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Research Article

Formulation and Evaluation of Controlled Release Salbutamol Tablets Using *Cissus Populnea* Gum as Matrix Former

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Abstract: Gums abound in nature and many have been extracted, characterized and used as excipients in dosage forms manufacture. In this study, gum obtained from *Cissus populnea* root was extracted and used as release retardant in the formulation of controlled release salbutamol tablets. Test gum, acrylate-methacrylate copolymer (Eudragit®RS100) and maize starch at varied concentrations were used to formulate tablets by wet granulation and the granules were characterized by measuring flow and packing properties. Granules with adequate flow properties were compressed into flat face tablets of 6 mm diameter at a compression load of 26.5 KgF on the load scale. Resultant tablets were evaluated for friability, hardness and drug release study. The pH of the gum was 8.03 and granules have angle of repose, bulk and tapped density and Carr's index ranging from 18.53 ± 0.98 to 22.49 ± 0.97º, 0.53 ± 0.01 to 0.64 ± 0.01 g/ml, 0.56 ± 0.15 to 0.69 ± 0.01 g/ml and 5.35 ± 1.54 to 17.66 ± 2.31% respectively. Hardness values ranged from 4.61 ± 0.42 to 8.61 ± 0.84 Kg/F and friability percentage of 0.01 to 1.88%. The test gum and formulated salbutamol granules exhibit adequate flow properties and compressibility. Over 50% drug release was achieved between 60 and 150 min depending on gum concentration. Drug release from the tablets were adequately retarded and showed good post-compression properties. The study revealed *Cissus populnea* gum has comparable effect with Eudragit®RS100 at a ratio of 2:1 and can be used to formulate controlled release salbutamol tablets.

Keywords: Gum, *Cissus populnea*, Acrylate-methacrylate copolymer, Salbutamol, Controlled release, Matrix tablets.

INDRODUCTION

Pharmaceutical excipients play important roles in pharmaceutical dosage forms. Different excipients play various functional roles in the design, quality and performance of dosage forms (Adeleye *et al.,* 2015). One of such excipients that has received tremendous attention over the ages is gum, especially the ones from natural sources (Bhosale *et al.,* 2014). Goswami and Naik (2014) buttressed the usefulness of natural gums in conventional and novel dosage forms. The interest in natural excipients is not unconnected with the facts that synthetic excipients are not only expensive but many also irritate gastric and intestinal mucosal (Adeleye *et al.,* 2015).

Natural gums as polymers are mainly polysaccharides obtained from woody and non-woody plant parts which include seeds, fruits, leaves etc. (Ghatage *et al.,* 2014). Gums are usually formed by a natural phenomenon called "gummosis" (Goswami and Naik 2014). In this process, plant tissues break down and cavities created. These cavities exude the gums. Gums are also exuded when the barks and stems are injured. Bacteria and fungi attack can also cause exudation of gums (Goswami and Naik 2014).

Gums play crucial role in formulation of conventional and controlled release dosage forms. Due to numerous advantages associated with controlled release dosage forms, the emphasis over the years is development of novel drug delivery systems (Nep and Conway, 2012). Besides consistent blood level and enhanced bioavailability, there is reduced dosing frequency and improved patient adherence with controlled release drug delivery system (Nouh *et al.,* 2010; Nokhodchi *et al.,* 2012). However, since natural gums are hydrophilic in nature and the test drug in this study – salbutamol – is water soluble, there is a great challenge in using natural gums to formulate a suitable oral drug delivery system for controlled delivery of salbutamol (Nep and Conway, 2010). Soluble drugs are not usually easy to formulate into modified release preparations (Kushal *et al.,* 2013).

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Salbutamol sulphate is soluble 1 in 4 parts of water; slightly soluble in ethanol, in chloroform and in ether. Pure salbutamol on the other hand, is sparingly soluble in water (1 in 70), 1 in 25 of ethanol; slightly soluble in ether (BPC, 2009). Experimental controlled release salbutamol sulphate (10.6 mg tablet) had been formulated with polymethacrylate (Eudragit RS100) as matrix former (Sanghavi *et al.,* 1990). Drug diffusion through the matrix was significantly retarded especially when magnesium oxide or calcium hydroxide was added as diluent. Other polymers which had been tried to achieve controlled release of salbutamol are: hydroxyl propyl methyl cellulose (HPMC), hypromellose, propyvinyl alcohol, xanthan gum etc.

Salbutamol (also known as albuterol) is a selective beta-2 adrenergic receptor agonist (Shaik *et al.,* 2011; Mote *et al.,* 2013). It is a widely used sympathomimetic drug for the management of asthma and other obstructive pulmonary diseases like bronchitis and emphysema (Karya *et al.,* 2010; Sunil *et al.,* 2013). However, this all-important drug is commonly marketed as conventional dosage forms (conventional tablets and simple liquid preparations). In the current study, gums were extracted from the plant, *Cissus populnea* and investigated as the retardant in the formulation of salbutamol sulphate matrix tablets.

Cissus populnea Guill & Perr, family Vitaceae, is a tropical plant and a woody climber of about 8 m high. It is found mainly in the tropical regions of North Mexico, Asia, Africa, Central and South America and Australia (Adeleye *et al.,* 2015). It is commonly called food gum and Okoho (Idoma) or Ager (Tiv). Idoma and Tiv are some local dialects spoken in Nigeria. The plant has several uses in different part of the world. It is used as a diuretic agent in Benin republic (Souza and Houngnon, 1985). It is used to improve genital erection, food thickener and antibacterial in Nigeria (Kone *et al.,* 2004; Ojekale *et al.,* 2006). In Ghana on the other hand, serves as post-harvest protectant (Belmain *et al.,* 2000). This gum has been characterized (Alakali *et al.,* 2009; Adeleye *et al.,* 2015) and some formulation studies done (Ibrahim *et al.,* 2002); However, there is little or no information on its ability to form matrices and retard drug release. The focus of this study is to investigate the ability of *Cissus populnea* gum to form matrix, retard salbutamol release and these effects will be compared with already established synthetic polymer.

MATERIALS AND METHODS

Materials: Materials used include, Salbutamol powder (obtained as a gift from Vitabiotics Ltd., 35 Mobolaji Johnson Avenue, Oregun ind. Estate, Ikeja, Lagos, Nigeria), fresh *Cissus populnea* roots were harvested from Iyorah in Edo state, Nigeria.), Eudragit RS100 (Free sample from Evonik Rohn GmbH, D-64293 Darmstadt, Germany) solvents used include, Isopropyl alcohol and Acetone (Guangdang Guanghua Chemical Factory Co. Ltd. Shanfau, Guandang China). All other reagents/chemicals such as Magnesium stearate, Talc, Maize starch BP and Lactose are of analytical grades and were used without further purification.

Methods:

(a) Extraction of *Cissus populnea* gum: The roots of *Cissus populnea* collected from the wild were thoroughly washed to remove adhering dirt and foreign materials. After washing, the roots were air dried and pulverized using mortar and pestle. The pulverized blend was sieved using a 1.18 mm standard test sieve to remove the shaft. A sample of the blend (100 g) was weighed and transferred into a clean bowl. Mucilage was formed by adding 1000 ml of distilled water to the powder, stirred properly and filtered with a muslin cloth to obtain viscous filtrate. A sample of the viscous mucilage (500 mL) was measured and the gum was precipitated with equal volume of acetone and isopropyl alcohol at a ratio of 1:1. The gum was collected through filtration and dried at 50 ± 1^0C in a hot air oven for 24 h. The dried gum was pulverized using a mortar and pestle and stored in an airtight container for further studies. The percentage yield of dried gun was determined with **Equation (1.1)**

$$\%\, Yield = \frac{Wf}{Wi} * \frac{100}{1} \ldots . (1.1)$$

Where: *Wf* represents final weight of dried gum, *Wi* represents initial weight of root before extraction.

(b) Phytochemical screening of *Cissus populnea* gum: A sample of the pulverized gum (1 g) was weighed, soaked in 100 ml of distilled water and was allowed to stand for 24 h. The mixture was filtered and phytochemical screening was performed using the filtrate to determine the components of the gum.

i. Determination of carbohydrate (Benedict Test): Two drops of benedict reagent was added to 2 ml of the filtrate in a test tube and was heated gently. The observation was recorded (Tiwari *et al.,* 2011).

Ii. Determination of protein (Biuret Test): Four drops of 1% copper sulphate solution was added to 2 ml of the filtrate. Thereafter, 2 ml of 1 % sodium hydroxide solution was added to the solution and stirred properly. Observation was made and recorded.

iii. Determination of alkaloid (Hager's Test): The filtrate (2 ml) was treated with 2 ml of Hager's reagent (Saturated picric acid solution). Formation of yellow precipitate confirmed the presence of alkaloid (Thakur, 2015).

iv. Determination of Flavonoids (Shinoda Test): A sample of the filtrate (2 ml) was treated with few drops of sodium hydroxide solution and dilute acid. Observation was made and recorded.

v. Determination of glycosides (modified Bontrager's test): To 2 ml of the filtrate, few drops of ferric chloride

solution was added and immersed in boiling water for 5 min. The mixture was cooled and extracted with benzene. The benzene layer was then treated with ammonia solution.

vi. Determination of saponin (Froth test): To the filtrate (2 ml), 20 ml of distilled water was added and shaken vigorously for 15 min and observations recorded (Tiwari *et al.,* 2011).

vii. Determination of Tannins (Gelatin test)*:* Gelatin solution (1 % w/v) containing 10% sodium chloride was prepared. A few drops of this solution were added to 2 ml of the filtrate. A white precipitate is an indication of tannins presence (Thakur *et al.,* 2015).

(c) Formulation of salbutamol granules: Seven batches of tablets were prepared according to the formulae in **Table 1**. To prepared controlled release salbutamol matrix tablets, 1.5 g (10% w/w) of the extracted gum was weighed, transferred into a beaker and formed into mucilage with sufficient quantity of water. A 2.1 g sample of salbutamol powder was weighed and transferred to porcelain mortal. Samples of magnesium stearate (0.15 g), talc (0.15 g) and lactose (11.1 g) was weighed and transferred to the mortal and blended with the salbutamol powder properly. The blend was kneaded properly with the gum mucilage to form a damp mass. The wet mass masses were screened through a 1.18 µm sieve and dried in hot air oven at 60 ± 0.5^0C. The dried mas was passed through a 710 µm sieve to form the required granules. Three other batches were prepared using 15%, 20% and 30% of gum mucilage. In other experiment, Eudragit RS100 was substituted for the extracted gum as matrix former. Finally, the granules were stored in air tight containers for further evaluation and compression into flat faced tablets.

Table 1: Composition of Controlled Release Salbutamol Tablets (Weight in mg)

Ingredients (mg)	Batches						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Salbutamol sulfate	14	14	14	14	14	14	14
Cissus populnea gum	10	15	20	30	---	---	---
Eudragit®RS100	---	---	---	---	10	15	---
Maize starch (binder)	---	---	---	---	---	---	3
Maize starch (disintegrant)	---	---	---	---	---	---	15
Magnesium stearate	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1
Diluent (lactose)	74	69	64	54	74	69	66
Total	100	100	100	100	100	100	100

(d) Pre-compression study:

i. ***Flow rate and Angle of repose (Θ)*:** A sample of the salbutamol granules (5.00 g) was weighed and transferred into a glass funnel with shutter at the orifice. The funnel was clamped to a retort stand at a distance of 5 cm from the horizontal flat surface and the granule was allowed to flow through the orifice by removing the shutter. The time taken for the granule to flow through the orifice was noted and the flow rate was calculated using the formula stated in **Equation 1.2**.

$$Flow\ rate = \frac{Mass\ of\ powder}{Time} \ldots . (1.2)$$

The height of the cone formed after the flow of the granule through the orifice and the radius of the cone were used to calculate the angle of repose using the formula in **Equation 1.3**. All determinations were in triplicate and mean values recorded.

$$\Theta = Tan^{-1}\frac{h}{r} \ldots .1.3$$

Where *h* is height and *r* the radius of the height of the heap so formed. While *θ* the angle of repose.

ii. ***Bulk Density and Tapped Density*:** To determine the bulk (poured) and tapped densities of the granules, a sample of granules (5.0 g) was weighed and transferred into the cylinder of a Jolting volumeter. The volume (V_i) occupied by the granules was recorded. The volumeter was a made to make 100 taps and the new volume (V_f) was recorded. The bulk and tapped densities were computed using the formulas in **Equations 1.4** and **1.5** respectively (Avbunudiogba *et al.,* 2012). All determinations were done in triplicates and mean values reported

$$Bulk\ density = \frac{W}{V_0} \ldots . (1.4)$$

$$Tapped\ density = \frac{W}{V_f} \ldots . (1.5)$$

iii. ***Carr's Index and Hausner Ratio:*** The Carr's index and Hausner ratio of the granules were determined based on the formulas in **Equation 1.6** and **1.7** respectively.

$$Compressibility\ index = \frac{Bulk\ volume - Tapped\ volume}{Bulk\ volume} \times 100 \ldots . 1.6$$

$$Hausner\ Ratio = \frac{Bulk\ volume}{Tapped\ volume} \ldots . 1.7$$

iv. ***Particle Size Analysis:*** A sample of the granules (5.0 g) was weighed and transferred into the top most sieve in a series of sieves arranged in descending order, mounted on a mechanical shaker (SW193TZ, England) and timed for 10 min. The powders retained in each sieve after 10 min has elapsed was weighed and recorded.

(e) Compression of granules: A sample of salbutamol granules (14.7 g) was thoroughly mixed with magnesium stearate (0.15 g), talc (0.15 g) and compressed into flat faced tablets using a single punch machine (Manesty type, F3) at a compression force of 26.5 arbitrary units on the load scale

(f) Post-compression studies:

i. *Weight Variation Test:* Twenty tablets from each batch were selected randomly and weighed individually. The average weights of the tablets were obtained and their percentage weight variations were calculated based on the formula in **Equation 1.8.**

$$Weight\ Variation = \frac{Iw - Aw}{Aw} * \frac{100}{1} \ldots . (1.8)$$

Where: *Iw* = Individual tablet weight, *Aw* = Average weight of tablets.

ii. *Friability Test*: Ten (10) tablets from each batch were selected randomly, weighed and transferred into a friabilator (VFT – DV, India) which was programmed to revolve at 25 rpm for 4 min. At the set time, the tablets were removed, dedusted and re-weighed. The percentage friability was obtained using the formula in **Equation 1.9.**

$$\%\ Friability = \frac{Initial\ weight - Final\ weight}{Initial\ weight} * \frac{100}{1} \ldots . (1.9)$$

(iii) *Tablets tensile strength (Ts) determination:* The thickness (***t***), diameter (***d***) and the crushing load of each 10 tablets selected at random were determined using Veego Digital Tablet Hardness Test Apparatus (Veego Instruments Corporation Mumbai - 400099 India. Model NO: VDIGITAB – 1. Sr. NO: 04-1112). Mean thickness value (***t***) and crushing load (***L***) were obtained and used to calculate the tensile strength (***Ts***) using **Equation 1.10**

$$Ts = \frac{2P}{\pi dt} \ldots . (1.10)$$

(iv) *Disintegration Test*: Six (6) tablets were selected at random from batch 7 (convectional tablets) and their disintegration times were determined using Erweka disintegration unit (Manesty Machine Limited Liverpool, TD29TIT6 England) containing distilled water and operated at 37 ± 0.5^0C. The average disintegration time were calculated and recorded.

(v) Salbutamol analysis (calibration curve): A standard calibration curve of salbutamol was prepared as follows (Kumar *et al*., 2013): A sample of salbutamol powder (100 mg) was weighed with analytical balance and dissolved in 100 ml of the medium (0.1 N hydrochloric acid) to obtain a solution of 1 mg/ml (stock). From the stock solution, 5 ml was measured into a test tube and made up to 10 ml with the dissolution medium to obtain a concentration of 500 µg/ml which was labeled "A". Concentration "B" was prepared by measuring 5 ml of concentration A and made up to 10 ml. concentration "C" was obtained from "B" and so on up to concentration "F". The absorbances of the various concentrations were obtained at wavelength of 276 nm using ultraviolet – visible spectrophotometer (PG Instrument, USA). The tests were done in triplicate and mean values recorded. Plots of mean absorbance against concentrations were made and a linear regression coefficient (R^2 value) of 1.000 obtained. The same procedure was used to compute the amount of salbutamol released into the dissolution medium at various time intervals.

(i) *Dissolution Test*: Tablet dissolution test was carried out using the rotating basket method (USP apparatus one). Hydrochloric acid (0.1 N) was used as dissolution medium. The apparatus consists of a Pyrex glass vessel containing 900 ml of the dissolution medium maintained at 37 ± 1^oC and a cylindrical basket made of stainless-steel wire mesh (aperture size, 425 µm). A tablet from each batch was placed in the basket and rotated at a speed of 100 rev. per min in the dissolution medium. Samples (5 ml) of the leaching fluid were withdrawn at specified time interval with a pipette plugged with cotton wool. The samples were filtered through a number 3 Whatman filter paper, diluted properly with fresh dissolution medium and analyzed with UV spectrophotometer (PG instrument, USA) at a wavelength of 276 nm. Fresh dissolution medium (5 ml) was added each time a sample was withdrawn in other to maintained sink condition. The absorbance was converted to percentage release and plotted against sampling time (in Minutes) (Adeleye *et al.*, 2011).

RESULT AND DISCUSSION

Gum from *Cissus populnea* root was successfully extracted using Isopropyl alcohol and acetone and the percentage yield obtained was 10.61%. The pH of the test gum (*Cissus populnea*) was 8.03 indicating that it is basic making it non-toxic and suitable for consumption. Thus, it can be used in the preparation of pharmaceutical product. Organoleptic test showed that the extracted gum is brownish in colour, tasteless, odourless and gritty texture.

Table 2: Phytochemical Screening of the Test Gum

Test	Observation	Inference
Benedict Test	Reddish brown precipitate	Carbohydrate present
Biuret Test	Violet colour	Protein present
Hager's Test	Yellow precipitate	Alkaloids present
Shinoda Test	Intense yellow colour turns colorless with dilute acid	Flavonoids present
Modified Borntrager's Test	Pink color at ammoniacal layer	Glycosides present
FrothTest	Foam formation	Saponin present
Gelatin Test	White precipitate	Tannin present

The results of phytochemical screening are presented in **Table 2. The** results revealed that the root of *Cissus populnea* is rich in phytochemicals (bioactive compounds) which have various medicinal uses. The presence of flavonoids is an indication of its anti-oxidant effect, thus, the plant can be used as an antibacterial, antiviral, antiallergic, anti-inflammatory agent (Alan & Miller, 1996). According to Asl and Hossein (2008), saponin has tumour - inhibiting effect thus the plant can be used in the treatment of cancer. The presence of tannin in *Cissus populnea* root also shows that it can be used in the formulation of antiviral and antibacterial agents. *Cissus populnea* root also contained carbohydrate and protein, hence a rich food source.

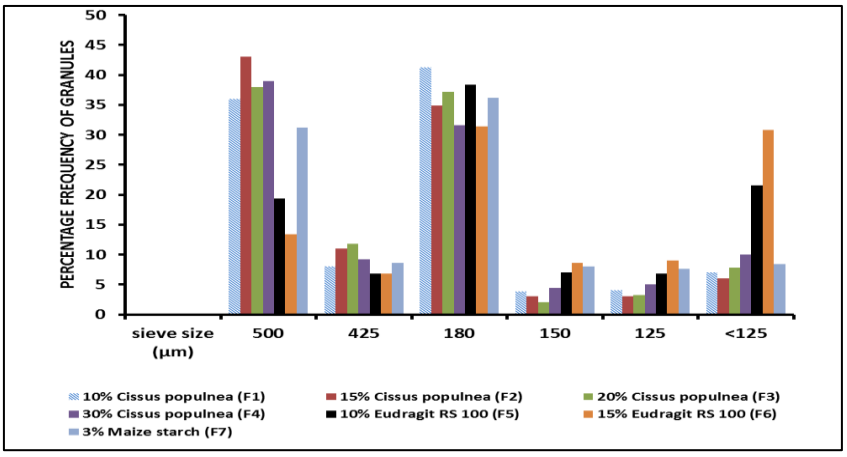

Figure 1: Particle size distribution of formulated salbutamol granule.

Figure 1 shows results of particles size distribution. Batch F6 had more percentage of fine particles (< 125 µm) leading to poor flow property. Batch F1 had larger particles (500 µm) and batch F4 had more particles at mesh size of 180 µm leading to excellent flow properties of these batches. The physical properties of formulated granules such as bulk and tapped densities, angles of repose and Carr's compressibility index are shown in **Table 3.** There was no significant difference in densities between the various batches of granules. Slight variations were noted but these were not statistically significant (P>0.05) when data were subjected to statistical analysis. These observations were further buttressed by the angle of repose values which ranged between 18^0 and 22^0. In other words, all granules exhibited excellent flow indicating the ability of the granules to compact and decrease in volume when pressure is applied which enhances the production of strong tablets that can withstand pressure. Granules prepared with *Cissus populnea* (F1 – F4), F5 (10 % Eudragit® RS 100) and maize starch all exhibited excellent flow with Hausner ratio ranging from 1.05 to 1.11. Granules prepared with 15 % Eudragit® RS 100 (F6) had fair flow with percentage compressibility of 17.66 and Hausner ratio of 1.21. Post compression properties of formulated tablets are shown in **Table 4.** Hardness values ranges from 3.99 KgF to 8.61 KgF, while percentage friability ranges from 0.01% to 1.88%.

Table 3: Flow/packing properties of formulated salbutamol granules

Batch	Flow rate g/s ± SD	Bulk density g/ml ± SD	Tapped densi-ty (g/ml) ±S D	Angle of Rep-ose (deg)±SD	Carr's Index (%) ± SD	Hausner ratio ± SD
F1	2.26±0.44	0.53±0.15	0.56±0.02	21.55±0.44	5.99±1.84	1.05±0.04
F2	2.30±0.28	0.54±0.01	0.58±0.01	21.17±0.57	6.90±0.95	1.07±0.01

F3	2.76±0.35	0.56±0.01	0.60±0.01	20.93±0.77	7.29±0.04	1.07±0.01
F4	4.28±0.31	0.64±0.01	0.69±0.01	19.35±1.49	7.58±1.98	1.08±0.02
F5	3.75±0.22	0.56±0.02	0.62±0.01	22.49±0.97	9.61±2.39	1.11±0.03
F6	4.47±0.14	0.53±0.01	0.64±0.01	18.53±0.98	17.66±2.31	1.21±0.02
F7	4.34±0.21	0.62±0.00	0.66±0.01	22.21±0.41	5.35±1.54	1.06±0.02

Table 4: Post-compression properties of formulated salbutamol tablets

Batch	**Weight varia-bility ± SD**	**Thickness ± SD**	**Diameter ± ± SD**	**Hardness (Kg/F) ± SD**	**Friability (%)**
F1	0.10±0.00	2.44±0.27	6.57±0.23	8.16±1.36	0.01 ± 0.00
F2	0.09±2.16	2.10±0.06	6.31±0.20	8.51±0.82	0.1 ± 0.00
F3	0.14±0.19	2.18±0.06	6.24±0.00	4.61±0.42	1.88 ± 0.01
F4	0.14±0.19	2.59±0.09	6.66±0.09	8.61±0.84	0.21 ± 0.01
F5	0.10±0.00	2.25±0.05	6.27±0.02	3.99±0.40	0.58 ± 0.00
F6	0.10±0.00	2.36±0.10	6.37±0.02	5.68±0.75	0.24 ± 0.02
`1F7	0.10±0.00	2.26±0.07	6.41±0.05	4.23±0.53	0.18 ± 0.01

Tablets formulated with test gum were generally harder than those prepared with Eudragit polymer and maize starch. However, concentration of gum has no effect on tablets prepared with test gum. All the batches met British Pharmacopoeia specification for friability except batch F3 that failed the test which could be due to experimental errors.

DISSOLUTION:

From the values obtained in **Figure 2**, Tablets produced with 10 %, 15%, 20 % and 30% of the test gum (*Cissus populnea* gum) released 50 % of the active in 75, 90, 60 and 150 minutes respectively. Based on the results obtained, as the concentration of the binder increased, the percentage of drug release decreased. This is due to the binding force of the binder. Tablets produced with 20 % gum released the active faster than those prepared with 15% gum. This could be due the hardness of the tablet and poor granulation. Tablets formulated with 10 % and 15 % Eudragit® RS 100 released 50 % of their active in 60 minutes and 150 minutes respectively while tablets formulated with 3 % maize starch released 50 % of the active in 5 minutes as shown in Fig 2. The fast dissolution of formulation containing maize starch could be due to the fact that the formulation contains disintegrant which affects the dissolution rate.

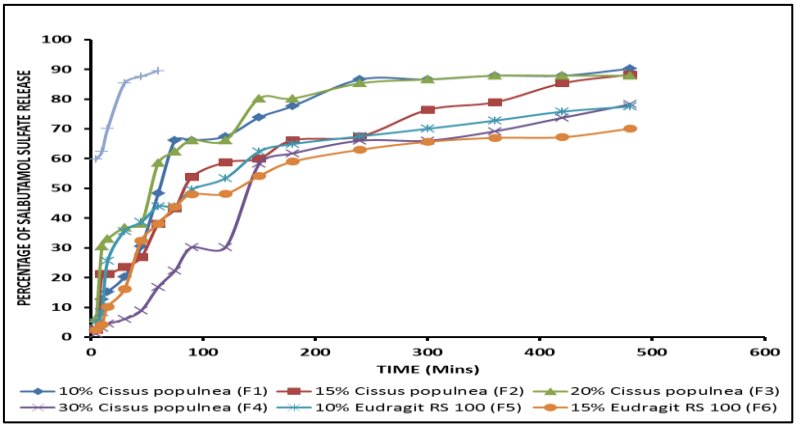

Figure 2: *In vitro* drug release profile of salbutamol sulfate prepared using *Cissus populnea*, Eudragit® RS 100 and Maize starch

From the results obtained, formulations containing 30 % of the test gum (*Cissus populnea*) and formulations containing 15 % of Eudragit ® RS 100 released 50 % of their active at the same time (150 minutes) and then there was gradual release of the drug with time. Hence based on this results, *Cissus populnea* gum will have the same retardant effect with Eudragit® RS 100 at a concentration of 2 : 1 thus controlling drug release.

Dissolution rate determines the extend of drug absorption and subsequent therapeutic outcome of a drug (Ngwuluka *et al*., 2010). The dissolution of a tablet is affected by factors such as concentration of

binder, type of binder, presence of disintegrant, hardness of tablet and solubility of the drug.

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