

“FORMULATION AND EVALUATION OF CARBOXY METHYL CELLULOSE BASED HYDROGEL FOR CONTROLLED DRUG DELIVERY OF ANTI HYPERTENSIVE DRUG”

Swaleha Patel*1, Dr. Remeth Dias.

YSPM's, YTC, Faculty of Pharmacy, Wadhe, Satara, 415011 India

Corresponding author

Swaleha Khansaheb Patel.
YSPM's, YTC, Faculty of Pharmacy (M.Pharm),
Wadhe, Satara, India 415011
E mail:swalehapatel89@gmail.com
Mobile No. +919960286894

Abstract

The main objective of present investigation is to formulate and evaluate Carboxy Methyl Cellulose Based Hydrogel for Controlled Drug Delivery of Anti-Hypertensive Drug as they are the multiple component system capable of swelling in aqueous mediums and retaining a large amount of water or biological fluids. they have emerged as one of the efficient carrier systems of therapeutic agents which are to be delivered in required amount at specific rate and site of action.

Key words: Hydrogel, CMC,MC,CA, Swelling index, Carboxyl Content, Sol-Gel Ratio, Drug Content, Drug Release

INTRODUCTION

Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical cross linking of individual polymer chains. Hydrogels are the main class of gels they are since the discovery of poly (2 hydroxyethyl methacrylate) by Wycherley and Lim in 1960, have been of great interest to biomedical scientists. They are defined as two or multi component systems, consisting of three dimensional networked hydrophilic polymer chains which are capable of swelling in aqueous mediums and retaining a large amount of water or biological fluids. Their ability to absorb water is due to the presence of hydrophilic groups such as OH, CONH, CONH₂, COOH, and SO₃H along the polymer chains. Hydrogels have emerged as one of the efficient carrier systems of therapeutic agents which are to be delivered in required amount at specific rate and site of action. Hydrogels are cross-linked networks of water soluble polymers which have tendency to swell under physiological conditions. Their rubbery consistency and high water content makes them an ideal material for biomedical and pharmaceutical applications.

Hydrogels can be prepared from natural or synthetic polymers. Besides few disadvantages related to pathogenicity and inflammatory responses, hydrogels made from natural polymers such as sodium alginate, chitosan, dextran etc. possess inherent biocompatibility, biodegradability and biologically recognizable moieties that support cellular activities. Cellulose is the most abundant renewable resource on the earth. The cellulose based hydrogels offer additional advantages which includes transparency and low cost. Hydrogel is a one of the good dosage form to achieve development in the field of controlled drug delivery system. Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical cross linking of individual polymer chains. Hydrogels have excellent application in the controlled drug delivery system delivery. They can be prepared by cross linking the polymer by means of suitable cross linking agent, which leads to the variety of physicochemical interactions such as hydrophobic interactions, charge condensation, hydrogen bonding, stereocomplexation, or supramolecular chemistry. These cross linkers prevent burst release of the medicaments. So all these chemical interaction causes entanglements of the polymer which provides the controlled release of the drug for extended period of time. Controlled release dosage forms cover wide range of prolonged

Perindopril terbutylamine:

It is a cardio selective β_2 -adrenergic blocking agent used for acute myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headaches the β_2 -selectivity of these agents is thought to be due in part to the large substituent's in the Para position. At low doses Perindopril terbutylamine, selectively blocks cardiac β_2 -adrenergic receptors with little activity against β_1 -adrenergic receptors of the lungs and vascular smooth muscle. Receptor selectivity decreases with higher doses. Unlike other drugs.

Materials and method

Materials

Perindopril terbutylamine, Carboxy Methyl Cellulose (CMC), Methyl cellulose (MC), Citric acid.

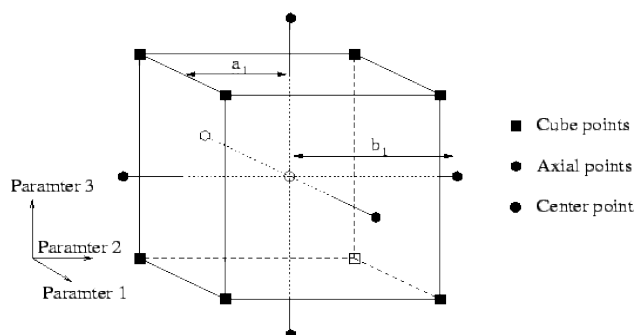
Preparation of Hydrogel

Hydrogel films were prepared according to the previously reported methods with certain modifications. Polymer solutions (2%w/v) containing CMC and MC in specific ratio were prepared using magnetic stirrer at room temperature. Citric acid was added to these solutions as a cross linking agent. The solutions were kept overnight to remove the air bubbles. The clear solutions were cast into Petri dishes of uniform size (9cm diameter) and dried in a hot air oven at 50°C for 24hr. The dried films were cured at 160°C for 20min. The curing temperature and curing time was sufficient to achieve cross linking. The cured Hydrogel films were washed with distilled water and isopropyl alcohol for 1h in order to remove the unreacted entities. Thereafter, the Hydrogel films were dried in a hot air oven at 50°C for 24hr. and stored in desiccators.

Experimental design for optimization:

In statistics, a central composite design is an experimental design, useful in response surface methodology, for building a second order (quadratic) model for the response variable without needing to use a complete three-level factorial experiment. The design consists of three distinct sets of experimental runs:

1. A factorial (perhaps fractional) design in the factors studied, each having two levels;
2. A set of center points, experimental runs whose values of each factor are the medians of the values used in the factorial portion. This point is often replicated in order to improve the precision of the experiment;
3. A set of axial points, experimental runs identical to the centre points except for one factor, which will take on values both below and above the median of the two factorial levels, and typically both outside their range. All factors are varied in this way.



A central composite design was employed for the optimization of CMC/MC Hydrogel films. The studied factors (independent variables) were concentration of cross linking agent (citric acid) (A) and ratio CMC and MC (B), while curing time and heating temperature were used as dependent variables.

Design–Expert software (V.7.0, Stat-Ease Inc, USA) was used for generation and evaluation of experimental design. Suitable polynomial equations involving individual factors and interaction factors were selected. The polynomial mathematical model generated by circumscribed central composite design is as follows: $Y = b_0 + b_1A + b_2B + b_3AB + b_4A^2 + b_5B^2$ (1) where Y is the response; b_0 is the intercept, and b_1, b_2, b_3, b_4, b_5 are regression coefficients. A and B are individual effects; A^2 and B^2 are quadratic effects; AB is the interaction effect.

Sr.No.	Runs	Block	Independent variable X ₁	Independent variable X ₂
1	1	Block 1	1	10
2	2	Block 1	3	10
3	3	Block 1	1	20
4	4	Block 1	3	20
5	5	Block 1	1	15
6	6	Block 1	3	15
7	7	Block 1	2	10
8	8	Block 1	2	20
9	9	Block 1	2	15
10	10	Block 1	2	15
11	11	Block 1	2	15
12	12	Block 1	2	15
13	13	Block 1	2	15

Table: Formulation of batches in a central composite design:

X₁-Concentration of citric acid (A), X₂-CMC: MC ratio (B)

Characterization of Hydrogel film:

IR Spectrum:

The main distinction of ATR-FTIR from other spectroscopic techniques is that it depends on total internal reflection and attenuation of a total reflection. ATR-FTIR allows us to study thin films, powders, surface layers of bulk materials, polymers, and strongly absorbing solutions such as various chromophores and dyes.

Scanning Electron Microscopy (SEM):

Scanning electron microscopy (JSM-5800; JEOL Ltd., Tokyo, Japan) was used to evaluate the shape and surface topography of the formulation. Beads were gold coated by mounted on a brass stub using double-sided adhesive tape and under vacuum in an ion sputter with a thin layer of gold (3-5 nm) for 75 s and at 15 kV to make them electrically conductive and their morphology was examined.

Evaluation of Hydrogel films

The formulated CMC/MC Hydrogel films were evaluated for different parameters like carboxyl content, thickness measurement, swelling studies, drug loading, drug release and release kinetics.

Carboxyl content:

Carboxyl content of the Hydrogel films were determined using acid-base titration. A known amount of Hydrogel film was dissolved in excess of 0.1N NaOH and stirred on a magnetic stirrer for 2hr. Sodium hydroxide breaks down the ester linkages and reacts with the free carboxyl groups to form sodium carboxylate (citrate). The excess amount of 0.1N NaOH was titrated with 0.1N HCl using phenolphthalein as an indicator. The carboxyl content in mill equivalents per 100g of Hydrogel films were calculated using formula,

$$\text{Carboxyl content} = \frac{(V_b - V_a) \times N \times 100}{\text{Weight of sample}}$$

Thickness measurement:

Thickness of the CMC/MC Hydrogel films was measured using 0-25 X 0.01mm micrometer (Aerospace).

Swelling studies:

The swelling ratio of the Hydrogel films was determined according to the previously reported method (Chen & Park, 2000) with certain modifications. Hydrogel films were immersed in 0.1 N HCl/PBS 6.8 for 24 hr. The swollen samples were

removed from 0.1 N HCl/PBS 6.8 after 15min and excess of 0.1 N HCl/PBS 6.8 was blotted using tissue paper. The weight of the swollen Hydrogel films (W_s) was measured and absorbency was calculated. The Hydrogel films were again immersed in the 0.1 N HCl/PBS 6.8 and absorbency was determined till 1h. Swelling ratio after 24h was determined in same way. Gel fraction was determined by immersing the pre-weighed Hydrogel films in 0.1 N HCl/PBS 6.8 at room temperature. After 24h, the Hydrogel films were removed and dried over night in a hot air oven at 40°C. The gel fraction was then measured as follows:

$$GEL\ FRACTION = \left(\frac{W_d}{W_i} \right) \times 100$$

Where,

W_i = initial weight of dry Hydrogel films

W_d = weight of dried insoluble part of Hydrogel films after extraction in PBS.

Drug loading and drug release:

Pre weighed Hydrogel films were placed in 20ml drug solution (5mg/ml) up to equilibrium swelling. Drug loaded Hydrogel films were then dried in hot air oven at 30°C for 24hr. In order to determine the amount of drug loaded, a small portion of drug loaded Hydrogel films were cutted into small pieces, weighed and immersed in the 20ml 0.1N HCl. The mixture was stirred on magnetic stirrer for 24h and amount of drug released in the solution was determined spectrophotometrically ($\lambda = 215\text{nm}$). Drug loaded dry Hydrogel films were immersed in 20 ml phosphate buffer (pH 6.8) for maintaining sink condition. Samples were withdrawn periodically and replaced with fresh medium in order to maintain constant volume of the liquid (dissolution medium). The amount of drug released within the samples was measured spectrophotometrically ($\lambda = 215\text{nm}$).

RESULTS AND DISCUSSION

Preformulation study

Estimation of by UV spectroscopy

i) Determination of λ_{max} of Perindopril terbutylamine in phosphate buffer 6.8

The λ_{max} of Perindopril terbutylamine was found to be 215 nm.

ii) Determination of λ_{max} of Perindopril terbutylamine in 0.1N HCl

The λ_{max} of Perindopril terbutylamine was found to be 215 nm.

Preparation of calibration curve of Perindopril terbutylamine in 0.1N HCl

Sr. No.	Concentration(mcg/ml)	Absorbance(A°)
1	2	0.113
2	4	0.196
3	6	0.276
4	8	0.327
5	10	0.365
6	12	0.424
7	14	0.510
8	16	0.536
9	18	0.542
10	20	0.607

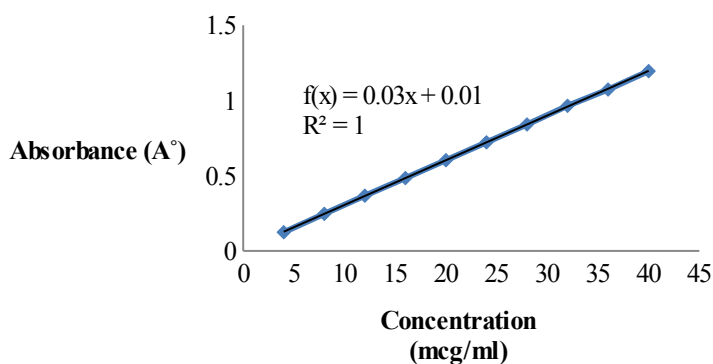


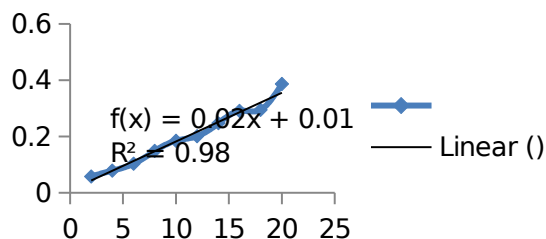
Figure: Calibration curve of Perindopril terbutylamine in phosphate buffer pH 6.8

Absorbance goes on increasing as we increase the concentration of Perindopril terbutylamine

Slope	0.0297
Intercept	0.0055
R ²	0.999

In Distilled Water

Sr. No.	Concentration(mcg/ml)	Absorbance(A°)
1	2	0.058
2	4	0.079
3	6	0.103
4	8	0.149
5	10	0.185
6	12	0.201
7	14	0.247
8	16	0.291
9	18	0.295
10	20	0.387



Calibration curve of Perindopril terbutylamine in Distilled water

Slope =0.017342
Intercept =0.008733
R ² =0.977

Absorbance goes on increasing as we increase the concentration of Perindopril terbutylamine

IR overlay Spectrum :

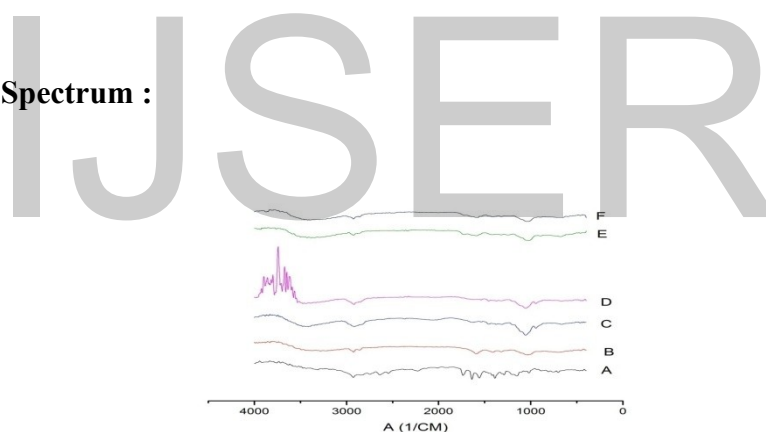


Figure .21 Overlay of IR Spectrum

So from the above figure it is clear that, characteristic peaks in the IR spectra of perindopril terbutylamine with physical mixtures CMC,MC and citric acid, 3138.18 cm⁻¹, 1556.55 cm⁻¹, 1238.30 cm⁻¹ are at same wave number as they are in the drug alone. Thus it is clear that perindopril terbutylamine is compatible with CMC,MC and citric acid.

DSC overlay spectra:

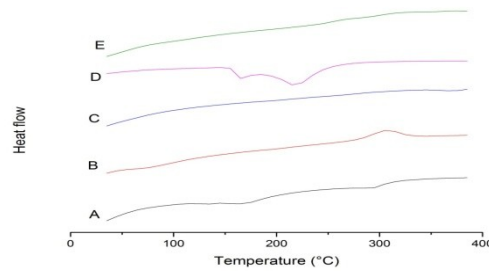
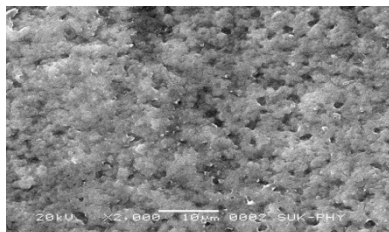


Figure 22: DSC overlay spectrum of (a)Perindopril terbutylamine,(b)CMC,(c)MC, (d)Citric acid,(e)Blank hydrogel,(f)Loaded hydrogel.

DSC thermo gram of hydrogel formulation showed endothermic peaks at 131.96, 308 and 155.46°C indicating melting points of Perindopril terbutylamine,CMC,and citric acid respectively, with somewhat decrease in intensities.

SEM analysis

Hydrogel Film(Loaded with drug)



Hydrogel Film(Blank)



The above mentioned hydrogel formulations Blank hydrogel and Drug loaded hydrogel have been formulated by varying the concentration of citric acid 10, 15 and 20% respectively.

Evaluation of hydrogel films:

Hydrogel formulations were prepared with different citric acid concentrations and checked for the various evaluation parameters to optimize the formulation

Carboxyl content of hydrogel films

Sr.No	Batch	Va(mL)	Vb(mL)	Wt=Weight of sample(mg)	Total Carboxyl Content(mL/mg)	Wt=Weight of sample in gram	Total Carboxyl Content(mL/g)
1	A	25.2	26.6	11.2	1.25	0.0112	123.66
2	B	25.1	26.6	9.5	1.578947368	0.0095	1578.947368
3	C	25.5	26.6	30.9	0.355987055	0.0309	355.987055
4	D	26.1	26.6	20	0.25	0.02	25.0
5	E	26.2	26.6	42.7	0.093676815	0.0427	93.676815
6	F	25.5	26.6	13.5	0.814814815	0.0135	814.814815
7	G	24.5	26.6	37.5	0.56	0.0375	56.0
8	H	24.8	26.6	28.2	0.638297872	0.0282	638.297872
9	I	25.8	26.6	20	0.4	0.02	40.0
10	J	25.4	26.6	22.7	0.528634361	0.0227	528.634361
11	K	25.2	26.6	17.4	0.804597701	0.0174	804.597701
12	L	23.9	26.6	29.3	0.921501706	0.0293	921.501706
13	M	24.6	26.6	27.5	0.727272727	0.0275	727.272727

a. Carboxyl content of hydrogel films

Batch B was found to be the one which is showing maximum carboxyl content and that is 1578.94 ml/g

Swelling studies of Hydrogel films:

Sol-Gel fraction of Hydrogel Films in PBS					
Sr.No.	Batch	WI(mg)	WF(mg)	Sol Fraction(mg/mg)	Gel Fraction(mg/mg)
1	A	24.9	23.3	6.425702811	93.57429719
2	B	21.9	21.8	0.456621005	99.543379
3	C	31.5	29.3	6.984126984	93.01587302
4	D	16.1	15.8	1.863354037	98.13664596
5	E	51.5	43.3	15.9223301	84.0776699
6	F	22.7	21.6	4.845814978	95.15418502

7	G	54.5	46.1	15.41284404	84.58715596
8	H	24.5	24.3	0.816326531	99.18367347
9	I	22	20.6	6.363636364	93.63636364
10	J	25.8	23.4	9.302325581	90.69767442
11	K	18.7	18.3	2.139037433	97.86096257
12	L	17.9	15.4	13.96648045	86.03351955
13	M	41.2	40	2.912621359	97.08737864

Sol-Gel fraction of Hydrogel Films in D e-ionised water

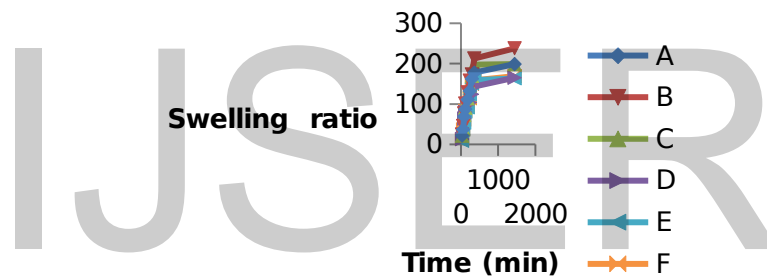
Sr.No.	Batch	WI(mg)	WF(mg)	Sol Fraction(mg/mg)	Gel Fraction(mg/mg)
1	A	24.9	23.8	4.417670683	95.58232932
2	B	20.5	19.3	5.853658537	94.14634146
3	C	32.7	31.5	3.669724771	96.33027523
4	D	23.1	22.2	3.896103896	96.1038961
5	E	23.8	21.4	10.08403361	89.91596639
6	F	47.9	45.8	4.384133612	95.61586639
7	G	45.1	44.3	1.77383592	98.22616408
8	H	39	36.9	5.384615385	94.61538462
9	I	33.6	32.1	4.464285714	95.53571429
10	J	39.4	35.6	9.644670051	90.35532995
11	K	14	12.8	8.571428571	91.42857143
12	L	26.6	24.5	7.894736842	92.10526316
13	M	48.5	45.8	5.567010309	94.43298969

Sol-Gel fraction of CMC:MC Hydrogel in 0.1 N HCL					
Sr.No.	Batch	WI(mg)	WF(mg)	Sol Fraction(mg/mg)	Gel Fraction(mg/mg)
1	A	44.2	42.7	3.393665158	96.60633484
2	B	39.4	37.3	5.329949239	94.67005076
3	C	45.9	44.1	3.921568627	96.07843137
4	D	47.5	46.2	2.736842105	97.26315789
5	E	50.1	48.8	2.594810379	97.40518962
6	F	48.5	46.1	4.948453608	95.05154639
7	G	53.2	51.2	3.759398496	96.2406015
8	H	48.5	47.2	2.680412371	97.31958763
9	I	50.1	48.9	2.395209581	97.60479042
10	J	39.8	37.7	5.27638191	94.72361809
11	K	40.4	38.9	3.712871287	96.28712871
12	L	48.5	45.6	5.979381443	94.02061856
13	M	38.7	36.7	5.167958656	94.83204134

Gel fraction of Batch B was found to be the maximum

Time	Swelling index (%)
-------------	---------------------------

(min)	A	B	C	D	E	F	G	H	I	J	K	L
30	22.12	24.76	22.10	13.33	8.98	13.1	14.96	19.20	20.25	16.66	18.20	11
60	36.97	45.76	39.61	24.12	36.9	37.32	32.58	33.65	35.05	32.55	36.55	34.54
90	68.55	76.96	72.77	64.03	54.48	61.42	56.87	60.14	61.90	42.87	57.22	60.04
120	87.02	101.44	91.40	79.98	81.11	83.38	77.42	87.80	83.50	68.57	65.87	73.98
180	111.03	129	114.47	98.30	91.92	93.32	83.99	99.25	112.82	79.83	87.45	91.96
240	132.47	158.24	145.80	103.45	124.44	114.25	119.32	118.54	139.26	96.15	93.58	110.22
300	162.81	173.04	169.59	124.11	151.43	149.89	125.87	123.54	159.82	111.24	99.80	121.24
360	178.02	212.98	197.50	143.65	159.14	158.78	133.65	132.15	173.92	128.30	114.22	126.50
1440	198.70	238.24	198.81	165.44	163.50	169.10	148.98	149.65	189.90	142.40	128.97	128.67



Comparison of swelling index from A to F

Comparison of swelling index from G to M

Drug content and release:

DRUG CONTENT IN 0.1N NaoH.											
Batch	Day	Abs	Slope	Intercep	C (µg/ml)	Vol. of Mediu	S	D	D	C (mg/10ml)	Loading

	Wt			t	in solution	m	v	v	F) in solution	(mg/g)
A	50.1	0.15	0.01734	0.00873	3.23	10	1	10	10	0.323	6.447105788
B	67.3	0.426	0.01734	0.00873	7.147	10	1	10	10	0.7147	10.61961367
C	71.8	0.51	0.01734	0.00873	8.05	10	1	10	10	0.805	11.21169916
D	40.4	0.535	0.01734	0.00873	15.024	10	1	10	10	1.5024	37.18811881
E	39.8	0.319	0.01734	0.00873	8.989	10	1	10	10	0.8989	22.58542714
F	56.8	0.568	0.01734	0.00873	11.35	10	1	10	10	1.135	19.98239437
G	53.2	0.219	0.01734	0.00873	6.1	10	1	10	10	0.61	11.46616541
H	48.5	0.228	0.01734	0.00873	5.19	10	1	10	10	0.519	10.70103093
I	50.1	0.263	0.01734	0.00873	5.84	10	1	10	10	0.584	11.65668663
J	47.5	0.15	0.01734	0.00873	3.41	10	1	10	10	0.341	7.178947368
K	45.9	0.134	0.01734	0.00873	3.13	10	1	10	10	0.313	6.819172113
L	39.4	0.053	0.01734	0.00873	1.29	10	1	10	10	0.129	3.274111675
M	44.2	0.147	0.01734	0.00873	3.59	10	1	10	10	0.359	8.122171946

Drug content in 0.1N NaOH

DRUG CONTENT IN DE-IONISED WATER											
Batch	Dry Wt	Abs.	Slope	Intercept	C(µg/mL)	Vol. of medium	Sv	Dv	DF	Drug Content	Drug Content

A	16.3	0.572	0.063864	0.081	7.688212451	10	1	10	10	0.768821245	47.16
B	9.4	1.171	0.063864	0.081	17.06751848	10	1	10	10	1.706751848	181.5
C	19.3	0.407	0.063864	0.081	5.104597269	10	1	10	10	0.510459727	26.44
D	20	1.011	0.063864	0.081	14.56219466	10	1	10	10	1.456219466	72.8
E	31	0.556	0.063864	0.081	7.43768007	10	1	10	10	0.743768007	23.99
F	12	1.026	0.063864	0.081	14.79706877	10	1	10	10	1.479706877	123.3
G	15	0.54	0.063864	0.081	7.187147689	10	1	10	10	0.718714769	47.9
H	16.1	1.054	0.063864	0.081	15.23550044	10	1	10	10	1.523550044	94.63
I	15.5	0.394	0.063864	0.081	4.901039709	10	1	10	10	0.490103971	31.6
J	19.5	0.602	0.063864	0.081	8.157960666	10	1	10	10	0.815796066	41.83
K	13.2	0.942	0.063864	0.081	13.48177377	10	1	10	10	1.348177377	102.1
L	12.3	0.687	0.063864	0.081	9.488913942	10	1	10	10	0.948891394	77.14
M	10.9	0.697	0.063864	0.081	9.64549668	10	1	10	10	0.964549668	88.49

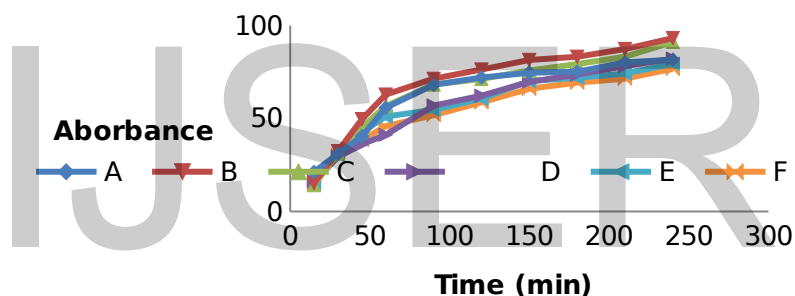
As reaction time increases there is increase in drug content of hydrogel and vice versa.

Again as the reaction time increases there is increase in drug release of hydrogel.

Drug release (A-F)

Time (min)	% Cumulative drug release (%CDR)					
	A	B	C	D	E	F

15	21.20±1.5	15.13±0.8	14.23±0.9	16.2±0.51	15.3±0.68	14.9±0.8
30	31.01±1.8	32.35±.6	31.29±0.5	29.23±0.8	30.2±0.41	30.28±0.21
45	40.47±1.0	49.68±0.5	45.23±0.2	36.2±0.9	42.65±0.12	38.32±0.8
60	55.74±0.8	62.89±0.5	56.65±0.61	41.23±1.6	51.12±0.58	45.81±0.78
90	68.10±1.5	71.38±1.0	68.23±0.3	56.9±0.21	54.71±1.5	51.8±0.91
120	71.98±1.5	76.35±1.5	71.26±0.9	62.32±0.8	60.65±0.6	58.6±0.71
150	74.63±1.0	81.51±1.8	75.69±0.6	69.8±0.9	70.2±0.94	65.92±0.54
180	75.2±0.21	83.21±0.5	79.35±0.2	73.65±0.8	71.95±0.26	69.32±0.53
210	80.2±0.9	87.33±1.8	83.21±0.5	78.21±0.75	74.21±0.5	71.5±0.81
240	81.6±0.2	93.23±0.5	91.23±0.1	82.3±0.21	79.5±0.54	76.81±0.68

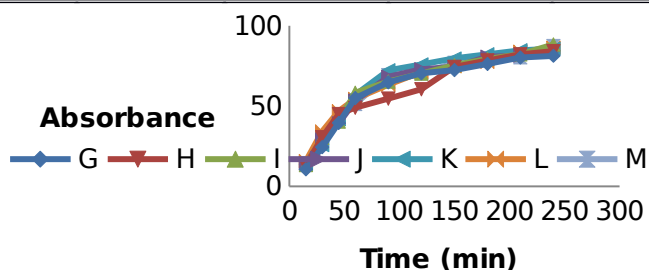


Comparison of % cumulative drug release from A to F

Drug release (G-M)

Time (min)	%Cumulative drug release (%)						
	G	H	I	J	K	L	M
15	10.53±0.8	12.83±0.8	13.2±0.9	14.2±0.8	13.80±0.5	15.80±1.5	14.3±0.12
30	24.35±0.5	30.53±0.9	30.21±0.3	29.23±0.2	25.68±1.0	34.16±1.8	31.21±0.5
45	39.38±1.0	44.95±1.5	40.32±0.8	39.2±0.8	41.80±0.8	46.77±1.5	44.21±0.9
60	54.89±0.8	48.83±0.5	58.23±0.9	53.26±0.9	56.83±1.5	54.41±0.8	51.2±1.2
90	64.71±1.8	54.53±0.8	65.21±1.2	68.21±0.3	72.23±1.5	63.13±1.5	69.2±0.6

120	70.32±1.0	60.35±1.5	70.2±0.5	72.9±0.5	75.74±1.8	71.09±0.5	70.23±0.8
150	72.27±1.8	74.36±0.8	75.32±0.7	74.23±0.41	79.57±1.0	74.60±1.5	76.9±0.61
180	76.21±0.8	78.24±0.5	79.3±0.21	80.7±0.5	82.12±0.5	77.39±1.0	79.21±0.62
210	80.12±1.8	82.12±1.8	82.15±0.54	81.3±0.3	84.66±1.5	83.81±1.8	80.23±0.8
240	81.2±0.5	84.1±0.84	88.2±0.75	84.3±0.7	85.63±0.8	86.24±1.5	87.2±0.84



Comparison of % cumulative drug release from G to M

Effect of reaction time on drug content as well as on drug release is much significant. As reaction time increases there is increase in drug content of hydrogel and vice versa. Again as the reaction time increases there is increase in drug release of hydrogel.

Release kinetics

Table 19: Results of curve fitting of the in vitro drug release data from hydrogel

Run	R ²				Release exponent (n)
	Zero order	First order	Korsmeyer Peppas	Higuchi	
A	0.880855	0.826255	0.914022	0.946638	0.383359
B	0.902471	0.797716	0.976115	0.964206	0.36409
C	0.934263	0.826843	0.987418	0.981883	0.419493

D	0.943091	0.878021	0.969981	0.981136	0.535334
E	0.933559	0.840579	0.98517	0.979681	0.388025
F	0.983945	0.903749	0.993362	0.993255	0.493439
G	0.938936	0.821059	0.979014	0.983269	0.454017
H	0.915462	0.815895	0.959102	0.965788	0.429927
I	0.866266	0.779643	0.911349	0.937483	0.408549
J	0.935811	0.839958	0.968872	0.981288	0.471253
K	0.911927	0.817764	0.956567	0.968881	0.438587
L	0.887376	0.796324	0.954743	0.952376	0.370301
M	0.865376	0.782769	0.914361	0.936221	0.388177

The curve fitting results of in vitro drug release data indicated that release of perindopril terbutylamine from hydrogel follows Korsmeyer Peppas model. The value of release exponent (n) determined from in vitro release data of various hydrogels ranges from, 0.383359 to 0.388177 indicating mostly the anomalous (nonfiction) diffusion mechanism of drug release demonstrates both diffusion controlled and swelling controlled drug release from hydrogel containing perindopril terbutylamine.

CONCLUSION

Hydrogel has been prepared by cross linking the polymer CMC,MC by means of suitable cross linking agent, citric acid. Due to the cross linking reaction hydrogel shows good swelling property. Formulated hydrogel of Perindopril terbutylamine would be a good alternative to the controlled release drug delivery system.

In this study Central composite design which was used by using Design-Expert 8.0.7.1. It has given 13 runs. From the results it can be concluded that the effect of citric acid concentration on drug content and drug release is nonsignificant. But the effect of citric acid concentration on swelling index is much significant. Effect of reaction time on drug content as well as on drug release is much significant. As reaction time increases there is increase in drug content of hydrogel and vice versa. Again as the reaction time increases there is increase in drug release of hydrogel.

From this entire discussion it can be concluded that the optimized batch from all prepared hydrogel runs is R2. So all responses, drug content, swelling index and drug release of this run are maximum. Drug content, swelling index of this run are 181.56mg/gm,94.14mg/mg, and drug release goes on increasing with respect to time. As all responses are maximum as expected therefore it can be concluded that the optimized batch from all runs of hydrogel formulations is R2. Further, their potential to improve bioavailability of a highly water soluble drug, Perindopril terbutylamine could be established by in vivo evaluation of hydrogel in animals and/or humans.

REFERENCES

1. Jain NK. Progress in controlled and novel drug delivery systems, New Delhi: CBS Publication. 2010; 341-360.
2. Vyas SP, Khar RK. Controlled drug delivery concepts and advances. New Delhi: Vallabh Publication. 2010; 155-170.
3. Drug bank. Available from: <http://www.drugbank.ca/drugs/DB00264>.
4. Florey K. Analytical profiles of drug substances. Volume 12, Elsevier Publication. 2005; 325-353.
5. Chein YW. Novel drug delivery systems. New York: Marcel Dekker Inc. 1992; 139-196.
6. Donald L. Handbook of pharmaceutical controlled release technology, New York: Marcel Dekker, Inc. 2008; 211-216.
7. Hoare TR, Kohane DS. Hydrogels in drug delivery: Progress and challenges. Cambridge: Polymer. 2008; 4(1): 1993-2007.
8. Donald L. Handbook of pharmaceutical controlled release technology, New York: Marcel Dekker, Inc. 2008; 217-224.
9. Chein YW. Novel drug delivery systems. New York: US Informa Healthcare, Inc. 2011; 91-93.
10. Vyas SP, Khar RK. Controlled drug delivery concepts and advances. New Delhi: Vallabh Publication. 2010; 171-195.
11. Sharaf S, Hashem M, Hady MM. Synthesis and characterization of novel carboxymethyl cellulose hydrogels and carboxymethyl cellulose hydrogels-ZnO-nanocomposites. Dokki: Carbohydrate Polymers. 2013; 2(1): 421– 427.
12. Ameduri B, Tillet G, Boutevin B. Chemical reactions of polymer cross linking and post-cross linking at room and medium temperature. Gerhardt: Progress in Polymer Science. 2011; 4(1): 191–217.
13. Martens PJ, Bryant SJ, Anseth KS. Tailoring the degradation of hydrogels formed from multivinyl poly(ethylene glycol) and poly(vinyl alcohol) macromers for cartilage tissue engineering. Biomacromolecules. 2003; 283-292.

14. Niamlang S, Sirivat A. Electrically controlled release of salicylic acid from poly(p-phenylene vinylene)/polyacrylamide hydrogels. *International Journal of Pharmacy*. 2009; 126-133.
15. Singh B, Chauhan N, Kumar S. Radiation crosslinked psyllium and polyacrylic acid based hydrogels for use in colon specific drug delivery. *Carbohydrate Polymer*. 2008; 1(2): 446-455.
16. Metters AT, Schoenmakers RG, Hubbell JA. Poly(ethylene glycol) hydrogels formed by conjugate addition with controllable swelling, degradation, and release of pharmaceutically active proteins. *Journal of Control Release*. 2005; 619-627.
17. Devine DM, Devery SM, Lyons JG, Geever LM, Kennedy JE, Higginbotham CL. Multifunctional polyvinylpyrrolidinone-polyacrylic acid copolymer hydrogels for biomedical applications. *International Journal of Pharmacy*. 2006; 50-59.
18. Chein YW. *Novel drug delivery systems*. New York: US Informa Healthcare, Inc. 2011; 92-93.
19. Gawish SM, Ramadan AM, Abo SM, Kheir AA. Citric acid used as a cross-linking agent for grafting β -Cyclodextrin onto wool fabric. *Polymer Plastic Technology and Engineering*. 2009; 701-710.

IJSER