International Journal of Enhanced Research in Medicines & Dental Care (IJERMDC),
ISSN: 2349-1590, Vol. 11 Issue 5, May 2024, Impact Factor: 8.325

Advancements in Nanoemulgel Formulation for Enhanced Drug Delivery: A Comprehensive Review

Aditya Kumar[1], Ritu Saini[2], Lokesh Kumar Mishra[3], Abhishek Anand[4]

[1,2]Smt. Tarawati Institute of Bio-Medical and Allied Sciences Roorkee
[3,4]Teerthanker Mahaveer College of Pharmacy Moradabad, Uttar Pradesh

ABSTRACT

Nanotechnology has revolutionized drug delivery systems, offering precise targeting and enhanced efficacy. Nanoemulgel, a hybrid formulation combining nanoemulsion and gel, presents a promising strategy for delivering drugs, particularly hydrophobic ones, through the skin. This paper discusses the formulation, optimization, and evaluation of nanoemulgel, highlighting its advantages such as enhanced drug penetration, improved stability, controlled release, and versatility in accommodating various drug types. The formulation process involves screening of components, preparation of nanoemulsion, and incorporation into the gel base. Evaluation parameters include pH, globule size, swelling index, bioadhesive strength, rheological properties, drug content, spreadability, skin irritation test, and in vitro release study. Nanoemulgel emerges as a valuable tool in pharmaceutical research, offering opportunities for developing novel and effective therapeutic interventions with improved patient outcomes.

Keywords: Nanoemulgel, Drug delivery, Nanotechnology, Formulation, Optimization and Evaluation, Skin penetration, Stability, Controlled release, Spreadability, Drug content, Skin irritation.

INTRODUCTION

The science and engineering used to the design process is known as nanotechnology, synthesis, characterization, and use of materials and devices whose smallest functional organization is on the nanoscale scale, or one billionth of a metre, in at least one dimension. At such scales, the significance of individual molecules and interacting molecular groups increases concerning the overall properties of the material or device, as they exert influence over the molecular arrangement, thereby allowing manipulation of the material's chemical and physical characteristics on a larger scale[1].

Over the last 50 years, nanotechnology has been used in a variety of sectors for a wide range of purposes and has grown rapidly[2]. In the pharmaceutical communities of practice, it has a major influence on medical devices such as imaging probes, drug delivery systems, and diagnostic biosensors. According to Hobson [3], nanotechnology is the development of artificially created or engineered particles having sizes between one and one hundred nanometers. An area of specialisation is the handling of materials and objects with nanoscale structures. It is said that nanotechnology has grown significantly in importance in the field of electronic devices as a result of its breakthroughs in computing, networking, and data processing[4]. Improved power densities for sustaining the storage charge used in different battery types with fewer flammable potential and for converting waste heat in nanomachines into usable energy have been made possible by nanotechnology[5-6].

Nanoemulgel is considered as one of the fitting candidates for medicating conveyance for skin since of its double characters which are nanoemulsion and gel base[7]. Nanoemulgel has found extensive application in the pharmaceutical field, yielding significant benefits[8]. Various considers and examinations have been done on the formulations and advancement of nanoemulgel for the endless conveyance frameworks such as transdermal, vaginal, visual, dental, and nose to the brain for the treatment of differing local people as well as systemic afflictions from both nanoemulsion and gel have caused nanoemulgel to realize tall persistent worthiness. Currently, there is a growing interest in the development of natural and environmentally friendly products with various beneficial bioactivities. The combination of nanoemulgel and plant based oils may be an extraordinary arrangement for the analysts to progress the definition of the application to fulfill the showcase needs[9-10].

Nanotechnology presents an appealing approach for drug delivery and targeting, offering significant potential and advantageous features[11-12] to specifically target sites of action with high therapeutic effectiveness while minimizing adverse reactions[13]. Nanoemulsions (NEs) possess numerous desirable attributes, including large surface area, high entrapment efficiency for hydrophobic drugs, kinetic stability, solubilization capability, high skin permeability, controlled release, and targetability as drug carriers[14-15]. They have been employed for topical delivery of various actives, such as naproxen[16], curcumin[17], mupirocin[18], and tamoxifen[19]. Nonetheless, challenges like low viscosity, limited spreadability[20], and inadequate skin retention can hinder theirapplicability. One potential remedy is integrating nanoemulsions into a hydrogel base to enhance formulation thickness, improve rheological behavior, and enhance physicochemical properties[21].

EMULGEL

Emulgels are a new and popular way to deliver drugs, especially those that don't dissolve easily in water. They are a special mixture of two types of substances: emulsion and gel.This combination allows for the effective delivery of hydrophobic drugs. Emulgels are considered a unique and innovative approach to drug delivery. Emulgel presents notable benefits compared to both traditional and innovative vesicular systems in numerous aspects. It possesses several desirable characteristics, including prolonged shelf life, emollient properties, non-staining nature, water solubility, thixotropic behaviour, greaseless texture, easyspreadability, rapid removal, translucency, and visual appeal. Emulgel serves as an ideal dosage form for administering steroids, antibiotics, analgesics, and antifungal medications and has recently witnessed expanded applications.

Topical use Emulgel has several favorable properties like simple unfold, fat-free, thixotropic properties, water-soluble, simple to get rid of, longer period, non-staining, and compatible love biology[22].

Advantages

Enhanced drug penetration: Emulgel formulations have the ability Emulgel compositions can improve drug absorption through the skin in contrast to traditional creams or ointments. The emulsion componentinemulgel helps solubilize lipophilic drugs, allowing them to better penetrate the lipid-rich outer skin's layer[23].

Improved stability: Stability of drug can be improved by protecting them from degradation, oxidation, or hydrolysis. The emulsion element serves as a shield, minimizing exposure to external elements that might degrade the drug. This is especially crucial for medications prone to degradation or with a short shelf life.

Controlled drug release: Emulgel formulations can be designed to control the release rate of the drug, allowing for sustained or controlled release over a longer period of time.

Versatility in formulation: Emulgel can accommodate a wide range of drug types, including hydrophilic, lipophilic, and amphiphilic drugs.

Non-occlusive and breathable: Emulgel formulations are non-occlusive, allowing the skin to breathe and reducing the risk of maceration or irritation.

Easy application and Spreadability: Emulgel can be easily applied and spread on the skin,
allowing for better coverage of the affected area.

Combination of gel and emulsion benefits: Emulgel combines the advantages of both gels and emulsions. It provides the viscosity and stability of a gel, while the emulsion component enhances drug penetration and solubilization[24].

IMPORTANT CONTENT IN NANO-EMULGEL

VEHICLE: To ensure that a medication effectively reaches and stays on the skin's surface, the vehicle (the substance carrying the medication) needs to distribute the active component evenly. The vehicle or solvent helps transport the medication to the intended location. It's required for the vehicle to maintain the therapeutic effect of the medication, allowing it to work better. The outermost layer of the skin called the stratum corneum, acts as a barrier for absorption of drug. The vehicle plays a role in determining how fast and what amount of the medication is absorbed through this barrier [25]. The vehicle are aqueous material (water and alcohols) and oils (mineral oils, castor oil, and vegetable oil).

Emulsifiers: Emulsifying agents are employed during the manufacturing process to enhance emulsification and ensure stability throughout the product's shelf life. The duration of shelf life can vary from a few days for freshly prepared

emulsions to several months or even years for long-term formulated products [26]. Commonly used emulsifying substances include sorbitan monooleate (Span 80), sodium stearate, polyethylene glycol 40 stearate, stearic acid, and polyoxyethylene sorbitan monooleate (Tween 80). These agents play an important role in facilitating the formation and maintenance of stable emulsions by reducing the interfacial tension between the oil and water phases.

Gelling Agent: Polymers essential to present the structural network for the preparation of gels are referred to as gelling agents. E.g. Natural - Agar, Tragacanth, Guar gum, Xanthan Gum, Semisynthetic and artificial Ca rbapol, Poloxamer, HPMC (cellulose derivatives)[27].

Carbopol: Carbopol is a versatile ingredient that can be used in different concentrations. It has a noticeable flow pattern and becomes thick even at low concentrations. It works well with various active substances, has good sticking power, and remains stable at different temperatures[28].

Preservatives: Antimicrobial preservatives are synthetic or non-synthetic substances used to
inhibit the growth of microorganisms in drugs, excipients, and formulations. Their purpose is to increase the shelf life of these products.

Humectant: Additives known as humectants aid in the retention of moisture in formulations. They are frequently included in skincare treatments that help with dry skin issues. Humectants' primary job is to maintain the skin's moisture content. The way that medications are absorbed through the skin can also be impacted by the skin's level of moisture. Humectants include things like urea, hyaluronic acid, propylene glycol, and glycerine.

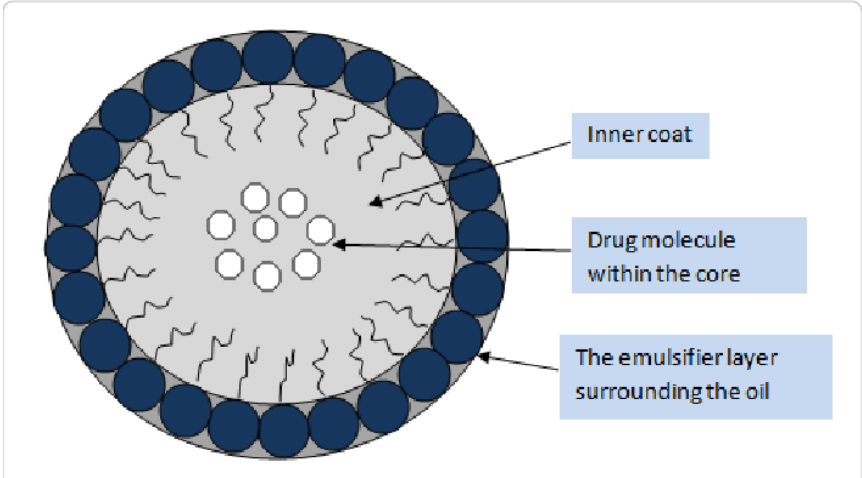

Figure No. 1: Diagram of stablilzed Nanoemulsion

Method of formulation
Formulation of Nanoemulsion-gel can be summed up into following steps,

a. **Screening of components**
b. **Preparation of Nanoemulsion**
c. **Preparation of Nano emulgel.**
The selection of ingredients, their proper concentration, order of addition, a suitable method of preparation, and an appropriate stirring speed or shear stress are the vital aspects that are considered before the formulation of an emulsion. Phase inversion emulsification or applying extreme shear should be used to assure the production of nanoscale droplets (Mason et al., 2006).Number of methods to create nanoemulsions (size range 20–200 nm) until this point, some of which are summarized here.

High-energy emulsification methods:
High-energy emulsification methods are employed to create thermo kinetically stable nanoemulsions. These techniques aim to overcome the intermolecular forces of attraction, such as hydrogen bonds and Van der Waals forces, which are present between liquids with extremely high or low surface tension. To achieve this, a more robust force is required. While these

processes generate elevated temperatures, external energy is applied through shear, ultrasonic waves, and pressure to disintegrate droplets into the nanoscale range.

Low-energy emulsification methods:
Low-energy emulsification methods have become widely favored because they harness the inherent energy within the system to create small droplets, resulting in stable nanoemulsions. These methods involve modifying parameters such as temperature or composition, which influence the balance between the hydrophilic and lipophilic properties of the system (referred to as the Hydrophilic-Lipophilic balance, or HLB). These techniques are gentle and do not cause any harm to the enclosed molecules. Moreover, they are energy-efficient, making them highly appealing for large-scale production.

Self-nano emulsification method:
The self-emulsification method enables the creation of nanoemulsions while retaining the surfactant's inherent properties. This technique involves the rapid diffusion of surfactant and/or co solvent molecules from the dispersed phase into the continuous phase, leading to turbulence and the formation of nano-sized emulsion droplets (Solans et al., 2016). It is commonly referred to as the spontaneous emulsification method. Self-nanoemulsifying drug delivery systems
(SNEDDS) are developed based on the principles of self-emulsification.

Screening of components:
Drug solubility was determined in different oils by adding more than drugs in different ingredients, then stirring continuously for 72 hr to reach equilibrium.

Psedoternary phase diagram:
Surfactant and co-surfactant (Nmix) are mixed in different ratios(2:1, 3:1, and 5:1). Each ratio was chosen as an increasing amount of surfactant over co-surfactant for the phase diagram study. Here aqueous phase (Distilled Water) is used as the dilution medium. Oil and Nmix were mixed at different ratios from 9:1 to 1:9 in different vials for each Nmix.

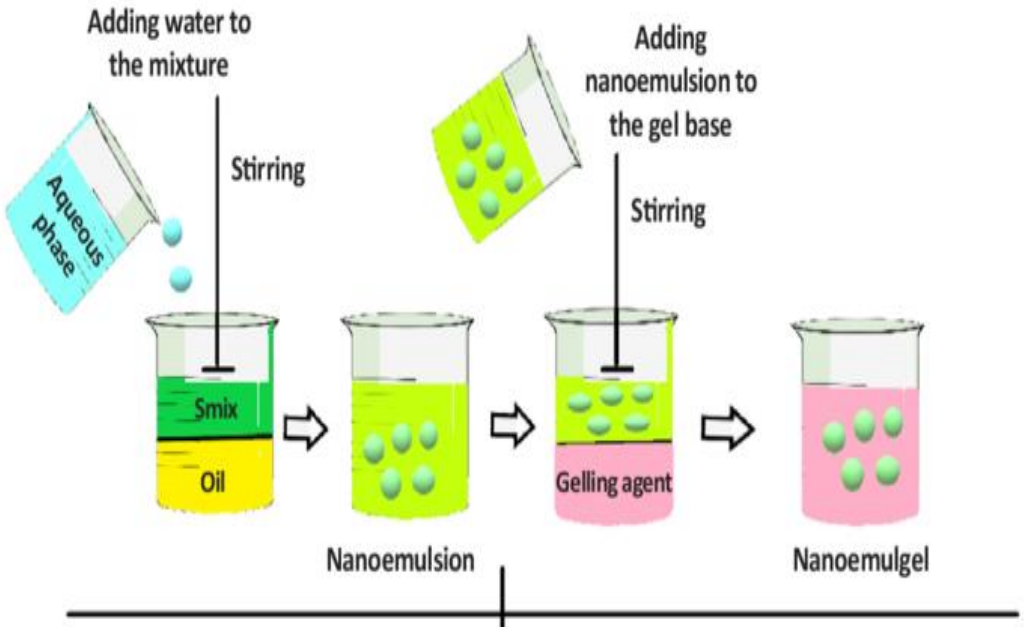

Figure No. 2: Preparation of Namo Emulgel.

Optimization and evaluation:
a. Measurement of pH: Several topical therapies have pH values between 5 and 6, according to a pH metre. For testing, 1g of gel is dissolved in 10ml of water. Every formulation's PH is measured 1 three times to ensure accuracy.

b. Size of globules: A 1.0 gramme gel sample was dissolved in water and agitated to achieve dispersion before being injected into the Malvern Zeta Sizer's photocell to measure this parameter.

c. Swelling Index: On a piece of porous aluminium foil, spread out 1 gm of the produced topical nanoemulgel. Top with 10 ml of 0.1 N NaOH solution. The sample is periodically taken out, and the weight is recorded until it stops changing:

Swelling Index (SW) % = [[Wt-Wo]/Wo]*100
Where, (SW) % = Percentage swelling,
Wo = Original weight of nanoemulgel
Wt = Weight of swollen nanoemulgel at time t

Measurement of Bioadhesive strength:
Two more glassed plates and one glass slide were situated on each arm of the contraption. The weight is added using a single plate. In the space between slides with rate skin pieces, One gramme of nanoemulgel is carefully injected. The sandwich of two slides may be separated by applying weight to one of the glass slides. 200 mg of additional weight is applied every minute until the skin's surface separates.

It is calculated by using the following equation:

Bioadhesive Strength = W / A

Where W denotes the desired weight (in gms) and A denotes the area (cm2)

Determination of Rheological properties Using a Brookfield viscometer with Spindle number S64, the viscosity of 20g of Nanoemulsion-gel in a 25ml beaker was determined.

Accelerated stability studies:
Every two weeks, analyse the drug content using the proper analytical techniques. The drug's breakdown or the gel's pH change are the basis for the stability measurement.

a. Determination of % drug content: Combine 25 ml of methanol with 1 g of Nanoemulgel. For thirty minutes, the solution was sonicated. Utilise suitable analytical techniques to determine the amount of drug present in this mixture.

Spreadability of Gellifed Nanoemulgel:
For measuring, you can use the sliding and dragging base that Mutimer suggests. Here, a 500 mg hook, a glass slide, and another glass slide of a comparable size are fastened to the lower glass slide, which has 2gm of Nanoemulgel glued to it with a piece of wood. Positioning of weight. Put more weight on the tray that is attached to the second slide after five minutes. To determine the spreading capacity, note how long it took the upper slide to travel 5 cm and apply this formula:

Spreading capacity (S) = M * L / T

Where M = the weight tied to the slide,

L = the size of the slide Length

T = Time required to move the distance with the upper carriage

Drug content determination:
By combining the right amount of the nanoemulgel formulation with an appropriate solvent, the drug content is ascertained. Subsequently, the solution is run through Whatman filter paper, and the filtrate is subjected to UV spectrophotometric analysis using the same standard plot and the absorbance value reported by More et al. to determine the drug concentration.

Skin irritation test (Patch test):
When the preparation was used on appropriately shaved rat skin, unwanted colour changes emerged. Skin morphological changes should be monitored for a maximum of twenty-four hours. The test is successful if there is no irritation.

In vitro release study:
Drug release investigations employ the Franz diffusion cell, which has an effective diffusion area of 3.14 cm2 and a cell volume of 15.5 ml. The diffusion cell's donor and acceptor chambers are encased in an even layer of the nanoemulsion that is applied to the membrane. To dissolve the medication, new phosphate-buffered saline (pH 5.5) is added to the receptor compartment. A magnetic stirrer is used to stir the receiving chamber. Gather samples (aliquots of 1.0 ml) at appropriate intervals. Following the appropriate dilution, UV-Vis was used to determine the drug concentration of the sample. Calculate the total amount of medication that has been released via the dialysis membrane.

CONCLUSION

Nanoemulgel, a combination of nanoemulsion and gel, offers a promising approach for drug 11 delivery due to its advantageous properties. It enhances drug penetration through the skin, improves stability, allows controlled release, accommodates various types of drugs, and is non-occlusive and breathable. The formulation process involves careful screening of components, preparation of nanoemulsion, and incorporation into the gel base. Evaluation parameters include pH, globule size, swelling index, bioadhesive strength, rheological properties, drug content, spreadability, skin irritation test, and in vitro release study. Overall, nanoemulgel shows potential as an effective and versatile delivery system for pharmaceutical applications, offering benefits such as enhanced efficacy, improved patient compliance, and expanded therapeutic possibilities.

REFERENCES

[1]. Saini R, Saini S, Sharma S. Nanotechnology: the future medicine. J Cutan Aesthet Surg. 2010 Jan;3(1):32-3. doi: 10.4103/0974-2077.63301. PMID: 20606992; PMCID: PMC2890134.
[2]. J. E. Hulla, S. C. Sahu, A. W. Hayes, Nanotechnology: History and future. Human & experimental toxicology, 34(12), 1318-1321, (2015).
[3]. V. J. Morris. Foods, Materials, Technologies and Risks, Encyclopaedia of Food Safety, (2014).
[4]. D. W. Hobson, Industrial Biotechnology and Commodity Products, Comprehensive Biotechnology, 2nd edition, (2011).
[5]. G. A Divesh. Literature review of Nanotechnology, Journal of emerging technologies and innovation research, Volume 6, Issue 1, Gaalgotias University, Uttar Pradesh, (2019).
[6]. F. A. Zaid, Nuha, A. A. Aklas. Effects of solvents on the size of copper oxide particles fabricated using photolysis method, Asian Journal of Chemistry, pp: 223-225, (2018).
[7]. Algahtani, M., Ahmad, M. and Ahmad, J., 2020. Nanoemulgel for Improved Topical Delivery of Retinyl Palmitate: Formulation Design and Stability Evaluation. Nanomaterials, 10(5), p.848.
[8]. Kaur, G., PMS, B. and Narang, J., 2017. Topical Nanoemulgel: A Novel Pathway for Investigating Alopecia. Journal of Nanomedicine & Nanotechnology, 08(06).
[9]. Panwar, N Upadhyay, M Bairagi, S Gujar, G Darwhekar (2011) Emulgel: A Review. Asian Journal of Pharmacy and Life Science 1
[10]. S Yadav, M Mishra, A Tiwari, Ashutosh Shukla (2017) Emulgel: A New Approach for Enhanced Topical Drug Delivery. International Journal of Current Pharmaceutical Research 9(1): 15-19.
[11]. DeLouise, L.A. Applications of nanotechnology in dermatology. J. Investig. Dermatol. 2012, 132, 964–975.
[12]. Hirose, A.; Nishimura, T.; Kanno, J. Research strategy for evaluation methods of the manufactured nanomaterials in NIHS and importance of the chronic health effects studies. Bull. Natl. Inst. Health Sci. 2009, 127, 15–25.
[13]. Saini, R.; Saini, S.; Sharma, S. Nanotechnology: The future medicine. J. Cutan. Aesthetic Surg. 2010, 3, 32–33.
[14]. Pawar, K.R.; Babu, R.J. Lipid materials for topical and transdermal delivery of nanoemulsions. Crit. Rev.TM Ther. Drug Carr. Syst. 2014, 31, 429–458.
[15]. 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.
[16]. Abd, E.; Namjoshi, S.; Mohammed, Y.H.; Roberts, M.S.; Grice, J.E. Synergistic skin penetration enhancer and nanoemulsion formulations promote the human epidermal permeation of caffeine and naproxen. J. Pharm. Sci. 2016, 105, 212–220.
[17]. Md Saari, N.H.; Chua, L.S.; Hasham, R.; Yuliati, L. Curcumin-loaded nanoemulsion for better cellular permeation. Sci. Pharm. 2020, 88, 44.
[18]. Alhasso, B.; Ghori, M.U.; Conway, B.R. Development of Nanoemulsions for Topical Application of Mupirocin. Pharmaceutics 2023, 15, 378.
[19]. Tagne, J.-B.; Kakumanu, S.; Ortiz, D.; Shea, T.; Nicolosi, R.J. A nanoemulsion formulation of tamoxifen increases its efficacy in a breast cancer cell line. Mol. Pharm. 2008, 5, 280–286.
[20]. Khurana, S.; Jain, N.; Bedi, P. Nanoemulsion based gel for transdermal delivery of meloxicam: Physico-chemical, mechanistic investigation. Life Sci. 2013, 92, 383–392.
[21]. Dhawan, B.; Aggarwal, G.; Harikumar, S. Enhanced transdermal permeability of piroxicam through novel nanoemulgel formulation. Int. J. Pharm. Investig. 2014, 4, 65–76.
[22]. K. Mohammed Haneefa and S. Easo and P Hafsa and Guru Prasad Mohanta and Chandini R. Nayar},year={2013},url={https://api.semanticscholar.org/CorpusID:617236}

[23]. Bashir M, Ahmad J, Asif M, Irfan M, Ibrahim AY, Asghar S, Khan IU, Iqbal MS, Haseeb A, Khalid SH, Abourehab MA. Nanoemulgel, an innovative carrier for diflunisal topical deliverywith profound anti-inflammatory effect: In vitro and in vivo evaluation. International Journal of Nanomedicine. 2021; 16:1457
[24]. Gorain B, Choudhury H, Kundu A, Sarkar L, Karmakar S, Jaisankar P, Pal TK. Nanoemulsion strategy for olmesartanmedoxomil improves oral absorption and extended antihypertensive activity in hypertensive rats. Colloids and Surfaces B: Biointerfaces. 2014 Mar 1; 115:286-94.
[25]. Abdallah MH, Lila AS, Unissa R, Elsewedy HS, Elghamry HA, Soliman MS. Preparation, characterization and evaluation of anti-inflammatory and anti-nociceptive effects of brucine-loaded nanoemulgel. Colloids and Surfaces B: Biointerfaces. 2021 Sep 1; 205:111868.
[26]. Ahmad J, Gautam A, Komath S, Bano M, Garg A, Jain K. Topical nano-emulgel for skin disorders: Formulation approach and characterization. Recent patents on anti-infective drug discovery. 2019 May 1;14(1):36-48.
[27]. Ahmad J, Gautam A, Komath S, Bano M, Garg A, Jain K. Topical nano-emulgel for skin disorders: Formulation approach and characterization. Recent patents on anti-infective drug discovery. 2019 May 1;14(1):36-48.
[28]. Patel J, Trivedi J, Chudhary S. Formulation and evaluation of diacerein emulgel for psoriatic arthritis. International Journal of Pharmaceutical Research. 2014;3(2):625 38.
[29]. Inouye, S.; Yamaguchi, H.; Takizawa, T. Screening of the antibacterial effects of a variety of essential oils on respiratory tract pathogens, using a modified dilution assay method. J. Infect. Chemother. 2001, 7, 251–254.
[30]. 71. Kumar, P.; Mishra, S.; Malik, A.; Satya, S. Repellent, larvicidal and pupicidal properties of essential oils and their formulations against the housefly, Musca domestica. Med. Vet. Entomol. 2011, 25, 302–310.
[31]. 72. Sugumar, S.; Clarke, S.; Nirmala, M.; Tyagi, B.; Mukherjee, A.; Chandrasekaran, N. Nanoemulsion of eucalyptus oil and its larvicidal activity against Culex quinquefasciatus. Bull. Entomol. Res. 2014, 104, 393–402.
[32]. Edris, A.E. Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: A review. Phytother. Res. 2007, 21, 308–323.
[33]. Deba, F.; Xuan, T.D.; Yasuda, M.; Tawata, S. Chemical composition and antioxidant, antibacterial and antifungal activities of the essential oils from Bidens pilosa Linn. var. Radiata. Food Control 2008, 19, 346–352.
[34]. Assali, M.; Zaid, A.N.; Abdallah, F.; Almasri, M.; Khayyat, R. Single-walled carbon nanotubes-ciprofloxacin nanoantibiotic: Strategy to improve ciprofloxacin antibacterial activity. Int. J. Nanomed. 2017, 12, 6647–6659.
[35]. Mayaud, L.; Carricajo, A.; Zhiri, A.; Aubert, G. Comparison of bacteriostatic and bactericidal activity of 13 essential oils against strains with varying sensitivity to antibiotics. Lett. Appl. Microbiol. 2008, 47, 167–173.