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Formulation and Evaluation Of Poly Herbal Anti-Diabetic Capsule Dosage Form

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ABSTRACT

Traditional herbal liquid remedies may be converted into solid dosage forms for enhanced product stability, patient convenience and compliance. Hidden Treasure mixture (HTM) is an herbal decoction produced and used by Hidden Treasure Herbal Clinic(HTHC) in Ghana for the management of diabetes. The objective of the study was to transform the HTM herbal decoction into oral capsules. The amount of dried extract per dose (120 ml) of HTM decoction was determined together with the maximum wavelength of absorption. Different adsorbents were incorporated in the HTM extract at 75, 150, 225 and 300 mg per dose of HTM to facilitate adsorption of water and enhance the processing of the dried extracts. The adsorbent-HTM extract mix were dried in hot air oven at 60 ºC 72 hours and subsequently processed into granules by dry granulation. The granules were evaluated for their ease of scrapping and processing, percentage loss in weight, flow properties and dissolution in aqueous medium. The weight of dried extract per dose was 350 mg. Light magnesium carbonate produced granules with the best ease of scrapping and processing and showed optimum release of 80.29% at 75 mg per dose. A maximum weight of 560 mg of HTM granules were used to fill size O capsule shells. Using LMC as adsorbent, the adsorbent-HTM granules were processed into capsules with talc and lactose as glidant and diluent respectively. The HTM capsules produced passed the stipulated British Pharmacopoiea quality control tests for hard capsules and can be used as replacement for the HTM decoction.

Keywords: Decoction, Adsorbent extract-mix, Dry granulation, percent release, Granules.

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1. Introduction

Plants are very important especially for their therapeutic purposes. The World Health Organization (WHO) defines medicinal plants as plants that contain substances or active ingredients that have therapeutic effects [1]. Therefore, the active ingredients of therapeutic plants are in high demand by pharmaceutical companies [2,3]. In this 21st century, diabetes remains one of the fastest growing maladies affecting almost 6% of the global population, with the number of affected people having more than tripled over the past 20 years [4]. The characteristics of the disease are changing rapidly in low as well as middle income countries including Ghana [5]. In addition, diabetes imposes a huge economic burden on communities and the nation at large. As a result, many Ghanaians have resorted to the use of phytomedicines or herbal formulations, which are relatively less expensive and have minimal side effects [6-10].

This situation has necessitated the need for research into effective, safe and cheap alternative treatments for the management of diabetes as the prevalence continue to increase. Diabetes mellitus remains a burden on healthcare systems due to increasing costs in managing the disease condition and its associated complications [11].

To address this challenge, this present study seeks to develop capsules from HTM, a liquid poly-herbal produced and used at Hidden Treasure Herbal Centre (HTHC), Weija, Ghana for the management of diabetes mellitus. The developed capsules will mask the bitter taste of the mixture and thereby increase the appeal of HTM to the general public, as well as prolong its shelf life. *Alstonia boonei* (*A. boonei*), *Rauwolfia vomitoria* (*R. vomitoria*), *Picralima nitida* (*P. nitida*) and *Gongronema latifolium* (*G. latifolium*) are well-known plants on the Ghanaian market that are frequently employed in the treatment of various ailments including diabetes mellitus. The polyherbal solid dosage form would be formulated using the aqueous extracts of the branches of *G. latifolium*, stem bark of *A. boonei*, root and stem bark of *R. vomitoria* and the seeds of *P. nitida* in the ratio of 4:3:2:1.

2. Methods

2.1. Materials: Light magnesium carbonate (Fisons Scientific, United Kingdom), maize starch, microcrystalline cellulose, kaolin and bentonite (Tradewinds Chemists, Ghana). Talc and Lactose were obtained from the chemical store, Department of Pharmaceutics, KNUST, Kumasi, Ghana. All additional chemicals and reagents utilised in this investigation were of analytical grade.

2.2. Sample collection and preparation: Branches of *G. latifolium*, stem bark of *A. boonei*, root and stem bark of *R. vomitoria* and the seeds of *P. nitida* used for the formulation of HTM were obtained from the premises of HTHC, Weija in the Greater Accra Region of Ghana. The plant materials were authenticated by Department of Herbal Medicine, KNUST, Kumasi, Ghana. The plant materials were combined and processed according to classified formula used by HTHC.

2.3. Preparation of HTM decoction

In the preparation of 3 L of decoction, 300 grams of the plant materials (branches of *G. latifolium*, stem bark of *A. boonei*, root and stem bark of *R. vomitoria* and the seeds of *P. nitida* in the ratio of 4:3:2:1) were weighed into a cooking pan containing 3300 ml (3.3 L)

of boiling water and allowed to boil for forty-five minutes [12]. The mixture was allowed to macerate for twenty-four hours after which it was filtered and the residue was washed with hot boiling water to make up to the 3 L volume. It was then dried in the oven at 60°C for three days, the yield of the extract was recorded and phytochemical tests were conducted on it. Quantities of plant materials used to make up the 300 grams in the preparation of HTM decoction are based on the formula used by HTHC. These quantities are noted to provide the required therapeutic effect to the patient.

2.4. Determination of maximum wavelength of absorption of HTM extract

One gram of the crude dry HTM extract was weighed and mixed with deionized water in a 100 ml volumetric flask. The solution was shaken after deionized water had been added to the 100 ml mark. Serial dilutions of the 100 ml solution produced concentrations of 0.0001, 0.001, 0.010, and 0.1%w/v [6]. The solutions were scanned using a UV- Vis Spectrophotometer to determine the maximum wavelength of absorption.

2.5. Calibration plot of HTM extract

The crude dried HTM extract was used to prepare concentrations of 0.0175, 0.015, 0.0125, 0.01, 0.0075, 0.0050, and 0.0025%w/v, and their corresponding absorbance values were measured using a UV-Vis spectrophotometer at a wavelength of 276 nm after which a calibration curve was plotted.

2.6. Determination of amount of extract per dose of decoction

A quantity of 120 ml portions of the HTM decoction were measured and transferred into three weighed, dry, clean stainless steel pans in order to determine the amount of extract per dose. A dose of HTM decoction is 120 ml. The mixtures were completely dried out using the oven and the weight of the extract and pan were both noted. The extract weight per dose was then determined.

2.7. Preparation of HTM granules

Five 3000 ml portions representing 25 doses of freshly prepared decoction of HTM were transferred into four different pans (labelled A, B, C and D) and placed in the oven with temperature set at 60^{o}C. The preparation was allowed to evaporate until a thin viscous extract was obtained. A quantity of 1.875 g light magnesium carbonate (LMC) representing 75 mg of light magnesium carbonate per dose of HTM was added to the thin extract in pan A and used to form a paste. The paste was allowed to dry completely at 60^{o}C. The ease of scrapping and processing of the adsorbent-extract mix was recorded. Processing involved passing the adsorbent-extract mix through sieve #20 (850 μm). Based on how much HTM extract could fill a 500 mg capsule, the weight of the adsorbent per dose was calculated. To calculate the maximum amount of adsorbent per dose, the weight of HTM extract per dose was subtracted from the total. Furthermore 3.750 g, 5.635 g and 7.500 g of light magnesium carbonate representing 150 mg, 225 mg and 300 mg respectively of light magnesium carbonate per dose of HTM was added to the thin extracts in containers B, C and D and used to form a paste. The above procedure was repeated. Using these same weights of adsorbent per dose, the same procedure was performed using bentonite, kaolin, maize starch and microcrystalline cellulose as adsorbents. This step was necessary to determine the most appropriate adsorbent for further formulation.

2.8. Determination of flow properties of granules

Bulk and tapped density determination

Ten grams of the powdered HTM granules was weighed and transferred through a funnel into a 100 ml measuring cylinder. The cylinder was then lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The initial volume, Vo was recorded. The cylinder was tapped from a height of 2.0 cm on a wooden bench top 100 times to attain a constant volume reading from the cylinder, Vf. The initial density was calculated as the bulk density using Do = mass/Vo. The final density was also calculated as the final tapped density using Df = mass/ Vf [13].

Hausner's ratio: $\frac{Df}{Do}$ was calculated as the Hausner's ratio.

Carr's index: Carr's index or percentage compressibility was then calculated using

Carr's index = $\left[\frac{\text{Tapped density (Df)} - \text{bulk density (Do)}}{\text{Tapped density (Df)}}\right] \times 100$ [7].

2.9. Angle of repose determination

The fixed height method was used in determining the angle of repose of the granules. A known quantity of the granules was allowed to flow through a funnel clamped at a fixed height unto a flat horizontal surface to form a cone. The diameter and height of the resulting cone were measured and the angle of repose calculated from the radius of the cone (r) and the height (h) using the relation, $\tan \theta = h/r$ [14].

2.10. Dissolution of HTM granules containing different adsorbents

The United States Pharmacopeia dissolution apparatus 2 (paddle) together with the procedure described in the BP 2013 [15] were used to determine the dissolution profiles of the granules in vitro. Each dissolution vessel was filled with 900 mL of distilled water. The temperature of the dissolution medium was kept at 37 ± 0.5 ^{o}C. A paddle speed of 50 revolutions per minute were set to maintain stirring. Six 350 mg samples of HTM extract-adsorbent mix were weighed out for the procedure. A volume of 10 mL was withdrawn from the dissolution vessel after start at time intervals 5, 10, 15, 30, 45 and 60 minutes. These samples were immediately filtered into appropriately labelled amber bottles. Ten milliliters of distilled water was taken to replace the 10 mL sample withdrawn from each vessel to maintain sink conditions [16]. The absorbance of the solutions in each amber bottle were determined by UV visible spectrophotometer at a wavelength of 276 nm. The blank solution was distilled water. The calibration curve was used to determine the sample concentrations. Each sample's percentage HTM extract release was estimated as well. The best extract-adsorbent combination was then determined by plotting the dissolution profile. Optimum release means that 75% of the API (extract) is dissolved within 45 minutes. The appropriate adsorbent for further study was determined based on how easily it could be scraped and processed as well as how much of the HTM extracts were released at 45 minutes in the dissolution studies.

Table 1: Formula for the preparation of HTM capsules

Ingredients	Quantity for one capsule (mg)	Quantity for 150 capsules (g)	Function of Ingredient
HTM extract	350	52.50	Serves as active pharmaceutical ingredient with glucose lowering effect
LMC	75	11.25	Acts as an adsorbent
Talc	5.6	0.84	Acts as a glidant
Lactose	129.4	19.41	Acts as a bulking agent
Capsule fill weight	560		

2.11. Formulation and production of HTM capsules

Based on the weight of the HTM extract per dose that was determined in triplicate, the size of capsule shell to be used was selected. Initial experimentation to determine the amount of granules that could fill a capsule shell was done. The required weights of the extract and the excipient were then calculated and weighed into a dry container and mixed well. Size '0'capsule shell was used, the shells were opened and were fixed into a manual capsule filling machine. The powder mixture was poured onto the powder bed on the machine and slowly filled with the aid of a plastic spatula to fill the shells uniformly. Excess granules was removed and apparatus was tapped to ensure powder was well inside the shells [17]. The shells were covered with the caps and placed in a well-covered container and stored at room temperature for further evaluation.

2.12. Evaluation of capsules

Uniformity of weight of HTM capsules

The test was performed in accordance with the BP 2013 [15] method for uniformity of weight of capsules. In this weight variation study, the mean weight of twenty randomly selected capsules was determined. Then the weight of each capsule was determined using an analytical balance. After which the capsules were carefully opened, making sure not to lose any shell material, and the contents removed totally. The difference between the weight of the intact capsules and the empty shells were calculated. The percentage deviations from the mean were determined.

2.13. Disintegration of HTM capsules

The disintegration time of capsules was determined according to the procedure described in the BP (2013) [15]. The bath of the disintegration tester was filled with distilled water to the desired mark and the temperature was set at 37 ± 0.5°C. The beakers were filled with 600 ml of distilled water and suspended in the main bath. The temperature was allowed to reach equilibrium with that of the bath. One capsule was placed into each of the six tubes. A disc was placed on each capsule to prevent it from floating. A stop watch was set and the apparatus operated until all six capsules had disintegrated leaving only remains of gelatin shell on the mesh. The time was recorded and the procedure was done in triplicate. The mean disintegration time of capsules was determined.

2.14. Dissolution of HTM capsules

The United States Pharmacopeia dissolution apparatus 1 (basket) together

Table 1: Formula for the preparation of HTM capsules

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Lactose	129.4	19.41	Acts as a bulking agent
Capsule fill weight	560		

with the procedure described in the BP 2013 (Appendix XII B) were used to determine the dissolution profiles of the capsules in vitro, as earlier described.

3. Results and Discussion:

The UV spectrum of HTM extract showed an observable peak at maximum wavelength of absorption of 276 nm (Figure 1) with an R^2 of 0.9976 (Figure 2). The calibration curve shows a good relationship between the concentration of the marker and the absorbance values recorded.

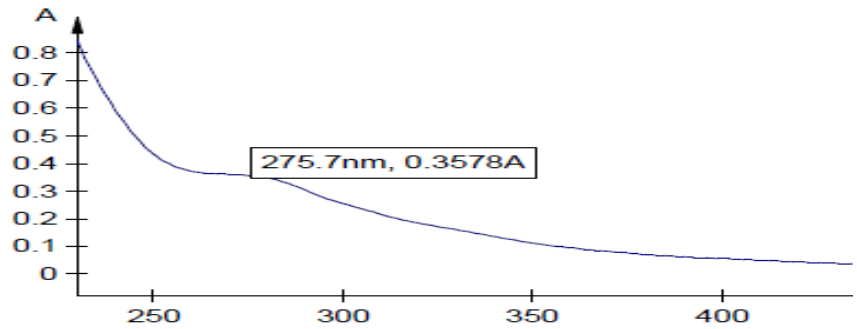

Fig. 1: UV spectrum of HTM extract

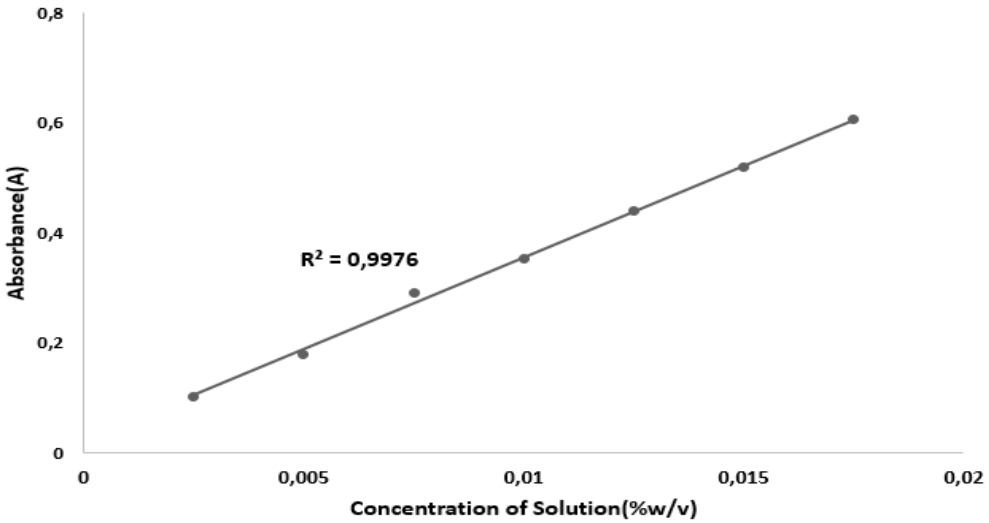

Fig. 2: calibration curve for HTM extract solutions

The average weight of HTM extract per dose of HTM decoction was 0.350 ± 0.01 g (Table 2). This means one Size 0 capsule could accommodate a dose of HTM granule.

Table 2: Determination of weight of extract per dose

Pan	A	B	C
Weight of pan + extract (g)	149.68	154.32	147.77
Weight of empty pan (g)	149.32	153.98	147.42
Weight of extract (g)	**0.36**	**0.34**	**0.35**

120 mls of HTM decoction was used for this procedure because that was the recommended dose for diabetes treatment at HTHC. As a result, the weight of the extract per dose used for future calculations was 350 mg.

Table 3: Ease of scrapping and processing of HTM extract-adsorbent mix after drying

	Weight of adsorbent per dose			
	75 mg	**150 mg**	**225 mg**	**300 mg**
Light magnesium carbonate	Very Easy	Very Easy	Very Easy	Very Easy
Microcrystalline cellulose	Very difficult	Very difficult	Very Easy	Very Easy
Bentonite	Difficult	Easy	Very Easy	Very Easy
Kaolin	Difficult	Very difficult	Very difficult	Very difficult
Maize starch	Very difficult	Very difficult	Very easy	Very Easy

Since a constant temperature is desired and the properties of the decoction cannot be ascertained, oven drying is a suitable method for drying extracts. The recommended temperature for the drying of plant extracts in the oven is between 50 – 80^{o}C [18]. Hence an optimum temperature of 60^{o}C was used for the drying of HTM decoction. To select the appropriate adsorbent needed for the formulation of HTM capsules, five adsorbents (bentonite, maize starch, light magnesium carbonate, kaolin and microcrystalline cellulose) were first evaluated for ease of processing. The method of choice in this study was the incorporation of the adsorbents which will be effective in the formation of flakes after drying and ensure the extract can be processed into granules. The adsorbents enhanced scrapping and further processing as well reduced the drying time. However, a hindrance to the use of adsorbents is the possible interference with the release of the API from the adsorbent-extract mix.

Table 3: Ease of scrapping and processing of HTM extract-adsorbent mix after drying

Absorbent	**Percentage loss in weight of adsorbent per dose (mg) ($^{W}/_{W}$%)**			
	75 mg	**150 mg**	**225 mg**	**300 mg**
Light magnesium carbonate	4.00±0.10	6.16±0.02	2.26±0.03	6.46±0.05

Bentonite	9.65±0.04	18.16±0.01	4.14±0.01	17.91±0.03
Maize starch	10.02±0.01	10.16±0.02	12.63±0.03	3.02±0.01
Kaolin	2.96±0.03	24.00±0.10	3.03±0.02	6.22±0.02
Microcrystalline Cellulose	3.53±0.06	12.96±0.02	4.00±0.16	18.52±0.09

Values are expressed as mean±SD, n=3

Table 4 shows the percentage loss in weight of HTM granules using different adsorbents. Results indicate that the loss in weight of granules was independent of the amount of adsorbent employed for granulation. Nonetheless, a lower loss and desirable ease of scrapping and processing granules was achieved when light magnesium carbonate was used as adsorbent as compared to the other four adsorbents. The percentage loss in weight has a direct correlation with difficulty in scrapping and processing. Hence, ease of granule processing should be a keenly considered factor when large scale production is desired.

Table 5: Flow properties of HTM granules using Hausner ratio (HR), Carr's index (CI) and Angle of repose

ADSORBENT	WT OF ADSORBENT /DOSE (mg)	ANGLE OF REPOSE (Ɵ)	BULK DENSITY (mg/ml)	TAPPED DENSITY (mg/ml)	H.R	C.I (%)
Light magnesium carbonate	75	33.69±0.01	0.36±0.01	0.44±0.02	1.22±0.02	17.86±0.02
	150	29.74±0.06	0.45±0.03	0.51±0.01	1.13±0.01	11.54±0.01
	225	28.72±0.02	0.44±0.02	0.54±0.03	1.23±0.01	18.75±0.06
	300	31.22±0.02	0.41±0.01	0.61±0.03	1.48±0.01	32.43±0.01
Bentonite	75	29.74±0.02	0.44±0.02	0.48±0.01	1.10±0.06	9.09±0.02
	150	37.04±0.01	0.60±0.02	0.68±0.03	1.13±0.01	11.76±0.12
	225	36.03±0.02	0.49±0.01	0.66±0.02	1.33±0.01	25.00±0.29
	300	29.75±0.01	0.70±0.02	0.83±0.01	1.19±0.01	15.79±0.01
Maize starch	75	29.75±0.02	0.48±0.01	0.64±0.03	1.33±0.01	25.00±0.35
	150	33.69±0.02	0.56±0.01	0.62±0.02	1.11±0.02	10.00±0.29
	225	36.03±0.02	0.47±0.02	0.50±0.01	1.08±0.02	7.41±0.01
	300	29.75±0.02	0.44±0.03	0.46±0.02	1.06±0.01	5.56±0.01

Kaolin	75	31.61±0.03	0.52±0.01	0.61±0.01	1.18±0.01	15.00±0.46
	150	33.69±0.01	0.35±0.03	0.45±0.01	1.29±0.02	22.22±0.17
	225	33.69±0.03	0.56±0.01	0.70±0.03	1.25±0.01	20.00±0.12
	300	29.75±0.02	0.53±0.01	0.61±0.02	1.16±0.01	13.79±0.01
Microcrystalline Cellulose	75	31.61±0.02	0.38±0.01	0.43±0.02	1.13±0.02	11.11±0.03
	150	30.84±0.00	0.44±0.03	0.49±0.01	1.14±0.01	12.00±0.00
	225	29.05±0.00	0.42±0.01	0.49±0.03	1.18±0.00	15.15±0.00
	300	26.57±0.01	0.41±0.02	0.55±0.01	1.33±0.01	25.00±0.29

Values are expressed as mean±SD, n=3

The flow properties of the extract-adsorbent mix varied between good and passable as shown in Table 5. Good flow properties facilitate uniform filling of capsules [19]. Furthermore, knowledge of flow properties of powders is important in operations such as granulation, tablet compression and capsule filling [20]. With Hausner‘s ratio, Carr’s index and angle of repose values of 1.22±0.02 %, 17.86±0.02 % and 33.69±0.01 % respectively, it can be said that all the parameters fell within the acceptable range as indicated in the BP 2013. Hence 75 mg LMC was a good choice for the formulation of HTM capsules.

Furthermore, the most important factor considered for selecting an adsorbent was the ease of release of the extract from the adsorbent extract-mix. Work was done to ascertain which adsorbent and at what weight will be suitable for the formulation of HTM capsules. At 75 mg of adsorbent per dose of HTM extract, light magnesium carbonate is the most suitable adsorbent for further work in the formulation of HTM capsules. Table 3 also shows that this adsorbent possessed good processing characteristics. Furthermore, at 150 mg, 225 mg and 500 mg (Figures 4-6) adsorbent per dose of HTM extract, the percentage release of HTM granules corroborated the earlier assertion that light magnesium carbonate is the most suitable adsorbent for formulating the capsules. Furthermore, the BP 2013 states that, for conventional dosage forms, not less than 75% of the drug must be released by the 45th minute. From the results discussed above, 75 mg LMC per dose of HTM was the best choice (Figure 3). The importance of the dissolution characteristics is key to the selection of adsorbents for use in the formulation of granules for encapsulation.

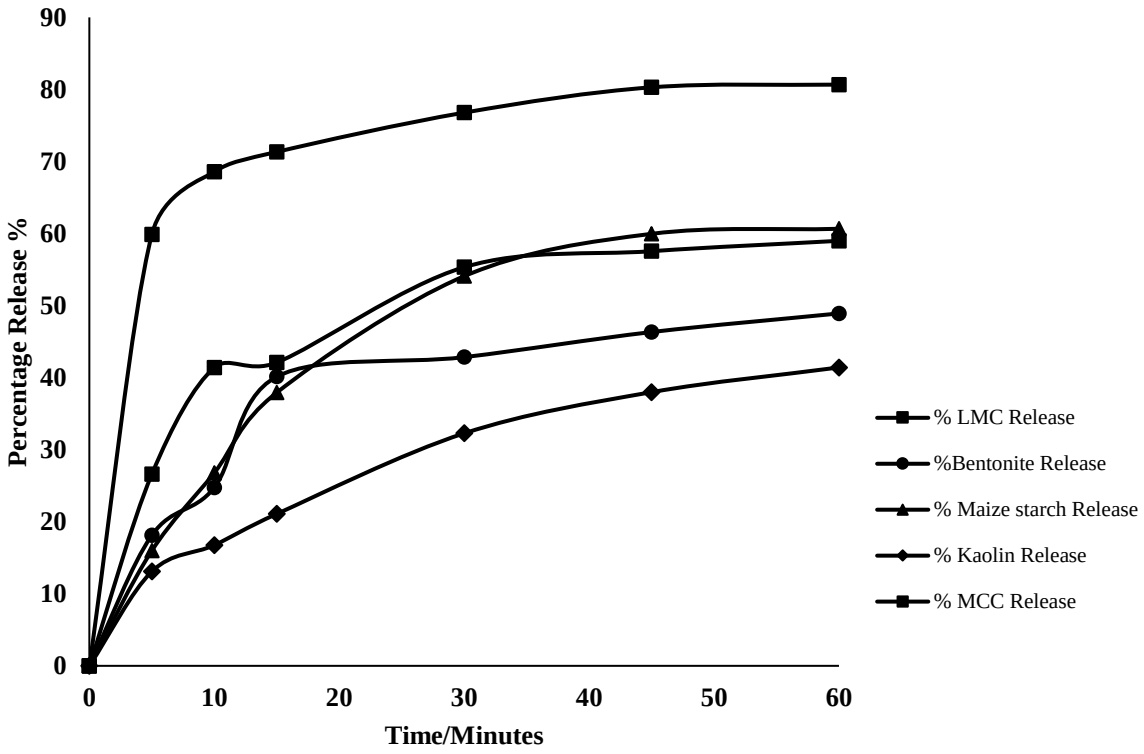

Fig. 3: Dissolution profiles of HTM granules using 75 mg adsorbent per dose of HTM

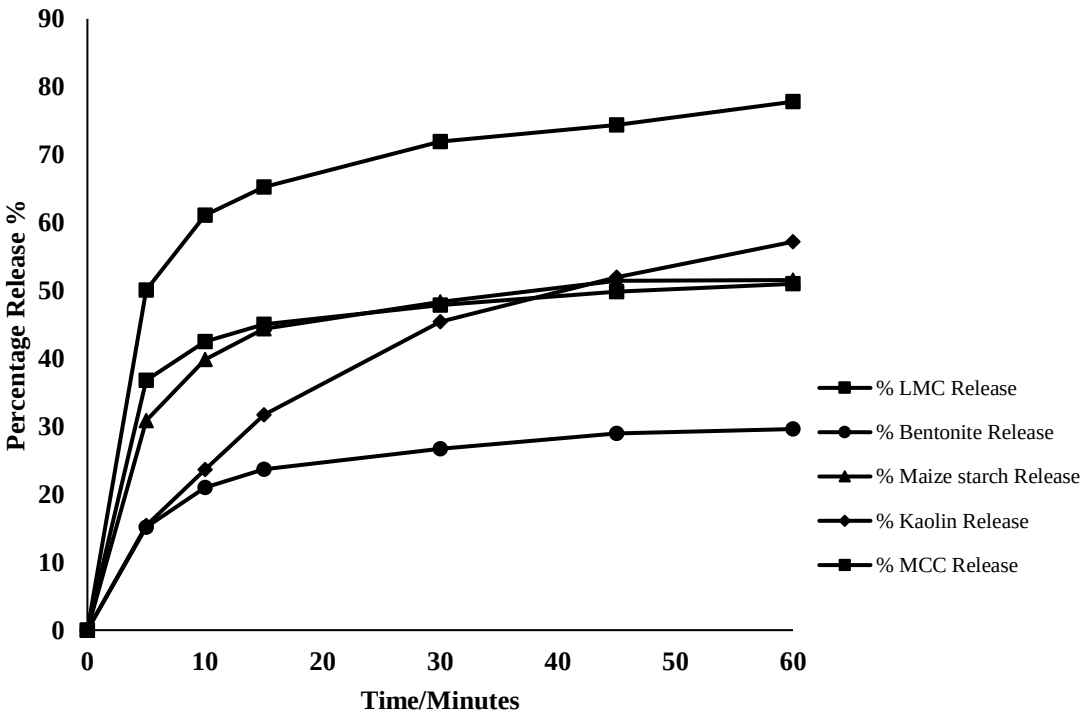

Fig. 4: Dissolution profiles of HTM granules using 150 mg adsorbent per dose of HTM

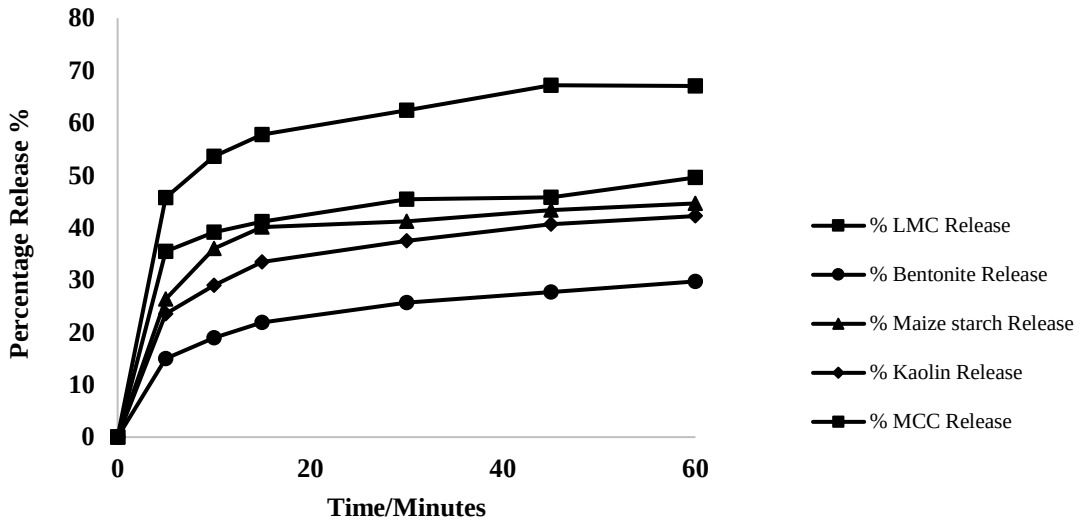

Fig. 5: Dissolution profiles of HTM granules using 225 mg adsorbent per dose of HTM

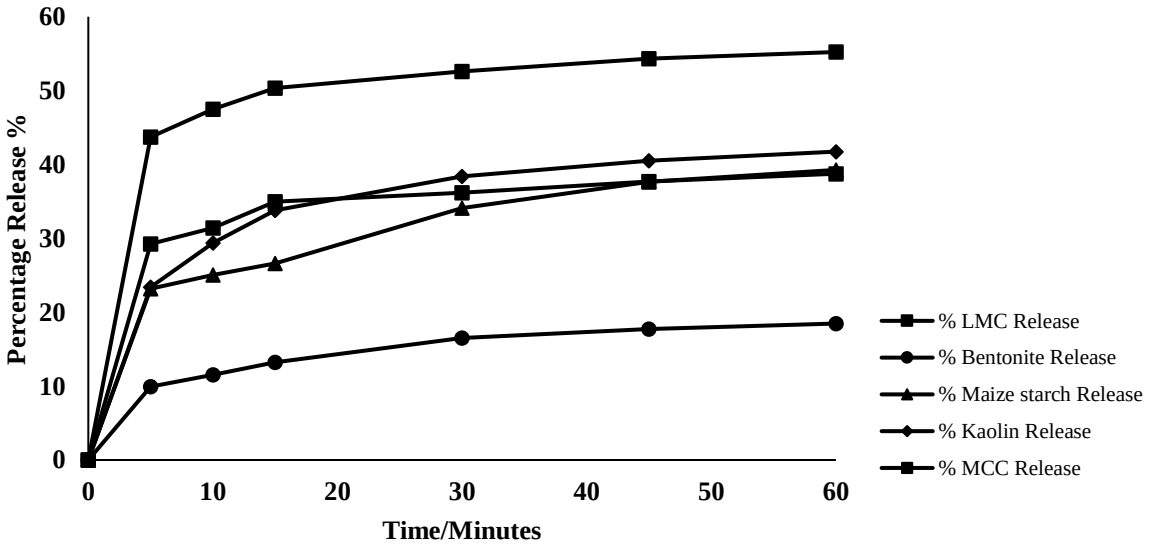

Fig. 6: Dissolution profiles of HTM granules using 300 mg adsorbent per dose of HTM

The uniformity of weight test results showed that all capsule weights were within the acceptable weight range. According to the BP 2013, for capsules which weigh 300 mg or more, not more than 2 capsules should deviate from the average weight by 7.5% and none should deviate by twice that. Good flow properties are a precondition for uniform filling of capsules. Hence the formulated capsules of HTM passed the uniformity of weight test. In addition, the BP 2013, the disintegration time of hard gelatin capsules should not be more than 30 minutes. Disintegration of capsules causes the capsule content to deaggregate into multiparticulate system to facilitate dissolution. Hence with a time of 7.69 ±

0.55 minutes, the formulated HTM capsules passed the BP 2013 specification for disintegration test.

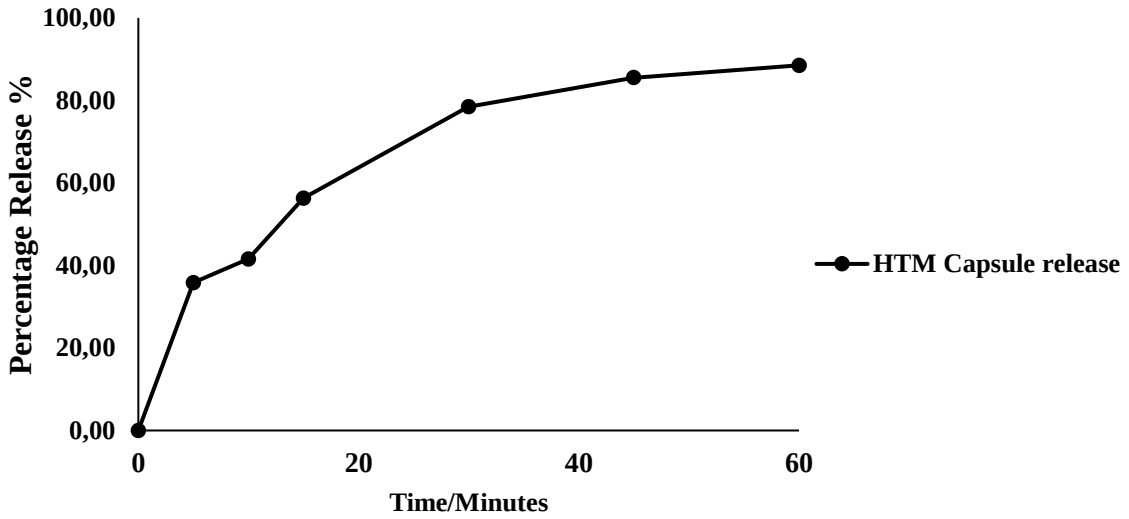

Fig. 7: Dissolution profile of HTM capsules prepared using 75 mg of light magnesium carbonate per dose of HTM

The dissolution of drugs is important in the absorption and subsequent therapeutic activity of the drug in the body. Dissolution tests on solid dosage forms measure the drug release from the drug product to determine the compliance with the dissolution requirements. The BP 2013 states that, for conventional dosage forms, not less than 75% of the drug must be released within 45 minutes. From the results as shown, the dissolution profile of HTM capsules showed a percentage release of 85.50 % at 45 minutes (Figure 7). This means that drug can dissolve in physiological solution to make available the active ingredients for absorption and subsequent pharmacological activity. It also showed that the drug is suitable for formulation into a solid dosage form. Thus the HTM capsules produced showed desirable dissolution properties. Further studies should be conducted to identify the efficacy of HTM capsule.

4. Conclusion

The formulated HTM capsules passed the uniformity of weight test, the disintegration and dissolution tests. Results from the study have shown that different adsorbents may be required in different preparations to ensure optimum release of API (extract) and the release of extract from adsorbent-extract mix depends on the amount of adsorbent used in the formulation. HTM can be formulated into solid dosage form which conforms to Pharmacopoeia standards and can be used as alternative to the HTM decoction in the management of diabetes.

5. Acknowledgement

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