



Research Journal of Pharmaceutical, Biological and Chemical Sciences

Evaluation of New Binder Isolated from *Tinospora cordifolia* for the Preparation of Paracetamol Tablets

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ABSTRACT

Pharmaceutical Manufacturing is an important enterprise and oral tablet manufacturing is the most significant of all, because more drugs are made as tablets than any other dosage form. The way of tablet manufacturing has been undergoing change in recent years and is likely to head in new directions. In this study *Tinospora cordifolia* (guduchi) a freely available, a climbing shrub belonging to the family Menispermaceae, a cheap source of starch has been chosen for isolation of starch (binder) and used for the preparation of paracetamol model drug. The tablets were prepared by wet granulation method using 4% w/v, 6% w/v, 8% w/v, 10% w/v and 12% w/v of *Tinospora cordifolia* starch and compared with maize starch (Standard) as binding agent. All the paracetamol tablets were evaluated for weight variation, hardness, friability, disintegration time and in-vitro drug release etc. The study results indicate the tablet with highest binder concentration showed maximum hardness and disintegration time and minimum friability compared with standard binder.

Keywords: Paracetamol tablet; Maize starch; *Tinospora cordifolia*.

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INTRODUCTION

Pharmaceutical tablets must have the mechanical strength to withstand the rigors involved in manufacture, packaging, transportation, dispensing and in the hand of the user. They must also release the drug content in the gastrointestinal tract for absorption. *Tinospora cordifolia* (Guduchi) is a large, glabrous, deciduous climbing shrub belonging to the family Menispermaceae and is a rich source of starch. Starch from different source is a well known tablet binder. Potato starch, corn starch and cassava starch are most commonly used. Binders are agents used to impart cohesive qualities to the powdered material during the production of tablets. They impart cohesiveness to the tablet formulation, which ensure that the tablet remains intact after compression as well as improving the free flowing quality. Binders have been used as mucilage and in dry powder form depending on the other ingredients in the formulations and the method of preparation. The choice of a particular binding agent depends on the binding force required to form granules and its compatibility with other ingredients particularly the active drug. The commercial sources of starch are wheat, barley, maize, potato, arrowroot and tapioca. In these, starch occurs in the form of loosely packed granules, which vary in shape and size. In the present study aimed to isolate the starch from fresh stems of *Tinospora cordifolia* as binder for the preparation of paracetamol tablets has been investigated in comparison with paracetamol tablet prepared with widely used maize starch [2, 3].

MATERIALS AND METHOD

Materials

Paracetamol (gift from Chethana pharmaceuticals, Thrissur, Kerala). Maize starch, magnesium stearate, talc, (Prowess Lab Chemicals Ottapalam), potato starch (s d fine- chemical limited, worli road, Mumbai), lactose monohydrate (Nice chemicals, Kochi, Kerala). Fresh stems of *Tinospora cordifolia* were collected from local area at Palakkad and authenticated.

Isolation of Starch

Tinospora Cordifolia collected and removes the physical impurities and washed thoroughly with water. Stem was made into pieces and crushed thoroughly to convert into slimy paste. This mass was further mixed with 4 times of Potable water in a stainless steel vessel and kept for soaking overnight (12hrs). Next morning this mass was macerated thoroughly in water for about 1 hour, filtered slowly through a clean four folded cotton cloth. The liquid was kept a side undisturbed for 4 hrs for settlement. The supernatant liquid was decanted carefully. Heavy starchy sediment, which was settled at the bottom, was shifted into tray, air dried under running fan, collected and stored in air tight jars [4].

Determination of Solubility

Solubility [5] is expressed in terms of “parts” representing the number of milliliters (ml) of the solvent in which 1g of the solid is soluble. Solubility of the powder was determined in different solvents at 20⁰ C (Table 1).

Total ash

The sample (3g) of the ground air – dried material in a crucible, spreading the material in a crucible, spreading the material in an oven layer and igniting it by gradually increasing the temperature to 550 °C until it is white, indicating that absence of carbon. The crucible was cooled in a desiccator, weighed and the content of total ash in mg/g of air-dried material was calculated. (Table 1)

Acid - insoluble ash

Residue obtained after boiling the total ash with dilute hydrochloric acid and igniting the remaining insoluble matter. To the crucible containing the total ash, 25ml of hydrochloric acid was added, covered with a watch glass and boiled gently for 5 min. The watch glass was rinsed with hot water this liquid was added to the crucible. The insoluble matter on an ash less filter paper was collected and washed with hot water until the filtrate is neutral. The filter paper containing the insoluble matter was transferred to the original crucible, dried on a hot plate and ignited to constant weight. The residue was allowed to cool in a desiccator for 30 min, weighed without delay and the content of acid insoluble ash in mg per g of air dried material was calculated⁶ (Table 1).

Loss on drying

The sample (1g) was heated at 105°C until loss on moisture on drying was calculated using the formula [7], (Table 1)

$$\text{LOD (\%)} = \text{initial weight} / \text{final weight after drying} \times 100$$

Rheological studies

Starch mucilage (8%) of *Tinospora cordifolia* and Maize starch were prepared. The rheological characteristics of mucilage were evaluated by using Brookfield viscometer [8]. (Table 1)

pH determination

pH was determined by shaking a 1% w/v dispersion of the sample in water for 5 min and the reading were noted by digital pH meter. (Table 1)

Limit test for chlorides, sulphates

It is highly impossible to remove all the impurities from pharmaceutical substance. So it is desirable if the substance is sufficiently pure and for this purpose Pharmacopoeias specify the

limits upto which various impurities can be tolerated. In limit test, opalescence, turbidity or colour is compared with the fixed standards as prescribed in the Pharmacopoeias [9].

Gelatinization and pasting characteristics of isolated starches

The moistened samples of starch powder were loaded in to a capillary tube by means of intrusion. The temperature of gelling and the time from swelling to full gelatinization were measured with a melting point apparatus. Pasting characteristics was observed by suspending 1g of starch in 10ml of distilled water and heating, with stirring, on water bath [9]. The time until paste formation was 3.8 ± 0.5 min.

Microstructure studies by SEM

The morphology of *Tinospora cordifolia* starch was investigated by using scanning electron microscope [10]. (SEM JSM – 6390 LU, JEOL, TOKYO, Japan.) (Fig.1).

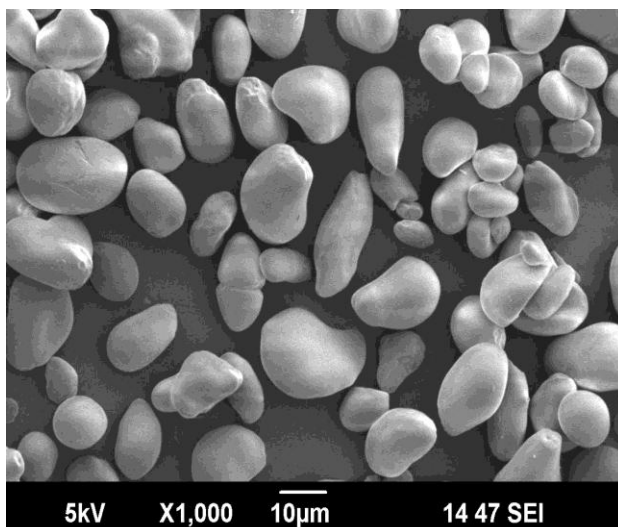


Fig. 1. SEM of *Tinospora cordifolia* starch

Particulate size analysis for starch grains

The diameter of starch grains was measured by using a eyepiece micrometer and a compound microscope. Powder was stained with N/20 iodine, mounted on a microscopic slide and the diameter of the starch grains was calculated randomly [9].

Preparation of tablets

Aqueous slurry of starch was made with distilled water and then heated over a water bath with stirring until a starch paste is formed. The resultant starch paste was used as a binding agent in the tablet formulations. The working formula for the assessment of *Tinospora cordifolia* starch as binder in paracetamol tablet is given in (Table 3).

Table 3. Formulae of the Paracetamol tablets prepared

Ingredient (mg/tablet)	Formulation				
	F1	F2	F3	F4	F5
Paracetamol					
Lactose monohydrate(qs)	500	500	500	500	500
Tinospora cordifolia starch	19.8	19.8	19.8	19.8	19.8
Potato starch	22.6	33.9	45.2	56.5	67.8
Magnesium stearate	28.25	28.25	28.25	28.25	28.25
Talc	5.65	5.65	5.65	5.65	5.65
Total weight	565	565	565	565	565

Wet granulation method was used for the tablet production. The calculation is made for 60 tablets in each batch. In case accurately weighed quantities of each ingredient were mixed in a mortar and an appropriate quantity of the starch mucilage was added as a granulating agent and mixed for 20 min in a mortar. The damp mass was sieved with sieve no. 12 and dried at 50 °C oven for 2 hrs. The dried granular mass was passed through sieve no. 16 to obtain uniform sized granules. The different batches of the granules specified amount of the disintegrant i.e. Potato starch (5%) were then mixed with calculated equal quantity of magnesium stearate (1%) and talc (2%) then compressed into tablets under constant pressure.

The prepared granules were then evaluated for loss on drying, flow properties, density related properties and compatibility studies by FTIR and DSC (Fig 2, 4) and tablet properties (crushing strength, weight variations, hardness, friability etc) were determined by standard procedure [8, 9, 11].

Compression and evaluation of tablets

The tablets were compressed using a Rotary tablet compression machine (10 station, Rimek, Ahmedabad, India). The tablets were evaluated for average weight and weight variation, content uniformity, thickness, hardness, friability, disintegration time and in vitro dissolution profile. Totally 10 batches out of this 5 batch tablets prepared by using Tinospora cordifolia starch and 5 batch tablets prepared by using maize starch [11].

Weight variation test

To study weight variation twenty tablets of the formulation were weighted using an Shimadzu digital balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation [12].

Hardness test

Five tablets were selected at random from each batch to perform this test. Pfizer hardness tester [12] (Elite, Mumbai, India) was used to measure the hardness. Tablet was placed between spindle and anvil of the tester and the calibrated scale adjusted to zero, then

applied a diametric compression force on the tablet and the position on the calibrated scale at which the tablet broke was recorded in kg units. A mean hardness was calculated for each batch. (Table 4)

Disintegration of tablets

Disintegration time was measured in distilled water at $37 \pm 1^{\circ}\text{C}$, pH 6.5, according to the method described by the US Pharmacopoeia USP XXIII (2040) Disintegration and Dissolution of National Supplements, using a tablet disintegration tester apparatus. The tablets were considered completely disintegrated. When all the particules passed through the wire mesh, tablets with a surface erosion disintegrateion patern retained their shape and only reduced their size with time. (Table 4)

Friability test

Ten tablets were selected at random, dusted and weighed (W_1) together using Shimadzu electronic balance and then placed in the friabilator [12]. The machine was operated for 4 min at 25 rotations per min and then stopped. The tablets were dusted and again reweighed (W_2). (Table 4)

The percentage losses were calculated for each batch of the tablets.

$$F\% = [(W_1 - W_2)/W_1] \times 100$$

Determination of drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and dissolved in phosphate buffer pH 7.8 stirred for 2hour. After 2 hour take the sample 0.1 to 10 ml standard flask. Measure the absorbance at 243 nm using a Shimadzu UV-Visible spectrophotometer 1800. Phosphate buffer is used as blank. (Table 4)

***In vitro* dissolution test**

The *in vitro* dissolution test of the compressed Paracetamol tablet was performed using USP 2nd dissolution apparatus. Phosphate buffer (pH 7.8) was used as dissolution medium. The temperature was maintained at $37 \pm 2^{\circ}\text{C}$ using rotation speed 75 rpm. Samples were withdrawn at regular intervals up to 1hour, replacing equal amount of fresh dissolution medium (phosphate buffer pH 7.8). Samples were analysed using Shimadzu UV-Visible spectrophotometer 1800 and % cumulative drug release was calculated. (Fig 4)

Statistical analysis

Statistical analysis was done to compare the effects of the starches on tablet properties using the analysis of variance (ANOVA) on a computer software GraphPad Prism[®] 4 (Graphpad software Inc.San Diego CA, USA). Tukey – kramer multiple comparison test were used to compare the difference between the starches. At 95% confidence interval, probability, *p* values less than or equal to 0.05 were considered significant.

RESULTS AND DISCUSSION

Table 1. PHYSICOCHEMICAL PROPERTIES

Some physicochemical properties of <i>Tinospora cordifolia</i> starch and Maize starch		
Parameters	<i>Tinospora cordifolia</i>	Maize starch
Solubility	soluble in cold water, ethanol, more soluble in hydrochloric acid	soluble in cold water, ethanol, more soluble in hydrochloric acid
Organoleptic characteristics		
Colour	Pale white	Pale white
Taste	Tasteless	Tasteless
Touch	Smooth	Smooth
Loss on Drying(%)	2.31	2.27
Total ash(%w/w)	7.5	7.3
pH	6.3 – 6.5	6.4 – 6.5
Viscosity (cps) 8%	8090	9578

Table 2. Identification test for starch

S.No	Chemical tests	Results
1	Molish's test	Presence of carbohydrates
2	Benedict's test	Absence of reducing sugars
3	Barfoed's test	Absence of reducing disaccharides
4	Iodine test	Presence of starch
5	Biuret test	Absence of proteins
6	Liebermann burchard test	Absence of steroids

Preformulation studies of *Tinospora cordifolia* starch as well as Maize starch was carried out (Table 1), both starch are comparatively soluble in cold water. The cold water solubility of starches depends on the amylose / amylopectin constituents. The higher the water soluble amylopectin constituent, the higher the cold water solubility, while the higher the cold water insoluble amylose, the reverse becomes the case (Table 2). Identification test for starch confirm that both starch give positive result in Molish's test as well as Iodine test. Both starches pass the limit test for chlorides as well as sulphates. Angle of repose of *Tinospora cordifolia* starch and Maize starch powders were 39.82° and 37.84° , respectively it indicate both are poor flow properties of powders. The confirmation of the non free flowing nature of *Tinospora cordifolia* starch and Maize starch powders were obtain from the fact their Hausner's ratio of 1.376 and 1.432 respectively, and these were greater than 1.2 which indicate low inter particulate friction

powder. So, *Tinospora cordifolia* starch possessed better flow properties than maize starch was confirmed by Carr's compressibility index of 27.37% and 30.18% respectively.

FTIR studies of *Tinospora cordifolia* starch with Paracetamol gave a characteristic peaks at 3325.28, 3165.19, 1654.93 and 1226.73 cm^{-1} . The appearance of the above peaks of NH, C=O, recommended a strong presence of Paracetamol molecule in the mixture. It has been concluded that, the *Tinospora cordifolia* starch doesn't have any functional incompatibility, when it is incorporated with the paracetamol.

The moisture content of the Paracetamol granules was found to increase with increase in binder concentration. The tapped and bulk densities of the Paracetamol granules were found to decrease with increase in binder concentration. This is consistent with the production of larger granules as the concentration of binder. Due to an increase in the formation of bonds between the paracetamol particles and other excipients with increase in binder concentration. The more the binder concentration the more the bond formation. This might also be due to increase in viscosity and stronger bridges between the granules increased. Flow properties were found to increase with increase in binder concentration. (Table 4) This was due to decrease in densities with increase in binder concentration and also due to resultant increase in particule size leading to decrease in surface free energy of the granule particles and decrease in frictional forces between the granules leading to faster flow. The angle of repose of various granules prepared with *Tinospora cordifolia* starch as well as maize starch mucilage at various concentration between 4 to 12%w/v., it was increased as the concentration of the binder is increased this provides an insight into the extent of the cohesiveness and flow ability of the granules. The angle of repose ranges from 33.10⁰ to 35.40⁰ for *Tinospora cordifolia* granules and from 31.80⁰ to 36.50⁰ for maize starch granules. Flow properties increased from low concentration. This was due to decrease in densities with increase in binder concentration.

Table 4. Comparison of binding properties of *Tinospora cordifolia* starch and maize starch using paracetamol

Binders	Granule Propertiees			Tablet Properties			
	Bulk Density (g/cm ²)	Tapped Density (g/cm ²)	Angle of Response	Hardness (Kg/cm ²)	Friability (%w/w)	Uniformity of weight	Disintigration time (min)
TS4%	0.35±0.04	0.41±0.02	30.90±0.33	3.4±0.18	0.44±0.03	0.565±0.08	0.60±0.03
TS6%	0.38±0.02	0.48±0.01	33.92±0.22	3.9±0.20	0.43±0.03	0.566±0.09	1.27±0.03
TS8%	0.43±0.02	0.51±0.01	35.43±0.24	4.4±0.15	0.41±0.03	0.568±0.01	1.31±0.03
TS10%	0.42±0.04	0.51±0.02	34.68±0.25	5.2±0.12	0.40±0.03	0.567±0.01	1.27±0.02
TS12%	0.37±0.02	0.45±0.02	33.10±0.26	5.3±0.20	0.38±0.03	0.567±0.08	1.28±0.02
MS4%	0.33±0.02	0.42±0.02	36.52±0.23	3.8±0.18	0.36±0.03	0.568±0.04	1.41±0.02
MS6%	0.39±0.02	0.47±0.01	33.42±0.23	4.2±0.21	0.33±0.03	0.564±0.09	2.07±0.02
MS8%	0.41±0.04	0.46±0.02	35.05±0.23	4.6±0.20	0.34±0.03	0.570±0.05	2.19±0.02
MS10%	0.48±0.03	0.50±0.02	31.84±0.21	5.0±0.20	0.31±0.03	0.573±0.06	2.27±0.02
MS12%	0.50±0.03	0.53±0.01	34.40±0.20	5.5±0.20	0.31±0.03	0.567±0.07	2.30±0.02

^a Each values are the mean ± S.E (n=3), ^b Each values are the mean ± S.E (n=6)

TS = *Tinospora Cordifolia* Starch, MS = Maize Starch

The effect of the two starch mucilage's concentrations on the paracetamol tablets the hardness/crushing strength, was found to be increase, with increase concentration of binder. (Table 4). It may be due to the adhesive nature the binder leading to increase the bond formation between granules as a result of formation of plastic and elastic deformation and melting of the particles during compaction hence the hardness of the tablets were consequent upon the amount of binder present (Table 4).

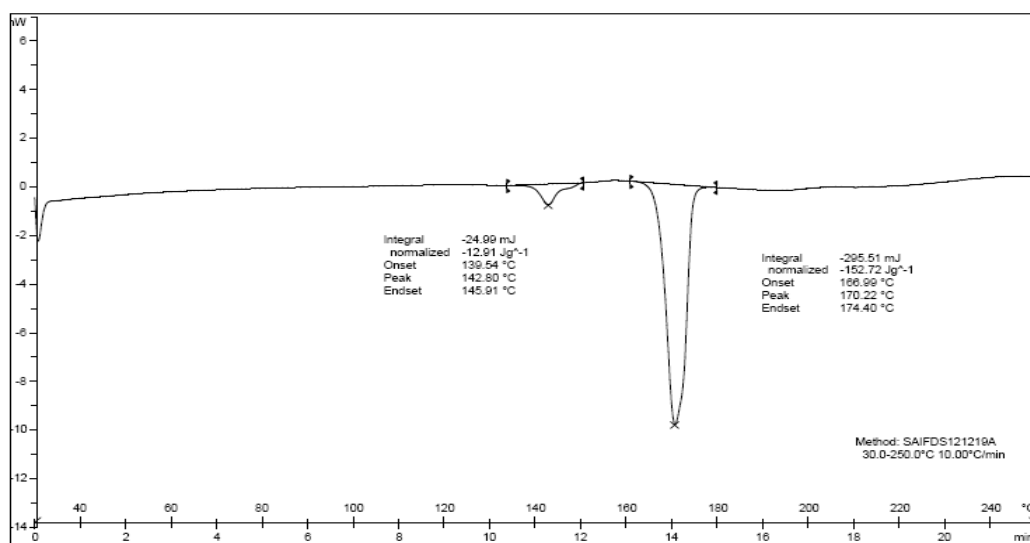


Fig. 2. Differential Scanning Calorimeter studies of Paracetamol + Tinospora cordifolia starch granules

Fig 3 Drug Polymer Interaction (FTIR) Study

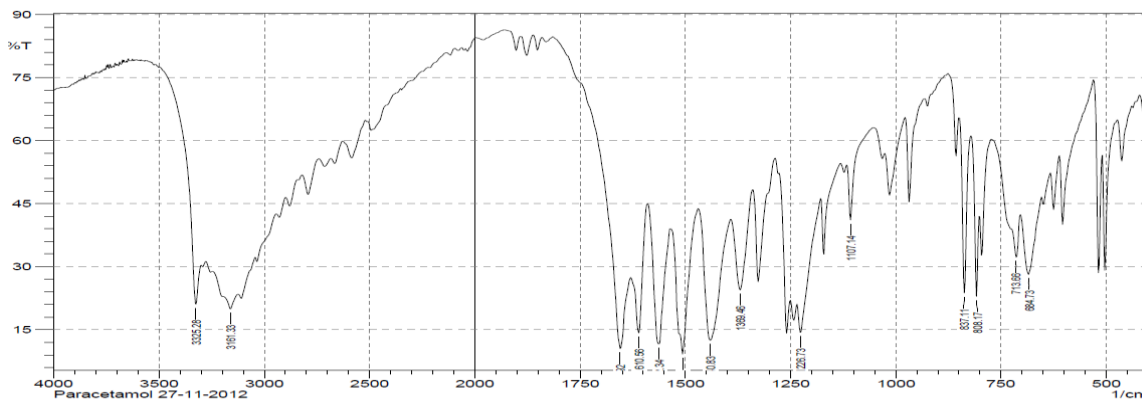


Fig 3a. IR Spectrum of Paracetamol

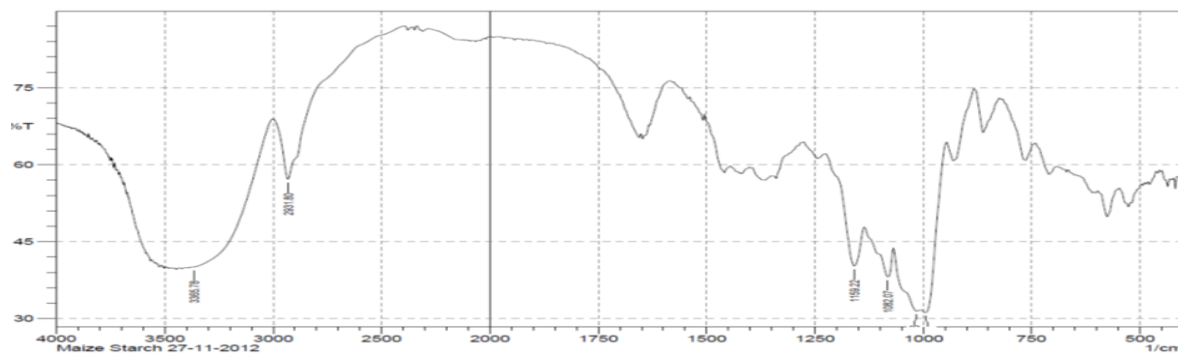


Fig 3b. IR Spectrum of Maize Starch

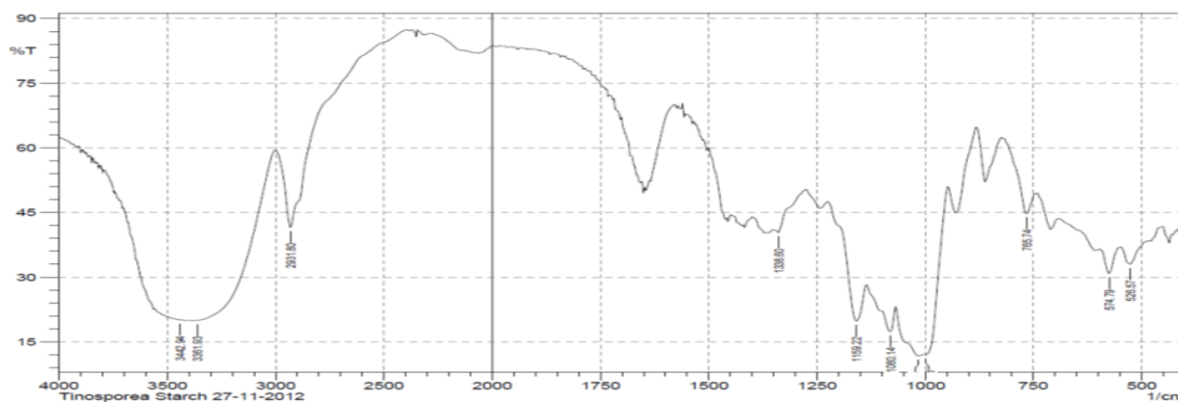


Fig 3c. IR Spectrum of Tinospora cordifolia starch

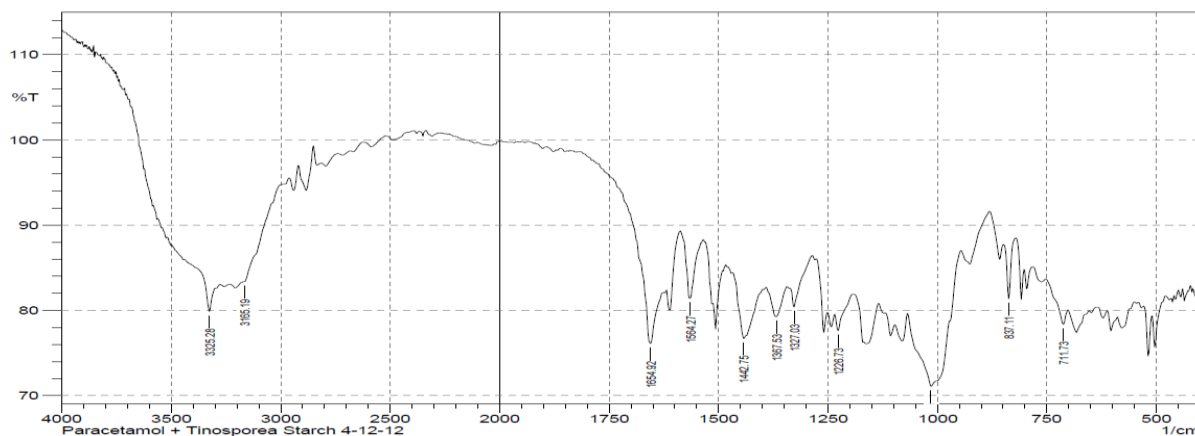


Fig 3d. IR Spectrum of Tinospora cordifolia starch + Paracetamol

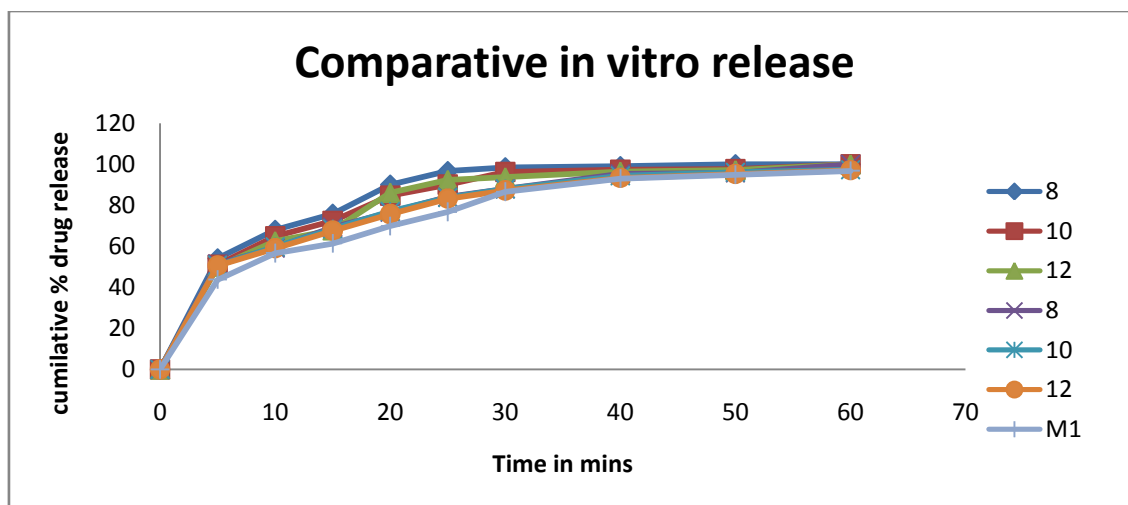


Fig 4. In-vitro release of optimized Paracetamol tablet by using *Tinospora cordifolia* starch as well as Maize starch as binder concentrations of 8,10,12%w/v & marketed tablet.

The friability value decreased as the concentration of starch mucilage binder increased. The hardness/crushing strength, friability is consequent upon interparticulate bonding and bridges in tablets. Increasing the binder concentration causes a corresponding increase in the disintegration times of all the tablet formulation. The results compliment the results of the crushing strength testing of the tablets. This indicates that the increase in disintegration time is attributed to an increase in the binding bridges and bonds of granules particles during compaction of the tablets mass, a series of linkages bridges and bonds formed in order to hold the tablet compacts. The bond formation tends to increase with increased starch mucilage binder concentration making the tablet compact difficult to be broken during disintegration there by prolonging the disintegration time. The dissolution time was also found to increase with increased concentration of binder. This might be due to the fact that dissolution is a subject of disintegration as tablet would most often disintegrate before it release the drug into solution.

CONCLUSION

From the results of the study conducted above it can be inferred that starch extracted from *Tinospora cordifolia* may be suitably used as binder to formulate Paracetamol tablets. Also the Paracetamol granules obtained from the extracted starch have similar physicochemical properties with that of the paracetamol granules prepared with Maize starch. The *Tinospora cordifolia* starch has same binding efficiency as that of maize starch as a binder at different concentrations in paracetamol tablets.

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