

Design and Evaluation of Verapamil Hydrochloride Controlled Release Hydrogel-Based Matrix Tablets

Vidyadhara Suryadevara, Sasidhar Reddyvalam Lankapalli, Balakrishna Thalamanchi, Anuradha Patcha, Lakshmi Harika Danda

Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur, Andhra Pradesh, India

Abstract

Aim: The present work was aimed to formulate Verapamil hydrochloride (HCl) an antihypertensive agent as controlled release (CR) matrix tablets using naturally occurring hydrophobic gum such as dammar gum as a polymer. **Methods:** In the present investigation, an attempt was made to induce hydrogel formation using polyelectrolytes such as calcium hydroxide and sodium hydroxide with the dammar gum in the presence of dissolution media and to extend the drug release up to 12 h. The hydrogels thus formed could be able to diffuse the drug through the channels present in the hydrogel-based matrix tablets. CR hydrogel-based matrix tablets were prepared using various concentrations of dammar gum, calcium hydroxide, and sodium hydroxide by wet granulation technique using isopropyl alcohol as a granulating fluid. The prepared tablets were evaluated for pre- and post-compression parameters. In vitro dissolution studies were performed in 0.1 N HCl for the first 2 h and in 6.8 pH phosphate buffer for next 10 h. **Results:** Among various formulations, dammar gum with calcium hydroxide and sodium hydroxide in the concentrations of 1 mg and 2.5 mg, respectively, were showed extended drug release up to 12 h in a steady state manner. The swelling index, Fourier transform infra-red, differential scanning calorimetry studies and scanning electron microscopy analysis were also performed on both the optimized formulations indicated that there were no drug and excipient interactions, and these formulations were found to be stable.

Key words: Calcium hydroxide, dammar gum, hydrogel, verapamil

INTRODUCTION

Recently, controlled and sustained drug delivery systems have become the standard in modern pharmaceutical design, and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. In this regard, many polymers are very useful. The science of drug delivery is always affected by the choice of polymers which act as carriers. Synthetic polymers frequently suffer from the problem of being non-biocompatible, non-biodegradable, and highly expensive. Natural polymers, therefore, are a promising solution to this problem.^[1]

Hydrogels are three-dimensional, hydrophilic, polymeric networks, with chemical or physical crosslinks, capable of imbibing large amounts of water or biological fluids.^[2-6] The hydrophilicity of the network is due to the presence of chemical residues such as hydroxylic (-OH), carboxylic (-COOH), amidic (-CONH-), primary

amidic (-CONH₂), sulfonic (-SO₃H), and other groups that can be found within the polymer backbone or as lateral chains.^[7] The networks are composed of homopolymers or copolymers and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), physical crosslinks, such as entanglements or crystallites.^[8,9] Cross-linking facilitates insolubility in water because of ionic interaction and hydrogen bonding. It also provides required mechanical strength and physical integrity to the hydrogels.^[10] Thus, hydrogels can imbibe water nearly 10-20 times its molecular weight and hence become swollen.^[11,12]

Address for correspondence:

Dr. Vidyadhara Suryadevara, Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chowdavaram, Chandramoulipuram, Guntur - 522 019, Andhra Pradesh, India. E-mail: svidyadhara@gmail.com

Received: 04-05-2015

Revised: 08-06-2015

Accepted: 13-07-2015

Hydrogels are smart enough to respond the fluctuations of environmental stimuli (pH, temp, ionic strength, electric field, presence of enzyme, etc.) and swell or shrink accordingly.^[13] The hydrophilic/hydrophobic balance of the hydrogels, the degree of cross-linking and especially, the degree of ionization and its interaction with counter ions are the important parameters which control the equilibrium swelling, dimensional change and the release patterns of drugs from these carriers.^[14]

The hydrophobic polymer, dammar gum, is used in tablet dosage forms to produce sustained and controlled drug release. Dammar gum, calcium hydroxide and Sodium hydroxide were used in the tablet formulations to form a hydrogel on exposure to dissolution media and to extend the drug release.

Verapamil hydrochloride (HCl) is a calcium channel blocker (acts on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thus reducing heart rate and blood pressure). Approximately about 90% of verapamil is absorbed from gastrointestinal tract, but is subjected to very considerable first-pass metabolism in the liver and the bioavailability is only about 20%. Verapamil exhibits bi-or-tri-phasic elimination kinetics and is reported to have a terminal plasma half-life of 2-8 h following a single oral dose or after intravenous administration. After repeated oral doses this increases to 4.5-12 h, it acts within 5 min of intravenous administration and in 1-2 h after an oral dose. There is considerable inter-individual variation in plasma concentrations.

Thus, there is a strong clinical need and market potential for a dosage form that will deliver Verapamil HCl in a controlled manner to a patient needing this therapy, thereby resulting in better patient compliance.

In the present study, an attempt was made to formulate controlled release (CR) hydrogel-based matrix tablets of verapamil HCl using various concentrations of dammar gum to form *in situ* gel formation with calcium hydroxide and sodium hydroxide by wet granulation technique so as to achieve steady state drug release over an extended period of time.

MATERIALS AND METHODS

Materials

Verapamil HCl was a gift sample from M/S AUROBINDO Pharma Ltd., Hyderabad. Dammar gum, sodium hydroxide, magnesium stearate and talc were procured from SD. Fine Chem. Ltd., Mumbai. Calcium hydroxide and avicel pH 102 were obtained from high pure fine Chem., Chennai; and Colorcon Chemicals Asia Pvt. Ltd., Mumbai, respectively.

Methods

Preparation of verapamil HCl CR hydrogel-based matrix tablets

Verapamil HCl CR hydrogel-based matrix tablets were prepared by wet granulation technique using various concentrations of dammar gum, calcium hydroxide, and sodium hydroxide. Isopropyl alcohol (IPA) was used as the granulating fluid. The raw materials were individually weighed, passed through sieve no. 80 and blended for 15 min using double cone blender. The powder mixture was then converted into damp mass by using IPA. The damp mass was passed through sieve no. 20 to obtain granules, which were kept in a tray dryer for drying at 60°C for 1 h. The dried granules were dry screened through sieve no 16 and uniform granules thus obtained were further subjected to compression. The prepared granules were lubricated with 1% talc and magnesium stearate and compressed into tablets by using 10 station clit minipress with 6 mm flat round punches. The compositions of various tablet formulations were given in Table 1.

Evaluation of pre-compression parameters on prepared granules

The pre-compression parameters such as angle of repose, Carr's index and Hausner's ratio were performed on prepared granules as per the standards. The results were given in Table 2.

Evaluation of post-compression parameters of hydrogel-based matrix tablets

The post-compression parameters such as weight uniformity, hardness, friability, and drug content were performed for prepared tablets. The prepared tablets were tested as per standard procedure for weight variation ($n = 20$), hardness ($n = 6$), and friability ($n = 20$) characteristics. The tablet hardness and friability were determined by using Monsanto tablet hardness tester and Roche friabilator, respectively. The results were given in Table 3.

Drug content uniformity

A matrix tablet of verapamil HCl from a batch was taken at random and was crushed to a fine powder. The powdered material was then transferred into 100 ml volumetric flask and few ml of 6.8 pH phosphate buffer was added to it. It was shaken occasionally for about 30 min and the volume was made up to 100 ml by adding 6.8 pH phosphate buffer.

The resulting solution was set aside for few minutes and the supernatant solution was collected, filtered by using Whatmann filter paper. Then, the filtrate was subsequently diluted and the absorbance was measured at 278 nm. This

Table 1: Composition of various verapamil HCl CR hydrogel-based matrix tablets

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Verapamil HCl	120	120	120	120	120	120	120	120	120	120	120
Dammar gum	120	120	120	120	120	120	120	120	120	120	120
Calcium hydroxide	-	1	2.5	5.0	7.5	10.0	-	-	-	-	-
Sodium hydroxide	-	-	-	-	-	-	1	2.5	5.0	7.5	10.0
Avicil pH102	103	102	100.5	98	95.5	93	102	100.5	98	95.5	93
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total weight	350	350	350	350	350	350	350	350	350	350	350

CR: Controlled release, HCl: Hydrochloride

Table 2: Pre-compression parameters of prepared granules of various hydrogel-based matrix tablets formulations

Formulation	Angle of repose (°)	Carr's index (%)	Hausner's ratio
F1	28.4±0.02	13.6±0.04	1.14±0.02
F2	25.6±0.04	12.4±0.02	1.13±0.01
F3	21.9±0.01	13.9±0.03	1.12±0.04
F4	23.5±0.01	13.6±0.03	1.08±0.04
F5	28.8±0.03	12.3±0.05	1.24±0.03
F6	29.6±0.04	14.5±0.02	1.06±0.01
F7	22.8±0.05	12.7±0.03	1.11±0.02
F8	24.6±0.02	13.5±0.04	1.14±0.02
F9	22.4±0.01	12.6±0.03	1.13±0.04
F10	25.5±0.04	14.5±0.02	1.13±0.04
F11	28.8±0.03	15.9±0.01	1.12±0.03

Table 3: Post-compression parameters of various verapamil HCl hydrogel-based matrix tablet formulations

Formulation	Weight uniformity (mg)	Hardness (kg/cm ²)	Friability % w/w	Drug content* (mg/tab)
F1	348±2.0	5.4±0.3	0.25	120±1.8
F2	350±3.0	5.3±0.3	0.23	119±1.2
F3	346±1.0	5.6±0.2	0.27	118±1.6
F4	355±4.0	5.5±0.2	0.28	119±1.8
F5	350±2.0	5.4±0.3	0.29	117±1.4
F6	345±1.0	5.4±0.2	0.26	118±1.2
F7	349±2.0	5.5±0.3	0.24	119±1.4
F8	347±2.0	5.5±0.3	0.23	120±1.8
F9	348±2.0	5.4±0.2	0.25	120±2.2
F10	346±2.0	5.6±0.2	0.27	119±1.6
F11	345±1.0	5.5±0.3	0.29	118±1.4

W/W: Weight-by-Weight, HCl: Hydrochloride

test was repeated 6 times ($n = 6$) for each batch of tablets for determining drug content in the prepared matrix tablets. The results were given in Table 3.

In vitro dissolution studies

The dissolution test was carried out in the United States Pharmacopoeia (USP) apparatus Type II (paddle) with 900 ml of 0.1 N HCl for 2 h then with 6.8 pH phosphate buffer for next 10 h. The temperature and rotations per minute (rpm) were maintained at $37 \pm 0.5^\circ\text{C}$ and 50, respectively. About 5 ml samples were withdrawn at 1, 2, 4, 6, 8, 10 and 12 h. A fresh volume of the medium was replaced with the same volume to maintain the sink conditions and the constant volume throughout the experiment. The samples withdrawn were suitably diluted with same dissolution medium, and the amount of drug dissolved was estimated by ultra-violet (UV) spectrophotometer at 278 nm. The dissolution studies were carried out in triplicate. Based on dissolution data, dissolution parameters such as zero order constant, first order constant, Higuchi's constant, and Peppas constant were determined for various tablet formulations. The results were given in Table 4.

Swelling behavior of CR hydrogel-based matrix tablets

The swelling behavior was determined by equilibrium weight gain method and studied using USP dissolution apparatus, Type I, to know polymer hydration and to evaluate extent of medium penetration into the tablets. The tablets were weighed, placed in dissolution basket and immersed in the vessel containing dissolution medium. At regular intervals, the weighed basket matrix system was withdrawn from the dissolution vessel, blotted with tissue paper to remove excess test liquid and re-weighed. The results were given Table 5.

SI of each tablet was calculated by the following equation:

$$SI = \{(W_t - W_0) / W_0\} * 100$$

Where, W_0 = Initial weight and W_t = Final weight.

Table 4: Evaluation of dissolution parameters for verapamil HCl hydrogel-based matrix tablet formulations

Formulation	Rate constant				Higuchi constant		Peppas constant	
	Zero order		First order		K (mg/h ^{1/2})	R ²	N	R ²
	K (mg/h)	R ²	K (hr ⁻¹)	R ²				
F1	9.80	0.829	0.270	0.992	27.80	0.982	0.890	0.996
F2	9.49	0.891	0.214	0.996	22.08	0.965	0.870	0.971
F3	8.89	0.868	0.179	0.965	19.01	0.963	0.818	0.957
F4	6.32	0.894	0.081	0.953	13.13	0.966	0.782	0.993
F5	5.20	0.746	0.054	0.973	13.84	0.971	0.629	0.984
F6	4.49	0.751	0.054	0.980	12.87	0.988	0.565	0.987
F7	9.21	0.839	0.196	0.953	28.41	0.987	0.880	0.984
F8	9.56	0.889	0.221	0.992	23.70	0.986	0.873	0.993
F9	8.21	0.842	0.126	0.980	20.15	0.991	0.809	0.996
F10	7.89	0.765	0.116	0.942	14.20	0.990	0.788	0.996
F11	7.30	0.776	0.103	0.960	11.15	0.996	0.688	0.998

HCl: Hydrochloride

Table 5: Percent SI values of various verapamil HCl CR hydrogel-based matrix tablet formulations

Formulation	% SI			
	1 h	3 h	6 h	12 h
F1	34.8	64.6	72.4	102.3
F2	46.8	66.5	82.6	152.3
F3	38.5	59.4	74.6	145.6
F4	36.6	52.4	74.9	116.4
F5	32.8	42.4	65.6	102.6
F6	30.6	36.6	52.6	82.8
F7	41.7	69.8	93.9	164.6
F8	42.3	67.6	88.7	158.4
F9	39.2	62.3	83.9	148.1
F10	34.8	58.9	75.8	122.5
F11	30.4	52.5	70.9	113.8

SI: Swelling index, CR: Controlled release, HCl: Hydrochloride

Characterization of matrix tablets

Based on the dissolution studies, the optimized formulations were selected and Fourier transform infra-red (FTIR) and differential scanning calorimetry (DSC) studies were performed on formulations F2 and F8 to know the drug and polymer interactions.

Scanning electron microscopy (SEM) analysis was performed on optimized formulations in dry and swollen state to know the surface erosion characteristics.

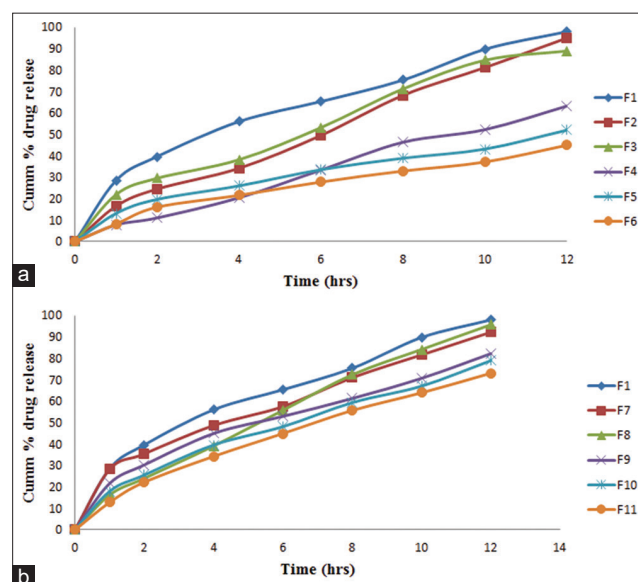
Stability studies

The optimized formulations (F2 and F8) were subjected to accelerated stability studies as per ICH guidelines. They were

kept in separate petridishes after preparation and stored in thermostated oven at a temperature and relative humidity (RH) of $25 \pm 2^\circ\text{C}$, $60 \pm 5\%$ RH for 6 months and $40 \pm 2^\circ\text{C}$, $75 \pm 5\%$ RH for 3 months. Then, they were evaluated for physical parameters, drug content and drug release studies.

RESULTS AND DISCUSSION

Verapamil HCl was estimated by spectrophotometric method in 6.8 pH phosphate buffer. The drug concentration was estimated at an absorption maximum of 278 nm by UV spectrophotometer. The pre-formulation studies were performed and indicated that there was no drug and excipient incompatibility. The FTIR spectra and DSC thermograms were given in Figures 1 and 2. Based on these studies,

**Figure 1:** (a and b) Dissolution profiles of verapamil hydrochloride controlled release hydrogel-based matrix tablet formulations

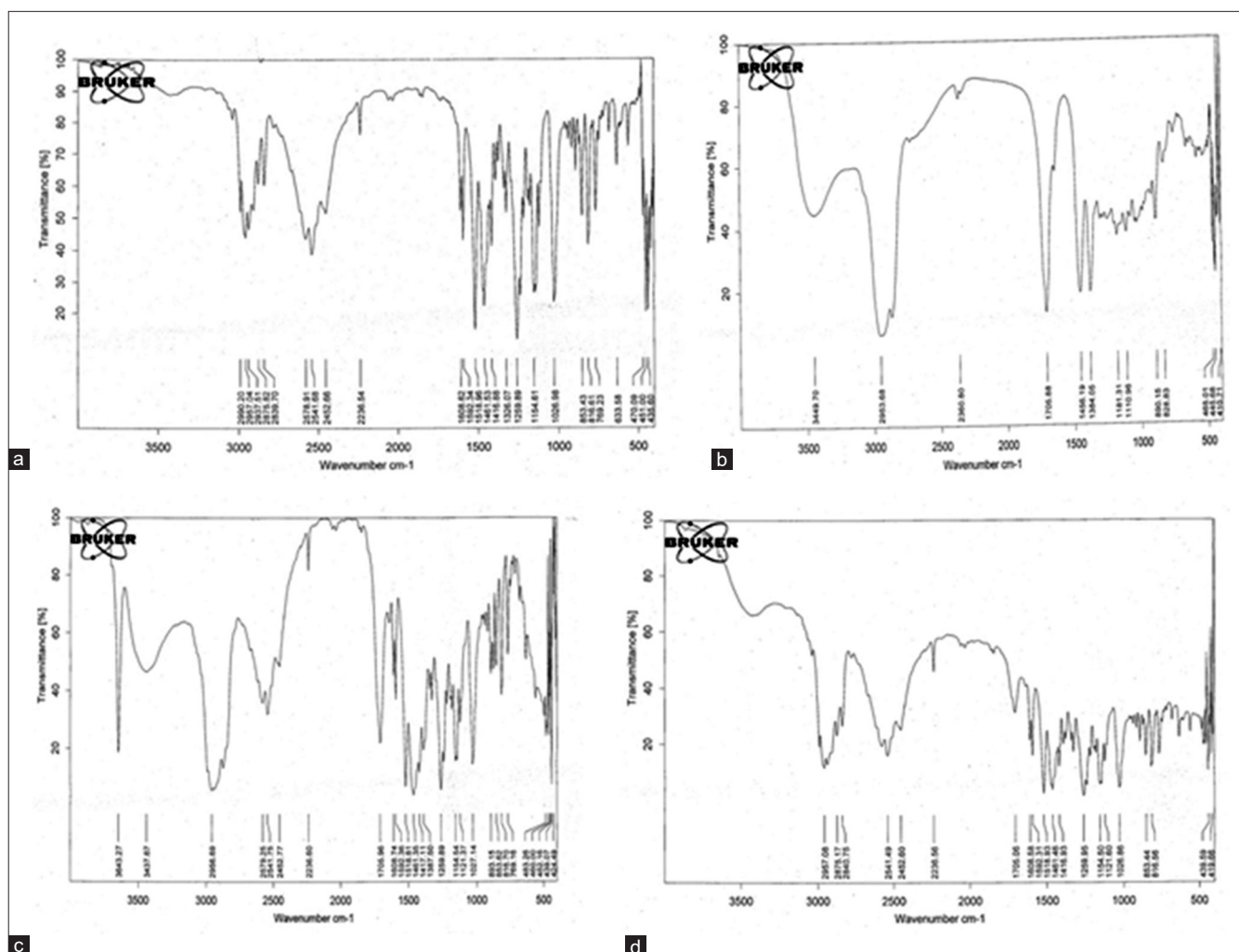


Figure 2: Fourier transform infra-red spectra of, (a) pure drug, (b) dammar gum, (c) F2, (d) F8

excipients were selected, and hydrogel-based matrix tablets were formulated. All the hydrogel-based matrix formulations that contained various concentrations of dammar gum, calcium hydroxide and Sodium hydroxide were prepared by wet granulation technique using IPA as the granulating fluid. Formulation F1 was prepared by utilizing drug and polymer at 1:1 ratio with Avicel pH 102 as diluent and without any polyelectrolyte. Formulations (F2-F11) were prepared by maintaining drug and gum concentrations at 1:1 ratio while polyelectrolytes concentrations were changed. Formulations F2-F6 were prepared by adding calcium hydroxide as polyelectrolyte at increased concentrations of 1-10 mg. Formulations F7-F11 were prepared by adding sodium hydroxide as polyelectrolyte at increased concentrations of 1-10 mg. The compositions were given in Table 1.

The pre-compression parameters such as angle of repose, Carr's index and Hausner's ratio were performed for various prepared granules. The angle of repose, Carr's index and Hausner's ratio values were in the range of 22.4-29.6, 12.3-15.9%, and 1.06-1.24, respectively, which indicated that the granules exhibited good flow properties. The results are given in Table 2.

After compression of granules along with lubricants into matrix tablets, the physical parameters such as weight uniformity, hardness, friability and drug content were evaluated. The weight uniformity, hardness, friability and drug content values were in the range of 345-355 mg, 5.3-5.6 kg/cm², 0.23-0.29% w/w and 117-120 mg, respectively, which indicated that the formulations were found to be stable and within the Indian Pharmacopoeia specified limits. The results are given in Table 3.

In vitro dissolution studies were performed on all the prepared matrix tablets by using USP apparatus II with 900 ml of 0.1N HCl as a medium for the first 2 h followed by 6.8 pH phosphate buffer as medium for remaining 10 h by maintaining temperature at 37°C with paddle rotating at 50 rpm speed. All the dissolution studies were performed in triplicate, and the average values were taken for further investigations.

Formulation F1 prepared without polyelectrolyte tend to exhibit a faster rate of drug release than compared to the other formulations. Formulations F2-F6 prepared using calcium hydroxide as polyelectrolyte were exhibited the extend drug release for more than 12 h. It was observed that as the concentration of calcium hydroxide increases the rate of drug

released is decreased due to intense formation of complex hydrogel by the polymer and polyelectrolyte. Formulation F2 containing 1mg of polyelectrolyte found to extend the drug release up to 12 h at a steady state manner and hence it is optimized for further investigations.

Formulations F7-F11 prepared using sodium hydroxide as polyelectrolyte were exhibited the extend drug release for more than 12 h. It was observed that as the concentration of sodium hydroxide increases the rate of drug released is decreased due to intense formation of the complex hydrogel by the polymer and polyelectrolyte. Formulation F8 containing 2.5 mg of polyelectrolyte found to extend the drug release up to 12 h at a steady state manner and hence it is optimized for further investigations.

It was observed that formulation F2 containing 1 mg of calcium hydroxide as polyelectrolyte and formulation F8 containing 2.5 mg of sodium hydroxide as polyelectrolyte were extended the drug release up to 12 h in a similar manner at a steady state patterns. The variations in the polyelectrolyte concentration in these formulations for extending the drug release may be due to intense formation of hydrogel complex with dammar gum by these polyelectrolytes. Calcium hydroxide a multivalent ion may form insoluble more complex hydrogel formation than compared to sodium hydroxide a monovalent ion which forms loosely networked hydrogel formation. This could be the main reason for the variation in the concentration of polyelectrolytes to form the stable and optimized hydrogel formation for extending the drug release at a steady state manner.

The dammar gum which is used as polymer for matrix tablets is basically hydrophobic in nature but possess net negative charge on its molecular structure which is responsible for inducing *in situ* hydrogel formation with disassociated polyelectrolytes in the presence of aqueous media. However, the intensity of gel formation depends on the type of polyelectrolyte used and its solubility in the dissolution media. Hence, formulations with calcium hydroxide could be able to retard the drug release from the formulations at lower concentrations than compared to the formulations prepared with sodium hydroxide.

The *in vitro* pharmacokinetic parameters such as zero order rate constant, first order rate constant, Higuchi's constant and Peppas constant were calculated for all the formulations and drug release was found to be linear with the first order release rate kinetics which was indicated by R^2 values in the range 0.942-0.996. Higuchi's constant values indicated that the drug release from tablet formulations was by diffusion process. The " n " values obtained by Peppas constant were in the range 0.565-0.890, which indicated that the drug release followed non-fickian anomalous drug release. Thus, the drug release from the tablet formulations was by diffusion of the drug from the hydrogel matrix followed by erosion of the hydrogel.

FTIR and DSC studies were performed on the drug, gum and optimized formulations. The results indicated that there were

no drug and polymer interactions. The results were shown in Figures 3-5, respectively. SEM analysis was performed on

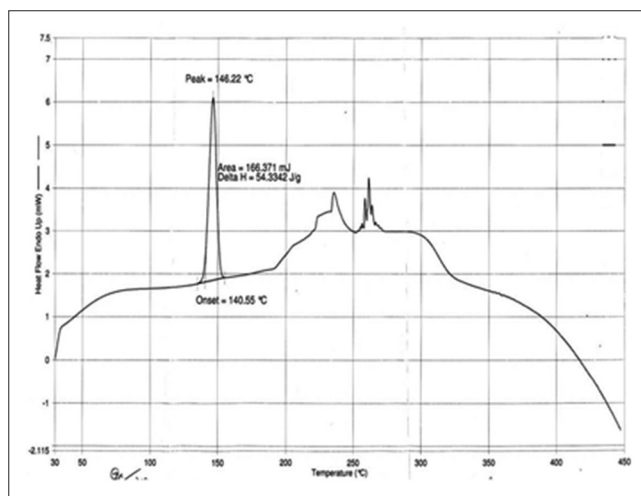


Figure 3: Differential scanning calorimetry thermograms of verapamil hydrochloride pure drug

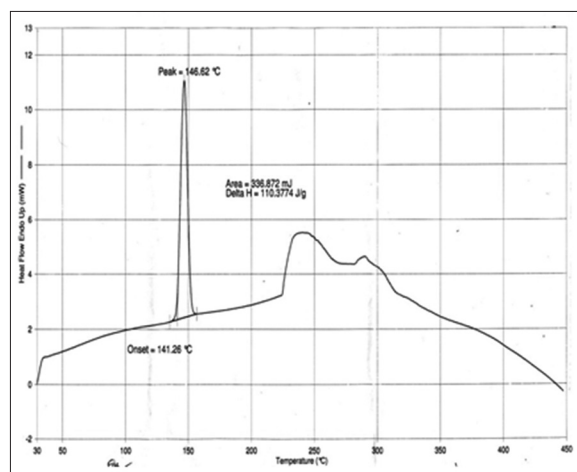


Figure 4: Differential scanning calorimetry thermograms of formulation F2

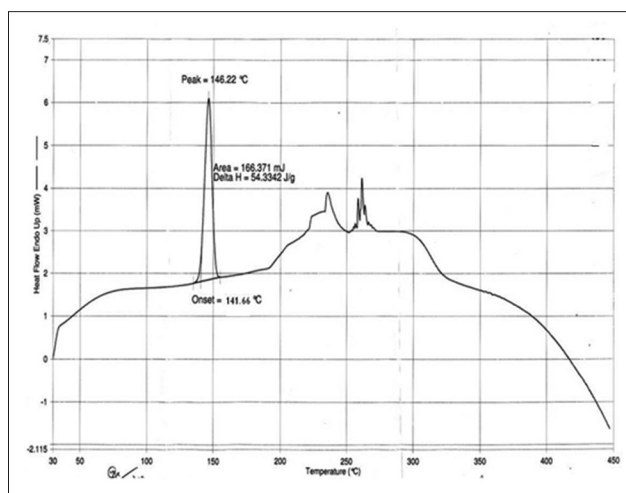


Figure 5: Differential scanning calorimetry thermograms of formulation F8

optimized formulations in dry and swollen state. The smooth surface was observed before dissolution and porous eroded surface as gel was observed after dissolution. The SEM figures were shown in Figure 6.

SI was performed on the tablet formulations F1-F12. The formulations F2 and F8 showed optimum swelling, i.e. they could form suitable gel matrix and showed the drug release up to 12 h. The results are given in Table 5. The photographs of F2 and F8 formulations before and after swelling were shown on Figures 7 and 8.

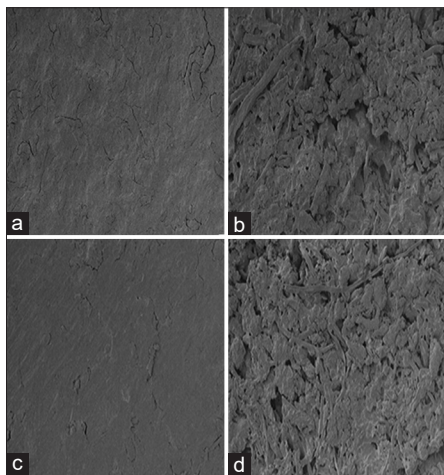


Figure 6: Scanning electron microscopy images of, (a) formulation F2 before dissolution, (b) formulation F2 after dissolution, (c) formulation F8 before dissolution, (d) formulation F8 after dissolution

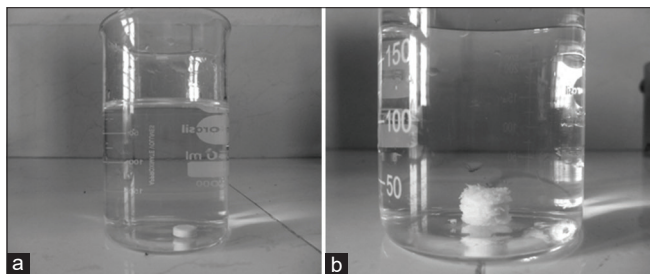


Figure 7: (a and b) Photographs of formulation F2 before and after swelling

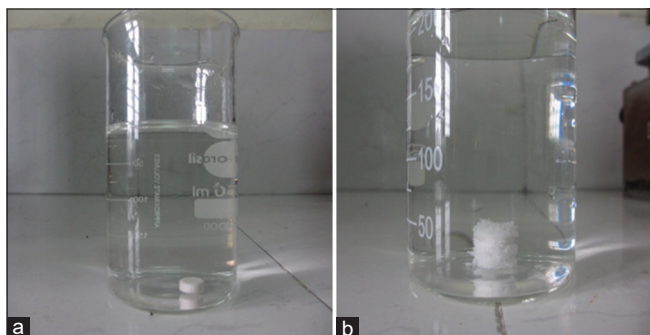


Figure 8: (a and b) Photographs of formulation F8 before and after swelling

The optimized formulations were subjected to accelerated stability studies as per ICH guidelines after storage at different conditions physical parameters and drug release studies were carried out on these formulations. There was no significant change observed in physical parameters and drug release even stability studies at various storage conditions and indicated that these formulations were found to be stable.

CONCLUSION

The present work provided an approach to formulate CR hydrogel-based matrix tablets which were designed to release the drug for extended period of time. Among various formulations based on drug release profiles, formulations F2 and F8 were optimized and *in vitro* pharmacokinetic parameters were also determined.

Based on the above studies, it may be concluded that verapamil HCl matrix tablets prepared using specific concentrations of dammar gum, calcium hydroxide, and sodium hydroxide showed drug release up to 12 h at a steady state.

ACKNOWLEDGMENTS

The authors are thankful to Aurobindo Laboratories Ltd., Hyderabad for gift sample of verapamil HCl and Chebrolu Hanumaiah Institute of Pharmaceutical Sciences for providing the facilities to carry out the research work.

REFERENCES

1. Saraswat R, Bhan CS, Gaur A. A review on polymers used in in-situ gel drug delivery systems. *Int J Pharm Innov* 2011;1:110-118.
2. Mikos AG. Preparation methods and structure of hydrogels. In: Peppas NA, editor. *Hydrogels in Medicine and Pharmacy*. Vol. 1. Boca Raton: CRC Press; 1986. p. 1-27.
3. Lee TW, Robinson JR, Remington I. *The Science and Practice of Pharmacy*. 2nd ed. Baltimore: Lippincott Williams and Wilkins; 2000. p. 903-29.
4. Brannon L. Preparation and characterization of cross linked hydrophilic networks. Harland RS, editor. *Absorbent Polymer Technology*. Amsterdam: Elsevier; 1990. p. 45-66.
5. Yadav R, Sharma A, Dubey A, Yadav SK. Hydrogels a boon to novel drug delivery system: An overview. *Invent Impact NDDS* 2012;1:1-5.
6. Madolia H, Sheo Datta M. Preparation and evaluation of stomach specific IPN hydrogels for oral drug delivery: A review. *J Drug Deliv Ther* 2013;3:131-40.
7. Fariba G, Samira VF, Ebrahim VF. Theoretical description of hydrogel swelling: A review. *Iran Polym J* 2010;19:375-98.

8. Rehner J. Statistical mechanics of cross-linked polymer networks. II. Swelling. *J Chem Phys* 1943;11:521-6.
9. Mongia NK. Ultrapure poly (vinyl alcohol) hydrogels with mucoadhesive drug delivery characteristics. *Eur J Pharm Biopharm* 1997;43:51-8.
10. Rowley JA, Madlambayan G, Mooney DJ. Alginate hydrogels as synthetic extracellular matrix materials. *Biomaterials* 1999;20:45-53.
11. Kim SW, Bae YH, Okano T. Hydrogels: Swelling, drug loading, and release. *Pharm Res* 1992;9:283-90.
12. Singh A, Pramod Kumar S, Kumar VG, Garima G. Hydrogels: A review. *Int J Pharm Sci Rev Res* 2010;4:97-105.
13. Das N. Preparation methods and properties of hydrogel. *Int J Pharm Pharm Sci* 2013;5:112-7.
14. Yin Y, Yang Y, Xu H. Swelling behavior of hydrogels for colon-site drug delivery. *J Appl Polym Sci* 2002;83:2835-42.

Source of Support: Nil. **Conflict of Interest:** None declared.