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Research

Tizanidine-Loaded Nanogel: Fabrication, Characterization, And Potential Biomedical Applications Of A Synthetic Polymer-Based Delivery System

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Abstract

Nanogels, defined as highly cross-linked nano-sized hydrogel systems, offer unique advantages for drug delivery due to their hydrophilic networks capable of imbibing water or physiological fluids. This study focuses on the fabrication, characterization, and potential biomedical applications of a tizanidine-loaded nanogel using synthetic polymers. The nanogel was prepared using a homogenization technique, resulting in a stable O/W emulsion that transformed into nanogel. Characterization included Fourier-transform infrared spectroscopy (FTIR) for compatibility studies, particle size analysis using Malvern Zeta sizer, and zeta potential measurement. The drug content and release profile were evaluated using spectrophotometry and Franz diffusion cell, respectively. The optimized formulation (F9) demonstrated superior drug release (83.62% over 24 hours) and stability, with a particle size of 449 nm and zeta potential of 13.3 mV. In vitro release studies confirmed a sustained release pattern, enhancing cellular uptake and bioavailability. The study concludes that the tizanidine-loaded nanogel, formulated using cost-effective methods, can effectively deliver drugs transdermally, reducing administration frequency and side effects, making it a promising candidate for muscle spasm treatment.

Keywords: Nanogel, Tizanidine, Drug delivery, Hydrophilic networks, Transdermal.

INTRODUCTION

Nanogels may be defined as highly cross-linked Nano-sized hydrogel systems that are either co-polymerized or monomers which can be ionic or non-ionic. The size of nanogels ranges from 20- 200 nm. They can escape renal clearance and prolonged serum half-life period due to their size. Nanogels are three dimensional hydrophilic networks that have the tendency to imbibe water or physiological fluid in a large amount, without changing in the internal network structure. Chemical modifications can be made to help incorporating plenty of ligands which can be used for targeted drug delivery, stimulus responsive drug release or preparation of composite

materials. Nanogels are known to exhibit great qualities that contribute to the drive towards it as a delivery system. They include remarkable thermodynamically stability, elevated capacity of solubilization, relatively low viscosity, and capability of undergoing vigorous sterilization techniques. Nanogels may entrap drugs and biological molecules. Therefore, they can be vastly employed in protein and gene delivery. Some nanogels possess a hydrophilic nature which limits good encapsulation property of hydrophobic drugs. This issue was faced with encapsulation of anticancer drugs which are hydrophobic in nature. For this purpose, suitable structure engineering of the polymer was adopted to permit high encapsulation of them. Thereby, Nanogels provided a new mean of drug delivery for poorly soluble drugs which doesn't only improve their solubility and stability but increasing the opportunity of their cellular uptake than the free drug. Since they reflect a relatively high affinity to aqueous solutions, an outstanding stability, inertness in the systemic circulation as well as the internal fluids, and appropriateness for molecular incorporation in bulk, they are considered promising carriers for delivery and cellular uptake of proteins, peptides, and other biological compounds.

MATERIALS AND METHODS

Experimental methods

Preparation of Phosphate buffer

50ml 0.2 M Potassium dihydrogen phosphate was taken in 200ml volumetric flask, to which 39.1ml of 0.2M Sodium hydroxide was added and the volume was made up to the mark with distilled water

Preparation of Potassium dihydrogen phosphate (0.2M) Solution

27.219g of Potassium dihydrogen phosphate was added in to a 1000ml volumetric flask containing distilled water and the volume was made up to the mark with distilled water

Preparation of Sodium hydroxide (0.2M) Solution

8g of sodium hydroxide was taken in 1000ml volumetric flask containing distilled water and the volume was made up to the mark with distilled water.

Excipient Compatibility Studies

Fourier transform infrared (FT-IR) spectra of the sample were obtained using a SHIMAZU spectrometer by KBR disc method. The spectrum was recorded for the pure drug and physical mixture of drug and polymer

Formulation of nanogel

Accurately weighed quantity of Drug, Eudragit S-100 (polymer) and Tween-80 as stabilizer are dissolved in glycerol while stirring. Prepared aqueous phase containing Carbopol-940 dissolved in water with continuous stirring and heat. These drugs containing phase is sonicated on Ultra sonic bath sonicated. The drug phase is added drop by drop into the aqueous phase during homogenization to form emulsion. The emulsion converted into nano drop lets by homogenizer which formed O/W emulsion. Homogenization was continued for one hour. Triethanolamine added to form the gel with continuous stirring to nanogel.

Fig 1: Nanogel

Batch - 1

Composition	Formulation - 1	Formulation- 2	Formulation-3
Tizanidine hydrochloride (mg)	10	10	10
Carbopol – 940 (mg)	750.100	0.	0.150
Glycerol (ml)	5	5	10
Propylene glycol	2	2	2
Tween – 80 (ml)	0.1	0.3	0.5
Water (ml)	10	10	15
Triethanolamine (ml)	2	2	4

Batch - 2

Composition	Formulation - 4	Formulation- 5	Formulation-6
Tizanidine hydrochloride (mg)	10	10	10
Carbopol – 940 (mg)	0.75	0.125	0.76
Glycerol (ml)	5	5	10
Eudragit S-100	2	4	4
Tween – 80 (ml)	0.1	0.3	0.5
Water (ml)	10	10	10
Triethanolamine	2	2	2

Batch - 3

Composition	Formulation - 7	Formulation- 8	Formulation-9
Tizanidine hydrochloride (mg)	10	10	10
Carbopol – 940 (mg)	0.75	0.130	0.150
Glycerol (ml)	5	5	10
Eudragit S-100	4	4	6
Tween – 80 (ml)	0.1	0.3	0.5
Water (ml)	10	10	15
Triethanolamine	2	2	2

Evaluation

Appearance

The prepared gel bases were inspected visually for clarity, color and presence of any particles.

Homogeneity

All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Measurement Of Particle Size Of Formulation

The mean size of the selected nanogels were determined by using Malvern Rasterizer 2000 MS. The mean particle size was recorded.

Ph Measurement

The pH measurement was carried out by using calibrated digital type pH meter by dipping the glass electrode and the reference electrode completely into gel system so as to cover the electrodes.

Drug Content

For the estimation of the drug in gel, Tizanidine hydrochloride was extracted from 1gm of gel formulation with 50ml of phosphate buffer 6.8 and mixture was filtered through membrane filter (pore size 0.4 µm) From this, 2 ml was pipette out and made up to 10 ml. The absorbance of the sample was determined spectrophotometrically at 270 nm. The concentration of Tizanidine hydrochloride was estimated from the calibration curve

Skin Irritation Test

A set of 8 rats was used in the study. The nanogel was applied on the properly shaven skin of rat. Undesirable skin changes, i.e., change in color, change in skin morphology were checked for a period of 24 hr.

In Vitro Release Studies

The drug release from the formulation was determined by using the apparatus known as Franz Diffusion

Cell, which consist of a cylindrical glass tube which was opened at both the ends. 1 gm of gel was spread uniformly on the surface of cellophane membrane (previously soaked in medium for 24 hrs.) and was fixed to the one end of tube. The whole assembly was fixed in such a way that the lower end of tube containing gel was just touches (1-2 mm deep) the surface of diffusion medium i.e., 100 ml of pH 5.5 acetate buffer contained in 100 ml beaker. The assembly was placed on thermostatic hot plate with magnetic stirrer and maintained at temperature 37°±2° the contents were stirred using magnetic bar at 100 rpm for a period of 24 hrs., 2 ml of samples were withdrawn at different time intervals. This 2 ml was diluted up to 10 ml of fresh acetate buffer (pH 5.5) and sample were analyzed at 270 nm in UV-Vis.

Spreadability

Spreadibility is determined by apparatus suggested by Multimer. It consists of wooden block, which is provided by a pulley at one end. By this method, spreadibilityby is measured on the basis of "Slip" and "Drag". A ground glass slide is fixed on this block. A sample of 0.1 g of nanogel under study is placed on this ground slide. The gel is fixed on the beach formula was pressed between two slides and a 1 kg weight is placed on the top of two slides and left for about 5 min to expel air and to provide a uniform film of the nanogel between two slides. Excess of the gel is scrapped from edges. The top plate is then subjected to pull the weight. With help of string attaches to the hook and the time required by top slide to cover the distance is noted. A shorter interval indicates better spreadibility, spreadability was calculated by using the formula,

S=M.L/T,

Where,

S=spreadability, L=Length of glass slide, M=weight tied to upper slide, T=Time taken to separate the slides.

Extrudability

It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting plug flow. The method adopted for evaluating nanogel formulation for extrudability is based upon the quantity in percentage of nanogel and nanogel extruded from lacquered aluminium collapsible tube on application of weight in grams required at least 0.5cm ribbon of nanogel in 10 sec. The measurement of extrudability of each formulation shows the triplicate and averages value is presented.

Extrudability = Applied weight to extrude the nanogel from tube (in gm)/ Area (in cm2).

Rheological Studies

Brookfield viscometer was used for the studies. First, the spindle was dipped into the gel till the notch on the spindle touched the gel surface. 3gm each of gel I and gel II (Stability chamber and Room temperature) was used in the study. The spindle no.61, 63, 64 was selected based on viscosity of gel. The dial readings were taken at 50, 100, 150, 250rpm and viscosity was measured.

RESULT AND DISCUSSION

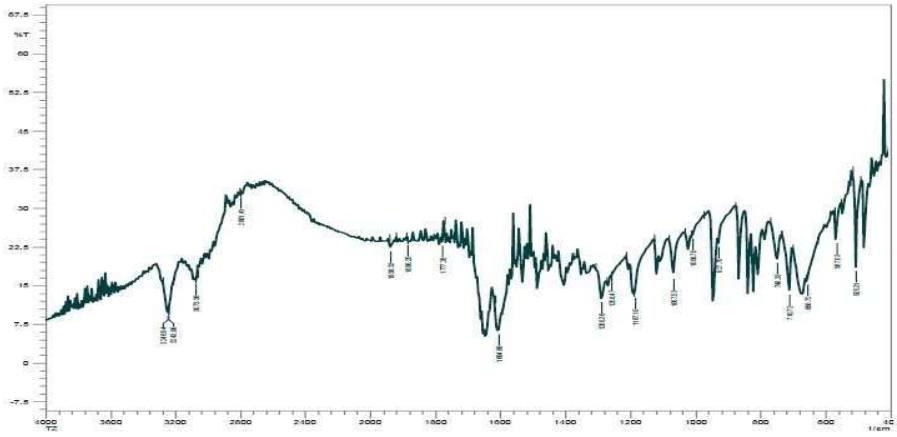

Fig 2: FTIR – Spectrum of Tizanidine hydrochloride

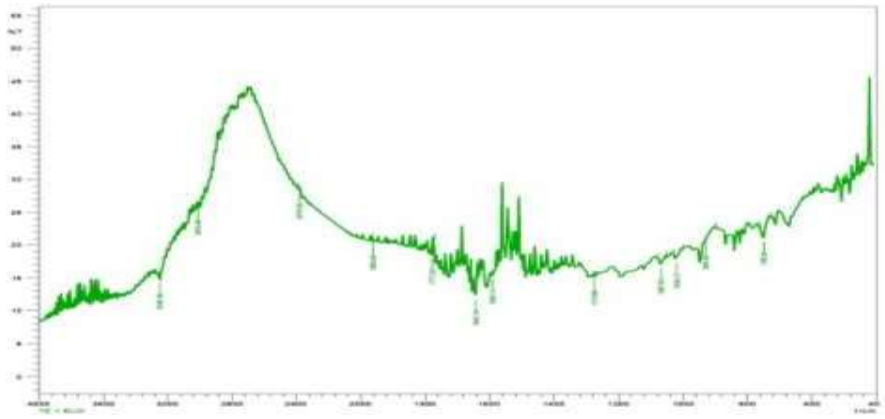

Fig 3: FT-IR Spectrum of physical mixture containing Tizanidine hydrochloride, eudragit

Materials	Standard wave number (cm-1)	Test wave number (Cm-1)	Functional group assignment
Mixture containing tizanidine hydrochloride and eudragit	1700 cm-1	1625 cm-1	Amine

Physical appearance

Formulation	Appearance	Homogeneity	Grittiness
F-1	White	Homogenous	NO
F-2	White	Homogenous	NO
F-3	White	Homogenous	NO
F-4	White	Homogenous	NO
F-5	White	Homogenous	NO
F-6	White	Homogenous	NO
F-7	White	Homogenous	NO
F-8	White	Homogenous	NO
F-9	White	Homogenous	NO

All the formulations show clear white appearance all the formulations were homogenous and free of grittiness.

PH

The pH values of all prepared formulations were ranged between 6.40- 6.94 which is considerable to avoid the skin irritation of the skin after application.

Spread ability coefficient

The spread ability of various concentration of Carbopol 940 is spread ability of nanogel was found to be in range of 6.2–7.9cm better spread ability.

Particle Size And Pdi

Particle size of optimized formulation is 449nm and PDI is 1.000 as the smaller particle size may in turn bring about more bio-availability.

Zeta Potential

The reduced zeta potential value of 13.3mV indicated that the prepared nanogel possess a higher degree of long- term stability.

Drug content determination

The drug content of Tizanidine hydrochloride from its various nanogel formulations are represented in the F9 showed better drug content as compared to other formulations. The percent drug content of these formulations was 87.06% respectively.

Formulation	pH	Spread ability (g.cm/s)	Drug content
F-1	6.40	6.9	55%
F-2	6.68	7.1	67%
F-3	6.80	6.8	71%
F-4	6.84	7.4	69%
F-5	6.50	7.3	73%
F-6	6.72	7.6	70%
F-7	6.62	6.3	77%
F-8	6.55	7.2	80%
F-9	6.90	7.9	87.06%

In-vitro drug release study

In-vitro release studies at different ratios, Tizanidine hydrochloride and Eudragit-S 100 performed at 24h using Franz Diffusion Cell apparatus. The in-vitro release results of nanogels F1-F9 were compared with Tizanidine hydrochloride. Nanogel of Tizanidine hydrochloride Eudragit-S 100 and prepared using homogenization method showed drug release in formulations such as F1, F2, F3, F4, F5, F6, F7, F8, and F9 were 52.28%, 53.71%, 71.71%, 56.71% 63.71 % 67.42% 71.90% 73.45%, and 83.62% respectively. Nanogel formulation-F9 elicited highest rate of drug release. In-vitro drug release profile of formulation-F6 was observed 83.42% release at 24hr.

Invitro Release

Table 1: Over All Cumulative Profile For Tizanidine Hydrochloride

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	12.8	19.7	16.7	0.09	0.21	1.047	1.907	1.804	2.604
2	13.45	28.0	22.96	0.11	0.96	1.504	6.701	7.405	9.576
3	23.1	32.0	32.45	0.14	1.38	5.604	8.504	14.66	18.45
4	28.0	38.5	38.91	12.8	12.8	11.77	13.44	25.46	28.16
5	34.8	41.1	47.95	16.17	28.0	22.55	19.56	31.77	36.21
6	41.7	48.2	53.60	20.55	33.45	32.49	24.72	42.55	42.81
7	45.6	51.6	55.4	20.98	36.4	37.38	28.7	45.05	46.04
8	52.28	53.7	60.62	21.35	41.7	45.95	36.09	48.71	51.20

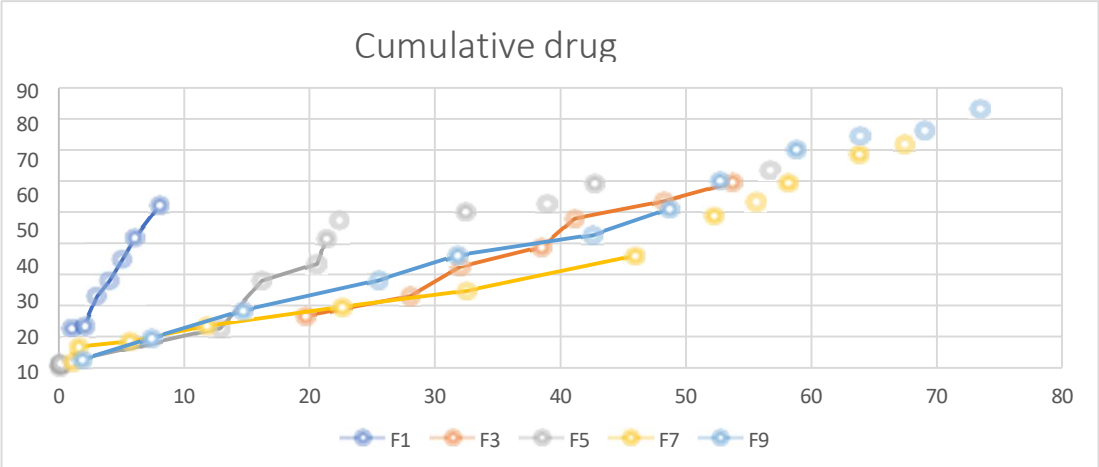

Fig 4: Cumulative release of Tizanidine hydrocholoride for various formulation

At the end of 10 hours, the *in vitro* release of the different formulations was found to be in the range of 60.62 **%** Here formulation 2 shows good release but it attains maximum release at 8hrs, when compared with the formulation 3. From the above *in vitro* release table, the optimized formulations were found to be F3 because of higher *in vitro* release of 60.62**%** when compared to the other formulations. As it is more hydrophilic it enhances

the release of the drug.

***In Vitro* Kinetic Profile For Formulation 9**

Formula Tion Code	Time (In Hrs)	S.Q.R.T. Of Time	Log Time	Cumulati Ve % Drug Release	Log Cumulative % Drug Release
F9	1	1	0	2.604	0.415
	2	1.414	0.301	9.576	0.981
	3	1.732	0.477	18.45	1.265
	4	2	0.602	28.16	1.449
	5	2.236	0.698	36.21	1.558
	6	2.449	0.778	42.81	1.631
	8	2.828	0.903	51.20	1.709

SUMMARY

Nanogel based materials have high drug loading capacity, biocompatibility and biodegradability which are key points to design the drug delivery system effectively. Drug molecules loaded into the nanogel need to be retained and not to be transported out or leak prematurely while circulating in order to provide maximum therapeutic effects and minimum toxicity or side effect. Main objective of this study was to formulate Tizanidine hydrochloride using polymer is an effective as vesicular system and can efficiently deliver the drugs through transdermal route to treat spasms, cramping and tightness of muscles.

The present work aimed at formulating Tizanidine hydrochloride nanogel with hydrophobic polymer using emulsion solvent diffusion method. This method was simple and cost effective. Pre-formulation studies were carried out to find out the solubility of Tizanidine hydrochloride. Solubility test gave an idea that Tizanidine hydrochloride is water soluble and soluble in solvents.

FTIR and UV spectral studies authenticate the spectra obtained with the sample drug matched with standard pure drug. UV spectra gave the maximum absorption peak at 228nm. Formulation was carried out by emulsion solvent diffusion method. Trial batches indicated that hydrophilic polymers are not suitable for the Tizanidine hydrochloride nanogel. The hydrophobic polymers produced good formulation. Eudragit were selected for further studies. Particle size and zeta potential was determined by Malvern Zeta sizer. The particle size analysis confirmed that the prepared sample were in the nanometer range. Average particle size obtained for the formulation F9 is 449.1 nm. Zeta potential values of nanogel indicated that the formulated nanogel are stable.

The amount of drug being entrapped in nanogel was calculated and all the prepared nanogel were found to possess very high entrapment efficiency. From the results of the present experimental investigation, it may be concluded that the formulation of Tizanidine hydrochloride nanogel showing small vesicle size, with desire release of Tizanidine hydrochloride nanogel Hence,F3 is the optimized formulation. The optimized formulation was found to follow zero order release pattern which was revealed by the linearity shown from the plot of Time vs Concentration. So, we can conclude that Tizanidine hydrochloride nanogel facilitate higher cellular penetration and possess high bioavailability and sustained release.

CONCLUSION

The Tizanidine hydrochloride nanogel can be formulated by cost effective and easy emulsion solvent diffusion method using hydrophobic polymers such as eudragit. The formulated Tizanidine nanogel can be used in the treatment of muscle spasms, muscle cramps. This can be targeted to the muscle and produce sustained drug delivery which in turn reduced the dose frequency of administration and the side effects. Thus formulation F3 shows the highest drug release and absorption.

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