RESEARCH ARTICLE

Influence of electrolytes on the controlled release of verapamil hydrochloride from HPMC K15M matrix tablets

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Verapamil hydrochloride was formulated as oral-controlled release matrix tablets using hydrophilic polymer such as hydroxypropyl methylcellulose K_{15} M (HPMC 15 M) along with electrolytes. In this work a new attempt was made for *in situ* interactions between drug and electrolytes were devised to control the release of highly water soluble drugs from oral hydrophilic monolithic systems. Electrolytes such as aluminum hydroxide and sodium carbonate were used at different concentrations in various formulations, while drug and polymer concentrations were maintained constantly at 1:2 ratios in all the formulations. These electrolytes were used to monitor matrix swelling and gel properties. Electrolytes at higher concentrations exhibited greater inhibition in drug release from the matrix and low concentrations were accounted for controlled release of the drug. The results indicated that the drug released at a controlled rate were due to differential swelling rate and matrix stiffening, and provides a uniform gel layer. These findings indicated that the swelling and gel formation in the presence of ionizable species within the hydrophilic matrices provide an attractive alternative for controlled drug delivery from a simple monolithic system. Accelerated stability studies were carried out as per ICH guidelines for some selected formulations, which indicated that these formulations were stable at accelerated storage conditions.

Key words: *Verapamil hydrochloride, HPMC K15M, alumnium hydrochloride, sodium carbonate*

INTRODUCTION

Recently numerous hydrophilic polymers have been investigated and are currently used in the design of complex controlled release systems.[1-3] The polymers that are most widely used in the design of controlled release of a drug include nonionic hydroxypropyl methylcellulose K_{15} M (HPMC K_{15} M) and polyethylene oxides (PEO'S). The major challenge in the development of new controlled release devices is to achieve optimal drug concentration at the site of action. To achieve optimal drug concentration at the site of action, liberation of the drug from the device must be controlled as accurately as possible.[4] The dissolution in a monolithic matrix for linear drug release over a prolonged period of time is not easily achievable and still remains a challenge. The limitation of a hydrophilic polymer may be circumvented through modification of physical and chemical infrastructure of the polymeric gel system by using electrolytes.

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In the present investigation, studies were under taken for design and development of oral controlled release drug delivery system of verapamil HCL tablets by matrix diffusion technique. Verapamil HCL is a calcium channel blocker, used in the treatment of variant angina, hypertension and supra ventricular tachyarrhythmia.[5] It is freely soluble in distilled water, chloroform and methanol. It has elimination half life of 3-5hrs. Based on these physicochemical and biopharmaceutical properties, verapamil HCL was selected as drug candidate for developing controlled release matrix tablet formulations.[6]

In the present work, a reliable process has been established for inducing *in situ* reactions between pharmaceutically acceptable electrolytes and drug which influences the intragel swelling dynamics and relative physical integrity of the swollen matrix

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structure. Furthermore, that may produce heterogeneous domains with in the swollen gel boundary.

In the past, alkaline compounds (or) buffers have been included in solid oral formulations for several acidic drugs that undergo dissolution rate limited absorption.[7] The same principle of addition of buffers, osmotically active agents, surfactants (or) combinations thereof has also been utilized to control the swelling of hydrophilic polymers with different coating and inclusion techniques.[8] However more specific strategy has been employed to apply the same principle to design a simple directly compressible, monolithic controlled release system. In general the application of buffers and ionizable compounds in dosage form design has essentially been limited to the minimization of localized GIT adverse effects and the solubility dependency of poorly soluble compounds.[9,10]

The aim of this work was to provide and expand on a means to design, formulate and develop a novel oral monolithic, controlled release tablet dosage form of a drug that may be tailored to provide quasi steady state drug release over an extended period of time.[11] The rationale behind the mechanism and dynamics of electrolytes induced matrix stiffening and structural changes to the gel is the basis of controlled drug release has also been elucidated.

MATERIALS AND METHODS

Materials

Verapamil Hcl (Gift sample from Pellets Pharma Limited, Hyderabad), Hydroxy propyl Methyl Cellulose K_{15} M (HPMC K_{15}M) (Gift sample from MS Colorcon Asia limited, Mumbai), Microcrystalline Cellulose (MCC) (Gift sample from Pellets Pharma limited, Hyderabad), Aluminum Hydroxide, Sodium Carbonate and Talc were of analytical grades procured commercially.

Preparation of matrix tablets

The controlled release monolithic tablet formulation consisted of a polymer, drug and electrolyte. The ratio of drug and polymer was always maintained at 1:1 levels, while the electrolyte content was varied. The materials are individually passed through sieve no: 60 and blended for 15mins in a double cone blender. The powder mixture was lubricated with 1% talc and compressed into tablets using a 10 station rotary punching machine (Minipress). To minimize processing variables, all batches of tablets were compressed under identical conditions.

Evaluation of physical parameters

The physical parameters such as hardness, friability, weight uniformity and drug content were evaluated for the prepared matrix tablets as per the standards of official compendium.[12]

Determination of swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium 0.1 N Hcl at 37±0.5°C. After 0.5, one, two, three, four, five, six, seven and eight hours. Each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance. The experiment was performed in triplicate for each time point the swelling index was calculated by the following formula.[13]

$$\text{Swelling Index} = \frac{\text{Wet weight of tablet - Dry weight of tablet}}{\text{Dry weight of tablet}}$$

Drug release studies

Dissolution studies on all the formulation were performed in a calibrated 8 station dissolution apparatus equipped with paddles employing 900 ml of 0.1N Hcl as a medium.[14] The paddles were operated to rotate at 100 rpm and the temperature was maintained at 37±1°C± throughout the experiment. Samples were withdrawn at regular intervals up to 12 hours and each time samples were replaced with equal volume of fresh medium to maintain the volume of dissolution medium constant throughout the experiment. Drug content of the samples were determined by ELICO Double beam UV spectrophotometer at 278 nm, after suitable dilution. To analyze the mechanism of drug release studies from the obtained data, various calculation were analyzed based on the equation, first order constant, Higuchi constant, and the koresmeyer peppas constant respectively. The following are the equations used:

$$\ln Q = k.t \quad (1)$$

$$Q = k.t \quad (2)$$

$$M_t/M_\infty = kt^n \quad (3)$$

where Q in the equation[1] is cumulative percent drug remained, while **Q** in the equation[2] is cumulative amount of drug released, M_t/M_∞ is the fraction of drug released, **t** is the release time and **k** is the constant incorporating the structural and geometrical characteristics of the release device. If the value of n=0.45 indicates Case I (Fickian) diffusion or square root of time kinetics, 0.45<n<0.89 indicates anomalous (non Fickian, drug diffusion in the hydrated matrix and the polymer relaxation) diffusion, n=0.89 indicates case II transport and n>0.89 indicates super case II transport (18). Linear regression analysis was performed for all these equations and regression coefficients (**r**) are determined.

RESULTS AND DISCUSSION

The present study was under taken for design and evaluation

Table 1: Composition of various controlled release matrix tablets of verapamil Hcl

S. no	Ingredients	Formulations											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Verapamil Hcl	120	120	120	120	120	120	120	120	120	120	120	120
2	HPMC K 15M	60	120	120	120	120	120	120	120	120	120	120	120
3	Sodium Carbonate	–	–	10	20	30	40	50	–	–	–	–	–
4	Aluminum Hydroxide	–	–	–	–	–	–	–	10	20	30	40	50
5	MCC	118	38	47	37	27	17	07	47	37	27	17	07
6	Talc	2	2	3	3	3	3	3	3	3	3	3	3
7	Total weight	300	300	300	300	300	300	300	300	300	300	300	300

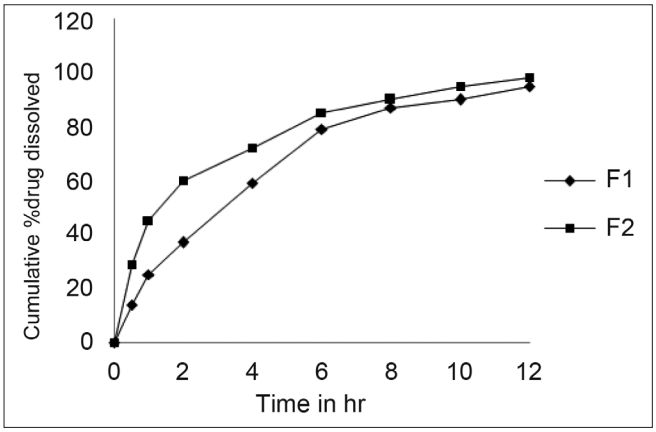

Figure 1: Drug release profiles of various controlled release formulations of verapamil hydrochloride with microcrystalline cellulose

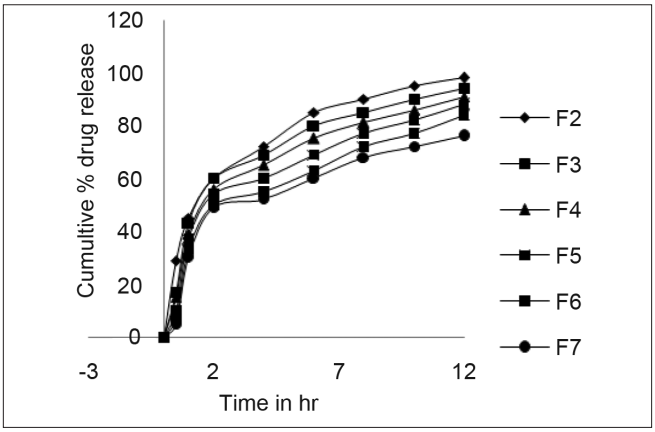

Figure 2: Drug release profiles of various controlled release formulations of verapamil hydrochloride with aluminium hydroxide

of the controlled release matrix tablets of verapamil hydrochloride with HPMC $K_{15}M$, by employing electrolytes as drug release retardants.

All batches of tablets were produced under similar conditions to avoid processing variables. The compositions of various matrix tablets were given in Table 1. These tablets were preliminarily evaluated for various physical parameters such as weight uniformity, hardness, friability and drug content.

All batches of tablets with different electrolyte composition were within the weight range of 290 -310 mg. Hardness of the matrix tablet formulations were constant for all batches maintained at 5 - 6 kg/cm^2. Friability loss for the formulations was negligible and was less than 0.2% for all the batches. Drug content was uniform in all the batches of matrix tablet formulations. All the matrix tablets were prepared under identical conditions and were found to be stable. The results of physical parameters evaluated for various matrix tablets were given in Table 2.

From the *in vitro* dissolution studies, showed greater inhibition of release rate of verapamil from the tablet matrix. The dissolution profiles of various matrix tablets were shown in Figures 1, 2 and 3 and then their corresponding kinetic data was shown in Table 3. By the incorporation of electrolyte into hydrophilic monolithic tablet matrices, it was possible to reduce the release rate of drug over an extended period

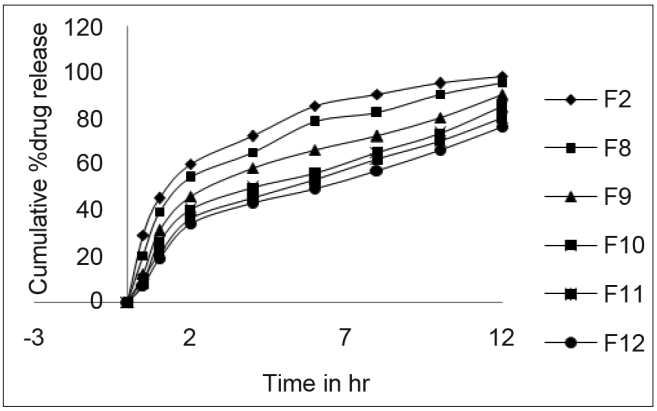

Figure 3: Drug release profiles of various controlled release formulations of verapamil hydrochloride with sodium carbonates

of time. The inclusion of electrolytes within a swollen matrix for controlling the release rate of verapamil may lead to the formation of free base of verapamil and fundamental structural changes in gel boundary, thus inducing the textual variations in the swollen matrix. It appears that electrolyte induced buffer threshold within the matrix place an essential role in effective interaction with drug and textural changes. Further it may be due to higher pKa values of electrolytes, which can display higher buffer threshold for maintaining suitable pH inside the matrix. Electrolytes such as aluminum hydroxide and sodium carbonate with pH values greater than 7.0 might exert a better and desired control on drug release from matrix tablet. The following mechanism may prevail

Table 2: Physical parameters of verapamil HCl matrix tablets

Formulations	Weight uniformity (mg) *n* = 20	Hardness (kg/m^2) *n* = 6	Friability (%) *n*= 20	Drug content (mg/tab) *n* = 6
F1	298±3.0	6.5±0.3	0.20	120±0.5
F2	299±3.0	5.9±0.5	0.21	119±0.4
F3	299±4.0	5.5±0.2	0.25	118±0.5
F4	298±3.0	5.7±0.4	0.20	119±0.7
F5	298±3.0	6.1±0.4	0.23	119±0.5
F6	300±2.0	6.4±0.2	0.25	120±0.4
F7	298±3.0	6.6±0.3	0.22	119±0.5
F8	299±2.0	7.0±0.4	0.23	119±0.4
F9	299±3.0	6.4±0.5	0.21	120±0.4
F10	300±2.0	6.1±0.2	0.25	119±0.5
F11	300±2.0	6.4±0.5	0.22	119±0.4
F12	298±3.0	6.6±0.4	0.24	120±0.5

Table 3: Kinetic Parameters of verapamil Hcl matrix tablets

S. no	Formulations	First Order (hr^{-1})	*r*-value	Higuchi Constant (mg$^{1/2}$)	*r*-value	Peppas Constant (*n*)	*r*-value
1	F1	0.347	0.994	80.09	0.984	0.154	0.981
2	F2	0.135	0.995	41.36	0.964	0.177	0.977
3	F3	0.186	0.993	41.37	0.974	0.300	0.968
4	F4	0.162	0.977	49.34	0.991	0.233	0.992
5	F5	0.218	0.902	49.89	0.996	0.324	0.980
6	F6	0.132	0.967	43.75	0.963	0.474	0.965
7	F7	0.069	0.954	65.62	0.967	0.525	0.977
8	F8	0.135	0.981	66.18	0.985	0.416	0.991
9	F9	0.107	0.964	65.78	0.986	0.546	0.968
10	F10	0.085	0.971	58.33	0.978	0.659	0.951
11	F11	0.180	0.948	8S0.21	0.964	0.216	0.991
12	F12	0.323	0.992	49.64	0.983	0.874	0.936

Table 4: Swelling characteristics of various matrix tablet formulations

Formulations	Swelling index (%) at various time intervals (hr)		
	2	6	12
F1	31.2	73.4	
F2	26.2	53.3	89.7
F3	22.4	52.1	88.6
F4	20.3	51.8	86.9
F5	18.9	49.9	76.2
F6	16.6	47.8	72.3
F7	11.3	47.2	66.7
F8	20.7	51.8	86.4
F9	18.2	50.7	82.8
F10	16.3	48.9	78.3
F11	12.1	48.2	72.1
F12	9.8	47.1	69.8

during the period of drug release from the swollen intragel structure. As the dissolution medium enters the periphery of the tablet, there is a rapid electrolyte water interaction with significant chemical reaction through electrolyte solubilization and subsequent events that may lead to both initial suppression and later enhancement of polymer swelling. During this infiltration process, the electrolyte present in the gel boundary could have been converted to chloride form (for example sodium carbonate and sodium chloride) due to which the hydrochloride form of Verapamil hydrochloride lead to the formation of free base of Verapamil. The formation of free base might cause matrix stiffening. The passive and actively formed electrolytes within the gel matrix would compete for water leading to dehydration of polymer molecules, thus leading to suppression of initial swelling which was seen up to 2 to 3 hours with formulations containing high concentration of electrolytes. After 3 hour the water attracted by electrolytes into the polymer matrix could result in solubilizing the drug molecules which would diffuse by penetration of water leading to enhancement of swelling. The swelling index characteristics of various matrix tablets were given in Table 4. From these alterations and mechanisms of intragel changes, it appears possibility to inhibit drug dissolution rate. This inhibition in dissolution rate appears to be a time- dependent phenomenon. Since, as more water enters the gel matrix layer -by- layer, the electrolytes and their by products are diluted and any drug base may revert to its hydrochloride form, which is subsequently released.[15]

CONCLUSION

This work has provided a novel and a simple approach to formulate an oral, swellable monolithic controlled release

drug delivery system designed for delivery of verapamil HCL over an extended time period. An important feature of this system is the potential for generating constant drug release The formulations F5 and F10 were found to extend the drug release over an extended period of time. Hence the formulations can be further evaluated for *in vivo* studies such as pharmacokinetic and pharmacodynamic studies in a suitable animal model. Their physical parameters were within IP specified limits.

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