

Formulation and Evaluation of Colon Targeted Matrix Tablets Containing Extract of *Haplophyllum Tuberculatum* (Hazaa) for Colorectal Cancer Management

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ABSTRACT

Objective: The objective of the present study is to formulate colon targeted matrix tablets containing *Haplophyllum tuberculatum* extract using guar gum alone or in combination with either HPMC K15M, with Eudragit S100, or with both them.

Methods: The Hazaa colon targeted matrix tablets were prepared by wet granulation method. The prepared matrix tablets were evaluated for the weight variation, hardness, friability, and in-vitro drug release study in three different media.

Results: Despite good understanding of the molecular basis of the disease and advances in treatment, globally cancer is still a major cause of death. Estimates are that it will surpass cardiovascular disease as the leading cause of death, with higher incidences in the developing countries that have minimal resources. The formulations showed compliance with Pharmacopeial standards except that containing guar gum alone. There was no interaction between drug, polymer and other excipients. It was confirmed by FTIR studies. Among the formulations, GHE2 (i.e. containing triple polymer mixture) showed good results in release retardation and other physicochemical properties of matrix tablets when compare to other formulations. The optimum formulation (GHE2) was stable when it was stored at 450/75% RH for 3 months.

Conclusion: The formulation (GHE2) is considered the most suitable formula for targeting the colon. The current results for the first time suggest that Hazaa plant water dry extracts are promising anticancer reagents. Subsequently, the results can be used to develop a prevention agent for the treatment of human cancers.

Keywords: *Haplophyllum tuberculatum*, Colon Targeted Matrix Tablets, Guar Gum, HPMC K15M, Eudragit S100, Hazaa Extract, Colorectal Cancer

Introduction

According to the World Health Organization (WHO) cancer today is one of the major causes of death among the world's population; in 2018, the number of deaths was 9.6 million people. Recently, the new methods of treating oncological diseases have appeared (nanotherapy, neutron capture, and low-intensity electroresonance therapy), and besides, classical methods are used – chemotherapy, surgery, and radiation therapy. However, all of the above methods are accompanied by a number of side effects, which also negatively affect the patient's health [1].

Therefore, the development of the cancer drugs from the plant materials and their use in the clinical practice are still today an urgent task. More than 60% of drugs based on the natural products or herbal raw material are currently used for the treatment of cancer. The recent scientific studies show that various food plants, medicinal plants, and spices contain the primary and secondary metabolites that help in the treatment of cancer [2].

Colon delivery systems are potential for delivering various drugs to treat the local diseases for colon including colon cancer [1]. Guar gum is reported to be potential carrier for colon specific drug delivery, due to its drug release retarding property and susceptibility to microbial degradation in the large intestine

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[2-5]. It is the best polymer for control release matrix tablets but it produces burst effect for water-soluble drugs in starting hrs. In order to minimize it a combination of guar gum with other polymers such as HPMC K15M or/and Eudragit S100 is necessary. Indeed, a combination of these polymers is an approach that may allow formulators to develop colon targeting dosage form that may exhibits performance improvements over the individual polymer components. It provides a neat and smooth means of combining desirable properties of different polymers [6,7]. Recently, a lot of studies reported that a combination of different gums or polymers to increase matrix viscosity and optimize release often leads to synergistic interactions [8,9]. To achieve colon delivery, preparation of matrix tablets is simple method when compared to other methods like tablets coated with different polymers and chemical conjugation of drug [10].

Colorectal cancer is one of the highest incidence and mortality cancers worldwide [11]. In Sudan, colorectal cancer is the fifth most commonly diagnosed cancer [12]. The serious side effects of chemotherapeutics and the resistance developed by tumor cells in addition to recurrence and metastasis highlighted the urge need for search to find more safe and efficient therapies [13,14]. Plant derived products have been valuable source for the discovery and development of unique anticancer drugs, which target multiple pathways in cancer cells and are associated with limited or no side effects [15,16]. Haplophyllum tuberculatum is one of the most commonly used medicinal plants in Sudan. Many of scientific studies have been carried out reporting that the extracts of Haplophyllum tuberculatum possess various antitumor activities [17-20]. The main objective of this study is to formulate, and evaluate a novel matrix tablet using the methanol extract of Haplophyllum tuberculatum (Hazaa) leaves to target a colon, for provide effective, and safe therapy for colorectal cancer.

Materials and Methods

Materials

Hazaa dried leaves were obtained from local market in Khartoum. Guar gum was procured from (Gitaf, Sudan). HPMC K15M was obtained from (Dow Chemical, Michigan, USA). Eudragit S100 was received from (Evonik, Germany). Lactose monohydrate was obtained from (Breckland scientific supplier, UK). MCC PH 101 and Talc were obtained from (A Johnson Matthey, UK).

PVP K30 and Magnesium stearate were obtained from (Techno pharmchem, India). All other chemicals used were of analytical grade.

Methods

Formulation of Hazaa Colon Targeted Matrix Tablets

Preparation of Haplophyllum tuberculatum (Hazaa) Extract

Hazaa dried leaves were cleaned from other parts of the plant and crushed by hand, then 1 kg of Hazaa dried leaves exhaustively extracted with 80% methanol in Soxhlet apparatus. The solvent was evaporated under reduced pressure using Rotary evaporator. The extract was maintained at 4 °C and protect from light [21].

The methanolic extract of Haplophyllum tuberculatum leaves was formulated as colon targeted matrix tablet by wet granulation method using different polymers include Guar gum, HPMC K15M, and Eudragit S100 in addition to other excipients such as MCC as filler, PVP K30 as binder, Mg stearate as lubricant, and Talc as glidant.

Compatibility Study of Hazaa Extract and Polymers

The infrared spectra of drug alone (Hazaa extract), and granules of Hazaa matrix tablet (G2, GH2, GE2, and GHE2) were recorded in range from 400 to 4000 cm⁻¹ on FTIR to detect the drug-polymers interactions. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer. The resultant spectra were compared for any possible changes in the peaks of the spectra [22].

Preparation of Hazaa Colon Targeted Matrix Tablets

Weighed quantity of Hazaa extract, Guar gum, HPMC K15M, Eudragit S100, and MCC were sieved and mixed properly in polybag for 15 minutes. A binder solution (PVP K30 in mixture of Isopropyl alcohol and water solution 3:1) was added to above blend to prepare a dough mass. The dough mass was granulated using a 14-mesh screen and the granules obtained were dried in oven at 80 °C for 2 hrs. The dried granules were passed through 20 # sieve. The dried granules were lubricated using talc and magnesium Stearate (2:1) for 5 minutes. The lubricated granules were compressed to tablets using a 12 mm concave single punch tablet machine (Korsch, Germany). Table 1 shows the compositions of Hazaa colon targeted matrix tablet of 12 Formulae.

Table 1: The Compositions of Colon Targeted Matrix Tablet

Ingredients	G1	G2	G3	G4	GH1	GH2	GH3	GE1	GE2	GE3	GHE1	GHE2
Hazaa Extract (mg)	90	90	90	90	90	90	90	90	90	90	90	90
Guar gum (mg)	90	180	180	180	90	180	90	90	180	90	90	180
HPMC K15M (mg)	-	-	-	-	90	90	180	-	-	-	90	90
Eudragit S100 (mg)	-	-	-	-	-	-	-	90	90	180	90	90
Lactose (mg)	-	-	-	70	-	-	-	-	-	-	-	-
MCC (mg)	30	30	100	30	30	30	30	30	30	30	30	30
PVP (mg)	18	18	18	18	18	18	18	18	18	18	18	18
Talc (mg)	8	8	8	8	8	8	8	8	8	8	8	8
Mg. Stearate (mg)	4	4	4	4	4	4	4	4	4	4	4	4

G: Guar gum, GH: Guar gum + HPMC K15M, GE: Guar gum + Eudragit S100, GHE: Guar gum + HPMC K15M + Eudragit S100

Evaluation

Evaluation of Granules

Angle of repose

The angle of repose was calculated using the following equation:

$$\tan \theta = \frac{h}{r}$$

Where,

$\tan \theta$ - tangent of angle

r - Radius of base of the heap (cm) and

h - Height of the heap (cm).

Bulk and Tapped density

To calculate the densities the following equations were used:

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{bulk Volume}}$$

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped Volume}}$$

Compressibility index

Carr's index was calculated according to equation given below:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

It is the ratio of tapped density to bulk density of the powder and measured by employing the following formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Evaluation of Hazaa Colon Targeted Matrix Tablets

Weight variation test

The weight variation test was analyzed by selecting twenty tablets randomly and average weights were determined. Then individual tablet weighed and compared with the average. The requirement met the (USP, 2016) if not more than two tablets differ from the average weight $\pm 5\%$ and no tablet differs in weight by double that percentage, the tablets will be accepted [23].

Hardness test

The resistance of tablets to shipping or breakage under conditions of storage, transportation, and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm. The test was conducted as per (USP, 2016) [23].

Friability test

Friability is the measure of tablet strength. Erweka Friabilitor was used to perform the test. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight

are generally considered acceptable. The test was conducted as per (USP, 2016) [23].

Thickness test

Thickness was calculated using vernier caliper. Ten tablets from each formula were used, and average values were calculated. The test was conducted as per (USP, 2016) [23].

In – Vitro drug release study

The drug release studies were carried out using USP dissolution test apparatus I (basket) at 50 rpm and $37 \pm 0.5^\circ\text{C}$ temperature using 500 ml of 0.1N HCl pH 1.2 (simulated gastric fluid) a dissolution medium in the first 2 h of study as the average gastric emptying time is about 2 h. At the end of 2 h, the dissolution media was replaced with 500 ml of phosphate buffer pH 6.8 (simulated intestinal fluid) and drug release study was continued for another 3 h as the average small intestine transit time is about 3 h (i.e., total 5 h). At the end of 5 h, the dissolution media was replaced with 500 ml of phosphate buffer pH 7.4 (simulated colonic fluid) and drug release study was continued for next 19 h. 10 ml samples were withdrawn at regular time intervals and correspondingly replaced with fresh media. The amount of drug release was analyzed spectrophotometrically at λ_{max} of 265 nm [24].

Stability Study

The best formulation was subjected to accelerated stability study according to ICH guidelines at temperature $45 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH (Relative Humidity) for 3 months in stability chamber. At the end of each month, the physicochemical properties of tablets including organoleptic properties, average weight, hardness, friability, and dissolution were evaluated.

Statistical Analysis

The results obtained are expressed as a mean $\pm$ standard deviation calculated using Microsoft excel 2010 software. Statistical analysis was performed using SPSS version 20.0 for windows (SPSS Inc. Sep 2011).

Results and Discussion

Compatibility Study of Hazaa Extract and Polymers

Figures 1 – 5 display the IR spectra of physical mixture of Hazaa extract and guar gum (G2), physical mixture of Hazaa extract, guar gum and HPMC K15M (GH2), physical mixture of Hazaa extract, guar gum and Eudragit S100 (GE2), and physical mixture of Hazaa extract, guar gum, HPMC K15M and Eudragit S100 (GHE2). From these Infrared spectra, it observes that Hazaa extract showed characteristic peaks at 3417.63 cm^{-1} (O-H bending), 2904.60 cm^{-1} (C-H stretching), 1737.74 cm^{-1} (C=O bending), and 1290.29 cm^{-1} (C-N bending). Furthermore, there is not significant change between these peaks and peaks obtained in the spectra of each physical mixture of Hazaa extract with polymers used. Therefore, the Hazaa extract is compatible with all polymers used.

Evaluation of Granules

Table 2 shows the results of Angle of repose, Bulk density, Tapped density, Carr's index, and Hausner's ratio for granules of all formulae. The results of granules evaluation summarized in (Table 2) indicate good flow properties of prepared granules for all formulae. This is observed from the obtained results of

angle of repose (25.15° - 32.83°) which indicate good flow properties of prepared granules. According to table 2, the compressibility index values up to 20% and hausner's ratio less than 1.25 indicate fair to good compressibility and flowability.

Table 2: Evaluation of Granules of All Formulate

Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's ratio
G1	33.24 ± 0.75	0.3774 ± 0.0071	0.4653 ± 0.0108	18.87 ± 0.36	1.23 ± 0.01
G2	32.83 ± 0.94	0.3394 ± 0.0149	0.4112 ± 0.0130	17.47 ± 1.92	1.21 ± 0.03
G3	31.67 ± 0.76	0.3509 ± 0.0062	0.4204 ± 0.0225	16.41 ± 2.97	1.20 ± 0.04
G4	33.24 ± 0.75	0.3871 ± 0.0044	0.4695 ± 0.0224	17.43 ± 3.44	1.21 ± 0.05
GH1	29.27 ± 1.10	0.3681 ± 0.0039	0.4584 ± 0.0162	19.63 ± 2.80	1.23 ± 0.03
GH2	27.89 ± 0.40	0.4317 ± 0.0053	0.5088 ± 0.0152	15.11 ± 2.18	1.18 ± 0.03
GH3	27.67 ± 1.26	0.3826 ± 0.0155	0.4584 ± 0.0162	16.55 ± 0.50	1.20 ± 0.01
GE1	27.11 ± 0.47	0.3297 ± 0.0062	0.3871 ± 0.0044	14.82 ± 1.41	1.17 ± 0.02
GE2	28.53 ± 0.06	0.3824 ± 0.0111	0.4446 ± 0.0099	14.00 ± 0.72	1.16 ± 0.01
GE3	27.17 ± 1.04	0.3593 ± 0.0037	0.4138 ± 0.0049	13.17 ± 0.97	1.15 ± 0.01
GHE1	25.15 ± 0.24	0.3410 ± 0.0066	0.3923 ± 0.0077	13.07 ± 0.89	1.15 ± 0.01
GHE2	27.37 ± 2.14	0.3243 ± 0.0031	0.3705 ± 0.0069	12.44 ± 1.00	1.14 ± 0.01

G: Guar gum, GH: Guar gum + HPMC K15M, GE: Guar gum + Eudragit S100,

GHE: Guar gum + HPMC K15M + Eudragit S100

Evaluation of Hazaa Colon Targeted Matrix Tablets

The colon targeted matrix tablets were prepared using guar gum alone, and in combination either with HPMC K15M, with Eudragit S100, or with both HPMC K15M and Eudragit S100. Thus, twelve formulations were prepared (Table 1). Table 3 shows the results of weight variation test, hardness test, friability test, and thickness test for prepared Hazaa colon targeted matrix tablets of all formulae. The results indicate that the weight variation for different formulations is found to be within the pharmacopeia limit of 5% as per USP standard. Also, the thickness is uniform and reproducible.

The results of hardness test demonstrated that matrices of guar gum alone (G1 – G4) failed in the test, this is attributed to the compaction properties of guar gum [25]. However, the hardness is a parameter which can be related directly to the compression force used that causes decreasing in the powder volume due to elastic and/or plastic deformation and the degree of particle attrition behaviors of the particle-particle bonds in the powder mass [26]. The hardness of the matrices containing a combination of guar gum either with HPMC K15M, with Eudragit S100, or with both them was found to be satisfactory and conformed to those given in pharmacopeia (USP, 2016). This finding similar to results obtained by [27]. The result indicates that incorporation of both HPMC K15M and Eudragit S100 to guar gum provides more mechanical strength for matrix tablets and, hence, resulted in successfully preparation of matrix tablets with a required hardness.

The results of friability test revealed that matrices containing guar gum only (G1 – G4) failed in the test, this is due to their hardness which is extremely low. However, the friability was affected by the content of guar gum where it showed higher with the large quantity of guar gum [28]. The friability of the matrices containing a combination of guar gum either with HPMC K15M, with Eudragit S100, or with both them was found to be reasonable and conformed to those given in pharmacopeia (USP, 2016).

Table 3: Evaluation of Prepared Hazaa Colon Targeted Matrix Tablets of All Formulae

Formulation code	Weight variation (mg) (n=20)		Hardness (kg/cm ²) (n=10)	Friability (%) (n=10)	Thickness (mm) (n=10)
	Weight variation	Deviation (%)			
G1	242.3 ± 3.8	1.5 ± 1.4	1.18 ± 0.06	93.5 ± 2.85	1.82 ± 0.01
G2	332.0 ± 0.7	1.1 ± 1.0	1.53 ± 0.12	87.2 ± 3.01	2.53 ± 0.03
G3	402.5 ± 0.9	1.1 ± 0.9	3.92 ± 0.28	1.2 ± 0.1	2.84 ± 0.01
G4	401.5 ± 1.1	1.0 ± 0.8	3.43 ± 0.09	1.4 ± 0.1	2.96 ± 0.01
GH1	332.8 ± 1.0	1.4 ± 1.0	3.23 ± 0.06	1.4 ± 0.1	2.48 ± 0.00
GH2	420.2 ± 0.9	0.9 ± 1.1	3.24 ± 0.10	1.3 ± 0.2	3.25 ± 0.01
GH3	418.5 ± 0.8	1.0 ± 0.9	4.50 ± 0.07	0.8 ± 0.1	3.18 ± 0.01
GE1	331.9 ± 1.1	1.0 ± 0.8	3.70 ± 0.07	1.0 ± 0.1	2.47 ± 0.01
GE2	419.5 ± 0.7	0.6 ± 0.7	4.25 ± 0.17	0.8 ± 0.1	3.12 ± 0.01
GE3	419.3 ± 0.5	0.9 ± 0.9	5.58 ± 0.09	0.7 ± 0.1	3.18 ± 0.00

GHE1	420.5 ± 0.8	0.8 ± 0.9	5.11 ± 0.06	0.4 ± 0.1	3.18 ± 0.01
GHE2	511.4 ± 0.7	0.6 ± 0.6	5.64 ± 0.12	0.3	± 0.1

In-Vitro Drug Release Study

The dissolution test was carried out for the twelve formulae using three different dissolutions medium (0.1N HCl pH 1.2, phosphate buffer pH 6.8 and pH 7.4). The following results were obtained after carrying the dissolution test for 24 hours, by measuring drug release from matrix tablets at different time intervals (2, 5, 8, 12, 16, 20, and 24 hour). The results of the dissolution test for 12 formulae are shown in (Fig. 6). The results demonstrated that the matrix tablets retained their physical integrity up to 24 h of the dissolution study conducted without rat caecal content in the dissolution medium except that containing guar gum alone which are divided into two parts. Matrix tablets containing guar gum alone showed higher percent release compared to others which are containing polymer combinations. According to fig. 6, the percent of drug released from matrix tablets containing guar gum alone was ranged between 30 – 35.74% after 5 h, while it was ranged from 13.9 – 28.2% for matrix tablets containing the polymer combinations. However, the drug release rate from matrix tablets is dependent on the formation and viscosity of gel layer and its swelling or erosion rate [29]. This result suggests that guar gum alone was unable to retard the drug release in the stomach and small intestine, while the matrices containing a polymer combination could be retarded the drug release in stomach and small intestine and, hence, capable to deliver the drug (Hazaa extract) to a colon.

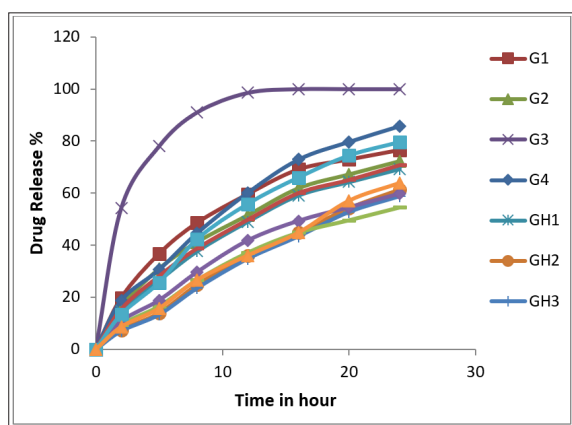


Figure 1: In Vitro Drug Release Profile of Hazaa Colon Targeted Matrix Tablets of All Formulae.

Stability study

The results of accelerated stability study test for the best formula (GHE2) revealed that the matrix tablets retained their organoleptic and physicochemical characteristics, over three months of storage. Therefore, it could be considered stable according to the ICH guidelines.

Table 4: The Accelerated Stability Study Test for the Formula (GHE2)

Test time	Color	Average weight (mg)	Hardness (kg/cm ²)	Friability (%)
Zero Time	Pale green	511.4 ± 0.7	5.64 ± 0.12	0.3 ± 0.1
1 month	Pale green	510 ± 0.7	5.53 ± 0.05	0.3 ± 0.1

2 months	Pale green	510.3 ± 1.0	5.68 ± 0.18	0.2 ± 0.1
3 months	Pale green	509.6 ± 0.3	5.72 ± 0.12	0.3 ± 0.0

Conclusion

Plants have always played an important role in the treatment and prevention of cancer and other diseases. Moreover, natural components from plants at the level of synthetic compounds are used in the creation of new drugs. The effective extract of *Haplophyllum tuberculatum* can be successfully formulated as colon targeted matrix tablet by wet granulation method. The results suggest that matrix tablet containing a combination of guar gum with HPMC K15M and Eudragit S100 (GHE2) was most likely to provide targeting of drug (Hazaa extract) for treatment colorectal cancer [28,29].

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