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Formulation And Evaluation Of Skeletal Muscle Relaxant Topical Gel

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ABSTRACT

The formulation and evaluation of a skeletal muscle relaxant topical gel aim to provide localized relief from muscle spasms and pain while minimizing systemic side effects. This study focuses on the development of a gel containing a selected muscle relaxant, which is optimized for skin permeability and therapeutic efficacy. Various gelling agents, such as carbopol and hydroxypropyl methylcellulose (HPMC), were employed to achieve the desired viscosity and stability. The gel's physicochemical properties, including pH, viscosity, and spreadability, were systematically evaluated. In vitro drug release studies were conducted using Franz diffusion cells to assess the permeation of the active ingredient through synthetic membranes. Additionally, stability testing was performed under different storage conditions to ensure product integrity over time. The formulation demonstrated promising results in terms of drug release kinetics and skin compatibility. Efficacy was further validated through in vivo studies, showcasing significant muscle relaxation effects in animal models. This topical gel represents a novel approach to managing musculoskeletal discomfort, offering a targeted and effective alternative to traditional oral medications.

KEY WORDS : Topical, Drug, Gel, Properties

INTRODUCTION

Topical drug delivery systems are gaining in popularity and several drugs have been successfully delivered by this route for both local and systemic action. Drug delivery through skin has been a promising concept for a long time because skin is easy to access, has a large surface area with vast exposure to the circulatory and lymphatic networks and route is non-invasive. Topical preparation avoids the GI-irritation, prevent the metabolism of drug in liver and increase the bioavailability of the drug. Topical preparations give its action directly at the site of action due to the first pass effect only 25-45% of the orally administered dose reaches the blood circulation. In order to avoid these problems the gel formulation have been designed for topical application.

Advantages

1. Minimizing the side effects associated with use oral therapy.
2. Enhanced penetration into the affected joints(s) or inflamed area(s).
3. Safe and effective as compared to oral and rectal routes.
4. Increase patient compliance.
5. Maintains constant blood levels for longer period of time.
6. Easy to discontinue in case of toxic effects.

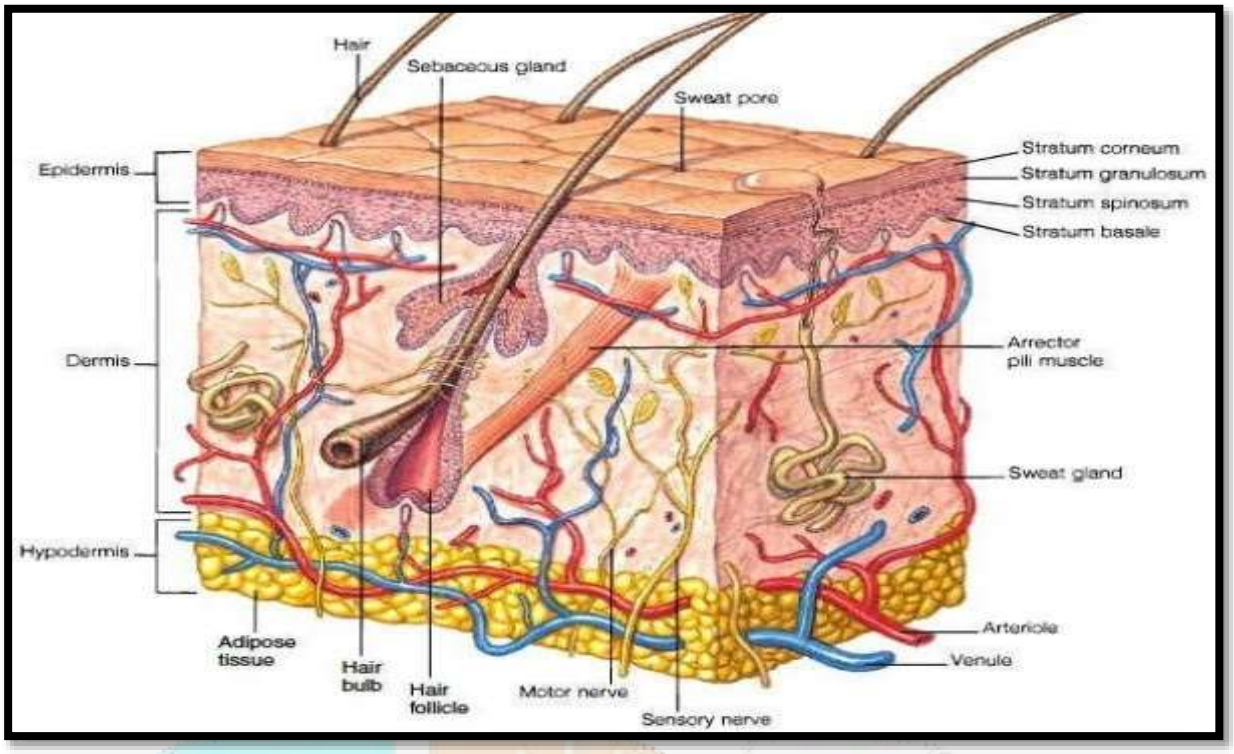
CRITERIA FOR THE SELECTION OF DRUG TOPICAL DRUG DELIVERY SYSTEMS

Physiochemical properties:-

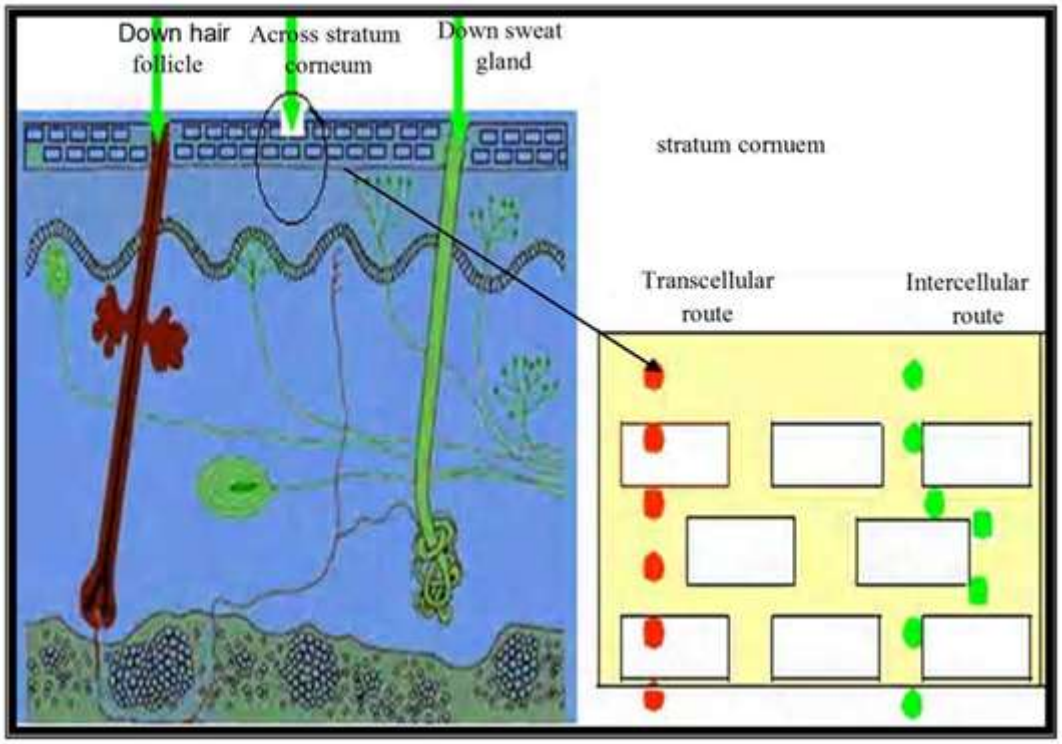
1. The drug should have a molecular weight less than approximately 1000 Daltons.
2. The drug should have affinity for both lipophilic and hydrophilic phases.
3. Extreme partitioning characteristics are not conductive to successful drug delivery via the skin.
4. The drug should have a low melting point.

Biological Properties:-

1. The drug should be potent with daily dose of the order of a few mg/ day.
2. The half –life (t/1/2) of the drug should be short.
3. The drug must not include a cutaneous irritant or allergic response.
4. Drug which degrade in GI tract or are inactivated by hepatic first pass effect are suitable candidates for topical delivery.
5. Tolerance to the drug must not develop under the near zero order profile to topical delivery.
6. Drugs which have to be administered for a long period of time or which cause adverse effect to non-target tissues can also, be formulated for topical delivery.
7. Drug should not get extensively metabolized in skin



Structure of skin



Permeation Route :- Transcellular route, Intercellular route, Transappendageal

Gel :

A gel is a two-component, cross linked three-dimensional network consisting of structural materials interspaced by an adequate but proportionally large amount of liquid to form an infinite rigid network structure which immobilizes the liquid continuous phase within.

Properties of gel :

- Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert safe and should not react with other formulation components
- The gelling agent include in the preparation should produce a reasonable solid- like nature during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube, or during topical application.
- It should possess the suitable anti- microbial to prevent from microbial attack.
- The topical gel should be non-tacky.

Gel are classified according to following ways :

1. According to source of gelling agent:
   Natural gel
   Synthetic gel
2. According to liquid medium entrapped
   Hydrogel
   Organogel
3. According to their cross-linkage:
   Chemical gel
   Physical gel
4. According to the chemical nature of the gelling agent:
   Organic gels
   Inorganic gels

Methods of Preparation of Gel :

- Dispersion Method
- Cold Method
- Chemical Reaction
- Temperature Effect
- Flocculation with Salts and Non-Solvents

Need For Study

- First pass metabolism.
- Shorter biological half –life 2.5 hours.
- Minimizing systemic side effects.

AIM :- Formulation and Evaluation of Skeletal Muscle Relaxant Topical Gel

OBJECTIVE OF THE STUDY

- To formulate the topical gel of Tizanidine hydrochloride by using Carbopol 934 as synthetic gelling agent and HPMC K100M as a semisynthetic agent separately and compare the effectiveness of them
- To study the effects of penetration enhancer conc. on drug release.
- To evaluate gel formulation with respect to various physiochemical parameters.
- To evaluate gel formulation for in- vitro release studies.
- To study ex-vivo permeation and skin irritation of gel formulation of optimized batches.
- To check the stability of gel formulation as per ICH guideline.

Plan of work

- Literature review
- Selection & procurement of drug & suitable excipients
- Pre-formulation study
- Formulation development
- Evaluation of formulation
- In-Vitro release study
- Ex-vivo, Skin irritation and
- Stability study of optimized batch
- Result and Discussion
- Summary & conclusion

List of Materials

Sr No	Name of Material	Manufacture
1.	Tizanidine HCL IP	Aarati Pvt. Ltd., Mumbai.
2.	Carbopol 934	Corel Pharma
3.	HPMC K 100M	Research Lab, Mumbai
4.	Methyl Paraben	Allay Pharma, Mumbai
5.	Propyl Paraben	Research Lab Fine Chemie Industries, Mumbai
6.	DMSO	Research Lab, Mumbai
7.	Propylene Glycol	Loba chemical Pvt. Ltd., Mumbai

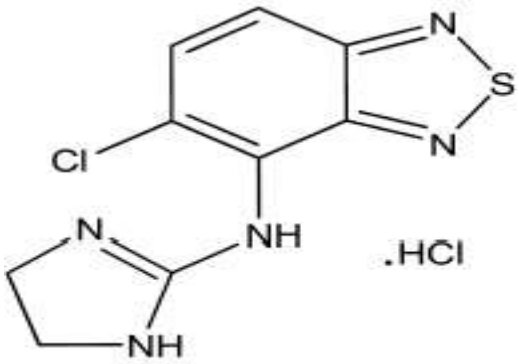
List of Instruments

Instruments	Manufacturer	Model No
Digital Electronic Balance	Schimadzu corporation Japan	AUX 220
FTIR	Jasco, Japan	FTIR 410
Lab Stirrer	Remi	RA-121-D
Digital pH meter	Equiptronics	CL 180
UV spectrophotometer	Jasco	V-550
Stability Chamber	Remi instruments	CNM 10 S
Franze Diffusion Cell	Logan Instruments Ltd.	SFDC- 6
Homogenizer	Remi Instruments	RQ- 127 A
Cooling Centrifuge	Remi Instruments	C-24BL
Bath Sonicator	Lab-Hosp Corporation	LHC- 670
Melting point apparatus	LABINDIA	MEPA

DRUG PROFILE

Name-Tizanidine Hydrochloride

Chemical name: 5-choro-N-(4, 5-dihydro-1H-imidazole 2-yl)-2, 1, 3-benzothiadazol-4-amine

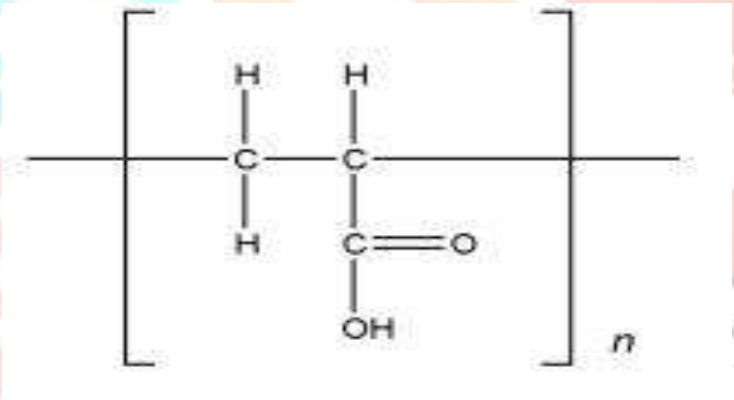


Physicochemical Properties	Parameters
Molecular formula	$C_9H_9ClN_5S$
Molecular weight	253.711dalton
Category	Skeletal muscle relaxant
Melting point	285-289^{0}C
Half life	about 2 - 2.5 h.
Solubility	slightly soluble in water and methanol also freely soluble in DMSO

Carbapol 934

Synonym: Acrylic acid

Functional Category: Viscosity increasing agent.



Acrylic acid monomer unit in carbomer resins.

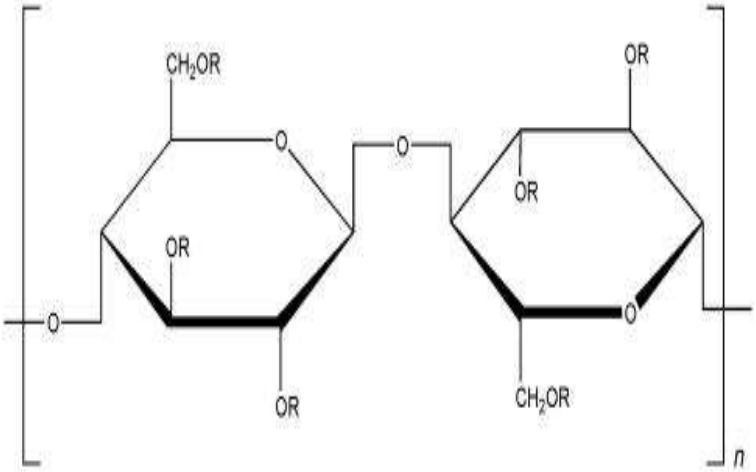
Physicochemical Properties

Properties	Parameters
Description	White or similar to white fiber or granular powder
Chemical name	carbomer 934.
Viscosity	4000 mPa
Solubility	Soluble in water, ethanol (95%), glycerin

Hydroxypropylmethylcellulose K100M

Synonym: Methocel K100M

Functional Category: Viscosity increasing agent



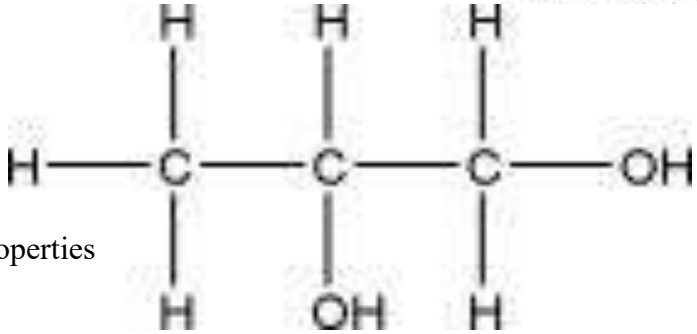
Physicochemical Properties

Properties	Parameters
Description	White or creamy white fibrous or granular powder.
Chemical name	Cellulose 2-Hydroxypropyl methyl ether
Viscosity	10,000 mPa
Solubility	Soluble in cold water, ethanol

Propylene Glycol

Synonyms: 1, 2- Dihydroxypropane

Functional Category: Penetration agent; solvent



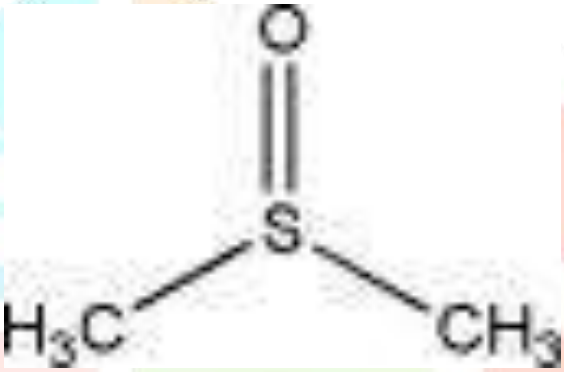
Physicochemical Properties

Properties	Parameters
Description	Clear, colourless, viscous, practically odourless liquid with a sweet, slightly acrid taste resembling that of glycerin.
Chemical name	Sulfinylbismethane
Viscosity	58.1mPas (58.1cP) at 20^0 C.
Solubility	Miscible with acetone, chloroform, ethanol (95%), glycerin, and water

Dimethyl sulphoxide

Synonym: Methylsuifoxide

Functional Category: Penetration agent; solvent



Physicochemical Properties

Properties	Parameters
Description	colourless, viscous liquid
Chemical name	Methylsuifoxide
Viscosity	1mPa s (1.1cP) at 27^0 C
Solubility	Miscible with ethanol (95%), ether and organic solvents. Practically insoluble in acetone, chloroform, ethanol (95%) and ether.

EXPERIMENTAL WORK

1. Melting point

It was determined by using melting point apparatus.

2. IR spectroscopy

The spectra were scanned over wavelength region of 4000 to 400 cm^{-1}at resolution of 4 cm^{-1}.

3. UV Spectroscopy

The spectra of Tizanidine hydrochloride in DMSO was examined between 200-400nm, the solution shows maxima at 320nm.

Polymer Authentication

IR spectroscopy: The spectra were scanned over wavelength region of 4000 to 400 cm^{-1}at resolution of 4 cm^{-1}

Preparation of Trial Batches

In this two polymers i.e. Carbopol 934 and HPMC K100M are used with four different concentrations as gelling agent

Carbapol 934 (0.25%, 0.50%, 0.75%, 1%)

HPMC K 100 M (0.50%, 0.75%, 1%, 1.5%)

After preparation of trial batches, concentration of Carbopol 934 and HPMCK100M was finalized.

Preparation of Trial Batches of Gel

Drug (mg)	Carbop-ol934 (g)	HPMCK 100M (g)	Propyl paraben (g)	Methyl paraben (g)	Ethanol (ml)	Propyl-ene glycol (ml)	TEA	Purified water upto (ml)
50	0.25	-	0.03	0.01	5		Adjust pH6-6.5	100
50	0.50	-	0.03	0.01	5	5		100
50	0.75	-	0.03	0.01	5	5		100
50	1	-	0.03	0.01	5	5		100
50	-	0.50	0.03	0.01	5	5		100
50	-	0.75	0.03	0.01	5	5		100
50	-	1	0.03	0.01	5	5		100
50	-	1.5	0.03	0.01	5	5		100

Optimization:

It is desirable to develop an expectable pharmaceutical formulation in the shortest period of time using minimum number of man-power and raw materials. In addition to the art of formulation, factorial design is an efficient method of indicating the relative significance of a number of variables and their interaction.

Factorial Design:

A 2^2 full factorial design with two independent variables at one levels were employed for study. 2^2 factorial design was used for study between DMSO conc. and Propylene glycol conc.

Independent Variables:

X_1 -Concentration of propylene glycol

X_2 - Concentration of DMSO.

Dependent variables:

Y_1 - Cumulative % of drug release at 6 hours

Level for optimization

Coded values	Actual Values	
	X_1(%V/W)	X_2(%V/W)
-1	5	7
+1	10	12

Scheme for 2^2 Factorial Design

Batches	Concentration of propylene glycol(%)	Concentration of DMSO (%)
C_1	10	7
C_2	5	7
C_3	10	12
C_4	5	12

Composition of Carbopol934 based batches

Ingredients	Formulation Batches			
	C_1	C_2	C_3	C_4
Tizanidine hydrochloride (mg)	50	50	50	50
Carbopol934 (g)	0.5	0.5	0.5	0.5
Propylene glycol (ml)	10	5	10	5
DMSO (ml)	7	7	12	12
Ethanol (ml)	5	5	5	5
Methyl paraben(g)	0.03	0.03	0.03	0.03
Propyl paraben(g)	0.01	0.01	0.01	0.01
Purified water (ml) Upto	100	100	100	100
Triethanolamine	Adjust pH 6-6.5			

Composition of HPMC K 100M based batches

Ingredients	Formulation Batches			
	H_1	H_2	H_3	H_4
Tizanidine hydrochloride (mg)	50	50	50	50
HPMCK100M (g)	1.5	1.5	1.5	1.5
Propylene glycol (ml)	10	5	10	5
DMSO (ml)	7	7	12	12
Ethanol (ml)	5	5	5	5
Methyl paraben(g)	0.03	0.03	0.03	0.03
Propyl paraben(g)	0.01	0.01	0.01	0.01

Purified water (ml) Upto	100	100	100	100
Triethanolamine	Adjust pH 6-6.5			

Preparation Of Gel

- Accurately weigh polymer and add in 50 ml of distilled water.
- Kept the beaker aside for half an hour to swell the polymer.
- Prepare solution of drug by using water.
- Then take propylene glycol and DMSO in another beaker and add preservative.
- Then by using mechanical stirrer at 1200 rpm mixed the prepared solution of drug and preservative.
- Then finally volume made upto 100ml by adding water and Triethanolamine added dropwise for adjustment of skin pH (6-6.5)
- Then kept the beaker 24 hours in dark.

Parameters and Optimized Condition

Parameters	Optimized Conditions
RPM for gel preparation	1200 rpm
Time for gel preparation	½ hour
Quantity of triethanolamine	q.s. to adjust pH (6-6.5)

Characterization of gel

- Physical appearance
- Extrudability
- Measurement of pH
- Spreadability
- Rheological study
- % Drug content
- In-vitro drug release

Characterization of optimized batches

- Ex-vivo permeation study
- Skin irritation study
- Stability study

In-vitro Characterization Optimized Condition

Parameters	Optimized condition
Receptor compartment	Phosphate buffer pH 7.4
RPM of diffusion cell	50 rpm
Systems temperature	37±0.5^{0}C
Sampling volume	1 ml

Results and Discussion

Preformulation Study

Drug Authentication

Organoleptic properties of Tizanidine hydrochloride

Criteria	Observation
Colour	White- yellowish
Odour	Odourless
Nature	Crystalline powder

Solubility of Tizanidine hydrochloride

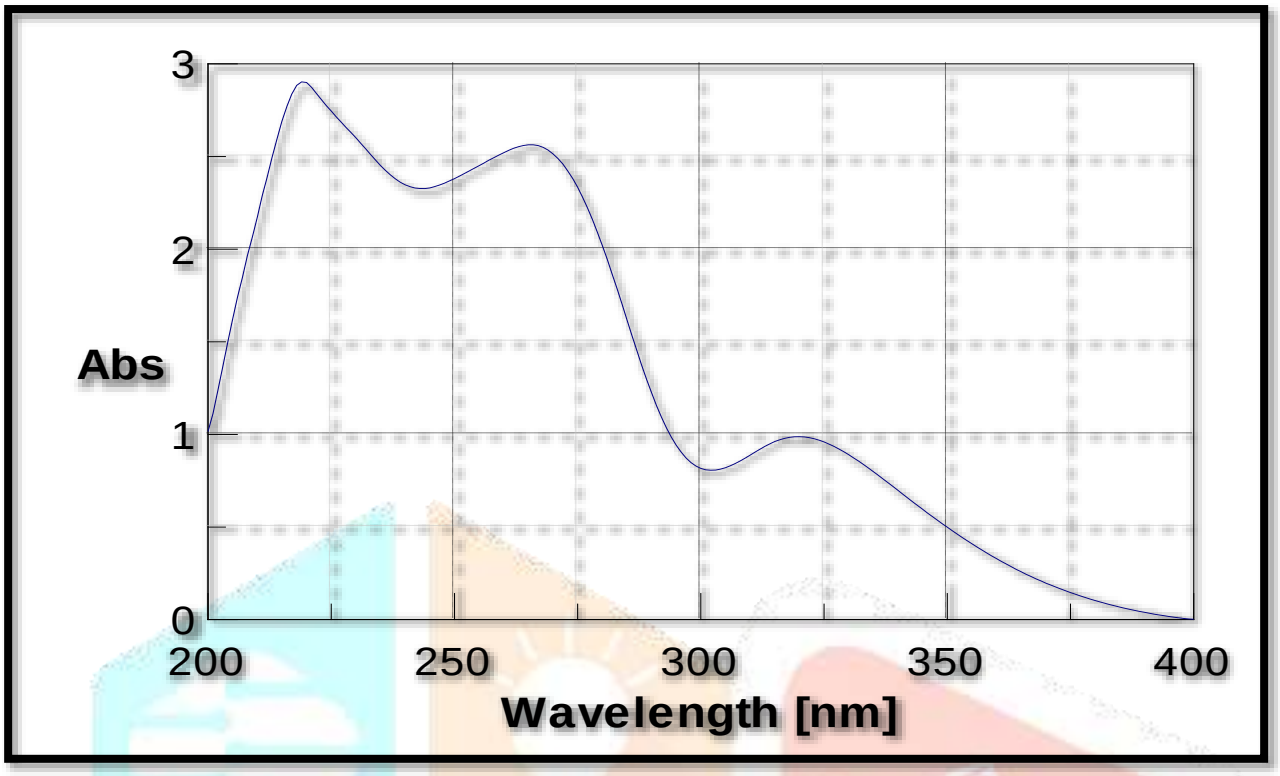
Medium	Tizanidine hydrochloride
Distilled water	Soluble
Methanol	Soluble
DMSO	Soluble
Phosphate Buffer pH 7.4	Soluble

Melting point:

Digital melting point apparatus: 285-288^0 C as per literature

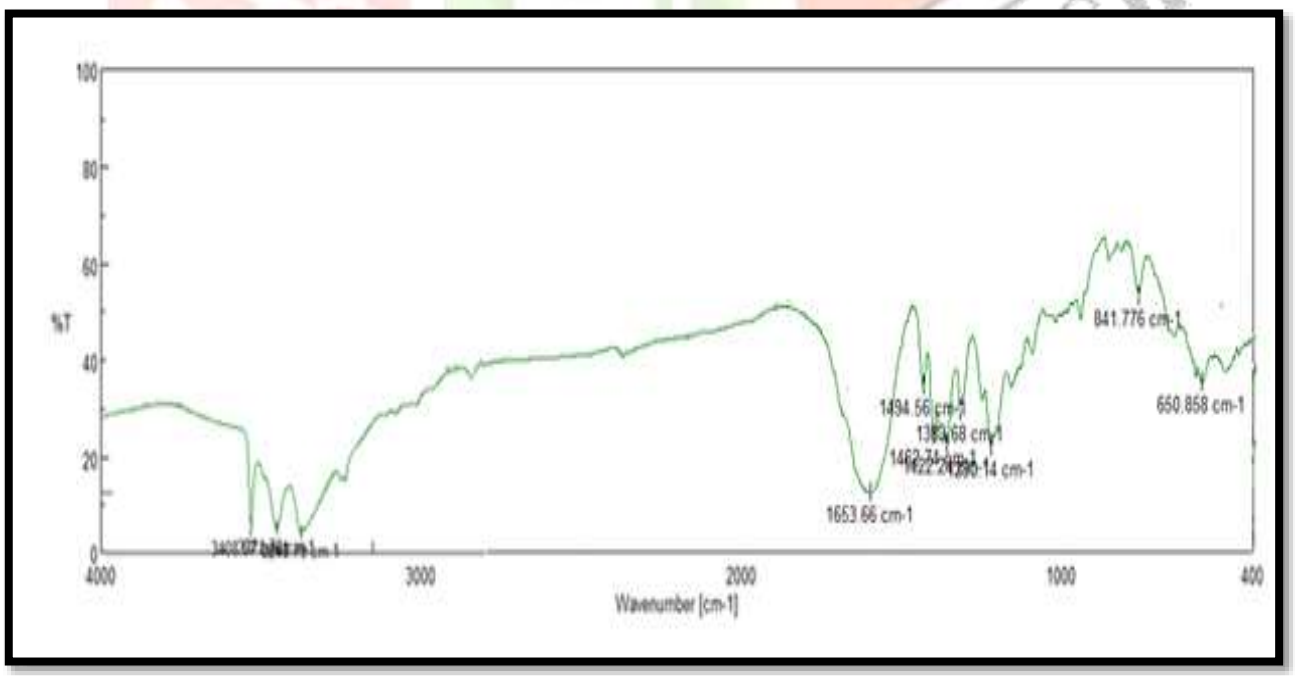
UV Spectroscopy

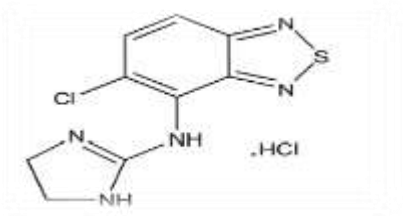
UV Scan of Tizanidine Hydrochloride in Phosphate Buffer pH 7.4



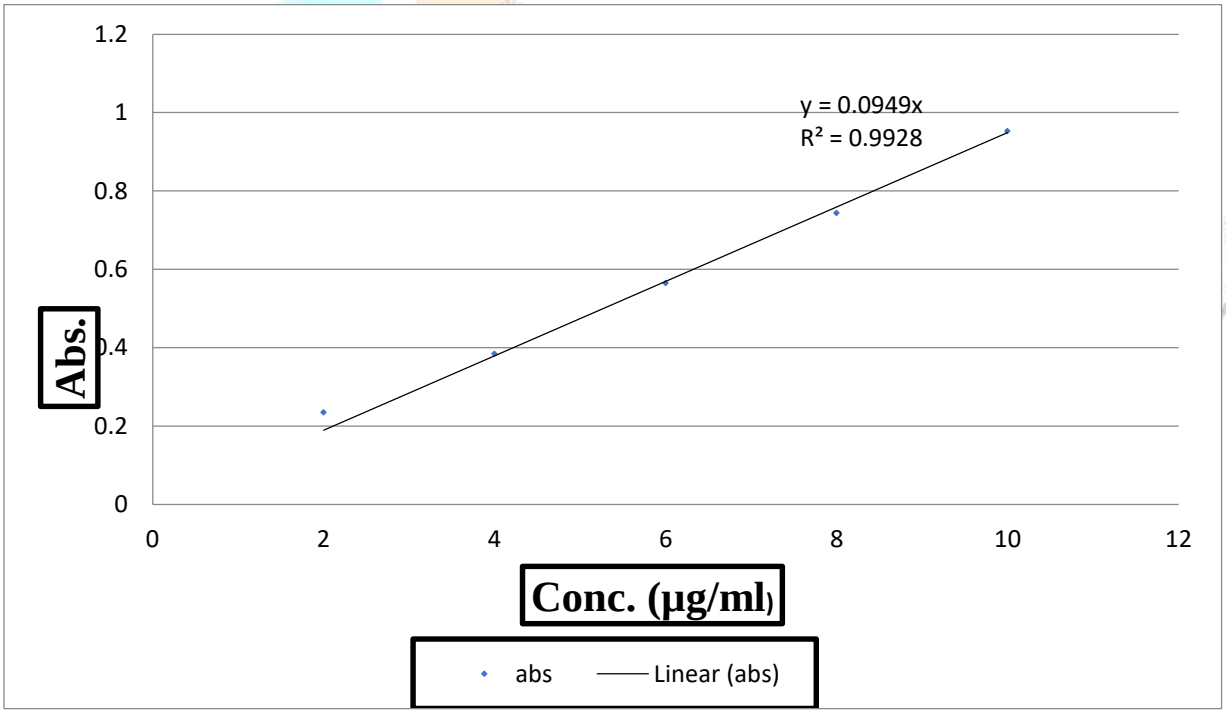
IR Spectroscopy

IR spectrum of Tizanidine hydrochloride



Sr no.	Tizanidine hydrochloride structure	Peaks cm^{-1}	Indication	Functional Group
1		3376.44	N=H Stretch	Amide group
2		1663.66	C=N Stretch	Nitriles
3		1473.64	C =C stretch	Aromatic ring
5		650.85	C-Cl Stretch	Alkyl halide

Calibration Curve of Tizanidine hydrochloride in Phosphate Buffer pH 7.4



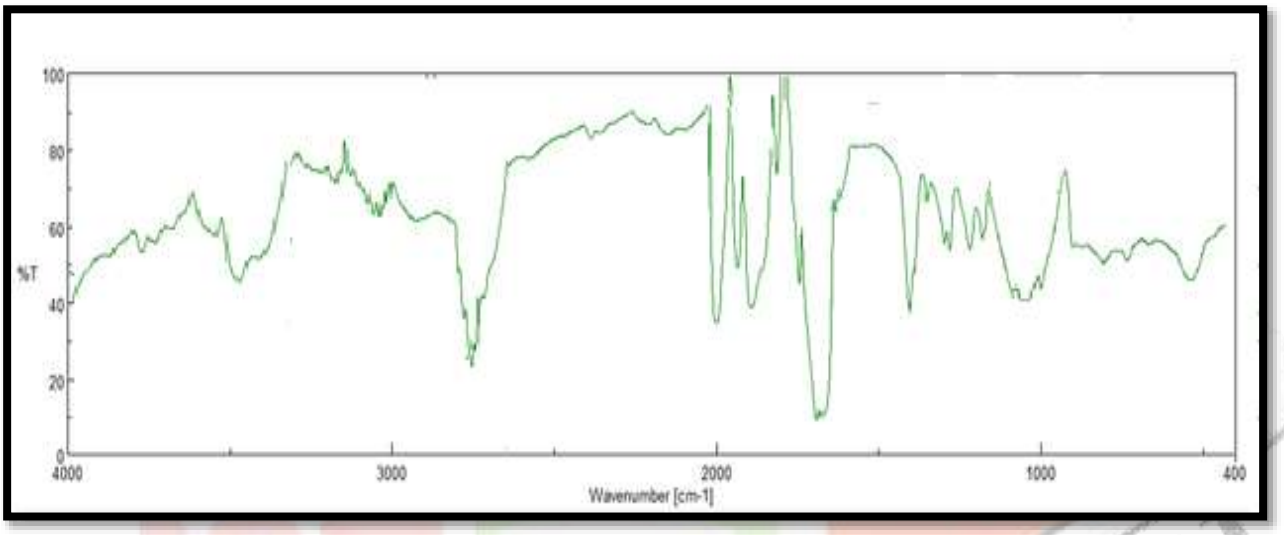
Absorbance of Tizanidine hydrochloride in phosphate buffer7.4

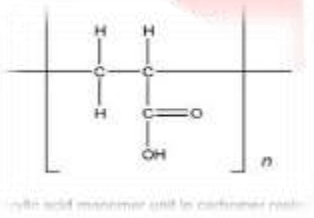
Sr. no,	Concentration (mcg/ml)	Absorbance
1.	2	0.235±0.011
2.	4	0.385±0.012
3.	6	0.565±0.013
4.	8	0.744±0.011
5.	10	0.953±0.013

Values of Tizanidine hydrochloride calibration curve

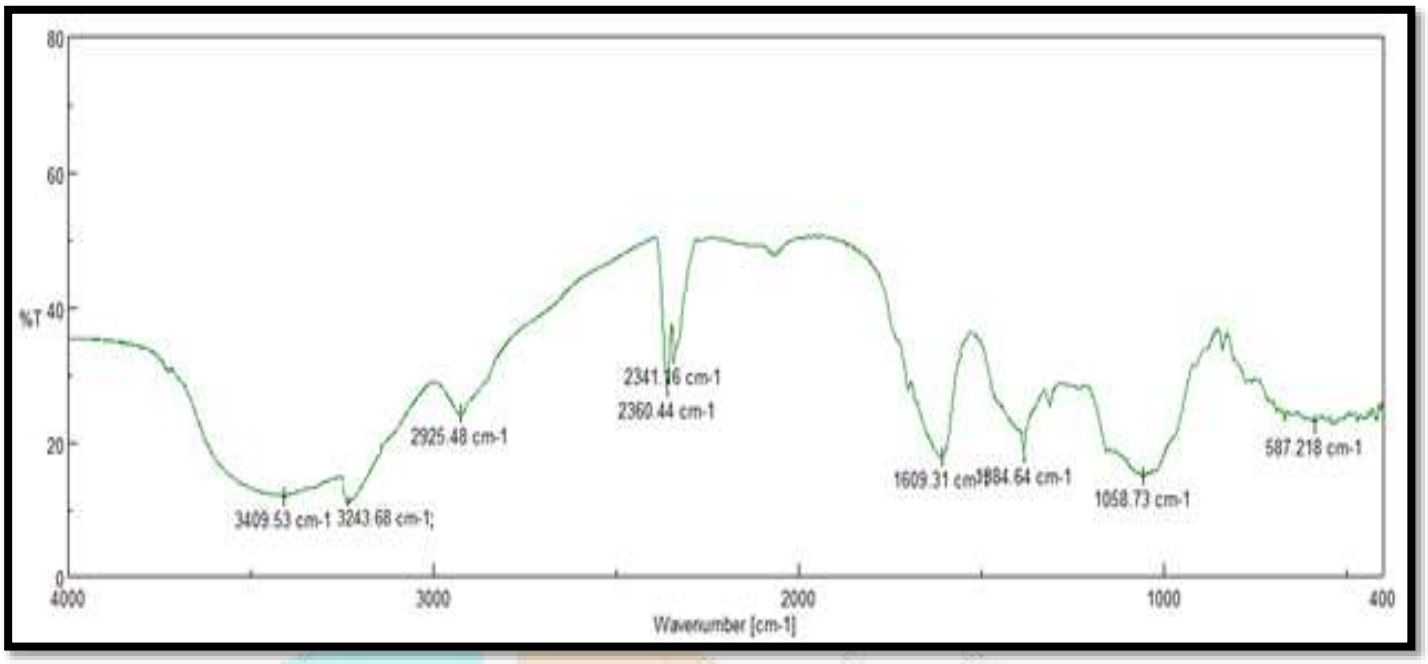
Absorption maxima(nm)	320
Slope(m)	0.0949
Intercept(c)	0
Coefficient of correlation(r)	0.9928

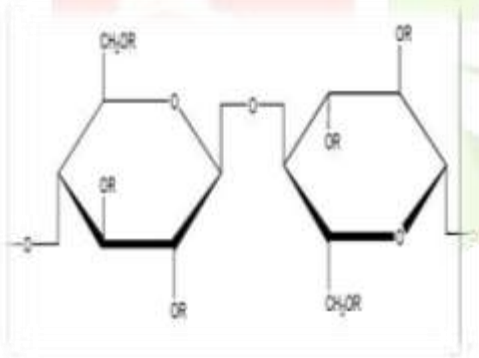
Polymer Authentication : IR of Carbopol 934



Sr. no.	Carbopol 934 structure	Peaks cm^{-1}	Indications	Functional Group
1		2950.33	O-H Stretching vibration	Hydroxyl group
2		1714.41	C=O stretching vibration	C=O group of acids
3		1450.35	C-O stretching vibration	Carbonyl group of acids
4		850.37	= C-H out of plane bending	Aromatics and enes

IR of HPMC K 100M



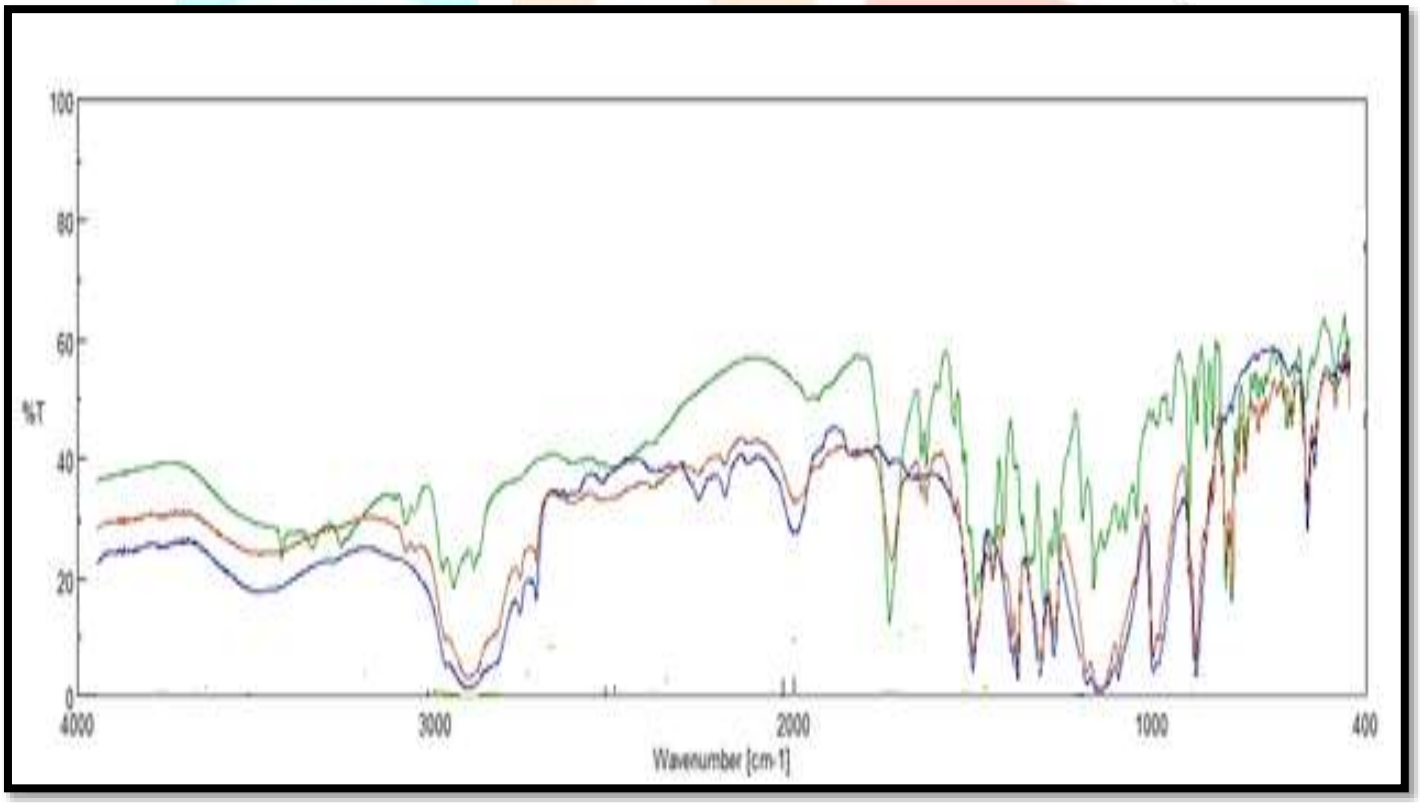
Sr. no.	HPMCK100M structure	Peaks cm^{-1}	Indications	Functional Group
1		1058.7	aliphatic C-O stretching	Ether group
2		2925.4	C-H Stretching	Benzene ring
3		3243.6	N-H Stretching	Primary amino group
4		3409.53	O-H Stretching	Alcohol

Compatibility by UV visible Spectroscopy

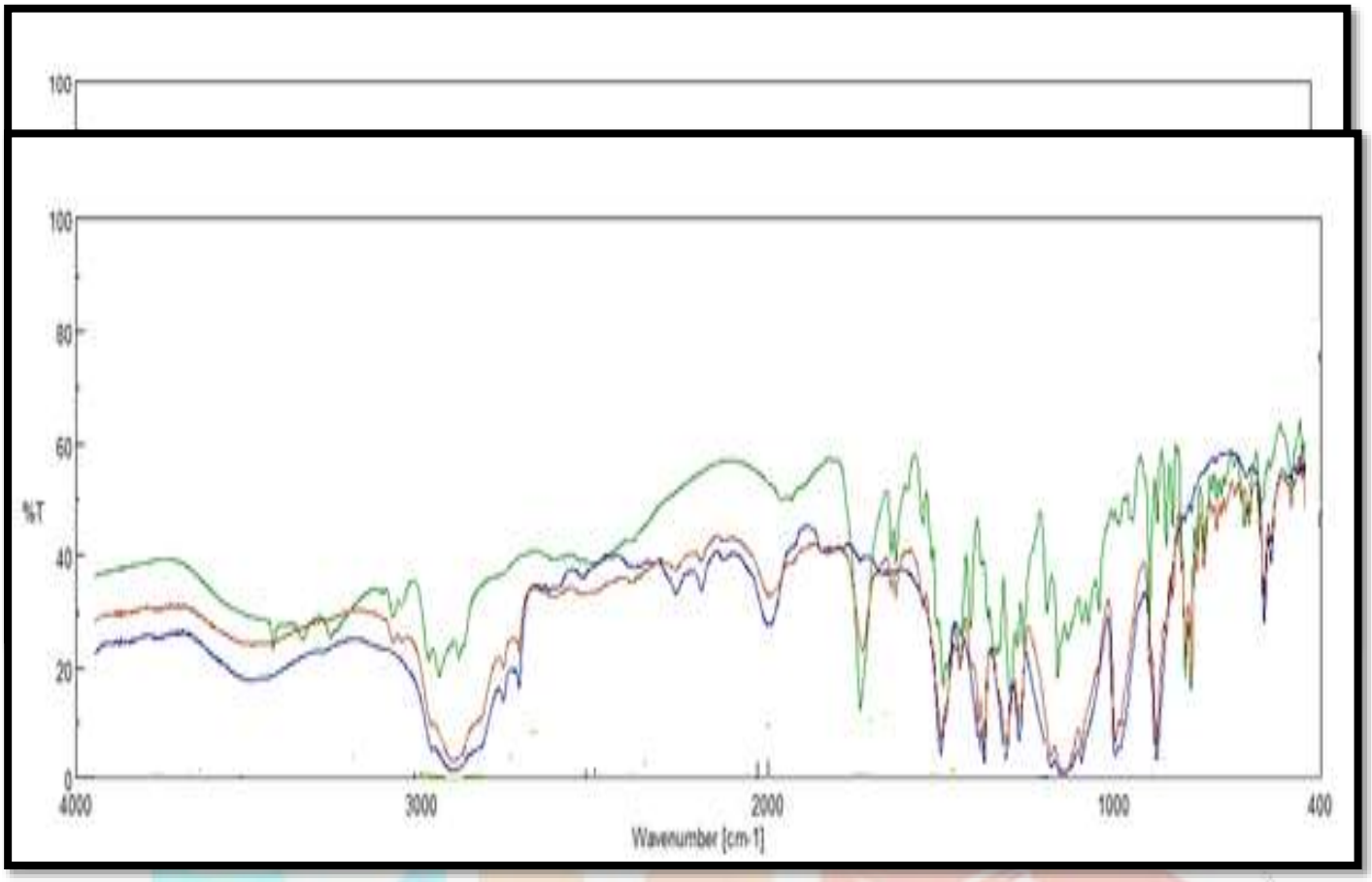
Compatibility study of Tizanidine Hydrochloride by UV Spectroscopy

Sr. No.	Name	Max. wavelength in nm		
		Initial	After 2 weeks	After 4 weeks
1	Physical mixture of Tizanidine hydrochloride + Carbopol934	320	318	320
2	Physical mixture of Tizanidine hydrochloride + HPMCK100M	318	320	320

Compatibility study by IR Spectroscopy



Initial Compatibility



Compatibility after 2 weeks

Compatibility after 4 weeks

Physical appearance of trial batches:-

Batches	Physical appearance
F_1	White transparent
F_2	White transparent
F_3	White transparent
F_4	White transparent
F_5	White transparent
F_6	White transparent
F_7	White transparent
F_8	White transparent

Viscosity of trial batches:-

Batches	Viscosity (cps)	Batches	Viscosity (cps)
F_1	12,440	F_5	11,210
F_2	15,450	F_6	11,409
F_3	17,450	F_7	12,224
F_4	17,421	F_8	13,750

Drug Release of trial batches at 6 hours

Batches	%drug release	Batches	%drug release
F_1	55.26	F_5	51.01
F_2	55.86	F_6	50.09
F_3	49.06	F_7	52.04
F_4	50.65	F_8	53.70

pH of trial batches

Batches	pH
F_1	6.2
F_2	6.4
F_3	6.4
F_4	6.5
F_5	6.6
F_6	6.7
F_7	7.1
F_8	6.5

From results of trial batches get the proper idea for preparation of further batches which gives best results.

Physical Appearance

All formulation batches were found to be homogenous. Clarity and homogeneity of final Carbopol934 based gel

Clarity and homogeneity of final HPMC K100M based gels

Formulation code	Clarity	Homogeneity
C1	+++	Excellent
C2	+++	Excellent
C3	+++	Excellent
C4	+++	Excellent

Formulation code	Clarity	Homogeneity
H1	+++	Excellent
H2	+++	Excellent
H3	+++	Excellent
H4	+++	Excellent

Extrudability of final batches

Batches	Extrudability amount (%)	Batches	Extrudability amount (%)
C1	89.80	H1	89.06
C2	82.81	H2	86.06
C3	85.58	H3	89.97
C4	86.05	H4	91.71

(mean ±(SD, n=3)

Measurement of pH of final batches

Batches	pH	Batches	pH
C1	6.4	H1	6.8
C2	6.2	H2	6.7
C3	6.4	H3	6.6
C4	6.2	H4	6.7

Spreadability of final batches

Spreadability is expressed in terms of time in seconds taken by two slides to slip off from formulation, placed between, under the application of a certain load. Lesser the time taken for the separation of two slides, better the spreadability.

Spreadability was calculated by using following formula:

$$S = M \times L / T$$

Where S = spreadability,

M= weight in the pain (tied to upper side),

L= length moved by the slide,

T = time (in sec).

Batches	Spreadability (gm.cm/sec)
C1	13.09 ± 0.66
C2	15.01± 2.66
C3	16.02± 1.66
C4	14.53±0.66

Batches	Spreadability (gm.cm/sec)
H1	10.05±0.1
H2	11..04±0.2
H3	10.03±0.1
H4	12.03±0.2

Rheological Study:

The measurement of viscosity of prepared topical gel was done with Brookfield viscometer of cone and plate type with spindle no.64

Batches	C1	C2	C3	C4
Viscosity (cps.)	20,334±0.66	16,646±2.66	14,947±1.66	22,703±0.66

(mean ± SD, n=3)

Batches	H1	H2	H3	H4
Viscosity (cps.)	14,666±1.66	13,999±2.29	13,925±0.66	12,999±0.66

(mean ± SD, n=3)

HPMC K 100M based formulation showed low viscosity than Carbopol 934 based formulations.

Drug Content Determination:

Drug content was calculated using the following equation, which was obtained by linear regression analysis of calibration curve. The drug content of all gel formulation is found within range i.e. 97.40±2.44 – 102.86±2.44.

$$Y = 0.0948x$$

$$R^2 = 0.9928$$

Batches	Drug Content	Batches	Drug Content
C1	98.81 ±3.22	H1	101.78±3.77
C2	97.56±2.86	H2	97.40±2.44
C3	99.49±2.99	H3	100.58±1.44
C4	102.63±4.3	H4	102.86±2.44

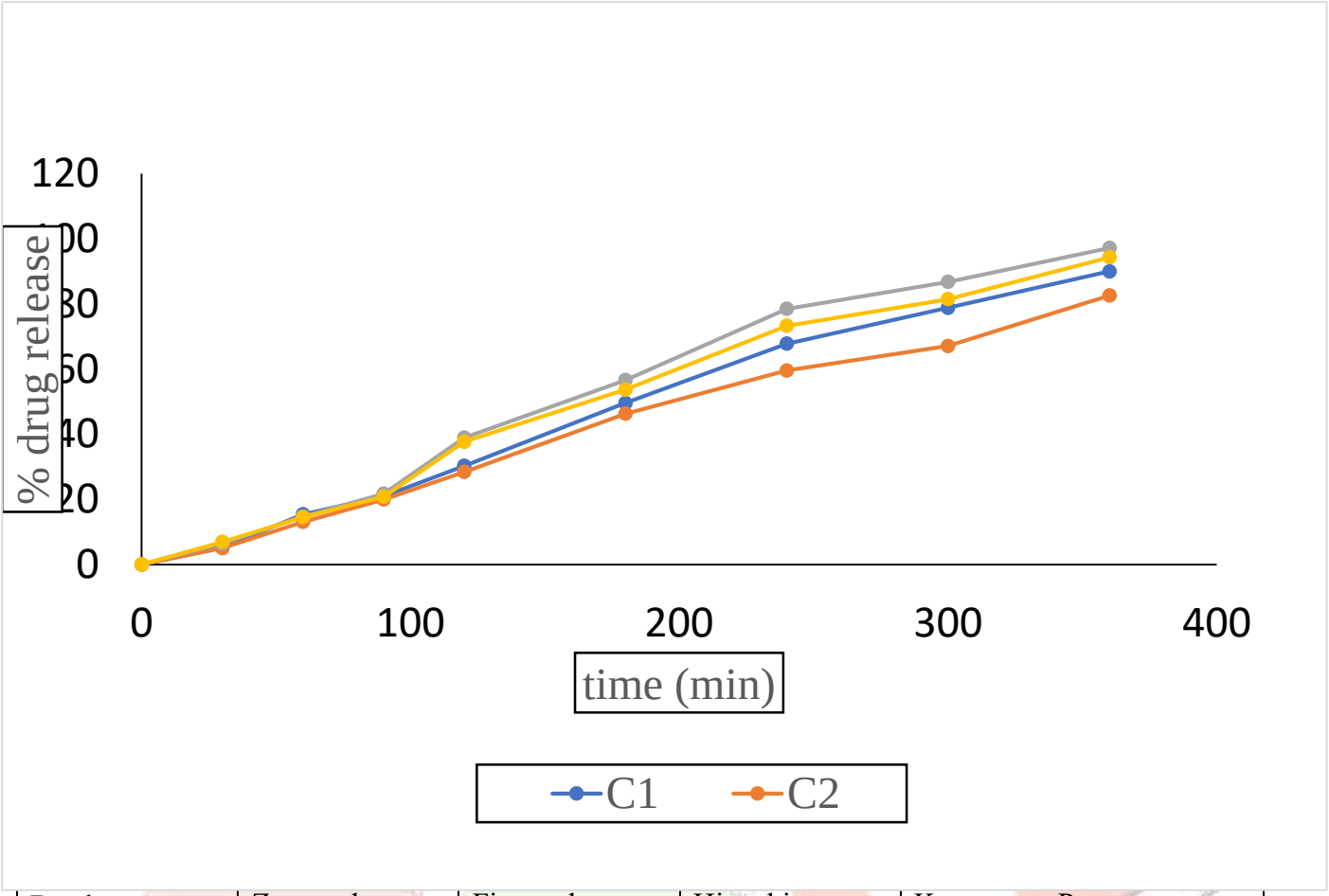
In –vitro Drug Release

In vitro diffusion test was carried out using the flow through method with Modified- Franze diffusion cell. All formulations weighed 1.0 g flattened above the membrane with a surface area of 1 cm^2. System's temperature 37±0.5^{0}C with the receptor phosphate buffer pH 7.4. The assembly was kept on a magnetic stirrer and stirred at 50 rpm. After specific time interval 1ml of sample was withdrawn and replaced with same medium after each sampling and absorbance was taken by UV spectroscopy.

Drug release from Carbopol 934 based formulations (C1-C4)

Time (min)	% in-vitro drug release			
	C1	C2	C3	C4
30	5.2±0.57	5.04±0.57	6.44±0.57	6.95±0.57
60	15.38±0.57	13.09`±1.15	14.70±1.15	14.55±1.15
90	20.92±0.57	19.98±2.30	21.72±2.30	20.81±1.15
120	30.31±1.55	28.45±0.57	38.93±2.37	37.71±0.57
180	49.62±1.73	46.29±1.73	56.64±1.73	53.69±0.57
240	67.79±1.15	59.55±0.57	78.51±0.57	73.31±0.57
300	78.83±1.15	67.08±0.57	86.79±1.15	81.50±.0.57
360	89.99±0.57	82.58±0.81	97.23±0.57	94.43±1.73

In-vitro drug release profile of Tizanidine HCL from (C1-C4) batches



Batches	Zero-order	First order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	N
C1	0.9927	0.9506	0.9150	0.9536	0.7948
C2	0.9931	0.9599	0.9197	0.9532	0.7747
C3	0.9815	0.8713	0.9171	0.9526	0.7461
C4	0.9862	0.9410	0.9196	0.9652	0.8022

Factorial design with surface plot % optimization of process variables

i) Carbopol 934

Coded &Actual value

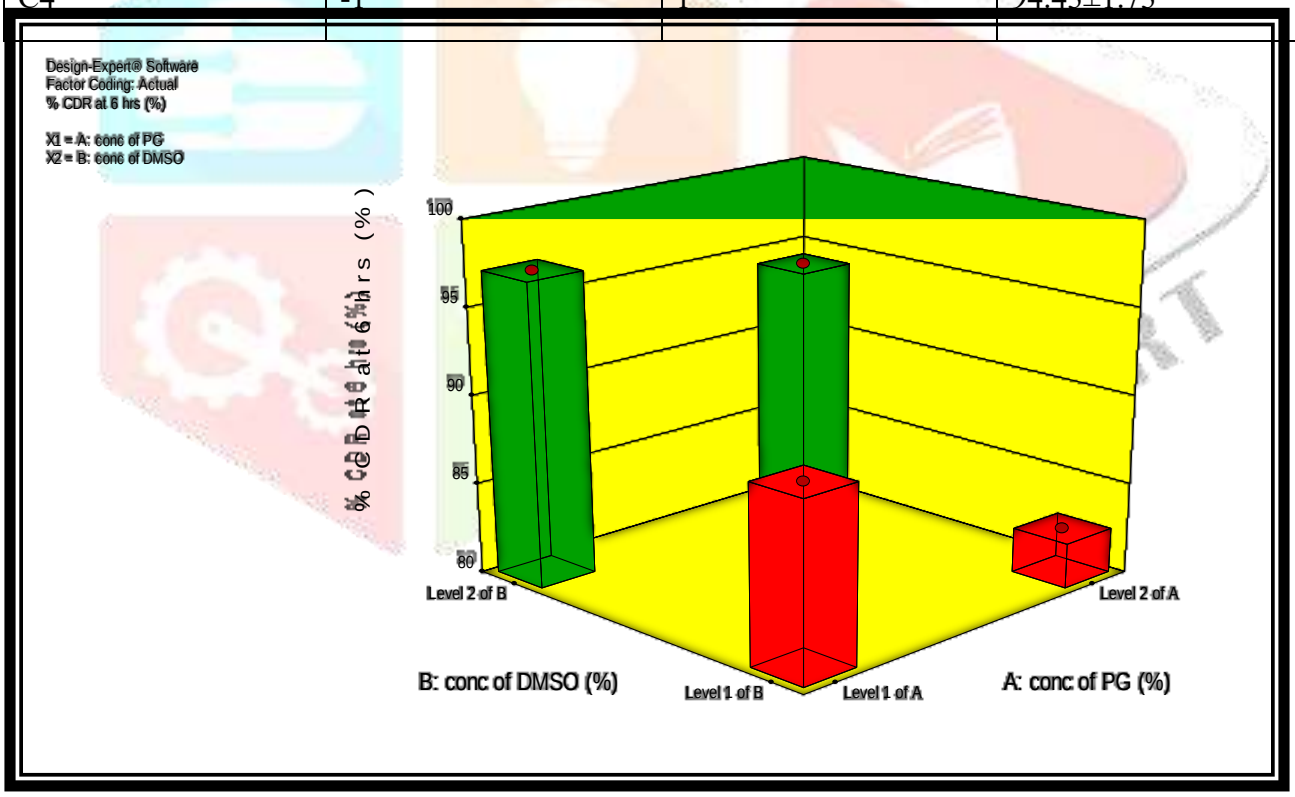
X_1 = Propylene glycol conc.

X_2= DMSO concentration

Coded value	Actual value	
	X_1 (%v/w)	X_2 (%v/w)
-1	5	7
+1	10	12

2^2 full factorial design layout for Carbopol 934 based batches

Batch No.	Variables in coded form		% CDR at 6 hrs
	X_1	X_2	
C1	1	-1	89.99±0.67
C2	-1	-1	82.58±0.81
C3	1	1	97.23±0.57
C4	-1	1	94.43±1.73



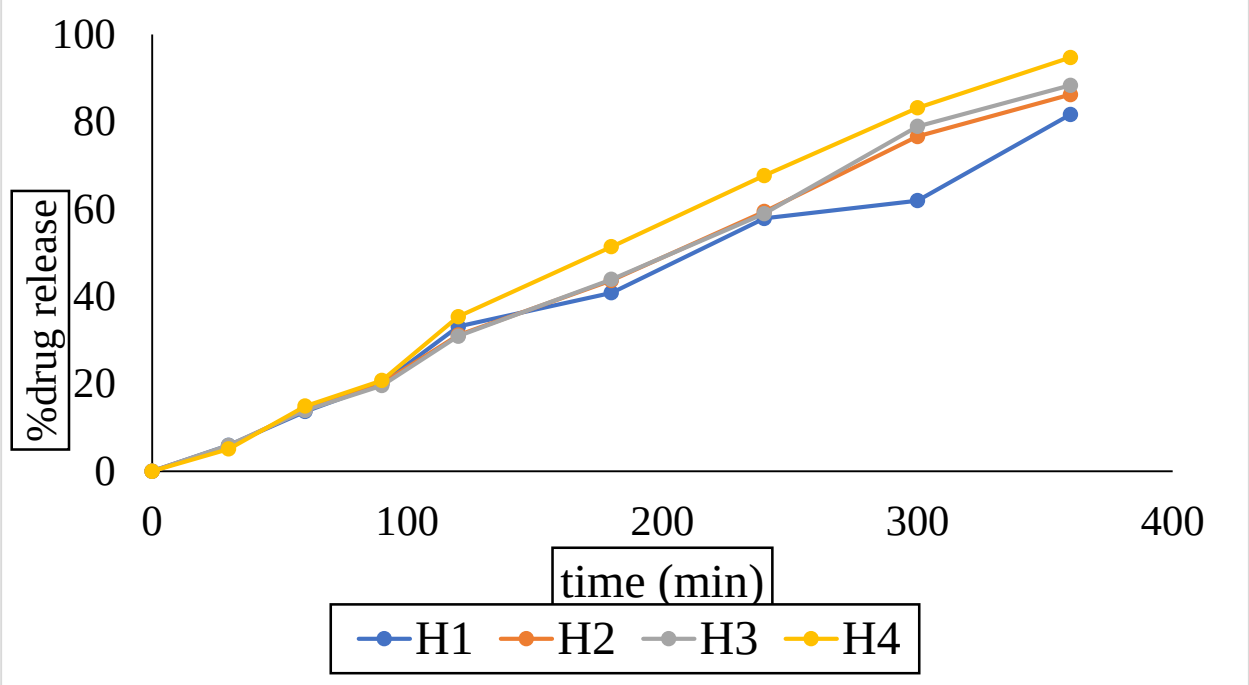
3D response plot for %CDR at 6 hours (C1-C4 batches)

Drug release from HPMCK100M based formulations (H1-H4) batches

Time (min)	% in-vitro drug release			
	H1	H2	H3	H4
30	5.93±1.00	5.76±0.57	5.93±0.57	5.10±1.00
60	13.69±3.46	14.13±1.15	13.94±0.57	14.93±1.00
90	20.08±1.15	20.08±1.00	19.61±1.15	20.79±0.57
120	33.12±0.57	31.17±0.57	30.92±1.73	35.42±0.57
180	40.87±1.15	43.68±0.57	43.93±1.00	51.41±1.00
240	57.92±0.57	59.47±1.13	58.99±1.00	67.71±1.15
300	61.96±0.57	76.47±1.15	78.99±1.55	83.24±1.15
360	81.73±0.57	82.27±0.57	88.40±1.73	94.78±0.57

In-vitro drug release of Tizanidine hydrochloride from

(H1-H4) batches



Drug release kinetics of H1-H4 batches

Batches	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	N
H1	0.9864	0.9370	0.9211	0.9609	0.7052
H2	0.9969	0.9484	0.9125	0.9547	0.7141

H3	0.9959	0.9304	0.9050	0.9544	0.7152
H4	0.9943	0.9064	0.9154	0.9495	0.8054

2^2 full factorial design layout forHPMCK100M based batches

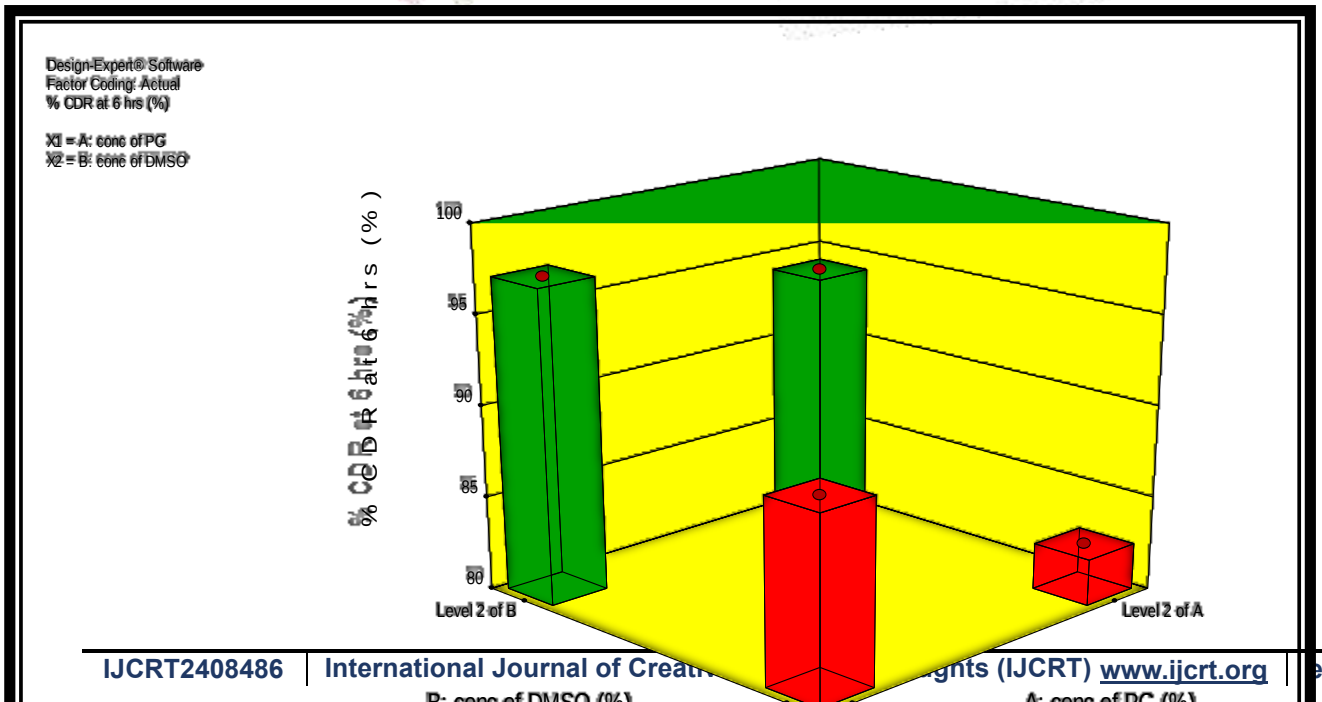
Coded &Actual value

X_1 = Propylene glycol conc.

X_2= DMSO concentration

Coded value	Actual value	
	X_1 (%v/w)	X_2 (%v/w)
-1	5	7
+1	10	12

Batch No.	Variables in coded form		% CDR at 6 hrs
	X_1	X_2	
H-1	1	-1	81.73±0.57
H-2	-1	-1	82.27±0.57
H-3	1	1	88.40±1.73
H-4	-1	1	94.78±0.57



Surface Response plot for % CDR at 6 hours (H1-H4)

It was concluded that the batch H4 and C3 showed good pH, viscosity, spread- ability and also maximum drug diffusion of 94.43% and 97.43% at 6 hours respectively.

Evaluation	C3	H4
pH	6.4	6.7
Spreadability (gm.cm/sec.)	14.53	12.03
Viscosity (cps)	13,999	16,646
% CDR at 6 hours	97.43	94.43

Optimized Batch Characteristics

Optimized Batch Characteristics of C3 and H4 batches

Ex-vivo Diffusion Study:

The gel formulations having maximum release were selected (C3 and H4) for further release study using rat abdominal skin as diffusion barrier

The result were depicted in table and plotted in four models of data treatments.

1) Zero order
2) First order
3) Higuchi model
4) Korsmeyer-peppas model

From the below plots the kinetics value were calculated and listed in table. The degree of linearity of this plots were tested by applying statistical regression analysis from correlation coefficient (R^2) and slope (n) were determined.

Drug Release kinetics of optimized C3 & H4batches

Optimized Batches	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	
	R^2	R^2	R^2	R^2	N
C3	0.953	0.909	0.818	0.890	0.719
H4	0.960	0.934	0.826	0.857	0.584

The drug release pattern from the optimized formulation (C3 & H4) was diffusion controlled obeying higuchi equation. However from the Korsmeyer-Peppas model the n value for C3& H4 was found to be 0.719 &0.584 respectively, thus indicating non-fickian diffusion.

Skin Irritation Study:

Skin irritation study was carried out by dividing animals in 2 groups each group consists of 4 rats

- ✓ Group 1 Control treated with normal saline.
- ✓ Group 2 was treated with optimized batch formulation.

The signs of skin irritation were observed for 24 and 72 hrs

Skin irritation study for optimized batch of C3 and H4 batch

No. of Animals	Edema				Erythema			
	C3		H4		C3		H4	
	24 hr	72hr	24 hr	72hr	24 hr	72 hr	24 hr	72 hr
Group 1	0	0	0	0	0	0	0	0
Group 2	0	0	0	0	0	0	0	0

Stability Study:

As per ICH guideline stability study was carried out at $40^0 \pm 2^0$C/ 75±5% RH up to 90 days. The results indicate that there is no so much change in appearance, pH, and drug content.

Stability study of optimized batches of C3 and H4 batches

Sr.No.	parameters	Optimized batches			
		C-3		H-4	
		Initial	After 3 month	Initial	After 3 month
1	Appearance	White transparent	No change	White transparent	No change
2	pH	6.4	6.3	6.7	6.7
3	Drug content	99.49±2.99	99.45±1.55	102.86±2.44	102.85±0.57

Summary and Conclusion

Summary

Optimization methodology helped to predict the best possible formulations. From drug release kinetics of all formulation it was concluded that all batches pass the zero order, first odder. Higuchi model and korsmeyer-peppas model. But among all gel formulation C3 which was carbopol 934 based and H4 which was HPMC

K100M based gel gave excellent pH value, rheological properties, spreadability homogeneity, consistency, drug content, % CDR and drug release kinetics. Optimization of parameters is powerful and efficient tool that shortens the time required for the development of pharmaceutical dosage forms.

From Ex-vivo study it was concluded that optimized batch passes higuchi model i.e. it is diffusion controlled. From peppas model it concluded that n value is between 0.5< n >1 so it was non-fickian diffusion.

Conclusion:

It can be concluded that from the above results that Tizanidine hydrochloride topical gel formulations prepared with Carbopol 934 and HPMCK 100M with combination of Propylene glycol and DMSO concentration showed acceptable physical properties, drug content and drug release.

Thus prepared skeletal muscle relaxant gel for topical drug delivery will avoid first pass metabolism.

The topical gel formulation administered directly on to the skin thus minimize the systemic side effects and will give best results.

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