CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.5996324

Available online at: http://www.iajps.com ***Review Article***

A REVIEW ON: HERBAL NANOGEL

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Abstract:

Increasing research interest has been focused on controlled as well as sustained drug delivery using natural and biocompatible constituents in recent years. Many of them herbal constituents are escape due to Pharmacokinetic and pharmacodynamic issues of herbal constituents. There are many new technological ways and comparisons have been studied to improve the herbal discoveries in pharmaceutical market. This review paper will highlight on the basic methodology of nanogels , Drug loading techniques, release mechanisms , and their application in industry for herbal medicines . The term "Nanogel" define as a hydrogel nanoparticle with a network of cross-linked hydrophilic polymers. Nanogels are nanoparticles made up of cross-linked polymer that swell in a suitable solvent. Nanogels have an strength of drug loading capacity and it shows better permeation capabilities due to smaller size. They can be administered by various routes such as oral, nasal, parenteral, pulmonary,intra-ocular etc .Nanogel favored for herbal medicines due to stability and for the comfort. Nanoges in terms of herbal drugs are hopeful and novel approach which also can be called as future generation drug delivery systems outstanding to high drug encapsulation capacity, uniformity, minimum toxicity, greater stability.

Keywords*: Herbal medicine, nanogel, basic methodology, drug loading technique, drug delivery*

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Please cite this article in press Priti Jadhao et al, ***A Review On: Herbal Nanogel.,*** *Indo Am. J. P. Sci, 2022; 09(02).*

INTRODUCTION:

Herbal medicines that are those with working ingredients made from plant parts, like leaves, roots or flowers. Herbal medicine is a special and remarkable form of traditional medicine in which the traditional healer,in this case known as the herbalist, specializes in the use of herbs to treat various ailments. Herbal medicine is often defined as "the therapeutic practices that are alive for many years, before the event and spread of recent medicines". This branch of other medicines that utilize medicinal plants for therapy is applied as herbal medicine which exploits medicinal plants for therapy is applied as herbal medicine which is mostly researched by many researchers. Herbal medicines from traditional herbs or natural herbs are logically considered as alternative medicines during this period to treat and cure most communicable diseases also as non-communicable diseases like cancer and diabetes. Herbal medicines have played an crusial role in fixing the inspiration for current pharmacopoeia which is within the pharmaceutical market. Herbal medicines get favour over modern medicines due to minimum side effects and also healthier option for the patients. Mostly 85% of Worlds population used herbal drugs to treat skin related diseases like viral, fungal, diabetic related issues, hypersensitive reactions etc. But in reality, despite their appropriate pharmacological activity, they are less used in medicinal practices due to many reasons like solubility issues, bioavailability problems, high dose requirement etc. They can be used in day-to-day medicinal practices by using them in a new way. And it results to reduces the dose of the herbs as a drug which is used for pharmacological activity, however easy accessibility and also cost effectiveness of these traditional medicines by making them more desirable as a alternative option for modern medicines. Curcumin is the most widely used herbal compound which has been studied extensively in cancer research. Herbal medicine have been widely use all over the world since age old times and have been know by physicians and patients for their better therapeutic value as they have fewer adverse effect as compared with modern medicines.

Nanotechnology, a novel technique which having the broad scope for the drug delivery. Development of novel drug delivery system has a impact on a disease prevention diagnosis,and treatments. This novel way have is overcome the issues by improving absorption of drugs sustained release of drugs, controlled release of drugs,by reducing toxicity of drugs etc.the application of nanotechnology to medicines has the development of nanoparticles which act as carriers can be loaded with drugs or genetic material which release in controlled orsustainble manner to specific target site . Many nanotechnological techniques available nowadays for drug delivery like nanoemulsion, nanosuspensions, nanotubes, and nanogels but despite other techniques nanogels are mostly available in market due to its advantages over the other formulations. A nanoparticle which contains hydrogel with cross linked polymer network called as "Nanogel". A nanogel which is nanosized hydrogels which is cross-linked, small swollen particles which is made up from amphilic or hydrophilic polymer networks, these networks might be anionic or ionic. They act as carrier for drug molecules and design in the way that can absorb active compounds by the formation of biomolecular interactions like hydrogen bonding, salt bonds etc. The main biological compound can be loaded into nanogels by allowing the interaction between matrix and active agent and these results more dispersed hydrophilic particles. And for that nanogels become the more flexible structure for controlled and sustained drug release to the target site.

Advantages of nanogel

1. Less amount of drug is required.
2. Provide protection from biodegradation of drug molecule inside the body system.
3. Size of nanogel can be adjustable according to delivery molecule.
4. Reduce the toxicity of drugs.
5. Nanogels are able to cross physiological barrier of skin also the blood brain barrier.
6. Nanogels with loaded drug can be delivered inside the body without any side effects and also can be applied topically.
7. Easy for scle up and biofriendly formulation route.
8. Appropriate for many of bioactive compounds like proteins, antibodies, peptides etc.

Disadvantages of nanogel

1. Sometimes particles of surfactant can cause toxicity.
2. It requires expensive techniques.

Routes of administration of nanogel:

- Topical
- Nasal
- Pulmonary
- Parenteral
- Intraocular
- Oral

Properties Of Nanogels:

There are following properties of nanogels-

Biocompatibility and Degradability: Nanogel based drug delivery system is highly biocompatible and biodegradable, due to this characteristic it is highly suitable for the patients.

Swelling Property in Aqueous Media: The most beneficial features of nanogels is their rapid swelling/de-swelling characteristics.

Higher Drug Loading Capacity: Drug loading capacities of nanogels depend on the functional group present in the polymeric unit. These functional groups have an effect on drug carrying and drug releasing properties, and some functional groups have the potential to conjugate with drugs/antibiotics for targeting for application.

Particle Size: Nanogels ranges in size of 200nm in diameter and therefore effect avoiding the rapid renal exclusion but are enough to avoid the uptake by the endothelial system.

Solubility: Nanogels are able to soluble hydrophobic drugs and diagnostic agents in core or network of gel.

Electro mobility: Nanogels could be prepare without employing energy or harsh condition such as sonication or homogenization, which is critical for encapsulating bio-macromolecules.

Colloidal Stability: Nanogels have better stability over the surfactant micelle concentrations, slower rate of dissociation, and longer retention of loaded drugs.

Herbal Medicines Nano formulations

For pharmaceutical companies, the development of a complete herbal medicine is very annoying, because many factors affect the biological efficacy of the plant herbal medicine and the reproducibility of its therapeutic potential. In some cases, due to certain complications, such as asthma, pain, fever, etc., drugs need to act quickly, while in controversial cases, chronic treatments such as hypertension, cancer, and diabetes also need to extend the duration of action. Due to its physical and chemical properties, herbal medicines are strictly restricted in both stages.These factors have undoubtedly reduced their dominance in modern medical practice. In recent years, many research investment have been made to bring effective deliverables in herbal medicines. However, in order to obtain the desired efficacy, nanotechnology strategies are needed to control the efficacy of the active plant ingredients in the system. Attempt to use nanomaterials (such as polymer nanoparticles, solid lipid nanoparticle, lipid crystal systems, liposomes and nanoemulsions) as carriers to protect the herbal medicines from external degradation and improve their biological utilization. Facts have proved that nanotechnology increases the chances of implementing herbal-based medicines by increasing the potential of drug action, promoting the sustained release of active ingredients, reducing the required dosage and improving biological activity. Due to its inherent site-targeting ability and response to external stimuli, the research on polymer nanoparticles has been greatly developed in the last decade. When designing polymer nanoparticles for herbal preparations, the biotoxicity and stability of the polymer should be considered. Therefore, through biodegradable and biocompatible polymers, such as PLA (polylactic acid), PLGA (polylactic-glycolic acid), chitosan, etc., the delivery mechanism of such herbal compounds can be very effectively practiced. Certain polymers such as chitosan provide a series of advantages for transdermal delivery applications by enhancing functions such as sustained, targeted drug release, high biocompatibility and biodegradability. Due to its good physical and chemical properties (controllable drug delivery and affinity for aqueous solutions), excellent colloidal stability, high cell internalization properties, and tendency to remain inert in the blood, nanogels are modern pharmaceuticals that need special consideration. In addition, nanogels can easily meet current challenges in herbal formulations.

Techniques Of Drug Loading In Nanogels

Nanomaterials and nanogel composites have the ability to interact with many inorganic and organic components.

The interaction between these components is mainly through hydrogen bonds, covalent bonds, electrostatic forces

and van der Waals forces . These interactions determine the effectiveness of nanogels for embedding drugs.

Biomolecules are released from the nanogel through various mechanisms, such as diffusion, degradation, pH and

environmental stimuli. The various methods are as follows:

Covalent conjugation

Self assembly

1. Covalent Conjugation

Nanosystems provide a convenient platform for drug delivery. This is the result of its inherent functional groups participating in determining the structure and properties of nanoparticles. The covalent conjugation of the drug to the

cross-linked nanogel provides additional stability to the encapsulated drug. Polysaccharides contain hydroxyl groups that are easy to interact with hydroxyl groups, which are formed by forming ester bonds with the carboxyl groups in the drug. In this case, due to the cleavage of functional groups by enzymes such as esterase's, the drug will be released prematurely.

2. Self Assembly

When the autonomous organization of components is gathered to a good structure-the definition is called self-assembly. Many molecules are self-assembled, which is characterized by diffusion, and then through non-covalent interactions, hydrophobic associations or including electrostatic, specific binding of molecules occurs. Because it involves a lot of interaction, it has weaknesses and dominates the structure and conformational behavior of the assembly. Polyelectrolyte-based nanogels have a tendency to self-assemble in the presence of oppositely charged solutes (such as surfactants, polynucleotides, proteins and synthetic polyions). Amphoteric molecules instantly form self-assembled nanoparticles in an aqueous environment, which facilitates better drug interaction and release from the nanogel. The orientation of the drug molecule should expose the hydrophilic part to polar or aqueous media, while the hydrophobic area should be fixed in the core of the component. From a physical and chemical point of view, the important feature is that the hydrophobic part accumulates in the inner core and hydrophilic region in to polar region. The concentration of polymer above which chains are aggregates is called critical micelle concentration or critical aggregate concentration.

Mechanism Of Drug Release from Nanogels

a. pH stimulus
b. Degradation of nanogel
c. Ionic exchange with environment
d. Simple diffusion
e. From external energy sources

The release by stimulation of pH from the gel is the result of side group ionization. Nanogel polymers are composed of anionic or cationic side groups. In an aqueous environment, these groups will ionize at the appropriate pH and ionic strength. This creates a fixed charge on the polymer, causing electrostatic repulsion, which enlarges the pores of the gel. As a result, the flow of water into the gel increases, leading to swelling of the nanogel and drug release.The degradable nature of the nanogel ensures low toxicity and prevents unnecessary accumulation after repeated administration. Easily cleavable bonds can be introduced into the polymer backbone. Degradation is for specific reducing compounds, pH or even enzymatic activity. The lowest critical solution temperature (LCST) of the thermosensitive nanogel poly(N-isopropylacrylamide) in an aqueous medium is 32°C. At a temperature lower than the LCST, the amide group of the polymer interacts with the hydrogen of water, so the polymer is hydrated.

When the temperature increases, the hydrophobic-hydrophobic interaction of the polymer becomes obvious. The hydrogen bond with water is broken, the water phase separates and nanogel aggregation occurs; thereby releasing the captured drug into the environment. The diffusion release of the drug from the gel is the result of the difference in environmental concentration. The drug moves from the higher concentration area (inside the gel) to the lower concentration area (around). Another method is displacement by ions which is present in environment. A lot of research work is developing nanogels that can release biological agents in response to environmental cues at specific sites of action . When a cationic nanogel containing a negatively charged drug interacts with negatively charged particles in the environment/cell surface, the drug will be exchanged for negatively charged particles.

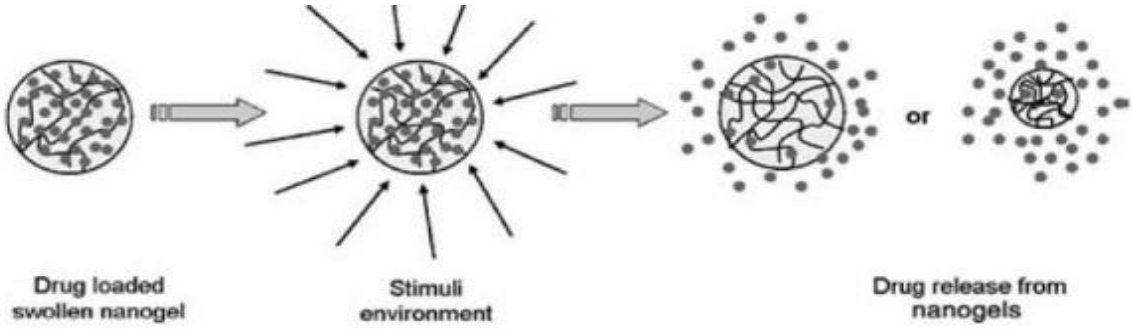

Figure1: drug release from nanogel

Basic method of preparation of nanogel

Method used for synthesis of nanogels are listed as follows:

a. Photolithographic Techni
b. Micro molding method
c. Biopolymer synthesis system
d. Water in oil (W/O) heterogeneous emulsion method
e. Inverse nanoemulsion method
f. Reverse micellar method
g. Membrane emulsification method
h. Heterogeneous free radical polymerization method
i. Conversion of microscopic gel technique
j. Chemical cross-linking method

Photolithographic techniques

Photolithography has been explored to fabricate hydrogel particles and microgel or nanogel rings for drug delivery.

The photolithographic method requires the development of techniques for surface treatment of stamps or new aterials for replica molds to permit the release of molded gels fro replica molds.

Photolithography consists of five steps. In the first step cross-linkable polymer, which possesses low surface energy, as a substrate is released on the pre-baked photo resist-coated water. The next step involves molding the polymer into patterns on the silicon wafer by pressing the quartz template onto the polymer and exposed it to the intense UV light. In the third step, the particles with a thin residual interconnecting film layer are uncovered by removing the quartz. template. Subsequently, this residual thin layer is removed by a plasma containing oxygen that oxidizes it. In the last step, the fabricated particles are directly collected by dissolution of the substrate in water of buffer . A top-down method called ‘‘Particle Replication In Nonwetting Templates (PRINT)’’was developed to fabricate submicron-sized microgels with control over particle size, shape, and composition. Using PRINT, DNA, proteins, and small-molecule therapeutics were incorporated into 200 nm PEG-based microgels by a simple encapsulation technique to demonstrate the compatibility of PRINT with (bio) molecules. Their sizes were ranged from 200nm to micron-scale in diameter with various shapes such as trapezoidal, bar, conical, and arrow . In addition, PRINT is a GMP-compliant (GMP=good manufacturing practice) platform amenable for particle fabrication on a large scale .

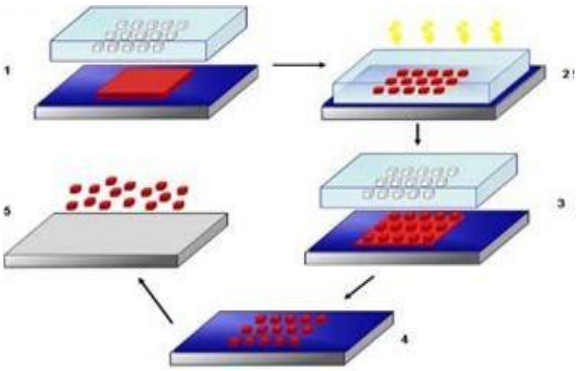

Figure2. Diagram of five steps involved in photolithography .

Micro molding method

The methods are similar to photolithographic techniques. However, they can minimize the need to use costly

lithographic equipment and clean room facilities. In the process, cells were suspended in a hydrogel precursor solution consisting of either methacrylated hyaluronic acid (MeHA) or PEGDA or a photoinitiator in water. The resulting mixture was deposited onto plasma-cleaned hydrophilic PDMS patterns and then photocrosslinked via exposure to UV light. The resulting cell-laden microgels were removed, hydrated, and then harvested. They were also molded into various shapes including square prisms, disks, and strings.

Fabrication of biopolymers

Chitosan (CS), hyaluronan (HA), and Dex are naturally occurring carbohydrate-based biopolymers. Many methods have been developed for the preparation of microgels of these biopolymers. They can be classified into four categories: waterin-oil (W/O) heterogeneous emulsion, aqueous homogeneous gelation, spray drying method, and chemical cross linking of Dex .

Water-in-oil (W/O) heterogeneous emulsion methods

W/O emulsion methods involve generally two steps: emulsification of aqueous droplets of water-soluble biopolymers in continuous oil phase with an aid of oil-soluble surfactants and cross linking of biopolymers with water-soluble cross linkers.

Inverse (mini) emulsion method

- A W/O emulsion is formed from a mixture consisting of aqueous biopolymer droplets and a continuous oil phase
- using either a homogenizer or a high-speed mechanical stirrer.

- Resulting aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents.
- then crosslinked microgel particles are prepared as dispersion in organic solvents
- purified by precipitation, centrifugation, washing with organic solvents such as isopropanol, and lyophilization.
- the size of the prepared microgel particles can be controlled by number of surfactants and crosslinking
- agents as well as stirring speed during the formation of inverse emulsion.

Example
preparation of HA-based microgels, carboxylic acids of HA were crosslinked with adipic dihydrazide (ADH) as a crosslinker in the presence of ethyl-3-[3-dimethylamino] propyl carbodiimide (EDCI) in aqueous droplets.

Reverse micellar method
Similar to the inverse (mini) emulsion method, the reverse micellar method also involves a W/O dispersion; however, a relatively large amount of oil-soluble surfactants is used to form a thermodynamically stable micellar solution consisting of aqueous droplets dispersed in the continuous oil phase .The resulting micellar droplets have a submicron size ranged from tens to hundreds of nanometers in diameter. Tumor targeted CS-based nanogels were prepared in inverse microemulsion of hexane containing Aerosol OT as a stabilizer in the presence of doxorubicin (Dox)-modified Dex. Aqueous glutaraldehyde was used to crosslink CS. The resulting Dox-encapsulating CS-based nanogels have a diameter of around 100nm.

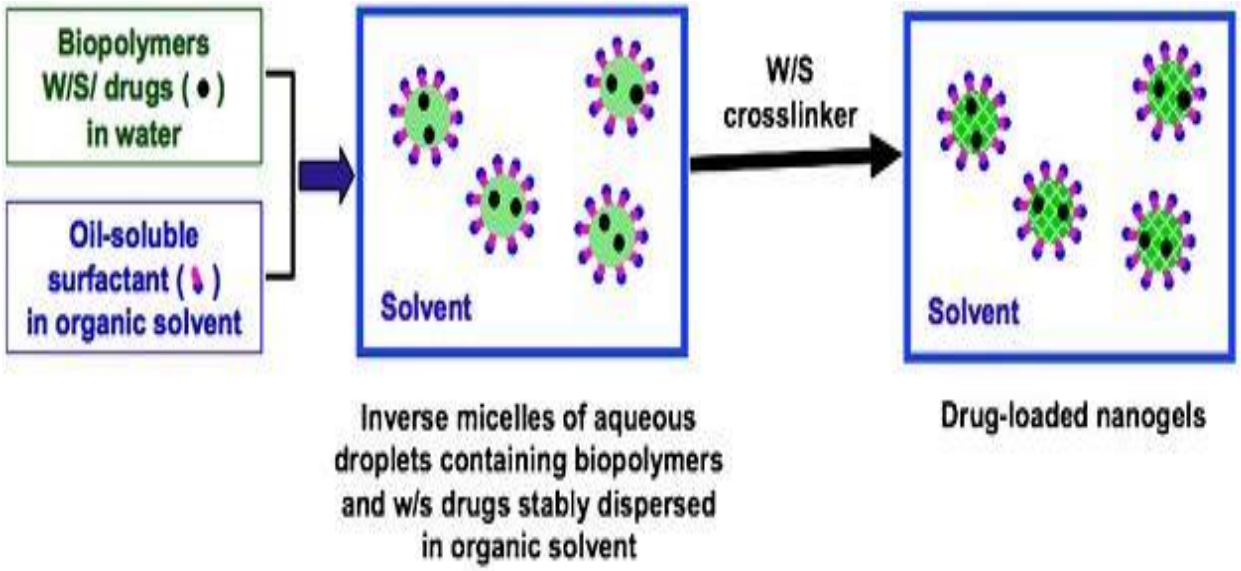

Figure3. Diagram of the reverse micellar method for the preparation of nanogels.

Membrane emulsification
In the membrane emulsification technique, the to-bedispersed phase is passed through the membrane (glass or ceramic), which possesses uniform pore size. Under certain conditions the emulsion droplets or microgels with specific morphology are formed on the surface of the membrane and afterwards, with a continuous phase that is flowing across the membrane, these fabricated emulsion droplets or microgels are recovered. These fabricated emulsiondroplets can be in different emulsion formation such as water-in oil (W/O), oil-in-water (O/W), oil-in-water-in-oil (O/W/O), and water-in-oil-in-water (W/O/W) . The size of the formed droplet is controlled by the membrane pore size, velocity of the continuous phase, and pressure of the trans-membrane.

Following figure represents the diagram using this synthesizing technique.

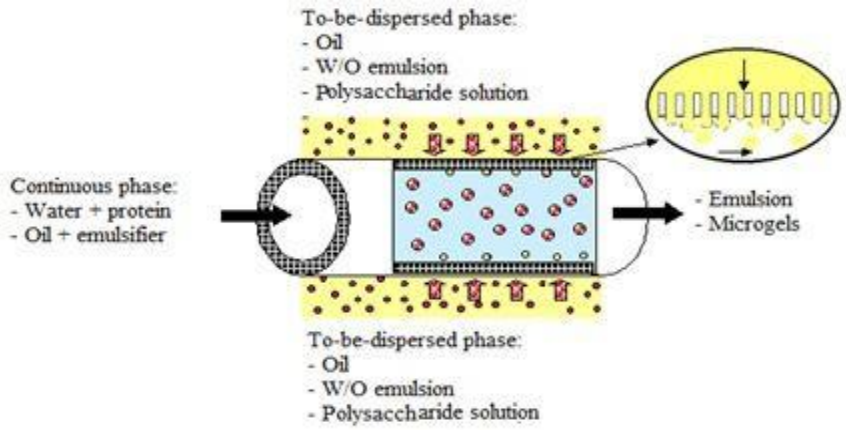

Figure4 Schematic diagram of the membrane emulsification technique.

Heterogeneous free radical polymerization

Various heterogeneous polymerization reactions of hydrophilic or water-soluble monomers in the presence of either difunctional or multifunctional crosslinkers have been mostly utilized to prepare well-defined synthetic microgels. They include precipitation, inverse (mini) emulsion, inverse micro emulsion, and dispersion polymerization utilizing an uncontrolled free radical polymerization process.

Conversion of Macroscopic Gels to Nanogels

Several synthetic methodologies are identified to prepare macroscopic gel networks (bulk gel networks or wall-to wall cross-links) and are easy to prepare, because it is not necessary to control the synthetic parameters as are required in nanogel or microgel synthesis to control the size. The macroscopic gel networks are generally prepared by bulk polymerization, which produce a solid and the network structure with macroporous blocks. These blocks are then crushed, grounded, and sieved to obtain gels of desired particle size. However, this is a time- and energy-consuming process and results in significant loss of material. Nevertheless, micro- and nanogels obtained from this method have particles of different shape and sizes .

Chemical cross linking

Biodegradable Dex-based microgels and hydrogels were prepared by various methods based on chemical cross linking including Carbodiimide coupling, Michael addition reaction, Free radical polymerization.

Evaluation parameter of nanogel

Evaluation parameters are used to evaluate the particle size, zeta potential, drug diffusion, permeation studies entrapment efficiency of formulated nanogel.

Particle size analysis: - By using particle size analyzer (Malvern instrument), we can analyze the particle size of the prepared nanogel particulate systems. For this purpose, nanogel particulate systems are suspended in ultra-pure water and particle size analysis is performed.

FTIR spectroscopy: - For this purpose, samples are prepared by mixing the prepared grounded formulations with potassium bromide and is placed on disc slit and then the IR spectra is recorded.

Entrapment efficiency: - In this, a small portion of the nano dispersion is centrifuged a unincorporated is measured using spectrophotometer.

Rheological measurements: - The rheological measurements can be performed on the Brookfield Rheometer RVDV Pro 11. All the measurements are carried out at room temperature 25+/-100C.

Experimental design: - In this study, a 32 factorial study is used to optimize the nanogel.

In vitro drug release: - A calibrated USP type-2 dissolution apparatus is used in order to perform the dissolution studies of drug loaded formulations at pH. 1.2 and 6.8 respectively. 900ml of each solution was used as a medium while maintaining the temperature at (37+/- 0.20C) and paddles speed at 50 rpm. After specified time interval 5ml of the sample are taken and replaced it with the same quantity of fresh medium. The cumulative drug released is calculated by measuring the absorbance with the help of UV spectrophotometer at 332nm.

Application of nanogel

Local Anesthetics: Local anesthetics are drugs which induce analgesia and give relief from pain. Local anesthetics give analgesic effect by blocking

nerve impulses in nerve cell membranes by blocking Na voltage gated channels .

Herbal nanogels:- Oral and transdermal applications of herbal nanogels are possible. Oral route is a most preferable route for delivery of many clinical drugs. But when drugs give orally there are many processes are seen such asabsorption,distribution, metabolism and elimination which takes time for drugs to show its effect. Apart from this oral administration also shows first pass metabolism effect, poor bioavailability, GI degradation. On the other hand, transdermal applications of herbal nanogel has various advantages over the other conventional drug delivery such as good patient compatibility, controlled release of drug, and it avoids first-pass metabolism effect of the drug. Curcumin based nanogel is one of the examples of the herbal nanogel.

CNS delivery: - Delivery of drugs (hydrophilic) to the brain is still challenge for the treatment of various CNS related disorders. Methotrexate loaded nanogel were prepared by using ionic gelatin method. Latest developments in studying the cell biology of BBB have opened new point of view in directing drugs to the CNS.

Protein delivery: - Nowadays, more therapeutically active proteins have been discovered and attracted attention in specific diseases such as malignant, viral and autoimmune disease.

Anticancer therapy: - Cancer treatment involves targeted delivery of drugs which has low toxic effects to surrounding tissues and have therapeutic efficacy. Many polymeric nanogels have been used for cancer therapy. Integrating chemotherapeutic drugs into the nanogel not only increases the bioavailability but also increases permeability and retention. Nanogel are being used to deliver drugs more successfully in cancer chemotherapy. One of the example of polymeric nanogels for use in patients with breast cancer, which has FDA approved, is Genexol-PM . Another example is Chitin-polymerized Doxorubicin nanogels are used for treatment of prostate, breast, lungs, and liver cancer.

Autoimmune diseases: - A study directed, designed and tested a novel nanogel drug delivery vehicle for the immunosuppressant mycophenolic acid (MPA). Study come to an end that there is a better efficacy of nanogel based local drug delivery for lupus erythematosus as it targets antigenpresenting cells. This new drug delivery system increases the survival of the patient and delays the onset of kidney damage, a common complication of lupus .

Challenges and Opportunity

According to the World Health Organization (WHO) report, 80% of the world's population will be highly dependent on herbal medicines to meet their health needs. A Nanogels formulated with herbs have opened a multibillion-dollar market for the growing pharmaceutical industry. As people's social, political and economic values have undergone major changes, the therapeutic application of herbal medicine has been greatly reduced. Nanogels can greatly help herbal medicine enter many applicable clinical practices through effective research programs. The fascinating properties of nanogels (such as biocompatibility and degradability, swelling properties in aqueous media, higher drug loading, permeability and particle size, non-immune reaction and colloidal stability) are always, There are new opportunities.Nanogels are useful for designing delivery systems that respond to external stimuli that control the rate of drug release at the site of action. This can make the herbs play a multifunctional role by improving their efficacy.

CONCLUSIONS:

Nanogel formulation is a versatile platform for enhancing herbal drug properties. Due to its flexibility and versatility nanogels have several opportunities in herbal formulations as a drug carrier. Herbal nanogels transform natural products into the most suitable drugs for the treatment of many diseases, such as cancer, skin diseases, diabetes, etc. Chitin, chitosan, PLGA, PEG and other polymers are generally used in the synthesis of cross-linked herbal nanogels. These cross-linked nanogels have excellent potential in delivering drugs through the transdermal route. Compared with oral drugs, this has less side effects on patients' compliance with herbal medicines. Although many natural medicinal products have been developed, not all of these products are safe. Some are highly toxic, can interact with conventional drugs and have adverse side effects. For herbal products to be accepted in modern medical systems, the quality of herbal products needs to be evaluated. Herbal nanogel formulations are currently expected in the pharmaceutical industry and can give the required synergistic effects at low drug concentrations and almost no side effects. In general, herbal nanogel products can be a practical new drug carrier system.

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