ejpmr, 2022, 9(11), 217-223

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

NANOEMULGEL – AN INNOVATIVE APPROACH FOR TOPICAL DELIVERY USING HIGH ENERGY METHOD

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Article Received on 28/08/2022 **Article Revised on 18/09/2022** **Article Accepted on 08/10/2022**

ABSTRACT

As an emerging transdermal delivery tool, nanoemulgel, has proved to show astonishing upshots for the lipophilic drugs over other formulations. The goal of this review is to formulate the nanoemulsion using microfluidizer to achieve better stability of formulations and to evaluate and report the current potential and future scope of nanoemulgel formulation for becoming an effective delivery system for poorly water-soluble drugs. Lipophilic drugs can be easily incorporated and the skin permeability of the incorporated drugs can be increased in several folds due to the finely distributed oil droplets in gel phase. Concurrently, it can be targeted more specifically to the site of action and can avoid first pass metabolism and aid the user from gastric/systemic incompatibilities. The nanoemulgel drug delivery system is a formulation related intervention to enhance drug absorption and therapeutic profile of lipophilic drugs. An emerging trend has been noticed in recent years in the use of nanoemulgel due to the better acceptability of the formulation to the patients due to their non-greasy nature which favours user compliance, convenience, spreadability, and easy applicability and good therapeutic and safety profile. Despite having few drawbacks, nanoemulgel formulation can be considered as potential and promising candidates for topical delivery of lipophilic drugs in the future.

KEYWORDS: Nanoemulgel; Nano emulsion; Topical drug delivery; High Energy Method.

INTRODUCTION

1.1 Topical drug delivery

It is the effortless route of localized drug delivery anywhere in the body by routes as ophthalmic, rectal, vaginal and skin. It can be elucidated as the topical application of a drug loaded formulation to treat cutaneous disorder directly. The topical delivery system bypasses first pass metabolism which is the main advantage of it. The topical drug delivery system is generally used where other routes (like oral, sublingual, rectal, parental) of drug administration fails or in local skin infection like a fungal infection Avoidance of the risks and inconveniences of intravenous therapy and of the varied conditions of absorption, like pH changes, the presence of enzymes, gastric emptying time are another advantages. The topical drug delivery system is used generally where the other systems of drug administration fails to enhance the permeation of drug through skin.

Topical drug delivery can be used to directly treat cutaneous disorders (e.g acne) or the cutaneous mainfestations of a general disease (e.g psoriasis) with the intent of confining the pharmacological or other effect of the drug to the surface of the skin or within the skin. Topical drug delivery system include a large variety of pharmaceutical dosage form like semisolids, liquid preparation, sprays, and solid powders. Most widely used semisolid preparation for topical drug delivery includes gels, creams, and ointments.[1]

1.2 Nanoemulsion

It refers to mini emulsion/ultrafine emulsion which is fine oil/water or water/oil dispersion stabilized by an interfacial film of surfactant molecule having droplet size range 100-400 nm.

Nanoemulsions are defined as transparent dispersions of oil and water stabilized as an interfacial film of surfactant and cosurfactant molecules having droplet size less than a micron. Nanoemulsions are thermodynamically stable dispersed system.[2] The long-term stability, ease of preparation and high-drug solubilization property, make nanoemulsions a promising tool for drug delivery.[2]

There are three types of nano emulsion which can be formed:

(a) oil in water nano emulsion (oil is dispersed in the continuous aqueous phase),
(b) water in oil nanoemulsion (water droplets are dispersed in continuous oil phase), and
(c) bi-continuous nanoemulsions.

In nanoemulsions lipid based formulations are excellent choice for delivering drugs which improve solubility and bioavailability of hydrophobic drugs.

In recent times, nanoemulsions have shown promising potential as transdermal drug delivery in delivering drug across the skin than other conventional transdermal delivery system.[3] There is increasing interest in utilization of NEs as carriers in the drug delivery systems due to their physicochemical properties and biological performance.[4] Natural oils can be utilized as oil phase of NEs.[5] Doing that, the oil not only plays the role of nanocarrier but also exerts its usual therapeutic properties. The stability and application of nano emulsions depend on the droplet size and physicochemical characteristics. The droplet characteristics are studied through the droplet size, droplet composition, droplet concentration, zeta potential, polydispersity, and interfacial tension.

The physicochemical properties are studied by their optical property, rheological property, gravitational separation, droplet aggregation, Ostwald ripening, and chemical stability. The emulsifiers and surfactants aid in the emulsification process and are selected according to the requirements of emulsification methods and expected nanoemulsion quality.
They are prepared by either *High energy methods* or *low energy* emulsification method (phase titration) by mixing appropriate amounts of oil, water, surfactant and cosurfactant. Only mild agitation is required as the process is almost spontaneous.

1.2.1 Screening of Nanoemulsion Components

Screening of Oil: The solubility of drug in various oils will be determined by adding an excess amount of drug in 2mL of the oils separately in 5mL capacity stopper vials, and mixed using a vortex mixer. The mixture vials were then kept at 25±1.0 °C in an isothermal shaker for 72 h to reach equilibrium. The equilibrated samples will be removed from shaker and centrifuged at 3000 rpm for 15 min. The supernatant will be taken and filtered through a 0.45 µm membrane filter. The concentration of the drug was determined in oils using a HPLC method or UV method.[5,6]

Screening of Surfactants: 2.5 mL of 15%w/w surfactant solution will be prepared in water and 4µL of oil will be added with vigorous vortexing. If a one phase clear solution is obtained, the addition of the oil will be repeated until the solution became cloudy or turbid.

Screening of Cosurfactants: Surfactant will be combined with six types of solubilizers as cosurfactants. At a fixed Smix ratio of 1:1, the pseudoternary phase diagrams will be constructed. 12 different combinations in different weight ratios of oil and Smix; 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 6:4 (1:0.7), 7:3 (1:0.43), 9:1; will be taken so that maximum ratios will be covered to delineate the boundaries of phases precisely formed in the phase diagrams.[6]

Effect of Surfactant and Cosurfactant Mass Ratio on Nanoemulsion Formation Surfactant will be blended with cosurfactant in the weight ratio of 3:1, 2:1, 1:1, 1:0, 1:2, and 1:3. These Smix ratios will be chosen in decreasing concentration of surfactant with respect to cosurfactant and increasing concentration of cosurfactant with respect to surfactant for detailed study of the phase diagrams. Aqueous titration method will be used for the construction of the pseudoternary phase diagrams which involves stepwise addition of water to the each weight ratio of oil and surfactants and then mixing the components with the help of vortex mixer at 25°C. The mixtures will be assessed visually and determined as being nanoemulsions, crude emulsions, nanoemulsion gel and emulgel. The nanoemulsion phase will be identified as the region in the phase diagram where clear, easily flowable and transparent formulations are obtained. Clear and highly viscous mixtures that did not show a change in the meniscus after tilted to an angle of 90°C were considered as nanoemulsion gel. If milky gel is obtained it was called as emulgel. 12 different combinations in different weight ratio of oil and Smix; 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 6:4 (1:0.7), 7:3 (1:0.43), 9:1 were taken.[6,7] One axis of the pseudo-three-component phase diagram represents the aqueous phase, the other represents the oil phase and the third represents a mixture of surfactant and cosurfactant at a fixed weight ratio (Smix).[6]

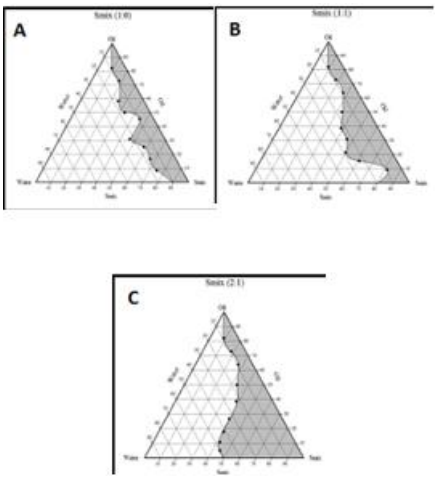

Figure:1 Pseudo ternary phase diagrams showing Nanoemulsion region.

1.2.2 Methods of preparation

High energy methods

i. High-pressure homogenization
ii. Microfluidization
iii. Ultrasonication

Low energy methods

i. Phase inversion emulsification method

- *Transitional phase inversion (TPI)*
- Phase inversion temperature (PIT)

- Phase inversion composition (PIC)
  - *Catastrophic phase inversion (CPI)*
- Emulsion inversion point (EIP)

ii. The self-nanoemulsification method

HIGH ENERGY METHODS: In the current review the high energy method have been discussed to formulate nanoemulsion. High mechanical energy is used that provides strong disruptive forces, which break up large droplets to nano-sized droplets and produce nanoemulsions with high kinetic energy.[8,9] The disruptive forces are created by using mechanical devices such as ultrasonicators, microfluidizer, and high-pressure homogenizers. By using high energy methods, we can achieve a greater control of particle size with a choice of formulation composition. High energy methods also provide controls for stability, rheology, and color of the emulsion. This method is inapplicable for thermolabile components.[8]

The operating parameters which effect the efficiency of High pressure homogenizer are as follows:

- Pressure
- Temperature
- Number of passes
- Flow rate

Microfluidization: Microfluidization technology is a patented technology generally used in large scale industries to produce NEs of desired size. This device uses a high pressure displacement pump (5000–40,000 psi) to produce NEs.

The device forces the product interaction chamber consisting of small channels called 'micro channels'. The product flows through the micro channels on to an impingement area resulting in very fine particles of submicron range. The two solutions (aqueous and oily phases) are combined together and processed in an inline homogenizer to yield a coarse emulsion. This coarse emulsion is further introduced into microfluidizer to obtain stable nanoemulsion after required number of cycles. This process is repeated until the desired particle size is obtained. Particle size reduction happens due to interaction of forces such *as Attrition, impaction, cavitation & shear pressure forces*, and also due to collision with the walls. With every **1000 psi** rise in pressure the 1 ˚C temperature rises, so in order to avoid degradation of thermolabile drug, ice will be added to the cooling chamber.

Figure: 2 Microfluidizer for the formulation of nanoemulsion.

Advantages of High energy methods

→ High pressure homogenizing technique produces stable nanoemulsions, reduce particle size or molecular weight of Vaccine Adjuvants, Lipid Nanoparticles, Cell Disruption, Nanoencapsulation, Liposomes, Deagglomeration.
→ More efficient reduction of particles to the nano level will yield greater stability, longer shelf life, more efficient use of raw materials, and significant potential savings in the filter area.
→ Achieve processing pressures up to 2068 bar (30,000 psi)
→ Produces product flow rate up to 120 ml/min (100 ml/min on 50 Hz model)
→ Highest shear rate
→ Guaranteed scalability
→ Customizable options to suit every application.

Limitations of High energy methods

→ Cleaning is labour-intensive and time-consuming.
→ High pressure homogenizers are unsuitable for applications requiring the processing of multiple samples.
→ Units will be large, heavy and cumbersome, so not very portable.
→ Requires high maintenance cost and voltage.
→ Formulation of nanoemulsions using this equipment is a highly expensive process.

→ Thermolabile drugs may degrade due to heating of samples during processing of nanomulsions.
→ The formulations dilute to greater extent while washing out the sample at the end of cycles.
→ Product wastage/loss from one cycle to another.

1.2.3 Characterization of nanoemulsion Nano emulsion were characterized in terms of various physicochemical parameters like morphology, refractive index, particle size and their distribution, zeta potential, percentage transmittance, drug content, viscosity and *invitro* drug release.

The nanoemulsion formulations were then optimized using design of experiment based on above characterization results. The optimized formulation will then be transformed into nanoemulgel using gelling agent.[14,15,16,17]

1.3 Nano emulgel

It is known as the formation of nanoemulsion based on hydrogel is the addition of nanoemulsion system intergraded into hydrogel matrix which influences a better skin penetration[10]. This mixture of nanomulgel has attracted the attention of many scientists for the development of numerous drugs that function to treat various kinds of skin disorders. The formulation of nanoemulgel for the topical delivery system acts as drug reservoirs which, influence the release of drugs from the inner phase to the outer phase and then further onto the skin.[11] These release mechanism depends on the composition of the network polymer chains and the crosslink density.[12] Besides that, the ability of a drug to permeate the skin and successfully release of therapeutic agent is influenced by drug affinity to diffuse out from the vehicle and permeate through barrier.[13] Nanoemulgel on intact with skin will release the oily droplets from the gel network. The oil droplets then will penetrate into the stratum corneum of the skin and directly deliver the drug molecules without a transfer via hydrophilic phase of nanoemulsions.[12]

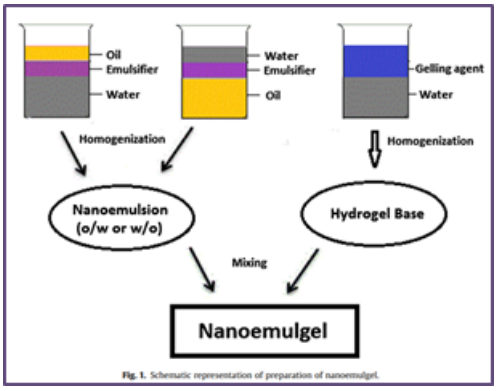

Fig. 1. Schematic representation of preparation of nanoemulgel.

1.3.1 Advantages of Nanoemulgel

It is currently of great pharmaceutical interest to the formulators because of several advantages such as:

→ A stable nanoemulsion formulation is enhanced through nanoemulgel, by decreasing surface and interfacial tension and which leads the viscosity of the aqueous phase to be increased.[14]
→ Emulsifier and thickeners been added to hold the gelling capability of hydrogel serves a better stability, permeation and suitable viscosity for the delivery of topical drug-loaded nanoemulsion.
→ In Nanoemulgel system, the stability of nanoemulsion is enhanced by the distribution of oily droplets in gel network.[12]
→ These oily droplets function as carrier for drugs, such as lipophilic drug. The stability of drugs loaded in the system is determined by the affinity of the drug to be solubilized in the oil phase.
→ Nanoemulgel attained a good adhesion property on the skin together with high solubilizing capacity leads to larger concentration gradient towards the skin that influence further skin penetration of drug as it move down the gradient.
→ Moreover, the Nanoemulgel formulation is known to support better delivery of lipophilic and poorly soluble drugs.
→ It also promotes improve patient compliance because the formulation is not sticky and easily spread as compared to other topical delivery system such as ointment and cream which are very sticky, troubled upon application and have reduced spreading coefficient, hence they require the mechanism of rubbing.
→ Besides that, nanoemulgel helps in controlling the release of drugs by extending the effect of drugs having shorter half-life.[14]

Despite of several advantages, nanoemulsion faces problems of low viscosity related spreadability issues and poor retention on the skin (Khurana et al., 2013). Such disadvantages restrict the clinical application of nanoemulsion platform for topical application (Mou et al., 2008). Incorporation of nanoemulsion to a gelling system has been evolved as a strategy to overcome this problem (Baibhav et al., 2011). Gels are produced by using high amounts of aqueous or hydroalcoholic bases in the colloidal solid particle network. Such network allows higher dissolution and easy release of drugs compared to cream or ointments because of the presence of higher aqueous materials (Dev et al., 2015). Hydrogel suffers from a limitation of incapability to incorporate hydrophobic molecules (Begur et al., 2015; Zhao et al., 2015). Fusion of nanoemulsion and gel system to produce nanoemulgel formulation overcomes the limitations of both nanoemulsion and hydrogel. Incorporation of drug into the oil phase of nanoemulsion followed by addition into gel base make it possible to incorporate hydrophobic molecules into a hydrogel (Eid et al., 2014). On the other hand gelling system enhances the viscosity of the nanoemulsion for making it topically applicable. Several biocompatible gelling agents such as carbomer 980, carbomer 940, carbomer 934, pluronics, xanthan gum and carrageenan have been identified which have weak interaction with surfactants and are capable to modify the viscosity of nano emulsion (Dhawan et al.,

2014). Topical nano emulgel has potential to improve patient compliance because of their non greasy, non-irritant and better drug release property (Dev et al., 2015). It has also been reported that, gel formulations release drug in a faster rate than ointments and creams (Jain and Gautam, 2010; Patel Chirag et al., 2013). The current increasing interests on nanoemulgels is also due to the homogenous behaviour and consistency of hydrogel matrix (Begur et al., 2015).

1.3.2 Composition of nanoemulgel

Nanoemulgels are composed of two separate systems; the emulsion containing nano sized droplets and a gelling system. The emulsion may be oil in water or water in oil type. The emulsions serve as the vehicles for delivering the drug and are stabilized by an emulsifier. The gels are made up of polymers that swell after absorption of liquid. In general, following are the major components of a nanoemulgel formulation (Dev et al., 2015; Eswaraiah et al., 2014).

Aqueous solvents: They are required for the aqueous phase of the emulsion. Water and alcohol are the widely used aqueous solvents in practice.

Oils: Mineral oils, singly or as a mixture with paraffin are used for the preparation of emulsions to be used externally.

Emulsifiers: In addition to their use in emulsification process, emulsifier also increases the stability when the product is stored for a long time. Polyethylene glycol, sorbitan mono-oleate (Span 80), polyoxyethylene sorbitan monooleate (Tween 80), stearic acid and sodium stearate are the commonly used emulsifier for this purpose.

Gelling agents: Gel forming agents are used to increase the thickness of the formulation. Carbapol 934, carbapol 940, hydroxyl propyl methyl cellulose (HPMC), HPMC-2910 are widely used for this purpose.

Preservatives: They are used to increase the self life of the product by protecting the formulation from microbial attack. Methyl paraben, propyl paraben, benzalkonium chloride, benzoic acid, etc. are amongst the commonly used preservatives.

Antioxidants: They protect the formulation components from degradation by oxidation. Butylated hydroxyl toluene, ascorbyl palmitate, butylated hydroxyl anisole is of great use as antioxidant.

Humectants: Humectants are used to stop the loss of moisture. Glycerine and propylene glycol is used for this purpose.

1.3.3 Preparation procedure for nanoemulgel

Nanoemulsion is a non-equilibrium system of structured liquids and high amount of energy, surfactant or both are necessary for their preparation. High energy or low energy methods may be adopted to formulate a nanoemulsion (Anton and Vandamme, 2009; Prakash and Thiagarajan, 2011).

Irrespective of the methods, there are three major steps involved in preparation of nanoemulgel (Dev et al., 2015).

Step 1: Preparation of the nanoemulsion

Screening is performed to select the oil phase, surfactant and cosurfactant based on solubility.

Emulsifiers are dissolved in the selected oil phase or aqueous phase. The drug is then solubilized in either oil or aqueous phase based on its solubility. After heating the individual oil and aqueous phases, they are mixed together by gradual addition of one phase into another with continuous stirring till it reaches room temperature.

Step 2: Preparation of gel The gel base is prepared by dissolving the appropriate polymer in purified water with continuous stirring using mechanical device and pH is adjusted.

Step 3: Preparation of nanoemulgel The prepared gel and nanoemulsion systems are mixed together slowly with continuous stirring to incorporate the nanoemulsion to the gel system.

1.4 Evaluation of nano emulgel

1.4.1 Physical Characterization

Visual Inspection

The formulated transdermal preparations were visually inspected for their color, appearance and homogeneity.

1.4.2 pH Measurement

The pH value of the formulations was detected at room temperature using a calibrated pH meter (MW802, Milwaukee Instruments, Szeged, Hungary).

1.4.3. Spreadability Test

The spreadability of the prepared transdermal formulations was measured using spreadability apparatus, which had a wooden board with a scale and two glass slides. It helps to determine the extent of the area that the formulation could freely spread over the affected part of the skin after being applied. One gram of gel, emulgel or nanoemulgel formulation was placed between two horizontal glass slides (25 cm × 25 cm) and a certain load (500 g) was applied for 1 min. The diameter of the spread of the formulations was measured as it represents the spreadability value.

1.4.4 Viscosity determination

A Brookfield viscometer (DV-II + Pro, USA) was employed to determine the viscosity of the formulated gel, emulgel and nanoemulgel using a spindle R5 rotated at 0.5 rpm at 25 ± 0.3 ◦C.

1.4.5. Size and Size Distribution

Particle size and polydispersity (PDI) of Cur-loaded gel, emulgel and nanoemulgel estimated via measuring their dynamic light scattering using a Zetasizer apparatus (Malvern Instruments Ltd., Worcestershire, UK). The formulations (10 µL) were diluted with 3 mL of distilled water.

1.4.6. Morphological Evaluation The morphology of the prepared nanoemulgel will be examined using a scanning electron microscopy (SEM). The morphology of the formulation will be considered at different magnifications (1000 to 95,000). One drop of sample

after being diluted will be coated with gold under vacuum on metal stubs, and then examined at 5 kv.

1.4.7 In Vitro Drug Release Studies The in vitro release of nanoemulgel from the various transdermal formulations and aqueous suspension will be investigated using the Agilent fiber optics dissolution system according to method previously described by Elsewedy et al. Briefly, 1 g of the formulations was added into glass tubes that were used instead of baskets, and covered with cellophane membrane from one side. The tubes will be maintained in 750 mL of phosphate buffer (pH 7.4) and rotated at 50 rpm at 37 + 0.5 ◦C. Samples measured spectrophotometrically at different time intervals (0.25, 0.5, 1, 2 until 6 h) at λmax 425 nm.

1.5 Ex-vivo/in-vitro permeation enhancement by topical nano emulgel Different group of researchers carried out various types of research work to evaluate the skin permeation from nanoemulgel formulation using different drugs (Table-1). Azeem et al. reported a 7.5 fold enhancement in skin penetration of ropinirole from nanoemulgel compared to a normal hydrogel. Furthermore, ropinirole showed an extended release pattern and the bioavailability was found to be twofold more compared to the gel formulation available in the market (Azeem et al., 2009). Another study by Hussain et al. reported that highest percutaneous permeation flux for Amphotericin-B was achieved with nanoemulgel (18.09 mg/cm2 /h) compared to nanoemulsion (15.74 mg/cm2 /h) and drug solution (4.59 mg/cm2 /h). A sustained drug release profile of Amphotericin-B from the nanoemulgel formulation was observed in their in vitro drug release study (Hussain et al., 2014).

Aparna et al. compared the ex vivo permeation profile of telmisartan from a nanoemulgel formulation with their corresponding nanoemulsion and conventional gel formulation. Permeability parameters including steady-state flux, permeability coefficient, and enhancement ratio were significantly increased in nanoemulsion and nanoemulsion gel as compared to the simple gel. The flux of nanoemulgel (1154.3 µg/cm2 /h) was much better than conventional gel (118.8 µg/cm2 /h) and the corresponding nanoemulsion (1393.2 µg/cm2 /h) (Aparna, Srinivas, & Patnaik, 2015).

As reported by Somagoni et al., nanoemulgel formulation produced 2.02 and 1.97 fold better penetration of aceclofenac and capsaicin, respectively than the marketed preparation through the dermatomed human skin. The amounts of aceclofenac and capsaicin retained for nanoemulgel after 24 h of application were 4.96 and 5.01-fold higher than drug solution and 1.78 and 2.28-fold higher than marketed formulation, respectively. Therefore, a controlled release of drug from the nanoemulgel formulation was evidenced (Somagoni et al., 2014). In general, drug penetration through the psoriatic inflamed skin becomes less due to the development of plaque, scaling, or alterations in epidermis, that act as barrier for drug permeation through skin. But, it has been reported by Somagoni et al. that nanoemulgel is capable to deliver the drugs into the deeper skin layer even through the psoriatic inflamed skin for complete inhibition of the inflammation. After 24 h, in vitro permeation experiment with nanoemulgel through the differently treated inflamed rat skin showed a significant improvement in aceclofenac and capsaicin permeation through nanoemulgel-post treated inflamed skin compared to marketed product and drug solution (Somagoni et al., 2014).

CONCLUSION

Topical nanoemulsion gel can be considered as a superior alternative to conventional formulations of lipophilic drugs due to its better permeation properties, improved pharmacokinetic profile and consequently better therapeutic efficacy. Less stickiness and better spreading characteristic of nanoemulgel formulation can be one of the major reasons for its better acceptability to the patients compared to other topical delivery options. In conclusion, nanoemulgel system has all the potential to become an effective, safe and well-accepted drug delivery system for topical delivery of lipophilic drugs. Inspite of few limitations, nanoemulgel formulation has the possibility to occupy the central place for topical delivery of lipophilic drugs replacing the conventional formulations in future.

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