Original Article

Topical Delivery of Methocarbamol Loaded Nanoemulgel - *in vitro* Characterization

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ABSTRACT

Background: Methocarbamol is used as skeletal muscle relaxant. Nanoemulgel is currently being developed as a transdermal drug delivery technology because to its nano-sized droplets, which provide superior effectiveness with reduced toxicity. **Aim:** The aim of the study is to prepare and characterize the Methocarbamol loaded nanoemulgel. **Materials and Methods:** The required quantity of Methocarbamol dissolved in Acconon oil, surfactant and co-surfactant used to prepare nanoemulsion with various ratios using probe sonicator and poured into the prepared carbopal gel with constant stirring. The prepared nanomelgel was characterized for its pH, viscosity, particle size and zeta potential, surface morphology by TEM, drug content and *in-vitro* Methocarbamol release from developed formulation. **Results:** The developed NEs formulation exhibited acceptable pH range around 6 to 7, viscosity was in the range of 38.26cps to 45.25cps. The average droplet size of the NE formulations varied from 20.1 to 56.4 nm. There is no much change of droplet size when varying the oil concentration of the NEs. The result of the droplet polydispersity index (PDI) shows the droplets are uniformly distributed. The zeta potential of the formulations ranging from -0.1mV to 0.3mV for NE and NE-Gel respectively. This is due to the presence of the non-ionic surfactant over the droplet. The TEM micrograph of the 10% NEs and NE-Gel appears spherical in nature with drug embedded in the oil droplet. The volume of drug release for 3% Nanoemulsion is 64.28%, 50.78%, 41.78%, 38.57% and 3% Nanoemulgel is 29.57%, 38.25%, 43.71%, 52.39% respectively. Due to higher quantity of oil phase of NE and rigid gel nature the *in-vitro* resulted in delaying and sustaining in drug release. **Conclusion:** Hence, we conclude that the developed NE, NE-Gel might be beneficial for the better topical delivery of muscle relaxant.

Key words: Methocarbamol, Nanoemulsion, Nanoemulgel, Topical Delivery, *In-vitro* characterization.

INTRODUCTION

A muscle cramp is an unexpected, automatic, excruciating compression of a muscle either part of it. This myoelectric movement could be mentioned as "cramp release". Cramps can happen in cases among low motor neuron disorder, metabolic disorder, neuropathies, and intense extracellular exhaustion. Moreover, they frequently occur in normal person along with no data of apprehensive or metabolic disorder, for example in rest, gestation and heavy physical workouts. The cramps have characterized as "benign cramps" or idiopathic cramps or spasms without clear reason.[1]

Lack of hydration (and additionally electrolyte consumption) frequently is inclined as a clarification for muscle cramps happening in laborers and sports person. The major risk factors for exercise were muscle cramp acquired from genetic history of cramping, any cramps by accident, over workouts or after workouts, insufficient stamina for the action.[2-4] Muscle relaxants is one of the several therapies recently worked in the system of normal low back pain.

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35% of patients concern to care doctors for low back pain are prescribed muscle relaxants.[5,6] It is feasible as a short-term symptomatic aid in patients suffering from severe and persistent low back pain. However, tiredness, dizziness, and other negative effects are common. Generally musculoskeletal conditions provoke fragility along with muscle pain contain fibromyalgia,[7] strain cerebral pains, myofascial agony, and mechanical low back or neck pain.

Skeletal muscle relaxant is one of a few classifications of medication as often as possible utilized to treat these cases.[7-11] Centrally acting medications are helpful in musculoskeletal pain and spastic neurological spasm, for example, cerebral paralysis and these drugs may cause many adverse side effects.[12,13]

Methocarbamol is a BCS class-II tranquilize, having low fluid dissolvability and high penetrability. Methocarbamol is carbamic acid ester, a secondary of guaifenesin carbamate. In market, it is available in film coated tablets but on set action slow while paining it gives muscle relaxation. Pharmacologically, methocarbamol is a centrally acting muscle relaxant, but in general it acts as antidepressant on central nervous system. Sedative and analgesic reaction has also been proved. Methocarbamol is a viable solution for neck and back pain, fibromyalgia, strain cerebral pains and myofascial torment disease[14-17] and well endured restorative choice for the intense low back pain patients. Topical delivery of these drugs provides better local action with less severe adverse effect. But the conventional topical delivery methods show lesser efficacy due to poor solubility of drugs.[18]

Nanoemulgels are utilized as potential drug delivery system with several routes such as topical, and oral.[19] The technical usage of nanoemulgel expandingly being utilized in variety of organization because of their typical properties, small globules size are 20-200 nm within huge interface area with increased solubilizing capacity, transparent, viscosity is low and enhanced kinetics stability, flocculation and coalescence in any cases.[20-23] Firstly, the solubility of lipophilic drug increased within the oil of the nanoemulsion followed by incorporated into a gel base has an important criterion to increase the colloidal stabilization[24-26] by improving its viscosity of aqueous phase for better treatment on topically.[27,28] Hence, we planned to develop the nanoemulgel for the better topical delivery of methocarbamol through the intact skin.

The present aim of this work is to develop and optimise a stable nanoemulgel loaded Methocarbamol, by ultra-sonication method. The excipients used such as oils, surfactants, co-surfactants possess various physico-chemical properties.[29] Further the developed formulations have determined the compatibility studies by FT-IR (Fourier Transform - IR Analysis), particle size and zeta potential by zeta sizer, pH, viscosity, gel spreadability, surface morphology by TEM, drug content and *in-vitro* release of methocarbamol with its release kinetic model.[30]

MATERIALS AND METHODS

Methocarbamol obtained as gift sample from Swapnroop Drugs, Maharashtra. Acconon oil gift sample from Abitec Corporation Limited, USA. The tween 80, carbapol 934, sodium benzoate, ethanol, triethanolamine and all other chemicals used in this study were purchased form Rankem Chemicals, Mumbai.

Methods

Excipient Compatability Studies

The drug is associated with one or more than one excipient, which influences the stabilization of the drug. The data of drug and other excipients relations is crucial for choosing proper ingredients which are done by using Fourier Transform-Infrared spectrophotometer (FTIR) study.

Fourier Transform-Infrared spectrophotometer Studies

FT-IR is basically used to measure the compatibility of drug and excipients. FT-IR is a better analytical instrument for transmission and describing of polymer. The FT-IR spectrum of pure drug, surfactant (Tween 80), other excipients and the final formulation with drug and surfactant were obtained to characterise the possible interaction between drug and excipients if any. FT-IR spectra of pure drug (Methocarbamol), surfactant (Tween 80), and a mixture of the drug with selected surfactant and oil are recorded via a KBr stub in FT-IR spectrophotometer. % Transmittance (%T) is documented in the spectral area of 4000- 400 cm^{-1}. The characteristic peaks of functional groups for distinct samples are done.

Preparation of Nanoemulgel

About 1% of drug (Methocarbamol) weight were taken and dissolved in oil (Acconon) in w/v. Nanoemulsion have prepared by selecting the various concentration of surfactant (Tween 80) with fixed concentration of oil. The formulation was prepared in various ratios of 1:2, 1:3, 1:5, 1:7.5, 1:10.

About 0.75g of Acconon oil weighed and 0.05g of drug dissolved, followed by Tween80 in various ratios were added. Further the required quantity of water has added and sonicated the mixture by ultrasonication method using probe sonicator for 20min to attain translucent nanoemulsion. Instantaneously preparing a gel formulation with appropriate weighed quantity (0.1g) of carbapol-934 have dissolved in sufficient quantity of double distilled water for swelling, followed by addition of 0.1 g of ethanol, 0.1g of sodium benzoate, 0.5mL of polyethylene glycol w/v and sufficient quantity of triethanolamine were mixed for thickening to the gel formation. The prepared Methocarbamol loaded nanoemulsion was poured into the gel formulation with constant stirring till the clear homogeneous nanoemulgel obtained. The developed Methocarbamol loaded nanoemulgel have store in eppendorf tubes at room temperature for further evaluations. The formulated nanoemulgel composition is given in Table 1.

Characterization of Methocarbamol Loaded Nanoemulgel

The nanoemulgel pH has measured using a pH meter (Pico pH Meter). The nanoemulsion and nanoemulgel viscosity was measured by a viscometer (Brookfield DV-E viscometer) which has twisted for 10mins at 100 rotations at the maximum per min within spindle. The spreadability evaluation were performed by aligning the spreading measurement conducted by keeping the formulated nanoemulgel between two glass slides. Briefly, the weighed amount (0.5g) of test and put at the focal point of the glass plate and squeezed between the slides then estimated the spreadabilty of the gel in cm following 5 min.

Particle Size and Zeta Potential

Droplet size and zeta potential of the formulated Methocarbamol infused nanoemulgel was analyzed with DLS (dynamic light scattering) method with the help of Horiba Particle Size Analyzer, USA. The nanoemulgel and nanoemulsion was diluted to 200µL in water, from that 50 µL diluted to 2mL with water and analysed.

Transmission Electron Microscopy (TEM)

The surface morphology of methocarbamol loaded formulations like both Nanoemulsion and Nanoemulgel has determined using a TEM (Transmission Electron Microscope) instrument. A droplet of formulation was kept in a membrane coated grid and dried in hot air oven. TEM images were analyzed from working on 200kV voltage.

Drug content

In the developed formulation the drug content was measured, about 1g of nanoemulgel were dissolving in PBS (pH7.4) and make up to 10mL. The solution was filtered with membrane filter 0.45µ and diluted preferably, further the absorbance was measured at 273nm. Buffer used as a blank solution. The formula for calculating the drug content as follows:

$$\text{Drug content (\%)} = \frac{\text{Weight of Methocarbamol in formulation}}{\text{Weight of formulation}} \times 100$$

In-vitro Methocarbamol Release Studies

In-vitro drug release studies was done for both the formulation of Nanoemulsions and Nanoemulgel for comparing the release of drug. The different ratio of formulation was performed in phosphate buffer solution (pH 7.4), under ideal sink conditions using dialysis membrane (M.Wt cut off 12 KD) on Franz diffusion cell technique. The 1g of formulation sample was placed on dialysis membrane mounted on the donor compartment of franz diffusion cell and

Table 1: Composition of Methocarbamol loaded Nanoemulgel.

S.No.	Formulation Code	Ingredients (10 gm)						
		Methocarbamol (g)	Acconan Oil (g)	Tween 80 (g)	Carbapol934 (g)	PEG (mL)	Sodium benzoate (g)	Triethanolamine
1.	Nanoemulgel 2%	0.05	0.75	0.1	0.1	0.5	0.1	Q.S
2.	Nanoemulgel 3%	0.05	0.75	0.15	0.1	0.5	0.1	Q.S
3.	Nanoemulgel 5%	0.05	0.75	0.25	0.1	0.5	0.1	Q.S
4.	Nanoemulgel 7.5%	0.05	0.75	0.375	0.1	0.5	0.1	Q.S
5.	Nanoemulgel 10%	0.05	0.75	0.5	0.1	0.5	0.1	Q.S

the reservoir part filled with 18mL of PBS (pH7.4) solution by appropriate temperature (37°C) with continuing magnetic stirring at 600 rpm. At relative time interval of 1 to 7 hr aliquot amount of sample (2 mL) was withdrawn and replace it with 2mL of pH 7.4 buffer solution poured into a receptor compartment to continue the perfect sink condition. The drug release content of the samples was measured by diluting with PBS solution (pH7.4) and by absorbing the nanometer using UV spectrophotometer at 273nm. The graph is plotted with % Drug release verses Time. The pattern of drug release mechanism of non-linear kinetic model was treated by fitting the various release kinetic models to evaluate the zero order, first order, higuchi release model, hixon crowell model and korsmeyer peppas model.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies

The drug's stability is influenced when it comes into contact with one or more excipients. The information of interactions of excipients with drug is essential for choosing appropriate excipients which are done by using Fourier Transform-Infrared spectrophotometer (FT-IR) study.

The FT-IR spectra of Methocarbamol shows the characteristic peaks of carboxylic acid (2943- 3439.08), NH bend (1508.33-1602), C=O stretch (1674.21), C-H bend (758.02-833.25), -C-H bend (960.55), C-O stretch (at 1249.87-1184.29) and C-O-C stretch (1060.85-1082.07). The projecting peak of Methocarbamol was observed and when incorporated with other excipient there was no interactions were found. The FT-IR spectra of Methocarbamol, Acconon oil, Tween 80, carbapol 934, Sodium benzoate, PEG, Triehanolamine and 10% Nanoemulgel formulation and drug excipient physical mixture were shown in Figure 1 to 8 and their respected peaks represented in Table 2 to 9.

The strong absorption peak observed at 1674 and 1695 cm^{-1} could be recognized to carbonyl group vibrational stretching of Methocarbamol in Nanoemulgel 10%. Spectrum of formulation shows mild shift towards 1643 evident that carbonyl group stretching of methocarbamol and confirms that there was no chemical change. The formation of intermolecular hydrogen bonding at 3500 to 3400 cm^{-1} indicating the enhancing the solubilization capacity of the formulation.

Physicochemical Characterization

The physicochemical characterizations of the developed Methocarbamol loaded nanoemulsion are represented

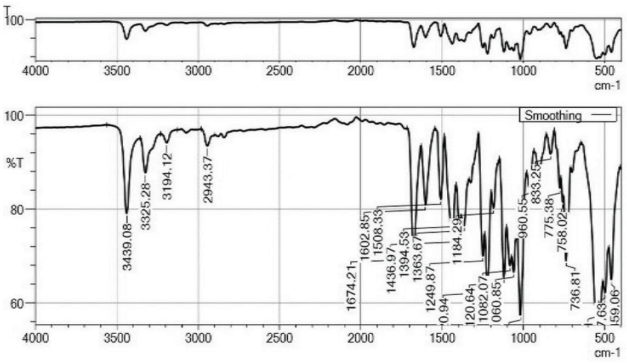

Figure 1: FT-IR spectra of Methocarbamol.

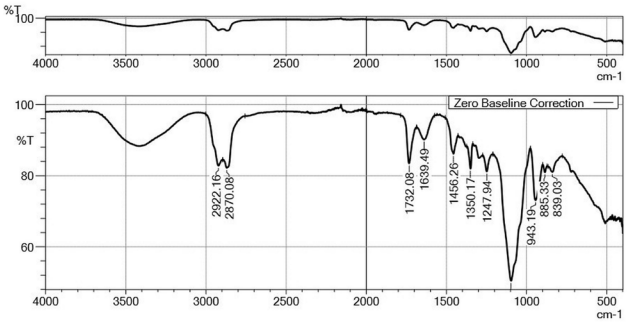

Figure 2: FT-IR spectra of Acconon.

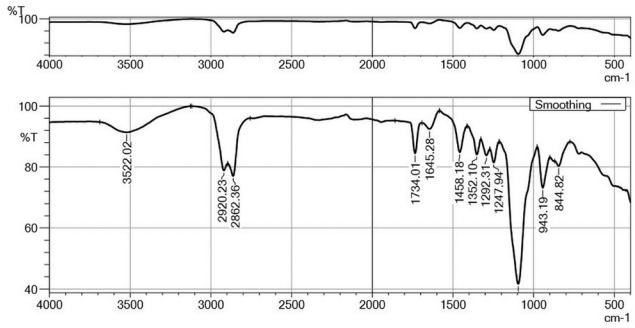

Figure 3: FT-IR spectra of Tween 80.

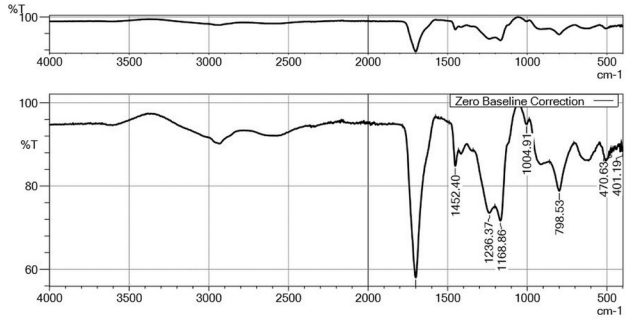

Figure 4: FT-IR spectra of Carbapol 934.

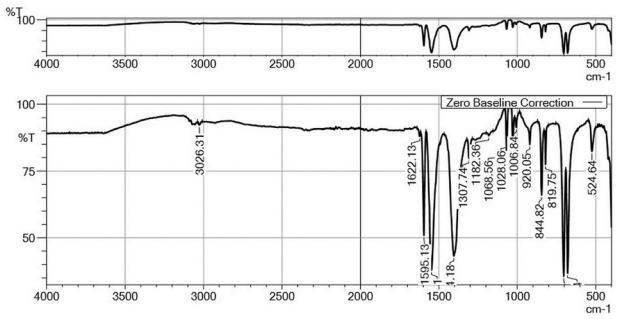

Figure 5: FT-IR spectra of Sodium Benzoate.

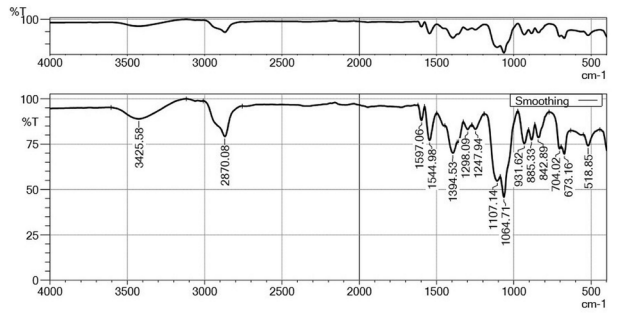

Figure 6: FT-IR spectra of Polyethylene Glycol.

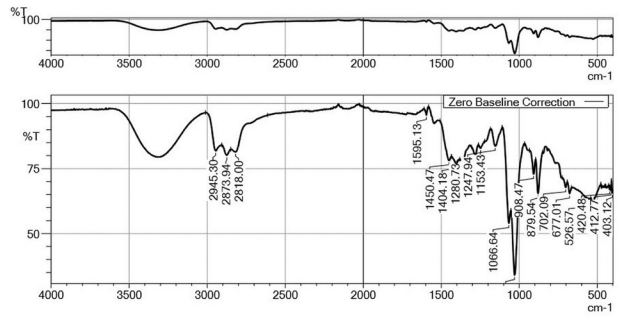

Figure 7: FT-IR spectra of Triethanolamine.

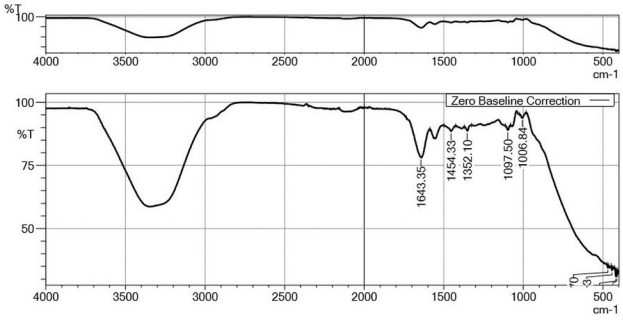

Figure 8: FT-IR spectra of Nanoemulgel 10%.

Table 2: The Main Characteristic Peak of Methocarbamol.

S No.	Functional group	Peaks (cm^{-1})	Bonds
1	Carboxylic	2943-3439.08	s, broad O-H stretch
2	NH bend	960.55	w-m N-H bend
3	Aldehyde	1674.21	s C=O stretch
4	Aromatics	758.02-833.25	s C-H bend
5	Alkenes	960.55	s =C-H bend
6	Alcohols	1184.29-1249.87	m-s C-O stretch
7.	Ether	1060.85-1082.07	s C-O-C stretch

Table 3: The Main Characteristic Peak of Acconon Oil.

S No.	Functional group	Peaks (cm^{-1})	Bonds
1	Alkanes and alkyls	2922.16-2870	s C-H stretch
2	Ketones	1639.49-1732	s C=O stretch
3	Alkanes and alkyls	1456.26	s C-H bend
4	Alkyl halides	1350.17	vs C-F stretch
5	Alkenes	885.35-943.19	s =C-H bend

Table 4: The Main Characteristic Peak of Tween80.

S No.	Functional group	Peaks (cm^{-1})	Bonds
1	Carboxylic acid	3522.02	s, broad O-H stretch
2	Alkanes and alkyls	2862.36-2920.23	s C-H stretch
3	Aldehydes	1645.28-1734.01	s C=O stretch
4	Alkanes and alkyls	1458.18	s C-H bend
5	Alkenes	885.33-943.19	s =C-H bend
6	Ethers	1247.94	m-s =C-O-C sym&asym stretch
7	Alkyl halides	1292.31	vs C-F stretch

Table 5: The Main Characteristic Peaks of Carbapol 934.

S No.	Functional group	Peaks (cm^{-1})	Bonds
1	Alkanes and alkyls	1452.40	s C-H bend
2	Ethers	1168.86	m-s =C-O-C sym&asym stretch
3	Alkyl halides	470.63	C-I stretch
4	Alkanes and alkyls	1456.26	s C-H bend
5	Alkyl halides	1004.91	vs C-F stretch
6	Alkenes	798.53	s =C-H bend
7	Alcohol	1236.37	m-s C-O stretch

in Table 10. The pH of all the Nanoemulsion (NE) formulations and Nanoemulgel formulations were around 5 to 7 and the viscosity was in the range of 18.22 to 45.25 cp. It has better spreadability range from 3.3cm to 7.2cm indicates the suitability of quick spreadable for the topical application.

Particle Size and Zeta potential

The mean globule size was found to be 20.1nm, 10.6nm, 73.8nm, 63.8nm and 56.4nm and zeta potential were found to be in the range of -0.1mV to 0.3mV respectively for the formulation of Nanoemulsion 3%, 5%, 7.5% and 10% accordingly. Zeta potential value is closer to zero owing to the appearance of tween 80 is non-ionic surfactant (Figures 9 and 10). Mostly attain using a various concentration of surfactant with optimal sonication.

Table 6: The Main Characteristic Peaks of Sodium Benzoate.

S No.	Functional group	Peaks (cm^{-1})	Bonds
1	Alkenes	3026.31	w-m =C-H stretch
2	Amides	1622.13	m-s N-H bend
3	Aromatics	1595.13	m-s ring C=C stretch
4	Alkanes and alkyls	524.64	C-I stretch
5	Alkyl halides	1307.74	vs C-F stretch
6	Alkenes	844.82-920.05	s =C-H bend
7	Alcohol	1182.36	m-s C-O stretch

Table 7: The Main Characteristic Peaks of Polyethylene Glycol.

S No.	Functional group	Peaks (cm^{-1})	Bonds
1	Carboxylic acid	2870.08-3425.58	s, broad O-H stretch
2	Amides	1450.47-1597.06	m-s N-H bend
3	Alcohol	1247.94	m-s C-O stretch
4	Alkanes and alkyls	524.64	C-I stretch
5	Alkyl halides	1064.71	vs C-F stretch
6	Alkenes	842.89-931.62	s =C-H bend
7	Alkenes	673.16-704.02	m-s =C-H bend

Drug Content

The drug loading study resulting that the formulations of 3%, 5%, 7.5% and 10% drug loading of 86.66%, 87.4%, 94.04%, and 97.77 respectively. This indicates increasing the oil concentration promotes the higher volume of drug loading capacity.

TEM (Morphology of the Formulation)

TEM for the processed formulation was studied using (TEM-2100 PLUS, Jeol ltd, UK) determined through

Table 8: The Main Characteristic Peaks of Triethanolamine.

S No.	Functional group	Peaks (cm^{-1})	Bonds
1	Carboxylic acid	2945.30	s, broad O-H stretch
2	Amides	1595.13	m-s N-H bend
3	Alkenes	2818-2873.94	s C-H stretch
4	Alkyl halides	403.12-420.48	C-I stretch
5	Alkanes and alkyls	1450.47	s C-H bend

Table 9: The Main Characteristic Peaks of the Nanoemulgel 10%.

S No.	Functional group	Peaks (cm^{-1})	Bonds
1	Alkenes	1643.35	vw-m C=C stretch
2	Alcohols	1097.50	s C-O-C stretch
3	Alkenes	1006-1352.10	vs C-F stretch
4	Alkanes and alkyls	1454.33	s C-H bend

Table 10: Characterizations of Developed Methocarbamol Formulation.

Formulation Code	Drug content* (%)	pH	Viscosity* (cps)	Spreadability* (cm)	Drug release* (%)
F1 NEs 3%	85.45±3.3	5.4±0.1	18.22±0.2	6.3±0.3	64.28±2.8
F2 NEs 5%	88.56±2.8	5.59±0.2	19.1±0.1	6.6±0.4	50.78±1.6
F3 NEs 7.5%	95.66±4.1	5.7±0.1	19.9±0.3	7.0±0.5	41.78±1.7
F4 NEs 10%	98.24±4.2	5.47±0.2	21.2±0.2	7.2±0.4	38.57±1.4
F5 GEL 3%	86.66±3.2	5.56±0.2	38.26±0.4	3.3±0.1	29.57±1.1
F6 GEL 5%	87.4±3.8	5.25±0.3	40.22±0.3	3.0±0.1	38.25±1.7
F7 GEL 7.5%	94.07±2.7	7.3±0.2	42.36±0.2	4.0±0.3	43.71±2.4
F8 GEL 10%	97.77±2.9	7.16±0.1	45.25±0.4	4.2±0.4	52.39±2.2

*number of experiment n=3.

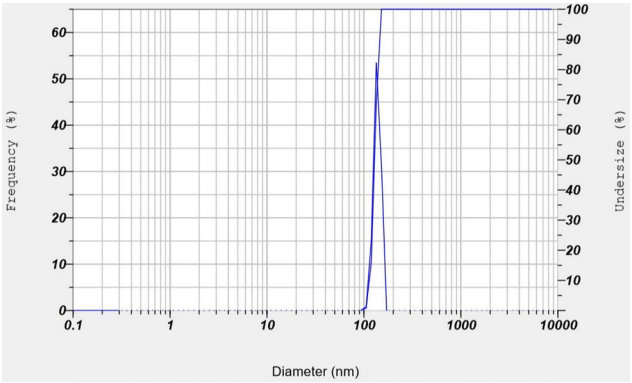

Figure 9: The particle size of 3% Nanoemulsion.

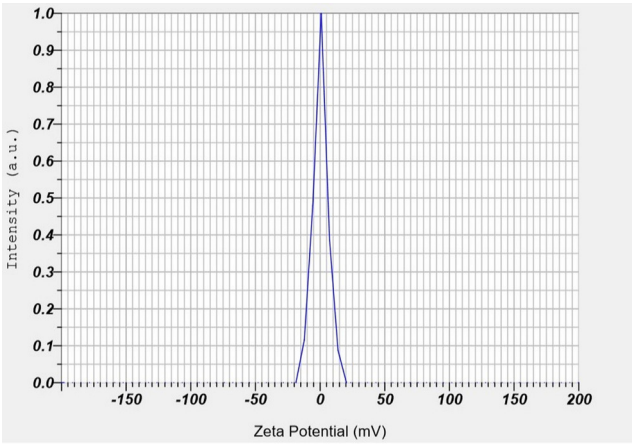

Figure 10: Zeta potential of 3% Nanoemulsion.

70-80KV at 5000 magnification. The TEM results displayed in Figure 11 a&b, that the droplet size was of nanometer in size range with uniform, spherical and smooth surface.

In-vitro Drug Release

The methocarbamol release studies of NEs, NE-Gel and conventional suspension were performed using dialysis membrane on the Franz diffusion cell, PBS (pH7.4) as release media with 37°C. The *in-vitro* drug release of drug from the NE, NEs-Gel after 7 hr showed the following order of release and the NE 3% and NE-Gel 10% showed the highest release of 64.28 and 52.39% at 24 hr, (Figure 12) which is due the presence of the higher amount ACCONON oil, in the formulation.

The *in-vitro* release data of Methocarbamol loaded NEs and NE-gel the rapid release followed along with steady manner of release was determined and the Methocarbamol release were accordingly with formulation of 3%, 5%, 7.5% and 10% respectively. The volume of drug release for 3% Nanoemulsion is

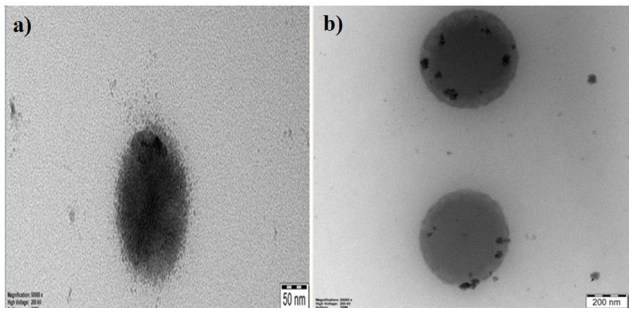

Figure 11: a) TEM image of Nanoemulgel and b) Nanoemulsion.

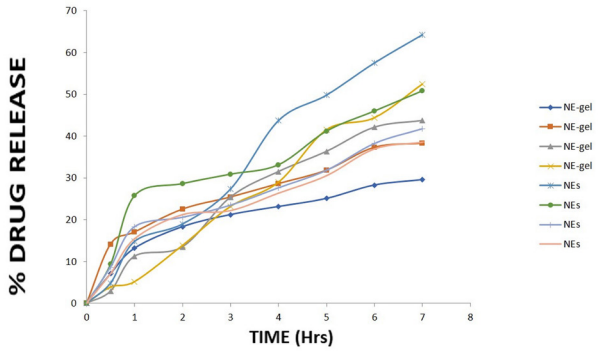

Figure 12: % Drug Release of All the Formulation.

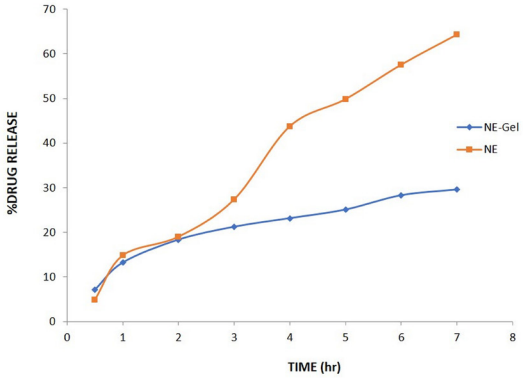

Figure 13: Comparing the both Nanoemulsion and Nanoemulgel drug release.

64.28%, 50.78%, 41.78%, 38.57% and 3% Nanoemulgel is 29.57%, 38.25%, 43.71%, 52.39% respectively. The *in-vitro* Methocarbamol release profile of 3% nanoemulsion has compared with its nanoemulgel due to higher quantity of oil, *in-vitro* resulting increased drug release are shown in Figure 13.

According to drug release kinetic model, various formulation of Nanoemulsion were prepared in that first order release kinetics shows best fit for 3%

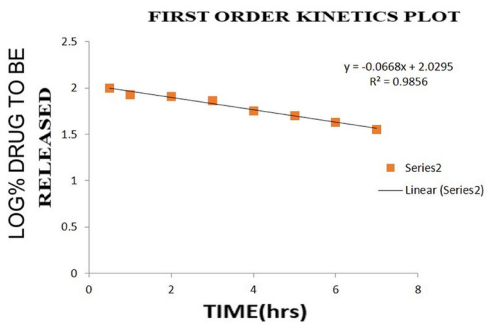

Figure 14: *In vitro* release kinetics of zero order kinetics model.

Nanoemulgel with its maximum R^2 value is 0.9856 are shown in Figure 6 and first order represents the systems where the drug release was dependent of its concentration. While zero order release model R^2 =0.9835, Higuchi model R^2 =0.6769, kormeyer peppas model R^2 =0. 9714 and Hixson crowell model R^2 =0.984 respectively. *In-vitro* release data were shown in Figure 14.

CONCLUSION

The aim of this work is to develop and optimise a stable nanoemulgel loaded with skeletal muscle relaxant drug Methocarbamol, by ultrasonication method of preparing oil in water type nanoemulsion. The primary objective of the work was the compatibility studies to characterize the nanoemulgel meant for the following Solubility, droplet size, zeta potential, pH, viscosity, spreadability, TEM for morphology of formulation, drug content and *in-vitro* release. Methocarbamol is skeletal muscle relaxant is used in the formulation of Nanoemulgel, to prove that nanoemulgel is having maximum drug release when comparing it with oil in water type nanoemulsion preparation and its prepared by sonication method using appropriate quantity of ingredients as Acconon is considered as oil phase, Tween80 is surfactant and co-surfactant, carbapol 934, sodium benzoate and triethanolamine these are all used for hydrogel preparation accordingly. The NEs were formulated using varying the concentration of Tween 80 by ultrasonication method to obtain stable NEs. The formulation was further evaluated for its physicochemical properties. It possess the pH of 5-7, viscosity of 18.22cps, droplet size of 10.6nm and zetapotential of 0.1mV. The formulated Nanoemulsion hydrogel preparation were admixed with carbapol hydrogel to form a nanoemulgel. Using franz diffusion cell, *in-vitro* release studies was performed and most of the formulation possess better quality of drug release. Based on *in-vitro* release it was found that 3% of Nanoemulsion possessed maximum drug release shows 64.28% when comparing with it 3% of nanoemulgel 29.57 %. The NE (3%) exhibiting the highest drug release and NE-Gel shows slower release due the amount of surfactant and hydrogel present in the formulation and maximum amount of Acconon oil content, lower size of the droplet when compared to the conventional formulation. Hence, we conclude that the developed NE, NE-Gel might be beneficial for the better topical delivery of muscle relaxant drug.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NE: Nanoemulsion; **FTIR:** Fourier Transform-Infrared spectrophotometer; **%T:** Percentage Transmittance; **DLS:** dynamic light scattering; **TEM:** Transmission Electron Microscope; **PBS:** Phosphate Buffer Solution; **M.Wt:** Molecular Weight; **UV:** Ultraviolet.

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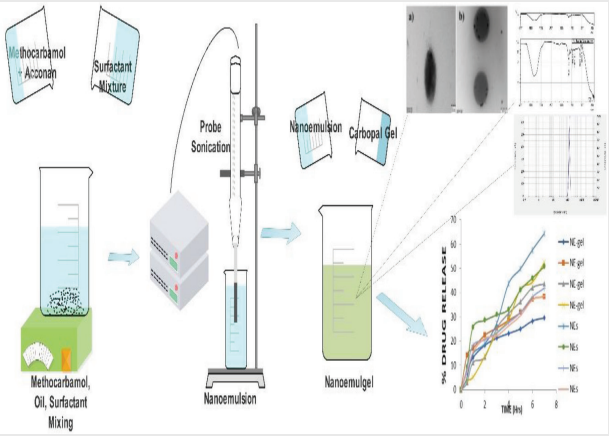
PICTORIAL ABSTRACT



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