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FORMULATION AND EVALUATION OF ANTIDIABETIC CAPSULES OF KAEMPFEROL-3-O-B-D-6''-(*P*-COUMAROYL) GLUCOPYRANOSIDE EXTRACTED FROM *ALLIUM CEPA* L.

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Keywords:

Kaempferol, Hypoglycemic Activities, Gelatin capsules, Normoglycemia, Alloxan

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ABSTRACT: *Allium cepa* L. has known potent antidiabetic effects due to several of its constituents, including kaempferol -3-O-β-D-6"-(*p*-coumaroyl) glucopyranoside (kaempferol). This preliminary work was aimed at preparing oral hard gelatin capsules of kaempferol obtained from *Allium cepa* L. In order to obtain more potent hypoglycemic activities, lower side effects with good patient compliance over the crude extract kaempferol were isolated from *Allium cepa* L. and formulated into capsule dosage form. The capsules were prepared by filling hard gelatin capsule shells with blends of kaempferol with excipients which included Avicel® PH102, agglomerated lactose®, Primogel®, Ac-Di-Sol®, maize starch, stearic acid, and talc. The blends were evaluated for their micrometric properties such as bulk densities, tapped densities, Hausner's quotients, compressibility indices, true densities, flow rate and angle of repose. Prepared capsules were evaluated for weight variation, disintegration time, content uniformity, dissolution profiles and antidiabetic properties in alloxan-induced diabetic rats with distilled water and glibenclamide respectively as negative and positive controls. The capsules were of good properties with disintegration time (2.75 ± 0.22 – 3.55 ± 0.55 min.). Drug release was within 92.12 – 99.57% within 30 min with faster drug release in batches containing Ac-Di-Sol® and Primogel® as disintegrants than those containing maize starch. Alloxanized diabetic rats attained normoglycemia within 2 weeks of continued daily administration of the capsule. Blood glucose reduction of 65.69 – 75.56% was attained within 3 weeks of continued daily administration of the drug. Kaempferol capsule dosage forms were effective in reducing blood sugar levels in alloxan-induced experimental diabetic rats.

INTRODUCTION: Diabetes mellitus is a disease of disorder in the metabolism of carbohydrates, proteins and fats as a result of lack, inadequate secretion and or decreased action of insulin [1].

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The disease is presently incurable with those affected growing in an epidemic manner. The number of those affected globally is estimated to be 415 million with type 2 diabetes mellitus constituting about 90%. The number affected may reach up to 642 million by the year 2040 with more increase coming from low and middle-income countries [2].

Current pharmacological treatment include: injectables with insulin and insulin analogs forming the mainstay, glucagon-like peptide 1 (GLP-1)

agonist, amylin analogues; oral hypoglycemic agents such as sulphonylureas, biguanides, meglitinides, glitazones, α-glucosidase inhibitors, dipeptidylpeptidase-4 (DPP) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and dopamine -2 agonist inhibitors [3].

Even though, a lot of progress has been made in the discovery of anti-diabetic drugs, search for new ones is still ongoing because of the inability of the present drugs to maintain normoglycemia, prevent complications of diabetes mellitus and are also of much cost to the greater number of diabetic population [3, 4].

Plant secondary metabolites are being researched as the possible source of new drugs for diabetes mellitus since plants have provided veritable sources of new drugs over time [3, 5]. Secondary metabolites naturally protect plants from predators, pathogens and also against herbivores and microbes [6]. These secondary metabolites of plants have been found to be the active principles responsible for the therapeutic effects of medicinal plants and provide great opportunity for new drug discovery due to their abundance and diversity [7].

Allium cepa as a potential source of new drug has the advantages of its cheapness and use as food condiment and this may suggest that it may not be toxic. Several of its constituents such as s-methyl cysteine sulphoxide and kaempferol-3-O-β-D-6"-(*p*-coumaroyl) glucopyranoside were found to have potent hypoglycemic effects [8, 9]. This work is aimed at preparing oral hard gelatin capsules containing kaempferol- 3- O- β- D- 6"- (*p*-coumaroyl) glucopyranose for use in management of diabetes mellitus. Capsule formulations offer the advantage of needing less excipients in addition to greater flexibility. They also have faster drug release due to faster disintegration and dissolution.

MATERIALS AND METHODS:

Chemicals: Alloxan monohydrate and glibenclamide were bought from Sigma Chemical CO, USA. Microcrystalline cellulose (Avicel® PH102) was a gift from FMC Corp. USA, Agglomerated lactose® was bought from Meggle, Germany. Kaempferol was extracted from *Allium cepa* L. Other chemicals used were bought from local vendors and used as such.

Animals: Male Wistar rats (110-150 g) were obtained from the animal house of the Department of Veterinary Physiology and Pharmacology, University of Nigeria, Nsukka. They were kept in standard cages at room temperature and fed with standard commercial pellets feed (Edo Feed and Flour Mill, Ewu, Nigeria) and allowed free access to potable water. All the procedures performed in this study that involved the use of animals were done in accordance with ethical standards of the Institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine, University of Nigeria, Nsukka (Approval Reference Number: FVM-UNN-IACUC-2018-059), which complied with all applicable national and international guidelines. The study was carried out in the Department of Veterinary Physiology and Pharmacology, University of Nigeria, Nsukka between October and December 2018.

Preparation of Kaempferol / Excipients Blends: Kaempferol powder was extracted from aqueous extract of *Allium cepa* L. by method described by Ogbonna and Ofoefule, 2016 [9]. The kaempferol powder blends were prepared by mixing a weighed quantity of the kaempferol and mixing it with weighed quantities of the respective filler and disintegrants as shown in **Table 1**. These weighed quantities of ingredients were mixed by shaking together in a bottle for 30 min resulting in a homogenous mass of powder which was stored in a well-closed bottle for further experiments.

TABLE 1: COMPOSITION OF THE KAEMPFEROL CAPSULES

Ingredients (mg)	Batch					
	K_1	K_2	K_3	K_4	K_5	K_6
Kaempferol	4	4	4	4	4	4
Avicel®	137	140	-	-	128	-
Ag. Lactose	-	-	137	140	-	128
Primogel®	6	-	6	-	-	-
Ac-di-sol®	-	3	-	3	-	-
Maize starch	-	-	-	-	15	15
Stearic acid	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	150	150	150	150	150	150

Micromeritic Properties of Kaempferol/ Excipients Blends: The different batches of the kaempferol/excipient blends were evaluated for various micrometric properties such as bulk density, tapped density, Hausner's quotient (HQ),

Carr's compressibility index (CI), true density, flow rate and angle of repose.

Bulk and Tapped Densities: A 10 g quantity of each the kaempferol/excipients blend was weighed out and put in a 50 ml measuring cylinder and allowed to drop on the table from a height of about 10 cm. The volume occupied by the kaempferol/ excipients blend was read directly from the measuring cylinder and recorded as the bulk volume. Tapped volume was obtained by fixing the measuring cylinder containing a known weight of each batch on an automatic tapping machine Stampf volumeter (Karl Klobb, Dreieich, Germany). The tapping by the machine continued until a constant volume was reached and this was recorded as the tapped volume. The bulk density (D_b) and tapped density (D_t) were the calculated from Equations (Eqn.) 1 and 2 respectively. A total of 3 observations (n = 3) were made.

$$D_b = M/V_b \text{ …..Eq (1)}$$

Where, M is the mass of the powder mixture (10g) and V_b is the bulk volume of the powder mixture

$$D_t = M/V_t \text{ …..Eq (2)}$$

Where, V_t is the tapped volume of the powder mixture.

Hausner's Quotient and Carr's Compressibility Index: Hausner's quotient (*HQ*) and Carr's compressibility index (C.I) were calculated using the Equations 3 and 4 respectively.

$$HQ = D_t/D_b \text{…..Eq (3)}$$

$$\text{C.I. (\%)} = D_t\text{-}D_b \times 100 /D_t \text{…..Eq (4)}$$

True Density: The true density (DT) of each batch was determined by fluid displacement method using xylene a non solvent fluid [10]. A 50 ml pycnometer or density bottle was used. The weight of the pycnometer was noted. The density bottle was then filled with xylene and the new weight (W_1) was noted. A known weight W (1 g) of each batch was added and the weight of the xylene with density bottle and the sample was noted as (W_2). True density was then calculated from Equation 5. Triplicate observations were made (n = 3).

$$DT = W \times S.G/W_1+W-W_2 \text{…..Eq (5)}$$

S.G. is the specific gravity of the non-solvent xylene

Flow Rate and Angle of Repose: Methods described by Hamzah *et al.*, 2018 were used in determination of the angle of repose [11]. A plastic funnel was placed in metal ring support clamped on to a retort stand and placed 10 cm above the bench. The orifice of the funnel was closed temporarily with small sheet of cardboard paper, and a 10 g quantity of each batch was put into the funnel. The sheet of paper covering the orifice was removed, and a stopwatch timer started simultaneously. The granules were allowed to flow freely on to a plain sheet of paper. The time of flow (t), *i.e.*, time taken for the sample to flow from the funnel till all the powder had passed through the orifice of the funnel, height of heap (h) formed and diameter (d) of heap formed were noted. The flow rate (F) and angle of repose (θ) were calculated using Equations 6 and 8 respectively.

$$F = \text{Mass/Time of flow…..Eq (6)}$$

$$\text{Tan } \theta = h/0.5d\text{…..Eq (7)}$$

$$\theta = \text{Tan}^{-1}h/0.5d\text{….Eq (8)}$$

Preparation of The Hard Gelatin Capsules Containing Kaempferol: Two diluents were used namely micro-crystalline cellulose and agglomerated lactose in preparation of the capsules. Three classes of excipients are usually added to powders filled into capsules [12]. These include fillers, glidants and lubricants. Disintegrants are at times added to quicken the release of drugs from granules. The kaempferol powder blends were prepared by mixing a weighed quantity of the kaempferol and mixing it with weighed quantities of the filler and disintegrants as shown in **Table 1**.

These weighed quantities of ingredients were mixed by shaking together in a bottle for 30 min resulting in a homogenous mass of powder which was stored in a well-closed bottle for further experiments. The homogenous mass of powder was lubricated prior to encapsulation by addition of appropriate quantities of talc and stearic acid and mixed for 5 min. The lubricated powder blends were manually filled into size 1 hard gelatin capsules and stored in airtight well-closed bottles.

Evaluation of the Hard Gelatin Capsules Containing Kaempferol Capsules: The capsules were evaluated for properties such as:

Weight Uniformity: The uniformity of weight was evaluated by selecting 20 capsules randomly from each batch. The weight of the 20 capsules was noted together with the average weight and the individual weight of each capsule. The percentage deviation of the weight of each capsule from the average weight was then calculated. The weight of a batch of capsules is considered uniform if the weight of the individual capsules falls within 90 - 110% of the average weight. If this condition is not fulfilled, the fill or net weight of each capsule is determined and compared with the average net weight of the capsules. Capsules are considered satisfactory if not more than 2 capsules are greater by 10% of the average net weight, or none is outside the range of 75 - 125%.

Content Uniformity: Content uniformity test was carried out by assaying individually 10 randomly selected capsules spectrophotometrically [13, 14]. The assay was carried out using an established standard Beer's plot for kaempferol obtained at 268 nm wavelength. A batch of capsules is said to be satisfactory if 9 out of the 10 assayed are within potency range of 85 - 115% and a tenth are within 75 - 125% [13]. If not more 20 are assayed and the requirement is met if all the 30 are within the 75 – 125% of the specified potency range and not less than 27 of the 30 are within the 85 - 115%.

Disintegration Time Test: Disintegration time test was carried out in the same apparatus as tablets; however a little strand of copper wire was attached to each capsule to ensure that they sink to the bottom of the disintegration cell. The disintegration time test was carried out using an Erweka disintegration machine (Erweka, type ZT4 Nr32440, Germany). Distilled water maintained at a temperature of 37.0 ± 1.0 °C was used as the disintegration medium. Six randomly selected capsules from each batch were put singly into each tube of the disintegration unit whose lower end was closed by a screen of 2 mm aperture. The tubes were raised up and lowered in a bath containing the disintegration medium steadily until the capsule breaks up and pass through the mesh of the tube. Capsules are said to be disintegrated if no particle of the capsule remains on the screen except fragments of the capsule shell. The time taken for this to happen was noted. The mean and the standard deviation were calculated.

Dissolution Rate: A standard Beer's plot was first constructed at the wavelength of maximum absorption (λ_{max}). The drug obeyed Beer's law at the concentration range of 0.01 - 0.08 mg/ml used and a regression equation of the Absorbance is 7.817 [Drug] - 0.080, R2 = 0.999 and at a maximum (λ_{max}) absorption of 268 nm in 0.1 N HCl. Dissolution studies were carried out using the dissolution apparatus with a paddle (U.S.P. model 2, Erweka, Germany) with 0.1N HCl as the dissolution medium. A 900 ml volume of the dissolution medium was measured into the dissolution apparatus maintained at 37.0 ± 1.0 °C. The machine was allowed to equilibrate for 30 minutes after which one capsule was introduced. The capsule was prevented from floating by attachment of a small strand of wire. A 5 ml volume of the dissolution medium was withdrawn after every 5 min and replaced with 5 ml of fresh 0.1 N HCl for 60 min. The samples withdrawn were then determined spectrophoto-metrically using ultraviolet spectrophotometer model (Shimadzu, Japan).

Drug Content: The percentage of drug content was determined for each batch spectrophotometrically. The contents of 10 randomly selected capsules were weighed and a quantity corresponding to the mean weight was taken and assayed using spectrophotometer as above.

Determination of *In-vivo* Antidiabetic Properties of the Capsules: Alloxan induced diabetic rat model was used. Male wistar rats were rendered diabetic by single intraperitoneal injection of freshly prepared alloxan monohydrate solution (150 mg/kg) and allowed free access to water and food for one week. On the 8th day the blood glucose levels of the rats were checked with Accucheck® Advantage Glucometer (Accucheck Germany) and those with fasting blood glucose greater than 180 mg/dl were selected for the study. The diabetic rats were grouped into 8 groups of 5 rats each representing the 6 batches and 2 control groups. Each group received one batch of the capsules

which was given orally through gastric intubation at the dose of 100 mg/kg (bodyweight) per day for 21 days. The control groups were respectively given glibenclamide at the dose of 2 mg/kg (body weight) and distilled water at 5 ml/kg (body weight) per day for 21 days. Fasting blood glucose was measured at predetermined time for each group including the control groups for 21 days.

Statistical Analysis: IBM SPSS statistics 21 (New York, USA) was used to analyze the results obtained from the experiments. Results were expressed as mean ± standard deviation (SD) where appropriate. Statistical significance among groups was analyzed by one-way analysis of variance (ANOVA). P values < 0.05 were considered significant.

RESULTS AND DISCUSSION:

Preparation and Evaluation of the Kaempferol / Excipients Blends: The powder blends of kaempferol and excipients were of good flow and also had good packing ability as shown by the Hausner's quotients and Carr's compressibility index values **Table 2**. Hausner's quotients less than 1.25 indicate good flow while from 1.25 -1.5 may need glidant to improve the flow 14. Successful filling of capsules requires good fluidity and packing properties of the fill material. The CI, HQ, flow rate and the angle of repose of the powder blends ranged from 12.24 to 19.05%, 1.14 to 1.23, 9.94 ± 0.19 to 16.72 ± 0.70 g/s and 28.52 ± 4.36 to 35.81 ± 3.26° respectively. All the values indicated good flow property of the powder blends.

TABLE 2: SOME PROPERTIES OF KAEMPFEROL/EXCIPIENTS BLENDS

Batch	Bulk density (g/ml)	Tapped density (g/ml)	CI (%)	HQ	Flow rate (g/s)	Angle of repose(°)
K_1	0.46 ± 0.03	0.53 ± 0.03	13.21	1.15	9.94 ± 0.19	28.52 ± 4.36
K_2	0.43 ± 0.09	0.49 ± 0.01	12.24	1.14	12.45 ± 0.85	31.20 ± 3.01
K_3	0.51 ± 0.05	0.60 ± 0.05	15.00	1.17	14.60 ± 1.05	35.81 ± 3.26
K_4	0.52 ± 0.01	0.64 ± b 0.06	18.75	1.23	16.72 ± 0.70	33.40 ± 2.35
K_5	0.48 ± 0.02	0.55 ± 0.04	12.73	1.15	13.24 ± 0.55	31.25 ± 2.33
K_6	0.51 ± 0.06	0.63 ± 0.08	19.05	1.24	10.66 ± 0.48	32.21 ± 3.83

*value expressed as mean ± standard deviation (SD) where appropriate, n = 3.

Physical Properties of the Kaempferol Capsules: The prepared capsules showed good weight uniformity as all the batches were within 90 –110% of the average weight which shows that the method of filling the capsules was satisfactory. This also reflected on the low variation in the content of the active ingredient **Table 3**. However, the standard content uniformity requirement is that if a batch of 10 capsules is assayed nine out of the ten will have weight uniformity within 85-115%. If not, more 20 are assayed and not less than 27 of the 30 should lie within 85-115%. It is an important test for capsule especially low dose capsules [15].

All the capsule batches also disintegrated within 5 min which is good for immediate therapeutic effect resulting in faster drug dissolution and absorption. Immediate-release capsules are however expected to disintegrate within 30 min except otherwise stated in the drug monograph.

The drug content was high in all the batches and very close to 100% in all the formulations. These values are reproducible even after more than three months at a temperature of 25 ℃ - 32 ℃ and relative humidity of 50-65%.

TABLE 3: SOME PROPERTIES OF KAEMPFEROL CAPSULES

Batch	Weight uniformity (mg)	Disintegration Time (min)	Drug content (%)	Content uniformity (mg)
K_1	153.33 ± 4.18	3.27 ± 0.15	101.09	4.5 ± 0.72
K_2	148.70 ± 3.49	3.44 ± 1.37	91.73	4.02 ± 0.56
K_3	145.46 ± 4.33	2.85 ± 0.36	96.25	3.95 ± 0.37
K_4	148.64 ± 2.55	3.55 ± 0.05	97.52	3.97 ± 0.54
K_5	152.35 ± 5.02	3.42 ± 0.76	103.45	4.11 ± 0.44
K_6	151.56 ± 6.27	2.75 ± 0.22	95.33	4.21 ± 0.28

*value expressed as mean ± standard deviation (SD) where appropriate

***In-vitro* Dissolution Profiles of the Kaempferol Capsules:** Drug release in the capsules was rapid because of the fast disintegration time and also a large volume of dissolution media in relation to the

quantity of active ingredient. All the batches achieved maximum release within 30 min **Fig. 1** and **2**. The drug obeyed Beer's law at the concentration range of 0.01 - 0.08 mg/ml used and a regression equation of y = 7.817x + 0.080, R2 = 0.999 and at a maximum (λ_{max}) absorption of 268 nm in 0.1 N HCl.

There was faster drug release in the batches with Primogel® and Ac-di-sol® as the disintegrants (K_1-K_4) than those containing maize starch (K_5 and K_6). Also, batches with Avicel® as the filler also had faster release than those containing lactose.

In all the batches maximum release (C_{max}) was in the range of 92.12 – 99.57% which was achieved in less than 30 min.

This implies that the capsules will have rapid *in-vivo* onset of action since drug absorption is dependent on the release behavior. Drug release in the capsules was rapid because of the fast disintegration time and also a large volume of dissolution media in relation to the quantity of active ingredient. All the batches achieved maximum release within 30 min as shown by **Fig. 1** and **2.**

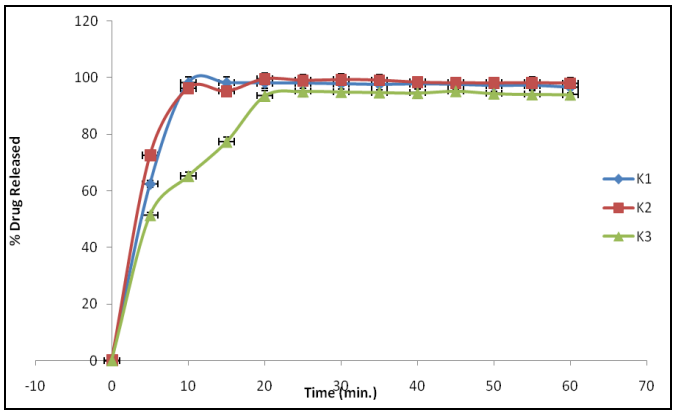

FIG. 1: DISSOLUTION PROFILES OF BATCHES K_1, K_2, K_3

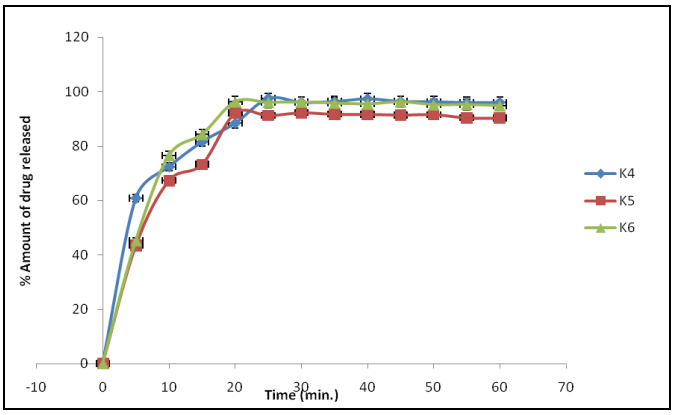

FIG. 2: DISSOLUTION PROFILES OF BATCHES K_4, K_5, K_6

Effect of Kaempferol Capsules on Blood Glucose Levels of the Diabetic Rats: The kaempferol capsules exhibited potent hypoglycemic action in alloxanized rats. Evidence of its blood sugar lowering effect was visible within one hour after administration of the drug. On continued administration of the capsules at the dose of 25 mg/kg body weight once daily the hypoglycemic effect was observed as shown by reduction in the fasting blood glucose levels. The rats were restored to normoglycemia within 2 weeks. Maximum reduction of blood glucose level of 70.71%, 65.69%. 75.56%, 64.21% 72.42% and 71.14% for batches K_1, K_2 K_3, K_4, K_5 and K_6 respectively were obtained **Fig. 3** and **4**. The potency of kaempferol as a hypoglycemic agent has earlier been confirmed in our earlier report [9]. Capsules are always the dosage form of choice for experimental new drugs because they can easily be prepared extemporaneously. The drug was given per oral and the observed *in-vivo* effect shows that the *in- vivo* release and absorption of the drug were adequate for possible therapeutic use.

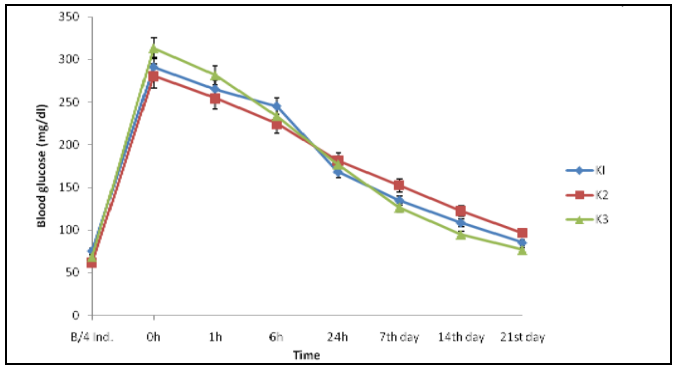

FIG. 3: ANTI-DIABETIC EFFECT OF BATCHES K_1, K_2 AND K_3

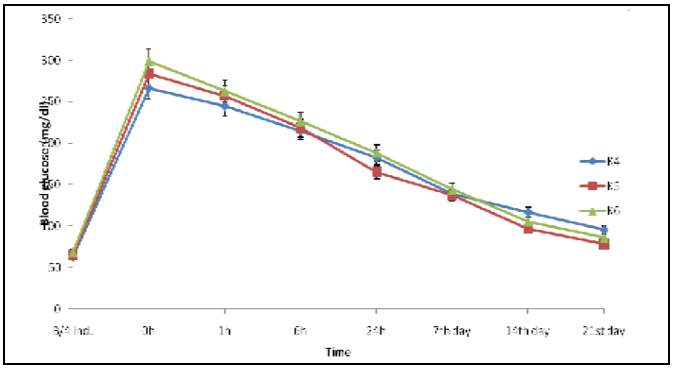

FIG. 4: ANTI-DIABETIC EFFECT OF BATCHES K_4, K_5 AND K_6

CONCLUSION: Formulation kaempferol into capsule form using suitable excipients was also found effective as an anti-diabetic drug as compared to the negative control. It is therefore suggested that while kaempferol can be formulated into capsules for better compliance and convenience based on this preliminary study, more studies are recommended to understand its possible interactions with excipients and stability problems that the capsules may encounter on storage, pharmacokinetics and potential adverse effects. Kaempferol has been found to exist in many plants as glycosides with different glycosidic links which have been shown to possess potent anti-diabetic properties together with other biological activities such as anticancer, antimicrobial, anti-inflammatory, antioxidant and anticholesterolemic properties [16].

Despite this reported effectiveness, *in-vivo* and *in-vitro* their safety is not fully understood and also requires further studies. There are available conflicting reports about the safety of kaempferol glycosides. Anti-mutagenic properties of kaempferol glycosides were observed by different researchers [17, 18]. The potential of kaempferol to induce genotoxicity has also been reported [19, 20, 21].

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CONFLICTS OF INTEREST: There is no conflicts of interest in this article.

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