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Influence of methacrylic acid and hydroxypropylmethyl cellulose on the tablet properties and *in vitro* release of dextromethorphan hydrobromide

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The release of dextromethorphan hydrobromide from matrices containing hydroxypropylmethyl cellulose (HPMC K100LV) and methacrylic acid copolymer (Eudragit® L100-55) has been evaluated at different ratios of the polymers. The physicochemical properties (including weight, thickness, crushing strength, friability and disintegration time) were also determined at 1000, 2000 and 4000 p compression forces. No significant differences in weight uniformity and thickness values were observed between the different formulations. The crushing strength of the tablets increased with increasing compression force and it reached a constant level at 4000 p. The formulations containing only HPMC K100LV resulted in an extended release pattern, however, Eudragit L100-55 alone could not effectively prolong the drug release. A combination of HPMC K100LV and Eudragit L100-55 in a 1:1 ratio at the 40% level provided an almost similar drug release profile than the marketed product.

1. Introduction

Matrix systems composed of drug and release retarding polymer offer the simplest approach to design an extended release dosage form. In matrix systems, the most commonly used polymers are hydrophilic polymers (cellulosic polymers, sodium alginate) and hydrophobic polymers (ethyl cellulose, methacrylic acid copolymers). Hydroxypropyl methylcellulose (HPMC) is the most used cellulosic polymer in controlling the release of drugs in the formulation of oral pharmaceutical dosage forms [1–3]. The mechanisms by which it retards drug release include its ability to form rapidly a gel layer at the matrix periphery exposed to aqueous fluids [4, 5]. As more fluid penetrates, the gel thickness increases and soluble drug diffuses out through the gel barrier. Therefore, the viscosity of the gel is critical to control drug release rates. For insoluble drugs, release occurs as a result of erosion of the fully hydrated outer layers [6].

Acrylic resins have also been used as a basis for compressed matrices. Many authors have described the prolonged release from acrylic polymer matrices [7–9]. Cameron and McGinity [8] reported that the combination of cationic and anionic resins as a retardant matrix in a tablet formulation has good potential in a controlled release dosage form. Vela et al. [7] reported that a direct compression technique using Eudragit L and S gave erodible matrix tablets of paracetamol. A greater delay in the dissolution process was created by increasing the amount of Eudragit without producing any change in the indicated release mechanism.

Admixing another polymer to the hydrophilic matrix may bring about different effects according to the type and

strength of the interactions between the polymers forming the matrix and also between polymer and drug. The use of mixtures of polymers represents a potential way of achieving particular release properties [10–12].

In a previous study, we evaluated the effect of different anionic polymers (Eudragit L100-55, Eudragit S and NaCMC) on pH dependent drug release from HPMC matrices. It has been found that the blends of HPMC and Eudragit L100-55 in 1:1 ratio succeeded in producing pH-independent extended release matrix tablets [11]. The possibility of the use of Eudragit RS as a sustained release matrix agent for the incorporation of water-soluble active compounds has been investigated by Plazier and et al. [12]. It has been concluded that Eudragit RS has a much smaller influence as a sustained release agent, however, the combination of polyvinylpyrrolidone/Eudragit RS decreased the release rate at the highest and lowest level.

Dextromethorphan hydrobromide (DMHBr) is a highly potent and commonly used antitussive agent. The usual therapeutic doses of DMHBr are 10–20 mg every 4 h or 30 mg every 6–8 h with a maximum of 120 mg daily [13–15]. Extended release cough products already exist in the European and Canadian market as suspension and capsule dosage forms. A DMHBr-resin complex in a solid or suspension based on ion-exchange technology (DELSYM) was developed to overcome the drawbacks of traditional syrup products [13]. Based on clinical observations and the results of pharmacokinetic studies that a controlled release DMHBr formulation given once every 12 h it was shown to be equally safe and effective as a traditional salt formulation given every 6 h.

In the present study, we developed extended release DMHBr tablets by a direct tablet compression method

Table 1: Physical properties of DMHBr tablets, expressed as mean $\pm$ SD

Formulation	Compression force (p)	Weight (mg)	Thickness (mm)	Hardness (Kp)	Friability
D1 (HPMC 20%)	1000	303 $\pm$ 2.36	5.18 $\pm$ 0.01	5.37 $\pm$ 0.38	5.1
	2000	302 $\pm$ 2.08	4.62 $\pm$ 0.03	9.24 $\pm$ 0.42	0.025
	4000	303 $\pm$ 2.06	4.56 $\pm$ 0.04	11.0 $\pm$ 0.84	0.095
D2 (HPMC 40%)	1000	304 $\pm$ 2.47	5.39 $\pm$ 0.02	6.09 $\pm$ 0.43	0.681
	2000	306 $\pm$ 2.77	4.94 $\pm$ 0.02	10.5 $\pm$ 0.75	0.043
	4000	301 $\pm$ 2.15	4.75 $\pm$ 0.06	11.3 $\pm$ 0.46	1 tb capped
D3 (HPMC 60%)	1000	302 $\pm$ 0.003	5.33 $\pm$ 0.01	6.61 $\pm$ 0.87	0.182
	2000	303 $\pm$ 0.003	4.86 $\pm$ 0.04	13.3 $\pm$ 0.99	0.024
	4000	298 $\pm$ 0.02	4.79 $\pm$ 0.09	12.8 $\pm$ 1.72	0.013
D4 (Eudragit 20%)	1000	304 $\pm$ 3.19	5.91 $\pm$ 0.02	0.87 $\pm$ 0.22	50.2
	2000	305 $\pm$ 2.23	4.79 $\pm$ 0.04	8.21 $\pm$ 1.04	0.047
	4000	302 $\pm$ 2.08	4.61 $\pm$ 0.03	7.68 $\pm$ 0.49	0.129
D5 (Eudragit 40%)	1000	306 $\pm$ 2.44	5.36 $\pm$ 0.03	2.48 $\pm$ 0.48	0.315
	2000	304 $\pm$ 2.21	4.93 $\pm$ 0.04	8.61 $\pm$ 0.74	12 tb capped
	4000	304 $\pm$ 2.20	4.89 $\pm$ 0.04	7.93 $\pm$ 1.32	0.192
D6 (Eudragit 60%)	1000	308 $\pm$ 0.002	5.63 $\pm$ 0.02	4.39 $\pm$ 0.92	4 tb capped
	2000	301 $\pm$ 0.003	5.29 $\pm$ 0.12	7.08 $\pm$ 1.48	10 tb capped
	4000	301 $\pm$ 0.001	5.11 $\pm$ 0.05	8.33 $\pm$ 0.51	10 tb capped
D7 (HPMC:Eudragit 20%)	1000	300 $\pm$ 2.36	5.28 $\pm$ 0.01	2.7 $\pm$ 0.41	0.511
	2000	302 $\pm$ 2.25	4.61 $\pm$ 0.02	10.3 $\pm$ 0.52	0.025
	4000	310 $\pm$ 2.17	4.66 $\pm$ 0.02	11.6 $\pm$ 0.98	0.016
D8 (HPMC:Eudragit 40%)	1000	303 $\pm$ 2.47	5.42 $\pm$ 0.01	3.54 $\pm$ 0.16	0.270
	2000	308 $\pm$ 2.25	4.95 $\pm$ 0.02	9.24 $\pm$ 0.70	0.013
	4000	311 $\pm$ 2.19	4.85 $\pm$ 0.03	13.8 $\pm$ 1.86	0.007
D9 (HPMC:Eudragit 60%)	1000	302 $\pm$ 0.002	5.48 $\pm$ 0.05	5.43 $\pm$ 1.67	0.262
	2000	305 $\pm$ 0.002	5.12 $\pm$ 0.02	8.81 $\pm$ 0.77	0.061
	4000	304 $\pm$ 0.002	5.04 $\pm$ 0.10	9.63 $\pm$ 1.59	5 tb capped

which will reduce the number of doses required and may lead to a better compliance with the minimum cost. The effect of HPMC K100LV, methacrylic acid copolymer (Eudragit L100-55) and their combination on the tablet properties and dissolution behaviour of DMHBr under different compression forces has been investigated to design a 12 h an extended release matrix tablet.

2. Investigations, results and discussion

2.1. Weight and thickness

The properties of the tablets prepared from different formulations are set out in Table 1. The results are expressed as mean $\pm$ standard deviation. For all the compression forces used the weight variation was under 3.5%. The tablet weight variation was found minimum for all the formulations. It is also observed that the variation of thickness was minimal. The standard deviation of tablet thickness in all the formulations was also quite uniform, ranging from 0.01% to 0.12%. As expected, a decrease in thickness was found with an increase in the compression force.

2.2. Crushing strength

The hardness values of DMHBr tablets compressed at three different compression forces are given in Table 1. Crushing strength of tablets clearly describes a certain mechanic property of a whole tablet. The crushing strength of the tablets increased with increasing compression force. At lower compression force, this increase was exponential but reached a constant level at a compression force of 4000 p. A plateau was observed for all the formulations (Fig. 1). This suggests that a maximum strength had been reached for tablets made from these polymers, and that further increases in compaction load would not result in stronger tablets. Increasing the amount of Eudragit L100-

55 or the blend of HPMC K100LV: Eudragit L100-55 increased tablet strength at 1000 p compaction force. The formulation containing only Eudragit had low tablet hardness values ranging from 0.87 ± 0.22 Kp with 20% level to 4.39 ± 0.92 Kp with 60% Eudragit level. The tablet strengths remained almost similar at 2000 and 4000 p compaction forces when the polymer level increased. The formulations containing only HPMC K100LV at 20, 40 and 60% levels generated tablets with crushing values of 9.24 ± 0.42 , 10.5 ± 0.75 , and 13.3 ± 0.99 Kp, respectively at 2000 compaction force. It is observed that tablet strength was strongly influenced by the type of polymer. The crushing strength of tablets containing only HPMC K100LV was higher than that of tablets containing only Eudragit L100-55. The major reason for this may be that Eudragit L100-55 has a rigid structure but HPMC K100LV exhibits plastic deformation properties. The higher crushing strength of HPMC K100LV is the result of relatively low methoxy and high hydroxylpropyl group content and also the high moisture content which may contribute to the development of relatively strong hydrogen bonds within the tablets.

2.3. Tablet friability

As expected, the friability decreased with increasing upper punch force. The results are shown in Table 1. A limiting value of 1% for friability tests of tablets has been suggested by the European and USA Pharmacopoeas. With compression forces with 2000 p, tablets provided a friability of $<0.5\%$. Extended release tablets based on Eudragit only were liable to capping in the friability test. Capping was particularly observed in the formulations containing Eudragit at 60% level under three applied compaction forces. The friability values of 60% Eudragit L100-55 under three compaction forces verified that it had limited potential for future development.

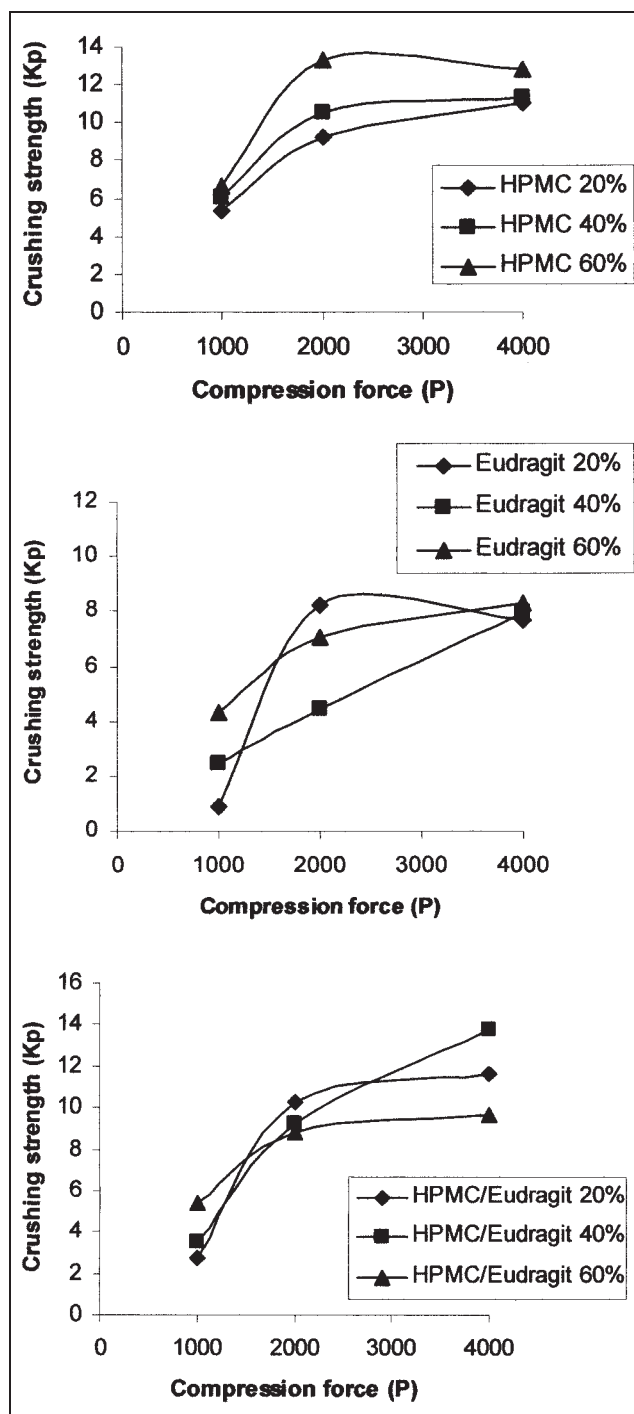


Fig. 1: Effect of compression force on the crushing strength of dextromethorphan hydrobromide tablets

2.4. Release of DMHBr from matrix formulations

The formulations which were tableted at 2000 p compaction pressure were used for the dissolution studies. The effect of the amount of HPMC K100LV (20, 40 or 60%) on the drug release is shown in Fig. 2. The DMHBr release decreased as the percent amount of HPMC K100LV increased. Drug release is controlled by the hydration of HPMC K100 LV, which forms a gelatinous barrier layer at the surface of the matrix. In addition, the resistance of such a gel layer to erosion is controlled by the viscosity of the HPMC. HPMC K100LV is a low viscosity polymer (100 cps), therefore, 20% polymer level

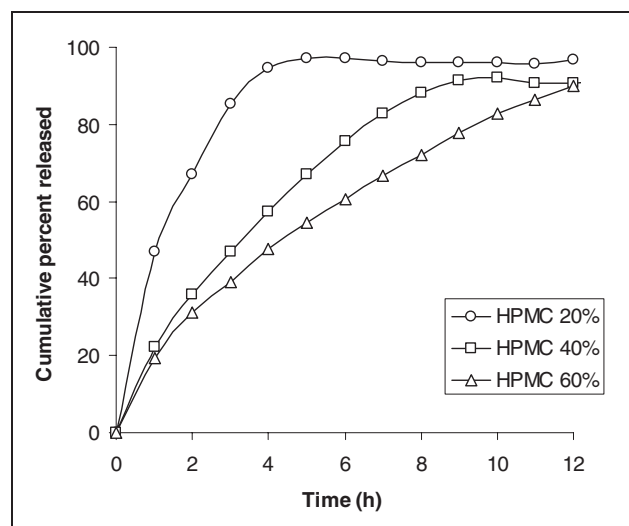


Fig. 2: Effect of HPMC K100 LV amount on dextromethorphan hydrobromide release

showed a fast drug release from the matrix. It is observed that after 3 h, 85.4% of the drug was released in the dissolution media. An increase in the polymer amount causes an increase in the viscosity of the gel as well as the formation of a gel layer with a longer diffusional path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate. In the present study, the results followed this predictable behaviour. The drug release from the formulations containing 40 and 60% HPMC K100LV was found to be 92.2 and 82.8%, respectively at 10 h (Fig. 2). The gel thickness might have prolonged the drug release from the formulations.

Matrices containing 20 and 40% Eudragit L 100-55 showed fast release of DMHBr because of disintegration (Fig. 3). The release rate data from these matrices were not calculated because of the fast release of the drug (Table 2). More than 82.1% release value was reached in 2 h from the matrices containing 60% Eudragit L 100-55.

Eudragit L100-55 was incorporated into the formulations containing HPMC K100LV to evaluate the modification of the drug release from HPMC matrices (Fig. 4). It was

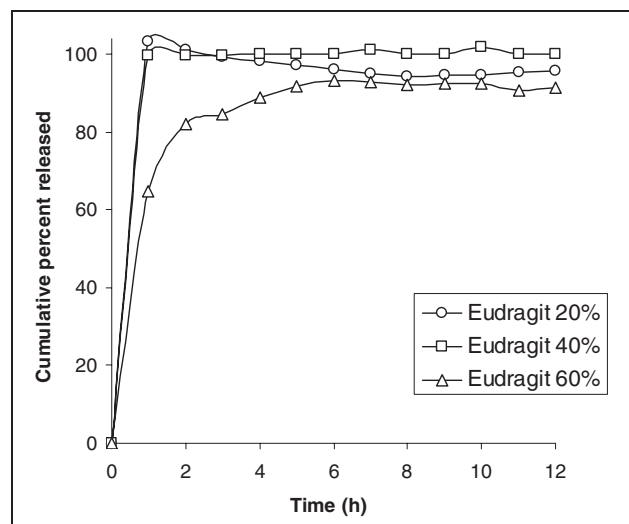


Fig. 3: Effect of Eudragit L100-55 amount on dextromethorphan hydrobromide release

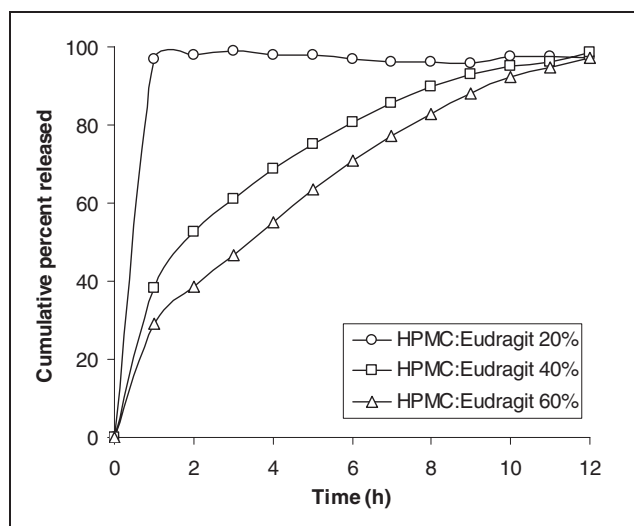


Fig. 4: Effect of amount of HPMC K100LV and Eudragit L100-55 combination on dextromethorphan hydrobromide release

observed that the combination of HPMC K 100LV and Eudragit L100-55 at 20% level did not retard the drug release. The low HPMC K100LV level probably played an important role for the faster release of DMHBr. The combination of HPMC and Eudragit L100-55 in a 1:1 ratio at 40 and 60% level, provided slow release of drug compared to the formulations containing only HPMC K100 LV at 40 and 60% level. The release rates were found to be 29.5 ± 0.23 and $24.5 \pm 0.45\% h^{-1/2}$ for the blends of HPMC K100LV: Eudragit L 100-55 at 40 and 60% level, respectively (Table 2). The pKa of DMHBr was found to be 9.12 by Gilligan and Po [16]. The retarding effect was probably caused by the interaction of the cationic DMHBr and with the anionic polymer Eudragit L100-55 in the dissolution medium.

The formulations which provided an extended release profile were also compared with the market product (Fig. 4). The extended release market product was prepared according to ion-exchange technology. The drug release rate of the blend of HPMC K100LV: Eudragit L100-55 at 40% were found to be very close to that of the market product. The release rates were found to be 29.5 ± 0.23 and $28.2 \pm 0.32\% h^{-1/2}$ for the blend of HPMC K100LV:

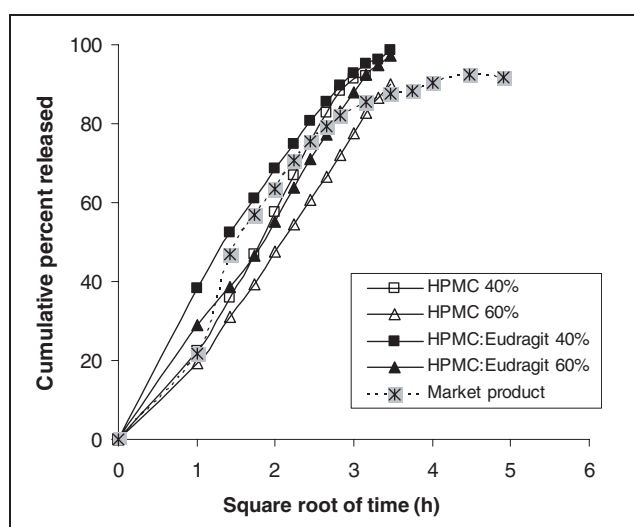


Fig. 5: Comparison of matrix formulations with the market product

Table 2: Release rates ($\%h^{-1/2}$) and correlation coefficients (r^2) according to Higuchi equation

Formulation	release rate	Correlation coefficient
HPMC 20%	42.5 ± 2.10	0.966
HPMC 40%	34.6 ± 1.65	0.999
HPMC 60%	29.2 ± 0.46	0.999
Eudragit 20%	—	—
Eudragit 40%	—	—
Eudragit 60%	18.3 ± 0.68	0.888
HPMC:Eudragit 20%	—	—
HPMC:Eudragit 40%	29.5 ± 0.23	0.995
HPMC:Eudragit 60%	24.5 ± 0.45	0.982
Market product	28.2 ± 0.32	0.933

Eudragit L100-55 at 40% level and the market product, respectively. The similarity factor was used to compare the dissolution profiles of optimum formulation (D8) and the market product. The percent average difference, based on f_2 values was 53.2% indicating similarities in the release profiles.

Based on our observations, the direct compression method using the low viscosity HPMC K100LV and Eudragit L100-55 combination offers a promising alternative for the controlled delivery of the antitussive agent DMHBr. This study demonstrates the feasibility of developing an extended release matrix tablet using the direct compression method on the basis of reliability and ease of manufacture. In order to confirm the *in vitro* release results, investigations will be pursued by doing *in vivo* studies.

3. Experimental

3.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: dextromethorphan hydrobromide (Roche Vitamins Inc., Parsippany, NJ, USA), Methocel® K100 LV (Dow Chemical Company, Midland, MI, USA), methacrylic acid copolymer (Eudragit® L100-55, Rohm America Inc, Somerset, NJ, USA), microcrystalline cellulose (Avicel pH 102, FMC Corp., Philadelphia, PA, USA), lactose anhydrous (Sheffield, Norwich, NJ, USA), magnesium stearate (Mallinckrodt Specialty Chem. Co., St. Louis, MO, USA).

3.2. Manufacturing procedure

The effects of varying the concentration (20–60%) of hydroxypropyl-methylcellulose (HPMCK100LV), methacrylic acid copolymer (Eudragit L100-55) and the combination of them in a 1:1 ratio were studied. DMHBr, polymers (HPMC K100LV and/or Eudragit L100-55) and the fillers (anhydrous lactose and Avicel pH 102) were passed through a 25-mesh sieve (USA Standard Testing Sieve, Gilson Company, Worthington, OH) and mixed 10 min in a Turbula mixer (WAB Maschinenfabrik, Basel, Switzerland). Magnesium stearate was then added, and blended for an additional 2 min. The blends were compressed using an instrumented Manesty D3B tablet press (Manesty Machines Ltd., Liverpool, England) at 1000, 2000 and 4000 p compression force. The compositions of these formulations are listed in Table 3.

Table 3: Composition of dextromethorphan hydrobromide matrix tablets

Ingredients	D1	D2	D3	D4	D5	D6	D7	D8	D9
DMHBr	20	20	20	20	20	20	20	20	20
HPMC K100LV	20	40	60	—	—	—	10	20	30
Eudragit L100-55	—	—	—	20	40	60	10	20	30
Avicel pH102	29.5	19.5	9.5	29.5	19.5	9.5	29.5	19.5	9.5
Lactose	29.5	19.5	9.5	29.5	19.5	9.5	29.5	19.5	9.5
Mg stearate	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100

3.3. Dissolution testing

Dissolution of DMHBr from the tablets was monitored using an automated VK 7010 dissolution tester coupled to an automated VK 8000 sample collector. (Vankel Technology Group, Cary, NC, USA). The release characteristics of the formulations were determined using USP 24 apparatus II, at 100 rpm, in 0.1 N HCl for 2 h, and then switching to pH 6.8 phosphate buffer solution at $37 \pm 0.5^\circ\text{C}$. Samples were collected hourly for 12 h. The release profile of the optimum formulation was compared to the market release profile using the FDA recommended model independent approach using the similarity factor (f_2) [17].

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^n (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\} \quad (1)$$

where n is the number of sample points; R_i is the percent dissolved of optimum formulation at each time point; T_i is the percent dissolved of market product at each time point.

3.4. HPLC

Samples collected were analyzed by HPLC. The HPLC equipment used was a Hewlett-Packard series 1100 equipped with a built in degasser, an autosampler and a variable wavelength UV-VIS detector (Hewlett-Packard, Analytical Group, Novi, MI, USA). Column used was a XTerra Rp18, 5 mm particle, 15 cm $\times$ 4.6 mm i.d. equipped with a 4.6 mm $\times$ 2 cm guard column (Waters Corporation, USA). The mobile phase was a mixture of 0.1 N acetic acid (J. T. Baker, USA) and HPLC grade methanol (J. T. Baker, USA) in the ratio of 65:35 with a detection at 280 nm. DMHBr is normally analyzed by reversed-phase HPLC with UV detection. The amine functional group in the compound produces tailing peaks on many silica-based stationary phases unless ion pairing agents are added. This method employs a specially deactivated stationary phase to minimize tailing effects and eliminates the need for modifiers in the mobile phase.

3.5. Tablet evaluation

3.5.1. Tablet weight variation

Twenty tablets were randomly selected and weighed using an analytical balance. Weight values were reported in mg. Mean and standard deviation values were calculated.

3.5.2. Tablet thickness

Tablet thickness of the ten randomly selected tablets used for the weight variation analysis using a micrometer (Starret Portable Dial Hand Micrometer; Starret, Athol, MA). Tablet thickness values were reported in mm. The mean and standard deviation values were calculated.

3.5.3. Tablet hardness/crushing strength

Crushing strength of the ten randomly selected tablets, previously used for weight variation and tablet thickness determination, was measured using a key hardness tester (Key hardness tester, Model HT500II; Key International Inc., Englishtown, NJ). Crushing strength values were reported in Kp. The mean and standard deviation values were calculated.

3.5.4. Tablet friability

Twenty tablets were weighed. The tablets were placed in a friabilator (Model 45–2000; Vankel, Edison, NJ) and subjected to 100 rotations (25 rotations/min). The tablets were then dusted and reweighed. Weight loss was calculated, and the friability as reported as percent weight loss.

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