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Impact of pH and Time-Dependent Polymers on Colon-Targeted Mebeverine Hydrochloride Drug Delivery System

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Abstract: The primary goal of this study is to formulate and assess sustained colon-targeted mebeverine hydrochloride (MbH) tablets using pH as well as time dependent coating polymers at different concentrations for the management of inflammatory bowel illness. Drug-polymer interaction did not occur according to the results of the DSC analyses. Cores containing 5% superdisintegrant C_1 (crosspovidone), C_2 (sodium starch glycolate) and C_3 (croscarmellose sodium) were chosen to be coated, since they achieved gradual release patterns. The drug core tablets were coated with different controlling release polymers (pH and time dependent polymers) via compression coating technique. Press coated tablets were assessed for their weight, thickness, hardness, friability and drug content and in-vitro release. The developed MbH tablets F8, F9, F11, F14 and F17 that displayed a 5- to 6 hours lag period before the full MbH release were chosen for short term accelerated test of stability at two different temperatures of 35 ± 2 and 45 ± 2 ºC/75 ± 5% relative humidity (RH). I*n-vivo* study was carried out formulated tablet (F14) that displayed the highest of both T_{90} value and similarity factor and commercial ones as they were administered to healthy human volunteers and the plasma MbH was analyzed. F14 exhibited the highest T_{max} and $AUC_{(0-24)}$ in comparison with the commercial tablets. According to the findings, this strategy can offer a practical way for colon targeting.

Keywords: Colon targeting; Inflammatory bowel disease (IBD); Lag time; In-vivo study.

1. INTRODUCTION

Inflammatory bowel disease (IBD) is an idiopathic, recurrent, and chronic gastrointestinal tract inflammatory disorder that mostly includes Crohn's disease (CD) and ulcerative colitis (UC). The main organs affected by inflammatory bowel disease are the small and large intestines, as well as the colon. The condition is characterized by persistent inflammation in specific mucosal or transmural regions. From a clinical standpoint, gastrointestinal bleeding is more commonly associated with ulcerative colitis, while Crohn's disease typically manifests as stomach pain and perianal illness[1]. The causes of IBD are numerous and complex. Due to aberrant intestinal barrier function, a person's intestinal microbiome and immune system interact dysfunctionally as a result of a combination of environmental factors (particularly diet, smoking, and infections) and hereditary factors.[2]. Colon targeted delivery is beneficial in treating colon disorders, as Crohn's disease, ulcerative colitis, carcinomas, and infections[3] and this approach is expected to be promising for delivering Mebeverine hydrochloride to the colon for its local impact, reducing the medication's systemic adverse effects. Time required to release about 20 % of drug content was considered as lag time[4]. Lag time of 5-6 hours was considered suitable for colon targeted application for colonic disease[5]. MbH is an antispasmodic musculotropic that acts directly on the smooth muscle of the gastrointestinal system, particularly the colon. MbH directly produces a cellular relaxation effect on the muscles of the gut. Its biological half-life is brief (2.5 hours), bonding of

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plasma proteins is about 75% and is rapidly absorbed after oral administration[6]. Drug delivery systems can be created by coating instant release core tablets using a compression coating process, which releases the drug after a lag period and dissolves or disintegrates gradually. This technique used to prepare compressed coated tablets solvent-free, making it a cheap, safe method that doesn't require specialized coating equipment and also offers greater stability[7].

In the present research, an effort was made to investigate the suitability of the approaches for colonic drug delivery utilizing different polymers (pH and time dependent) using MbH as a model drug. The weight, thickness, hardness, friability, drug content, and in vitro release of the generated formulations were evaluated. The formulation exhibited lag time of 5–6 h followed by complete drug release were chosen for stability test. Finally, the most stable formula with highest T_{90} value and similarity factor was compared to commercial tablet to investigate the pharmacokinetic parameters for each.

2. METHODS

2.1. Materials

MbH freely provided by EIPICO Pharma (Egypt). Sodium starch glycolate (SSG), Croscarmellose sodium (CS), Crosspovidone (CP) were kindly supplied by AUG Pharma for Pharmaceutical Industries (Egypt). Polyvinyl pyrrolidone (PVP k30) and Avicel PH101 were obtained as gift samples from Sigma Pharma (Egypt). Magnesium stearate was received as a supportive sample from Hikma Company (Egypt). The supplier of hydroxy propyl methyl cellulose (HPMC k4m) was Dow Chemical Co. (USA). Cellulose acetate phthalate (CAP) was gratefully provided by Delta Pharma in Egypt. Eudragit L100 (Ed 100) was provided by Al- Nile pharmaceutical Co. (Egypt). Hydrochloric acid, di-sodium hydrogen orthophosphate, and potassium dihydrogen orthophosphate were provided by El-Nasr Pharmaceutical Company (Egypt).

2.2. Compatibility study of MbH with suggested polymers using Differential scanning calorimetry

Differential scanning calorimetry (DSC) was employed to study the compatibility of MbH with the recommended polymers. DSC was employed to create thermograms of the pure substance as well as physicochemical combinations of the medication and suggested polymers in a 1:1 (w/w) ratio. About 3 mg of the samples were hermetically placed in an aluminum crucible and heated at a rate of 10 °C per minute between 25 and 400 °C. while being scanned at a 25 ml per minute flow rate in a dynamic N2 environment. Compatibility of both was determined by detecting any modifications to the drug's melting point[8].

2.3. Pre-Compression study of suggested core tablet formulations

Six core tablet formulations were made in the manner indicated by table (1), To ascertain the flow characteristics of the powdered blend, the powder blend of each formulation was assessed for a number of pre-compression parameters, including angle of repose, powder density, tapped density, compressibility index, and Hausner's ratio.

2.3.1. Angle of repose

It is described as the greatest angle that can exist between the powder pile's surface and the horizontal plane. The funnel method was used to calculate the angle of repose[9].

The following formula determines the angle of repose:

$$\tan \theta = h/r \quad \ldots\ldots\ldots\ldots (1)$$

Where, θ is the angle of repose, h is the cone's height, r is the cone base's radius.

2.3.2. Powder density

It is the proportion of the powder's total mass to its bulk volume. After the powder had been passed through sieve No. 20, its weight was determined by pouring it into a measuring cylinder and recording the original weight[10]. This original volume is called the bulk volume. It is stated as g/ml and is given by:

$$\text{Bulk density} = \text{Mass of the powder} / \text{Bulk volume} \quad \ldots\ldots\ldots\ldots (2)$$

2.3.3. Tapped density

It is the proportion of the powder's total mass to its tapped volume. A graduated cylinder with a known powder weight is placed, and a mechanical tapper device is used to tap the powder bed a set number of times until the minimum volume is reached[10].

$$\text{Tapped density} = \text{Mass of the powder} / \text{Tapped volume} \quad \ldots\ldots\ldots\ldots (3)$$

2.3.4. Compressibility index (Carr's index, (CI))

It is stated using the subsequent equation[11].

Carr's index = (Tapped density – Bulk density / Tapped density) X 100……(4)

2.3.5. Hausner's ratio

An indirect measure of the ease of powder flow is Hausner's ratio[12]. It is computed using the subsequent formula:

Hausner's ratio = Tapped density / Bulk density……(5)

2.4. Formulation of MbH core tablets

Every 200 mg core tablet contained MbH, PVP K30 as polymer, Avicel PH101 as filler and magnesium stearate as lubricant. CP or SSG or CS was included in either 5% or 7.5% level of concentration to acquire features of rapid disintegration. The composition of the prepared cores is displayed in Table (1). After blending the powder mixture for around ten minutes, it was sieved through a No 16 sieve and compressed using a tablet compression machine and single punch tablet press, Shanghai, China. The resulting tablets had an 8 mm diameter and weighed 200 mg apiece[12].

Table 1. Core formulations composition of formulae (C1 to C6).

Ingredients (mg)	MbH core formulations					
	C1	C2	C3	C4	C5	C6
MbH	135					
CP	10	-	-	15	-	-
SSG	-	10	-	-	15	-
CS	-	-	10	-	-	15
PVP K30	6					
Avicel PH101	47	47	47	52	52	52
Mg.stearate	2					
Total	200					

2.5. Post compression evaluation of core tablets

Core tablets passed through physicochemical assessment procedures[13], such as weight homogeneity, thickness, hardness, friability, in vitro disintegration., content uniformity and in-vitro dissolution. All measurements were done in triplicate.

2.5.1. Uniformity of weight

From each formulation twenty tablets were taken, which were then carefully weighed once using an electronic balance.

2.5.2. Uniformity of thickness

From each formulation, three tablets were chosen at random, and the average value was recorded using Planimeter, an Indian tablet thickness device, to measure thickness (mm).

2.5.3. Hardness

Hardness in Kg/cm^2 was measured by Pharma test Tablet Hardness Tester (Germany). A triplicate of the test was administered.

2.5.4. Friability

The Tablet Friability Test Apparatus (VEEGO, model: FT-2D, Progressive Instrument, Bombay, India) was used to determine friability. The tablets

were placed in a plastic drum that rotates at a speed of 25 rpm for four minutes, falling the tablets to a distance of six inches every revolution, exposing them to the combined effects of shock and abrasion. The friability chamber was filled with pre-weighed tablets and rotated 100 times. After brushing off any remaining dust, the tablets were weighed again. A triplicate of the test was administered. The following formula was used to get the percent friability (% F):

$$\% F = (w1-w2)/w1\times100 \ldots\ldots\ldots\ldots(6)$$

Where F is the % loss in weight, W1 is the original weight of each tablet; W2 is the weight of each tablet after rotation[14,15].

2.5.5. In vitro disintegration time

Using USP disintegration device and phosphate buffer with a pH of 6.8, the disintegration time (DT) was calculated. The medium had a volume of 900 ml and a temperature of 37±0.5 °C. The duration in seconds required for the tablet to completely disintegrate and leave no appetizing bulk inside the device was recorded[16]. Every tablet's disintegration time was noted, and the average time was used to compare other formulations examined in the same settings. The test was run three times, and the findings are shown as means ± SD.

2.5.6. Content uniformity

Tablet content uniformity was determined using 10 tablets of each formula. Powdered tablets were dissolved in 250 ml of phosphate buffer pH 6.8, the solution was then filtered, and the filtrate was then further diluted using the same buffer solution until achieve the desired concentration, then assayed spectrophotometrically at 263 nm with respect to the standard calibration curve of MbH in the same pH. Three readings were taken, and the average value was recorded[17].

2.5.7. In vitro dissolution study

A USP Type II dissolution equipment (Paddle type) was used to evaluate the in vitro dissolution of core tablets at a speed of 50 revolutions per minute. The dissolving medium used was 900 ml of phosphate buffer pH 6.8. The medium was kept at a constant temperature 37±0.5ºC. Five ml aliquots of the dissolution medium were taken at predetermined intervals (10, 20, 30, 40, 50, 80, 90, and 100 minutes) and filtered through 0.45µm filter paper. Immediately following each withdrawal, the same volume of novel, pre-warmed dissolving medium was added to replace the amount removed. A UV-Visible spectrophotometer set at 263 nm was used to measure the quantity of medication in each sample[16]. The experiment was conducted in triplicate, and the sink condition was maintained the entire time.

2.6. Formulation of press-coated tablets

Combination between pH and time dependent polymer is better than the use of each one alone. Since in pH dependent polymer, Significant differences exist in pH between the various GIT regions. A diet high in carbohydrates may have an impact on the pH of the colon. It has also been found that intestinal disease states such as ulcerative colitis (UC) influence the colon's pH. The pH of the colon has an impact on the pharmacokinetic and pharmacodynamic behaviour of a colon drug delivery device because it influences the solubility of medications in the colonic fluid, Moreover, the impact of colonic pH on drug release is even more noticeable if one or more dosage form components such as a pH-sensitive coated membrane are pH-sensitive[18].

Additionally, in the case of time-dependent polymers, the amount of food consumed also affects the gastric emptying time, which varies from person to person. Furthermore, conditions related to the colon, such ulcerative colitis (UC) and irritable bowel syndrome (IBS), might affect how long something takes to go through the colon.[18].

In order to assure no release in the upper gastrointestinal system and accomplish site-specific drug delivery to the colon, a combination of polymers can be used in the coat to overcome the drawbacks of each one alone and result in varied coat permeabilities.

Based on results obtained from tests carried on core tablets, cores showed gradual release profile were chosen to be coated with a combination of time dependent coat as hydroxy propyl methyl cellulose (HPMC k4m) with pH dependent coat as cellulose acetate phthalate (CAP) or eudragit L100 (Ed 100).

In order to construct press-coated tablets using the direct compression method, this process allowed the core tablet to be press-coated with 300 mg of coating mixture. Press coating ingredients (Table 2) were weighed, mixed for approximately 10 minutes, and 150 mg of coating material was added to a 10 mm die to create a powder bed then the previously manufactured core tablet was positioned in the center of the polymer bed then the remaining 150 mg of coating material was poured into the die. After that, the contents were compressed using a tablet compression machine to create a tablet with a 10 mm diameter[19].

2.7. Post compression evaluation of MbH press-coated tablets

The press-coated tablets were subjected to the same physicochemical testing as core tablets, which included assessments of the tablets' weight, thickness, hardness, friability, and drug content.

2.7.1. In-vitro dissolution study of press-coated tablets

Dissolution was done with a USP type II equipment running at 50 rpm in a 900 ml volume of dissolving media, 0.1N HCl at pH 1.2 for two hours, and phosphate buffer at pH 6.8 for the rest of twenty-four hours. Aliquot samples were taken at prearranged intervals, passed through Whatman filter paper with a pore size of 0.45 µm, and then examined at 263 nm using a double beam UV-visible spectrophotometer. Using the Beer-Lambert equation produced in the appropriate medium, the cumulative percentage release for MbH was determined. The drug release experiments were conducted in triplicate, and the mean cumulative percentage of drug (± SD) was determined[17]. Sink state was kept the entire time.

Table 2. Suggested core and coating layer composition.

Formula code	Core (mg)			Coat (mg)		
	CP	SSG	CS	HPMC	CAP	Ed
$F_1CP_{HPMC\text{-}CAP\ (Mix1:1)}$	10	-	-	150	150	-
$F_2CP_{HPMC\text{-}CAP\ (Mix1:3)}$	10	-	-	75	225	-
$F_3CP_{HPMC\text{-}CAP\ (Mix1:5)}$	10	-	-	50	250	-
$F_4SSG_{HPMC\text{-}CAP\ (Mix1:1)}$	-	10	-	150	150	-
$F_5SSG_{HPMC\text{-}CAP\ (Mix1:3)}$	-	10	-	75	225	-
$F_6SSG_{HPMC\text{-}CAP\ (Mix1:5)}$	-	10	-	50	250	-
$F_7CS_{HPMC\text{-}CAP\ (Mix1:1)}$	-	-	10	150	150	-
$F_8CS_{HPMC\text{-}CAP\ (Mix1:3)}$	-	-	10	75	225	-
$F_9CS_{HPMC\text{-}CAP\ (Mix1:5)}$	-	-	10	50	250	-
$F_{10}CP_{HPMC\text{-}\ Ed\ (Mix1:1)}$	10	-	-	150	-	150
$F_{11}CP_{HPMC\text{-}\ Ed\ (Mix1:3)}$	10	-	-	75	-	225
$F_{12}CP_{HPMC\text{-}\ Ed\ (Mix1:5)}$	10	-	-	50	-	250
$F_{13}SSG_{HPMC\text{-}\ Ed\ (Mix1:1)}$	-	10	-	150	-	150
$F_{14}SSG_{HPMC\text{-}\ Ed\ (Mix1:3)}$	-	10	-	75	-	225
$F_{15}SSG_{HPMC\text{-}\ Ed\ (Mix1:5)}$	-	10	-	50	-	250
$F_{16}CS_{HPMC\text{-}\ Ed\ (Mix1:1)}$	-	-	10	150	-	150
$F_{17}CS_{HPMC\text{-}\ Ed\ (Mix1:3)}$	-	-	10	75	-	225
$F_{18}CS_{HPMC\text{-}\ Ed\ (Mix1:5)}$	-	-	10	50	-	250
Total weight(mg)	200			300		

2.8. Accelerated stability study

Stability studies were conducted on the chosen formulation to evaluate its stability with regard to its release characteristics, T_{90} and similarity factor after six months of storage in ovens at 35 and 45 degrees Celsius with 75% relative humidity.

The dissolving characteristics of selected tablets before and after storage at 35 and 45 degrees Celsius were compared using the similarity factor (f2), which was computed using the following equation[20].

$$f_{2 = 50 \cdot \log \{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \cdot 100\}} \ldots\ldots\ldots\ldots (7)$$

where Rt and Tt, for fresh and preserved tablets, respectively, represent the percentage of medication dissolved at each time point.

2.9. In vivo studies on human volunteers

2.9.1. Study design

The study's protocol was examined and approved by the Ethics Committee of the Faculty of Pharmacy for Girls Al-Azhar University (190).

Each volunteer provided written agreement after being told of the potential risks and side effects of taking the medication. The volunteers were between the ages of 25 and 30, had no prior medical history, and were not currently taking any medications. The research was planned as a cross-over study. Two equal groups (group I and group II) of volunteers were formed. Three volunteers from group I (n = 3) were given immediate release (commercial) tablets containing 135 mg MbH, which are known as (Duspatalin)® tablets. Three volunteers from group II (n = 3) were given colon targeting tablets (F_{14}). The tablet formulations were given to the volunteers with a glass of water (250 ml) and on an empty stomach. Group I volunteers received the colon-targeted tablets after a seven-day washout period, while Group II volunteers received an immediate-release tablet. Drinks and food were avoided for at least two hours following the dosage. A 12-hours fast was required of the human subjects before to the trial. Until the completion of the trial, their nutritional and liquid intake was strictly regulated. During the research, they underwent medical observation.

2.9.2. Collection of blood samples

Five ml of blood per person were drawn into heparinized tubes at 0 (pre dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24hours. After thoroughly mixing the blood samples, they were quickly centrifuged at 5000 rpm, and the plasma was separated., transferred by micropipette into new screw-cap tubes and kept cold at -20ºC until HPLC analysis.

2.9.3. Chromatographic system and Conditions

A simple, rapid, and sensitive RP-HPLC method was developed and validated for the simultaneous determination MbH degradation product (veratric acid) as mebeverine is a prodrug upon its absorption rapidly metabolized and converted into veratric acid, in human plasma. Separation was achieved within 9 min on a BDS Hypersil phenyl column (4.5 mm × 250 mm, 5 µm particle size) using a mobile phase consisting of acetonitrile: 0.1 M potassium dihydrogen phosphate: triethylamine (35 : 65 : 0.2, v/v/v) in an isocratic mode at a flow rate of 1 mL/min and retention time 3 min. The pH of the mobile phase was adjusted to 4.5 with orthophosphoric acid and UV detection was set at 260 nm. The mobile phase was freshly prepared. Chromatography was carried out at ambient temperature[21].

2.9.4. Stock and working standard solutions

Standard stock solutions of veratric acid were prepared individually in methanol (200.0 µg/mL), and then serial dilution with mobile phase to give working standard solutions at concentration range 2.0–40.0 µg/mL (2,5, 10, 20, 40 ug/ml. Twenty µL aliquots were injected in triplicate and eluted under the optimum chromatographic conditions. Average peak areas of each compound were plotted versus the corresponding concentration (µg/mL) to obtain the calibration graph and the corresponding regression equations[21].

2.9.5. Procedure for spiked human plasma

Suitable aliquots of mixture of MbH metabolite (veratric acid) were transferred into centrifugation tubes. 1.0 ml of human plasma was added to each tube. Then, alkalinization was achieved by addition of 0.1 mL of NaOH (1.0 M) and the tubes were shaken for 1 min. The samples were mixed well using a vortex mixer and then extracted with 3 × 3 mL of ethyl acetate/dichloromethane (5:1 v/v) by centrifugation for 5 min at 4000 rpm. The organic layer was transferred into an evaporating dish and evaporated till dryness. The residue was reconstituted in 3 mL methanol The procedure described under calibration curve and the nominal content of the drug was determined[22].

2.9.6. Determination of pharmacokinetic parameters

For both developed MbH press coated tablet and commercial tablets (Duspatalin)®, pharmacokinetic parameters such as C_{max}, T_{max}, area under concentration-time curve (AUC), elimination rate constant (Ke), and elimination half-life (t½) were computed. Un-Paired two-tailed t-test was performed on T_{max}, AUC_{0-24}, and MRT.

3. RESULTS and DISCUSSION

3.1. Compatibility study of MbH with suggested polymers using Differential scanning calorimetry

The thermal behaviors of MbH alone as well as its physical mixtures with the suggested polymers were illustrated in figure (1). A distinct endothermic peak was visible in the DSC thermogram of pure MbH at 130.92 ºC as a result of melting of the drug.

The endothermic peak of MbH was seen in all of the acquired thermal profiles of the drug-polymer combinations, demonstrating the drug's compatibility with the employed polymers[23].

3.2. Pre-compression evaluation of MbH core tablets

The powder used for preparing the core tablets were evaluated for angle of repose, bulk density, tapped Density, compressibility index and Hausner's ratio.

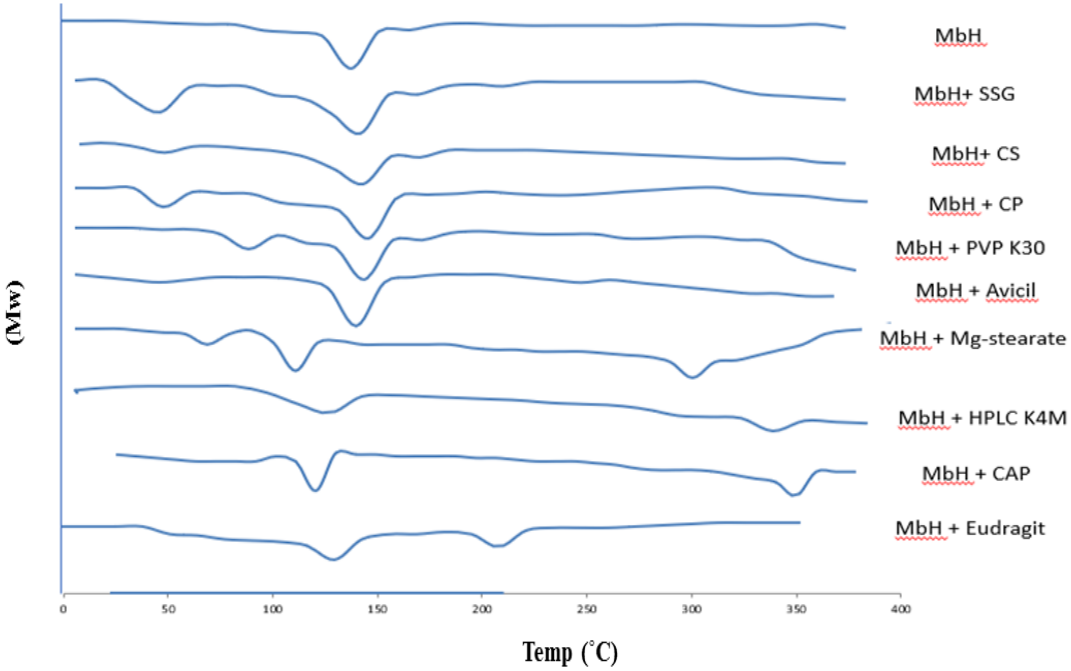

Figure 1. DSC thermogram of MbH and its physical mixture with suggested polymers.

Table 3. Pre-compression evaluation parameters of core tablet.

Pre-compression evaluation parameters	Mebeverine	Pre-compression mixture					
		C1	C2	C3	C4	C5	C6
Angle of Repose (θ)	30.91± 0.89	22.02± 0.16	23.50± 0.14	25.30± 0.12	23.4±0.45	25.8±0.32	22.6±0.41
Bulk Density (gm/ml)	0.168± 0.10	0.824± 0.24	0.612± 0.28	0.722± 0.32	0.844±0.25	0.70±0.31	0.73±0.4
Tapped Density (gm/ml)	0.179± 0.22	0.915± 0.28	0.642± 0.32	0.812± 0.22	0.92±0.33	0.65±0.24	0.82±0.23
Compressibility Index	6.15 %	9.94 %	8.77 %	11.08 %	9.98%	8.81%	11.1%
Hausner's Ratio	1.07	1.11	1.08	1.12	1.16	1.14	1.18

Since the flowability of the powder mixture are important for the content uniformity of the drug in the tablet, the flow properties were estimated before compression of the tablet and compared with that of MbH alone. From results obtained, it was found that the flow properties of MbH was fair to passable, while the six core tablets of MbH exhibited excellent flow properties with respect to the angle of repose (< 25°), Carr's index (< 12%), and Hausner ratio (< 1.25).

3.3. Post compression evaluation of core tablets

Every tablet was white in color, and according to USP, thickness, hardness, percentage of friability, disintegration, and the drug content, were all within pharmacopeial requirements. (Table 4).

Table 4. Physical Characteristics of Core Tablets Following Compression**.**

Core	Weight (mg) ±SD	Thickness (mm) ±SD	Hardness (Kg/cm^2) ±SD	Friability % ±SD	Disintegration time (DT) (sec.) ±SD	Drug content (%) ±SD
C1	199.85±0.21	3.13±0.035	2.97±0.035	0.36±0.028	41.00±1.50	98.85±0.42
C2	200.15±0.14	3.17±0.028	3.125±0.10	0.26±0.056	38.00±1.47	99.61±0.57
C3	200.70±0.07	3.16±0.014	3.075±0.07	0.33±0.070	36.00±1.41	100.3±0.22
C4	198.72±0.24	3.23±0.025	3.97±0.035	0.65±0.041	23.00±2.12	99.09±0.33
C5	200.05±0.17	3.19±0.005	3.17±0.027	0.42±0.051	19.00±1.15	99.50±0.70
C6	200.18±0.35	3.21±0.025	3.27±0.14	0.32±0.050	16.00±3.24	100.08±0.4

The in- vitro disintegration time (DT) of the core tablets was found to be less than 3 minutes. Tablets containing 5 % from super disintegrants showed disintegration time ranged from 36-41 sec. by increasing the conc of super disintegrants to 7.5 % it results in decrease in the disintegration time ranged from 16-23 sec. This was mainly due to the easy and high swelling abilities of super disintegrants which can swell many times of its original volume when contact with fluid[15]. The water uptake is of critical importance for tablet disintegration since the contact with water causes swelling which reduce adhesiveness of tablet ingredients resulting in break apart of tablet constitution.

The presence of super disintegrants in tablet cores exerts pressure on the coating layer. Super disintegrant swells after the ingress of water which leads to the rupturing the coat[24].

From the results it was evident that the mebeverine release from the core tablets depends on the concentration of super disintegrants.

Formulations C1, C2, C3 containing 5 % of super disintegrant showed gradual release of the drug which is suitable for preparing sustained release press- coated tablets. By increasing the concentration of super disintegrant to 7.5 % in C4, C5, C6 it results in rapid dissolution and the drug released at the end of 10 min was more than 98 %. So, it will not be suitable for preparing sustained release press-coated tablets.

Formulations C1, C2, C3 containing mebeverine showed satisfactory hardness, friability, % drug content, disintegration time, and gradual drug release. So, C1, C2, C3 were considered as the chosen formulation, and they were taken as a core tablet for further studies.

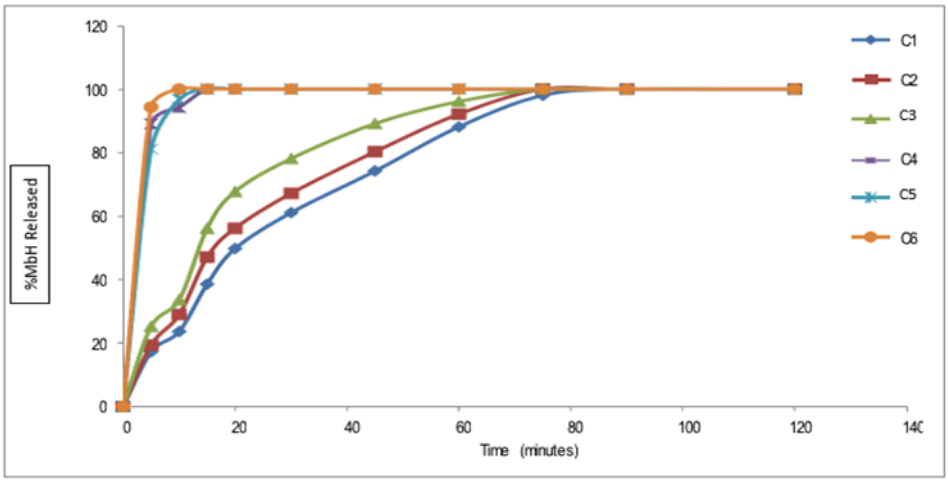

Figure 2. In-vitro release of MbH core tablets.

3.4. Post compression evaluation of MbH press-coated tablets

Every tablet is round and white in color. Every tablet met the acceptable standards for weight, thickness, hardness, percentage friability, and content consistency as shown in (Table 5).

Table 5. Physical Parameters of MbH Press-Coated Tablets.

Formulae	Weight (mg) ± SD	Thickness (mm) ± SD	Hardness (Kg/cm2) ± SD	Friability (%) ± SD	Drug content (%) ± SD
F1	0.4993±0.40	4.49±0.01	7.17±0.30	0.270±0.01	99.20±1.9
F2	0.4987±0.80	4.48±0.05	7.47±0.04	0.350±0.03	100.6±0.72
F3	0.4998±1.04	4.46±0.03	6.99±0.20	0.220±0.02	99.31±0.40
F4	0.4996±2.1	4.60±0.05	7.01±0.55	0.15±0.01	99.30±0.46
F5	0.4999±1.4	4.58±0.03	6.21±0.2	0.30±0.05	100.0±0.75
F6	0.4985±1.27	4.43±0.02	6.00±0.12	0.29±0.04	98.60±0.35
F7	0.4989±1.00	4.45±0.01	7.15±0.42	0.24±0.01	99.10±0.46
F8	0.4992±1.17	4.41±0.03	7.00±0.20	0.31±0.04	99.60±0.70
F9	0.4991±0.69	4.43±0.02	7.17±0.70	0.20±0.04	99.30±0.21
F10	0.4969±0.57	4.65±0.02	7.17±0.36	0.16±0.03	99.10±0.12
F11	0.4995±0.28	4.52±0.01	6.90±0.60	0.30±0.06	99.89±0.14
F12	0.4950±0.02	4.49±0.07	7.12±0.95	0.20±0.11	99.50±1.04
F13	0.4994±1.6	4.47±0.02	7.38±0.58	0.19±0.01	99.60±1.2
F14	0.4980±0.02	4.64±0.05	7.87±0.31	0.45±0.03	98.70±0.42
F15	0.4997±1.00	4.41±0.01	6.99±1.00	0.28±0.01	99.80±1.2
F16	0.4991±0.28	4.47±0.02	7.06±0.36	0.30±0.03	99.50±0.70
F17	0.500±1.70	4.65±0.05	8.10±0.06	0.16±0.04	100.5±0.80
F18	0.4999±0.57	4.50±0.07	7.40±0.80	0.50±0.11	99.80±0.30

3.4.1. In-vitro dissolution study of press-coated tablets

The polymer used acts by gel formation; HPMC K4M (time dependent polymer) containing tablets Figure (3). It hydrates the tablet's outer surface to create a gel layer when it comes into touch with water. The overall rate of dissolution and delivery of the active ingredient is determined by the rate of diffusion out of the gel layer and the rate of tablet erosion[25].

Cellulose acetate phthalate (pH dependent polymer) provides enough gut protection with 0.1N HCl. There was no evidence of drug leakage from these formulations, and the coated tablets stayed intact in 0.1N HCl. Cellulose acetate phthalate dissolves at pH greater than 6[26].

The pH-sensitive polymer Eudragit L100 dissolves at 6-7, so it will resist gastric acidity and start to dissolve at pH 6.8[27].

It was found that, formulations (F_1-F_3) containing CP as a core disintegrant and a coat of HPMC: CAP (Mix 1:1, 1:3 and 1:5) shown in figure (3a), (F_4-F_6) containing SSG as a core disintegrant and a coat of HPMC: CAP (Mix 1:1, 1:3 and 1:5) shown in figure (3b) and (F_7-F_9) containing CS as a core disintegrant and a coat of HPMC: CAP (Mix 1:1, 1:3 and 1:5) shown in figure (3c) demonstrate no release within the initial two hours, suggesting that the coat is stable in acidic media. Less than 20% of the drug was released in the next three hours, and between six and twenty-four hours, other formulations showed another pattern.

The presence of HPMC may interact with CAP by hydrogen bonding between the hydroxyl group of cellulose in HPMC and the carbonyl group of the ester linkage I n CAP, which could explain the observed slowdown in the % drug release[28].

It was observed that increasing CAP concentration with respect to HPMC, (HPMC: CAP 1:1) (HPMC: CAP 1:3), (HPMC: CAP 1:5) there was a decrease in hydroxyl group of cellulose in HPMC that form hydrogen bond with carbonyl group in the CAP's ester linkage that result in increase of MbH release.

By adjusting ratios of HPMC K4M and CAP in formulations (F8 and F9) lag time of about five hours could be obtained with complete medication release which is (96.43±1.8 and 98.6± 1.6 respectively) at the end of 24 hours, making them suitable as colon targeted dosage forms.

It was found that, formulations (F_{10}-F_{12}) containing CP as a core disintegrant and a coat of HPMC: Eudragit (Mix 1:1, 1:3 and 1:5) shown in figure (3d), (F_{13}-F_{15}) containing SSG as a core disintegrant and a coat of HPMC: Eudragit (Mix 1:1, 1:3 and 1:5) shown in figure (3e) and (F_{16}-F_{18}) containing CS as a core disintegrant and a coat of HPMC: CAP (Mix 1:1, 1:3 and 1:5) shown in figure (3f) demonstrate no release within the initial two hours, suggesting that the coat is stable in acidic media. Less than 20% of the drug was released in the next three hours, and between six and twenty-four hours, other formulations showed another pattern.

From results, it was obvious that the combination of Eudragit with HPMC, it will increase the release of drug. This is because the polymer is anionic and easily soluble in neutral to slightly alkaline conditions at pH within 6 to 7, increasing the ratio of Eudragit gradually and decreasing the ratio of HPMC leading to elimination of lag time and increasing the release[28].

Adjusting the ratio of HPMC: Eudragit (F11, F14 and F17) provided lag period of about 5-6 hours, then a full release of drug which is (99.6± 3.2, 98.11±2.2 and 98.7±4.1) at the end of the 24-hours period making them suitable as colon targeted dosage forms.

By comparing formulations of the same coat but containing different cores, it was obvious that the pattern of release in formulation containing Croscarmellose in the core was higher than those containing Crosspovidone or Sodium starch glycolate. This is explained by the fact that the core comes into contact with the dissolving liquid once the coat erodes or dissolves. There are two ways in which croscarmellose sodium causes disruption. When it comes into touch with water, it could first expand and develop core fissures that allow water to seep further into the core. Second, the particles could create a pathway for water to seep through[29].

3.5. Accelerated stability study

Stability study was conducted for the selected formulations (F8, F9, F11, F14 and F17) at 35 and 45°C with RH 75±5% for 6 months as they provide lag period 5-6 hours followed by complete drug release at end of 24 hours. Figure (4) represents percent MbH retained from different press coated tablets formulations. It revealed that percent MbH retained was ≥ 96.12% at 35°C and ≥ 94.1% at 45°C. The degradation reaction was a zero-order reaction. The T_{90} values for the selected formulations F8, F9, F11, F14 and F17 were 676.47, 415.43, 711.16, 974.29 and 804.72.

Similarity factors were found to be between 64-89 for tablets stored at 35ºC and between 53- 78 for tablets stored at 45ºC which indicated similarity between selected tablets before and after storage, regarding dissolution profiles since values were greater than 50[30].

F14 showed the highest stability results that was indicated by its T_{90} and similarity factor values after six months of storage at both 35ºC and 45ºC compared to other formulations, thus chosen for further investigation.

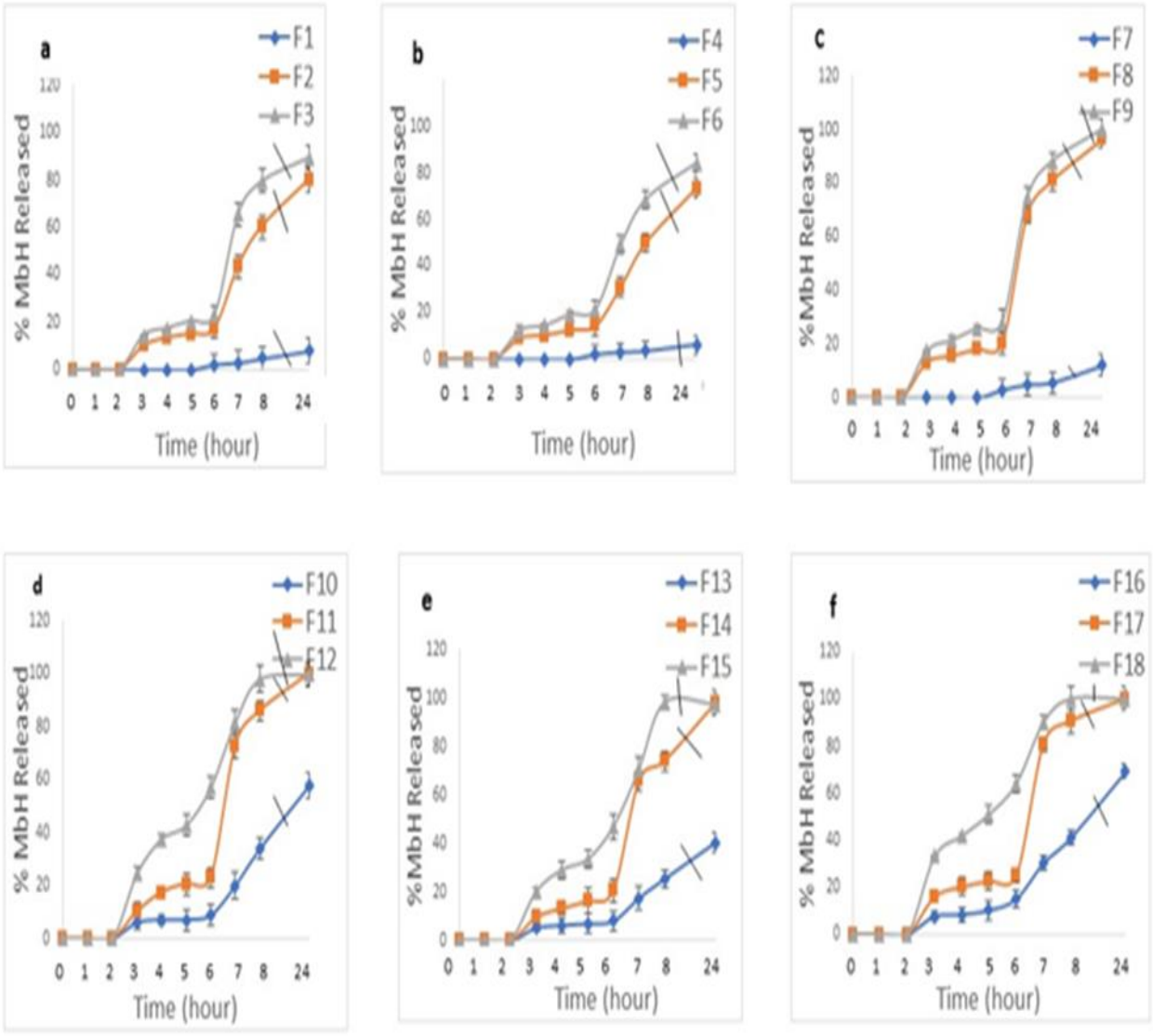

Figure 3. In-vitro release of MbH press-coated tablets.

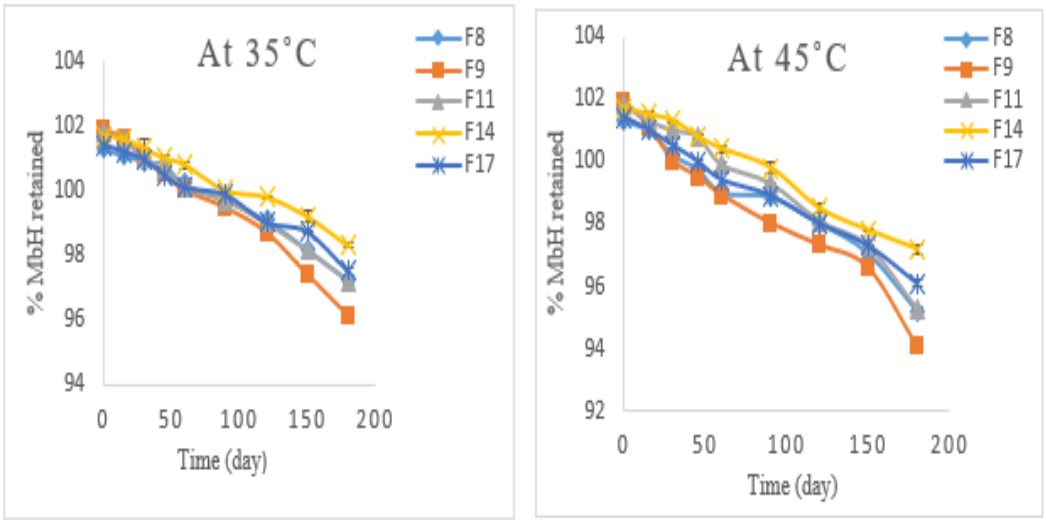

Figure 4. Percent retained of selected formulations of MbH press coated tablets stored at both 35 and 45°C/RH 75±5%.

3.6. In vivo studies on human volunteers

MbH being an ester, it is rapidly and thoroughly hydrolyzed into mebeverine alcohol and veratic acid in the gut and/or liver during presystemic (first-pass) hydrolysis. Studies revealed that only traces of MbH were detected in plasma following oral administration of the drug, while veratic acid appeared at the same time. As a result, the quantities of veratic acid in plasma were measured to track the effectiveness of MbH as a therapy[31].

Plasma drug concentration after oral administration of test formulation F14 and commercial tablet are shown in Figure 12. The pharmacokinetic findings are shown in Table 6. Significantly higher values of peak time, T_{max} (11.3 vs 2 hours) mean residence time, MRT (13.27 vs 7.19 h) were observed for tested tablets compared to commercial ones ($P < 0.05$), indicating presence of lag time for the formulations that were studied. The test formulations' bioavailability was noticeably higher than that of the reference formulation. The relative bioavailability of MbH press-coated F14 was found to be 135.75%.

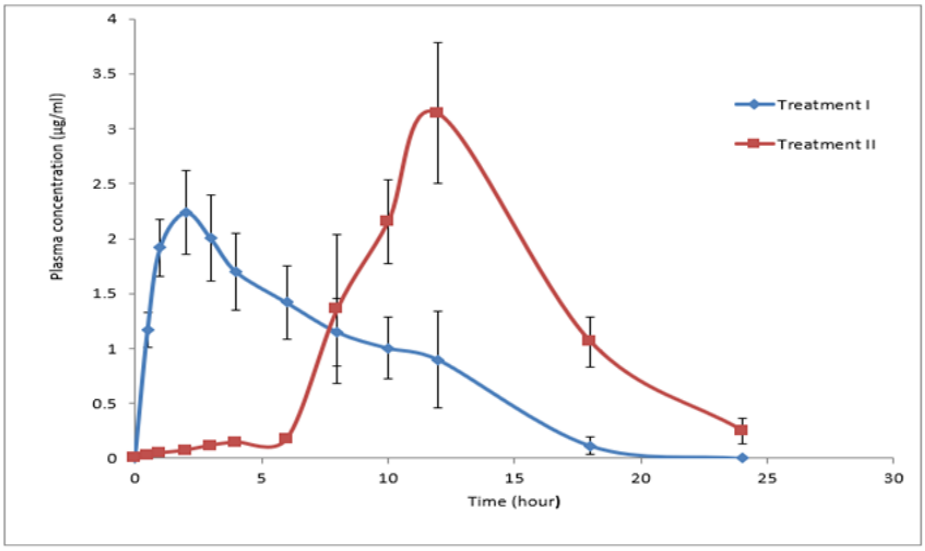

Figure 5. Mean veratric acid plasma conc. (µg/ml) versus time curve ± SD in participants getting tested and commercial tablets.

Table 6. Mean pharmacokinetic parameters following the oral administration of MbH tablets that have been tested and purchased.

Parameter	Commercial formula	F14
C_{max} (µg/ml)	2.24±0.44	3.14±0.56
T_{max}(hour)	2	11.3
K_{el} (hour^{-1})	0.410±0.61	0.240±0.05
$t_{1/2el}$ (hour)	1.689±0.54	2.877±0.96
V_d (L)	0.341±2.71	0.330±1.53
AUC_{0-24} (µg.hr/ml)	20.250±10.15	27.490±2.07
$AUC_{0-\infty}$ (µg.hr/ml)	20.981±58.52	28.736±2.18
MRT (hour)	7.199±1.15	13.273±0.40
RB %	-	135.75%

4. CONCLUSION

In this study, colon targeted MbH press coated tablets were successfully prepared using pH and time dependent coating polymers for treatment of inflammatory bowel disease. Cores with 5% CP, SSG, and CS that achieved gradual release pattern were coated and evaluated for their physical characteristics of drug content and in vitro release. All prepared MbH press coated tablets displayed acceptable physicochemical properties and complied with pharmacopeial requirements for their content uniformity. Based on the in vitro release pattern, tablets F8, F9, F11, F14 and F17 that showed 5-6 hours lag period, before full MbH release at the end of 24 hours were further studied for their short term accelerated stability. F14 (containing 5% SSG in the core and coated with HPMC: Eudragit 1:3) displayed the highest T_{90} value (974.29 days) and similarity factor (89 at 35˚C and 78 at 45˚C) was compared with commercial tablet (Duspatalin)® for their pharmacokinetic parameters. The pharmacokinetic data showed significant higher values of peak time,

T_{max} (11.3 vs 2 hours), mean residence time, MRT (13.27 vs 7.19 h) and the relative bioavailability of MbH press-coated F14 was found to be 135.75%. According to these findings the authors believe this would be a significant step forward to the broader application and manufacture particularly in areas of clinical development.

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Conflicts of Interest: There is no Conflict of interest.

Ethical Statement: The protocol for in vivo study was reviewed and approved by the ethical committee, Faculty of Pharmacy, Al-Azhar University (Approval number: 190).

Author Contribution: methodology -writing, Reem A. Selim; review and editing, Maha A. M. Marzouk, Amal A. E. Ammar and Zeinab A. M. Zalat. All authors have read and agreed to the published version of the manuscript.

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