Proceeding Paper

Development and Evaluation of Nanoemulsion Loaded Metaxalone for the Treatment of Pain and Injury †

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Abstract: Spasticity is a disorder characterized by an unnatural rise in muscular tone or stiffness, which may impair speech or movement and be accompanied by discomfort or pain. Spasticity can occur due to upper motor neuron dysfunction, which comes about when there is a disturbance of the inhibitory descending spinal motor pathways. The aim of the present work is to formulate nanoemulsion-loaded metaxalone and evaluate it for various parameters. Metaxalone is used with rest, physical therapy, and other measures to relax muscles and relieve pain and discomfort caused by strains, sprains, and other muscle injuries. The phase titration method was used to plot a pseudo ternary phase diagram to select the ratio of the oil to surfactant. The nanoemulsion was prepared using the high-speed homogenization method and an in vitro drug release study was conducted using a Franz diffusion cell. The optimized batch showed the highest entrapment efficiency, up to 93%, and the zeta potential -33 mV and PDI 0.321 showed the stable and homogenous behavior of the globule formed. It also showed an in vitro release of up to 8 h following a zero-order release. Therefore, we conclude that the nanoemulsion containing metaxalone showed a prolonged effect compared to plain metaxalone and can effectively work to improve the muscle conditions to relieve pain and injury.

Keywords: spasticity; nanoemulsion; muscle relaxant; spasm

1. Introduction

Spasticity is a clinical condition of upper motor neuron dysfunction, which comes about when there is a disturbance of the inhibitory descending spinal motor pathways. It is portrayed by a velocity-dependent increment in tonic stretch reflexes (muscle tone) with heightened tendon jerks, caused due to hyper excitability of the stretch reflex. It has been assessed that the pervasiveness of spasticity worldwide is more than 12 million patients. The reason behind such a surge in the velocity-dependent increase in tonic stretch reflexes is neurological disorders such as cerebral palsy (CP), spinal cord injury (SCI), and stroke [1]. Cerebral palsy is the most common cause of physical disability in children, with a reported incidence of 2 to 2.5 per 1000 live births. Approximately 90% of affected children present with clinical symptoms of spastic paresis, a muscle-tone and muscle control–regulation disorder [2]. Spasticity is a common symptom after stroke, arising in about 30% of patients, and usually occurs within the first few days or weeks [3]. The spinal cord carries all of the messages between the brain and the rest of the body that involve voluntary motion, sensory perception, and muscle tone. The prevalence of SCI is 250,000 to 300,000 plus 10,000 new injuries per year [4].

Nanoemulsions are transparent or translucent systems of nanometric size (10–500 nm) consisting of a dispersed phase and a continuous phase, which is stabilized by a surfactant and cosurfactant [5]. Unlike micro emulsions which are thermodynamically stable,

nanoemulsions are stable kinetically. This long-term physical stability property of nanoemulsions without any flocculation or coalescence makes them exclusive systems. A nanoemulsion is a biphasic system, i.e., it has both hydrophilic and lipophilic heads, and it is thermodynamically unstable and stabilized with the addition of an emulsifying agent. Nanoemulsions are made up of oils, emulsifying agents (surfactants/co-surfactants), and an aqueous phase [6–8].

Metaxalone, a muscle relaxant, is used with rest, physical therapy, and other measures to relax muscles and relieve pain and discomfort caused by strains, sprains, and other muscle injuries. Metaxalone comes as a tablet to take by mouth. It is usually taken three or four times a day [9]. Side effects may include drowsiness, dizziness, nausea, vomiting, and an upset stomach [10]. Metaxalone has an onset of action of 1 h, a plasma half-life of 2 to 3 h, and a duration of action of 4 to 6 h. This drug is supplied as 400 mg tablets and has a recommended dose of 800 mg 3 or 4 times daily [11].

The aim of the present study was to formulate and evaluate a metaxalone-loaded nanoemulsion suitable for oral delivery which would be more effective as a skeletal muscle relaxant for the treatment of pain and injury.

2. Materials and Methods

Metaxalone was received as a gift sample from Micro Labs Pvt. Ltd., Mumbai, Maharashtra, India. Sesame oil, Tween 80, PEG400, dichloromethane, triethanolamine, methyl paraben, propyl paraben were purchased from Research-Lab Fine Chem Industries, Mumbai, Maharashtra, India.

Preparation of Metaxalone Loaded Nanoemulsion

Optimized metaxalone nanoemulsion was prepared via high-speed stirring, followed by probe sonication. Two phases, namely, oil phase (P1) and aqueous phase (P2), were compounded separately. In P1, 400 mg metaxalone was dissolved in 5 mL methanol and this was added to oil (10 mL) with continuous stirring for 3 h at 50 °C for complete removal of solvent, and then, the surfactant was added to it. For P2, the co-surfactant was solubilized in distilled water (20 mL) and stirring was carried out for 30 min (Table 1). Then, P1 was gradually added into P2 with continued high-speed stirring (21,500 rpm) using Ultraturrax T25 (IKA WERKE, Bengaluru, India) to form a coarse emulsion (Table 1). The formed coarse emulsion was then probe sonicated to obtain fine nano-sized emulsion (Figure 1).

Table 1. Formulation table for metaxalone-loaded nanoemulsion.

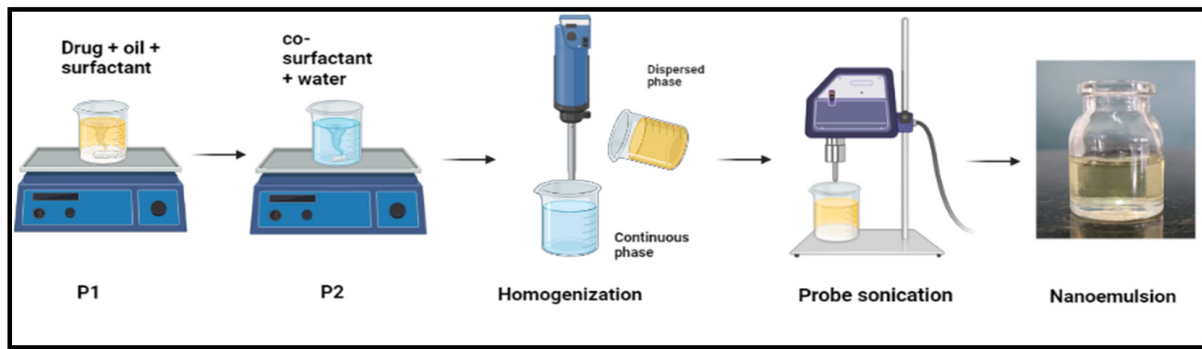| Formulation | Oil (mL) | Drug (mg) | Smix (mL) | Tween 80: PEG 400 [3:1] Smix | | Water (mL) |
				Surfactant (mL)	Co-Surfactant (mL)	
NE1	10	400	30	18	6	60
NE2	10	400	20	15	5	70
NE3	10	400	50	37.5	12.5	40
NE4	10	400	60	45	15	30
NE5	10	400	70	52.5	17.5	20
NE6	20	400	50	37.5	12.5	30
NE7	20	400	20	15	5	60
NE8	20	400	55	18.75	6.25	25
NE9	20	400	60	45	15	20
NE10	20	400	40	30	10	40

Figure 1. Method for preparation of metaxalone-loaded nanoemulsion.

The prepared nanoemulsion batches were optimized using metrics such as entrapment efficiency, TEM analysis, polydispersity index, and zeta potential. Optimized batch was used for further characterization.

3. Results and Discussion

UV spectrophotometry was used for determination of λ_{max} and plotting of the calibration curve of the drug in methanol and in 0.1 N HCL for the confirmation of the drug. The compatibility between the drug and the excipients was confirmed using the FTIR method.

3.1. Characterization of Metaxalone-Loaded Nanoemulsion

3.1.1. % Entrapment Efficiency

The highest entrapment efficiency of 93.85 ± 1.19% was shown by formulation NE5 as compared to the other formulations.

3.1.2. Transmission Electron Microscopy (TEM)

TEM image (Figure 2) of globule shows a particle size of 300–500 nm, which might be acceptable for delivery of the nanoemulsion through the oral route.
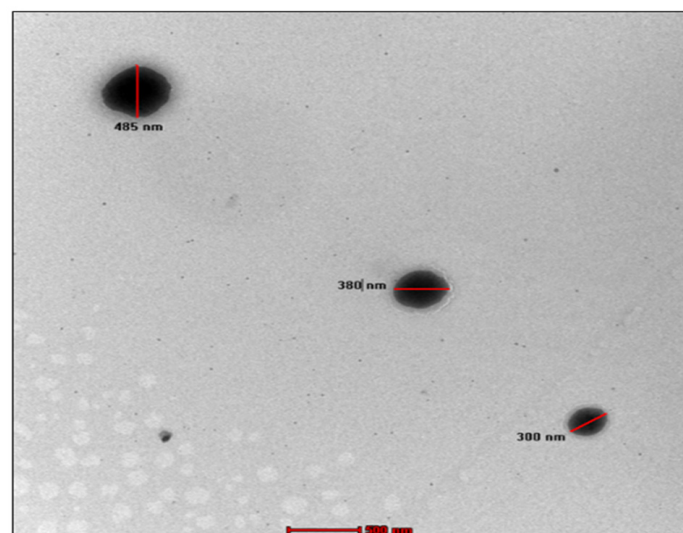

Figure 2. TEM image of optimized nanoemulsion globules.

3.1.3. Zeta Potential

The zeta potential of the NE5 formulation was calculated using a zeta sizer. The zeta potential was determined to be −33.3 ± 8.29 mV, which indicates that the globules were stable in the prepared formulation (Figure 3a).
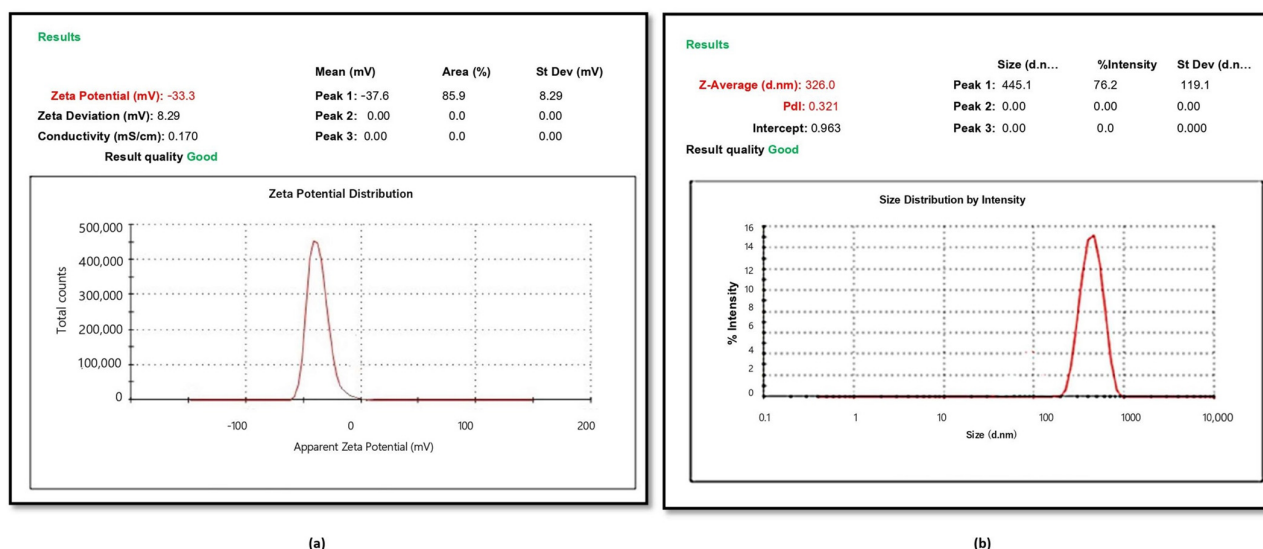
(a)

(b)

Figure 3. (**a**) Zeta potential; (**b**) particle size and polydispersity index of metaxalone-loaded nanoemulsion formulation.

3.1.4. Particle Size and Polydispersity Index (PDI)

The average size of globules was found to be 326 ± 91.21 nm and polydispersity index (PDI) was found to be 0.326, which estimates the homogeneity of the particles within the formulation (Figure 3b).

3.2. Characterization of Metaxalone-Loaded Nanoemulsion
3.2.1. Determination of pH

The pH of nanoemulsion was found to be in the range of 1.5–3.5. This range of pH is acceptable for the gastrointestinal tract.

3.2.2. Viscosity

The viscosity of the nanoemulsion was evaluated using a Brookfield viscometer (DV2T model) with a LV-62 cylindrical. NE5 had a suitable viscosity when compared to the other formulations.

3.2.3. % Drug Content

Formulation NE5 has shown the highest drug content of $95.67 \pm 3.81\%$. The drug content was found to be in range of $88.62 \pm 4.51\%$ to $95.67 \pm 3.81\%$.

3.2.4. In Vitro Release and Kinetic Modelling

The NE5 formulation showed the maximum drug release of up to $94.54 \pm 5.82\%$ at 8 h. The kinetic studies state that the NE5 formulation follows the zero-order model.

3.2.5. Stability Studies

The optimized nanoemulsion formulation was stored at $40 \pm 2\ °C/75\%$ RH in a stability chamber for 90 days. The sample was withdrawn periodically and evaluated for pH and % drug content, and the in vitro drug diffusion was found to be optimum and satisfactory, and there was no significant change in the formulation.

4. Conclusions

A metaxalone-loaded nanoemulsion was prepared using a combination of homogenization and sonication techniques and appears to be effective for the preparation of a drug-loaded nanoemulsion for oral drug delivery. The characterization of the metaxalone-loaded nanoemulsion demonstrated the highest entrapment efficiency of up to $93.92 \pm 1.19\%$.

The nanoemulsions' polydispersity index (PDI) was 0.321, and their zeta potential was -33.33 ± 4.84 mV, showing that the formulation was stable. The nanoemulsion's drug content was found to be $95.67 \pm 3.81\%$. The best results were obtained with a nanoemulsion made with 70% Smix, which demonstrated in vitro release for up to 8 h and followed a zero-order kinetic model. This nanoemulsion type is more flexible than other conventional systems, making it ideal for a low-aqueous-soluble drug.

References

1. Gillies, A.R.; Lieber, R.L. Structure and Function of the Skeletal Muscle Extracellular Matrix. *Muscle Nerve* **2011**, *44*, 318–331. [CrossRef] [PubMed]
2. Beckung, E.; Carlsson, G.; Carlsdotter, S.; Uvebrant, P. The Natural History of Gross Motor Development in Children with Cerebral Palsy Aged 1 to 15 Years. *Dev. Med. Child Neurol.* **2007**, *49*, 751–756. [CrossRef] [PubMed]
3. Pandyan, A.; Gregoric, M.; Barnes, M.; Wood, D.; Wijck, F.V.; Burridge, J.; Hermens, H.; Johnson, G. Spasticity: Clinical Perceptions, Neurological Realities and Meaningful Measurement. *Disabil. Rehabil.* **2005**, *27*, 2–6. [CrossRef] [PubMed]
4. McKinley, W.; Santos, K.; Meade, M.; Brooke, K. Incidence and Outcomes of Spinal Cord Injury Clinical Syndromes. *J. Spinal Cord Med.* **2007**, *30*, 215–224. [CrossRef]
5. Rai, V.K.; Mishra, N.; Yadav, K.S.; Yadav, N.P. Nanoemulsion as Pharmaceutical Carrier for Dermal and Transdermal Drug Delivery: Formulation Development, Stability Issues, Basic Considerations and Applications. *J. Control. Release* **2018**, *270*, 203–225. [CrossRef] [PubMed]
6. Hung, W.-H.; Chen, P.-K.; Fang, C.-W.; Lin, Y.-C.; Wu, P.-C. Preparation and Evaluation of Azelaic Acid Topical Microemulsion Formulation: In Vitro and in Vivo Study. *Pharmaceutics* **2021**, *13*, 410. [CrossRef]
7. Kriwet, K.; Müller-Goymann, C. Diclofenac Release from Phospholipid Drug Systems and Permeation through Excised Human Stratum Corneum. *Int. J. Pharm.* **1995**, *125*, 231–242. [CrossRef]
8. Trotta, M. Influence of Phase Transformation on Indomethacin Release from Microemulsions. *J. Control. Release* **1999**, *60*, 399–405. [CrossRef] [PubMed]
9. Metaxalone. Available online: https://medlineplus.gov/druginfo/meds/a682010.html (accessed on 10 June 2023).
10. Metaxalone: Uses, Interactions, Mechanism of Action. Available online: https://www.webmd.com/drugs/2/drug-7898/metaxalone-oral/details (accessed on 10 June 2023).
11. Waldman, S.D. Skeletal Muscle Relaxants. *Pain Rev.* **2009**, *28*, 651–656. [CrossRef]