Design and Evaluation of 1- and 3-Layer Matrices of Verapamil Hydrochloride for Sustaining Its Release

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ABSTRACT

The present study was performed to design oral controlled delivery systems for the water-soluble drug, verapamil hydrochloride, using natural and semisynthetic polymers as carriers in the forms of 1- and 3-layer matrix tablets. Verapamil hydrochloride 1-layer matrix tablets containing hydroxypropylmethylcellulose, tragacanth, and acacia either alone or mixed were prepared by direct compression technique. 3-layer matrix tablets were prepared by compressing the polymers as release retardant layers on both sides of the core containing the drug. The prepared tablets were subjected to in vitro drug release studies. Tragacanth when used as the carrier in the formulation of 1- and 3-layer matrices produced satisfactory release prolongation either alone or in combination with the other 2 polymers. On the other hand, acacia did not show enough prolonging efficiency in 1- and 3-layer matrix tablets. The results also showed that the location of the polymers in the 3-layer tablets has a pronounced effect on the drug release. Kinetic analysis of drug release from matrices exhibiting sustained release indicated that release was predominantly attributable to the contribution made by Fickian diffusion, while the erosion/relaxation mechanisms had a minor role in the release.

KEYWORDS: verapamil, sustained release, 1- and 3-layer matrix, tragacanth, acacia, HPMC.

INTRODUCTION

Developing oral controlled release tablets for highly water-soluble drugs with controlled release rate has always been a challenge to the pharmaceutical technologist. Most of these highly water-soluble drugs, if not formulated properly, may readily release the drug at faster rate than desired and are likely to produce toxic concentrations, on oral administration. Hence, it is a challenging task to formulate a suitable tablet dosage form for prolonged delivery of highly water-soluble drugs.

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Diffusion-controlled polymeric matrix devices have been widely used as drug delivery systems mainly owing to their low manufacturing cost.[1] Generally, in conventional diffusion-controlled matrix systems, in which the drug to be released is uniformly dispersed throughout the polymer, the release inherently follows first-order diffusion with an initially high release rate followed by a rapidly declining rate. To overcome this undesired behavior, various matrix geometries have been employed over the last 2 decades resulting in almost constant release of the drug with time.[2,3] A proper technique relies on the use of multi-layer matrix devices where the matrix core, containing the drug or any other active solute, is covered by one or more modulating layers that act as rate-controlling barriers.[4-6]

In this research, verapamil hydrochloride was chosen as model drug. Because of high solubility, short half-life, and therapeutic use of verapamil in chronic diseases, it was considered an ideal drug candidate for the design of oral controlled release dosage forms.

Different polymers have been employed for sustaining the drug delivery. In the present investigation, we have used tragacanth, acacia, and hydroxypropylmethylcellulose (HPMC) as release retardant carriers in the design of 1- and 3-layer matrix tablets.

Tragacanth is a naturally occurring dried gum obtained from *Astragalus gummifer* Labillardiere and other species of Astragalus grown in western Asia. The gum consists of a mixture of water-insoluble and water-soluble polysaccharides. Bassorin, which constitutes 60% to 70% of the gum, is the main water-insoluble portion, while the remainder of the gum consists of the water-soluble material, tragacanthin. Tragacanth gum is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations. It is used in creams, gels, and emulsions at various concentrations according to the application of the formulation and the grade of gum used.

Acacia is a complex, loose aggregate of sugars and hemicelluloses with a molecular weight of ~240 000 to 580 000. Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges, and as tablet binder.[7]

The purpose of the present study was to evaluate the potency of tragacanth and acacia to sustain the release of a water-soluble drug, verapamil hydrochloride, and the effect of the geometry and design of the 3-layer tablet on drug release.

Materials and Methods

Verapamil hydrochloride was obtained from Sobhan Pharmaceuticals (Rasht, Iran). Tragacanth, acacia, and magnesium stearate were purchased from Merck (Darmstadt, Germany). HPMC K15M was kindly provided as gift by Colorcon (Dartford Kent, UK).

Preparation of Verapamil Hydrochloride 1-Layer Matrix Tablets

One-layer matrix tablets containing 120 mg of verapamil hydrochloride were prepared by direct compression method. The composition of each tablet is shown in Table 1. All the components of each formulation except magnesium stearate were thoroughly mixed in a bottle using tumbling method for a period of 15 minutes. Magnesium stearate was added to the formulations at the end of mixing period and mixed for 2 more minutes. Tablets were directly compressed on a hydraulic press (Riken, Japan) using flat-faced 8-mm-diameter punch and die set at a pressure of 4.5 to 6.9 MPa to have a crushing strength of 5 to 6 Strong Cobb (equivalent to 37-41.2 N according to technical brochure of the hardness tester, Erweka, Heusenstamm, Germany). Tablets were kept in tightly closed containers for further studies.

Preparation of 3-layer Matrix Tablets

3-layer matrix tablets were prepared by compressing different amounts of polymers on both sides of tablet containing 120 mg verapamil hydrochloride by means of the same compressor used to compress the 1-layer tablets. A preweighed amount of polymer as the bottom layer was taken and placed in die cavity and slightly compressed for uniform spreading. The upper punch was lifted and powders of the matrix core formulation were placed over the bottom layer in the die cavity and again slightly compressed for uniform spreading. The remaining volume of the die cavity was filled with the preweighed amount of polymer as the top layer and compressed with a 6.9 MPa pressure to obtain 3-layer matrix tablets. The top and bottom layers of the 3-layer matrix tablet acted as release-retardant polymer layers. Table 2 indicates the composition and polymer locations of different layers.

Table 1. Composition of 1-Layer Matrix Tablets*

Code	Verapamil HCl (mg)	Tragacanth (mg)	Acacia (mg)	HPMC K15M (mg)
F1	120	-	80	-
F2	120	-	120	-
F3	120	-	160	-
F4	120	-	200	-
F9	120	-	80	80
F10	120	160	-	-
F11	120	200	-	-
F12	120	240	-	-
F13	120	280	-	-
F24	120	80	-	80

*HPMC indicates hydroxypropylmethylcellulose. All of the formulations have 1% wt/wt magnesium stearate.

Drug Release Studies

Drug release studies were performed using *United States Pharmacopeia* (*USP*) 26 apparatus I (basket), (Erweka, Heusenstamm, Germany). The dissolution medium was 900 mL of distilled water maintained at 37°C ± 0.5°C. The basket rotation speed was kept at 100 rpm. In all experiments, an aliquot of 5 mL sample was withdrawn at predetermined time intervals and replaced with an equal volume of the fresh medium to maintain the total volume constant. The samples were assayed using UV spectrophotometer at 278.4 nm. Cumulative percentage of drug released from the tablets was calculated and plotted as a function of time. Each formulation was tested in triplicate and a mean of 3 measurements was reported.

Analysis of Drug Release Data

For the evaluation and comparison of the release profiles, dissolution efficiency (DE) as a model independent criterion was used.[8] DE can be calculated according to Equation 1:

$$DE_T = \frac{\int_0^T y dt}{y_{100} T \times 100}, \quad (1)$$

in which the integral represents the area under the dissolution curve between times zero and T; y is the percentage drug released up to time t and y_{100} indicates 100% release. T in our study was 480 minutes.

In order to establish the kinetic mechanisms of drug release from matrices exhibiting sustained release, the data were fitted to a 2-term power law (Equation 2)[9] using the SPSS package Version 11.5.0 (SPSS Inc, Chicago, IL):

$$Q = \frac{M_t}{M_\infty} = K_1 t^m + K_2 t^{2m}, \quad (2)$$

Table 2. Composition of 3-Layer Matrix Tablets*

	Core (mg)				Each Layer (mg)		
Code	Verapamil	Tragacanth	Acacia	HPMC K15M	Tragacanth	Acacia	HPMC K15M
F5	120	-	80	-	-	40	-
F6	120	-	40	-	-	60	-
F7	120	-	80	-	-	-	40
F8	120	-	-	80	-	40	-
F14	120	160	-	-	40	-	-
F15	120	140	-	-	50	-	-
F16	120	100	-	-	70	-	-
F17	120	80	-	-	80	-	-
F18	120	40	-	-	100	-	-
F19	120	-	-	-	120	-	-
F20	120	-	-	80	60	-	-
F21	120	-	-	40	80	-	-
F22	120	80	-	-	-	-	40
F23	120	-	-	80	40	-	-
F25	120	-	100	-	70	-	-
F26	120	100	-	-	-	70	-

* HPMC indicates hydroxypropylmethylcellulose. All of the formulations have 1% wt/wt magnesium stearate.

where Q denotes the fraction of drug released in time t, ($Q \leq 60\%$); M_t and $M\infty$ are the amounts of drug released at time t and the overall amount released, respectively; K_1 and K_2 represent kinetic constants associated with diffusional and relaxational release, respectively; and m is the purely Fickian diffusion exponent. Depending on the aspect ratio of the device, m varies between 0.42 and 0.5. The diffusional/erosional contribution can be obtained by comparison of the diffusional and relaxational constants obtained from Equation 2.

Results and Discussion

Drug Release Studies on Acacia 1- and 3-Layer Tablets

Figure 1 shows the release profiles of the drug from 1-layer matrices prepared of acacia. It can be seen from the figure that the release of the drug from the matrices was fast and the increase in the amount of acacia from 80 to 200 mg did not affect the release rate significantly.

Acacia 3-layer tablets have been designed to evaluate the effect of geometry and design of tablet on drug release profile. Formulation F3 with 160 mg acacia has been selected and 2 different 3-layer formulations have been prepared (F5, F6). The release of drug from 3-layer tablets of acacia is shown in Figure 2. Similar to 1-layer matrices, the release was rapid. This result can be because the acacia chains are short, and their hydration is too fast, together with low viscosity and rapid diffusion of drug molecule from loose acacia gel,[10,11] which results in rapid disintegration and dissolution. Also the drug release from these matrices does not appear to be geometry and design dependent. An important point that should be considered is that in none of the acacia-containing formulations has verapamil release reached 100%. This phenomenon can be related to the interaction between the cationic verapamil and anionic acacia.[12] Because of fast release rates of drug from 1- and 3-layer formulations of acacia, Equations 1 and 2 were not applied to their corresponding data.

Drug Release Studies on 1- and 3-layer Tablets Containing Acacia-HPMC

Acacia did not show enough prolonging effect when it was incorporated as the only polymer into the tablets, either in 1- or 3-layer forms. Therefore, HPMC K15M was incorporated into the formulations to evaluate the effect of the tablet design and the location of polymer in either core or outer layers in 3-layer tablets. Figure 3 shows the drug release from 1- and 3-layer formulations containing acacia

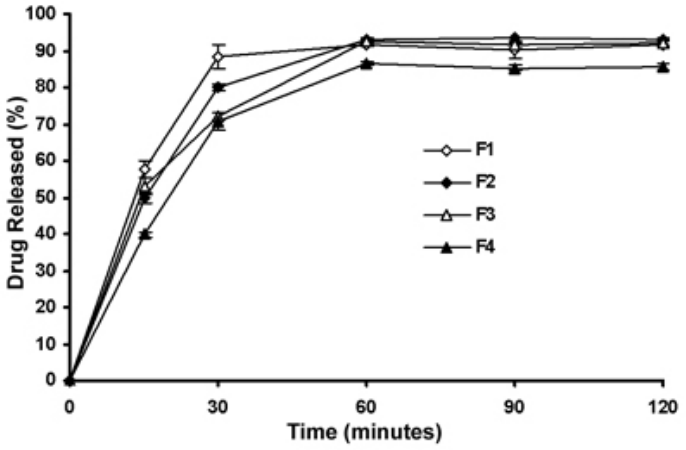

Figure 1. The release of drug from 1-layer tablets of acacia.

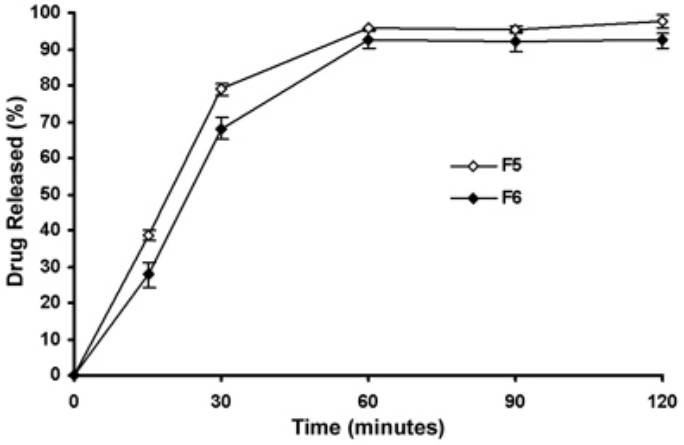

Figure 2. The release of drug from 3-layer tablets of acacia.

and HPMC (F7-F9). Verapamil has been released with a faster rate from F7, in which acacia was located in the core of the matrix. This phenomenon can be related to the above mentioned properties of acacia. Acacia in comparison with HPMC forms a gel with lower viscosity and higher permeability. Drug can easily diffuse out of the gel formed by acacia, but the HPMC gel has greater rigidity; then there is a barrier for penetration of dissolution medium into HPMC gel and diffusion of drug out of that. It can be seen from the results of formulations F7-F9 that when a polymer with higher capability to form a more viscous gel either is placed in the core of the 3-layer tablet (F8) or incorporated in 1-layer (F9), the drug release slows down.

Table 3 shows the values of DE_{480} for different formulations. According to the concept of DE, formulations with more sustained action show smaller DE values. DE_{480} value for formulation F7 is 79.51, whereas for formulation F8 it is 47.6, which shows the effect of incorporation of HPMC in the core of the tablet.

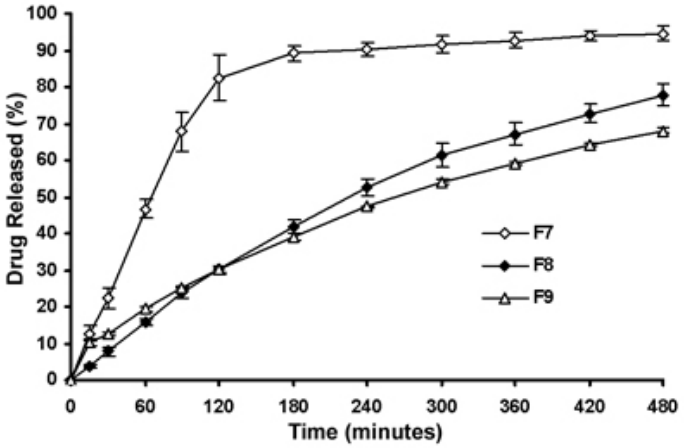

Figure 3. The release of drug from 1- and 3-layer tablets containing acacia and HPMC K15M.

Table 3. DE_{480} Values for Different Formulations*

Code	DE	Code	DE	Code	DE
F7	79.51	F14	48.21	F21	37.98
F8	47.6	F15	49.55	F22	43.76
F9	43.71	F16	53.25	F23	39.58
F10	63.01	F17	53.50	F24	44.57
F11	54.48	F18	54.49	F25	91.12
F12	53.92	F19	60.9	F26	78.61
F13	53.49	F20	33.65		

*DE indicates dissolution efficiency.

Drug Release Studies on 1- and 3-layer Tragacanth Tablets

Figure 4 shows the drug release from 1-layer tragacanth matrices containing different amounts of the gum (F10-F13). The higher the amount of the gum, the more efficient is prolongation. Formulation F10, which has less tragacanth content, shows a higher drug release rate (DE_{480} = 63.01) than formulations F11-F13 (DE_{480} = 54.48-53.49). However the release did not differ from the latter 3 despite having increased amounts of the gum contents. Similar to acacia, tragacanth, owing to its anionic nature, prevents 100% release of the cationic verapamil from the matrices.[13] Comparing the DE_{480} values of 1-layer tragacanth matrices with those of 1- and 3-layer acacia matrices indicates the superiority of the prolongation effect of tragacanth with respect to acacia. The prolongation efficiency of tragacanth was also demonstrated for chlorpheniramine tablets by other workers.[14,15]

The release profiles of 3-layer tragacanth matrices containing equal amounts of gum but with different geometry and design (F14-F19) are shown in Figure 5. The figure shows that when the drug alone was located in the core (F19), the fastest release (DE_{480} = 60.9) was achieved, accompanying the burst release during the early time. This result is because the drug is in direct contact with dissolution medium

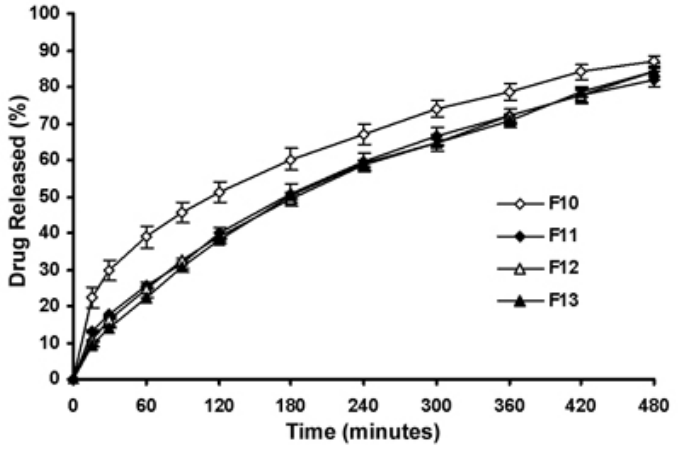

Figure 4. The release of drug from 1-layer tablets of tragacanth.

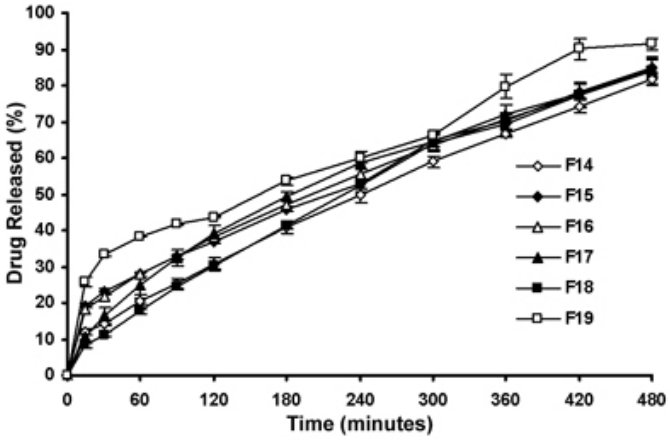

Figure 5. The release of drug from 3-layer tablets of tragacanth.

from the peripheral side of the tablet. The slowest release was seen with F14 and F15, where the gum content was maximum in the core (DE_{480} = 48.21, 49.55). This result is because of the highest polymer/drug ratio in the core of these formulations. However, the amount of drug released in 480 minutes from formulations was approximately the same. Therefore it can be concluded that the geometry and design of the tablet can mostly affect the rate of release not the overall amount of drug released in 8 hours.

Drug Release Studies on Tragacanth-HPMC 3-Layer Tablets

Figure 6 shows the release profiles of 3-layer matrices containing tragacanth in outer layers and HPMC in the core, but with different amounts. Formulation F20, which had a higher amount of HPMC in the core, showed slower drug release (DE_{480} = 33.65) as compared with F21 (DE_{480} = 37.98). These results indicate the efficiency of HPMC for prolonging the drug release. Increased amount of tragacanth in layers of formulation F21 did not compensate for the decreased amount of HPMC in core, compared with formulation F20.

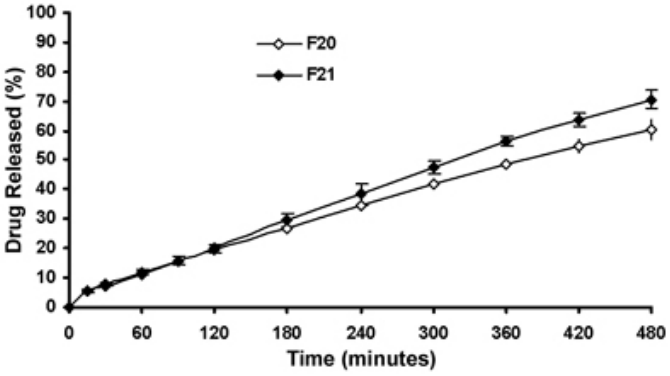

Figure 6. The release of drug from 3-layer tablets of tragacanth and HPMC K15M (total amount of polymer is 200 mg).

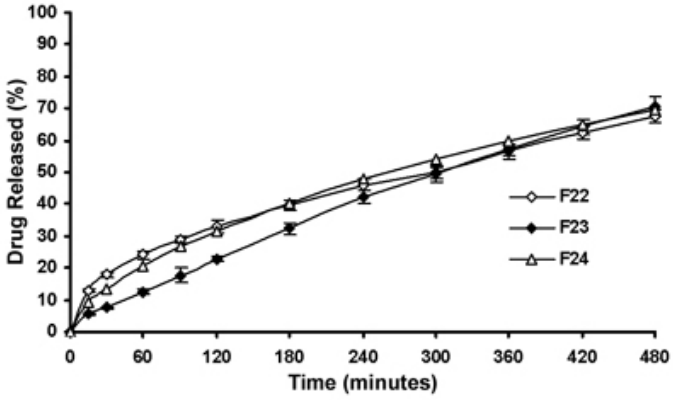

Figure 7. The release of drug from 3-layer tablets of tragacanth and HPMC K15M (total amount of polymer is 160 mg).

Figure 7 shows the release profiles of 3-layer matrices with outer layers of HPMC and the core consisting of tragacanth (F22), with outer layers of tragacanth and the core of HPMC (F23), and with a 1-layer matrix containing total amount of both polymers equal to the previous ones (F24). It can be seen that when a polymer with higher gel strength and viscosity is incorporated into the core (F23), the drug is released more slowly (DE_{480} = 39.58), while the corresponding DE_{480} values for F22 and F24 are 43.76 and 44.57, respectively.

In the first 4 hours, the drug has been released from F23 at a slower rate, but after this time there is no pronounced difference between the release profiles of drug from these 3 formulations (F21-F23). The total amount of drug released after 480 minutes is nearly the same for these formulations. It can be concluded that HPMC can greatly control the release of drug in the first hour when it is incorporated in the core of the 3-layer matrix tablet; this may advantageous in preventing the side effects of drug if such effects are induced by rapid drug release.

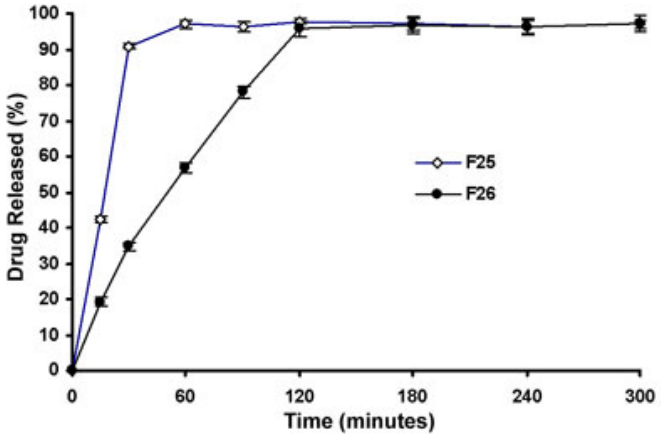

Figure 8. The drug release profiles from 3-layer matrices containing acacia in the core, tragacanth in the outer layers (F25), and tragacanth in the core and acacia in the outer layers (F26).

Table 4. The Results of Fitting Drug Release Data to Peppas-Sahlin Equation

Code	K_1	K_2	K_2/K_1	m	R^2
F10	6.7242	0.0000	0.0000	0.4250	0.9946
F11	3.0112	0.2744	0.0911	0.4250	0.9978
F12	2.6629	0.3034	0.1139	0.4250	0.9984
F13	1.8104	0.3946	0.2180	0.4250	0.9976
F14	2.1692	0.1410	0.0650	0.4626	0.9946
F15	5.0526	0.0000	0.0000	0.4250	0.9778
F16	4.7307	0.0524	0.0111	0.4250	0.9885
F17	2.6629	0.3034	0.1139	0.4250	0.9984
F18	1.3649	0.0748	0.0548	0.4354	0.9989
F19	6.1305	0.0000	0.0000	0.4250	0.8399
F20	0.7566	0.1384	0.1829	0.4720	0.9993
F21	0.6824	0.0398	0.0583	0.5774	0.9983
F22	3.9214	0.0529	0.0135	0.4250	0.9992
F23	0.4832	0.2552	0.5281	0.4495	0.9988
F24	2.5736	0.1965	0.0764	0.4250	0.9986

Drug Release Studies on Tragacanth-Acacia 3-Layer Tablets

Figure 8 shows the release curves of drug from 3-layer matrices with the outer layers of tragacanth and the core of acacia (F25), and acacia in the outer layers with the core of tragacanth (F26). As was predicted, since a polymer with the capability of producing a higher gel strength, tragacanth, was located in the core, (F26) exhibited a pronounced slower drug release (DE_{480} = 78.61) than F25, which contained acacia in the core (DE_{480} = 91.12).

Evaluation of the Release Kinetics

Drug release from swellable water-soluble polymer systems is typically described in terms of 2 simultaneously operating mechanisms. These are Fickian diffusion through the hydrated outer layers of the matrix and matrix relaxation/erosion.[16,17]

The contributions of these 2 mechanisms to the overall release are considered additive. A well-known empirical model that describes these phenomena is that of Peppas and Sahlin (Equation 2).[9] The model was applied to formulations F10-F24, which demonstrated sustained release properties. The results of the analysis are shown in Table 4. Considering the values for K_1, K_2, and K_2/K_1, it is clear that for these formulations, overall release is predominantly attributable to the contribution made by Fickian diffusion with a minimal contribution offered by matrix erosion/relaxation.[18,19] However, the extent of the Fickian diffusion contribution to the overall release is vastly different among the formulations. It is maximum in the case of F10 and minimum for F23. Moreover, the ratio of erosion constants to that of diffusion is also very different, indicating that the integrity of matrices during the release process was variable. The matrix with higher K_1 value retained its integrity for a longer time.

CONCLUSION

The results of our study show that the polymers possessing higher gelling ability (ie, tragacanth and HPMC) have the potential for sustaining and/or controlling the release of water soluble drug, verapamil hydrochloride, whereas a polymer with a weaker gel forming ability (ie, acacia) lacks such a potential. Also the geometry and design of the matrices has a pronounced effect on slowing the drug release during the first hours, though in most cases the total amount of drug release is not changed considerably. Kinetic analysis shows that the release is predominantly attributable to the contribution made by Fickian diffusion with a minimal contribution made by matrix erosion/relaxation.

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