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Research

Formulation and evaluation of baclofen nanogel by using synthetic polymer

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Abstract

Nanogels, highly cross-linked nano-sized hydrogel systems, offer significant potential as drug delivery vehicles due to their unique properties such as high water content, biocompatibility, and the ability to encapsulate both hydrophilic and hydrophobic drugs. This study focuses on the formulation and evaluation of Baclofen nanogel using synthetic polymers. The nanogels were prepared via the emulsion solvent diffusion method, incorporating Baclofen hydrochloride with Eudragit S-100 and Carbopol-940. The formulations were characterized by particle size, zeta potential, pH, viscosity, spreadability, drug content, and in vitro drug release. The optimized formulation (F9) demonstrated a mean particle size of 449 nm and a zeta potential of 13.3 mV, indicating good stability. The pH of the formulations ranged between 6.40 to 6.94, suitable for topical application. Drug content analysis showed formulation F9 had the highest drug content at 87.06%. In vitro release studies using Franz Diffusion Cell revealed that formulation F9 had the highest cumulative drug release of 83.62% over 24 hours, following zero-order release kinetics. The study concluded that Baclofen nanogel, prepared using synthetic polymers, is effective for transdermal drug delivery, offering sustained release and enhanced bioavailability. The nanogel formulation provides a promising approach for treating muscle spasms and related conditions, reducing the frequency of administration and potential side effects.

Keywords: Baclofen Nanogel, Synthetic Polymer, Transdermal Drug Delivery, Emulsion Solvent Diffusion, Sustained Release

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.

Properties of Nanogels

Biocompatibility and degradability

Nanogel are made up of either natural or synthetic polymers. They are highly biocompatible and biodegradable thereby avoiding its accumulation in the organs. Chitosan, ethyl cellulose, methyl cellulose and various polysaccharide-based polymers like dextran, pullulan and dextrin can be used to prepare the nanogel. Polysaccharides are mostly carbohydrate-based polymers, formed of repeating monosaccharide units linked by glyosidic bonds. These polymers are stable, non-toxic, hydrophilic and biodegradable in nature.

Swelling property in aqueous media

Due to the fact that Nanogels are very small, soft materials, they have the ability to swelling presence of an aqueous medium. It is considered to be the fundamental property influencing the mechanism of action followed by this drug deliverysystem. The structure of Nanogels: This includes the polymer chain's chemical nature as well as cross- linking degree and in case of polyelectrolyte gels; the charge density. Environmental parameters which are related to the variables of the aqueous medium. For instance, in polyelectrolyte gels pH as well as ionic strength and ions' chemical nature are influential factors. Likewise, temperature is a trigger of swelling in case of thermo responsive gels. Providing appropriate circumstances allows rapid swelling/deswelling. Regardless of the trigger, swelling takes place only when the osmotic pressure exerted by medium ions and the polymer's network swelling pressure are imbalanced.

Higher drug loading capacity

Just like any other Nano delivery system, nanogels are expected to have greater loading capacity compared to conventional dosage forms. This is mainly due to the swelling property which allows the formulation to absorb large quantity of water. Thus, upon incorporation and loading the water will provide cargo space sufficient to contain salts and biomaterials. Loading takes place through three methods: Physical entrapment: it can refer to the linkage between hydrophilic chains and hydrophobic regions of the polymer or to dissolving hydrophobic molecules in hydrophilic vehicle. Covalent attachment of bioactive molecules which leads to the formation dense drug-loaded core. Controlled self-assembly: which is generally for polyelectrolyte-based nanogel. The high loading efficiency is attributed to interaction between oppositely charged electrolytes. Other factors also contribute to the high loading capacity, such as: the composition, molecular weight, the possible interactions between the drug and the employed polymer and the different functional groups in each polymeric unit.

Permeability and particle size

What distinguish nanodelivery systems is that a tiny manipulation in particle size, surface charge and hydrophobicity can remarkably improve permeability. In spite of the fact that nanoparticles are capable of permeation by diffusion through tissues or compromised areas of endothelium and in some cases through a particular transport system, they created a challenge crossing Blood brain Barrier (BBB). So, in order to overcome such dilemma, nanogels were formulated in a way where they possess a diameter of 20-200 nm. It's small enough to cross (BBB) and in the same time avoid rapid clearance mechanisms.

Non-immunologic response

Any agent that enters systemic circulation is rapidly eliminated by the Mononuclear Phagocyte System through opsonization and phagocytosis. Opsonization is nothing but marking foreign agents and make them visible to phagocytes. Opsonin's bind on the surface of nanoparticles and facilitate the attachment of phagocytes. Few methods are adopted to help nanoparticles flee recognition and remain longer in bloodstream. All of which are based on minimizing protein binding. For example, hydrophilic polymers can act as a shield that hindersor delays binding with opsonin's rendering them unnoticeable by immune system and its defenses.

Colloidal stability

When handling nanoparticle, there is always a propensity of aggregation that compromises the colloidal stability. Formulators tend to alter the surface charge to avoid the formation of aggregates in bloodstream and further complications. It can be achieved through increasing zeta potential (minimum of ± 30 mV) that results in larger repulsive forces between particles that electrostatically stabilize them. Other techniques involve the incorporation of a surface modifier like PEG that produce steric effects and hydration forces to give a stable nanosuspension. If we compare polymeric micellar nanogel systems and surfactant micelles on basis of stability we will find that the former exhibits better stability lower critical micelle concentrations, decrease in dissociation rates, and longer retention of loaded drugs. They also have a high-water content that assure good dispersion stability.

Advantages of Nanogels

Nanogels are considered advantageous over other drug delivery systems for a number of reasons including:

- Nanogels are administered via a variety of routes including oral, pulmonary, nasal, parenteral, intra-ocular and topical routes of administration.
- Nanogels are suitable to administer both hydrophilic and hydrophobic drugs, as well as charged solutes and other diagnostic agents. This property is highly influenced by the type of functional groups present in the network of polymer chains, the crosslinking density and the type of crosslinking agent incorporated in the polymeric network.
- Nanogels have a high affinity to aqueous solutions, resulting in their ability to swell or Deswell, imbibing water when placed in an aqueous medium. This is the most beneficial characteristic of nanogels as it makes them ideal candidates for the uptake and delivery of proteins, peptides, bio- macromolecules as well as bulky drugs.
- Drug loading in nanogels is relatively high when compared to other nanocarriers and drug delivery systems. This is due to the effect of the functional groups present in the polymeric network. By forming hydrogen bonds or other weak linkages within the polymeric network and interacting with drug or protein molecules at the interface, functional groups on the polymeric network tremendously increase the drug loading capacity of nanogels.
- Incorporating drug into the nanogels is easy, spontaneous, and does not necessarily require any chemical reactions. This makes the process of preparing nanogels efficient, since the drug is not needed in the initial steps of the manufacturing process and can be introduced to the nanogel network in subsequent steps when the nanogel swell with water or aqueous biological fluids [7].
- Nanogels are prepared to be capable of releasing drug in a controlled and sustained pattern at the target site, thereby enhancing the therapeutic efficacy of the drug and avoiding its adverse reactions.
- Targeted drug delivery is possible in nanogels due to the presence of functional groups that conjugate with antibodies and/or drugs resulting in high selectivity and preventing the accumulation of drug in non-target tissue like muscular and adipose tissue. Moreover, the chemical modification of nanogels to incorporate ligands leads to targeted drug delivery and triggered drug release.
- The synthesis of nanogels is generally a stress-free process since mechanical energy is not employed and harsh conditions like sonication or homogenization are not involved [9]. Also, there is no introduction of organic solvents to the process in any of its steps. Hence the drug can be easily loaded without being exposed to any sort of vigorous conditions throughout the preparation process.
- Nanogel dispersions are known to have and exceptionally large surface area which is essential for a variety of in vivo applications.
- Bio-macromolecules as well as delicate compounds with low or high molecular weights can be successfully and efficiently encapsulated in the nanogels for the purpose of prolonging the activity of these molecules in the biological environment.
- Nanogels can be formulated in the form of polymeric micellar nanogel systems that exhibit slower rates of dissociation, better stability over the surfactant micelles, lower critical micelle concentrations, and, most importantly, longer retention of loaded drugs.

Limitations of Nanogels

The only limitations to using nanogels include: It is expensive to remove the surfactant and the solvent at the end of the preparation process although the manufacturing process itself is not very pricey. Adverse effects may occur if any traces of polymers or surfactant remain in the body.

Drug Release Mechanism of the Nanogels

There are multiple mechanisms to which the release of the drug or the biomolecule is attributed to including: simple diffusion, degradation of nanogel structure, pH and temperature changes, counterion displacement or induced due to external energy source [9].

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 nanodroplets by homogenizer which formed O/W emulsion. Homogenization was continued for one hour. Triethanolamine added to form the gel with continuous stirring to nanogel.

Batch- 1

Composition	Formulation - 1	Formulation- 2	Formulation-3
Baclofen hydrochloride (mg)	10	10	10
Carbopol – 940 (mg)	0.75	0.100	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
Baclofen hydrochloride (mg)	10	10	10
Carbopol – 940 (mg)	0.75	0.75	0.125
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
Baclofen hydrochloride (mg)	10	10	10
Carbopol – 940 (mg)	0.75	0.125	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, Baclofen 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 Baclofen 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 minto 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.

RESULTS AND DISCUSSIONS

Standards Curve Of Baclofen Hydrochloride

S.NO	CONCENTRATION (mcg/ml)	ABSORBANCE
1	0	0
2	2	0.241
3	4	0.432
4	6	0.631
5	8	0.853
6	10	1.093

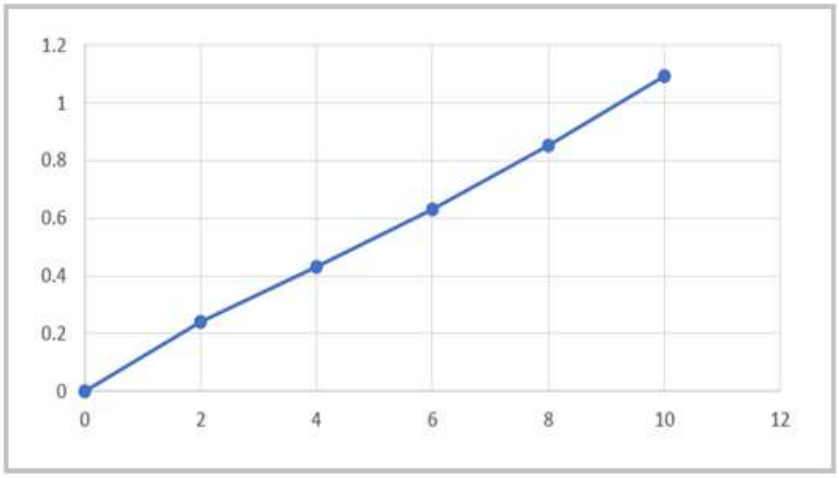

Fig 1: Standards Curve Of Baclofen Hydrochloride

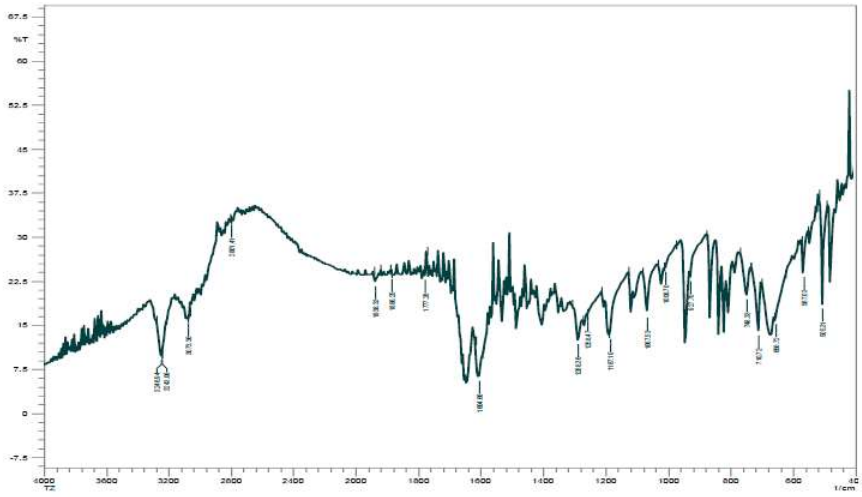

Fig 2: FTIR – Spectrum of Baclofen hydrochloride

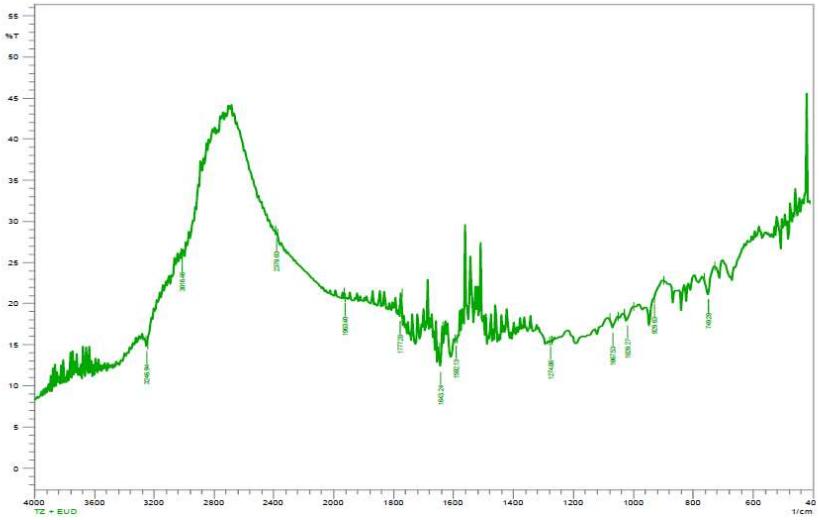

Fig 3: FT-IR Spectrum of physical mixture containing Baclofen hydrochloride, eudragit

Table 1: Standards Curve Of Baclofen Hydrochloride

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

Table 2: 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 Baclofen 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.

Table 3: Formulation value

Formulation	pH	Spreadability (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, Baclofen 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 Baclofen hydrochloride. Nanogel of Baclofen 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.

Table 4: Cumulative Profile For Baclofen Hydrochloride

TIME	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
8	52.28	53.7	59.62	21.35	41.7	45.95	36.09	48.71	51.20

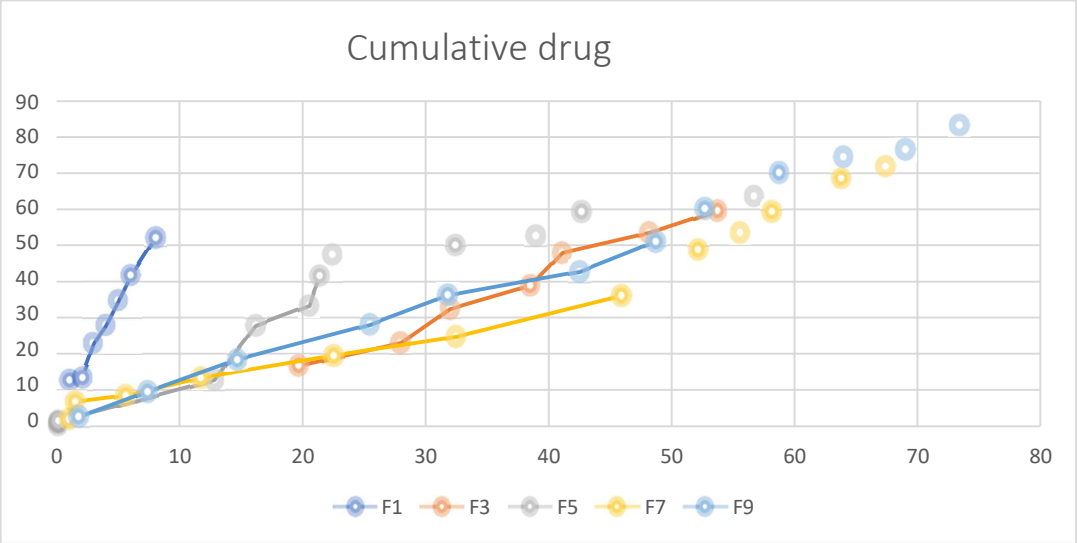

Fig 4: Cumulative release of Baclofen hydrocholoride for various formulation

At the end of 24 hours, the *in vitro* release of the different formulations was found to be in the range of 83.4 % Here formulation 3 shows good release but it attains maximum release at 10hrs, when compared with the formulation 9. From the above *in vitro* release table, the optimized formulations were found to be F9 because of higher *in vitro* release of 83.4 % when compared to the other formulations. As it is more hydrophilic it enhances the release of the drug.

Table 5: *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 AND CONCLUSION

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 Baclofen 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 Baclofen 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 Baclofen hydrochloride. Solubility test gave an idea that Baclofen 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 Baclofen 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 Baclofen hydrochloride nanogel showing small vesicle size, with desire release of Baclofen hydrochloride nanogel Hence,F9is 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 Baclofen hydrochloride nanogel facilitate higher cellular penetration and possess high bioavailability and sustained release.

CONCLUSION

The Baclofen hydrochloride nanogel can be formulated by cost effective and easy emulsion solvent diffusion method using hydrophobic polymers such as eudragit. The formulated Baclofen 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 F9 shows the highest drug release and absorption.

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