Journal of Pharmacognosy and Phytochemistry

Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
https://www.phytojournal.com
JPP 2023; 12(1): 130-134
Received: 18-11-2022
Accepted: 22-12-2022

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Formulation and characterization of analgesic and anti-inflammatory transdermal Nanogel containing combination of herbal extract and synthetic drug

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Abstract
The main aim of the study is preparation and characterization of the analgesic and anti-inflammatory nanogel containing the combination of herbal extract and synthetic drug. An oil-in-water nanoemulsion containing drugs such as gingerol, capsaicin and nimesulide and mixture of oil, surfactants and co surfactants [Coconut oil: Tween 80: Polyvinyl alcohol] prepared by spontaneous emulsification method. The prepared nanoemulsion formulations were evaluated for the further optimization of the system, which characterized by the particle droplet size, pH, spreadability and drug release.

Keywords: Herbal nanogel, transdermal nanogel, nanoemulsion

1. Introduction
Nanoemulsions are submicron-sized emulsions that are being investigated as drug carriers to improve the delivery of therapeutic agents. It is a thermodynamically stable isotropic system in which two immiscible liquids are mixed into one phase using a suitable surfactant and co-surfactant [1]. Due to their very small droplet size in the range of 20-500 nm, they can penetrate rough skin and improve the penetration of active substances [2]. However, to achieve the desired efficacy of herbal medicines, nanotechnology is incorporated to control the effectiveness of the active phytoconstituents in the system. The Nano drug delivery system is one of the new approaches to increase the use of plant-based drugs by improving the onset of action and releasing active ingredients [3]. Ginger is a spicy substance with a bitter taste. It is easily soluble in organic solvents, but slightly soluble in water. 6-Gingerol has a variety of pharmacological and physiological activities, such as anti-inflammatory, analgesic, antitumor and antiemetic activities [4]. Ginger oleoresin is a lipid extract of ginger. Capsaicin is the pungent principle of the hot chilli pepper (*Capsicum spp*.). Upon initial application, capsaicin appears to cause selective stimulation of afferent C fibers and the release of substance P and other neuropeptides. This is responsible for the initial analgesic effect associated with topical application of capsaicin. Continued application causes depletion of substance P from sensory nerve endings and long-lasting desensitisation to burning and pain. These effects are reversible after the withdrawal of capsaicin. Topical capsaicin is available in 2 strengths, 0.025 and 0.075%. Both preparations are currently indicated for use in neuralgia (e.g. postherpetic neuralgia and diabetic neuropathy); a 0.025% preparation is also indicated for use in osteoarthritis and rheumatoid arthritis [5]. Nimesulide is a NSAID with the good anti-inflammatory, analgesic, and antipyretic effects expected of these compounds. In addition, however, it has some unique therapeutic and pharmacological activities. Novel therapeutic aspects include relatively low toxicity to the gastrointestinal tract and kidneys, it can be administered to most patients who have respiratory problems with other NSAIDs, and the onset of analgesia is relatively rapid. The main novel pharmacological effects obtained by using nimesulide *in vivo* at therapeutic doses and *in vitro* at a concentration in the therapeutic range of the free drug, include: preferential inhibition of prostaglandin synthesis via COX-2 and reduction of the effect/release of cytokines, release of histamine, release of enzymes that degrade cartilage [6].

2. Materials and Methods
2.1 Materials
6-Gingerol resin (Plants lipids private ltd. Kolenchery-Kerala), Capsaicin resin (Plants lipids private ltd.Kolenchery-Kerala) Nimesulide(SDFCL, Mumbai), Tween 80(SDFCL, Mumbai),

Polyvinyl Alcohol(SDFCL, Mumbai), Coconut oil(local market) Carbopol 934(SDFCL Mumbai), Water(DW) Magnetic stirrer(Remi Instruments Ltd, Mumbai, India), Probe sonicator (Bandelin electronic, Berlin, Germany), UV-Visible spectrophotometer(UV 1601, Shimadzu, Japan), Diffusion cell apparatus(Orchid Scientifics), pH meter (Elico LI 617), Malvern ZetasizerNano ZS(Malvern instruments, UK).

2.2 Methods

2.2.1 Preparation of Nanoemulsion

The nanogel containing the combination of herbal extracts (Gingerol and Capsaicin resin) and synthetic drug (Nimesulide) was prepared by the ultrasonication technique using the Bandelin probe method. The accurately weighed quantity of drug was transferred to the narrow and conical shaped vessel using a micropipette and further mixed with surfactant (Tween 80) and co-surfactant (Polyvinyl Alcohol) respectively. Later, the oil (coconut oil) and water are added for the preparation of the nanoemulsion. The ultrasonication method was done by using a probe sonicator. It was kept for sonication using a Bandelin probe sonicator for 3 cycles of sonication for 15 min, appropriately varying the level of all surfactants, and secondary surfactants, it is possible to achieve the desirable properties. Table no 1.

2.2.2 Characterization of nanoemulsion

2.2.2.1 Mean particle size and Particle size distribution:

Particle size and distribution of the formulated nanoemulsion was analyzed by Photon Correlation Spectroscopy using Malvern particle size analyzer (Zetasizer) equipped with Malvern photo correlation spctroscopy software (The Malvern instruments, UK). The Zetasizer system determines the size by measuring the Brownian motion of the particles in a sample using Dynamic Light Scattering, and the samples were measured after appropriate dilution with distilled water (millipore). The reading was carried out at 90° angle with respect to the incident beam. The zeta potential was measured by a laser Doppler Anemometer coupled with the same instrument.

2.2.2.2 pH of the formulation.

The developed formulations were evaluated for pH using a digital pH meter (Elico LI 617), The pH meter probe was immersed in the formulation for 5 min and then the readings were taken [7].

2.2.2.3 Spreadability test

Two glass plates of 5×20cm and a weight of 30 gm each were used for the study. About 100 mg of the test formulation was placed over one glass plate. Then the second glass plate was placed over the first glass plate in such a way that the formulation was sandwiched between the 2 glasses. An extra weight of about 10gm was placed over the sandwiched glass plate for uniform spreading, then after five minutes, the diameter of the spreaded formulation was measured using a scale. An average of these readings was taken [8].

2.2.3 Preparation of nanoemulsion gel

In order to prepare a topical gel, Carbopol was selected as gel matrix base. In the optimized prepared nanoemulsion containing gingerol (5%w/w), capsaicin 0.025%(w/w) and nimesulide 0.3%(w/w)and mixture of oil, surfactants and co surfactants0.4% (w/w) Carbopol was added and stirred slowly with magnetic stirrer at a speed of 300 rpm for about 12 h at room temperature. pH of the sample was then adjusted to 7.0–7.5 by adding NaOH 1 N to form the gel [9].

2.2.4 *In vitro* permeation study using dialyzing membrane:

The *in vitro* permeation study of the transdermal nano gel was performed in a Franz diffusion cell with 10 mL of phosphate buffer solution (pH 6.8) in the receiving chamber. The dialysis membrane was clamped between the donor and recipient chambers. The phosphate buffer solution (pH 6.8) in the acceptor chamber was maintained at 37 ± 0.5 °C with constant stirring. The formulation was placed in the donor compartment and moistened. Diffusion took place for 6 hours. The amount of drug permeating the membrane was determined by periodic sampling and replacement with an equal volume of phosphate buffer solution (pH 6.8). The amount of drug in each aliquot was assayed on a UV spectrophotometer (Shimadzu 1601, Japan) using an appropriate blank.

3. Result and Discussion

3.1 Nanoemulsion formulation

The nanoemulsions were prepared by the self-emulsification method. Tween 80 and PVA were used as surfactants and cosurfactants, coconut oil as the oil phase, and water as the external phase (1). To prepare the nanoemulsion formulation, oil, surfactants, co-surfactants, and distilled water were weighed and mixed together and then sonicated using a Bandelin Probe sonicator. Samples in which no signs of phase separation, flocculation, and sedimentation were visually observed and were selected as stable formulations. Furthermore, the droplet size of the nanoemulsion was checked for 30 days at room temperature, and samples with a significant increase in particle size were removed from the screening process.

3.2 Physical characterization of nanoemulsion

3.2.1 Spreadability

Spreadability is very important because it shows the behaviour of the gel that comes out of the tube. The spreadability values shown in Table (2) show that all the polymers used gave gels spreadable with little shear. The diameters of the extended circles ranged from 3.7 cm for formulation F1 and 3.9 cm for formulation F2 with carbopol gel. The data in Table (2) revealed that an increase in the concentration of any of the gelling agents was always associated with a decrease in spreadability as expressed by the bottom diameter of the spread circle. Table No. (2)

3.2.2 pH Determination

The pH values of 2 developed formulae was in range 5-6 which is considered acceptable to avoid the risk of irritation upon application to the skin. Drug Content determination with the exception of pectin gel; pH was about 3.5; results are tabulated in table no (2)

Table 1: Shows the Composition of Nanoemulsion

Formulation	Gingerol (ml)	Capsaicin (ml)	Nimesulide (gm)	Surf: Cosurfactant (Tween 80:PVA)	Coconut oil (ml)	Water (ml)
F_1	0.5	0.025	0.3	6ml(3:3)	1	3
F_2	0.5	0.025	0.3	6ml(4:2)	1	3

Table 2: Shows the physical properties of Nanoemulsion gel

Formulations	Colour	Spreadability (cm)	pH
F_1	Translucent yellowish	3.7	6.4
F_2	Translucent yellowish	3.9	6.5

3.3. Mean particle size and Particle size distribution report by intensity using Malvern instruments

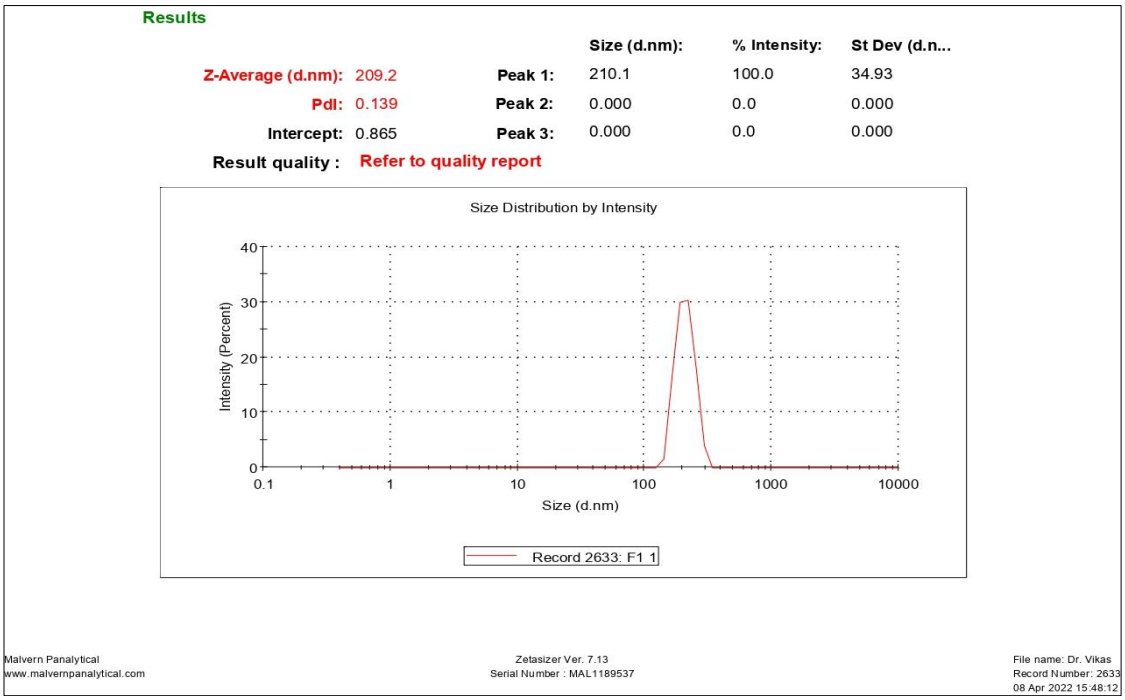

Fig 1: Mean particle size and Particle size distribution report of $\mathbf{F_1}$ formulation

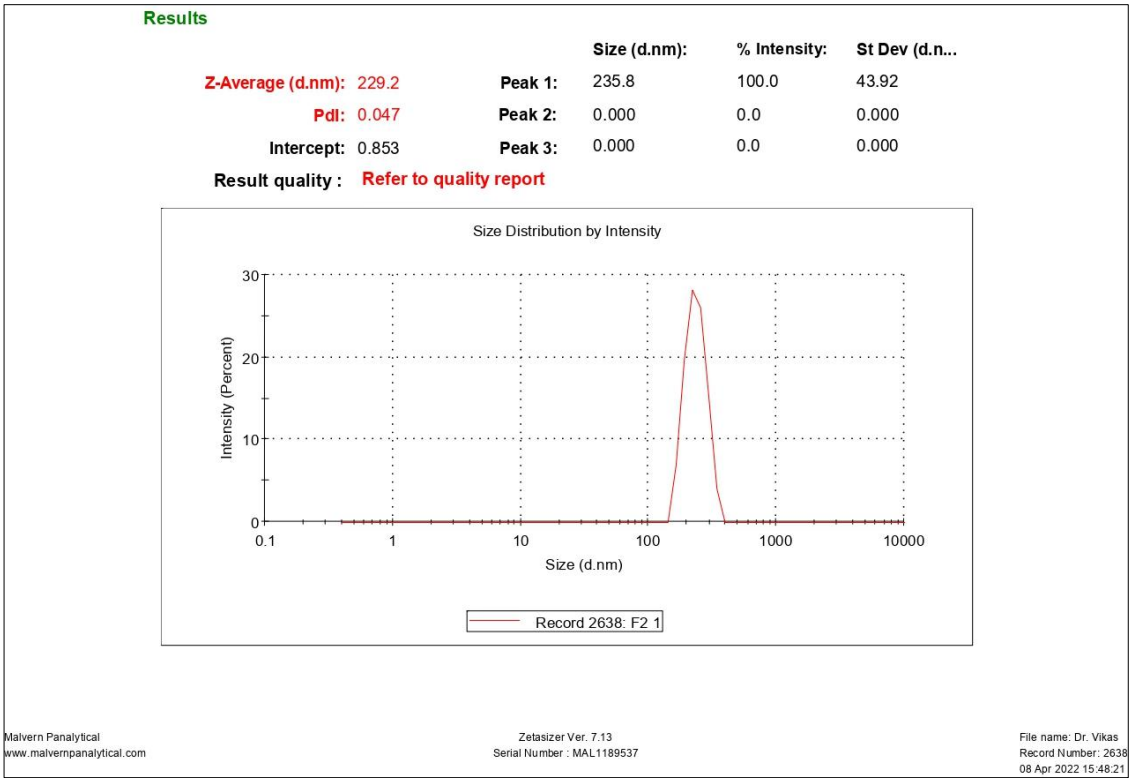

Fig 2: Mean particle size and Particle size distribution report of F_2 formulation

3.4. *In vitro* drug permeation study using dialyzing membrane: In-vitro drug release data of prepared transdermal nano gels in phosphate buffer solution (pH 6.8) are showed table no 3.

Drug release from the dosage form plays an important role in the drug delivery system and in determining the therapeutic effect of the drug. The effect of polymer concentration on drug release was analyzed and it was found that drug release *in vitro* depends on the concentration of the polymer used.

In-vitro release of the drug from the formulation F1, F2 transdermal nanogels was carried out for up to 6 hours (table no. 3 and table no. 4). Drug release from the formulations was dependent on the amount of polymer present in the formulations. Formulations containing lower polymer concentration showed higher drug release compared to formulations containing higher polymer concentration. As the amount of polymer in the formulations increased, the rate of drug release from the formulations decreased, as well as increasing the polymer concentration will increase the viscosity of the transdermal gel and also cause the gel to have a longer diffusion path length, causing more retardation of drug release. This effect on the rate and extent of drug release is inversely proportional to the thickness of the transdermal gel because it takes time for the drug molecules to pass through the gel and reach the dissolution medium. This effect on the rate and extent of drug release is inversely proportional to the thickness of the transdermal gel because it takes time for the drug molecules to pass through the gel and reach the dissolution medium. The results showed that formulation F2 was considered optimized.

Table 3: Shows the In-vitro drug permeation study of **F_1** nanoemulsion loaded Transdermal gel using dialyzing membrane.

Time	% Cumilative drug permeation[CDR]		
	CDR of Gingerol	CDR of Nimesulide	CDR of Capsaicin
0	0	0	0
0.5	1.1111111	0.2059448	2.4173554
1	2.7333333	0.379724	4.5010331
1.5	4.1227778	0.6359873	7.1993802
2	5.4305556	0.8744161	9.6497934
3	6.7938889	1.1338641	12.742769
4	7.7683333	1.4191083	14.97624
5	9.5761111	1.8073248	17.72624
6	11.946111	2.2181529	21.159091

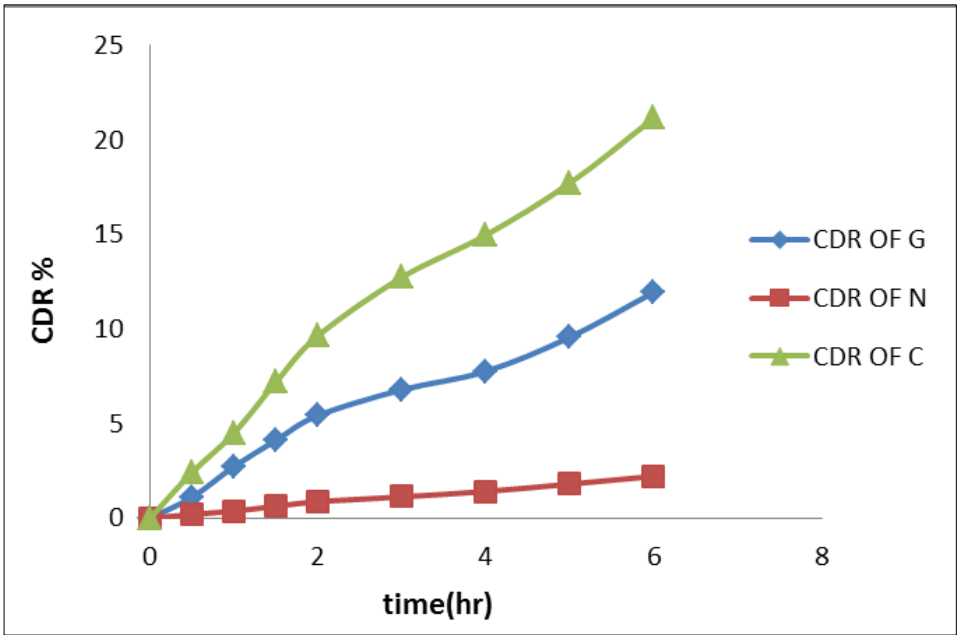

Fig 3: In-vitro drug permeation profile of F_1 formulation

Table 4: Shows the In-vitro drug permeation study of F_2 nanoemulsion loaded Transdermal gel using dialyzing membrane.

Time	% Cumilative drug permeation[CDR]		
	CDR of Gingerol	CDR of Nimesulide	CDR of Capsaicin
0	0	0	0
0.5	1.3555556	0.3163482	2.2107438
1	2.6566667	0.4616773	4.7592975
1.5	4.2194444	0.6771762	7.6363636
2	5.7538889	0.9532909	10.418388
3	7.2883333	1.233121	13.094008
4	8.4083333	1.5502123	15.982438
5	10.201111	1.8761146	19.853306
6	12.753889	2.4165605	22.642562

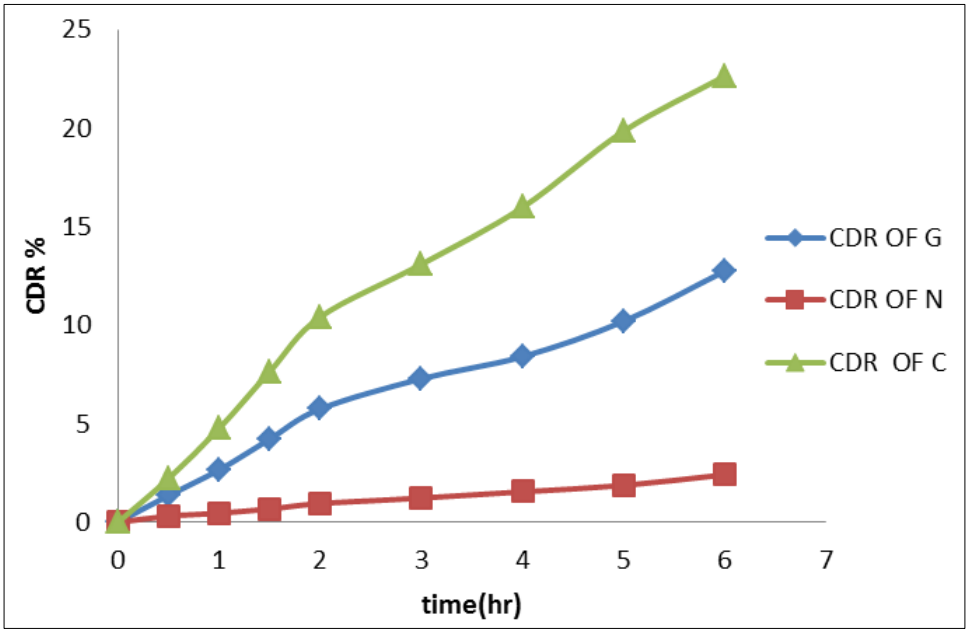

Fig 4: In-vitro drug permeation profile of F_2 formulation

4. Conclusion

In this study, coconut oil nanoemulsion was developed as a carrier for topical delivery containing the combination of herbal extract and synthetic drug bearing nanoemulsion was successfully formulated. The transdermal nanoemulsion were prepared by Bandelin probe method using Carbopol-934 as a gelling agent and surfactant: co-surfactant (Tween 80:PVA). The system exhibited enhanced diffusion rate due to decreased particles size. The ultrasonication showed to be a simple and efficient technique for particle size reduction and the parameters effecting performance of the formulation were optimized. The nanoemulsion were characterized by particles size, formulation were shown optimized range. The nanoemulsionin corporated into transdermal gel were characterized by appearance, Mean particle size and Particle size distribution, pH, spreadability and *in vitro* permeation study using dialyzing membrane. It concluded that, F2 formulation showed desired drug release up to 6 hours.

5. Acknowledgement

The authors are thankful to Principal & Teachers & Non-teaching staffs of National College of Pharmacy, Shivamogga for providing guidance and facilities to carry out the research work and heartly thankful to Asist. Prof. M.C Ravi for guidance in present work.

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