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Study of Verapamil hydrochloride release from compressed hydrophilic Polyox-Wsr tablets

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Abstract

This study deals with Verapamil hydrochloride release from tablets based on high molecular weight poly(ethylene oxide) (PEO). The drug release proceeds as a controlled diffusion ($n = 0.44–0.47$), which rate is dependent on the molecular weight of PEO. Independent from it, under the conditions of the Half-change test, the drug release practically ceases after 4 h as a result of obtaining low soluble in the water base. The introduction of hydrophilic polymers with pH dependent solubility (Eudragit L, Eudispert hv and Carbopol 934) at concentrations of $10 \div 50\%$ with respect to PEO amount keeping constant the ratio drug: matrix insures relatively complete release both in alkali medium and under the conditions of the Half-change test. Meanwhile drug release kinetics also changes — the release of all models studied runs as a typical abnormal diffusion ($a = 0.66–0.87$), i.e. like a diffusion-relaxation controlled process. The decrease in drug concentration leads not only to retarded release of the drug sample but also to changes in the kinetics of the process. At lower drug concentrations on the matrix from a typical abnormal diffusion it turns into a relaxation controlled diffusion ($n_{10\%} = 1$).

Keywords: Verapamil hydrochloride; Hydrogels; Polyethylene oxide; Controlled drug release; Solute transport

1. Introduction

Nowadays polymers with their unique properties (harmlessness and availability) have been widely applied in the development of drug delivery systems. (Dittgen et al., 1997). Hydrophilic polymers like hydroxy propyl methyl cellulose (HPC), polyvinyl alcohol (PVA), as well as acrylacid derivatives, PHEMA (hydroxyethylmethyl acrylate) methyl methacrylate, vinyl acetate, ethylene oxide, etc., have been already used for preparation of oral drug release systems (Zhang et al., 1990). Recently, it has been established that noncrosslinked low molecular weight poly(ethylene oxide) (PEO) ($M_w = 0.6 \times 10^6$) insures constant release rate by means of forming a homogeneous gel of even thickness. When the drug is loaded onto model matrices, based on PEO of higher molecular weight (4×10^6 and higher), the release is controlled by the swelling of the polymer, not by its erosion. This leads to the

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inconstant rate of release, inducing by the diffusion of the drug through the swollen gel layer (Kim, 1995). Being harmless and stable makes PEO a suitable carrier for drug delivery systems. Its good compressibility allows the preparation of hydrogel matrices by direct compression.

This paper presents the study on the release of Verapamil hydrochloride. Which characterizing with pH dependent water solubility, loaded onto hydrogel matrices based on high molecular weight PEO. The aim of the investigation was to clarify the possibility of improving the drug release. The effect of PEO molecular weight and the concentration of the drug loaded onto the matrix, are major factors determining the drug release from hydrogels, they been investigated as well as the possibility for increasing the PEO matrix permeation, by addition of polymeric supplements, with a view to insure a uniform and complete drug release.

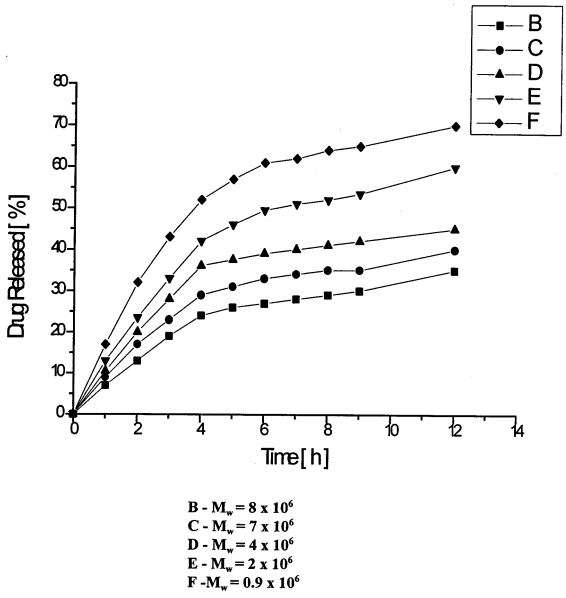

Fig. 1. Release of Verapamil hydrochloride from matrix tablets (PEO), with different molecular weights under conditions of the Half-change test.

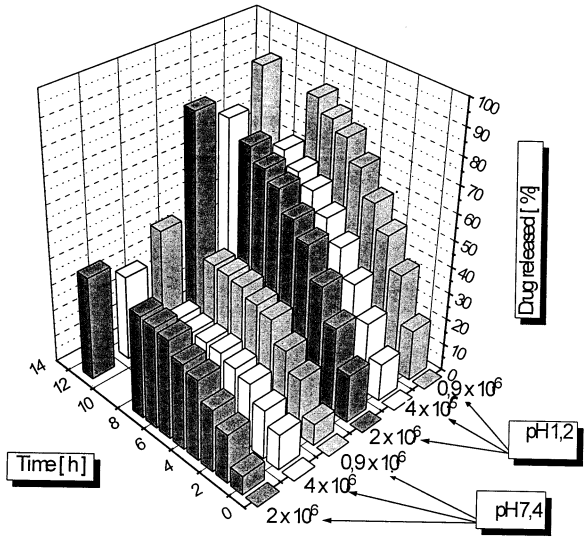

Fig. 2. Release of Verapamil hydrochloride from PEO matrix with different molecular weights in artificial gastric (pH 1.2) and intestinal (pH 7.4) juice.

2. Materials and methods

2.1. Materials

Polyox-Wsr NFs of average molecular weight from 0.9×10^6 to 8×10^6 were supplied by Union carbide corp., USA. Verapamil hydrochloride was purchased from Pharmachim, AG, Sofia, Bulgaria. Carbopol 934 was purchased from Hercules and Eudragit L and Eudispert hv were purchased from Rohm pharma G.m.b.H. Germany. The materials were used as received.

2.2. Preparation of tablets

The ingredients (PEO, drug, magnesium stearate and Eudragit L or Eudispert hv or Carbopol 934) were mixed and then tableted using a single punch tablet machine (Korch-EKO). A set of tablet punches with flat surfaces was used to prepare tablets with a 9-mm diameter. The breaking load of the resulting tablets was 90–110 N (Erweka TBH 30).

2.3. Testing of tablets

In vitro release study of the drug, from the different formulation tablets was carried out using method II (Paddle) of USP XXIII (Erweka DT

Table 1
Dependence of n and f from PEO's molecular weight

PEO's molecular weight models	Half-change test		pH 1.2	
	n[a]	f[b]	n	f
0.9×10^6	0.47	1.13	–	–
2×10^6	0.44	1.28	0.43	1.34
4×10^6	0.46	1.18	0.47	1.13
7×10^6	0.45	1.23	0.47	1.13
8×10^6	0.44	1.28	–	–

[a] n: an exponent in Peppas equation, which describing the kinetics.
[b] f: factor indicating the drug portion which was released by $\sqrt{t}$ kinetics.

8). At a stirring rate of 100 rpm (900 ml eluent) and a temperature of 37°C, under conditions of the Half-change test (Münzel, 1960) — artificial stomach juice (pH 1.2) and artificial intestinal juice (pH 7) according to USP XXIII. The amount of released drug was determined spectrophotometrically (Hewlett Packard 8452 A diode array spectrophotometer) at λ-280 nm.

The release kinetic data (up to 60% release) were analyzed by the following equation (Ritger and Peppas, 1987):

$$M_t/M_\infty = k \cdot t^n \quad (1)$$

where, M_t, M_∞, k, and n are the amount of drug released at time t, the total amount of drug in tablet, a constant, and the exponent for the release kinetics, respectively. According to the criteria for release kinetics from a swellable matrix (cylindrical shape), zero order and anomalous transport kinetics are represented by $0.89 < n < 1.0$ and $0.45 < n < 0.89$, respectively. A linear regression analysis (Origin 5.0) of the logarithmic form of Eq. (1) was carried out with $R^2 \geq 0.99$. A 95% confidence level is indicated in parenthesis beside the exponent.

The amount of drug (f_1), which was released by $\sqrt{t}$ kinetics, [whereas $(1-f_1)$ — describes part, which was released by zero order mechanism] was calculated by Eq. (2) (Möckel, 1990):

$$n = \left[\frac{7f_1 + 20}{7f_1 + 5}\right]^{0.5} - 1 \quad (2)$$

2.4. Scanning electron microscopy

Photomicrographs of the surface of tablets with Polyox, molecular weight 2×10^6 and supports of Eudragit L, Eudispert hv and Carbopol 934 were taken using a Jeol Scanning Microscope JSM-5300 at magnification, 200 × and 1000 ×, as well as a surface view at 1000 ×. Samples were sputter-coated with gold prior to microscopic examination

3. Investigations, results, and discussion

Matrix tablets were prepared from Polyox-Wsr of various molecular weights (0.9×10^6, 2×10^6, 4×10^6, 7×10^6, and 8×10^6 Da) by direct compression. The release of the model compound was

Table 2
Dependence of n and f from type and concentration of polymer supplements on the matrix

Sample (%)	pH 1.2		pH 7.4		
	n	f	n	f	
Eudragit L	10	0.83	0.19	0.87	0.14
	30	0.78	0.27	0.801	0.24
	50	0.77	0.29	0.77	0.29
Carbopol 934	10	0.8	0.24	0.86	0.16
	30	0.73	0.36	0.78	0.27
	50	0.73	0.36	0.75	0.32
Eudispert hv	10	0.67	0.49	0.74	0.34
	30	0.66	0.5	0.7	0.42
	50	0.66	0.5	0.71	0.39

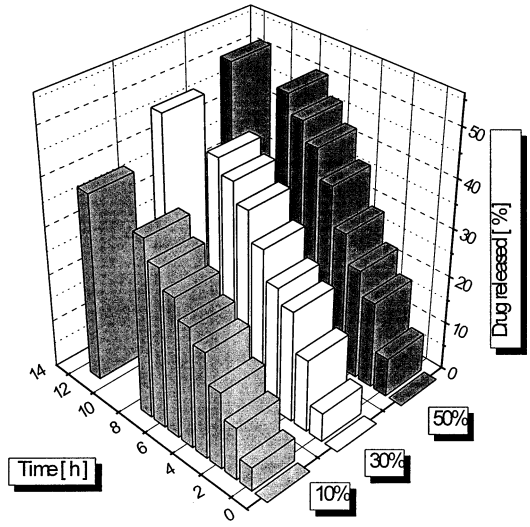

Fig. 3. Release from matrix of PEO with molecular weight 2×10^6 with addition of Carbopol 934 with different concentration in artificial intestinal juice (pH 7.4).

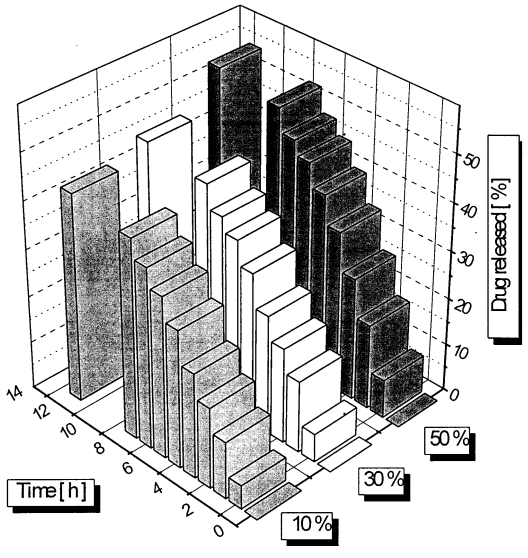

Fig. 4. Release from matrix of PEO with molecular weight 2×10^6 with addition of Eudragit L with different concentration in artificial intestinal juice (pH 7.4).

studied under the conditions of the Half-change test. Summary results from in vitro drug release experiments, are shown in Fig. 1. As seen the molecular weight of the polymer affects significantly the drug release — the higher the molecular weight, the smaller the amount of the drug released. While more than 50% of Verapamil hydrochloride loaded onto PEO of $M_w = 0.9 \times 10^6$ are released after 4 h, the released drug from the model compounds of $M_w = 8 \times 10^6$ is hardly 25%. There is a pronounced linear dependence between the amount of the drug released and the molecular weight of the polymer, e.g. after 4 h (Fig. 2). It proves that the molecular weight of the matrix determines the release rate of the model drug. Noteworthy is another fact: the release practically ceases after 4 h. The difference between the amounts of the drug released after 24 h is not greater than 3–6% regardless of the molecular weight of the polymer carrier. It is known that the permeation of the hydrogel PEO based matrices is not sensitive to pH of the medium (Kim, 1995). Then the only possible reason for the sudden interruption of the release of the model drug could be the change in its water solubility caused by the increased pH of the medium. Probably higher pH leads to separation of the low soluble in water base. Hence the concentration gradient is drastically decreased. This hypothesis was proved by the experiments performed in vitro in artificial gastric and intestinal media. As the experiments

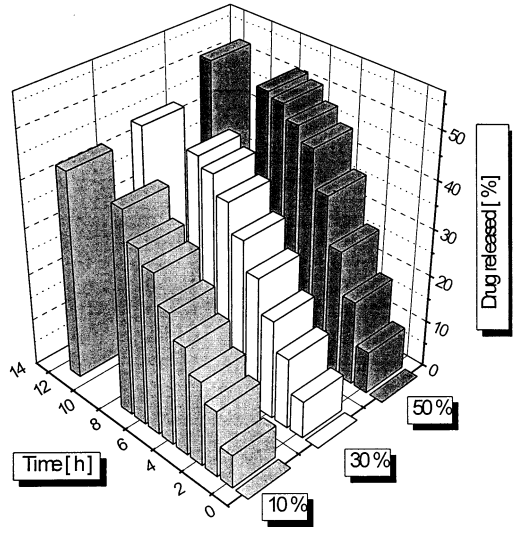

Fig. 5. Release from matrix of PEO with molecular weight 2×10^6 with addition of Eudispert hv with different concentration in artificial intestinal juice (pH 7.4).

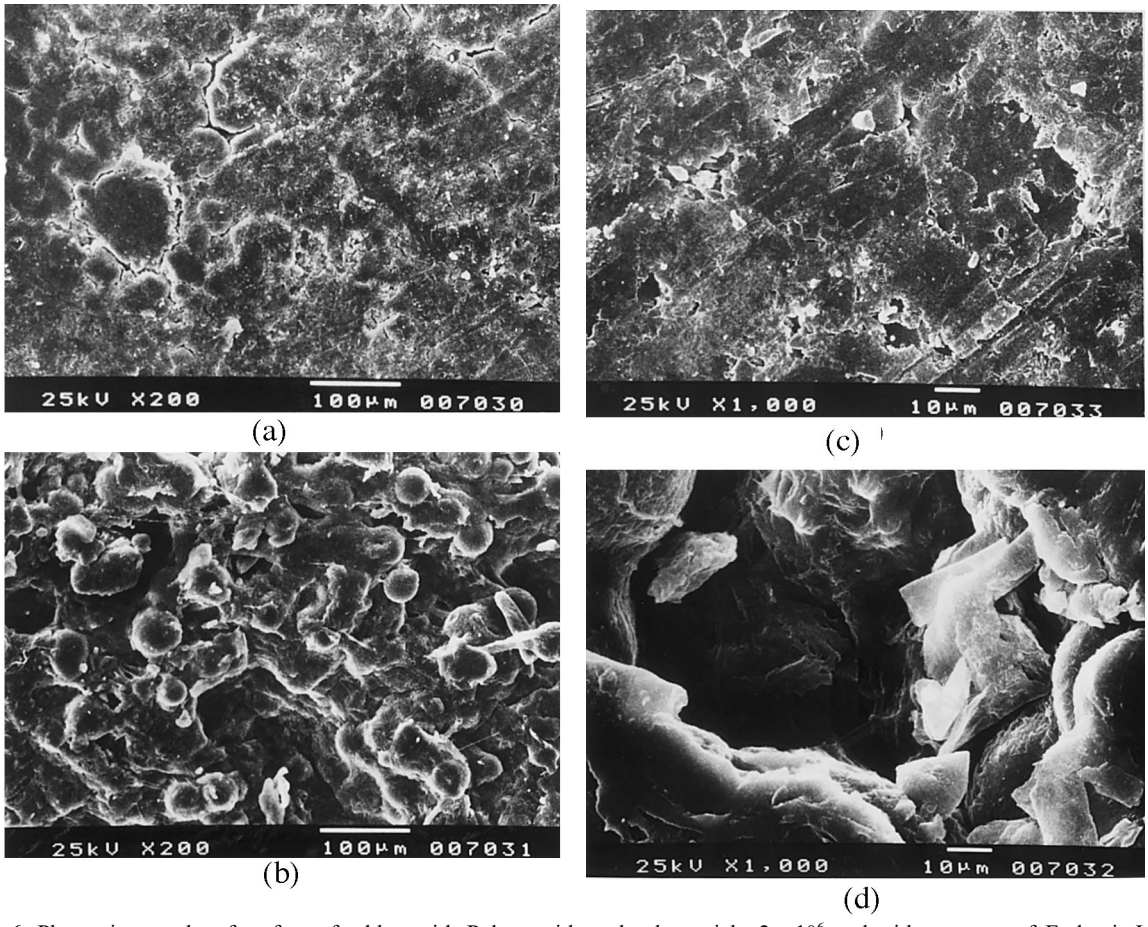

Fig. 6. Photomicrographs of surface of tablets with Polyox with molecular weight 2×10^6 and with supports of Eudragit L at magnification, 200 × and 1000 × . A, Polyox 2×10^6 at 200 × ; B, Polyox + 30% Eudragit L at 200 × ; C, Polyox 2×10^6 at 1000 × ; and D, Polyox + 30% Eudragit L at 1000 × .

carried out in a slightly alkali medium (pH 7.4), showed the release profiles of the three types of tablets are almost identical to those obtained from samples studied under the conditions of the Half-change test. The relatively faster release at the beginning is as a result of the fact that the greater part of the drug available in the matrix is in the form of salt. Later because of the much quicker diffusion of hydrogen cations (their size is smaller than that of Verapamil molecule) the drug is transformed into a base which release is hindered. Under the conditions of artificial gastric medium (pH 1.2) the release process runs uniformly till the moment when 70–90% of the drug is released. The gradual retardation of the release after 4–6 h results most likely from the decrease in the concentration gradient, which is typical of such systems. The diffusional exponent values (n) in the Peppas equation (Ritger and Peppas, 1987), shows that the release of all models studied under the Half-change test conditions proceeds as a diffusion controlled process ($n = 0.440 \div 0.47$; Table 1) (Kim et al., 1992). In acid (pH 1.2) and slightly alkali medium the release diffusional exponent (n) rises and varies in the range $0.610 \div 0.70$ which is characteristic of the abnormal diffusion, i.e. the release of the drug appears to be a diffusion-relaxation process. The amount of the

drug released at a rate close to zero order increases significantly and exceeds 50% in acid medium.

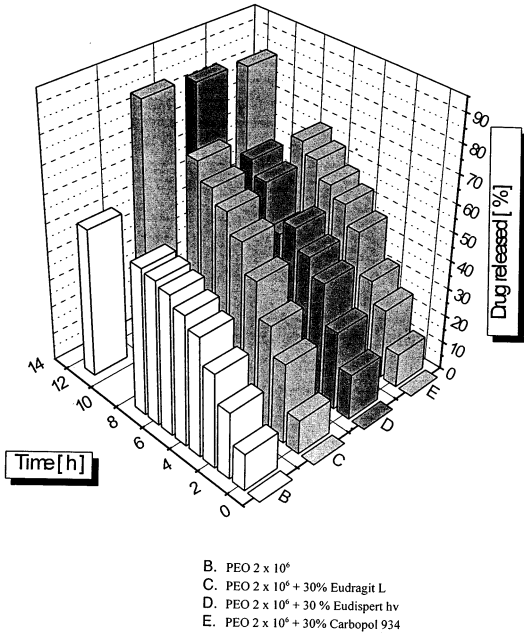

Fig. 7. Release from PEO matrix with molecular weight 2×10^6 under conditions of the Half-change test.

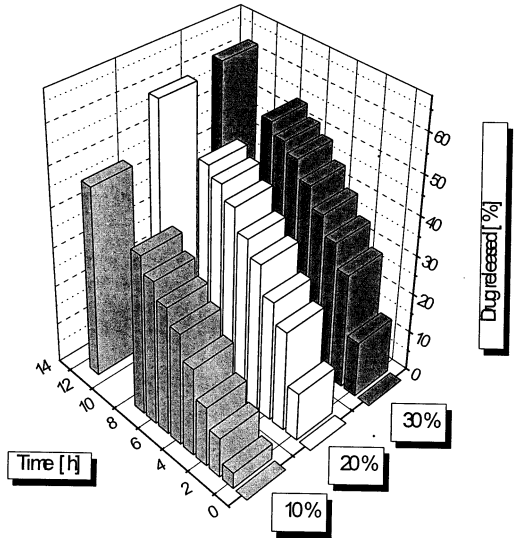

Fig. 8. Release from PEO matrix with molecular weight 2×10^6 including drug with different concentration.

The results show the necessity of improving the drug release with the goal of achieving uniformly and complete drug release. With membrane systems it is accomplished by introduction of weak organic acids capable of keeping optimal pH on the system (Thoma and Zimmer, 1989).

Our previous investigations have shown that it is not worth while for monolith systems as they are rapidly released (Tsankov et al., 1992). In our opinion a better route is to add a support compound where solubility is sensitive to pH changes in the medium and is able to affect the permeation of the system.

In order to accelerate the drug release in neutral and slightly alkali media, polymers with pH dependent solubility were introduced into the matrix. The solubility of these polymers at pH over $5 \div 6$, increased drastically. As the supporters Eudragit L, Eudispert hv, Carbopol 934 at concentrations of 10, 30 and 50% with respect to PEO amount keeping constant the ratio drug, matrix, were used. The results from the experiments run under the Half-change test conditions indicate that the release of all three model tablets is more complete and uniform, than that of the tablets which matrix is only PEO ($M_w = 2 \times 10^6$) based.

In the first case over 80% of the drug loaded are released within 12 h. There is another advantage, the mechanism of the release process changes. It takes place as an abnormal diffusion ($n = 0.71 \div 0.87$, Table 2), but with the addition of any of the three supports the amount of the drug released drastically increases (surmounting 80%) at a rate close to zero order (Fig. 7). While the results obtained from the investigations on PEO ($M_w = 2 \times 10^6$) based models without addition of a hydrophilic polymer, appears according to Higuchi equation ($r = 0.99$). Those from the experiments run with addition of soluble polymer supports, appears according to the zero order ($r = 0.98 \div 0.97$); (Lindner et al., 1996).

Figs. 3–5 present a notable acceleration of the release process in artificial intestine medium. According to us, a principal reason for the changes on the drug release, when the polymeric supplements included on the matrix appear, the changes in the matrix permeation with the changes of pH of the eluent under conditions of the Half-change

test. On one hand at this pH the permeation of the supports is higher, and on the other hand with their separation from the matrix the effective interface is augmented on account of their slow dissolving in the dissolution fluid. The electron micrographs showed significant breaks and cracks, which leads to an increase in free effective surface (Fig. 6). As a result, conditions for the faster diffusion of the low soluble base were created. The changes occurring in acid medium are not significant negligible. The polymeric supporters including in matrix, are not soluble and have a affect on its permeation. In the case of introducing hydrophilic polymer supporters, their concentration is a determining factor for the release rate of Verapamil hydrochloride. Generally, increasing the concentration of the polymer supporters in the matrix, one can increase the drug release rate, within certain limits. In all cases drug release appears as an abnormal diffusion.

The concentration gradient is known to be a factor in determining the diffusion rate. Therefore the influence of the drug concentration on the matrix, was studied. Reduction of the amount of Verapamil loaded onto the system slows the release rate sharply (Fig. 8). However an increase in the drug concentration to the same extent, does not have a pronounced effect on the releasing process. Probably, above a certain concentration the drug approximates its 'equilibrium' solubility in the hydrogel. Further release rate is insignificantly affected by an increase in its concentration. Moreover, the decrease in the drug concentration influences not only the release rate. A reduction in the concentration to 10% leads to a drastic change in the nature of the drug release process. From a typical abnormal diffusion ($n_{20\%} = 0.65$; $n_{30\%} = 0.62$) it is transformed into a relaxation controlled diffusion ($n_{10\%} = 1 \gg 0.89$) during which, the drug release proceeds as a reaction of almost zero order.

The experiments carried out allow the conclusion that the main factors determining the drug release rate are the molecular weight of the polymer in the matrix and the drug concentration (to a lesser extent). In addition, the problems with the sensitiveness of Verapamil hydrochloride solubility to higher pH of the medium can be solved via supporting the matrix by polymers with pH dependent solubility (Eudragit L, Eudispert hv, Carbopol 934).

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