Original Article

Comparison Drug Release from Simple and Layered Matrix Systems Containing Hydroxypropyl Methylcellulose

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ABSTRACT

Objective: The aim of this investigation was to compare the release behavior of propranolol HCl from simple matrix and layered tablets containing HPMC and phytowax as matrix component using direct compression technique.

Method: The test of drug release was performed in distilled water during 26 hrs using a dissolution apparatus and thereafter the dissolution profile fitting to different mathematical equations was carried out using least square fitting with a nonlinear computer program, Scientist for Windows, version 2.1.

Results: Covering both planar surfaces of drug-loaded middle layer was able to attain a more sustainable drug release than a simple matrix which composed the same amount of matrix component. Additionally, the near-zero order release could be obtained for the first system whereas the drug release from simple matrix tablet was diffusion-controlled. As the number or amount of coating layer, and amount of matrix component in middle layer were increased, the drug release was noticeably prolonged. Drug release from layered tablets was influenced by hydrodynamic force and incorporated diluents.

Conclusion: Effective near-zero order controlled release of hydrophilic drug was obtained from three-layered matrix tablets comprising HPMC as main matrix component. Modulation of drug release could be conducted by addition or increasing amount of water soluble substances into the matrix component of three-layered tablets.

Key words: drug release, comparison, simple layered-matrix, layered-matrix, hydroxypropyl methylcellulose

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Introduction

Hydroxypropyl methylcellulose (HPMC) is non-ionic aqueous-soluble cellulose ether derivative for a use in controlled-release dosage forms. Owing to high swellability and high gelling strength formation this polymer effectively prolongs drug release which has a significant effect on the release kinetics of an incorporated drug. Profound discussion of the mathematical modeling for drug release from HPMC-based delivery devices has been reviewed and described.[1] Typically, surface area/volume is one of the key variables in controlling drug release and can be employed to modulate drug release from tablet.[2] Design parameters such as the geometry or the amount and hydrophilicity of incorporated diluents should be considered as the important aspect when developing the effective controlled-release systems. Suitable geometric design of matrix systems has been employed to modulate drug release behavior. One of useful techniques is based on the fabrication of matrix into three-layer tablets. Select polymeric matter used in this system plays an important role in the modulation of drug release. The barriers made of HPMC seem more efficient

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in reducing drug delivery than poly(ethylene oxide) (PEO) barriers, and their efficiency in drug release modulation depended on the viscosity generated from polymer.[3] Layering with polymeric matrix containing chitosan and xanthan gum could prolong the drug release in HCl buffer pH 1.2 and shift the release pattern approach to zero order.[4] In addition, increasing the amount of this matrix component in coating layer or in core tablet could apparently prolong the drug release.

Several variables, such as the presence of diluents and compression force could modify the drug release from the simple monolithic matrices.[5,6] The varying loading dose of diltiazem HCl in three-layer tablets (prepared using polyethylene oxide combined with HPMC K4M) did not affect the drug release behavior.[7] However, an increase in stirring rate during dissolution of those systems enhanced the drug release rate with the linearity of release profiles remained unaltered.

Gastrointestinal drug absorption from developed dosage forms is reflected by *in vitro* dissolution rate. Agitation intensity, hydrodynamic force and hydrodynamic condition could influence the drug dissolution rate in dissolution medium during dissolution test or during drug distribution in gastrointestinal tract. As the agitation intensity of the paddle or the basket increased, the percent drug dissolved from tablets and mass transfer coefficient were increased, but the film thickness was diminished.[8] Most previous investigations have been concentrated on effect of the type of polymer and drug or compression force used, with scant attention given to test the effect of amount of coating barrier or middle layer, and the adjustment of matrix hydrophilicity on release characteristic of three-layer tablets.

The purpose of this study is to investigate the effect of the amount of coating barrier or middle layer on the drug release from layered matrix tablets comprising HPMC K15M and phytowax as the main matrix component. Effect of an addition of hydrophilic substances into the system was also studied. Propranolol HCl was used as the model drug in this study.

Materials and Methods

Materials

Hydroxypropyl methylcellulose (HPMC) type K15M, lot No. PH26012N31 (Dow Chemical, USA) was used as received. Propranolol hydrochloride (Batch No. 941002) was purchased from China National Chemical Imp. & Exp., Shanghai, China. Magnesium stearate (Lot No. MAF 07, P. C. Drug Center Co.) was passed through sieve No. 80 mesh before use. Phytowax (Phytowax® Olive 14L 48, hydrogenated myristyl esters of olive oil), purchased from Sophim, Parc de la Cassine, France), Avicel PH 101 (Lot no. 2784, Asahi Chemical Industry, Japan), polyethylene glycol 4000 (PC Drug, Thailand), sodium bicarbonate (AF310196, Asia Pacific Specialty Chemicals Ltd., NSW, Australia) were passed through sieve No. 60 before use and sodium chloride (Lot k20420804, Merk, E Merck, Darmstadt, Germany) was used as received. All other reagents were of analytical grade.

Preparation of Matrix Tablets

The single layer 200-mg tablets containing propranolol HCl were prepared by direct compression. The concentration of drug was kept constantly at 80 mg/tablet. To make the powder mixture, 40% w/w drug, 23 %w/w phytowax and 35 %w/w HPMC were mixed with 2% w/w magnesium stearate for 10 minutes using mortar and pestle. Then the blended powder of 200 mg was compressed into a tablet at a compression force of 1.5 tons using 12 mm round, flat and plain punches using a hydraulic press (Carver Press, WI). The combined two- or three-layered tablets containing 35% w/w HPMC were also prepared with the composition formula as shown in Table 1 using the method previously mentioned. For layered tablets, there was a barrier layer on upper or lower part of core tablet. Layered matrix tablets were prepared by adding the preweighed amount of the powder mixture without drug (containing 2% magnesium stearate) in the die cavity and the

preweighed amount of the powder mixture with drug was placed over the first layer compressed with a 1.5-tons force using a hydraulic press to obtain the two-layer tablet. The dwell time after target pressure achieved was 10 sec. To prepare the three-layer tablet, the preweighed amount of the powder mixture without drug was placed over the well spread second layer and was compressed with a 1.5-tons force. The three-layer tablets with different amount of barrier (100, 150 and 200-mg for each side of barrier) were prepared using the formulation containing 35 %w/w HPMC (Table 2). For the formula, the number before the letter "L" in the first term of formula represents the number of layer, and the first and third number in the second term multiply with 100 represents the amount (mg) of each barrier layer and the second number in the second term multiply with 100 represents the amount (mg) of core tablet. Layered tablets containing 10 or 20%w/w different additives (PEG 4000, Avicel, sodium chloride and sodium bicarbonate) were also prepared.

Table 1 Percent composition of different single layer formulations containing lactose.

Substances	Formulation (mg)		
	Core tablet (1L 2)	Combined 2-layered tablet (2L combined)	Combined 3-layered tablet (3L combined)
Propranolol HCl	80	80	80
HPMC	70	140	210
Phytowax	46	172	298
Magnesium stearate	4	8	12
Total	*200*	*400*	*600*

Table 2 Composition of barrier.

Substance	Formulations (mg)
HPMC	70
Phytowax	126
Magnesium stearate	4
Total	200

The Evaluation of Matrix Tablets

The hardness of tablets was determined using a hardness tester (Pharmatest, USA). The tablet thickness was measured using a thickness tester (Teclock, Japan). The friability was determined as the percent weight loss from 20 tablets. Twenty tablets were weighed and rotated for 100 revolutions in 4 min in a friabilator (Yieheng Engineering, Bangkok, Thailand). A test of drug release was undertaken using a dissolution apparatus (type 1) (Prolabo, France) with the basket method at 100 rpm. A 900-mL distilled water equilibrated at 37 ^{o}C was used as dissolution fluid. Samples were collected at specific time intervals and assayed by a UV-Vis spectrophotometer (Perkin-Elmer, Germany) at a wavelength of 320 nm. The operation was continued until completing 26 hours. During the drug release studies, the tablets were observed for physical integrity. To study the effect of hydrodynamic force on drug release, the tablets were tested for dissolution at different basket rotational speeds of 50, 100 and 150 rpm.

Dissolution Profile Fitting

Least square fitting the experimental dissolution data (cumulative drug release > 10% and up to 80%) to the mathematical equations (power law and zero order) was carried out using a nonlinear computer program, Scientist for Windows version 2.1 (MicroMath Scientific Software, Salt Lake City, UT, USA). The coefficient of determination (r^2) was used to indicate the degree of curve fitting. Goodness-of-fit was also evaluated using the Model Selection Criterion (MSC)[9], given below.

$$MSC = \ln\left\{\frac{\sum_{i=1}^{n} w_i\left(Y_{obs_i} - \overline{Y}_{obs}\right)^2}{\sum_{i=1}^{n} w_i\left(Y_{obs_i} - Y_{cal_i}\right)^2}\right\} - \frac{2p}{n}$$

Where Y_{obsi} and Y_{cali} are observed and calculated values of the *i*-th point, respectively, and w_i is the weight that applies to the *i*-th point, n is number of points and *p* is number of parameters.

Results and Discussion

The Physical Properties of Matrix Tablets

The data on weight, thickness, friability and hardness of single, combined and layered tablets are presented in Table 3. The hardness of tablet tended to increase as the amount of matrix or barrier was increased. The rather high % friability (>1%) was found in case of 1L 2 and layered-tablets of NaCl10% 2L 2/2 and $NaHCO_3$10% 3L 2/2/2. Replacement of phytowax with other additives except sodium chloride enhanced the tablet hardness. Since this production was one step manufacturing process, the commercial products can be scaled up by the high speed three-layer tableting machines.

Table 3 Physical properties of prepared tablets.

Formulation	Weight ± S.D. (mg) (n=20)	Thickness ± S.D. (mm) (n=10)	Friability (%)	Hardness ± S.D. (Kp) (n=10)
1L 2	200.6 ± 6.2	1.45 ± 0.02	1.91	2.54 ± 0.70
2L 2/2	401.0 ± 6.5	3.19 ± 0.04	0.74	3.70 ± 0.21
3L 1/2/1	403.3 ± 8.5	3.18 ± 0.20	0.62	3.21 ± 0.31
3L 2/2/2	602.7 ± 10.1	4.38 ± 0.09	0.58	4.43 ± 0.19
2L combined	402.4 ± 8.7	3.05 ± 0.06	0.51	1.12 ± 0.18
3L combined	608.5 ± 6.9	4.54 ± 0.07	0.73	2.24 ± 0.33
NaCl10% 2L 2/2	395.7 ± 8.3	2.90 ± 0.07	1.11	1.86 ± 0.41
NaCl 10% 3L 2/2/2	603.6 ± 6.3	4.23 ± 0.09	1.44	3.44 ± 0.16
NaCl 20% 3L 2/2/2	599.9 ± 6.9	3.96 ± 0.07	0.72	2.89 ± 0.48
PEG4000 10% 3L 1/2/1	396.3 ± 6.4	2.70 ± 0.11	0.53	7.71 ± 0.46
Avicel 10% 3L 1/2/1	403.8 ± 5.4	2.85 ± 0.05	0.41	5.34 ± 0.47
$NaHCO_3$10% 3L 2/2/2	598.8 ± 9.6	4.55 ± 0.12	1.14	4.91 ± 0.30
$NaHCO_3$ 20% 3L 2/2/2	598.0 ± 8.3	4.19 ± 0.04	0.81	5.25 ± 0.30

In Vitro Drug Release

Apparent drug release prolongation could be attained for three-layered tablets (Fig. 1). By comparison with the same amount of component, the drug release retardation was more evident from three-layered tablets than that of combined tablets. Barriers without drug covering onto core tablet effectively modulated the diffusion of dissolved drug molecule into dissolution medium since they could diminish the drug deposited on tablet surface to expose the dissolution medium. Rather initial fast drug release was noticeable for the single layer or combined tablets because of rapid drug dissolution and outward diffusion from tablet surface. This evidence indicated that the high water soluble drug could rapidly diffuse from this compressed matrix. Drug release of 100% over 4 hr was ostensible for single-layered tablet. Slow release of combined tablet was due to the formation of a thick gel structure after extensive swelling of HPMC that delayed drug release from the tablet matrix. Combined three-layered tablet showed greater retardation of drug release than combined two-layered tablet since higher amount matrix component promoted the longer distance for water penetration into tablet mass to dissolve the drug particles and for dissolved drug molecules inside matrix to diffuse outward into dissolution medium. Drug release rate from three-layer tablet was obviously less than that of two-layer tablet and single-layered tablet, respectively. High gelling formation with the sticky property of HPMC promoted the good adhesion between layers during immersion of the layered tablets in a dissolution medium. Both covering barriers played importance role on retardation of drug release, since this layer diminished the contact area of core matrix to the dissolution medium. Therefore one of the benefits of using the three-layer tablet was to reduce dose dumping for high

solubility drug substances. Additionally, this system could change the drug release behavior of typical simple matrix which would be subsequently analyzed.

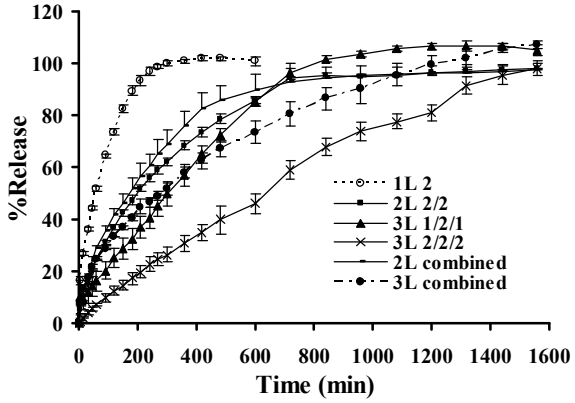

Figure 1 Dissolution profiles of propranolol HCl from single-layered, two-layered, three-layered and combined tablets containing HPMC and phytowax in distilled water. Each point represents the mean ± S.D., n=3.

Increasing amount of barrier apparently retarded the drug release as shown in Fig. 1. Drug release from the middle layer could be modified by the delayed diffusion from the two coated surfaces as a result of simple diffusion. From one planar drug release study, apparent lag time was observed for drug release of three-layer tablets and tended to prolong as the amount of barrier was increased.[4] The result suggested that the barrier layer plays a significant role in modifying the lag time and the drug release. Increasing matrix quantity of barrier resulted in a substantial retardation of drug release. Therefore, the apparent release rate was determined by the summation of release rates from the lateral surface of middle layer and from two covering barriers, which would vary, depending on the formulation variables of the barrier layer including thickness and composition.

Typically, agitation intensity or hydrodynamic force could influence drug release from dosage forms because of the alteration of drug diffusion rate. Effect of hydrodynamic force on drug release from prepared tablets was carried on using different rotational basket speeds during dissolution test. Increasing the basket rotational speed increased the drug dissolution from combined tablet and three-layer tablet as presented in Fig. 2. However, the drug release from three-layered tablet at 100 rpm was slightly slower than at 50 rpm. Therefore, the hydrodynamic force could affect the drug release of layered tablets.

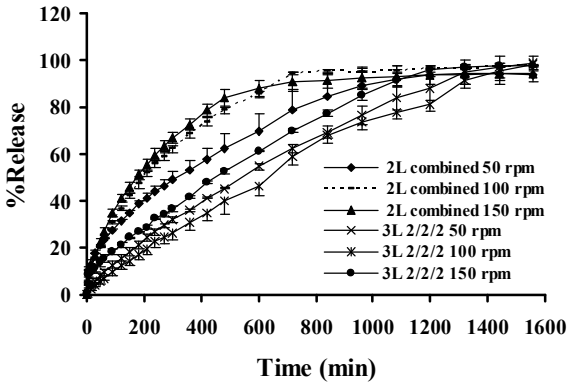

Figure 2 Effect of rotational speed on dissolution of propranolol HCl from combined tablet and three-layered tablets containing HPMC and phytowax in distilled water. Each point represents the mean ± S.D., n=3.

Phytowax is the hydrophobic material which is hydrogenated myristyl esters of olive oil. Utilizing this material as matrix component decreased the hydrophilicity of the matrix tablet. Incorporating some additives influenced the drug release as presented in Fig. 3. Water soluble additives including PEG4000 and sodium chloride apparently enhanced drug release. These two substances, by their water soluble and hydrophilic nature, facilitated HPMC gel formation and the time taken for the dissolution medium to permeate to the core was shorter as the amount of this soluble substance was increased. Moreover, soluble substance acted as a channeling agent, by rapidly dissolving and easily diffusing outward, therefore allowed a decrease in tortuosity and/or an increase in the matrix porosity.[10-12] The drug release from three-layered tablet containing sodium chloride was slower than that of two-layered

tablet. An addition or increasing amount of sodium bicarbonate noticeably retarded the drug release from three-layered tablets. Some research work indicated that the release rate of metoprolol tartrate was rather constant from polyethylene oxide containing electrolytes such as sodium bicarbonate since it changed the gel strength or there was the interaction of drug molecule with this substance.[13] Electrolytes such as adipic acid and sodium deoxycholate in polyethylene oxide matrix could capture the water molecules from polymer and promoted the gel strength.[14] Incorporation of sodium bicarbonate in the polymeric matrix (based on polyethylene oxide and HPMC) salted out the macromolecules and increased gel strength and gel viscosity has been reported.[15] Therefore, the outward drug diffusion was controlled by an inwardly progressing water penetration and higher viscous gel structure from HPMC matrix. Sodium chloride was able to diminish the polymer hydration[16,17] but due to its high water solubility it could enhance drug release. Similar result was also found for additions of PEG4000 and Avicel as shown in Fig. 3.

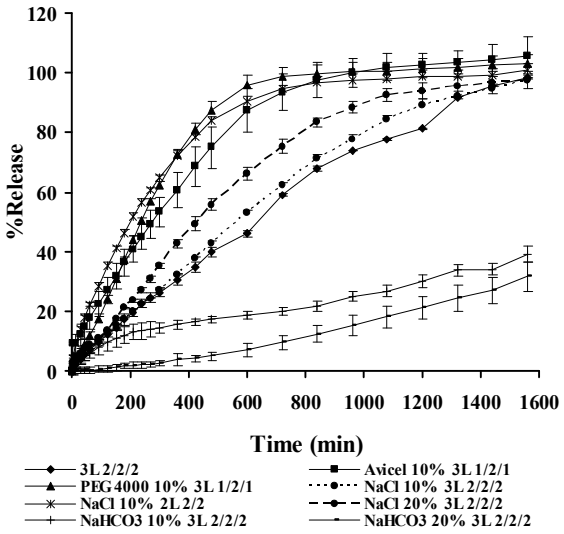

Figure 3 Effect of additives on dissolution of propranolol HCl from combined tablet and three-layered tablets containing HPMC and phytowax in distilled water. Each point represents the mean ± S.D., n=3.

However, Avicel increased drug release by enhancing tablet disintegration and promoting tablet erosion. Such similar effect of Avicel has been reported on drug release from acetaminophen bi-layered matrix tablet.[18]. The observed differences in the dissolution properties of the tablets were due to the differences in the solubility, swellability and density of the filler excipients. Therefore, the adjustment for type and amount of matrix component of the layered tablets exhibited as important factors affecting the modulating efficacy of the drug release.

Dissolution Profile Fitting

Large value of the coefficient of determination (r^2) or model selection criteria (MSC) indicated a superiority of the dissolution profile fitting to mathematical equations. Comparison of goodness of fitting drug dissolution profiles to power law and zero order equations is presented in Table 4A. Additional fitting to first order and Higuchi's was performed for drug release from combined tablet. Fitting experimental drug dissolution profiles to the power law equation provided high r^2 (0.9955 to 0.9997) and MSC (5.00 to 7.82) indicating a superiority of this model. Estimate parameters from curve fitting to power law and zero order equations are shown in Table 4B. Kinetics of drug release from the developed matrices was analyzed using the power law expression. This equation (an empirical equation) gained popularity for analysis of release data.[19] The n value from power law is the diffusional exponent which characterizes the transport mechanism of the drug. The transport mechanisms are classified based on the value that n assumes. For a cylinder, the drug transport mechanism is by Fickian diffusion when n = 0.45. If 0.45 < n < 0.89, it indicates anomalous (non-Fickian) transport. For values of n = 0.89, case II or zero order release kinetics is indicated. Case II relates to polymer relaxation, while non-Fickian release is described by two mechanisms; the coupling of drug diffusion and polymer relaxation.[19,21] The n values from the fitting of most drug dissolution profiles of combined, single-layered and two-layered tablets were

close to 0.45, indicating the nearly Higuchi's release. Prominent better fit to Higuchi's equation was observed for drug release from combined tablets as shown in Table 4A. Therefore, the drug release from these systems was the diffusion control. Similar result was reported for drug release from simple starch-borate-urea matrix tablet.[22] Near zero order release was evident for drug release from three-layered tablets since large r^2 and MSC values were obtained and the n value was close to 0.84. These results suggested that the developed three-layer tablets showed near zero-order or Case II release. The values of the kinetic constant (k) were in accordance with the values of n, the diffusion exponent, with k having lower values when the transport mechanism was Case II and higher values for systems that the drug release obeyed the Fickian diffusion kinetic. Alteration of these estimated parameters as mentioned above was previously mentioned.[20,21] Compression with polymeric layer on both sides of middle tablet could prolong and modify drug release to achieve a constant release rate.

Table 4 Comparison of degree of goodness-of-fit from curve fitting of drug dissolution to different release models (A) and estimate parameters (B) from curve fitting of drug dissolution to power law expression.

(4A)

Tablet	Power law		First order		Higuchi's		Zero order	
	r^2	MSC	r^2	MSC	r^2	MSC	r^2	MSC
1L 2	0.9995	6.65					0.9698	3.00
2L combined	0.9997	7.75	0.9973	5.60	0.9989	6.45	0.9731	3.31
3L combined	0.9990	6.58	0.9963	5.36	0.9990	6.62	0.9619	3.02
2L 2/2 50rpm	0.9985	6.12					0.9985	6.12
2L 2/2 100rpm	0.9990	6.55	0.9981	6.01	0.9966	5.41	0.9551	2.84
2L 2/2 150rpm	0.9991	6.60					0.9548	2.81
3L 1/2/1 50rpm	0.9997	7.82					0.9940	4.86
3L 1/2/1 100rpm	0.9955	5.00	0.9843	3.89	0.9404	2.55	0.9939	4.83
3L 1/2/1 150rpm	0.9994	7.04					0.9946	5.00

(4B)

Tablet	K ± S.D. *10-3	n ± S.D.
1L 2	55.43 ± 6.14	0.5377 ± 0.0212
2L combined	31.07 ± 1.26	0.5435 ± 0.0100
3L combined	28.14 ± 1.81	0.5108 ± 0.0104
2L 2/2 50rpm	23.39 ± 1.98	0.5299 ± 0.0132
2L 2/2 100rpm	30.93 ± 1.75	0.5275 ± 0.0096
2L 2/2 150rpm	35.75 ± 1.99	0.5148 ± 0.0096
3L 1/2/1 50rpm	4.65 ± 0.37	0.7447 ± 0.0114
3L 1/2/1 100rpm	3.84 ± 0.42	0.7818 ± 0.0154
3L 1/2/1 150rpm	2.10 ± 0.95	0.8520 ± 0.0625

Typically, the initial rapid drug release of deposited drug on matrix surface and the decreasing release rate at late state were exhibited for diffusion-controlled release of simple matrix. The layering on both planar surfaces of three-layered tablet with drug-free polymeric matrix by compression could diminish the initial rapid release and also delayed the medium penetration and hydration of middle layer. Therefore, the initial drug release was only from cylindrical side surface of tablet. Dissolved drug molecules gradually delayed diffusion through both covering barriers as a result of increasing polymer hydration/dissolution over time. External

hydrated barriers would disappear gradually with time and diffusional path-length was subsequently decreased promoting drug release at late state. Therefore the counterbalance was occurred as described above during dissolution test and the zero-order release could be achieved for three-layered matrix systems.[7] Type and amount of covering barrier, therefore, affected directly the drug release rate of three-layered system. Fig. 4 shows photoimages of 3L 1/2/1 before and after dissolution at different time intervals. The gel was formed around the tablet after dissolution and the dimension of tablet was increased with time. However, the tablet dimension was decreased after dissolution for 26 hrs. High gel forming efficiency of HPMC could maintain the cylindrical shape during dissolution and there was no tablet disintegration in the late stage of dissolution. Although the drug diffused outward but with its high hydrophilicity this also enhanced the water penetration and promoted the polymer hydration with viscous texture therefore the apparent erosion of middle layer was not found

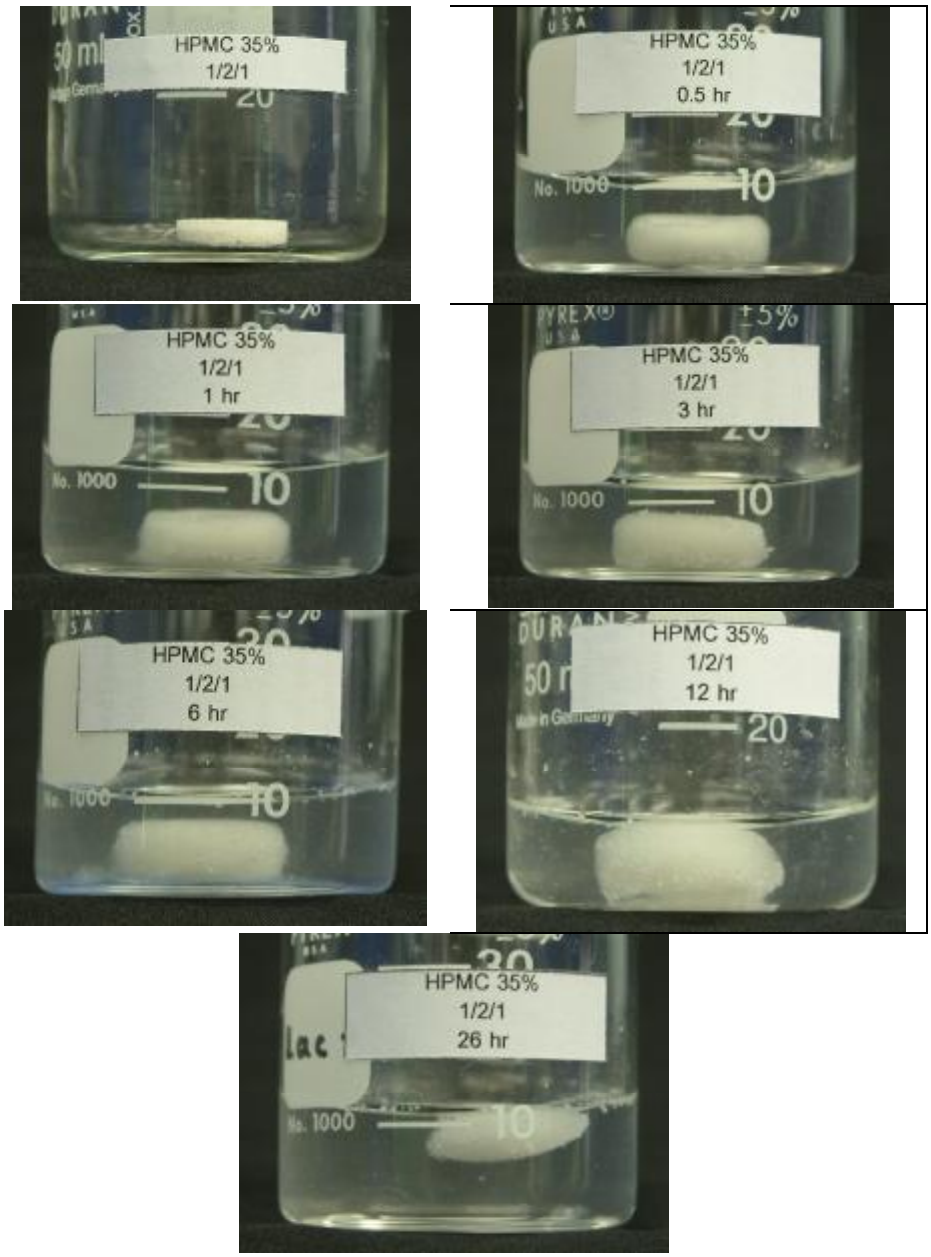

Figure 4 Appearance of three-layered tablets (3L 1/2/1) after dissolution test in distilled water at different time intervals.

Replacement the amount of phytowax with some additives did not significantly shift the release kinetic since the n value signified the Case II release (Table 5). Lower k value from curve fitting to power law equation was found for three-layer tablet containing different additives but not for two-layered tablet. Addition of PEG4000 and sodium chloride or increasing amount of sodium chloride increased the drug release rate as shown from the result of curve fitting to zero order equation. Dramatic low release rate was found for drug release from tablet containing sodium bicarbonate. In addition, the n value higher than 1 for these tablets indicated the super case II which was found for upward or sigmoid profile drug releases.[23,24]

Table 5 Comparison of degree of goodness-of-fit and estimate parameters from curve fitting of drug dissolution from three-layered tablets containing different additives to different release models.

Tablet	Power law				Zero order		
	r^2	MSC	K ± S.D. $*10^{-3}$	n ± S.D.	r^2	MSC	K ± S.D. $*10^{-3}$
NaCl10% 2L 2/2	0.9989	6.40	16.65 ± 1.53	0.6411 ± 0.0155	0.9789	3.58	1.73 ± 0.00
NaCl10% 3L 2/2/2	0.9984	6.01	1.42 ± 0.40	0.9196 ± 0.0393	0.9978	5.87	0.80 ± 0.00
NaCl20% 3L 2/2/2	0.9971	5.39	4.11 ± 1.07	0.8026 ± 0.0391	0.9924	4.57	1.07 ± 0.03
PEG4000 10% 3L 1/2/1	0.9980	5.66	6.21 ± 1.50	0.8186 ± 0.0393	0.9993	4.80	1.93 ± 0.05
Avicel 10% 3L 1/2/1	0.9998	8.38	5.34 ± 0.30	0.7966 ± 0.0088	0.9956	5.17	1.42 ± 0.03
$NaHCO_3$10% 3L 2/2/2	0.8225	1.27	0.23± 0.3.99	0.9342 ± 2.026	0.9850	3.99	0.18 ± 0.00
$NaHCO_3$ 20% 3L 2/2/2	0.9979	5.43	0.00 ± 0.00	1.4607 ± 0.2726	0.9903	4.13	0.24 ± 0.01

Conclusion

At the same amount of matrix component, the design of the system into three-layered tablet which covered both planar surfaces with polymeric barrier more effectively prolonged drug release than simple matrix system. Interestingly, the near-zero order drug release was also achieved for three-layered tablets whereas the diffusion control mechanism was evident for drug release from simple matrix tablet. Increasing the amount of matrix component in covering barriers could apparently prolong the drug release. The drug release from two-layered or three-layer tablet was influenced by hydrodynamic force. Drug release from three-layered tablet was noticeably increased after replacement of phytowax with hydrophilic excipients. Since this production was one step manufacturing process, the commercial products can be scaled up by the high speed three-layer tableting machines.

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