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CLAY COMPOSITE HYDROGEL FOR MODIFIED DRUG DELIVERY: A REVIEW

K. N. Sukanya* and Dr. M. Sunitha Reddy

CPS-IST, JNTU-H, Kukatpally, Hyderabad-500085
knsukanya16@gmail.com

Abstract:
Clay minerals are used in many pharmaceutical formulations (US-FDA declared as excipients). The necessity for safe, inexpensive and compatible drug delivery system led to the synthesis new material known as clay composite hydrogels. The clay minerals had a considerable effect in the properties of the hydrogels. Many clay mineral forms like montmorillonite, attapulgite, layered double hydroxide, saponite etc., are used in composite hydrogels. In recent years, the research on the clay composite has been increased due to improvement in mechanical properties, swelling kinetics, biocompatibility, and controlled release of drugs, proteins etc. Different systems (nanoparticles, microparticles, beads, films, matrices etc.) of clay composites were synthesized with variations in the amount of clay in the systems. This review contains the detailed study of the clay composite hydrogel materials, preparation methods, characterization and evaluation.

Key Words: *Clay minerals, clay composite hydrogels, controlled release.*

Corresponding author:
K. N. Sukanya,
CPS-IST, JNTU-H,
Kukatpally, Hyderabad-500085
E-Mail:Knsukanya16@gmail.com

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INTRODUCTION:

The clay minerals are hydrated alumino-silicates containing mostly the group I and II elements of the periodic table [1]. The utilization of clay in pharmaceutical formulations was started around 1960's as pharmaceutical excipients [2]. The monographs of clay minerals were found in United States Pharmacopeia (USP) and the European Pharmacopeia (EP) [3]. The clay composites were designed to modify the drug release patterns, reduce the side effects and to avoid fluctuations in the plasma drug concentrations [4]. The clay composite hydrogels contain polymers and clay minerals as main components.

Hydrogels are cross-linked three-dimensional hydrophilic polymeric networks. They swell enormously in the presence of water [5, 6]. Based on the network driving forces, the hydrogels are of two types- the physical gels in which the ionic bonds/hydrogen bonding/hydrophobic forces are involved in the gel formation. In chemical gels, the network is formed by covalent bonds caused by chemical agents (free radical generating agents) or even by radiation [7].

The clay minerals are different types of which only few forms were used after purification process as excipients in pharmaceutical industry [1]. The clay contains silica and it has layered structure hence known as layered structure, mostly belonging to the phyllosilicate family [8]. The structures of the clay minerals play an important role in the application such as excipients, active ingredients, adsorbents etc. The applications of layered silicates are lubricants, diluents, disintegrating agents, emulsifying agents, pigments, flavouring agents etc [3, 9].

The clays when administered with the drugs showed a considerable effect on absorption, promazine anti-depressing agent absorption has been decreased when administered along with attapulgite. The effect of interactions between clay and drug/API (active pharmaceutical ingredient) need not be negative always, which lead to the utilization of clay in drug delivery systems [2]. The composite hydrogel is formed by mixing the layered silicate with the polymers or its solutions. The intercalation of the polymer in the composite is studied by XRD and TEM which indicate the state of intercalation i.e. microcomposite or intercalated composite or exfoliated composite[8]. The composites were used earlier in industries, polymers were added with particles to improve its properties like mechanical strength, resistance to flame etc., also to reduce the cost[8]. These systems found their way to the biological applications due to these properties [10].

MATERIALS:

Clay minerals:

The clay minerals have alternating negatively charged alumino-silicates which are balanced by the exchangeable cations of the alkaline and alkaline earth metals [4]. They are used in medicinal formulations due to its large surface area, adsorptive properties, swelling behaviour and intercalative properties [11]. The clay minerals contain structural units made of aluminium or magnesium octahedral and silica in tetrahedral giving a layered structure [3]. In recent years the use of clay in the modified drug release has been increased drastically [12].

Table 1: The clay minerals used in dosage forms [13]

S.no.	Clay	Dosage forms
1.	Kaolin	Solid (modified release tablets and capsules, powders) Liquid (syrups)
2.	Talc	Solid (conventional tablets, modified release capsules and tablets, chewable tablets, granules and powders) Liquid (drops, mucilage, solutions, elixir, suspensions, and syrup, Lotions) Semi- solid (ointments)
3.	Bentonite	Solid (tablets, capsules). Films. Liquid (suspending agents)
4.	Activated attapulgite	powders

The clay minerals used in the synthesis of composite hydrogels are
Montmorillonite
Attapulgite
Bentonite
Vermiculite
Layered double hydroxide etc [4] .

Polymers:
The polymers are used to form the matrix or the support system in the composites. The selection of the clay and the polymer depends on the parameters of the individual components. The use of single clay and polymer combination cannot meet the requirements; hence a combination of polymers is preferred [11].

The addition of the clay minerals to the polymers helps in improving the properties of the material or to modify the release of drugs. Bhavesh et al. synthesized polyacrylamide/montmorillonite composite hydrogel for controlled release of anti-cancer drug 5-Flourouracil. The composite showed increased swelling when compared to the pristine hydrogel and was also tested for cyto-toxicity [14].

Table 2: commonly used polymers

S.no	Type of polymer	Examples
1.	Natural polymers	Chitosan Alginate Dextran Cellulose
2.	Synthetic polymers	
	a. Biodegradable polymers	Polyvinyl alcohol Polyvinyl pyrollidone
	b. Non-biodegradable polymers	Ethyl cellulose Cellulose acetate Polyurethanes

Methods:
The preparation methods of layered silicate composite are mostly done by the following methods.

Exfoliation-adsorption method:
This technique is otherwise called polymer or pre-polymer intercalation [4.] The clay is exfoliated in the solvents in which the polymers are soluble. The polymers enter into the layers of the clay and when the evaporation of the solvent takes place, the entrapment of the polymer between the layers/ sheets of the clay occurs [15].
Water soluble polymers are mostly used to produce intercalated composites by this method.

Solution exfoliation:
The clay is dispersed in the solvent before the addition of the polymer which helps in the easy penetration of the polymer into the layers in the clay. The polymer is added to the solution and dispersed for ample amount of time for proper interaction of clay and polymer, the evaporation of the solvent leads to the entry of the polymer within the clay layers [15].

Gu et al. have reported the synthesis of composite hydrogel by solvent intercalation method of organo-montmorillonite (OMMT)/polybutadiene rubber composite. The organo-modified MMT is dispersed in solvent oil then the polybutadiene rubber solution is added and stirred at 60º C for half an hour and then solvent evaporation is done. The XRD data showed an increase in the d-spacing from 1.55nm to 3.63nm when compared to the original montmorillonite and organo-MMT composite respectively [16].

Emulsion exfoliation:
In the emulsion method there is addition of an emulsifying agent which aids the formation of the clay composite, then the solvent is removed [15].

Melt intercalation method:
This method involves high temperature in the formation of the clay composite. The melted polymer is mixed with the layered silicate and the kneading of the material is done for the uniform distribution of the polymer [15]. The polymer enters into the layers of clay minerals and formation of exfoliated or intercalated composite takes place and a

slight increase in the space between the layers is seen [4].

Advantages:

1. This process is ecofriendly due to no utilization of solvents.
2. The solvent effect on the drugs can be avoided.

Disadvantages:

1. Utilization of high temperature in this method may lead to the deterioration of the drug activity.
2. Mostly thermoplastic polymers can be used in this process.
3. The drugs resistant to the heat range can only be used.
4. The optimization of the temperature parameter should be done in consideration with the properties of the polymer, clay and drug.

Campbell et al. have synthesized polyethylene glycol loaded with paracetamol and a clay composite material by the melt interposition method. The clay used is Closite 20A which is a modified form of montmorillonite. There was a slight decrease in the crystallinity of polyethylene glycol relative to the compound. There was an alteration in the drug release from the compound [17].

Insitu-polymerisation:

This process is also called as in-situ-intercalative polymerization. The clay minerals are dispersed in the monomeric solution and the polymerization of the monomer is initiated by external stimuli i.e. heat, radiation, catalyst or suitable initators [15]. This method over comes the problems of the solution method and melt intercalation [4].

W. Cui et al. A polyethylene terephthalate / double layer hydroxide compound was prepared by in situ polymerization. The terephthalate monomer is interposed in the hydroxide layers in different proportions. The thermal stability of the composite material has been enhanced, which has been affirmed by thermo gravimetric investigation [18].

Characterization:

The characterization of the composite is useful in determining the formation of the material and also to study the interaction of the clay minerals with the polymers. The selection of appropriate interpretation is also important as incorrect or lack of sensitivity in the instrument leads to wrong confirmation about the clay composite.

Fourier-transform infrared spectroscopy (FT-IR):

The use of IR spectroscopy can be done to determine the elements and functional groups in clay minerals. The elemental analysis of the clay minerals gives the detailed information about elements present.

X-ray diffraction (XRD):

XRD is used to determine the variations in the layers of clay minerals due to the composite hydrogel formation. XRD determines the spaces between the layers in the clay. The peaks of x-ray diffractogram confirm the layer separation or d-spacing in the layered structure of clay.

The increase in the d-spacing indicates entry of polymer between the layer spaces and intercalated structure. The absence of peaks which appeared in the pure clay x-ray diffractogram indicates the exfoliation of clay in composite hydrogel [19].

Elena et al. incorporated closite 30B (montmorillonite) into polyvinyl alcohol and chitosan polymers for the composite. Increase in the d-spacing from 1.81 to 1.89nm and lowering of 2θ from 4.85° to 4.66° indicating the intercalation of the polymers into the layers of closite 30B [20].

Surface morphology

The surface morphology of the clay composite hydrogel helps in understanding the interaction of polymer clay and also to determine the intercalation. The absence of peaks is not prominent to indicate that the exfoliation of the clay is obtained.

Transmission Electron Microscopy (TEM):

The TEM helps in studying the spaces in nm range due to which the clay exfoliation can be determined properly. The disappearance of the peaks doesn't confirm the exfoliation of the layered silicates [19].

Scanning Electron Microscopy (SEM):

SEM is used to determine the morphology of the material like the optical microscopy but this has an efficiency to analyze in nm range. The composite morphology study helps to determine the particle size (if nanocomposites), to check presence of any pores in the composite.

Thermal analysis:

The thermal analysis of the composite hydrogel is compared with the hydrogel without clay and the change in the thermal degradation process due to the addition of the clay is studied. In many cases the addition of the clay has improved the thermal stability of the composite when compared to the polymer or the hydrogel. Campbell et al, the composite of montmorillonite (MMT)/hydroxyl ethyl methacrylate showed an improvement the thermal stability with the addition of MMT. There was no change when a very small portion of 2% is added,

10% and 20% MMT showed a better thermal stability which could be due to heat barrier effect of MMT [10].

Swelling studies:
The swelling behavior of the composite hydrogel helps in estimating the release pattern of the drug, as the water intake helps in release of the drug. The swelling studies are carried in suitable solutions like water, simulated gastric fluids or pH solutions.
Swelling ratio = $(W_2 – W_1/ W_1) * 100$
Where, W_1 = weight of dry composite hydrogel, W_2 = weight of swollen composite hydrogel.

The swelling studies can be used to determine nature of composite like pH, temperature effect on the composite [10].

Drug loading methods:
The drug loading is done by adsorption or direct addition. In the adsorption method, drug loading is done after the complete synthesis of the composite. The material is soaked/ allowed to swell in the drug solution until maximum or complete entrapment of the drug. Then the composite is dried. In direct addition, drug is added to the composite during the synthesis process, into the polymer solution. Wen Fu Lee and others loaded different substances in mucoadhesive acrylic acid, composed of poly (ethylene glycol) methyl ether acrylate bentonite by adsorption. These release studies showed the effect of drug loading, polymer-drug interactions, the nature of the swelling of the material in the release models [21]. Qin Wang et al have loaded Diclofenac sodium into the composite by direct addition and the amount of loading of drug has been improved with increase in clay content [22].

Entrapment efficiency:
The amount of drug loaded in the composite is been estimated by studying entrapment efficiency of the material. It is performed by adding a known weight of the composite to release the drug in the required media of known volume. After the determined time, the solution is filtered to microfilter or centrifuged to remove the particles and the drug loaded is analyzed using the UV-visible spectrophotometer [4, 21, 22].

Entrapment efficiency% = (amount of drug in composite/ initial weight of drug) X 100

Drug release studies (*in vitro* and *in vivo*):
Based on the route of administration and the site of action of the composite hydrogel the in vitro studies are performed as follows. If topical administration or diffusion is involved then Franz diffusion cell is used. For GIT, the dissolution apparatus with the simulated gastric fluid as media is used. The UV-Visible spectrophotometer is used in the analysis of samples collected at predetermined time intervals for estimation of drug release[4, 14, 17, 21, 22].

In vivo analysis is performed on animals or tissues to study the effect. The selection of the tissue or animal depends on the route of administration [4, 23].

CONCLUSION:

The composite hydrogels have gained lot of research value in the recent years for modified drug delivery systems. The material carries the properties of the hydrogel along with it even in the composite form and most of the properties are improved.

The composite hydrogels can be used in drug delivery systems for its targeted site action, prolonged release, inexpensive and of all the clay are biocompatible and used as excipients, fillers in the pharmaceutical industry and even in composites. The composite hydrogels can be used for hydrophilic and hydrophobic drug delivery because the presence of clay material has improved the solubility and also the drug entrapment efficiency due to increased surface area.

LITERATURE ON COMPOSITE HYDROGEL:

S.no.	Clay	Drug and category	Materials	Results	Reference no.
1.	Montmorillonite (MMT)	Paracetamol-NSAID	2-hydroxy ethyl methacrylate, N, N-MBA, KPS.	The addition of MMT to hydroxyl ethyl methacrylate decreased the burst release of paracetamol from composite hydrogel.	10
		5- fluorouracil-Anti cancer drug	Acrylamide, TEMED, N, N-MBA, APS, sodium dodecyl sulphate.	The characterization of polyacrlamide/MMT revealed the increase in swelling and good conglomerated material. The controlled drug release was analyzed in vitro by MCF-7 and Hela cells.	14
2.	Bentonite	Vitamin B2, B12 and release of phenol red, crystal violet.	Acrylic acid, poly(ethylene glycol) methyl ether acrylate, N, N-MBA, diethyoxyacetaphenone (photo initiator).	Photopolymerisation technique. The increase in bentonite didn't decrease the mucoadhesive nature and increased the drug release time.	21
3.	Attapulgite	Ciprofloxacin-antibiotic drug.	N-isopropyl Acrylamide, N, N-MBA, cetyl trimethyl ammonium bromide, sodium metabisulfite	With the addition of attapulgite, improvement of drug relese rate in pH 7.4 buffer at 37° C. The swelling studies showed temperature dependency as the polymer is temperature sensitive.	24
		Diclofenac sodium- NSAID	Chitosan	The spray drying of the clay polymer solution produced microspheres of narrow size distribution. There was improved entrapment efficiency and controlled drug release.	22
		Diclofenac sodium- NSAID	Guar gum, sodium alginate, acrylic acid, APS, N, N-MBA.	The attapulgite in the hydrogel beads decreased the burst release of the hydrogel.	25
4.	Vermiculite	Diclofenac sodium- NSAID	Chitosan, acrylic acid, sodium alginate.	The composite showed pH sensitivity as the hydrogel and drug release is remarkably slowed from composite	26

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CONFLICT OF INTEREST:
The authors declare no conflicts of interest.

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