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A Comprehensive Approach to Hydrogel Nanoparticles and Nano Emulsions

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Abstract : Nanocarriers are used to transfer the drugs at the specific site of action without getting any systemic toxicities. They are sized from 1 to 100 nm. Different techniques can be used to encapsulate drug into the nanocarriers. Hydrogel nanoparticles and Nanoemulsions can serve as nanocarriers for drug delivery. In this review drug loading and release of drugs from these nanocarriers along with various drugs encapsulated in them is been focused. Their composition, mechanism of action, preparation, surface modification, advantages and disadvantages with their applications are also mentioned.

Index Terms **– Nanoencapsulation, Hydrogel Nanoparticles, Nano Emulsions, Nanocarriers.**

INTRODUCTION

Nanocarriers are colloidal nanoparticles with broadness from 1 to 100 nanometers (nm) which are often used to carry medications or other molecules to a specific target location [1,2]. They are biocompatible and deemed safe carriers since they are inert. Therapeutic nanocarriers, on the other side, has to be less than 200 nm since the diameter of the body's microcapillaries is the same, according to [3].

Nanoencapsulation of therapeutic pharmaceuticals can increase their effectiveness, precision, and target specific [4]. The nanocarriers can avoid the endosome–lysosome pathway, allowing for a longer circulation time and continuous medication release [5]. Nanocarriers' surface, composition, and shape may be changed to boost their activity and lessen their negative effects, and as a result, they play an important role in drug delivery[6]. Notwithstanding this, just a small number of carriers are capable of delivering the drug to the intended area. Nanocarriers are employed for sustained and targeted drug administration because they have improved biodistribution and pharmacokinetics, stability and solubility, and decreased toxicity [7].

Drugs and tiny compounds can be nanoencapsulated in nanocarriers (NCs), which might be a promising technique for nanomedicine development. Newer drug encapsulation methods allow therapeutic compounds to be loaded efficiently into NCs, reducing drug-related cytotoxic effects. The quantity of nanonencapsulated medication that reaches the damaged region can be increased with the aid of NCs [8].

1. HYDROGEL NANOPARTICLES

1.1 INTRODUCTION OF HYDROGEL NANOPARTICLES

Polymeric nanogels or macromolecular micelles are other names for hydrogel nanospheres/nanoparticles [9]. These are cross-linked polymers that contain water-loving groups that allow them to consume high quantities of water (hydroxyethyl methacrylate (HEMA)). These are hydrophilic polymers containing cross-links that form a polymeric network (Figure No. 1) that allows particles to absorb water up to thousands of times their weight [10,11]. Chemically cross-linked or irreversible hydrogels, which are resistant to degradation during swelling, and physically cross-linked or reversible hydrogels, which disintegrate and dissolve with water absorption, are the two types of hydrogels [10,12].

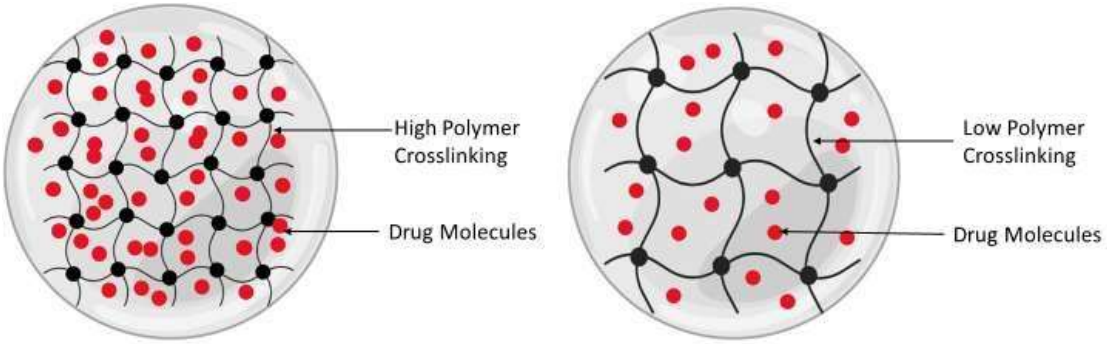

Figure No. 1. Structure of Hydrogel Nanoparticles

1.2 COMPOSITION OF HYDROGEL NANOPARTICLES

Natural or synthetic polymers could be utilized to make hydrogels (Table No. 1). Monomers, cross-linkers, and activators are the most critical elements in hydrogel manufacture. Hydrogels are classified as Homo-polymeric networks, Co-polymeric networks, multi-polymeric networks, or multi-polymeric networks with single, two, or more than two independent cross-linked polymers, depending on the technique of preparation [13]

Natural polymers	**Synthetic polymers**	**Semisynthetic polymers** (Cellulose derivatives)
Chitosan, Hyaluronic acid, Carrageenan, Alginic acid, Collagen, etc.	Polyethylene glycol (PEG), Polylactic acid (PLA), Poly lactic-co-glycolic acid (PLGA), Polyvinyl alcohol (PVA), Polycaprolactone (PCL), etc.	Carboxymethyl cellulose (CMC), Hydroxyethyl cellulose (HEC), Methylcellulose (MC), Hydroxypropyl cellulose (HPC), Hydroxypropyl methylcellulose (HPMC), etc.

Table No. 1. Composition of Hydrogel Nanoparticles

1.3 MECHANISM OF ACTION OF HYDROGEL NANOPARTICLES

These could be employed to supply drug substances in an active/direct or passive/indirect manner. Passive delivery attributes to passive diffusion into tumor interstitium and cells through leaky capillary fenestrations [14]. The EPR effect causes the selective accumulation of nanoparticles and drugs. The employment of peripherally coupled attacking elements for increased delivery to a particular region, depending on molecular acknowledgment, is known as active targeting.

1.4 PREPARATION / FORMATION OF HYDROGEL NANOPARTICLES

Lipophilic chains attached to the lipophobic backbone, lipophobic chains fixed to a lipophilic pillar (grafted polymers), or alternate lipophobic along with lipophilic sections can all be used to make amphiphilic polymers (block polymers). Amphipathic polymers voluntarily make self-accumulated nanoparticles when coming in relation to hydrous surroundings, principally to reduce the interfacial free energy, by means of intra- or intermolecular interactions in the middle of the lipophilic elements. Critical Micelle Concentration (CMC) is the concentration over which polymeric chains assemble. Direct dissolving, solvent extraction, dialysis, emulsion, and co-solvent removal have all been utilized in nanoparticles formation. The utilization of possibly harmful organic solvents and surface-active agents, which are generally inadmissible for parenteral delivery, limits the commercialization of nanodevices made with these technologies [9].

1.5 SURFACE MODIFICATION OF HYDROGEL NANOPARTICLES

The drug concentration at a desirable location has to be perpetuated at an active dose for the right time period to achieve maximal therapeutic efficacy, with minimum dose accumulation at off-target locations. Attentive sketch of multi-functional drug carriers with nano measurements has been a high-demand explored topic for these goals. Although reversely charged polysaccharides actively connect due to electrostatic attractions[15], interconnections between neutral polysaccharides are weaker or airy, requiring a change in chemical entities capable of triggering aggregation.

1.6 DRUG LOADING AND RELEASE OF HYDROGEL NANOPARTICLES

The most common loading technique for drug delivery administration is physically drug entrapment. In pursuant to the physicochemical features of pairing drug-carrier, the optimum incorporation approach for effective entrapment must be chosen. Dialysis, nanoprecipitation, solvent displacement/evaporation, desolvation, and direct dissolving have all been utilized to load drugs. The process of drug physical loading could be accomplished by integrating it into the nanoparticles as they are being made, or by the process of incubation, where the concentrated drug is being incubated with a nano-carrier that has already been created. Solubility in the polymeric matrix affects drug loading and entrapment efficiency, which is influenced by polymer configuration, molecular mass, drug-polymer interconnections, and existence of functional units (i.e., ester or carboxyl)[16,17].

The particle size has an impact on drug release. Because the surface-area-to-volume ratio of smaller ones is higher, majority of the drug resides nearby the particle surface, resulting in rapid drug release. Bigger particles, on the other hand, permit a higher amount of medication to be contained in the internal cores, resulting in a gradual release. The molecular mass and two or more polymer mix utilized could also influence the process of release. It shows that the larger the molecular mass of a polymer, the more gradual the drug delivers in vitro [14,18].

The releasing system is made of 3 different steps.

- **Diffusion-controlled (drug diffusion)**

The most prevalent method of drug release from hydrogels is diffusion-controlled release. Fick's diffusion theory is employed for kinetic modeling in this form of drug release Drug diffusion from hydrogels having full of pores with an opening size bigger than the drug molecular dimensions may be allied to the porousness and tortuousness of the hydrogels (Figure No. 2). Hydrogels with diffusion-controlled release could be used as a reservoir or matrix [9,19].

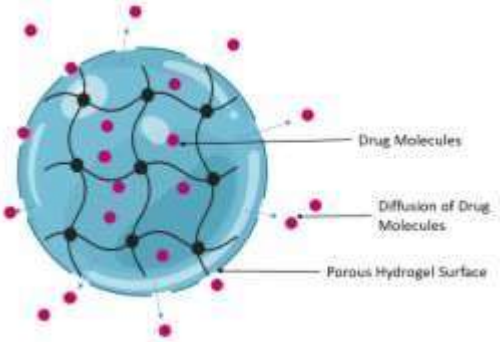

Figure No. 2. Diffusion-controlled Release

- **Swelling-controlled (Matrix swelling)**

Edema-controlled drug release may occur if the pace of drug dissipation is quicker to hydrogel bulging rate (Figure No. 3). The kinetic model of release could be mostly fitted to a zero-order model for purely swelling-controlled release of drug. Because pace and capacity of water absorption by hydrogels, as well as the dimensions of polymeric gels, are essential parameters in this type of regulated delivery systems, the higher the rate of drug release [9,19].

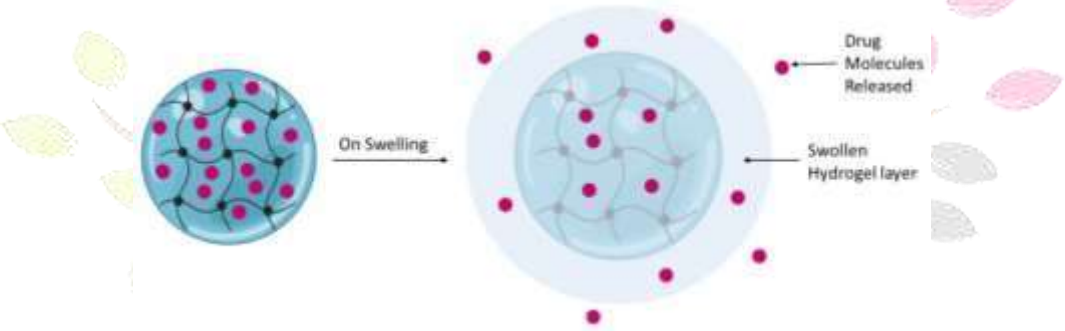

Figure No. 3. Swelling-controlled Release

- **Chemically-controlled (chemical reaction of the drug/matrix)**

Drug release in a hydrogel matrix is caused by enzymatic or hydrolytic breakdown of the polymeric network. Drug release in chemically controlled delivery systems might be caused by breakage of polymeric chains by bulk or surface erosion (Figure No. 4), and the entrapped or tethered drug would be released from hydrogels as a result of these mechanisms [9,19].

Biopolymers are those that respond to biological factors like pH, temperature, and external stimuli like light to cause controlled liberation of the curative substance.

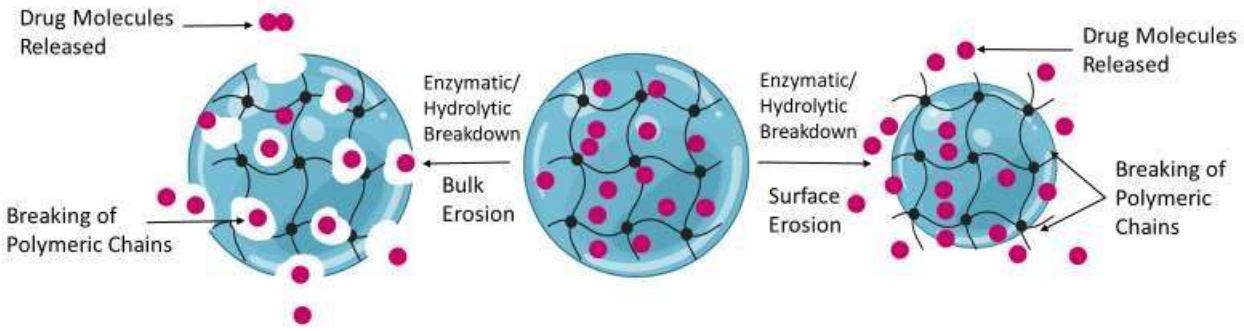

Figure No. 4. Chemically-controlled Release

1.7 DRUGS ENCAPSULATED USING HYDROGEL NANOPARTICLES

Drugs that are encapsulated using Nanoparticles of hydrogel are been mentioned in the below Table No. 2.

Sr. No.	Drug	Category	Modification and Characteristics	Outcome	Ref
1	Flavin mononucleotide	Function in oxidation-reduction reaction	Albumin-crosslinked polyvinylpyrrolidone hydrogels were used	Blood steadiness was maintained for more than 24 hr in fast state	[20]
2	chlorhexidine gluconate	antifungal	Gels or film forms of chitosan were used	prolonged release was observed	[21]
3	dexamethasone	Anti-Inflammatory	H2O2 and horse-radish peroxidase was used in making hydrogels	Decreased IL-6, PGE2 and 4 kinds of chemokine	[22]
4	valproate	antiepileptic	Ionotropic gelation was employed.	extended drug release manner above 3 weeks	[23]
5	doxorubicin	anticancer	nucleolin-aiming NP, copolymer of acrylamide (AAm) and 2-carboxyethyl acrylate (CEA) was used.	elevated fill-up and steady liberation of doxorubicin	[24]
6	magnolol	Anti-Inflammatory, anticancer	magnolol-polyvinylpyrrolidone (PVP) core phase enveloping by an amphipathic carboxymethyl-hexanoyl chitosan (CHC) shell was been used.	sustained-release was determined, outstanding cellular uptake efficiency, increased antiproliferative outcome and powerful hindrance of VSMC movement	[25]
7	5-fluorouracil	anticancer	chitosan-carbopol enclosed FerricOxide magnetic nanogelic key-casing formed in the existence of glutaric aldehyde was employed.	improved the 5-FU discharge rate	[26]
8	epigallocatechin gallate (EGCG) and hyaluronic acid	Anti inflammatory, antioxidant	advanced therapeutic hydrogel sheet (THS) of poly[2-(methacryloyloxy)ethane], a positively charged chitosan, and zinc oxide nanosized particles were used.	own a notable treatment efficacy for restoring wounded eye cells and illustrates a proportionate healing of more than 90%	[27]
9	metronidazole	antimicrobial	cellulose hydroxyethylate (HEC)-ground gel carrying metrogel (MTZ) packed in solid lipid nanoparticulates were used.	Outside of body it showed a continuous drug release, effective passability, and increased anti-infective exercise post 1 day therapy	[28]
10	gemcitabine and doxorubicin	anticancer	consists of glycol chitosan (GC), telechelic difunctional poly(ethylene glycol) (DF-PEG).	exhibits excellent filling to gemcitabine and doxorubicin at any congregation (10, 40 and 80 percent)	[29]

Table No. 2. Drugs Encapsulated Using Hydrogel Nanoparticles

1.8 ADVANTAGES AND DISADVANTAGES OF HYDROGEL NANOPARTICLES

Here in Table No. 3. advantages and disadvantages of Hydrogel nanoparticles are been mentioned.

Advantages [9]	**Disadvantages** [19,30]
• The size of the nanoparticles and surface features can be tweaked to avoid phagocytic cell clearance, allowing for both passive and active drug delivery. • The dimension of the nanoparticles and external features can be tweaked to avoid phagocytic cell clearance, allowing for both passive and active drug delivery.	• Some hydrogels have non-biocompatible and non-biodegradable characteristics. Because of their restricted magnitude, the capacity to access the smallest capillary veins and permeate tissues via paracellular or transcellular routes. • The response time of stimuli-sensitive hydrogels is too slow. • During hydrogel swelling, there is a rapid burst of drug release, as well as rapid drug release from large porous hydrogels. • In the entrapment approach, there is the possibility of drug deactivation and initial burst rerelease.

• Drug encapsulation is quite excessive and can be accomplished without use of chemicals; this is a key component in maintaining drug activity. • Oral, pulmonary, nasal, parenteral, intra-ocular, and other modes of delivery are also possible. • Due to their tiny size, the ability to access the smallest capillary veins and permeate tissues via paracellular or transcellular pathways;	• In the covalent binding approach, there is the possibility of drug deactivation during polymer binding.

Table No. 3. Advantages and Disadvantages of Hydrogel nanoparticles

1.9 APPLICATIONS OF HYDROGEL NANOPARTICLES

- Small molecular weight drug delivery
- Protein, peptide and oligosaccharide delivery
- Vaccine delivery
- Gene delivery [9]

2. NANOEMULSIONS

2.1 INTRODUCTION OF NANOEMULSIONS

Nano-emulsions are a mixture of two unmixable liquid phases which are thermodynamically unstable but kinetically stable. They can even be called mini emulsions, ultrafine emulsions, and submicron emulsions. [31,32,33]. The dispersed state is formed by one of the liquids, while the dispersing medium is formed by the other liquid [34].

Oil-in-water (o/w) emulsions having a mean globule width covering around 50 to 1000 nm are known as nanoemulsions. The average droplet size is usually in the middle of 100 and 500 nanometers. These may exist in two forms: oil-in-water and vice-versa, with the main component of the particle being either oil or water (Figure No. 5). Surfactants permitted for the use of humankind and daily food ingredients which are "Generally Recognized as Safe" (GRAS) by FDA were used to create nanoemulsions [31]. These are dis-equilibrium systems of organized fluids [35,36,37], and their making demands the addition of a significant amount of energy or surface-active agents or a mixture of the two.

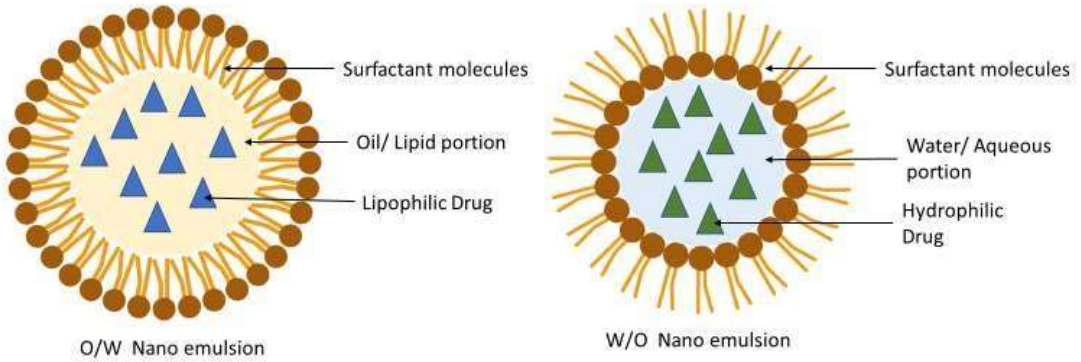

Figure No. 5. Nano Emulsions

2.2 COMPOSITION OF NANOEMULSIONS

Composition of nano emulsions is been described in the Table No. 4.

Oils and Lipids	Surfactants	water-soluble co-solvents / co surfactants	water
• Triglycerides such as triacylglycerols, diacylglycerols, and monoacylglycerols, as well as vegetable oils, mineral oils, and free fatty acids [38]. • The solubility of the medicine is usually taken into account when choosing an oil. • Oil phases with high drug loading are commonly used in nanoemulsion development [39].	• spans (sorbitan fatty acid esters) • tweens [span with corresponding polyoxyethylene (POE) derivatives], • CremophorR EL (polyoxyl-35 castor oil), lauroyl macrogolglycerides (GelucireR 44/14), • polysaccharides (gum and starch derivatives), • phospholipids (egg, soy, or dairy lecithin) • amphiphilic proteins [40,41].	• Nanoemulsion generation necessitates extremely low negative interfacial tension. • Co-surface-active agents or co-solvents were employed in conjunction along with a surfactant for this purpose. • polyethylene glycol, propylene glycol, ethanol, transcutol-P (diethylene glycol monoethyl ether), ethylene glycol, glycerin, and propanol are examples of polyethylene glycol, propylene glycol, ethanol, transcutol-P (diethylene glycol monoethyl ether), ethylene glycol, glycerin, and propanol [41,42].	• It is used as aqueous phase.

Table No. 4. Composition of Nano emulsion

2.3 MECHANISM OF ACTION OF NANOEMULSIONS

The cell-mediated response to nanoparticles is influenced by the size, which is an important physical characteristic. Nanoparticles smaller than 50 nm possess the most cellular grasp, while particles bigger than 60 nm and smaller than 20 nm are quickly removed by the renal and RE systems [43]. As the size of nanoparticles grows larger, the cellular uptake methods used change, with small nanoparticles under 200 nm that are being occupied by pinocytosis methods, 250 nm are engulfed by phagocytosis, and huge micrometer particles via physical or chemical ways [44].

2.4 PREPARATION / FORMATION OF NANOEMULSIONS

Overall preparation methods of nano emulsions are enlisted in Figure No. 6.

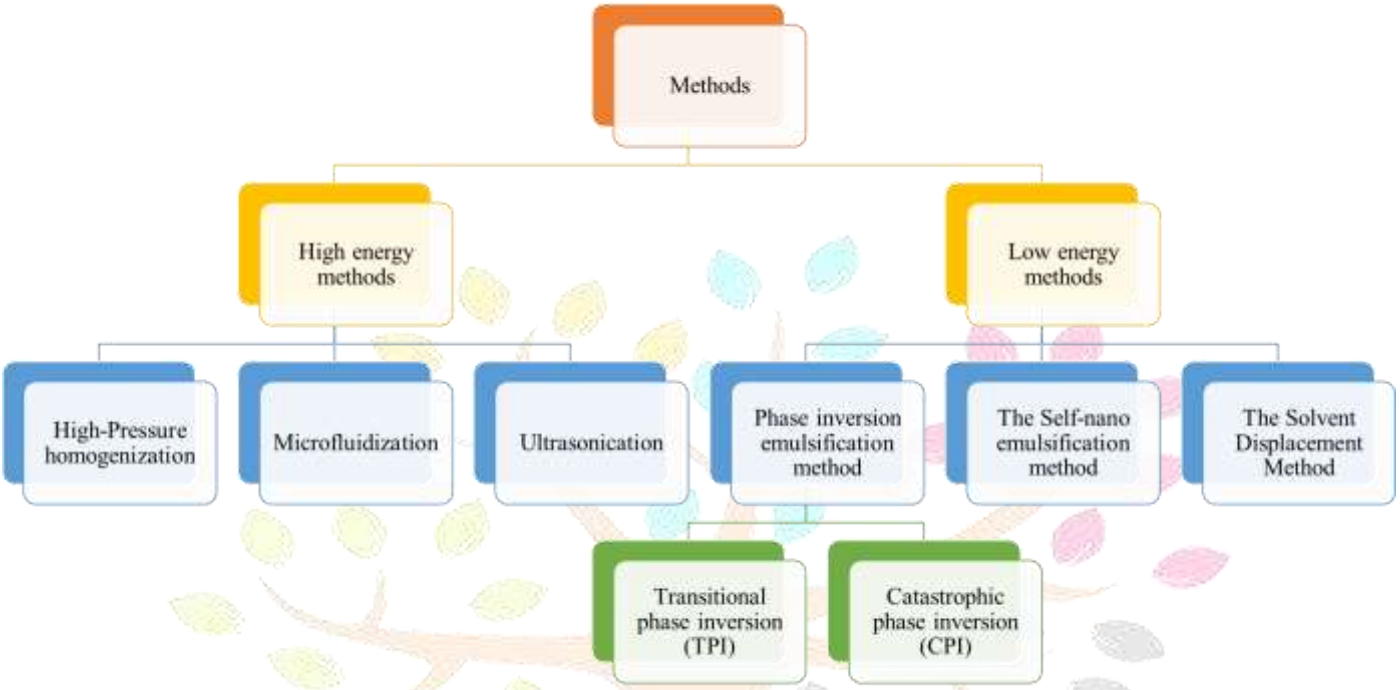

Figure No. 6. Preparation methods of Nano Emulsion

2.4.1 High energy methods:

2.4.1.1 High-Pressure homogenization

To manufacture nanoemulsions with extremely small particle sizes, this method uses a homogenizer that works with elevated pressure (up to 1 nm). Several factors, including hydraulic shear, severe turbulence, and cavitation, combine along with this mechanism to produce nanoemulsions with incredibly small and tiny droplet sizes [31].

2.4.1.2 Microfluidization

Microfluidizer is a device that is used. A high-pressure positive transposition pump is utilized in this gadget (500 - 20,000 psi) [31]. Fluids are pushed to pass through microchannels, which are micro-sized channels that allow high-pressure mixing at the microscale [39,45].

2.4.1.3 Ultrasonication

Ultrasonic waves create cavitation pressures which shatter the macroemulsion into nanoemulsions under ultrasonic emulsification. Ultrasonicators, that contain a probe that produces ultrasonic waves, are utilized in this procedure. It allows acquiring a required particle size and steadiness of the nanoemulsion by adjusting the ultrasonic energy input and time. Formationand collapse of bubbles in sa ample produces physical shear [46].

2.4.2 Low energy methods:

2.4.2.1 Phase inversion emulsification method

Due to characteristics such as temperature, composition, and others, the immediate curvature of the surface-active agent induces state change along the emulsification procedure in this approach [47].

a. Transitional phase inversion (TPI)

It happens when the surfactant's spontaneous curvature or affinity alters as a result of changes in factors such as temperature and composition [47,48,49].

- **Phase inversion temperature (PIT)**

Changing the temperature causes the spontaneous curvature of surfactants to reverse.

- **Phase inversion composition (PIC)**

Rather of modifying the system temperature, you can change the system composition.

b. Catastrophic phase inversion (CPI)

A catastrophe is an abrupt shift in a system's behavior as a result of varied environment. For this phase inversion to take place, the surface-active agent must be mostly there in the dispersed phase, resulting in an elevated rate of agglomeration and speedy phase inversion [50].

– **Emulsion inversion point (EIP)**

It is generated by modifying the fragmented volume of a dispersed phase instead of surfactant characteristics [48,51,52].

2.4.2.2 The Self-nanoemulsification method

This was accomplished without altering the surfactant's natural curvature. Surface-active agents or co-solvent particles or in combination dissolve quickly from immersed phase to the immersion phase, causing disturbance along with the formation of nano-sized emulsion globules [32].

2.4.2.3 The Solvent Displacement Method

The non-aqueous phase is dispersed in organic solvents that are water miscible, like acetone, ethanol, and butanone. By rapidly diffusing organic solvent, the organic state runs towards a liquid state having surface-active agent to produce instinctive nanoemulsion. An appropriate method, known as vacuum evaporation, is employed to draw out the organic solvent remaining in the nanoemulsion [31].

2.5 SURFACE MODIFICATION OF NANOEMULSIONS

When droplet sizes are reduced to the nanoscale, some unexpected physical features emerge, including as optical transparency and peculiar elastic behaviour [31].

2.6 DRUG LOADING AND RELEASE OF NANOEMULSIONS

Encapsulation and/or conjugation are two ways of medication loading that can be used to efficiently deliver active cargo substance to diseased locations using nanoemulsions. The hydrophobic medication is loaded within lipoidal portion of the emulsion throughout the encapsulation process. Encapsulation could be done before emulsification, resulting in great efficiency of encapsulation and little medication waste [39]. Conjugation is the process of forming covalent bonds between the drug and the emulsion surface. The proportion of functional groups on the active ingredient and emulsion, as well as the reaction rate, influence the efficiency of conjugation drug loading [53].

In physiological media, a precise blend of lipid oil, drug, surface-active agents, and co-surfactants generates a nanoemulsion which protects the cargo while controlling the drug release mechanism [54,55].

2.7 DRUGS ENCAPSULATED USING NANOEMULSIONS

Drugs that can be encapsulated using nano emulsions are enlisted in the Table No. 5.

Sr. No.	Drug	Category	Modification and Characteristics	Outcome	References
1	risperidone	Anti psychotic	Nasal drug delivery to the brain	Nasal route was found to be efficient compared to IV route	[56]
			Continuous emulsification process was used	mucoadhesive formulation displayed highest diffusion coefficient	[57]
2	Caffeine	anticancer	Water-in-oil nanoemulsion was used.	Showed a notable rise in permeability parameters	[58]
3	Carbamazepine	anticonvulsant	Used for IV	Exhibited desired in vitro release rate	[59]
4	amlodipine besilate	Anti-hypertensive	developed by spontaneous emulsification method	Release, bioavailability of drug from NEs was remarkably superior, the overall residence time multiplied by threefold	[60]
5	docetaxel	anticancer	fish oil, tween 80 and PEG 400 were used to load docetaxel in PUFA's	rapid release of DTX, increased drug permeation and cancer cells killing was observed	[61]
6	Curcumin	Antioxidant, anti-inflammatory	Given orally to cerebrally damaged rats with diabetes caused by streptozotocin	reduced brain damage	[62]
7	cephalexin	antibiotic	Hydrous titration process utilizing Lauroglycol 90, Poloxamer 188, and Transcutol-HP	greater antibacterial efficacy, sustained release profile, oral bioavailability is 3.48 times higher	[63]
8	Costunolide	anticancer	Controlled usage of a certain experimental design	Notable series of events seize at S phase, leads to reduced effect of TNF-α and NF-κB, elevated	[64]

				caspase-3, Bax, Bcl-2, and p53 mRNA	
9	Fisetin	antioxidant reduces inflammation, and anti-cancer	self-nano emulsifying drug delivery system was employed	Increased solubility and bioavailability enhanced the anti-parkinsonian activity	[65]
10	basil oil	Anti bacterial, anti microbial	Ultrasonication method was employed	enhanced antibacterial activity, Superior antibiofilm activities is achieved	[66]

Table No. 5. Drugs Encapsulated Using Nano emulsions

2.8 ADVANTAGES AND DISADVANTAGES OF NANOEMULSIONS [67,68].

Advantages and disadvantages of Nano emulsions are given in the Table No. 6.

Advantages	Disadvantages
• The gravity is greatly reduced, and randomness may be adequate to overcome it. This makes certain that during storage, there is no creaming or sediment formation. • The tiny globule size also restricts them from agglomeration. • The microscopic droplets also inhibit coalescence, and because they are elastic, they prevent surface fluctuations. • Nanoemulsions are perfect for delivering active chemicals to the exterior of the skin due to their broad surface. • It gives a soothing aesthetic aspect and skin feel. • Lower surfactant concentrations like 5% to 10% may be sufficient for a 20 percent o/w nanoemulsion. • These could be used to transport fragrances • Nanoemulsions can be used to replace liposomes.	• Nanoemulsion preparation frequently necessitates the employment of specialised application techniques like high-pressure homogenisers and ultrasonics. Only recently has such equipment (such as the Microfluidiser) become accessible. • Nanoemulsions were thought to be expensive to make in the personal care and cosmetics business. Big-budget apparatus is essential, as is the usage of high emulsifier concentrations. • The function of surfactants and cosurfactants in the formation of submicron droplets is not well understood. • There is no evidence of the advantages of employing nanoemulsions over traditional macroemulsion systems. • Deficit knowledge of the interfacial chemistry associated with the manufacture of nanoemulsions.

Table No. 6. Advantages and disadvantages of Nano emulsions

2.9 APPLICATIONS OF NANOEMULSIONS

- Intranasal Drug Delivery
- Transdermal Delivery
- Delivery of drug bypassing intestine
- Drug Targeting
- Vaccine Delivery
- Pulmonary Drug Delivery
- Prophylactic in intentional attack of microbes [31]

REFERENCES

1] Qian X, Peng XH, Ansari DO, Yin-Goen Q, Chen GZ, Shin DM, Yang L, Young AN, Wang MD, Nie S. In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags. Nature biotechnology. 2008 Jan;26(1):83-90

2] Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nature nanotechnology. 2007 Dec;2(12):751-60.

3] Singh R, Lillard Jr JW. Nanoparticle-based targeted drug delivery. Experimental and molecular pathology. 2009 Jun 1;86(3):215-23.

4] Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. Journal of controlled release. 2001 Jan 29;70(1-2):1-20.

5] Kingsley JD, Dou H, Morehead J, Rabinow B, Gendelman HE, Destache CJ. Nanotechnology: a focus on nanoparticles as a drug delivery system. Journal of Neuroimmune Pharmacology. 2006 Sep;1(3):340-50

6] Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y. Engineered nanoparticles for drug delivery in cancer therapy. Angewandte Chemie International Edition. 2014 Nov 10;53(46):12320-64.

7] Chamundeeswari M, Jeslin J, Verma ML. Kumari A, Singla R, Guliani A, Yadav SK.

8] Nanoencapsulation for drug delivery. EXCLI journal. 2014;13:265.Environmental Chemistry Letters. 2019 Jun;17(2):849-65.

9] Gonçalves C, Pereira P, Gama M. Self-assembled hydrogel nanoparticles for drug delivery applications. Materials. 2010 Feb;3(2):1420-60.

10] Hoffman AS. Hydrogels for biomedical applications. Advanced drug delivery reviews. 2012 Dec 1;64:18-23.

11] Omidian H, Park K. Swelling agents and devices in oral drug delivery. Journal of drug delivery science and technology. 2008 Jan 1;18(2):83-93.

12] Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Advanced drug delivery reviews. 2008 Dec 14;60(15):1638-49.
13] Ahmed EM. Hydrogel: Preparation, characterization, and applications: A review. Journal of advanced research. 2015 Mar 1;6(2):105-21.
14] Zambaux MF, Bonneaux F, Gref R, Dellacherie E, Vigneron C. Preparation and characterization of protein C-loaded PLA nanoparticles. Journal of controlled release. 1999 Aug 5;60(2-3):179-88.
15] Rinaudo M. Non‐covalent interactions in polysaccharide systems. Macromolecular bioscience. 2006 Aug 7;6(8):590-610.
16]Govender T, Riley T, Ehtezazi T, Garnett MC, Stolnik S, Illum L, Davis SS. Defining the drug incorporation properties of PLA–PEG nanoparticles. International journal of pharmaceutics. 2000 Apr 10;199(1):95-110.
17] Panyam J, Williams D, Dash A, Leslie‐Pelecky D, Labhasetwar V. Solid‐state solubility influences encapsulation and release of hydrophobic drugs from PLGA/PLA nanoparticles. Journal of pharmaceutical sciences. 2004 Jul 1;93(7):1804-14.
18] Mittal G, Sahana DK, Bhardwaj V, Kumar MR. Estradiol loaded PLGA nanoparticles for oral administration: effect of polymer molecular weight and copolymer composition on release behavior in vitro and in vivo. Journal of controlled release. 2007 May 14;119(1):77-85.
19] Ghasemiyeh P, Mohammadi-Samani S. Hydrogels as drug delivery systems; pros and cons. Trends in Pharmaceutical Sciences. 2019 Mar 1;5(1):7-24.
20] Shalaby WS, Blevins WE, Park K. In vitro and in vivo studies of enzyme-digestible hydrogels for oral drug delivery. Journal of controlled release. 1992 Mar 1;19(1-3):131-44.
21] Şenel S, İkinci GÜ, Kaş S, Yousefi-Rad A, Sargon MF, Hıncal AA. Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. International journal of pharmaceutics. 2000 Jan 5;193(2):197-203.
22] Kim KS, Park SJ, Yang JA, Jeon JH, Bhang SH, Kim BS, Hahn SK. Injectable hyaluronic acid–tyramine hydrogels for the treatment of rheumatoid arthritis. Acta biomaterialia. 2011 Feb 1;7(2):666-74.
23] Hamidi M, Rafiei P, Azadi A, Mohammadi-Samani S. Encapsulation of valproate-loaded hydrogel nanoparticles in intact human erythrocytes: a novel nano-cell composite for drug delivery. Journal of pharmaceutical sciences. 2011 May 1;100(5):1702-11.
24] Qin M, Zong H, Kopelman R. Click conjugation of peptide to hydrogel nanoparticles for tumor-targeted drug delivery. Biomacromolecules. 2014 Oct 13;15(10):3728-34.
25] Wang YJ, Chien YC, Wu CH, Liu DM. Magnolol-loaded core–shell hydrogel nanoparticles: drug release, intracellular uptake, and controlled cytotoxicity for the inhibition of migration of vascular smooth muscle cells. Molecular Pharmaceutics. 2011 Dec 5;8(6):2339-49..
26] Kheiri K, Sohrabi N, Mohammadi R, Amini-Fazl MS. Preparation and characterization of magnetic nanohydrogel based on chitosan for 5-fluorouracil drug delivery and kinetic study. International Journal of Biological Macromolecules. 2022 Jan 13.
27] Kheiri K, Sohrabi N, Mohammadi R, Amini-Fazl MS. Preparation and characterization of magnetic nanohydrogel based on chitosan for 5-fluorouracil drug delivery and kinetic study. International Journal of Biological Macromolecules. 2022 Jan 13.
28] Ho HN, Le HH, Le TG, Duong TH, Ngo VQ, Dang CT, Tran TH, Nguyen CN. Formulation and characterization of hydroxyethyl cellulose-based gel containing metronidazole-loaded solid lipid nanoparticles for buccal mucosal drug delivery. International Journal of Biological Macromolecules. 2022 Jan 1;194:1010-8.
29] Huang TH, Hsu SH, Chang SW. Molecular interaction mechanisms of glycol chitosan self-healing hydrogel as a drug delivery system for gemcitabine and doxorubicin. Computational and Structural Biotechnology Journal. 2022 Jan 25.
30] Ghasemiyeh P, Samani SM, Azadi A. Hydrogels as Novel Drug Delivery Systems; Limitations and Solutions.
31] Lovelyn C, Attama AA. Current state of nanoemulsions in drug delivery. Journal of Biomaterials and Nanobiotechnology. 2011 Dec 9;2(05):626
32] Kumar M, Bishnoi RS, Shukla AK, Jain CP. Techniques for formulation of nanoemulsion drug delivery system: a review. Preventive nutrition and food science. 2019 Sep;24(3):225.
33] Wilson RJ, Li Y, Yang G, Zhao CX. Nanoemulsions for drug delivery. Particuology. 2021 Jun 8.
34] McClements DJ. Nanoemulsions versus microemulsions: terminology, differences, and similarities. Soft matter. 2012;8(6):1719-29.
35] Thiagarajan P. Nanoemulsions for drug delivery through different routes. Research in Biotechnology. 2011.
36] Anton N, Vandamme TF. The universality of low-energy nano-emulsification. International journal of pharmaceutics. 2009 Jul 30;377(1-2):142-7.
37] Mason TG, Graves SM, Wilking JN, Lin MY. Extreme emulsification: formation and structure of nanoemulsions. Condensed Matter Physics. 2006.
38] Gonçalves A, Nikmaram N, Roohinejad S, Estevinho BN, Rocha F, Greiner R, McClements DJ. Production, properties, and applications of solid self-emulsifying delivery systems (S-SEDS) in the food and pharmaceutical industries. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2018 Feb 5;538:108-26.
39] Qadir A, Faiyazuddin MD, Hussain MT, Alshammari TM, Shakeel F. Critical steps and energetics involved in a successful development of a stable nanoemulsion. Journal of Molecular Liquids. 2016 Feb 1;214:7-18.
40] Komaiko JS, McClements DJ. Formation of food‐grade nanoemulsions using low‐energy preparation methods: A review of available methods. Comprehensive reviews in food science and food safety. 2016 Mar;15(2):331-52.
41] Singh Y, Meher JG, Raval K, Khan FA, Chaurasia M, Jain NK, Chourasia MK. Nanoemulsion: Concepts, development and applications in drug delivery. Journal of controlled release. 2017 Apr 28;252:28-49.
42] Khan AW, Kotta S, Ansari SH, Sharma RK, Ali J. Potentials and challenges in self-nanoemulsifying drug delivery systems. Expert opinion on drug delivery. 2012 Oct 1;9(10):1305-17.
43] Jiang W, Kim BY, Rutka JT, Chan WC. Nanoparticle-mediated cellular response is size-dependent. Nature nanotechnology. 2008 Mar;3(3):145-50.
44] Foroozandeh P, Aziz AA. Insight into cellular uptake and intracellular trafficking of nanoparticles. Nanoscale research letters. 2018 Dec;13(1):1-2.
45] Whitesides GM. The origins and the future of microfluidics. nature. 2006 Jul;442(7101):368-73.

46] Jayasooriya SD, Bhandari BR, Torley P, D'arcy BR. Effect of high power ultrasound waves on properties of meat: a review. International Journal of Food Properties. 2004 Dec 31;7(2):301-19.
47] Solè I, Pey CM, Maestro A, González C, Porras M, Solans C, Gutiérrez JM. Nano-emulsions prepared by the phase inversion composition method: Preparation variables and scale up. Journal of colloid and interface science. 2010 Apr 15;344(2):417-23.
48] Ishak KA, Annuar MS. Phase inversion of medium-chain-length poly-3-hydroxyalkanoates (mcl-PHA)-incorporated nanoemulsion: effects of mcl-PHA molecular weight and amount on its mechanism. Colloid and Polymer Science. 2016 Dec;294(12):1969-81.
49] Solans C, Solé I. Nano-emulsions: formation by low-energy methods. Current opinion in colloid & interface science. 2012 Oct 1;17(5):246-54.
50] Armanet L, Hunkeler D. Phase inversion of polyacrylamide ‐ based inverse ‐ emulsions: Influence of inverting ‐ surfactant type and concentration. Journal of applied polymer science. 2007 Mar 15;103(6):3567-84.
51] Fernandez P, André V, Rieger J, Kühnle A. Nano-emulsion formation by emulsion phase inversion. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2004 Dec 20;251(1-3):53-8.
52] McClements DJ, Rao J. Food-grade nanoemulsions: formulation, fabrication, properties, performance, biological fate, and potential toxicity. Critical reviews in food science and nutrition. 2011 Mar 25;51(4):285-330.
53] Yousefpour P, Atyabi F, Vasheghani-Farahani E, Movahedi AA, Dinarvand R. Targeted delivery of doxorubicin-utilizing chitosan nanoparticles surface-functionalized with anti-Her2 trastuzumab. International journal of nanomedicine. 2011;6:1977.
54]Alshahrani SM, Alshetaili AS, Alalaiwe A, Alsulays BB, Anwer M, Al-Shdefat R, Imam F, Shakeel F. Anticancer efficacy of self-nanoemulsifying drug delivery system of sunitinib malate. Aaps Pharmscitech. 2018 Jan;19(1):123-33.
55] Chaudhary S, Aqil M, Sultana Y, Kalam MA. Self-nanoemulsifying drug delivery system of nabumetone improved its oral bioavailability and anti-inflammatory effects in rat model. Journal of Drug Delivery Science and Technology. 2019 Jun 1;51:736-45.
56] Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. International journal of pharmaceutics. 2009 Sep 8;379(1):146-57.
57] Kumar M, Pathak K, Misra A. Formulation and characterization of nanoemulsion-based drug delivery system of risperidone. Drug development and industrial pharmacy. 2009 Apr 1;35(4):387-95.
58] Shakeel F, Ramadan W. Transdermal delivery of anticancer drug caffeine from water-in-oil nanoemulsions. Colloids and Surfaces B: Biointerfaces. 2010 Jan 1;75(1):356-62.
59] Kelmann RG, Kuminek G, Teixeira HF, Koester LS. Carbamazepine parenteral nanoemulsions prepared by spontaneous emulsification process. International Journal of Pharmaceutics. 2007 Sep 5;342(1-2):231-9.
60] Chhabra G, Chuttani K, Mishra AK, Pathak K. Design and development of nanoemulsion drug delivery system of amlodipine besilate for improvement of oral bioavailability. Drug development and industrial pharmacy. 2011 Aug 1;37(8):907-16.
61] Chaudhuri A, Shrivastava N, Kumar S, Singh AK, Ali J, Baboota S. Designing and development of omega-3 fatty acid based self-nanoemulsifying drug delivery system (SNEDDS) of docetaxel with enhanced biopharmaceutical attributes for management of breast cancer. Journal of Drug Delivery Science and Technology. 2022 Jan 12:103117.
62] Saleh DO, Nasr M, Hassan A, El ‐ Awdan SA, Abdel Jaleel GA. Curcumin nanoemulsion ameliorates brain injury in diabetic rats. Journal of Food Biochemistry. 2022 Jan 30:e14104.
63] Zafar A, Yasir M, Alruwaili NK, Imam SS, Alsaidan OA, Alshehri S, Ghoneim MM, Alquraini A, Rawaf A, Ansari MJ, Sara UV. Formulation of Self-Nanoemulsifying Drug Delivery System of Cephalexin: Physiochemical Characterization and Antibacterial Evaluation. Polymers. 2022 Mar 7;14(5):1055.
64] Alhakamy NA, Badr-Eldin SM, Ahmed OA, Aldawsari HM, Okbazghi SZ, Alfaleh MA, Abdulaal WH, Neamatallah T, Al-hejaili OD, Fahmy UA. Green Nanoemulsion Stabilized by In Situ Self-Assembled Natural Oil/Native Cyclodextrin Complexes: An Eco-Friendly Approach for Enhancing Anticancer Activity of Costunolide against Lung Cancer Cells. Pharmaceutics. 2022 Feb;14(2):227.
65] Kumar R, Kumar R, Khurana N, Singh SK, Khurana S, Verma S, Sharma N, Vyas M, Dua K, Khursheed R, Awasthi A. Improved neuroprotective activity of Fisetin through SNEDDS in ameliorating the behavioral alterations produced in rotenone-induced Parkinson's model. Environmental Science and Pollution Research. 2022 Mar 1:1-2.
66] Chinnaiyan SK, Pandiyan R, Natesan S, Chindam S, Gouti AK, Sugumaran A. Fabrication of basil oil Nanoemulsion loaded gellan gum hydrogel—evaluation of its antibacterial and anti-biofilm potential. Journal of Drug Delivery Science and Technology. 2022 Jan 20:103129.
67] Tadros T, Izquierdo P, Esquena J, Solans C. Formation and stability of nano-emulsions. Advances in colloid and interface science. 2004 May 20;108:303-18.
68] Aboofazeli R. Nanometric-scaled emulsions (nanoemulsions). Iranian journal of pharmaceutical research: IJPR. 2010;9(4):325.