Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(2):31-39

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Preliminary evaluation of *Sesamum radiatum* leaf mucilage as release modifier in potassium chloride matrix tablets

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ABSTRACT

The objective of this study is to evaluate the use of Sesamum radiatum leaf gum as a potential excipient for modifying the release of potassium chloride tablets. The gum was precipitated from the aqueous maceration of the leaves and then characterized to determine some of its physicochemical properties. Potassium chloride granules were prepared by the wet granulation method of massing and screening using 30 %w/w each of Sesamum radiatum gum, hydroxypropylmethylcellulose and 1:1 concentration of both polymers. The granules were analysed for flow parameters and then compressed into tablets in the ErwekaAR 400 single punch laboratory tableting machine using the 12mm punch and die assembly. The tablets were evaluated for uniformity of weight, tablet diameter and thickness, friability, crushing strength and disintegration time. In-vitro studies on the tablets was carried in acid medium (0.1 N HCl) and alkaline medium (phosphate buffer 7.4). The results showed that tablets containing Sesamum radiatum gum were able to modify/sustain the release of potassium chloride for up to 9 h, the gum was also able to offer barrier to drug release in the upper gastrointestinal tract (acidic medium). The kinetics of drug release was observed to be zero order which was controlled by swelling and subsequent erosion.

Keywords: Potassium chloride, *Sesamum radiatum* gum, hydroxypropylmethylcellulose, kinetics, swelling and erosion.

INTRODUCTION

The conventional delivery systems are designed for immediate drug release and absorption [1] but are usually plagued with setbacks such as drug degradation or loss and reduction in bioavailability. Other associated problems include increased drug accumulation at certain sites in the body, fluctuations in drug plasma concentrations leading to under or over-medication and also increase in emergence of adverse effects. The development of delivery systems capable of addressing the setbacks or problems of the conventional systems is therefore a potent area of research for drug formulators. These systems in addition to addressing the limitations of the conventional systems are capable of controlling drug release rates; examples are the prolonged, delayed, targeted and sustained release systems [2]. The sustained delivery is designed to achieve slow release of the drug over an extended period of time i.e. the system maintains a constant drug level in the cells or tissues[3]. A major advantage of the sustained release system is its ability to reduce the dosing frequency of the drug and increase the efficiency of the drug by providing uniform release. Sustained release systems can be achieved by a number of ways one of which is formulation into a matrix using a polymer i.e. homogenously dispersing the drug in a polymer [4]. Polymers ranging from natural, semi-synthetic to synthetic have been used in the development of these sustained release systems examples are eudragit,

hydroxypropyl methylcellulose, *aloe vera* mucilage, *Sesamum indicum* gun, *Moringa oleifera* gum, cashew gumamong others [5-8].

Sesamum radiatum is a flowering plant that belongs to the family Pedaliaceae and genus Sesamum. This plant originated from Africa and grows wildly in West and Central Africa but is also cultivated on a small scale mainly for home consumption. It is commonly known as benniseed, black benniseed and vegetable sesame. In Nigeria however, it is known among the Yoruba as Eku, and Karkashi among the Hausas[9].The fresh leaves of *Sesamum radiatum* are eaten as a popular leafy vegetable; its young shoots are finely cut and used in soups or sauces and the cooked leaves which is slimy in texture is also eaten as a staple soup in the rainy seasons[10].This work therefore seeks to explore the use of *Sesamum radiatum* leaf gum as a release modifier in the formulation of sustained-release potassium chloride tablets.

EXPERIMENTAL SECTION

2.1. Materials

Sesamum radiatum leaves (gotten from Samaru market, Zaria, Kaduna State, Nigeria).Acetone (BDH Chemical Ltd Poole England). Hydroxypropylmethylcellulose (HPMC) low grade; 80 -120 cp (H9262 Sigma-Aldrich, USA),Potassium chloride crystals (BDH Chemicals Ltd, England).All other chemicals and reagents used were of analytical grade.

2.2. Methods

2.2.1. Extraction of gum

Fresh *Sesamum radiatum* plant was collected from Samaru market, Zaria, Nigeria. The sand from the stalk of the plant was dusted off and then the leaves were plucked off the stalks. Five hundred (500) grams of the leaves was weighed on an electric balance and 1000ml of hot water was added unto the leaves. The leaves were stirred and squeezed in the water for about 15mins (to release the slime) then sieved using a muslin cloth. Equal volume of acetone was added to the filtrate and stirred to precipitate the gum. The precipitate was washed four times with acetone until all the gum was precipitated, air dried over-night and then dried again in the Gallenkamphot air oven for 2 hours at 40^0C. The dried gum was weighed, powdered and then preserved in a desiccator for further use.

2.2.2. Evaluation of Gum

2.2.2.1. Particle Size Distribution: The Endecott sieve shaker was used to determine the particle size distribution. Twenty (20) grams of the powdered gum was place unto a set of sieves arranged in decreasing order (500µm, 250µm, 150µm, 90µm, 75µm and pan).They were allowedto vibrate at 100rpm for 10 mins; the weight retained on each sieve was weighed and the percentage by weight was calculated thus:

$$\frac{weight\ retained\ on\ ech\ sieve}{total\ weight\ of\ powdered\ gum} X100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots equation\ 1$$

A portion of the gum was mounted in glycerol and viewed under the microscope at a magnification of X10. Two hundred (200) particles were counted and their particle sizes determined.

2.2.2.2. Angle of Repose: The set up involved a glass funnel clamped on a retort stand at a height of about 10cm from the table top. Twenty (20) grams of the powdered gum was poured into the funnel and allowed to flow. The height and the base of the heap were measured and the angle of repose was calculated as:

$$Tan\ \theta = \frac{h}{r} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots equation\ 2$$

2.2.2.3. Bulk Density and Tapped Density: Twenty (20) grams of the gum powder was poured into a graduated measuring cylinder and the volume occupied by the powder was noted and used to extrapolate the bulk density (g/ml). The cylinder was then tapped 100 times and the volume occupied by the powder was noted. The ratio of the weight to the tapped volume was calculated as the tapped density (g/ml).

2.2.2.4. Carr's index and Hausner ratio: The Carr's (compressibility) index (CI%) was calculated using the following formula:

$$CI\% = {Td - Bd}/{Td}\, x100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \; equation\ 3$$

Where Td = tapped density and Bd = bulk density.

The Hausner ratio was calculated as the ratio between the tapped density and bulk density.

2.2.2.5. Flow Rate: Twenty (20) grams of the powdered gum was placed into the funnel of the Erweka flow-tester and the time taken for the powder to flow through the funnel was recorded. Three readings were taken, the average obtained and the flow rate was calculated as:

$$\frac{weight\ of\ powdered\ gum}{time\ taken} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \; equation\ 4$$

2.2.2.6. Moisture Sorption Studies: One (1) gram of the powdered gum was weighed unto a dry petri dish of known weight and placed in a desiccator over water for 5 days. The petri dish was then removed and weighed and the water sorption of the gum was calculated as:

$$\frac{initial\ weight - final\ weight}{initial\ weight} X100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \; equation\ 5$$

2.2.2.7. Determination of Solubility: About 25 ml of cold water was added to 500 g of the gum in a beaker and left overnight. The clear supernatant (about 12.5 ml) was put into an evaporating dish and heated to dryness over a water bath. The weight of the dried residue in reference to the volume of the solvent was gotten and the percentage solubility was calculated. The solubility was repeated with hot water, ethanol and chloroform.

2.2.2.8. Swelling capacity: Five (5) grams of the gum powder was poured into a 100 ml measuring cylinder and the tapped volume was noted. Water was added to obtain 85 ml dispersion of the gum and this was then made up to 100 ml and left for 24 h. The ratio of the swollen volume to the tapped volume was calculated as the swelling capacity of the gum[11].

2.2.2.9. Viscosity: The apparent viscosity of 1 %w/v aqueous dispersion of the gum was determined using spindle 62 of the digital Brookfield viscometer (model DV-1 PRIME).

2.3. Preparation of granules

The granules were prepared by wet granulation method of massing and screening. The appropriate quantities of microcrystalline cellulose (MCC), potassium chloride crystals and *Sesamum radiatum* gum (SRG) were weighed (table 1) and geometrically mixed in a porcelain mortar. Distilled water (5 ml) was added to the powdered mix to form a wet mass which was screened through a 1.7 µm sieve and dried in the GallenKamp oven at 40^0C for 10 mins. The dried granules were further screened through 0.8 µm sieve to obtain uniformed sized granules and dried again in the oven until constant weight was obtained. The same procedure was employed in the production of granules containing hydroxylpropylmethylcellulose(HPMC).

Table 1: Composition of batches of Potassium chloride tablets

Ingredients/ tablet (mg)	Batches SR 30	HP 30	SR-HP 30
Potassium chloride crystals	500	500	500
Sesamum radiatum gum (SRG)	231	-	-
Hydroxypropylmethylcellulose (HPMC)	-	231	231
SRG+HPMC (1:1)	-	-	-
Microcrystalline cellulose (MCC)	15.9	15.9	15.9
Talc	15.4	15.4	15.4
Magnesium stearate	7.7	7.7	7.7
Total	770	770	770

SR 30 – formulation containing 30 %w/w of Sesamum radiatum gum
HP 30 - formulation containing 30 %w/w of Hydroxypropylmethylcellulose
SR-HP 30 - formulation containing 15 %w/w each of Sesamum radiatum gum and Hydroxypropylmethylcellulose

2.4. Analysis of granules
Moisture content, flow rate test, angle of repose, particle size distribution, bulk and tapped densities, Carr's index and Hausner ratio of the granules were evaluated following the already described procedure for *Sesamum radiatum* powder.

The granules were then mixed with the appropriate amounts of extra-granular excipients (table 1) and compressed into tablets in the Erweka AR 400 (Germany)single punch laboratory tableting machine at compression pressure of 6 metric tons for batch SR 30, 11.5 metric tons for batch HP 30 and 9 metric tons for batch SR-HP 30.

2.5. Evaluation of Tablets
2.5.1. Weight uniformity test: Twenty (20) tablets from each batch were weighed individually and the mean weight of each batch was obtained [12].

2.5.2. Tablet thickness and diameter: The thickness of 10 tablets was determined using a digital verniercalliper TOH-700K (USA). The mean thickness was calculated and recorded.

2.5.3. Friability: Five (5) Tablets were weighed collectively and allowed to rotate at 25 r.p.m for 4 min in the Erweka friabilator TA3R, Western Germany. The tablets were dusted, re-weighed and the loss in weight determined and expressed as:

$$F\ \% = {}^{Twi - Twf}/_{Twi\ x\ 100} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots equation\ 6$$

Where Twi = initial tablet weights, Twf = final tablet weights.

2.5.4. Crushing strength: Five (5) tablets were selected at random from each batch and the crushing strength of each tablet was determined using the hand operated Monsanto hardness tester (Phillips, England). The mean crushing strength (kgF) was determined

2.5.5. Disintegration Test: One (1) tablet was placed in each tube of the Erweka disintegration apparatus thermostated at 37^0C. The time taken for each tablet to disintegrate was noted and the mean time was calculated.

2.5.6. Dissolution Test: The DGN multipurpose, dissolution apparatus (Shanghai China) thermostated at 37±1°C and 100 rpm was used. One tablet was placed in the basket lowered into a vessel containing 900ml of acidic media (0.1NHCl).Five (5) ml aliquots were withdrawn at intervals of 30 mins and replaced with the same volume of the media. The amount of potassium chloride released in the medium at the specified times was obtained by titration using the official method [12]. The dissolution was also repeated with new tablets from each batch in phosphate buffer pH 7.4.

2.5.7. Release kinetics and mechanism of release: The data from the dissolution studies were fitted into various kinetics models such as zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas using the equations [13].

RESULTS AND DISCUSSION

3.1. Preliminary characterization of *Sesamum radiatum* gum (SRG)
The percentage yield of the gum extracted from the fresh leaves of *Sesamum radiatum* was 10 %w/w (table 2) which was similar to the previous reports [14]. The extracted gum powder was light brown in color; it had a mild acidic taste and characteristic smell. The gum was observed to have a moisture sorption capacity of 30 % this shows that the gum has high affinity for moisture and should therefore be stored in airtight containers. The presence of excessive moisture has been reported to influence the flow and mechanical properties of powders and also cause microbial growth in tablet formulations during the process of packaging and storage [15, 16].

The angle of repose of a powdered material indicates its flow-ability; values between 23 ^{o} and 35 ^{o} are considered to be good flow while values between 40 ^{o} and 60 ^{o} indicate that the materials do not flow properly [17]. *Sesamum radiatum* gum (SRG) showed an angle of repose of 20.3 ^{0} (table 2) indicating it is a good flowing powder. However,

the Hausner ratio revealed that the powder is cohesive in nature with a value of 1.84 and it was also observed to be poorly compressible (Carr's index of 45.75 %). Materials with Hausner ratio ≤ 1.25 have been reported to flow freely and are less cohesive and those with Carr's index (percentage compressibility) ≤ 15 % are said to have excellent flow [18]. SRG was observed to have small mean particle size and this might be a contributing factor to its cohesiveness as powders with small sizes (< 20 µm) have been reported to have greater interparticulate attractive forces which cause a restriction in flow [19].

Table 2: Physicochemical properties of *Sesamum radiatum* gum (SRG)

Parameters	Results
Percentage yield (%)	10
Odour	Characteristic smell
Colour	Light brown
Ttexture	Fine powder
Taste	Mildly acidic
Moisture sorption capacity (%)	30
Swelling capacity (%)	136
Solubility (%w/w)	
In cold water	9.6
In Hot water	9.4
In Chloroform	0.0
In Ethanol	0.1
Flow rate (g/sec)	3.76
Angle of repose (^{o})	20.3
Bulk density (g/ml)	0.45
Tapped density (g/ml)	0.83
Carr's index (%)	45.75
Hausner ratio	1.84
Mean particle size (µm)	12
Viscosity	Pseudoplastic and Thixotropic

3.2. Evaluation of Potassium chloride granules

All the formulated granules had Hausner ratio and Carr's index within the accepted range for good flowing powders (table 3). This can be attributed to the process of granulation as granulation makes powders flow better [20].

Table 3: Physicochemical properties of the granules

Parameter	SR 30	HP 30	SRHP 30
Angle of repose (^{o})	26.6	26.1	26.2
Bulk density (g/ml)	0.56	0.22	0.44
Tapped density (g/ml)	0.67	0.43	0.57
Carr's index (%)	16.4	23.3	29.8
Hausner ratio	0.84	0.77	1.43
Flow rate (g/sec)	4.93	3.41	6.2

SR 30 – formulation containing 30 %w/w of Sesamum radiatum gum
HP 30 - formulation containing 30 %w/w of Hydroxypropylmethylcellulose
SR-HP 30 - formulation containing 15 %w/w each of Sesamum radiatum gum and Hydroxypropylmethylcellulose

Table 4: Physicochemical properties of Potassium chloride tablets

	Batches		
Parameters	SR 30	HP 30	SR-HP 30
Mean weight (mg)	778 (0.03)	772 (0.01)	765 (0.003)
Thickness (mm)	4.35(0.022)	5.02(0.011)	4.75(0.024)
Diameter (mm)	12.07(0.014)	12.05(0.006)	12.12(0.014)
Friability (%)	0.27	0.78	0.26
Crushing strength (kgF)	10.4	9.9	10.4
Disintegration time (h)	3.3	1.4	3.0

SR 30 – formulation containing 30 %w/w of Sesamum radiatum gum
HP 30 - formulation containing 30 %w/w of Hydroxypropylmethylcellulose
SR-HP 30 - formulation containing 15 %w/w each of Sesamum radiatum gum and Hydroxypropylmethylcellulose

3.3.Evaluation of Potassium chloride tablets

Tablet weight

The average weights of all tablets ranged between 765 mg and 778 mg (table 4) with minimal deviation; these values are within the specification for tablets ≥ 324 mg [12] and indicate there was uniform filling of the die as a result of adequate flow of granules into the die.

Tablet crushing strength

This is a measure of the structural strength of a tablet and has been reported to be hard but also capable of disintegrating and releasing the drug for absorption. A crushing strength of 4-8 kgF is said to be acceptable for conventional tablets but this requirement usually varies dependent on the intent of the formulation and the type of materials used in the formulation [21]. All the tablets had high crushing strength > 9 kgF(table 4) and this could be attributed to the polymers used in the formulation.

Tablet friability

The hard tablets were observed to have low friability values (<0.78) due to the strength of the bonds which provided resistance to fracture. Although, friability is not an official test but values ≤ 1 %w/w are reported to be satisfactory [22].

Tablet disintegration time

All the formulated tablets exhibited long disintegration times due to the high crushing strength of the tablets making penetration of the fluid more difficult. The tablets formulated with HPMC however, exhibited the shortest disintegration time (table 4) indicating that it would probably go into solution before the other formulations.

***In-vitro* drug release**

Hydration and subsequent gel formation is an important property of polymers responsible for controlling drug release. Hydration of a polymeric matrix with simultaneous swelling, gel formation and increase in swollen gel density serves as barrier to influx of fluids, increasing the diffusional path-length for drug transport and thus, retardation of drug release [23]. The degree of gelatinous layer produced around matrix tablets are usually dependent on the amount and type of polymer used in the formulation.

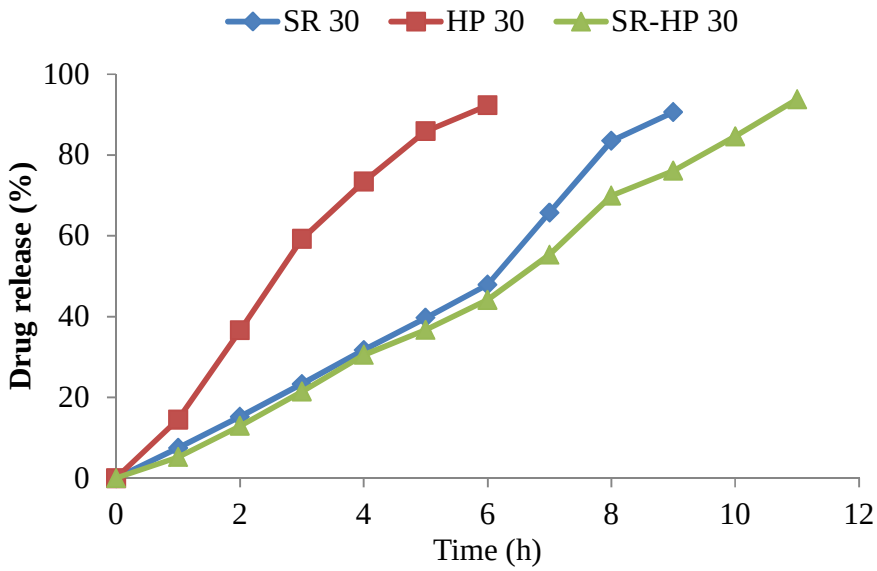

Figure (1): Release of potassium chloride from tablets formulated with 30 %w/w of *Sesamum radiatum* gum (SR 30), 30 %w/w of Hydroxypropylmethylcellulose (HP 30) and 15 %w/w each of both polymers (SR-HP 30) in acidic medium

Drug release in the acidic medium was observed to be at a gradual rate, meaning the drug was been released slowly with time. Although drug release from all the tablets was low within the stomach resident time (2 h), no “burst effect” (<30 % drug release in 1 h) was observed from any of the tablet formulations. Tablets formulated with

HPMC (HP 30) were observed to have the fastest release followed by SR 30 and then SR-HP 30 as shown in figure (1). The formulation SR 30 proved to be able to sustain the release of potassium chloride in the acidic medium for about 9 h and it was also capable of providing barrier to drug release in the upper GIT. The formulation SR-HP 30 was however capable of sustaining the release of potassium chloride for about 11 h, and providing barrier to drug release in the upper GIT. This could be attributed to the synergistic interaction between both polymers leading to the formation stronger elastic gel around the tablet than when the tablets were used alone.

Drug release from all the formulated tablets was generally faster in phosphate buffer than in acidic medium as shown in figure (2). Release from tablets formulated with HPMC was observed to be fastest and this is in agreement with a reports[24] which stipulates that HPMC formulations do not hydrate rapidly therefore, they are incapable of forming sustainable gels around the tablet and this would lead to faster granule dissolution.

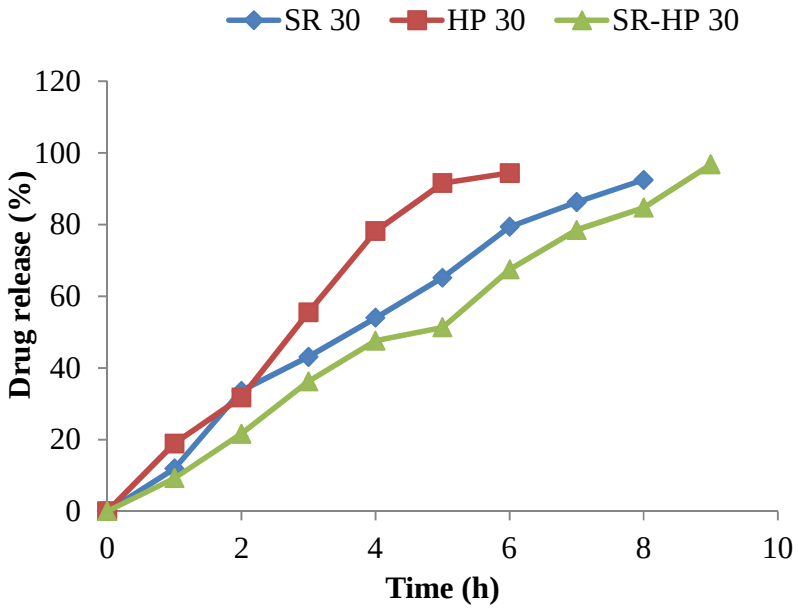

Figure (2): Release of potassium chloride from tablets formulated with 30 %w/w of *Sesamum radiatum* gum (SR 30), 30 %w/w of Hydroxypropylmethylcellulose (HP 30) and 15 %w/w each of both polymers (SR-HP 30) in phosphate buffer

Dissolution parameters

The t50 % from SR 30 was lower in phosphate buffer (7.6 h) than in acidic medium (9.0 h) showing that drug release was faster at higher pH than at lower pH (table 5); the values from SR-HP 30 were also observed to be significantly lower in the phosphate buffer (8.4 h) than in the acidic medium (10.6 h). The t50 % values from HP 30 however, were similar in both acidic and phosphate buffer media. About 90 % drug release was achieved by 9 h in SR 30 and 10.6 h in SR-HP 30 (table 5) indicating that combination of both polymers was able to provide greater sustaining property than when the polymers were used alone.

Table 5: Dissolution parameters for potassium chloride tablets

	t50 %	t70 %	t90 %
distilled water			
HP 30	3.4 h		
SR 30	3.6 h		
SR-HP 30	3.7 h		
acidic medium			
HP 30	2.6 h	3.8 h	5.8 h
SR 30	6.1 h	7.2 h	9.0 h
SR-HP 30	6.5 h	8.0 h	10.6 h
phospahte buffer			
HP 30	2.8 h	3.6 h	4. 9 h
SR 30	3.6 h	5.3 h	7.6 h
SR-HP 30	4.6 h	6.2 h	8. 4 h

Potassium chloride is used as an electrolyte replenisher or potassium supplement in hypokalemia. The potassium salt after ingestion causes gastrointestinal upset which may include symptoms such as nausea, vomiting, diarrhea, ulceration of the gastrointestinal wall and bleeding. Its formulation is usually intended to slow the release of potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced [3]. The minimal amount of drug release from formulations SR 30 and SRHP 30 *in-vitro* suggests the ability of these formulations to provide barrier to release of potassium chloride in the upper GIT thereby, minimizing the undesirable effects of potassium salt in the GIT while sustaining the release of the drug.

Release kinetics and mechanism of release:
The mechanism and kinetics of drug release from the tablets formulated with *Sesamum radiatum*, hydroxypropylmethylcellulose and their combination *in-vitro* were studied. The kinetic model with the highest coefficient was accepted as the appropriate model that describes the possible mechanism of drug release.

The most predominant kinetics of release from all the media was observed to be the zero order (table 6) indicating that drug release was independent of time and concentration of drug in the matrix. The release mechanism from the tablets was also confirmed by the Korsmeyer-Peppas model with "n" values > 0.89 signifying that drug release is controlled by swelling and then simultaneous erosion of the polymer. Drug release from hydrophyllic matrices has been reported to be governed by hydration followed by gel layer formation then drug diffusion into the gel layer and then finally into the dissolution media. Polymer erosion has also been implicated as a major role in releasing drug from these matrices[25].These considerations indicate that *Sesamum radiatum* gum has the potential to sustain the release of drug from matrix tablets.

In conclusion, *Sesamum radiatum* gum has greater sustaining power than hydroxypropylmethylcellulose and thecombination of both polymers has also proved to have better sustaining ability than each of the polymers alone.

Table 6: Kinetic Values and Mechanism of Release

	Zero order r^2	First order r^2	Higuchi model r^2	Hixson crowell r^2	Korsmeyers Peppas r^2	n
Batches			**Distilled water**			
SR 30	0.9979	0.9748	0.8819	0.7155	0.9965	1.0047
HP 30	0.9996	0.9781	0.8882	0.7168	0.9999	1.0272
SR-HP 30	0.9897	0.9632	0.8496	0.7656	0.9171	1.1567
Acidic medium						
SR 30	0.9759	0.9555	0.9217	0.3170	0.9509	0.9384
HP 30	0.9733	0.9661	0.9080	0.5528	0.9742	1.0469
SR-HP 30	0.9885	0.8394	0.8061	0.5446	0.9978	1.1963
Phosphate buffer						
SR 30	0.9759	0.9555	0.9217	0.3170	0.9509	0.9384
HP 30	0.9737	0.9598	0.8906	0.5458	0.9807	0.9708
SR-HP 30	0.9941	0.8628	0.9235	0.4400	0.9904	1.0477

Acknowledgement
The authors are thankful to the Department of Pharmaceutics, Ahmadu Bello University, Zaria for providing the facilities to carry out the work.

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