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REVIEW ARTICLE

Comprehensive Review of Novel Drug Delivery Systems of Anti-histaminic Drugs

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ABSTRACT

Antihistaminic drugs are used to treat different types of diseases which usually involve an inflammation reaction. These agents will inhibit the release and the effects of inflammatory mediator histamines in the target area. In order to solve some of the physicochemical drawbacks and the limitations associated to conventional formulations of antihistaminic drugs, novel drug delivery systems, such as niosomes, liposomes, hydrogel, nano and micro particles, have been developed. Evolution of an existing antihistaminic drug molecule from a conventional form to a novel delivery system can significantly improve its performance in terms of patient compliance, safety and efficacy. In the form of a Novel Drug Delivery System an existing antihistaminic drug molecule can get a new life. Depending on the inflammation site and allergic condition, different types of administration routes also used to deliver the antihistaminic drug. The aim of the present review article is to compile the recent improvements of novel drug delivery technology of antihistaminic drug delivery.

KEYWORDS

Niosome, Liposome, Hydrogel, Nano particle, Antihistamines, Novel drug delivery

INTRODUCTION

Nanogels Antihistaminic drugs will inhibit the actions of histamine at H1 receptors. Histamine is a physiologically active, endogenous substance that binds to H1 and H2 receptors in the respiratory tract (including the nose), the gastrointestinal tract[1, 2] brains, skin vasculature, and the heart etc.[3] During allergic conditions, histamine and other substances are being secreted from mast cells, basophils, and other cell types. Histamine then binds to, and activates, specific receptors, causing smooth muscle constriction, vasodilation, endothelial permeability, and sensory nerve stimulation.[2]

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These actions of histamine will shows allergic signs and symptoms: sneezing, rhinitis, rhinorrhea, erythema, pruritus, and urticaria[I2] hence antihistamines are chiefly used to treat all these allergic conditions like sneezing, rhinitis, insomnia, rhinorrrhea etc.[2] Antihistamines are classified[4] as first generation (sedating, including chlorpheniramine,diphenhydramine, promethazine, and hydroxyzine) second generation. The second generation antihistamines are relatively non-sedating, including terfenadine, astemizole, loratadine, cetirizine, and levocetirizine and third generation including fexofenadine, norastemizole, and descarboethoxyloratadine.

Different forms of anti-histaminic formulations are available in the market. They include tablet, capsules, eye drops, ointments, etc. But the lipophilic drugs may cause a wide range of stability as well as technical problems towards the formulation process. Conventional

formulations of antihistaminic shows poor bio-availability due to drug degradation, poor penetration through the skin, drug loss etc. Miraculous prosperity of novel drug delivery systems like localized action, controlled, sustained and targeted delivery may instigate to convert the drugs in novel form.

To minimize degradation of drug and drug loss, to prevent harmful side-effects and to improve drug bioavailability and the fraction of the antihistaminic drug accumulated in the required zone, various drug delivery and drug targeting systems are developed. These new strategies, often called novel drug delivery systems (NDDS), which are based on ambidextrous approaches that combine polymer science, pharmaceutics, bio conjugate chemistry, and molecular biology. Conventional drug delivery concerns the formulation of the drug into a convenient form, such as a compressed tablet for oral administration or a solution for intravenous administration. These dosage forms have been found to have serious limitations in terms of higher dosage require, lower effectiveness, toxicity and adverse side effects.[5]

Thus inorder to comply with the need of health care profession all the limitations of conventional drug delivery systems are being surpassed by the development of new and recent drug delivery systems.

The therapeutic benefits of these new systems include

- Increased efficacy of the drug
- Site specific delivery
- Decreased toxicity/side effects
- Increased convenience
- Viable treatments for previously incurable diseases
- Potential for prophylactic applications
  Better patient compliance.

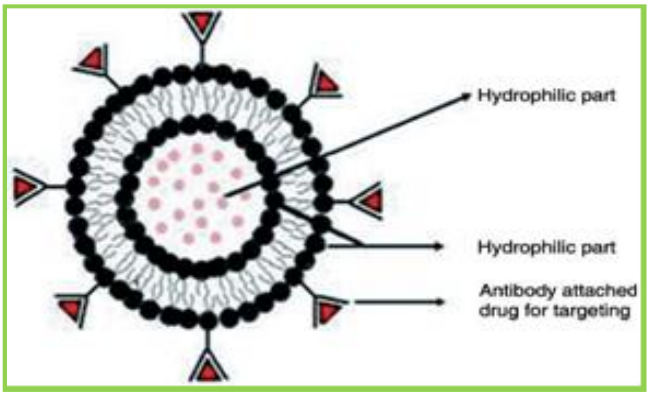
Various Novel Drug Delivery Systems are available for anti-histaminic drugs, some of them are;

- Niosomes,
- Liposomes,
- Hydrogel,
- Nano particles
- Niosomal in-situ gel

❖ **Niosomes**

Niosomes are one of the best drug delivery system among these carriers. Structurally, niosomes are similar to liposomes and also are equiactive in drug delivery potential but high chemical stability and economy makes niosomes superior than liposomes. Both consist of bilayer, which is formulated by using non-ionic surfactant in the case of niosomes and phospholipids in case of liposomes. Niosomes have size range between 10 to1000 nm and consists of biodegradable, non-immunogenic and biocompatible surfactants.[6]

The niosomes are amphiphillic in nature because hydrophilic drugs will entrap within the core cavity and hydrophobic drugs in the non-polar region present within the bilayer hence both hydrophilic and hydrophobic anti-histaminic drugs can be incorporated into niosomes[7]



***Types of niosomes*[8]**

1. Multilamellar vesicles (mlv):

It consists of a number of bilayer surrounding the aqueous lipid compartment. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes because these vesicles are highly suited as drug carrier for lipophilic compounds.

2. Large unilamellar vesicles (luv):

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of drugs can be entrapped with a very economical use of membrane lipids

3. Small unilamellar vesicles (suv):

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method,

***Method of preparation* [7, 6]**

1. Ether injection method

In this method, slowly introducing a solution of surfactant dissolved in diethyl ether into warm buffer at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into the buffer. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm.

2. Hand shaking method (Thin film hydration technique)

The mixture of surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0- 60°C with gentle agitation. This process forms typical multi lamellar Niosomes.

3. Sonication

In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield Niosomes.

4. Reverse Phase Evaporation Technique (REV)

Cholesterol and surfactant are dissolved in a organic solvent. An aqueous phase containing drug is added to this and the resulting mixture is sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of buffer. The organic phase is removed at 40°C under reduced pressure. The resulting viscous niosome suspension is diluted with buffer and heated on a water bath at60°C for 10 min to yield Niosomes.

Advantages of anti-histaminic niosomal formulation [9]:

The vesicles help to releasing the drug in a controlled manner especially in eye. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. The surfactants used are biodegradable, biocompatible and non-immunogenic, so it will not cause any inflammation and other adverse reaction to the sensitive part of the body. They improve oral bioavailability of drugs and enhance skin penetration of drugs in case of anti-allergic gels and other formulations. Due to the unique infrastructure consisting of hydrophilic, amphiphillic and lipophilic moieties together they, as a result can accommodate drug molecules with a wide range of solubility.

Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.[7] Niosomes will localize the drug action in eyes skin mouth etc.

❖ Liposomes

Liposomes are microscopic artificial vesicles in which lipid bilayer structure is present with an aqueous compartment entirely enclosed by a membrane, composed of lipid molecules. There are number of components present in liposomes, with phospholipid and cholesterol being the main ingredients. The type of phospholipids includes phosphoglycerides and sphingolipids, together with their hydrolysis products. Liposomes are structurally almost same as that of niosomes. Participation of nonionic surfactants instead of phospholipids in the bilayer formation results in niosomes.[10]

Classification of liposome[11]

Oligolamellar vesicles (OLV) 0.1-1 μm

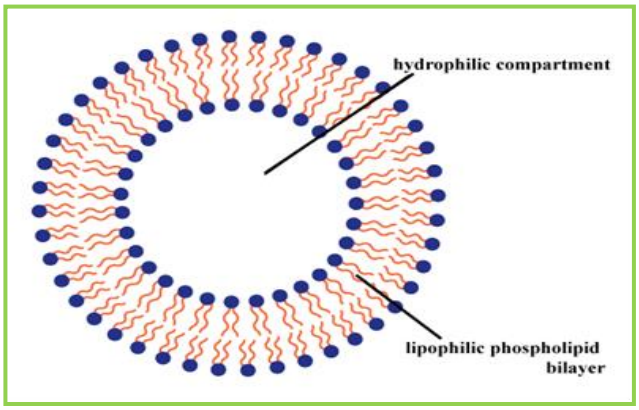
Unilamellar vesicles (UV) All sizes

Small unilamellar vesicles (SUV) 20-100 nm

Medium sized unilamellar vesicles (MUV)

Large unilamellar vesicles (LUV) >100 nm

Giant unilamellar vesicles (GU) >1 μm



Method of preparation

Some important general method of preparation of liposomes includes

1. Ether injection (solvent vaporization)[10]

A solution of lipids and cholesterol dissolved in diethyl ether mixture is gradually injected to an aqueous solution of the material to be encapsulated at 55°C to 65°C or under reduced pressure. The consequent removal of ether under vacuum leads to the creation of liposomes

2. Dialysis[30]

Here lipid will solubilize in detergents at their critical micellar. As the detergent is detached, the micelles become increasingly better-off in phospholipid and lastly combine to form LUVs. The detergents will remove by dialysis. A commercial device called LipoPrep, which is used for the elimination of detergents. The dialysis can be performed in dialysis bags engrossed in large detergent free buffers (equilibrium dialysis)

3. Reverse Phase Evaporation Method[31,32]

This method is similar to the preparation of non-ionic surfactant bilayer. Here water in oil emulsion is formed by brief sonication of two phase system containing phospholipids in organic solvent and aqueous buffer. The organic solvents are removed under vaccum, resulting in the formation of a viscous gel. At a critical point in this process, the gel state collapses, and some of the inverted micelles were disturbed. The excess of phospholipids in the environment donates to the formation of a complete bilayer around the residual micelles, which results in the creation of liposomes.

4. Thin film hydration technique[31,32]

The mixture of lipid and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask.

The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried lipid film can be rehydrated with aqueous phase at 0- 60°C with gentle agitation.

Advantages of anti-histaminic liposomal formulation[12]

Liposomes are biocompatible, completely biodegradable, non-toxic in nature, so it will not cause adverse reaction. They are suitable for delivery of both hydrophobic and hydrophilic anti-histaminic drugs. They protect the encapsulated sensitive antihistamines from external environment. They reduce toxicity and increase stability-Since therapeutic activity of anti-allergic agent can be improved through liposome encapsulation. This reduces deleterious effects that are observed at concentration similar to or lower than those required for maximum therapeutic activity. It reduces exposure of sensitive tissue to toxic drugs.

❖ **Hydrogel**

Hydrogels are three –dimensional cross linked water soluble polymers and that absorb substantial amount of water.[13] Cross linking produce insolubility in water because of ionic interaction as well as hydrogen bonding.[14] It also provides required mechanical strength and physical scrupulosity to the Hydrogels.[15] Thus, hydrogels can imbibe water nearly 10-20 times its molecular weight and hence become swollen.[16] Some examples of Hydrogels include contact lenses,[17] wound dressing[18,19] super-absorbents[19]

In general, hydrogels can be prepared from either synthetic polymers or natural polymers. The synthetic hydrophobic polymers are in nature and chemically stronger compared to natural polymers. They shows slow degradation rate due to good mechanical strength, but on the other hand, mechanical strength provides the durability as well. These two opposite properties should be balanced through optimal design.

Method of preparation [33]

Some of the important methods are:

1. ***Bulk polymerization***

Bulk polymerization is the simplest technique which involves only monomer and monomer-soluble initiators. Many vinyl monomers can substantially be used for the productions of hydrogels. Bulk hydrogels can be prepared with one or more types of monomers. Usually, a small amount of cross-linking agent is added in any hydrogel formulation. The polymerization reaction is normally initiated with radiation, ultraviolet, or chemical catalysts. The choice of a suitable initiator depends upon the type of monomers and solvents being used.

2. ***Solution polymerization/cross-linking***

In this reaction, the ionic or neutral monomers are mixed with the multifunctional cross linking agent. The polymerization will initiate thermally by UV-irradiation or by a redox initiator system. The presence of solvent serving as a heat sink is the major advantage of the solution polymerization over the bulk polymerization. The prepared hydrogels need to be washed with distilled water to remove the monomers, oligomers, cross-linking agent, the initiator, the soluble and extractable polymer, and other impurities.

3. ***Suspension polymerization or inverse-suspension polymerization***

This polymerization is referred to as ‘‘inverse suspension’’. In this technique, the monomers and initiator are dispersed in the hydrocarbon phase as a homogenous mixture. The viscosity of the monomer solution, agitation speed, rotor design, and dispersant type mainly governs the resin particle size and shape.

Classification of hydrogels [20]

- Based on the methods of preparation - Homo-polymeric Hydrogel,
  -Co-polymeric hydrogel,
  -Inter Penetrating Network,
- Stimuli-sensitive hydrogels
  -Temperature-sensitive hydrogels,
  -pH-sensitive hydrogels,
  -Dual pH-thermal sensitive systems
- Based on mechanism of release- Diffusion controlled,
  -swelling controlled.

Advantages of anti-histaminic Hydrogel formulations[15]:

They are biocompatible, biodegradable and can be injected. Hydrogels possess wide range of flexibility similar to natural tissue; hence it is effective for antihistaminic delivery. Have good transport properties and easy to modify. Timed release of drug content will ensure proper and sustained drug delivery. Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature or the concentration of metabolite and release their load as result of such a change. This technique is used to deliver drugs in eye, nose, etc.

- **Nano particles**

Nanoparticles can be defined as the colloidal particles either amorphous or crystalline having size ranging from 10 to 1000 nm. They are able to absorb and encapsulate a drug, in that way protect the drug against chemical and enzymatic degradation. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organ or tissue.[21, 22]

The reason why these nanoparticles (NPs) are attractive for anti-histaminic drug delivery purposes is based on their important and unique features. The surface to mass ratio of the nano particle is much larger than that of other particles. Their quantum properties and their ability to absorb and carry other compounds also attracted for this purpose. NPs have a relatively large (functional) surface which is able to bind, adsorb and carry other compounds such as drugs, probes and proteins

Method of preparation [34, 36]

1. Emulsification solvent evaporation technique

It is basically used for encapsulating hydrophobic drugs. In this technique polymer and the compound are dissolved in an organic solvent such as chloroform, ethyl acetate, or methylene chloride and then it is emulsified in an aqueous phase containing a stabilizer (e.g., PVA). Just after formation of the nanoemulsion the solvent diffuses to the external phase until saturation. The diffused solvent molecules will evaporate from water-air interphase, which vanguard to continuous diffusion of the solvent molecules from the inner droplets of the emulsion to the external phase; simultaneously, the precipitation of the polymer leads to the formation of nanospheres. In many cases, the induction of nanosized polymer droplets can be done by sonication or homogenization. The organic solvent is then evaporated and the nanoparticles are usually collected by centrifugation and lyophilization.

2. Emulsification Diffusion method

The polymer and the drug will dissolve in water-soluble solvent like acetone or propylene carbonate and it is emulsified in the aqueous phase containing the stabilizer. The stabilizer will prevent the aggregation of emulsion droplets by adsorbing of the surface of the droplets. Addition of water to the emulsion leads to the diffusion of the solvent into the water. Nano precipitation of the particles will produce by stirrering. Further, it can be collected by centrifugation, or dialysis. The main problem with this method is that the water soluble drugs tend to leak out from the order to avoid this problem the dispersing

medium changed from aqueous medium to medium chain triglycerides and a small amount of surfactant is added into it. The nan-poarticles are collected from the oily suspension by centrifugation.

3. Nanoprecipitation method

In this method, polymer and drug will dissolve in acetone, ethanol, or methanol and acclimatize with aqueous solution of the surfactant under magnetic stirring. The organic solvent diffuses promptly to the external aqueous phase, followed by precipitation of the polymer and drug. After formation of the nanoparticles, the solvent will remove under reduced pressure.

Advantages of anti-histaminic nano-particle based formulations [23]

Drug targeting is possible for allergic conditions, active targeting of carriers to specific cells using antibodies or sugars has been attempted and sustained release of drug is possible for chronic allergic conditions. They can be formulated for targeted delivery to the lymphatic system, brain, arterial walls, lungs, liver, spleen, or made for long-term systemic circulation. A large number of drugs can be delivered using nanoparticulate carriers via a number of routes; these include many hydrophilic and hydrophobic anti-histaminic drugs. They will reduce toxicity while maintaining therapeutic effects, greater safety and biocompatibility and faster development of new safe medicines.

❖ Niosomal *in-situ* Gel

These are the combination of two drug delivery systems, noisome and *in-Situ* gel.[24] It appears in liquid form, when the ph of the environment changes, the liquid form will change into a gel form. Such delivery systems consist of phase transition polymers that are in liquid form at the time of instillation into the eye and thereafter shift to the gel phase.[25] that is the basic principle of *in-Situ* gels. We will get conglomerated advantages of both the noisome and the gel in a single formulation. Here the formulated noisome will convert into a gel formulation by using a suitable gelling polymer.[26, 27]

Method of preparation

This preparation includes two steps,

1. **Preparation of Niosomes**
2. **Preparation of *in-situ* gel**

Niosomes were prepared by using general formulation technique of non ionic surfactant bilayered vesicle. Formulated niosomes further converted into gel formulation.

Various water soluble polymers such as carbopol systems, hydroxyl propyl methyl cellulose system, are comes under pH induced *in situ* precipitating polymeric systems. This type of polymeric system will act as the principle component of niosomal *in situ* gel. Niosomal *in situ* gels were prepared by adding viscosifier (Eg;HPMC K4M) to the niosomal suspension and then gelling agent (Eg;carbopol) was added and allowed to hydrate overnight.

Advantages of anti-histaminic Niosomal *in-Situ* gel:

We can improve the bioavailability of antihistamines through incorporating into a niosomal gel. It helps to increase the contact time of the drugs in eye nose etc. The gel part and the noisome will control and prolong the drug release. This formulation is more reformative for localizing the antihistamines in eye and nose, that way we can improve the drug action in this part. This is considered as one of the patient complying drug delivery system for antihistamines.

CONCLUSION

Obviously, Novel Drug Delivery Systems of anti-histaminic drugs will shows advanced drug delivery to the body than conventional drug delivery systems. Bioavailability, therapeutic

effect and other important characters of the drug can be improved by this way. Many research works has proved the best part of using novel drug delivery system as compared to conventional delivery system.

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