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COLON TARGETED MORINGA GUM COMPRESSION COATED TABLETS OF CAPECITABIN: A FACTORIAL APPROACH

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ABSTRACT

Objective: Colon targeting would be valuable for delivery of anticancer drugs like capecitabine, a prodrug, which is enzymatically converted to fluorouracil (antimetabolite) in a tumor by thymidine phosphorylase, where it inhibits DNA synthesis, and slows down the growth of tumor tissues of the colon. The major objective of this study was to prepare compression coated tablets by using moringa gum as a carrier based on a microbially triggered mechanism to target colonic cancer; so that adverse effects associated with oral administration of the drugs can be minimized. The most important object in such a dosage form was to target the drug to the colon by providing the minimal amount of the drug release in the physiological environment of the upper GI tract. Methods: The preparation of compressed coated tablets was done using moringa gum and HPMCK100M as the coating material followed by optimization by ANOVA using 3^2 full factorial design, whereby the weight of total coat on core (X_1) and % of MG present in coat (X_2) were taken as independent variables, and % drug release in upper GIT (Rel_{5h}) was taken as a response. Prepared tablets were evaluated for in vitro characterizations including hardness, weight variation, friability, drug content, and dissolution study in the presence or absence of 4%w/v rat cecal content and stability. Results: Formulation (C8) of moringa gum: HPMC K100M with 500 mg coat weight containing 50 % of gum was found to be a promising batch because it had restricted the drug release in upper GIT (LT 10 %), and when it reached the colon, there was a complete drug release in the presence of rat cecal content which might get acted upon moringa gum showing its suitability as a colon targeting carrier. The stability study of C8 formulation revealed that there was an insignificant change in the characteristics of tablets after the storage at 40^0 C for 1 month. Conclusion: Based on the results obtained, it was found that moringa gum would be an alternative as a carrier for colon in the form of compression coated tablets.

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Introduction

In the last 25 years, oral colon targeted drug delivery system of various drugs such as anticancer, anti-inflammatory, antihelminthics and proteins has been used with the aim of the enhancement of the therapeutic benefits. It has got many other advantages as well like the usefulness to treat local colonic disorders and the improvement in proteins and peptides delivery. Moreover, it is also preferred for those drugs which are unstable in the acidic media of stomach, which have low solubility, short half-life, a large volume of distribution, absorption problem and low therapeutic index. But, the most important challenge in designing the colon targeted formulation is to protect the drug during its transit from upper GIT viz. stomach and first six meters of the small intestine [1]. To accomplish this, many approaches have been used by various researchers like the prodrug approach, pH-sensitive drug delivery, time-dependent delivery systems, and microbial degradation methods and formulated tablets, capsules, multiparticulates, microspheres, and liposomes [2]. Amongst these, a microbially triggered method has been the most popular and successful approach to design colon-specific drug delivery system, which is capable of restricting the drug release in the upper GIT and giving complete drug release once it reaches the colon [3-7]. The abrupt drug release in the colonic environment has been attributed to the presence of anaerobic bacteria in the colon which produces many enzymes responsible to break the glycosidic linkage present in such natural polysaccharides.

Moringa oleifera gum (MG), a natural polysaccharide, can be easily collected without any complicated procedure and it is also available in huge amount. The naturally occurring gum exudate from the plant contains galactose 41.5 %, arabinose 26.9 %, xylose 25.9 %, rhamnose 5.6 % and a trace amount of uronic acid which can be isolated by the process of mild hydrolysis

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of the whole gum with acid. Various researchers have found that moringa gum (MG) can have medicinal as well as additive properties, and its swelling property can be helpful for preparing the sustained release formulation [8-14]. Additionally, it has also been studied as a suspending agent, a surface active agent, a film former, a stabilizer, a binder as well as a disintegrant by various groups of researchers. The normal microbiota of colon which is capable of degrading natural polysaccharides in a well-defined way which can trigger the release of the entire content of that formulation can be taken as a basis for localized colonic delivery or systemic absorption through the colon. Thus, the aim of this study was to prepare a formulation which consists of natural polysaccharides like MG to target the drug (capecitabine) in the colon [9, 15-18].

Capecitabine, a prodrug, is an orally-administered chemotherapeutic agent used in the treatment of colorectal cancer and metastatic breast cancer. Orally administered capecitabine can be readily absorbed from the gastrointestinal tract. When it reaches tumor tissue post-absorption, it is enzymatically converted to fluorouracil (antimetabolite) by thymidine phosphorylase, where it inhibits DNA synthesis and slows down the growth of tumor tissues. The recommended daily dose was large, i.e., 2.5 g/m^2, and it had a relatively short elimination half-life of 0.5–1 h [19]. Thus, the development of colonic delivery of Capecitabine can be appropriate to achieve high local drug concentrations in the colonic tumor to minimize the adverse effects associated with conventional oral administration.

Thus, in the present investigation, core tablets containing capecitabine as a model drug were prepared, and subsequently were compressed coated with MG and HPMC K100M by using 3^2 factorial design to characterize them as a colon targeted dosage form by using in vitro methods.

Materials and Methods

Materials

Moringa Oleifera gum was Isolated from moringa trees. Capecitabin was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, India. HPMC K100M was purchased from S.D Fine Chemicals, Mumbai. All the other materials were purchased from a chem dyes corporation, Vadodara.

Isolation of Moringa gum [18]

After collecting 500 g Moringa oleifera Lam. Gum was dissolved in 900 mL distilled water, and kept overnight at the room temperature. It was then subjected to the filtration, and the filtrate was precipitated out with 2 Litres of ethanol which had yielded 310 g of crude gum. To remove the resinous matter (50 %), the crude gum was further extracted using Soxhlet apparatus with 400 mL hot ethanol for 10 hrs. The obtained deresinified crud gum (200 g) was size reduced to fine powder, and added to 900 mL distilled water with continuous stirring till 8 hrs. The supernatant brown liquid was filtered, and the obtained filtrate was acidified with hydrochloric acid. The resultant acidified solution was then added slowly into absolute alcohol (4 Litre) using mechanical stirrer which resulted in precipitation of gum polysaccharide which was collected by filtration. The obtained residue was subjected to the purification process by repeating the process 4 times which resulted in a slightly brown powder. The final purification of gum polysaccharide was carried out by passing its aqueous solution through Amberlite Ion Exchange resins IR-120 (H^+) and IR-45 (OH^-) to yield (130 g) of pure white colored gum. It did not reduce the Fehling's solution, and it showed negative tests for nitrogen, halogens, sulfur, acetyl groups, and methoxyl contents.

Drug-excipient compatibility study

To check any possibility of the drug-excipients' compatibility, FTIR spectra of the pure drug and the mixture of the formulation were prepared in the ratio of 1:1 using mortar pestle, and then recorded using FTIR instrument between the wave numbers of 4000 cm^- to 500 cm^- (Shimadzu Model 8400 FTIR).

Preparation of capecitabine core tablets

The fast disintegrating core tablets of Capecitabine (200 mg) were prepared by the direct compression using a variable quantity of additives to achieve the disintegration time (Table 1). Drug and additives were weighed as per the experimental table and mixed thoroughly by passing through a mesh (100#) to ensure the complete mixing. The resultant mixture was subjected to the compression force using a 10-station tablet punching machine to get core tablets. The prepared core tablets were assessed for the characterizations viz. thickness, hardness, weight variation, friability, content uniformity, and disintegration. The disintegration test was performed as per Indian Pharmacopoeia 2007 in pH 6.8 PBS to check the fast disintegrating property of the prepared tablets.

Preparation of Compression Coated Tablets by Factorial design

A 3^2 Full Factorial Design was used in the present study to obtain an optimized formulation based on a preliminary study (Table 2). In this design, 2 factors were evaluated, each at 3 levels, and the experimental trials were performed at all 9 possible combinations which were run using STATE-EASE Design Expert 9.0 Demo version. The weight of the total coat (X_1) and the ratio of MOG: HPMC K100M in the coating (X_2) were chosen as independent variables (Factor) while the % Drug release in 5 hr (Rel_{5h}) was selected as a dependent variable (response). The core tablets of capecitabine were compression coated using a uniformly mixed polymer blend of MG and HPMC K100M in different ratios at three levels, as mentioned in the 3^2 factorial design layouts (Table 3 & 4). About one-third of uniformly blended coating mixture was placed in 12mm die cavity, the fast disintegrating core tablets (8 mm) were carefully positioned in the center of the die cavity, and filled with the remainder of the coating mixture. They were then directly compressed around the core tablets at a maximum

compression force on 10-station tablet punching machine using 12 mm round flat faced punches that had been surface lubricated, and when necessary magnesium stearate and talc mixture were used.

Evaluation of Capecitabine Core Tablets

Hardness

The hardness of the prepared tablets (five tablets) was identified using a hardness testing apparatus (Monsanto Type) as reported in the literature.

Friability test

The friability of the tablets (six tablets) was measured in a Roche friabilator (DBK friability test apparatus, India). Tablets of known weight (W_0) were taken and subjected to a friabilator for 100 revolutions and re-weighing (W). The percentage friability was calculated from the loss in weight as given in the equation as below:

$$\% \text{ Friability} = (W_0\text{-}W)/ W_0 \times 10$$

Weight Variation Test

20 tablets were picked up randomly from each formulation, and were weighed using an electronic balance. The percentage weight variation was then calculated from the magnitude of the difference between the weighed tablets and the label claim weight.

Disintegration study

The in vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Tablets from each formulation were taken and placed; each tube of apparatus was previously filled with phosphate buffer saline, pH 7.4 was maintained at 37 ± 2^0 C. The process of disintegration was observed, and the time taken in seconds for complete disintegration was noted down.

Drug Content

Ten tablets were finely powdered, and an amount equivalent to 150 mg of Capecitabine was accurately weighed and transferred to a 100 mL volumetric flask, and extracted with phosphate buffer saline (pH 6.8). The mixture was then filtered through a 45 µ membrane filter to remove the undissolved particles, and 1mL of the filtrate was suitably diluted and analyzed for Capecitabine content at 303.0 nm using double beam UV/Visible spectrophotometer.

Evaluation test for Compression Coated Tablets

The prepared compression coated tablets were subjected to various evaluation parameters like hardness, friability, and weight variation as per the reported method [20, 21] as described in the previous section. Further, these tablets were evaluated for In vitro dissolution studies in various simulated GI fluids and stability studies.

In Vitro Drug Release Studies without rat cecal content

Drug release studies were carried out using USP Dissolution Test Apparatus (Type I, 100 rpm, $37^0C \pm 0.5^0$ C). The tablets were tested for drug release for 2 h in 900 mL, 0.1 N HCl, pH 1.2 called simulated gastric fluid (SGF) as the average gastric emptying time was about 2h. Then, the dissolution medium was replaced with 900 mL, Phosphate buffer saline, pH 7.4 called simulated intestinal fluid (SIF) and tested for drug release for 3h as the average small intestine transit time was about 3 h. At the end of the time periods, two samples, each of 1 mL, were taken, suitably diluted and analyzed for the drug content at 303.0 nm λ_{max} .

In Vitro Drug Release Studies in the presence of rat cecal content

To check the susceptibility of prepared compression coated tablets to the colonic enzymes, in vitro drug release studies were performed in 100 mL of Phosphate buffer saline (PBS), pH 6.8 pH 6.8 PBS containing 4 % wt/vol of rat cecal contents as per the guideline of CPCSEA (Committee for the purpose of control and supervision of Experiments on animal, Ministry of Culture, Government of India) and all the study protocols were approved by the Local Institutional Animal Ethics Committee. To get the cecal contents, male albino rats (weighing 150-200 g) were sacrificed. The collected cecal content was immediately transferred in PBS, pH 6.8 to get a final cecal dilution of 4 % wt/vol called simulated colonic fluid (SCF). The drug release studies were carried out in USP dissolution rate test apparatus (Type II, 100 rpm, 37°±0.5° C) with a slight modification of apparatus design. A 150 mL capacity beaker (beaker A) containing 100 mL of dissolution medium was immersed and fixed by rubber packing in the 1000mL vessel (beaker B) of the dissolution test apparatus. The 1000 mL vessel was added with 200mL of warm water maintained at 37^0 C temperature. The tablets were placed in the beaker A containing 4 % wt/vol of rat cecal contents in 100 mL PBS, pH 6.8. During the whole study, continuous N_2 gas supply was given to beaker A to simulate an anaerobic environment of the cecum. The drug release studies were carried out for 3 h and 1mL samples were taken at different time intervals without filtration, and replaced with 1mL of fresh pH 6.8 PBS bubbled with N_2 gas. To the samples, 1 mL of methanol was added to solubilize the released drug from tablet formulations due to the break down of MG by the cecal enzymes. 1mL sample was withdrawn and diluted to 10 mL with pH 6.8, phosphate buffer saline, then it was centrifuged and the supernatant was collected. The collected supernatant was filtered through a bacteria-proof filter (45 µm), and the filtrate was analyzed for drug content at the respective λ_{max} as a procedure described in the methodology section. The study was carried out for all the formulations with rat cecal contents, and without cecal contents in pH 6.8 phosphate buffer saline which was called (control).

Stability study

The study was carried out to assess the stability of the prepared formulation. The optimized formulation (C8) was subjected to the accelerated stability studies according to ICH Guidelines for a period of 1 month in a stability chamber. The samples were evaluated for the drug content and In vitro drug release characteristics.

Discussion

The aim of the present investigation was to prepare colon targeted compression coated tablets of capecitabin by using moringa gum; so that such formulations would restrict their drug content in upper GIT, but once it reached colon it should release their entire content within a short span. Fast disintegrating core tablets of capecitabine were prepared by using a direct compression method that would allow the core tablets to disintegrate rapidly, once the coating material was digested by the colonic microflora. Tablet formulations (A1-A9) were prepared by using various disintegrating agents like cross carmellose sodium, sodium starch glycolate, and cross-povidone, along with lactose as diluent and magnesium stearate as a lubricant for different tablet formulations. The compressional force was adjusted to give core tablets with a hardness of 3 to 4 kg/cm^2. The prepared formulations were evaluated in weight variation, friability and disintegration time as per the methods mentioned in the methodology section. The results of weight variation (LT 7.5 %), hardness (3 to 4 kg/cm^2), drug content (96.29 % - 100.88 %) and DT (45 sec – 88 sec) have been depicted in table 5. Based on these results, the formulation A3 was selected for further study as it gave relatively fast disintegration.

To achieve the restricted drug release in upper GIT, core tablets were then coated with different quantities of moringa gum alone as well as with HPMC K100M to evaluate their synergistic effects on the characteristics of tablets. Those compression coated tablets then were evaluated for friability, hardness, weight variation, swelling index, erosion studies and in vitro dissolution studies as per the procedure mentioned in the methodology section.

Compression coated tablets (F1-F8) were prepared as per table 6 , and their results of hardness (5-6 Kg/cm^2), friability (0.10 %-0.17 %), weight variation (within 5 %) and rel_{5h} have been depicted in table 6. It was found that the coat weight of 300mg was able to restrict the drug release in upper GIT to LT 10 %. Thus, it was decided to go further to apply the factorial design to study the synergistic effect of MG and HPMC K100M.

Factorial batches (C1-C9) were prepared, and were subjected to the evaluation tests such as weight variation, hardness, friability, drug content, and dissolution study (in presence and absence of rat cecal content) as per the methodology section. The results of weight variation (LT 5 %), hardness (5 to 6 Kg/cm^2), friability (LT 1%) and drug content (97 to 99 %) have been shown in table 7. Drug release study was performed for factorial batches in upper GIT for 5 h (Table 8). It was found that the tablets containing 300 mg coat with 50% concentration, each of MG and HPMC K100M, could be able to restrict the drug release (7.99 %). This might be attributed to the synergistic effect of MG as well as HPMC K100M. Further to check their feasibility to release the restricted drug content in the colonic environment, this formulation was subjected to further drug release study in presence or absence of rat caecal content till 9 h. It was found that when the formulation C8 was placed in rat caecal content, there was a drastic increase in the release in the presence of rat caecal content. Whereas the same formulation when placed in the absence of rat caecal content, there was a limited drug release till 9 h (Table 9). This difference in drug release pattern in the presence of rat caecal content was attributed to enzymes liberated from rat caecal matter which might get acted upon the MG; and being natural polysaccharides, the glycosidic linkage of the gum was broken which released the drug drastically.

Further, the data obtained from the factorial batches were subjected to analysis using ANOVA for the quadratic model in DESIGN-EXPERT 11.0 demo version software (STATE-EASE), and the results have been shown in table 10.

The equation generated for Rel_{5h} was as follows:

$$Rel_{5h} = +13.25 - 7.65A + 1.02B - 0.0075\,AB + 2.98\,A^2 + 5.98\,B^2$$

The Model F-value of 28.70 and p-values less than 0.0500 implied that the model was significant. The results of checkpoint batch (CP1) have been given in table 11, and the insignificant difference was found between the predicted value and obtained value. Contour plot and surface plot for the effect of the weight of coat and percentage of MG on rel_{5h} were plotted and depicted as figure 1 and 2. As per these plots, it was observed that with an increased concentration of MG in the formulation, there was the corresponding decrease in percentage drug release in upper GIT.

As per the results obtained, batch C8 was found to restrict the drug release in upper GIT with a complete release of their entire content once it reached to the colonic region and hence, it was considered to be an optimized batch with respect to our cited objectives. Thus, batch C8 was subjected to the stability study for 1 month, and then evaluated for hardness, friability, drug content, and drug release as per the methodology section. The results were compared with the previous results, and the differences were found to be insignificant (Table 12).

Conclusion

Based on the obtained results, it can be concluded that MG in compression coated form had the capability to protect the release of active drug capecitabine in the physiological environment of the stomach and small intestine as established by the in vitro drug release studies under the condition of mimicking mouth to colon transit. Further, the susceptibility of MG to colonic bacteria and drug release in the colon was also assessed using in vitro drug release study of the rat caecal contents. Thus, it was clearly represented by the study that moringa gum, in the form of compression coat, can be a potential carrier of drugs targeting to the colon.

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References

1. Vemula SK, Bontha VK (2013) Colon Targeted Guar Gum Compression Coated Tablets Of Flurbiprofen: Formulation, Development, And Pharmacokinetics. Biomed research international, Article ID 287919, pp. 1-8.
2. Vemula SK, Veerareddy PR (2009) Different Approaches to Design and evaluation of colon specific drug delivery systems. International Journal Of Pharmtech Research.1.1–35.
3. Sinha VR, Kumria R (2002) Binders For Colon Specific Drug Delivery: An In Vitro Evaluation. International Journal Of Pharmaceutics, 249, 23–31.
4. Saini N, Bajaj A, Prashar M (2014) Colon Specific Drug Delivery System: A Review. International Research Journal For Inventions In Pharmaceutical Sciences 2(2): 75-85.
5. Sachin B, Sheetal P (2012) Different Approaches For Colon Drug Delivery Systems: A Review. International Journal of Research and Reviews in Pharmacy and Applied science 1(11-12):718-726.
6. Sarasija S, Hota A (2002) Colon- Specific Drug Delivery Systems. Ind. J. Pharm. Sci. 62(1): 1-8.
7. Gupta V, Gnanarajan G, Kothiyal P (2012) A Review Article On Colonic Targeted Drug Delivery System. The Pharma Innovation 1(7), 14-24.
8. Panda D, Swain S, Gupta R, Kanungo S (2006) Preparation And Evaluation Of Gels From Gum Of Moringa Oleifera. Indian Journal of Pharmaceutical Sciences 68(6):777–780.
9. Panda D, Choudhury N, Yedukondalu M, Gupta R (2008) Evaluation Of Gum Of Moringa Oleifera As A Binder And Release Retardant In Tablet Formulation. Indian Journal Of Pharmaceutical Sciences 70(5):614–618.
10. Patel B, Patel D (2011) Study Of Disintegrant Property Of Moringaolei Feragumandits Comparison With Other Super Disintegrants. International Journal of Chemtech Research 3(3):1119–1124
11. Shivalingam M, Arul K, Reddy Y, Jeslin D, Tejaswini M, Rao C, Chaitanya BS (2010) Evaluation Of Binding Properties Of Moringa Oleifera Gum In The Formulation Of Paracetamol Tablets. Drug Invention Today 2(1): 69-71.
12. Fahey JW (2005) Moringa Oleifera A Review Of The Medical Evidence For Its Nutritional, Therapeutic, And Prophylactic Properties. Part 1. Tree For Life Journal. 1-2.
13. Bhattacharya BS, Das K, Baneriji N (1982) Chemical Investigation On The Gum Exudate From Sajna (Moringa Oleifera). Carbohydrate Research 102: 253-262
14. Jarald E, Sharma S, Sheejae, Ahmad S, Patni S, Daud A (2012) Characterization Of Moringa Oleifera Lam. Gum To Establish It As A Pharmaceutical Excipient. Ind J Pharm Edu Res Vol 46: 211-216.
15. Gupta DP. The Herb. (2008) 1st Ed. Indore: Smt. Prem Lata Gupta, Smt. Prem Lata Gupta Is A Name Of Publication House P. 315.
16. Vyas Sp, Khar RK (2002) Controlled Drug Delivery Concept And Advances. 1st Ed. India: Vallabh Prakashan; Pp. 218–247.
17. Jain A, Gupta Y, Jain SK (2007) Perspectives Of Biodegradable Natural Polysaccharides For Site-Specific Drug Delivery To The Colon. J Pharm Pharm Sci. 10:86–128.
18. Pal A, Singh RB (2014) Nature Of Gum Polysaccharide Extracted From Moringa Oleifera Lam. (Sainjna) Plant. Advances In Applied Science Research. 5(6):1-3.
19. Agrawal D, Ranawat MS, Chauhan CS, Kamble R (2013) Formulation And Characterisation Of Colon Targeted Ph Dependent Microspheres Of Capecitabine For Colorectal Cancer. Journal Of Drug Delivery & Therapeutics 3(6): 215-222.
20. Kotadiya RM, Patel VA, Patel HV (2012) An In Vitro And In Vivo Assessment Of Okra Gum Matrices For Colon Delivery Of Theophylline. International Journal Of Pharmaceutical And Chemical Sciences 1 (1): 29-40.
21. Lachman L., Lieberman H. A., Kanig J. L. (1991) The Theory And Practice Of Industrial Pharmacy Varghese Publ. House: Hind Rajasthan Building, P. 293.

Table 1: Composition of Core tablets containing various disintegrating agents.

Ingredients (mg)	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
Capecitabine	150	150	150	150	150	150	150	150	150
Croscarmellose sodium	8	12	16	-	-	-	-	-	-
Sodium Starch glycolate	-	-	-	8	12	16	-	-	-
Cross Povidone	-	-	-	-	-	-	8	12	16
Lactose	24	20	16	24	20	16	24	20	16
Magnesium striate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Mannitol	15	15	15	15	15	15	15	15	15
Total wt	200	200	200	200	200	200	200	200	200

Table 2: Preliminary compression coat given to core tablets (A3)

Ingredients(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
MG	100	200	300	50	100	150	200	100
HPMC K100M	-	-	-	50	100	150	100	200

Tablet 3: Formulation of coat using factorial design (3^2) given to core tablets (A3)

Independent Variables (Factors)	COADED VALUE			ACTUAL VALUE		
	Low	Medium	High	Low	Medium	High
X_1:- Weight of total coat	-1	0	+1	250	275	300
X_2:- % of MOG in coat	-1	0	+1	25	50	75

Table 4: Composition of factorial formulations (Coded and Actual Value)

Run	Coded Values		Actual Values	
Batch Code	X_1	X_2	X1:- Weight of total coat on core	X2:- % of MOG
C1	-1	-1	250	25
C2	-1	0	250	50
C3	-1	1	250	75
C4	0	-1	275	25
C5	0	0	275	50
C6	0	1	275	75
C7	1	-1	300	25
C8	1	0	300	50
C9	1	1	300	75

Table 5: Post compression study of capecitabine core tablets

Formulations	Weight Variation (mg)	Hardness (Kg/cm2)	Friability (%)	Disintegration time (sec)	Drug Content (%)
A1	200 ± 0.010	3.3 ± 0.023	0.12	78.65 ± 0.06	97.32
A2	200 ± 0.009	3.6 ± 0.026	0.32	59.27 ± 0.07	99.61
A3	200 ± 0.005	4.5 ± 0.032	0.30	45.33 ± 0.60	98.20
A4	200 ± 0.011	3.6 ± 0.029	0.30	85.99 ± 0.90	99.82
A5	200 ± 0.013	4.6 ± 0.022	0.45	85.98 ± 0.02	98.21
A6	200 ± 0.006	3.5 ± 0.051	0.49	76.38 ± 0.06	100.88
A7	200 ± 0.008	3.6 ± 0.021	0.45	88.64 ± 0.07	96.29

A8	200 ± 0.009	4.5 ± 0.027	0.33	79.33 ± 0.03	99.42
A9	200 ± 0.010	3.3 ± 0.029	0.41	66.65 ± 0.04	98.46

Table 6: Post compression characteristics of prepared compression coated tablets as per Factorial design

Formulation	Weight Variation (mg)	Hardness (Kg/cm2)	Friability (%)	Drug Content (%)	Rel5h (%)
F1	300 ± 0.25	4.8 ± 0.023	0.37	98.29 ± 0.28	62.23
F2	400 ± 0.22	4.9 ± 0.052	0.24	98.36 ± 0.22	57.45
F3	500 ± 0.15	5.5 ± 0.024	0.26	97.41 ± 0.28	42.62
F4	300 ± 0.24	4.9 ± 0.043	0.34	97.22 ± 0.22	60.12
F5	400 ± 0.22	4.0 ± 0.064	0.32	98.08 ± 0.34	52.15
F6	500 ± 0.17	4.7 ± 0.033	0.27	98.68 ± 0.06	10.21
F7	500 ± 0.15	5.0 ± 0.075	0.32	97.10 ± 0.81	12.71
F8	500 ± 0.21	4.6 ± 0.034	0.33	100.64 ± 0.05	10.14

Table 7: Post compression characteristics of prepared compression coated tablets as per Factorial design

Formulation	Weight Variation (mg)	Hardness (Kg/cm2)	Friability (%)	Drug Content (%)	Rel5h (%)
C1	500 ± 0.15	5.8 ± 0.23	0.17	98.29 ± 0.28	29.14
C2	500 ± 0.19	5.9 ± 0.52	0.14	97.36 ± 0.22	23.24
C3	500 ± 0.15	5.5 ± 0.24	0.21	99.41 ± 0.28	31.31
C4	500 ± 0.14	5.9 ± 0.43	0.14	98.22 ± 0.22	17.24
C5	500 ± 0.12	6.0 ± 0.64	0.12	99.08 ± 0.34	15.14
C6	500 ± 0.17	5.7 ± 0.33	0.21	98.68 ± 0.06	19.22
C7	500 ± 0.15	6.0 ± 0.75	0.12	97.10 ± 0.81	13.21
C8	500 ± 0.11	5.6 ± 0.34	0.23	99.64 ± 0.05	7.92
C9	500 ± 0.14	5.7 ± 0.15	0.22	98.68 ± 0.35	16.25

Table 8: In vitro drug release study of prepared compression coated tablets in upper GIT

TIME (h)	**Cumulative Percentage Drug Release (%)**								
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
0	0	0	0	0	0	0	0	0	0
1	8.36± 0.55	5.14± 0.60	10.88 ±0.41	3.94± 0.60	2.98± 0.72	5.15± 0.74	2.31± 0.64	1.54± 0.32	2.87± 0.94
2	13.26 ±0.39	10.82 ±0.77	15.77 ±0.40	5.97± 0.77	3.23± 0.79	7.68± 0.32	3.06± 0.96	2.03± 0.24	4.64± 0.45
3	17.93 ±0.96	15.45 ±0.32	18.96 ±0.96	9.63± 0.14	5.45± 0.66	10.79 ±0.77	5.09 ±0.14	3.81± 0.63	7.27± 0.63
4	20.98 ±0.14	18.54 ±0.13	22.56 ±0.16	12.07 ±0.75	10.17 ±0.13	13.95 ±0.13	7.52± 0.36	5.92± 0.42	10.62 ±0.54
5	29.34 ±0.95	23.94 ±0.22	31.01 ±0.96	17.14 ±0.46	15.56 ±0.82	19.42 ±0.42	13.61 ±0.68	7.99± 0.95	16.35 ±0.14

Table 9: In vitro drug release study of prepared compression coated tablets (C7) in the absence or presence of 4% w/v rat caecal content

TIME (h)	**Cumulative Percentage Drug Release (%)**	
	Without rat caecal content	**With rat caecal content**
0	0	0
1	2.62 ± 0.64	2.48 ± 0.23

2	3.56 ± 0.96	3.96 ± 0.28
3	5.49 ± 0.14	5.94 ± 0.21
4	7.22 ± 0.36	7.62 ± 0.32
5	13.41 ± 0.68	13.21 ± 0.15
6	16.87 ± 0.35	39.08 ± 0.65
7	22.46 ± 0.47	56.63 ± 0.56
8	25.13 ± 0.64	83.37 ± 0.72
9	32.34 ± 0.45	98.21 ± 0.15

Table 10: ANOVA For Response surface Quadratic Full Model (Rel_{5h})

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	446.90	5	89.38	28.70	0.0098	significant
A-Weight of Coat	351.44	1	351.44	112.83	0.0018	
B-% of MG	6.18	1	6.18	1.98	0.2537	
AB	0.0002	1	0.0002	0.0001	0.9938	
A^2	17.72	1	17.72	5.69	0.0972	
B^2	71.56	1	71.56	22.97	0.0173	
Residual	9.34	3	3.11			
Core Total	456.25	8				

Table 11: Evaluation of tablets by check point batches

Formulation	Factor	Level	Parameters	Predicted Value	Obtained Value(C3)	% Error
CP1	Wt of Coat	300	% Drug release in 5 hrs	8.56889	7.98	6.8
	% of MOG	50	% Drug release in 8 hrs	82.3811	82.13	0.30

Table 12: Stability study of optimized formulation (C8)

Parameters	**Before 1 month**	**After 1 month**
Hardness	5.6± 0.034	6.0
Friability	0.23	0.12
Rel_{5hr}	7.98	7.12
Rel_{8hr}	82.13	81.98
Drug content	99.64±0.05	98.71

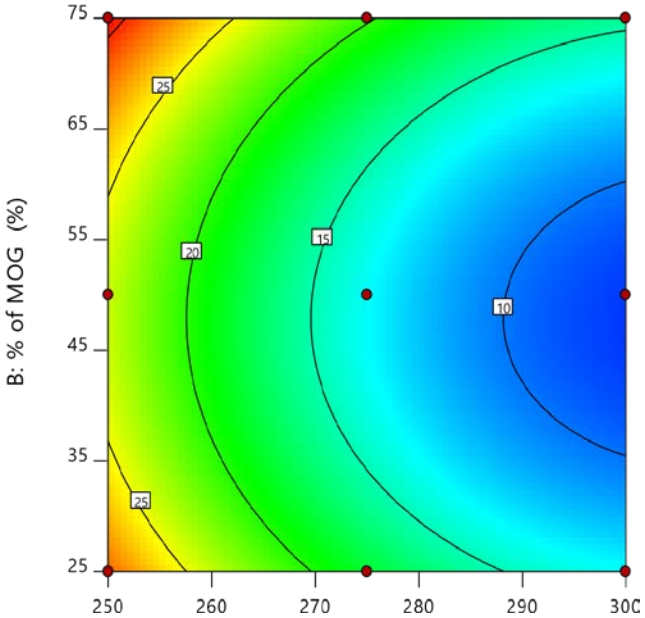

Figure 1. Contour plot showing the effect of the weight of coat and % of moringa gum on % drug release in 5 hrs

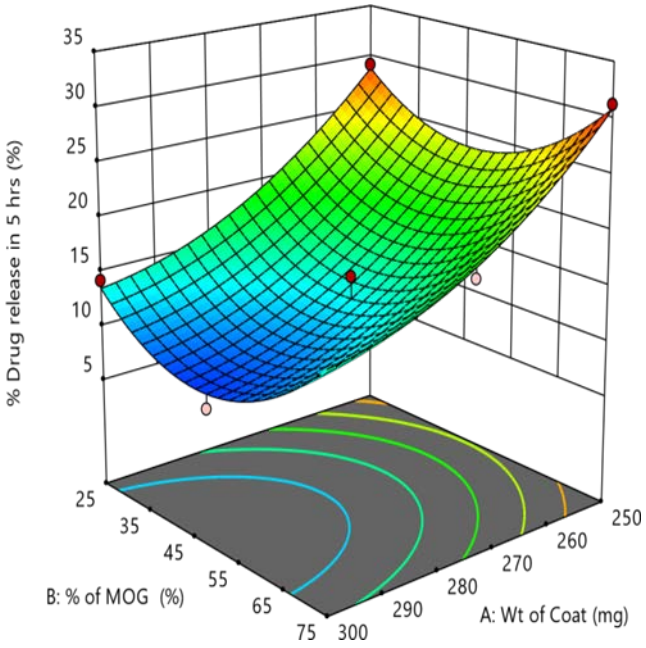

Figure 2. Response surface plot (3D) showing the effect of the weight of coat & % of moringa gum on % drug release in 5 hrs