Research Article

Formulation and *In vitro* Evaluation of Modified Release Oral Hydrogel Driven Drug Delivery Systems of Diethylcarbamazine Citrate

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ABSTRACT

Objective: Hydrogels are three dimensional polymer matrices that are capable of imbibing large quantity of water, and biological fluids and used in the modifying release of the drugs. The present work was aimed to study oral hydrogel driven drug delivery systems of Diethylcarbamazine Citrate as a model drug. **Methodology:** The Hydrogels were composed of Poly acrylamide, Hydroxyethyl methacrylate using ionotropic gelation method using starch. **Results:** Thermographs showed no incompatibility between the drug and the polymers. Scanning Electron photomicrographs showed a rough contour surface. Drug release studied by High Pressure Liquid Chromatography using acetonitrile/0•01M phosphate buffer pH 6•8 at 210 nm showed that Formulation 9 released 98.67% of the dose in 16 h as compared to the marketed formulation which released 98.66% up to 6 h. The release followed first order kinetics and non-fickian diffusion by super case-II transport mechanism. Accelerated stability studies performed as per ICH guidelines at 40° ± 2° and 75 ± 5% RH and at ambient conditions of 25° ± 2° and 60 ± 5% RH showed that the hydrogel was stabile. **Conclusion:** It is concluded that hydrogel can be recommended as modified release dosage forms for industrial applications.

Key words: Hydrogels, Ionotropic gelation, Modified release, Non-fickian diffusion, Super case–II transport.

Received Date : 20/02/2015
Revised Date : 07/05/2015
Accepted Date : 15/05/2015

DOI: 10.5530/rjps.2015.2.2

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INTRODUCTION

The field of pharmaceutical science has been developing steadily over the years, and has today become valuable in helping to keep us healthy and prevent disease. An avenue of research that has progressed a great deal in the past few decades is the treatment of diseases via bio-molecules such as drugs, proteins etc. Initially these could only be administered in limited manner, due to limitations of drug delivery through harmful environments in the body. Thus limited mobility reduced the effectiveness of administered drugs.[1] The development and continuous research on the biomaterial carriers led to formulation of dosage forms by encapsulating drugs, thus targeting them to safely reach the desired site without harm. These biomaterial carriers allowed for the release of drug in sites which were previously inaccessible. The nature of these carriers progressed over the years from ceramics, to natural, to synthetic materials.[2] Considering factors such as integrity, biocompatibility and flexibility the use of hydrophilic three dimensional matrices as carrier materials is gaining more importance. This class of materials known as Hydrogels is three dimensional polymer matrices that are capable of imbibing large quantity of water, and biological fluids. This property of hydrogels is the reason behind its varied applications ranging from food additives to pharmaceuticals and clinical applications. They have the ability of

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Table 1: Formulation of Hydrogels of Diethylcarbamazine Citrate

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Starch (gm)	1.33	0.665	0.337	1.25	0.665	0.337	0.665	0.337	0.665
PAA(gm)	1	1	1	1	1	1	1	1	1
HEMA(gm)	-	-	-	-	0.5	0.5	1.0	1.0	1.5
DEC(gm)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Distilledwater (ml)	35	35	35	35	35	35	35	35	35
NaOH(ml)	10	10	10	10	10	10	10	10	10
Acetic acid(ml)	50	50	50	50	50	50	50	50	50
Ethanol(ml)	200	200	200	200	200	200	200	200	200

PAA: Polyacrylamide; HEMA: Hydroxyethyl methacrylate; DEC: Diethylcarbamzine Citrate; NaOH: Sodium Hydroxide.

sensing the changes of temperature, pH, or the concentration of metabolite etc.[3] Natural and synthetic polymer has wide application as wound dressings for wound healing,[4] encapsulation of cells and recently are being used in the new-fangled field of tissue engineering as matrices for repairing and regenerating a wide variety of tissues and organs along with their versatile types of drug delivery like oral topical, intravenous route etc.[5] Filariasis is a parasitic disease (usually an infectious tropical disease) that is caused by thread-like nematodes. It is estimated that more than 120 million people worldwide are infected. More than 90 percent of such infections are due to *Wuchereria bancrofti*, while the remainder is largely due to *Brugia malayi*.[6] The disease is symptomised by edema with thickening of the skin and underlying tissues, skin rashes, hyper or hypo pigmented macules, frequent chills and pyrexia.[7] Treatment generally includes diethyl carbamazine three times a day for three weeks and also five days each six month period with 100 mg doses and albendazole (a broad-spectrum anthelmintic) combined with ivermectin.[8,9]

A combination of diethylcarbamazine and albendazole is also effective. Diethylcarbamazine Citrate is a white, crystalline powder freely soluble in water and alcohol and practically insoluble in acetone, benzene, chloroform and ether. It is readily absorbed from the gastrointestinal tract and has a half-life of 8 hours.[10]

The present approach was designed to formulate and evaluate oral hydrogel based drug delivery system containing starch as a gelling and swelling agent and to study the effect of PAA (Poly acrylamide) and HEMA (Hydroxyethyl methacrylate) in the release of the Diethylcarbamazine Citrate, an anti-filarial drug from the hydrogel driven drug delivery systems.

MATERIALS AND METHODS

Materials

Diethylcarbamazine Citrate (DEC) was procured from Altocare Life Sciences Pvt. Ltd, Hyderabad, PAA, HEMA, and all other chemicals were procured from S.D. Fine Chemicals Limited, Mumbai. All other reagents used were of analytical grade.

Methodology

Accurately weighed quantity of starch was dissolved in 35 ml of double distilled water using thermostatic hot plate with magnetic stirrer (Remi motors). Polyacrylamide and Hydorxyethyl methacrylate in required quantities were then added. Stirring was continued for 2 h after addition of 50 ml of 10% sodium hydroxide. The paste thus formed was cooled to room temperature to which 10 ml of 10% acetic acid solution was added. The entire setup was kept aside for 24 h. The smooth gel so obtained was cut into pieces and stored in 200 ml ethanol for 5 h. The hardened hydrogel particles were collected by filtration and dried at 50º for 10 h. The dried particles were immersed in 50 mg/ml solution of drug incubated at 10º for 25 h. The swollen hydrogel particles were dried using vacuum oven and used for further studies. Nine Hydrogel formulations were prepared as shown in Table 1.

An equivalent quantity of 100 mg of the hydrogel obtained was mixed thoroughly with accurately weighed quantities of 137 mg microcrystalline cellulose as diluent and 3 mg of magnesium stearate as a lubricant and prepared in the form of tablets of total weight 240 mg.

Characterization of hydrogels

Differential Scanning Calorimetry (DSC)

The hydrogels were further studied for thermal behaviour using DSC-60 (Shimadzu, Tokyo, Japan) Calorimeter. The samples were heated in sealed aluminium pans under nitrogen gas at a flow rate of 80 ml/min and scanned at a rate of 10º/min to a temperature from 25° ± 1° to 450°. The heat flow as a function of temperature was measured for the drug-polymer mixture. The Thermograms of DSC are shown in Figure 1 (a) and 1 (b).

Scanning Electron Microscopy

The surface morphological characteristics of hydrogels were determined by scanning electron microscopy (JSM, 35CF, Jeol, Japan) using gold sputter technique. The vacuum dried particles were coated to 200 Å thickness with an alloy of gold-palladium. A working distance of 20 nm, a tilt of zero-degree and accelerating voltage of 15 kV were the operating parameters. Photomicrographs were taken within a range of 10-100 magnifications as shown in Figure 2a and 2b before and after drug loading.

In vitro Drug Release Studies

The *in vitro* dissolution studies were carried out by using USP II paddle apparatus (TDT-08L, Electrolab, India) at 50 rpm maintained at 37 ± 0.5° using 900 ml of dissolution medium of pH 1.2 for 2 h and then replaced by pH 6.8 phosphate buffer up to 16 h. Aliquots of 5 ml samples were withdrawn at scheduled time intervals and replaced with same volume of fresh medium. The withdrawn samples were filtered through a 0.45 µm membrane filter and after appropriate dilution, estimated for drug content using High pressure Liquid Chromatography (Shimadzu LC 2010 AHT, Mumbai) equipped with a wavelength detector at 210 nm and a Kromasil C18 (250×4.6 mm ID, 5 µm pore size) column with auto integrator using acetonitrile/0·01M phosphate buffer pH 6·8 in 65:35 v/v ratio at a flow rate of 1·0 mL/min at 50° for 15 min run time with a 1500 psig. The calibration curve at concentrations varying from 0.5 µg/mL to 25 µg/mL was used to evaluate all the samples using 20 µL injection volumes. The drug release from different formulations of hydrogels were performed and compared with that of the marketed formulation.

The release profiles are shown in the Figure 3.

Evaluation of release kinetics

The mechanism of the drug release from the hydrogels of DEC was investigated by fitting the *in vitro* release data using zero order, first order, Higuchi model, Hixson-Crowell model, Korsmeyer–Peppas equation[11] models as shown in the Table 2.

Stability studies

The optimized best Hydrogel formulations were taken separately in High density Polyethylene screw capped bottles, labeled accordingly and subjected to accelerated stability studies at 40°C ± 2°C and 75 ± 5% RH and at

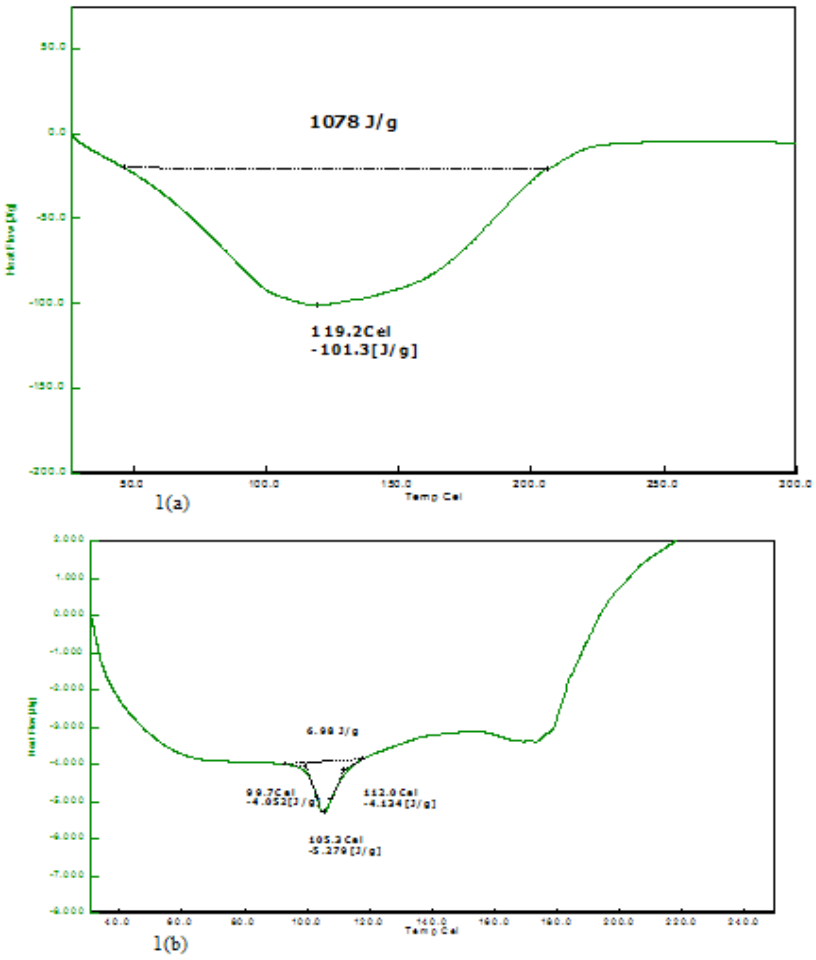


Figure 1: DSC Thermograms of (a) pure drug and (b) Hydrogel Formulation

ambient conditions of 25° ± 2°C and 60 ± 5% RH (as per ICH guidelines). Samples were withdrawn at predetermined time points i.e., at the end of 15, 30, 45 and 60 days at accelerated conditions. Similarly at the end of 1st and 2nd month at ambient conditions and evaluated for the drug content, physical appearance, dissolution profile and any changes in the same are reported in Table 3.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry (DSC)

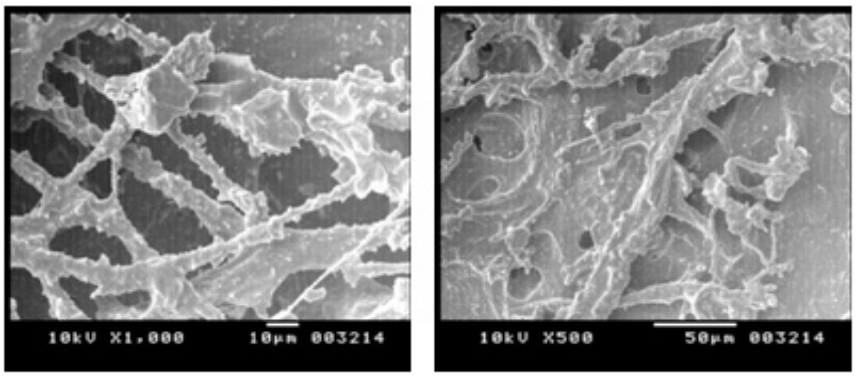
DSC is a well established method often used as a qualitative technique to characterize physical and chemical changes in either enthalpy or heat capacity of a crystalline drug in the polymer matrix during the manufacturing process. The thermal behavior of the pure drug and drug loaded Hydrogel formulation is shown in Figure: 1 (a) and 1 (b). A sharp endothermic peak was found with pure drug at 119.2° while the formulation showed a peak at 105.3°.

Scanning Electron Microscopy (SEM)

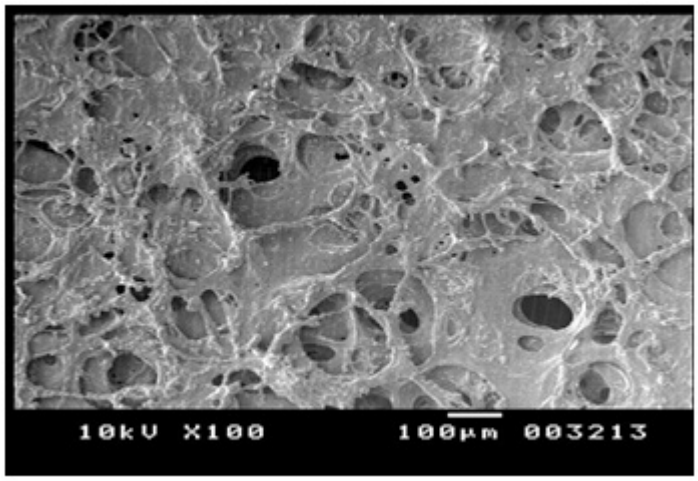
The surface of the hydrogels observed under Scanning Electron Microscope exhibited a rough network like morphology, which may be due to the presence of acrylamide and the crosslinking agent. The SEM photomicrographs of the hydrogel formulation before and after drug loading are shown in Figures: 2a and 2b respectively.

In vitro Drug Release Studies

The dissolution studies of Hydrogel Formulations F1to F4 showed a release of 91.55%, 87.13%, 90.33% and 91.86% respectively in 6 h which might be due to the concentrations of starch and soluble nature of the drug that resulted in faster dissolution and due to the non-existence of the cross linking agent. Starch was used as a gelling agent. The presence of the starch within the polymeric networks makes it suitable to release the drug faster because of its gelation which enables the hydrogel to swell and imbibe surrounding water thus releasing



2(a)



2(b)

Figure 2a: Scanning Electron Microscopic picture of Hydrogel Formulation before drug loading. 2b Scanning Electron Microscopic picture of Hydrogel Formulation after drug loading.

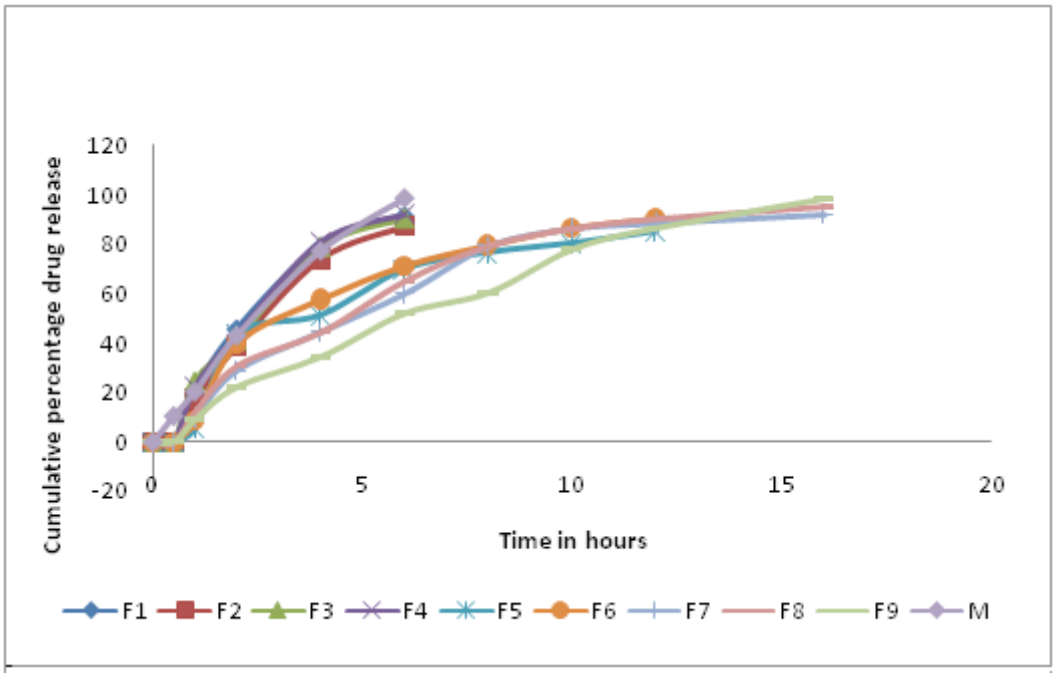


Figure 3: *In vitro* Drug Release Profile of Hydrogel and Marketed formulations

Table 2: Evaluation of release kinetics

Formulation Code	Zero order plot	First order plot	Higuchi plot	Hixson-Crowellplot	Korsmeyer-Peppas plot		
	R^2	R^2	R^2	R^2	R^2	n value	Transport mechanism
F1	0.9518	0.9917	0.9586	0.9945	0.9906	0.95	Super case II
F2	0.9648	0.9904	0.9428	0.9890	0.9947	1.05	Super case II
F3	0.9553	0.9887	0.9613	0.9882	0.9961	0.84	Non-fickian
F4	0.9525	0.9883	0.9558	0.9887	0.9997	0.92	Super case II
F5	0.7987	0.9162	0.9119	0.8819	0.8033	1.15	Super case II
F6	0.8362	0.9705	0.9419	0.9343	0.8676	1.00	Super case II
F7	0.9229	0.9752	0.9605	0.9688	0.9650	0.93	Super case II
F8	0.9176	0.9561	0.9550	0.9571	0.9760	0.88	Non-fickian
F9	0.9863	0.9511	0.9520	0.9837	0.9798	0.89	Case-II (relaxational)

the drug. Formulations F5 and F6 showed a varied rate of release of 85.12% and 90.31% for 12 h which might be due to the presence of the cross linking agent that restricted the drug release from the polymeric network. Further upon increasing the concentration of cross linking agent in formulations F7, F8 and F9 release was found to be 92.25%, 95.33% and 98.67% respectively, for an extended time for 16 h.

This modified release can be explained due to the soluble nature of the drug and the cross linking network formed by the Polyacylamide and Hydroxyethyl methacrylate. The marketed formulation when studied showed a release rate of 98.66% within 6 h which is shown in Figure 3. Thus the concentration of the cross linking agent influences the drug release from the cross linked hydrogel networks. The drug release also depends on the type and nature of the polymer.

Evaluation of release kinetics

The employment of mathematical models enables the prediction of release kinetics and release characteristics. Further the models facilitate the design and development of well defined and optimized formulations. Higuchi model describes the drug release mechanism from the matrix system. Hixson-Crowell model describes the dissolution of tablets recognizing that the particle regular area is proportional to the cubic root of its volume. Korsmeyer-Peppas model is used for drug diffusion from a controlled release polymeric system. If n value is around 0.45, it indicates, the apparent dif-

Table: 3 Accelerated Stability data of Hydrogel Formulation

Test	Specification	Time in days				
		0	15	30	45	60
Morphology	White in color, rough texture	No change in the morphology				
Assay (% w/w)	90-110	100 ± 0.00	96.18 ± 0.1	95.67 ± 0.1	94.18 ± 0.1	94.1 ± 0.1
Dissolution profile						
Time (hrs)	**Limits**	**Time in days**				
		0	**15**	**30**	**45**	**60**
0	0	15.13 ± 0.01	15.13 ± 0.01	15.13 ± 0.01	14.99 ± 0.01	14.91 ± 0.01
1	NMT 10%	36.73 ± 0.01	35.78 ± 0.01	35.83 ± 0.01	35.83 ± 0.01	35.83 ± 0.01
2	10-25%	48.16 ± 0.01	46.76 ± 0.01	47.16 ± 0.01	47.16 ± 0.01	47.16 ± 0.01
4	30-50%	63.99 ± 0.1	61.97 ± 0.1	63.99 ± 0.1	63.99 ± 0.1	63.99 ± 0.1
8	55-85%	85.29 ± 0.1	85.29 ± 0.1	84.69 ± 0.1	85.29 ± 0.1	85.29 ± 0.1
12	NLT 85%	94.99 ± 0.1	94.99 ± 0.1	94.99 ± 0.1	93.95 ± 0.1	92.98 ± 0.1

Accelerated stability studies at 40° ±2° and 75 ± 5% RH and at ambient conditions 25° ±2° and 60 ± 5% RH (as per ICH guidelines).

fusion is of Fickian mechanism, n value ranging from 0.45 to 0.89 indicates the anomalous Fickian transport or non-fickian mechanism and values of 0.89 and more than 0.89 are indicative for the case II (relaxational) and Super case II transport mechanism.

The results as shown in Table 2 indicated that the optimized hydrogel formulation followed zero order case II relaxational dissolution mechanism.

Stability studies

The stability studies proved that the hydrogel formulations prepared using starch and hydroxyethyl methacrylate offers good stability to the drug at 40° ± 2° and 75 ± 5% RH as shown in Table 3.

CONCLUSION

The hydrogel formulations using starch, PAA and HEMA using ionotropic gelation method can be successfully applied for soluble drugs like Diethylcarbamazine Citrate to achieve modified release for an extended period, reduce the dose frequency, minimize the side effects, and maximize the therapeutic efficacy. With increasing efforts devoted to the modified release, the applications of hydrogel technology will continue to grow in future.

ACKNOWLEDGEMENT

The authors are thankful to Malla Reddy College of Pharmacy for providing the facilities to carry out the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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