed into tablets on a single punch machine (Modern Engineering, New Delhi, India) with a 6.5 mm diameter die. After ejection, the tablets were stored over silica gel for 24 h to allow for elastic recovery.

Tablet properties

Twenty tablets from each batch were selected randomly and weighed individually using a Mettler Toledo electronic balance (Zurich, Switzerland). Their mean weights were calculated.

The crushing strength of the tablets was determined using a Monsanto hardness tester (MAC, Macro Scientific Works, Delhi, India). Six tablets were used for each batch and the results are given as the mean±SD.

Friability test was carried out on a friabilator (MAC, Macro Scientific Works, New Delhi, India) operated at 25 rpm for 4 minutes. Determinations were done in quadruplicates.

The disintegration test was carried out in distilled water at 37°C ±0.5°C using a Mac disintegration test apparatus (Macro Scientific Works, New Delhi, India). Determinations were done in quadruplicates.

The *in vitro* dissolution test was carried out in 900 mL of 0.1M HCL maintained at a constant temperature of 37±0.5°C using a USP Type 2 dissolution test apparatus (Labindia Dissolution test apparatus DISSO 2000, Labindia instruments

PVT Ltd, Thane, India) rotated at 50 rpm. Samples (5 mL) were withdrawn at different time intervals and replaced with fresh medium. The samples were diluted and the amount of carvedilol released was determined using a UV spectrophotometer (Genesys 6, Thermospectronic, USA) at a wavelength of 242 nm. Determinations were done in quadruplicates.

Determination of drug content

Ten tablets were finely powdered and an amount equivalent to the weight of 6.25mg of carvedilol was weighed into a 100mL volumetric flask and 0.1N HCL was added. The solution was sonicated for 15mins to allow for proper solubility of the drug. The solution was made up to volume and filtered. The samples were diluted and the drug content was determined using a UV spectrophotometer (Genesys 6, Thermospectronic, USA) at a wavelength of 242 nm.

Statistical analysis

Statistical analysis was done to compare the effect of the different binders on the tablet properties using ANOVA (GraphPad Software Incorporation, San Diego, USA). At 95% confidence interval, p values of ≤ 0.05 were considered significant.

Results and Discussion

The average particle size of the Terminalia gum was found to be 117 μm. The scanning electron micrograph of Terminalia gum is presented in Figure 1. The micrographs show that the particle of the powdered gum is polygonal. The particle shape of powders can affect the packing and compaction characteristics of powders. It has also been reported that particle size and specific surface area influence the hydration behavior of gums, which in turn influence their intrinsic viscosity and molecular mass (Wang et al. 2003). It has been shown experimentally that particle size influenced the hydration kinetics and molecular mass of guar gum (Wang et al. 2003).

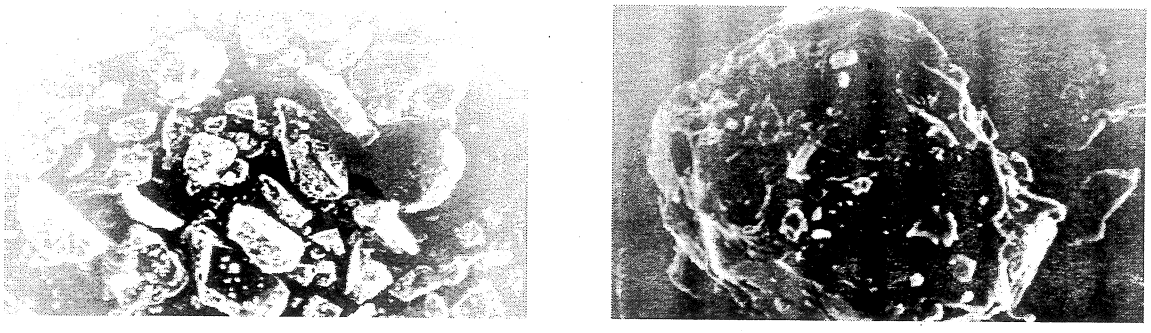

Figure 1. Scanning electron micrographs of Terminalia gum

The binding application of polymer gums depends on their hydrophilic and viscoelastic properties which are quantifiable by certain physicochemical properties such as the viscosity. The change in the viscosity of the Terminalia gum with change in shear rate is presented in Figure 2. Terminalia gum exhibited thixotropy which is the ability of some non-Newtonian pseudoplastic fluids to show a time-dependent change in viscosity; the longer the fluid undergoes shear stress, the lower its viscosity. Non Newtonian fluids do not settle easily and they undergo shear thinning which is time dependent. The viscosity of a 1% w/v of Terminalia gum at room temperature was 27.5cp. The viscosity of the polymer solution also increased with increase in the concentration of the gum. The pH of Terminalia gum at a temperature of 31.4°C was 4.56. This indicates that the gum is acidic in nature. This is expected as gums are generally macromolecular acids (Odeku and Fell 2004).

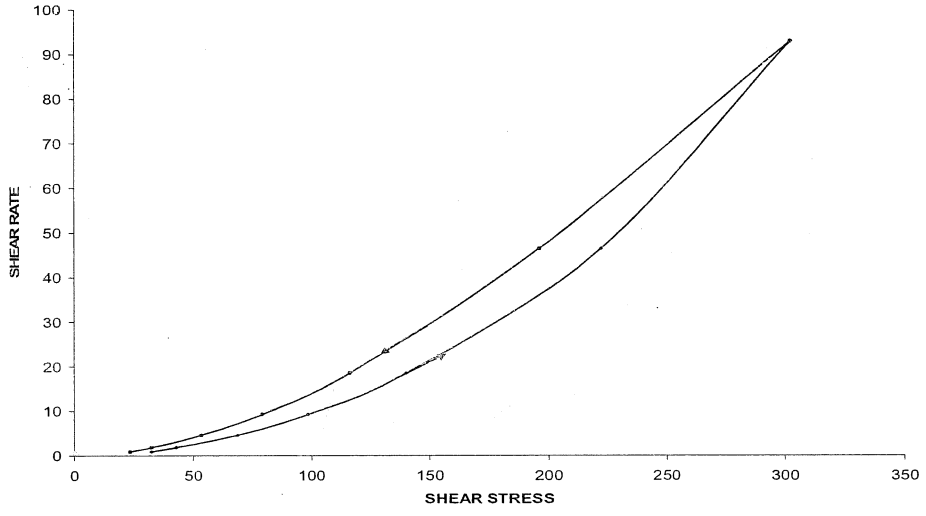

Figure 2. Plot of shear rate versus shear stress of Terminalia gum at 5% w/w concentration

The FT-IR spectrum of Terminalia gum is shown in Figure 3. Wave numbers between 4000 cm^{-1} and 2800 cm^{-1} are the stretching zone of C-H (alkanes) (3000-2850 cm^{-1}), C-H (Aromatic) (3100-3000 cm^{-1}), -OH (alcohol) (3720-3200 cm^{-1}), C-H (alkenes) (3100-3000 cm^{-1}), wave numbers between 1700-1850 cm^{-1} corresponds to stretching zone of C= O (carbonyl), CH_2 of cyclohexane (1422.2 cm^{-1}), CH_3-OH (1030.3 cm^{-1}), Aromatic ring (837.7 cm^{-1}). These functional groups are present in the materials like carbohydrates, starch, lactose and some natural gums (Malik et al. 2002). Thus, there are possibilities of formation of some weak bonding such as hydrogen bonding, Van der Waals forces or dipole-dipole moment and these forces could help the molecules to adhere to each other and thereby, the Terminalia gum may provide binding effect with the other excipients present in the tablet.

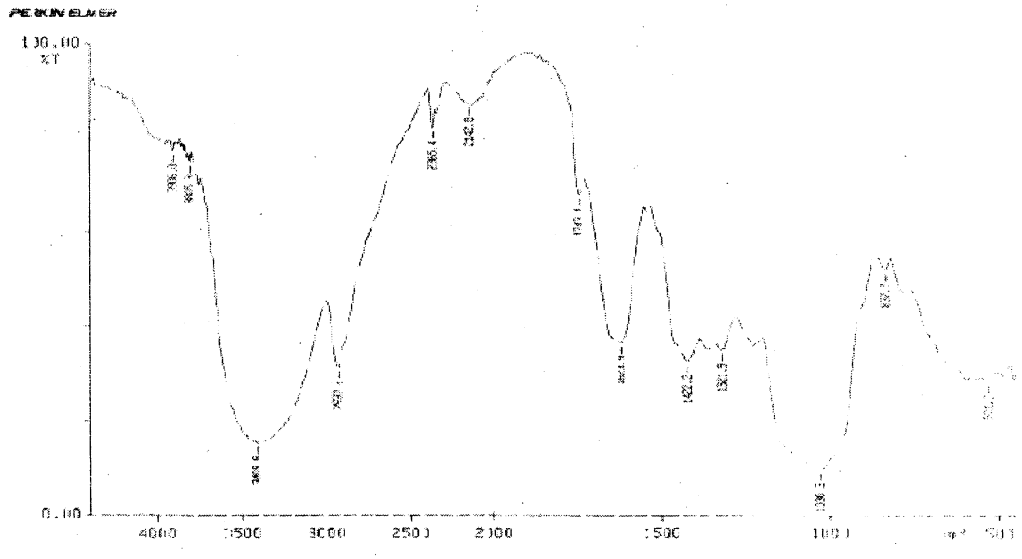

Figure 3. FT-IR spectrum of Terminalia gum

The X-ray powder diffraction spectrum of Terminalia gum is shown in Figure 4. The spectrum shows a single broad peak at 20° 2 Theta without any other characteristic peaks. This indicates that Terminalia gum is amorphous in nature. Natural gums such as arabic, guar and karaya have also been found to be amorphous in nature (Malik et al. 2002, Murali Mohan Babu et al. 2002, Reddy et al. 2004).

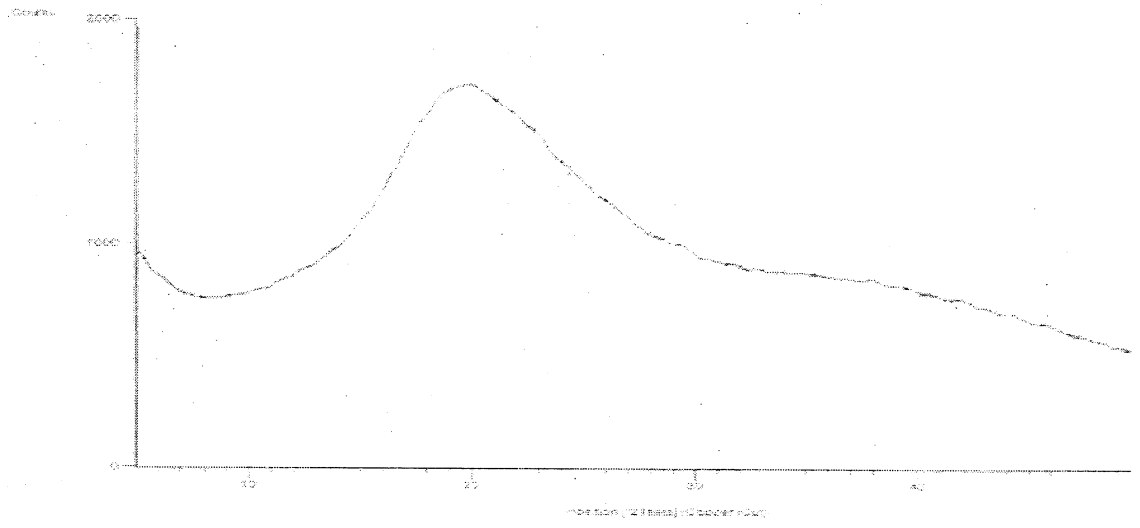

Figure 4. X-ray powder diffraction spectrum of Terminalia gum

The results of the granule properties when the gum was used as a binding agent in carvedilol tablet formulation are presented in Table 1. The results show that the granule size and granule properties depended on the type and concentration of binding agent used in the formulation. The mean granule size increased with increase in binder concentration except for formulations containing PVP as binder which showed a decrease. The ranking of the mean granule size and the angle of repose for the formulations was generally corn starch > PVP > Terminalia gum. The angle of repose for formulations containing Terminalia gum as binding agent was less than 30° indicating that the granules possessed better flowability than the granules prepared using the other binding agents (Martin et al. 2002).

Table 1. The properties of carvedilol granules containing different concentration of binders

Binder	Concentration (% w/w)	Mean granule size (μm)	Bulk density (g/mL)	Tapped density (g/mL)	Angle of repose (°)	Hausner's ratio	Carr's index (%)
	0.00	48.64	0.61	0.80	31.90	1.32	24.32
Terminalia gum	7.50	64.27	0.53	0.59	27.60	1.12	10.48
	10.00	242.73	0.56	0.65	27.90	1.16	14.01
Starch	7.50	104.12	0.50	0.59	34.00	1.17	14.89
	10.00	382.53	0.59	0.67	32.00	1.13	11.75
PVP	7.50	226.52	0.54	0.59	32.00	1.06	5.41
	10.00	64.93	0.53	0.67	30.90	1.27	21.14

The compressibility index is a measure of flowability and compressibility of a material. The lower the Carr index of a material, the better the flowability and the poorer the compressibility of the material. The compressibility index of granules prepared with Terminalia gum was < 15%, which indicates good to excellent flow properties (Staniforth 2002). The ranking of compressibility index was PVP > corn starch > Terminalia gum. This result is in line with those obtained for the angle of repose. The bulk and tapped densities of granules also increased with increase in binder concentration. This may be due to the differences observed in the mean granules size.

The mechanical properties of the tablets are indicators of the ability of the tablets to withstand the rigors involved in manufacture, transportation, dispensing and usage (Banker and Anderson 1986). Two important parameters used to quantify the mechanical properties of tablets are crushing strength and friability and the results for carvedilol formulations are presented in Table 2. The crushing strength which provides as measure of the tablet strength, increased with increase in the concentrations of the binding agents except for formulations containing Terminalia gum which showed a decrease. The ranking of crushing strength was generally formulation containing PVP > Terminalia gum > corn starch. Statistical analysis showed that there were no significant difference ($p>0.05$) in the crushing strength values of the tablets prepared using Terminalia gum and the other binders. The friability which is a measure of tablet weakness, decreased with increase in the concentrations of the binding agents in the rank order of formulations containing PVP < corn starch < Terminalia gum. All the tablet formulations passed the friability test by showing friability values of < 1% w/w (BP 1998). This suggests that all the binding agents including Terminalia gum should be able to provide adequate protection for tablets against abrasive motions during handling.

Table 2. The mechanical strength and drug release properties of carvedilol tablets containing different concentration of binders

Binder	Concentration (% w/w)	Crushing strength (N)	Friability (%)	Disintegration (min)	t_{50} (min)	t_{80} (min)	Drug content (%)
	0.0	37.53±5.06	0.64±0.00	0.80±0.29	7.05±	12.00	96.58±1.25
Terminalia gum	7.5	62.72±3.69	0.48±0.09	5.75±0.60	7.23	13.23	97.85±0.56
	10.0	51.45±6.00	0.45±0.04	23.70±4.65	13.23	25.23	98.12±2.47
Starch	7.5	55.57±9.64	0.45±0.02	2.06±0.14	10.24	19.14	96.29±1.37
	10.0	58.80±9.80	0.40±0.05	4.76±0.43	9.36	18.00	97.34±0.89
PVP	7.5	63.70±8.77	0.35±0.01	15.38±1.32	7.23	13.23	96.44±1.46
	10.0	72.72±11.77	0.40±0.01	23.42±2.22	7.24	13.25	97.57±2.65

It is well known that disintegration of tablets plays an important role in the dissolution process in determining to a large extent, the area of contact between solid and liquid. (Odeku 2005). The release properties of the carvedilol tablet were assessed by the disintegration and dissolution times (t_{50} and t_{80} - time required for 50 and 80% of the drug to be released respectively) and the results are presented in Table 2. The results indicate that the disintegration time of the tablets to be increased with increase in concentration of binder. Furthermore, all the tablets except tablets containing with 10% w/w Terminalia gum and PVP,

conformed to the official requirements for uncoated tablets on disintegration by showing disintegration time ≤ 15 min (BP 1998). When used at a concentration of 10% w/w, formulations containing Terminalia gum showed the highest disintegration time while those containing corn starches exhibited the lowest values.

The release profiles of the carvedilol tablet formulations are shown in Figure 5 while the dissolution parameters obtained from the plots are presented in Table 2. The values t_{50} and t_{80} of the tablets depended on the type and concentration of binding agent used in the tablet formulation. Tablets containing Terminalia gum as binder generally gave the highest dissolution times while those containing PVP gave the lowest values. It is notable that formulation containing 10% w/w Terminalia gum which showed the highest disintegration time also gave the highest dissolution time even though the crushing strength of the tablets was slightly lower than those of the other formulations. Thus, Terminalia gum would be useful when slower drug dissolution rate is desired. This finding highlights the need for careful selection of binder and binder concentration to achieve tablets with the desired strength and drug release properties.

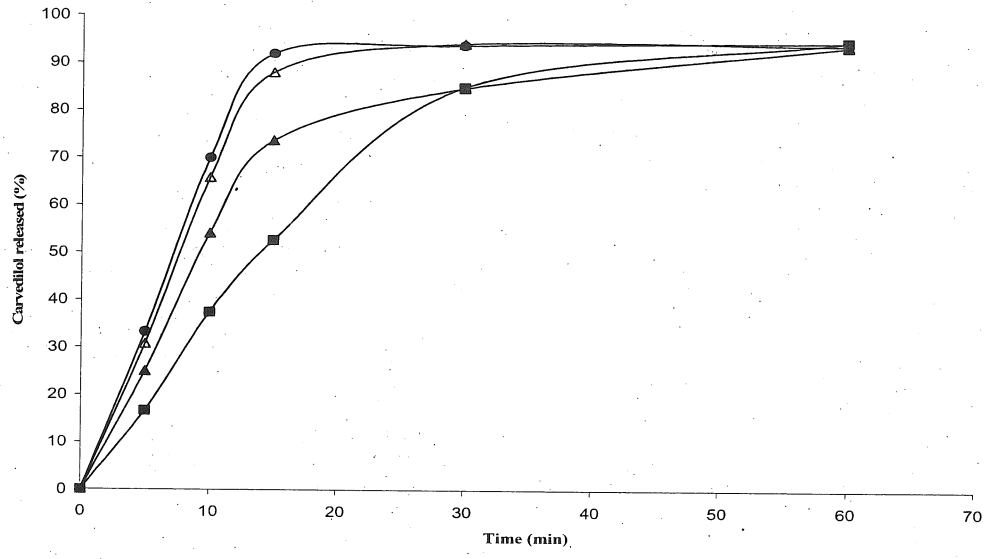

Figure 5. The release profile of carvedilol tablets containing the various binders: ◆, 0% Binder; ■, 10% Terminalia gum; ▲,10% corn starch; ●,10% PVP.

Conclusion

The results indicates that binding properties of Terminalia gum compared favorably with those of the standard binders and could also find application in controlled release tablet formulations.

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