# Colon Targeting of Mebeverine HCl from pH-Dependent Tablet Formulations

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**Abstract:** Inflammatory Bowel Syndrome (IBS), is an inflammatory disease affecting the bowel in which gastrointestinal tract (GIT) is more sensitive to many stimuli causing it to contract abnormally. Mebeverine HCl "as an intact drug" is a musculotropic antispasmodic agent with a direct non-specific relaxant effect on smooth muscles, especially the colon. In an attempt to restrict its action locally to the colon, avoiding its first-pass effect, its metabolic changes in the small intestine and its absorption along the GIT, mebeverine HCl polymer based formulations were designed for colon targeting. Tablet core containing drug, Avicel PH101 and carboxymethylcellulose sodium (CMC Sod.), 1:1:2 was compression coated. A set of tablets was coated with hydroxypropylmethyl cellulose 4000 (HPMC 4000) and cellulose acetate phthalate (CAP) 1:1 (F1), 1:3 (F2), 1:5 (F3), and with HPMC 4000 and Eudragit L100 (EL100) 1:3 (F4). Another set was coated with HPMC 6cp, then dipped in solution of 12.5% w/v Eudragit L100 in isopropyl alcohol containing 1.25% w/w polyethylene glycol 400 (PEG 400) (F5). Swelling index was calculated for most formulations. Coated tablets were tested for release at pH 1.2 (2 hours) and pH 6.8 (28hours). No or negligible release occurred in the first 2 hours. After 3 hours, less than 20% of drug was liberated. Results of dissolution were consistent with those of swelling. Differential Scanning Calorimetry (DSC) and Infra Red Spectroscopy (IR) studies were also performed. A selected formulation was tested ex-vivo on isolated guinea pig colon. Formulations were stable for at least one year except for F3 (after 6 months).
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**Keywords:** Mebeverine HCl; polymer; colon targeting; compression coating; guinea pig colon

## 1. Introduction

Colonic drug-targeting has several therapeutic advantages. Like in any other organ targeting, only a small dose of the drug is required, which subsequently results in fewer adverse drug reactions (1-2). Diseases of the colon such as irritable bowel syndrome are effectively treated when the drug is applied directly to the affected area (3). Mebeverine hydrochloride ,as intact drug, is an antispasmodic agent with a direct, non specific relaxant effect on smooth muscle especially the colon.

Kristinsson *et al.,* (4) studied the urinary metabolites of orally administered mebeverine hydrochloride (270 mg) in healthy volunteers. No altered mebeverine was detected in the pooled urine samples, which is in agreement with earlier findings (5). These findings suggested that the ester functional group of mebeverine was rapidly and extensively hydrolyzed *in vivo*, and did not reach the systemic circulation in detectable amounts. The first metabolic step takes place in the small intestine and liver, and the remaining steps possibly take place in the liver. The drug is completely metabolized to at least six metabolites following oral administration to man. On the other hand, assuming the gut is the main site of hydrolysis, the effect of mebeverine on irritable bowel syndrome might be explained by the local action of some unabsorbed drug or of its hydrolysis products (6).

Colonic targeting would ensure arrival of the intact drug to the affected contracted area and would avoid undue load to the liver especially in patients suffering from hepatic diseases.

Seventy-one patients with functional abdominal pain lasting more than three months were randomized to receive either mebeverine or dicyclomine. More unwanted side effects were reported in the dicyclomine group(7).

Dose for dose, the compound was found to be three times as potent as papaverine for inhibiting the peristaltic reflex of the guinea-pig ileum (6).

Site-specific drug delivery to the colon may be achieved by different approaches. In this study, a combination of pH and time dependent technique was adopted to prepare easily formulated mebeverine coated tablets using mixture of polymers through the common tableting and coating processing.

The use of mixture of polymers in the coat and manipulation of the proportion of its components can lead to different coat permeabilities which would ensure no release in the upper gastrointestinal tract followed by almost complete delivery to the colon.

## 2. Materials and Methods

### Materials

Mebeverine HCl (Meb. HCl) powder was a courtesy of Amriya Pharm., Ind., Alexandria, Egypt. Eudragit L-100 (EL100) was obtained from Rohm Pharma, Darmstadt, Germany. Hydroxy propylmethylcellulose (HPMC 4000) (Methocel K4M) and Carboxymethylcellulose Sodium (CMC Sod., degree of substitution not less than 0.4; a viscosity of

1% w/v solution in water is 8 cp at 20$^0$C) were BDH Chemicals Ltd., Poole, England. Cellulose acetate phthalate (CAP) and hydroxypropylmethyl cellulose (HPMC 6 cp) were purchased from Alexandria Pharmaceuticals, Alexandria, Egypt. Avicel PH101 (MCC) was a courtesy of Pharco Pharmaceuticals, Alexandria, Egypt.

All other chemicals were of analytical or pharmaceutical grade.

**Preparation of mebeverine HCl coated tablets**

All powders used were sieved and fractions corresponding to particle size range 71µ-1.25mm were used for tablet preparation.

The tablet core (Tc) (average weight 200 mg) was prepared by direct compression of a physical mixture (PM) of mebeverine HCl, Avicel PH 101 and CMC Sod. in a ratio 1:1:2. The composition of the tablet core is given in Table1.

A first set of tablet formulations (F1-F4) was prepared by compression coating of the prepared core with a mixture of HPMC 4000 and CAP in a ratio 1:1 (F1), 1:3 (F2) and 1:5 (F3) or HPMC 4000 and EL100 1:3 (F4) using 12-mm round, concave punches.

A second set of tablet formulations (F5) was prepared by compression coating of the prepared core tablets with low MW HPMC (6cp) using the same previous punch, followed by dipping in isopropyl alcohol containing 12.5% w/v EL100 and 1.25% w/w PEG 400 as a plasticizer (Table 2) .

The compression-coated tablets were tested for hardness, drug content, weight variation and thickness with a suitable number of tablets for each test.

The hardness of the compression-coated tablets was determined using Monsanto Hardness Tester.

**Table 1:** Composition of mebeverine HCl tablet core

| Ingredients | Quantity (mg) |
|---|---|
| Mebeverine HCl | 50 |
| Avicel PH 101 | 50 |
| CMC Sod. | 100 |

**Table 2:** Composition of coats for different mebeverine HCl tablet formulations

| Formulation | Ingredients (mg) | | | |
|---|---|---|---|---|
| | HPMC 4000 | CAP | EL100 | HPMC 6cp |
| F1 | 150 | 150 | - | - |
| F2 | 75 | 225 | - | - |
| F3 | 50 | 250 | - | - |
| F4 | 75 | - | 225 | - |
| F5 | - | - | - | 300* |

*dipped in isopropyl alcohol containing 12.5% w/v EL100 and 1.25% w/w PEG 400

**Determination of tablet porosity**

The total porosity of the compressed coated tablets (F1-F4) was calculated as follows:

$\epsilon_{total} = 1 - \rho_b/\rho$ (8) {1}

$\epsilon_{total}$ is total porosity.

$\rho_b$ is bulk density.

$\rho$ is approximate true density, was determined by compressing the powder to the maximum possible compressional force (8)

**Swelling studies**

The prepared tablet formulations were subjected to swelling studies at 37± 0.1$^0$C. The weight of the tablet was determined ($W_1$). Each tablet was placed separately in a 20 ml beaker containing 7.3 ml 0.1N HCl for 2 hours, then 2.7 ml 0.2M tri sodium phosphate (to adjust pH of the medium to 6.8) were added. Tablets were removed at different time intervals (2,5,8,12,24 and 28 hours), wiped with filter paper and reweighed ($W_2$). The swelling index was calculated as follows:

Swelling index = $W_2$-$W_1$/$W_1$ {2}

***In vitro* release studies**

Studies were carried out using USP dissolution apparatus II, at 37± 0.5$^0$C.The dissolution medium, stirred at 50 r.p.m., consisted of 730 ml 0.1N HCl for 2 hours followed by a buffer of pH 6.8 adjusted by the addition of 270 ml of 0.2M tri sodium phosphate (9-10) for 28 hours. Samples (5ml) were withdrawn at predetermined time intervals, compensated with fresh dissolution medium and assayed spectrophotometrically at 263nm in 0.1N HCl and pH 6.8. No interference occurred due to other tablet excipients at this wavelength.

**Differential scanning calorimetry (DSC)**

Thermal analysis by DSC (Perkin Elmer DSC 6 thermal analyzer) was carried out on mebeverine HCl, the individual excipients, physical mixture (PM), tablet core (Tc) and compressed tablet of drug and CMC Sod. (1:2). Samples (20 mg) were weighed in flat bottom aluminium pans. Temperature calibration was made using indium as a standard. An empty pan, sealed in the same way as the sample was used as reference. All samples were run at a rate of 10$^o$C/min, from 40$^o$C to 400$^o$C in an atmosphere of nitrogen.

**IR analyses**

Samples were mixed with KBr and compressed into discs using a hydraulic press under pressure of about $10^5$ N. The spectra were recorded over a range of 4000-500 cm$^{-1}$.

***Ex-vivo* studies using isolated guinea pig colon**

The experiment was carried out in compliance with the regulations of the Committee for animal experiments, Alexandria University. A selected formulation was subjected to further ex-vivo studies on isolated guinea pig colon.

**Preparation of the colon**

Female guinea pigs (weighing 450 g) were kept fasted for 24 hours prior to the experiment but were allowed free access of water. Guinea pigs were killed, the cecum was located and followed posteriorly to locate the colon. The colon was free from attached fat and ligaments. Pieces of colon 2.5cm long were cut at a distance 7cm from the cecal junction. Each tissue segment was suspended in 10ml oxygenated Tyrode's solution at $37^0$C and subjected to a tension of 1 g. Isometric contractions were measured using an isometric transducer connected to a Nacro-physiograph (11-12).

**Spasmolytic activity**

A concentration of drug solution (36 µg/ml) was selected to study its ex-vivo spasmolytic effect. Contractions were induced in the tissue using 0.1, 0.2 and 0.3 ml acetyl choline (30 µg/ml) or 0.3 ml barium chloride (5%). Contact time was 30 seconds followed by the addition of 0.1 ml of the drug solution for 2 minutes. The tissue was then retreated with the same volume of acetyl choline (30 µg /ml) or barium chloride (5%). Percentage inhibition induced by a selected treatment was calculated (11-12).

$$\% \text{ inhibition} = \frac{[\text{mean height of control (mm)} - \text{mean height of treated tissue (mm)}] \times 100}{[\text{mean height of control (mm)}]} \quad \{3\}$$

**Effect of ageing**

Tablet formulations were stored in airtight containers, at room temperature not exceeding $30^o$C and protected from light in a desiccator for 3,6 and 12 months. The solid drug was reported to be chemically stable under these conditions(6) and (13). Tablets were assessed for any change in physical properties and drug release which was conducted under the same conditions mentioned above.

**Statistical data analyses**

Statistical data analyses were performed using the Student t-test with $p<0.05$ as the minimal level of significance. Calculations were done using the online calculation programme (14).

All experiments were done in triplicates. SD values were calculated.

## 3. Results and Discussion

All quality control tests done on the prepared tablets were satisfactory.

**Swelling studies**

Swelling index of coated tablets are shown in Fig.1. In the first 2 hours, in 0.1N HCl, swelling index increased slightly but was in all cases less than 2 and the tablets were intact as shown by visual observation.

At pH 6.8, the swelling pattern was bimodal indicating the presence of two different processes possibly corresponding to two different water uptake mechanisms that contributed simultaneously to the overall phenomenon. The initial process was slow, probably due to water diffusion through available pores in the tablets. This process was soon accompanied by a more rapid water uptake process that is presumably linked to a gradual dissolution of the coat with pore widening. Progressive swelling will cause sudden opening of the pores possibly due to bond disruption between particles. It is to be noted that till 5 hours, only a part of the coat was dissoluted. A four times increase in swelling index was obtained after 28 hours and complete erosion was seen. A similar bimodal swelling was observed in a previous work (15), in which the matrix consisted of microcrystalline cellulose or cross povidone.

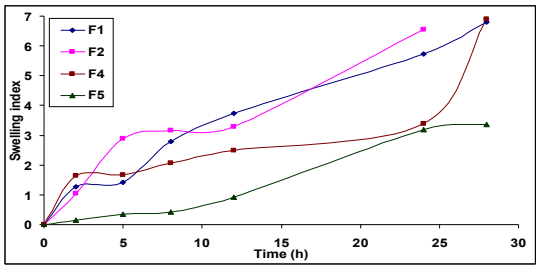


**Figure 1:** Swelling index profiles of F1, F2, F4 and F5 at $37^0$C in 0.1N HCl (2hrs), at pH 6.8

**Release studies**

Results of release study are shown in Fig.2. as well as Tables 3 and 4. The latter gives values for $t_{50\%}$, % dissolution efficiency, DE (16-17) and mean dissolution time, MDT (18).

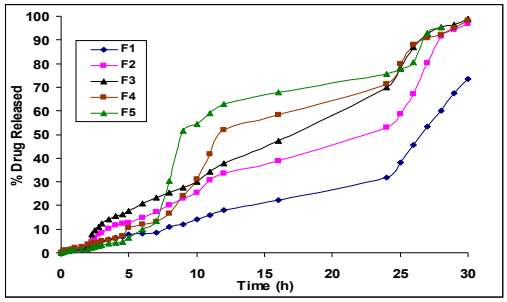


**Figure 2:** Release profiles of mebeverine HCl from different compressed coated tablets with a mixture of HPMC 4000 and CAP in a ratio of 1:1 (F1), 1:3 (F2) or 1:5 (F3) and a mixture of HPMC 4000 and EL100 in a ratio of 1:3 (F4) or from dipped coated tablets in EL100 solution (F5); in 0.1N HCl (2hrs) and pH 6.8 (28hrs).

No or negligible release occurred in the first 2 hours indicating coat stability in acid. In the following 3 hours, less than 20% of the drug was released (19). From 5 to 12 hours, another pattern was exhibited by the different formulations. Formulations containing CAP (F1, F2 and F3) exhibited a slow release (Table 4). However, this result is unexpected as CAP is known to dissolve at pH 6 (10). Such retardation in release is suggested to be due to the presence of HPMC which may interact with CAP through hydrogen bonding between carbonyl group of the ester linkage in CAP and hydroxyl group of cellulose in HPMC. On the other hand, formulations containing EL100 (F4 and F5) gave a rather obvious increase in release (Table 4). This is due to the anionic nature of the polymer which is readily soluble in neutral to weakly alkaline conditions (pH 6-7) (20). After 12 up to 24 hours, the release was more or less gradual in all formulations. Such observation may be explained as follows: upon hydration, the mixture of Avicel and CMC Sod. would generate a rheological system showing thixotropic properties. This latter behavior results from the formation of a three-dimensional gel structure, leading to immobilization of water molecules inside it (21).

In the last 6 hours (24-30 hours), an unexpectedly high release was obtained from all formulations. It was reported that in a thixotropic mixture of CMC Sod. and Avicel, agitation by time causes breakdown of the network structure of the formed gel with subsequent decrease in viscosity, resulting in an obvious increase of drug release (21).

Concerning the mechanism of release, it can be stated that the release of the drug from all tablet formulations is complex and cannot be effectively described by a single mechanism of release. A more or less similar release pattern was obtained in previous studies (22-23). This may be partly attributed to the polymer mixture used. A statistical approach in the determination of the predominant release mechanism was suggested (Table 3). Correlation coefficients (r) calculated for the first order and Higuchi plots were both high. Thus, the release mechanism of the drug from the tablets may be mixed consisting partially of diffusion and partially of first order.

**Table 3:** Correlation coefficients for the release of mebeverine HCl from different tablet formulations according to First order and Higuchi plots

| Formulation | Correlation coefficient (r) | |
|---|---|---|
| | First order | Higuchi |
| F1 | -0.9192 | 0.9073 |
| F2 | -0.8704 | 0.9454 |
| F3 | -0.9058 | 0.9671 |
| F4 | -0.9385 | 0.9577 |
| F5 | -0.9539 | 0.9339 |

**Table 4:** Values of $t_{50\%}$, mean dissolution time &% dissolution efficiency for different mebeverine HCl tablet formulations in 0.1 N HCl (2hrs) and pH 6.8 (28hrs)

| Formulation | $t_{50\%}$(h) | MDT*(h) | % DE** |
|---|---|---|---|
| F1 | 26.75 | 22.9 | 23.8 |
| F2 | 22.00 | 18.4 | 38.8 |
| F3 | 16.75 | 16.2 | 46.8 |
| F4 | 11.50 | 15.4 | 48.7 |
| F5 | 8.80 | 13.3 | 50.6 |

$*MDT = \int_0^\infty M_\infty - M_{(t)} dt / M_\infty$ (18) {4}

**% DE = % Dissolution efficiency (16-17)

In the first order release, the limiting step in the liberation of the drug becomes the water penetration rate and diffusion of the dissolved drug out of the tablet through the gel layer. On the other hand, according to Higuchi model, the penetration of the medium occurs through the available pores in the tablet (24).

However, differences in porosity of the tablets were found to be only a few percent units, unable to promote differences in release. This suggests the presence of other factors controlling release (25).

In the fresh F3 tablet, the low content of HPMC gives, upon hydration in the dissolution medium (pH6.8), a rather thin gel coating the external surface of the tablet. Such thin gel layer would not result in clogging of the tablet pores, thus rendering release fast compared to the other formulations of higher HPMC content (F1, F2, F4 and F5).

Also after 6 months storage, F3 with a low content of HPMC showed an increase in drug release, compared to the initial one. This phenomenon can be explained by the enhancement of polymer chain flexibility causing shrinkage of the polymer embedding the drug in the matrix, therefore increasing the penetration of the aqueous dissolution medium into the porous skeletal structure of the tablet during release. Furthermore, a lowering of the glass transition temperature of the polymer may occur with an increase in the polymer chain flexibility as well (26-28). The difference was significant as tested by Student t-test.

In the same context, F1 which showed the slowest release, contained the highest amount of HPMC. It is noteworthy that the release after 12 months was slower compared to that after 6 months. During storage, the tablet may adsorb some humidity on its surface, which may form a thin gel layer with a subsequent blocking of available pores. This will slightly hinder the entrance of the dissolution medium. However, the change was not significant.

Results of swelling were parallel to those of release. Figure 3 showed at 5 hours an increase in swelling accompanied by a corresponding increase in release for all formulations. Moreover, Figure 4 is representative for all time intervals (F4).

A significant difference was observed in the amount of mebeverine HCl released after 8 hours in case of F1 and F4 compared to the tablet core.

However, the release was considered too slow in case of F1 (31.8% at 24 hours) while F4 showed a suitable release (71.5% at 24 hours and complete release at the end of the dissolution run). So F4 was selected for further ex-vivo study.

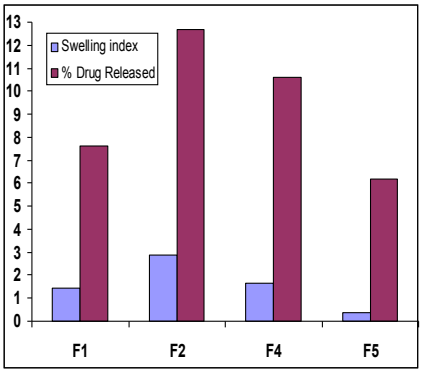


**Figure 3:** Plot of values of swelling index and % drug released from different mebeverine HCl tablet formulations at 5 hours

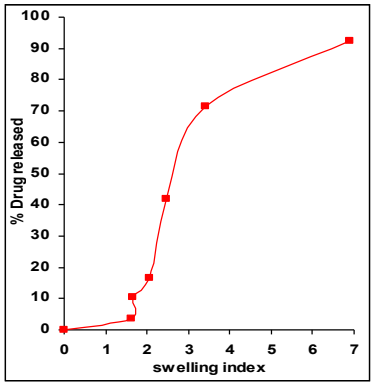


**Figure 4:** Correlation between % mebeverine HCl released & swelling index for F4 at different time intervals

**DSC studies**

The results of analyses by DSC for mebeverine HCl, tablet core, physical mixture, CMC Sod. and compressed tablet of the latter with the drug (2:1), are shown in Fig.5. The excipients used showed no endothermic peaks in the range of 100-300°C. Avicel, not shown in the figure, exhibited a sharp endothermic peak at 341.791°C. Under used experimental conditions, no oxidation or decomposition phenomenon was observed before the drug melting process. The drug thermal curve was typical of crystalline anhydrous substances and was characterized by one sharp endotherm at 138.137°C due to melting with an onset (thaw point) at 132.616°C and an end at 144.915°C. The enthalpy of fusion $\triangle$ H, was calculated to be102.621 j/g.

A rather different behavior was observed for the drug in its blend with the excipients. In fact, the thermal profile of the physical mixture showed after the broad shallow endotherm due to the hydration process of the excipients, a substantially affected drug melting peak in its shape which appeared broadened and shifted slightly to lower temperature, indicating a decrease in its original crystallinity and a rather high degree of amorphization. The extent of drug amorphization was much more positively influenced by compression which caused nearly the disappearance of its melting endotherm.

The $\triangle$ H value for physical mixture and the corresponding one for the tablet core was about 27.110 and 13.832 j/g respectively. Both were smaller than that of pure drug, indicating a decrease in crystallinity (29-30). The decrease in the enthalpy of the overall thermal effect per mass unit is a general observation when the surface of contact between drug and excipients is increased by compression. The relative degree of crystallinity of the drug (Drug $_{RDC\%}$) in the physical mixture and tablet core, was estimated by the ratio between the heat of fusion of the drug calculated in the sample and that of the pure drug (pd), according to the following equation: (31)

Drug $_{RDC\%}$ = $\triangle$H blend/ $\triangle$H pd x100 {4}

This equation is suitable to evaluate the amorphizing power of excipients. Values obtained for the physical mixture and tablet core were 26.42 and 13.48% respectively. The value of the relative degree of crystallinity in case of the tablet suggests the presence of a significant proportion of the drug homogeneously dispersed in the polymer matrix.

Avicel particles have a relatively large cohesive force and inner frictional coefficient, resulting in a good tablet hardness. In this connection, it is considered that Avicel might take a plastic deformation during compression (32-33). That is why the peak was much more affected in the thermogram of the tablet core compared to that in the physical mixture.

It was previously reported (34) that a possible interaction occurs between the drug and the CMC Sod. in a mixture 1:1 as exhibited from DSC thermogram.

Therefore, a DSC analysis for the drug and each excipient alone was prompted in this study. The result obtained in the case of physical mixture of CMC Sod. with the drug (1:2) showed an endothermic peak for the drug at 130.382°C with obvious decrease in both peak area and height. However, in case of compressed tablet the changes were of lower magnitude. However, the interaction was rather weak, since the drug was completely released from the tablet core at the end of the release run.

Such interaction did not occur with Avicel, where the drug peak remained almost unchanged either in the tablet or the blend form.

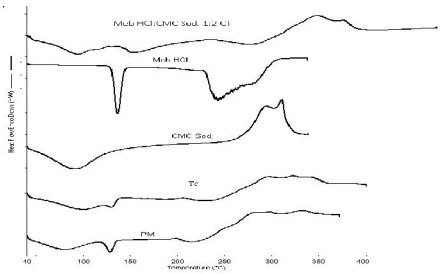


**Figure 5:** DSC thermograms of mebevrine HCl, CMC Sod., compressed tablet of drug and CMC Sod. (1:2), tablet core (Tc) and physical mixture (PM)

**IR analyses**

Among the principal peaks of the drug, the one occurring at 1750 $cm^{-1}$ corresponding to C=O stretching was taken to characterize the drug alone and when present with the excipients. The spectrum of mebeverine HCl in the PM was similar to that of the drug alone. However, for the Tc, the stretching band of the drug appeared as a broad band shifted to1762.5$cm^{-1}$ (Fig. 6). This shift might be due to the association of the carbonyl group of the drug with an electron accepting hydrogen in CMC Sod. The applied pressure during tablet compression would facilitate the attraction process between the two species.

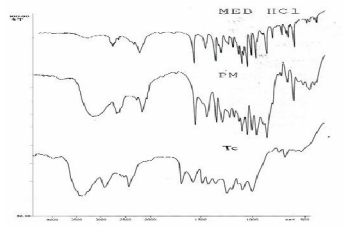


**Figure 6:** IR spectra of mebeverine HCl, physical mixture and tablet core

**Ex-vivo study**

Results showed an obvious direct relaxation of muscle by the drug (Fig.7). Percentage inhibition due to 0.1 ml mebeverine HCl (35.8 µg/ml) to contraction induced by 0.2 ml acetyl choline (30µg/ml) and 0.3 ml barium chloride solution (5%) was 60.8% and 82.1% respectively.

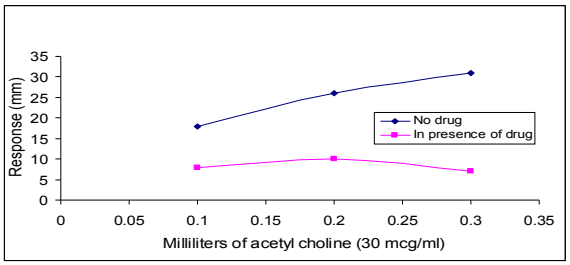


**Figure 7:** Response curve for the effect of mebeverine HCl (35.8mcg/ml) on acetyl choline induced contraction of isolated guinea pig colon

**Effect of ageing**

In view of the potential utility of mebeverine HCl formulations for colon targeting, stability studies were carried out. After storage, the formulations were observed for physical change and subjected to assay of the drug and in vitro drug release studies. No change appeared either in physical appearance or in drug content. The effect of ageing on drug release was mentioned above.

The values for correlation coefficients were nearly the same as before ageing. (Table 3), indicating nearly no change in the mechanism of release. SD values for all performed experiments ranged from 0.013 to 7.450.

**Conclusion**

Successful and stable tablet formulations of mebeverine HCl for selective delivery to the colon were developed resulting in:

- Lowering the required dose and frequency of administration.
- Reduction of systemic side effects of the drug.
- Avoiding undue load to liver especially in patients with hepatic diseases.
- Extension of drug action for 24 hours, thus ensuring prolonged direct spasmolytic effect on colonic smooth muscles.

Moreover, the technique adopted is non-expensive, simple and no organic solvent was required in majority of formulations. Polymers used are recognized as safe.

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**References**

(1) Ofori-Kwakye K and Fell JT., 2003. Biphasic drug release from film-coated tablets. Int. J. Pharm.; 250:431-440.
(2) Ofori-Kwakye K, Fell JT, Sharma HL and Smith A., 2004. Gamma scintigraphic evaluation of film-coated tablets intended for colonic or biphasic release. Int. J. Pharm.; 270: 307-313.
(3) Kalala W, Kinget R, Van den Mooter G and Samyn C., 1996.Colonic drug-targeting: *in vitro* release of ibuprofen from capsules coated with poly(ether-ester) azopolymers. Int. J. Pharm.; 139: 187-195.
(4) Kristinsson J, Snorradottir I and Johannsson M., 1994. The metabolism of mebeverine in man: identification of

urinary metabolites by gas chromatography/mass spectrometry. Pharmacol. Toxicol.; 74(3): 174-180.
(5) Dickinson RG, Baker PV, Franklin ME and Hooper WD.,1991. Facile hydrolysis of mebeverine *in vitro* and *in vivo*: negligible circulating concentrations of the drug after oral administration. J. Pharm. Sci.; 80(10): 952-957.
(6) Radwan MA, Foda NH and Al Deeb OA.,1998. Mebeverine HCl In: Florey K editor. Analytical profiles of drug substances, vol.25. New York: Academic press;. p.165-207.
(7) Grillage MG, Nankani JN, Atkinson SN and Prescott P. ,1990. A randomized, double-blind study of mebeverine versus dicyclomine in the treatment of functional abdominal pain in young adults. Br. J. Clin. Pract.; 44(5): 176-179.
(8) Martin A., 1993.Micromeretics In: Physical Pharmacy, fourth ed. Philadelphia: Lea Febiger;. p. 443-446.
(9) Sinha VR and Kumria R, 2002. Binders for colon specific drug delivery: An *in vitro* evaluation. Int. J. Pharm.; 249: 23-31.
(10) Sinha VR and Kumria R, 2003. Coating polymers for colon specific drug delivery: A comparative *in vitro* evaluation. Acta Pharm.; 53: 41-47.
(11) Abd ElHady SS, Mortada ND, Awad GAS, Zaki NM and Taha RA, 2003. Development of in sutu gelling and mucoadhesive mebeverine hydrochloride solution for rectal administration. Saudi Pharm. J.; 11(4): 159-171.
(12) Al Gohary OMN and Foda NH, 1993. Availability of mebeverine hydrochloride from Suppositories. Pharm. Ind.; 55(4): 396-400.
(13) "Mebeverine HCl"., 2007. In: Sweetman SC, editor, Martindale, The complete drug reference. 35th. ed., London, Chicago: The Pharmaceutical Press;. p.1572.
(14) http:// www.physics.csbsju.edu/stats/t-test.
(15) Ferrari F, Rossi S, Bertoni M, Caramella C and Geddo M.,1991. Modelling of water penetration into fast disintegrating tablets. S.T.P. Pharm. Sci.; 1(2): 137-144.
(16) Khan KA.,1975. The concept of dissolution efficiency. J. Pharm. Pharmacol.; 27: 48-49.
(17) Dreyfuss MF, Brossard D and Chaumeil J-C.,1986. Contrôle de la vitesse de dissolution à partir de comprimés de β-bloquants par la méthode à la palette tournante. S.T.P. Pharma Sci.; 2(14): 245-250.
(18) Rao BS, Seshasayana A, Saradhi SVP, Kumar NR, Narayan CPS and Murthy KVR, 2001. Correlation of *in vitro* release and *in vivo* absorption characteristics of rifampicin from ethylcellulose coated nonpareil beads. Int. J. Pharm.; 230: 1-9.
(19) Ofori-Kwakye K and Fell JT, 2001. Biphasic drug release: the permeability of film containing pectin, chitosan and HPMC. Int. J. Pharm.; 226: 139-145.
(20) Rowe RC, Shesky PJ, Owen SC. editors. 2006. "Polymethacrylates" In: Handbook of Pharmaceutical Excipients 5th ed. London, Chicago: The Pharmaceutical Press; p.553-560.
(21) Dolz-planas M, Gonzalez-Rodriguez F, Belda-Maximino R and Herraez Dominguez V., 1988. Thixotropic behavior of a microcrystalline cellulose-sodium carboxymethylcellulose gel. J. Pharm. Sci.; 77(9): 799-801.
(22) Adikwu MU.,1992. Release behaviour from microcapsules of chloroquine phosphate treated with polymerized latex of Landolphia dulcis. S.T.P. Pharm. Sci.; 2(3): 285-289.
(23) Proikakis CS, Tarantili PA and Andreopoulos AG., 2006. The role of polymer/drug interactions on the sustained release from poly(DL-lactic acid) tablets. Europ. Polymer J.; 42 : 3269-3276.
(24) Bamba M, Puisieux F, Marty JP and Carstensen JT, 1979. Release mechanisms in gel forming sustained release preparations. Int. J. Pharm.; 2: 307-315.
(25) Zecchi V, Tartarini A, Orienti I, Rodriguez L, Cini M, Conte U *et al.,* 1986. Chemical properties-dissolution of nonsteroidal anti-inflammatory drugs II. Factors affecting the release of NSAID from monoliths. Pharm. Acta Helv.; 61(12) : 322-325.
(26) Nagakami H, Keshikawa T, Matsumura M and Tsukamoto H, 1991. Application of aqueous suspensions and latex dispersions of water-insoluble polymers for tablet and granule coatings. Chem. Pharm. Bull.; 39(7): 1837-1842.
(27) Amighi K and Möes A, 1996.Influence of plasticizer concentration and storage conditions on the drug release rate from Eudragit RS30D film-coated sustained- release theophylline pellets. Europ. J. Pharm. Biopharm.; 42: 29-35.
(28) Rafiee-Tehrani M, Toliat T and Nedjadhashemi S, 1997. Dissolution and stability studies of the controlled release glyceryl trinitrate matrix tablets. Acta Pharm.; 47(4): 255-265.
(29) Prabhu S, Sullivan JL and Betageri G, 2002. Comparative assessment of in vitro release kinetics of calcitonin polypeptide from biodegradable microspheres. Drug Deliv.; 9: 195-199.
(30) Kim KH, Frank MJ and Henderson NL, 1985. Application of differential scanning calorimetry to the study of solid drug dispersions. J.Pharm. Sci.; 74: 283-289.
(31) Mura P, Maestrelli F, Cirri M, Furlanetto S and Pinzauti S, 2003. Differential scanning calorimetry as an analytical tool in the study of drug-cyclodextrin interactions. J.of thermal analysis and calorimetry ; 73: 635-646.
(32) Nogami H, Nagai T, Fukuoka E and Sonobe T, 1969. Disintegration of the aspirin tablets containing potato starch and microcrystalline cellulose in various concentrations. Chem. Pharm. Bull.; 17(7): 1450-1455.
(33) Rippie EG and Danielson DW, 1981. Viscoelastic stress/strain behavior of pharmaceutical tablets: Analysis during unloading and postcompression periods. J. Pharm. Sci.; 70(5): 476-481.
(34) Foda NH, 1992. Compatibility study between fluvoxamine maleate, mebeverine hydrochloride and tablet excipients using Differential Scanning Calorimetry, Egyp. J. Pharm. Sci.; 33(1-2): 73-81.