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Research Article

Polymeric *In-situ* Gels as Smart Carriers for Pesticide Delivery in Agricultural Practice

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ABSTRACT

Agriculture is the backbone of our economic system which had been associated with the production of basic food crops. Tremendous benefits have been derived from the use of pesticides in agriculture, forestry and other sectors. They are used to control pests, diseases and weeds, but conventional pesticides can contaminate surface water through runoff from treated plants and soil which results in incomplete release of the molecules and short residence time at the required sites. To overcome this drawback and to maximize the utilization of these pesticides, *in-situ* gel formulation would be an effective alternative. *In-situ* gelling polymeric delivery system is a novel technique in which the active ingredient present in the form of solution gets converted into a gel upon application to the site of action. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation; the *in-situ* gel formulation can sustain the release and also reduce the frequency of administration. So it is widely applied in drug delivery for ophthalmic, nasal, rectal and vaginal route of administration for improving both local and systemic effects of drug, and thereby its bioavailability. The objective of this review is to explore such new trends adapted for pesticide delivery systems to enhance the food production. Recently, these types of approaches are being explored in pesticide delivery systems to control various infections.

Key words: Agriculture, weed, conventional, *in-situ*, pesticide.

INTRODUCTION

*Importance of agriculture:*India is an agricultural country and, demographically agriculture is the broadest economic sector and it also plays an important role in the overall socio-economic fabric of India. Agriculture provides food and raw materials; in addition to that it also provides employment opportunities to around 70 percent of the total population. An impressive growth has been attained in the Indian agriculture in the production of food grains after the production and usage of pesticides and high yielding varieties of seeds. Wheat and rice are the world's major food staples and India ranks second in its production and ranks third in the production of dry fruits. India also accounts for 10 percent of the overall world fruit production and ranks first in the production of sapota and banana. In the economic survey of 2013, it has been stated that the agricultural growth rate was falling short of the 4 percent target in the last five years due to plant diseases, pests affecting crops and absence of high yielding varieties of seeds and lack of research and development in this area. Therefore the agricultural sector requires further reforms to achieve greater productivity and efficiency for sustaining growth. The survey also noted that for India, improvement in the crop yields holds the key to remain self-sufficient in food grains, which requires better research and development skills [1]. Research scientists are now working on new fields like nanotechnology, stem cell research and also in novel formulation approaches for the delivery of pesticides.

Uses of plants: Plants are the backbone of all life on the earth and it also acts as an essential source of proteins and other essential nutrients for human being. The process of producing sugar and oxygen from carbon dioxide and water with the help of sunlight is called photosynthesis. As a result of reaction between carbon dioxide and water, oxygen is formed and through the stomata of the leaves, it is expelled from plants. Plants are more essential for human nutrition because they provide fruits which are rich in vitamins, carbohydrates, fiber and vegetables which are rich in minerals and vitamins and therefore play a key role in maintaining health. They are also essential for animals since they act as the ultimate source of metabolic energy and food for most of the herbivorous animals [2]. Plants also have many industrial uses such as wood for furniture, doors and beams. They also provide paper pulp, fibers and components such as tannin for tanning leather, soaps, shampoos, essential oils and perfumes for the cosmetics industry and plastics, lubricants and rubbers for the automotive industry. Plants bring natural beauty to the houses; when the interior spaces are embellished with house plants, more than adding greenery these living organisms make an interaction with human body, mind and home in such a way that it enhances the quality of human life. Recently, herbal plants are largely used to develop

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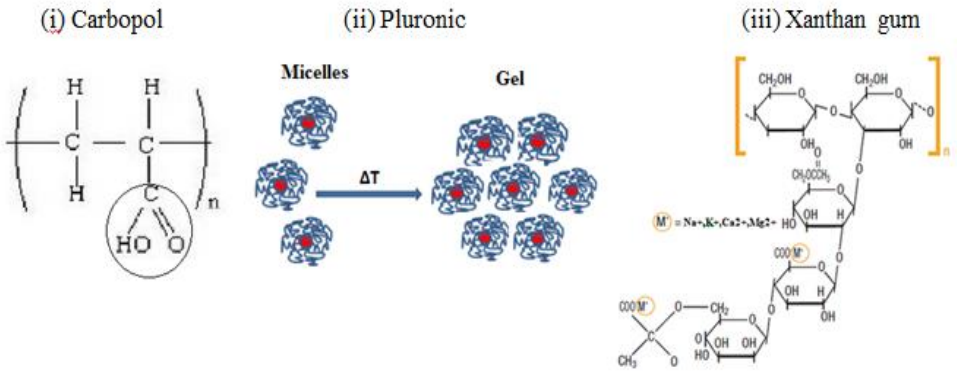

Fig 1: Gelling mechanisms of different polymers

cosmetics, toiletry formulations, personal care products and pharmaceuticals.

Table 1: Mechanisms of *in-situ* gelling using different polymers:

S.No	Type	Condition of gelling	Polymers
(i)	pH	pH-7 and above.	Carbopol, Para – Methoxy – N-Methylmphet Amine (PMMA), Poly Ethylene Glycol (PEG) [12].
(ii)	Temperature	Temperature raise of 30 to 35° C	Pluronics, Tetronics, Xyloglucans [13].
(iii)	Presence of ions	Presence of divalent cations (K^+, Ca^{2+}, Mg^{2+}, Na^+)	Gelrite, Gellan gum, Alginate.

Plants are the natural medicines; since ancient times the properties of medicinal plants have been used to cure various diseases. Medicinal plants are very promising therapy at present and natural remedies are gaining much interest with a basic approach towards nature. Medicinal properties that are obtained from the plants could come from different parts of a plant including leaves, roots, fruits, flowers, seeds and bark [2]. Many infectious diseases are being treated with herbal plants; some plants are considered as the most important source of nutrition and therefore recommended for their therapeutic activities.

Functions of different plant parts: The major sites of nutrition production for plants are the leaves and they are considered to be the powerhouse of plants. The molecule which utilizes the energy in sunlight and converts carbon dioxide and water into oxygen and sugar is chlorophyll and this process is also called photosynthesis. Leaves are made up of different layers which are sandwiched between two layers called epidermis. Chloroplasts are absent in the upper and lower epidermis and therefore photosynthesis do not occur there. In the epidermal cells, a pair of sausage shaped guard cells is present which forms pores called stoma which are responsible for air exchange; they let the gas carbon dioxide in and oxygen out. Photosynthesis occurs in the mesophyll cells where chloroplasts are present. Production of nutrition takes place in the elongated cells called palisade mesophyll. Gas exchange specifically takes place between the air spaces which are present between the oddly shaped cells of spongy mesophyll. Veins that are filled with vessels support the leaf and help in transportation of water, food and minerals to the plants [3].

Roots that grow under the ground act like straws and help in absorbing water and nutrients from the soil, tiny roots that stick out of the root help in efficient absorption. Roots also help in anchoring the plant in the soil. Stems act like the plumbing system of the plant by holding the leaves, roots and flowers. They provide support to the plant by distributing nutrients from the roots; they also supply food from the leaves in the form of glucose to other parts of the plant [3]. Flowers contain pollen and ovules; pollination occurs in flowers and therefore called as reproductive part of most plants. Flowers play a major role by providing covering for seeds; they also help in scattering the seeds away from the parent plant. Seed that form in fruits are the fundamental means of reproduction; which contain the new plants.

Diseases of plants: Diseases occurring in plants lead to the impairment of the normal state of the plants that modifies or interrupts the vital functions of the plant. Plant diseases causing pathogens take away energy from the plants on which they survive: the pathogens can be viruses, bacteria, fungi, nematodes, oomycetes, protozoa, parasitic plants and phytoplasmas. The pathogens are responsible for a huge deal of damage and they are characterized by scabs, rusts, wilting, mouldy coatings, blight, damping-off, rotted tissues and blotches. The symptoms of these diseases include death and destruction of host tissues, abnormal growth, wilting and discoloration of host tissues[4]. Many crop plants provide ample of food for human consumption and there are also numerous plants that have nutritional values that are grown very intensively. Loss of crops due to the occurrence of plant diseases would result in hunger and starvation and this has an immense impact in the less developed countries. Pesticides are effectively used to overcome the occurrence

Table 2: *In-situ* gelling system of drugs using different mechanisms:

Drug	Route of drug delivery	*In-situ* gelling mechanism	Polymers	Inference
Hp-β-CD-Voriconazole	Ocular	Temperature	Pluronic F-127 (or) Pluronic F-68 + Sodium Alginate	Prolonged drug release and retained its properties against fungal infection [14].
Itraconazole	Vaginal	Temperature	Poloxamer 407 and 188 + HPMC	Effective alternative for the treatment of vaginal candidiasis with suitable textural and rheological properties [15].
Clotrimazole	Oral	pH	Carbopol 934+ HPMC	Therapeutically efficacious, stable and provided controlled release upto 6hrs [16].
Diclofenac potassium	Ocular	Ion	Sodium alginate + HPMC	Sustained release, improved patient compliance [17].
Brimonidine tartrate	Ocular	Ion	Gelrite	Sustained release over a period of 8hrs [5].
Clindamycin HCl	Vaginal	Temperature	Poloxamer 127 + 188	Formulation- isotonic, Easy to administer, good bioadhesion and retention property [16].
Levetiracetam	Intragastric	pH	Sodium alginate + Calcium carbonate.	Extended drug release – 12 hrs [17].
Salbutamol Sulphate	Nasal	pH	Carbopol 934 + HPMC	Sustained release over 8 hr. and better patient compliance [13].
Betaxolol	Ocular	Temperature	Pluronic F-127 + HPMC E50LV	Controlled drug release, greater potential for glaucoma therapy [6].
Diltiazem HCl	Oral	Ion	Sodium alginate + HPMC	Sustained release over 8hours [20].
Nimesulide	Rectal	Temperature	Poloxamer 407 + Sodium Alginate	No mucosa irritation, higher Cmax and AUC of Nimesulide compared to solid suppository [21].

of plant diseases and to reduce the damage caused by them.

Pesticides: Tremendous benefits have been derived from the use of pesticides in agriculture, forestry and other sectors: Pesticides are also used in the protection and enhancement of lawns, public parks, gardens, playing fields, ponds and lakes for public enjoyment. Pests are considered as a menace by the farmers; pesticides play a major role in controlling the pests. To reduce the level of crop damage by pests, weeds and diseases, pesticide use is highly appreciated. Pesticides are the substances which prevent, destroy and mitigate any pest; commonly used as plant protection products. Generally, a pesticide is a biological or chemical agent which detects and kills the pests [4]. Target pests include insects, plant pathogens, roundworms and microbes that could destroy the plant property and spread diseases. The other indirect benefit of pesticides is decrease in the cost of food, as the use of pesticides leads to the improvement in the crop yields. The crop protection technologies impact the price of food. Because without the crop protection chemicals, production of food would decline; this would result in short supply and high price of many fruits and vegetables.

Pesticides are of many types: organophosphate pesticides, carbamate pesticides, Organochlorine pesticides, sulfonylurea pesticides, pyrethroid pesticides and biopesticides. Each type of pesticide is meant to be effective against specific category of pests.

Limitations of conventional pesticides

Pesticides are found to have the following limitations

a. By the action of rain water, pesticides percolate into the soil and get mixed with ground water which results in contamination.
b. Lighter and toxic compounds get suspended in to the air while spraying the pesticides which in turn results in nasal infection and air borne diseases for people who inhale the compounds.
c. Due to over use of the chemicals, resistance can be developed in the target pests towards the pesticide.
d. Runoff of chemicals and careless application can lead to environmental pollution which results in wildlife and fish losses.
e. Pesticide active ingredient loss can occur in the atmosphere through several pathways. The main pathway is found to be evaporation drift [4].
f. The main problem with conventional agrochemical applications is using greater amounts of agrochemicals, over a long period of time, than what is actually needed, possibly leading to crop damage and environmental contamination The local concentration of the active

ingredient is not maintained in case of conventional formulations.

g. Short residence of the pesticide formulation on the surface of the plant which may lead to incomplete absorption of the active ingredient by the plant.
h. Increased frequency of administration and poor availability for its action.

In-situ gelling systems:

In-situ gel forming systems have been known for their uses in various biomedical applications including the drug delivery systems. *In-situ* gels are polymer based liquids and they are colloidal solution in nature; these systems on exposure to the physiological conditions undergo sol to gel phase transition. *In-situ* gelling systems can be classified as ion activated systems, temperature dependent systems and pH triggered systems. The main advantage of *In-situ* gel over conventional formulations is that they can prolong the residence time of the drug due to the gel formation [5]. The sol-gel-sol transition occurs by physical and chemical changes that are induced by the physiological environment. This approach combines the advantages of both solutions and gels, such as accuracy in the amount of dose as solution or spray and prolonged residence time of the drug in the form of gel [6].

In-situ gelling polymeric drug delivery system can also be applied for the delivery of pesticides in agriculture. The system delivers accurate dose as well as prolongs residence time of drug, thus overcomes the problems generally encountered in conventional agrochemicals. Sustained release polymer matrix systems are more advantageous that it allows the automatic release of the agent to the target at a controlled rate and to maintain its concentration in the system within the optimum limits over a required period of time, thereby providing great specificity and persistence without diminishing efficiency [7]. Controlled release of agrochemicals (pesticides, herbicides, nutrients) is used to maintain the local concentration of active ingredients in the soil and to reduce losses due to run off.

The macromolecular nature of polymers is the key for the reduction of chemical loss throughout the production. Controlled release is a method by which the active agents are provided to certain plant species at predetermined rates and times. Controlled release polymer systems can be divided into two major categories. In the first category, the active agent is dissolved, dispersed, encapsulated or coated within the polymeric matrix. Through diffusion or after the biological or chemical breakdown of the polymer, the release of the active agent takes place. In the second category, the active agent either constitutes a part of the macromolecular backbone or attached to it. In the case of pesticides, the release of the active agent is the result of biological or chemical cleavage of the bond between bioactive agent and the polymer [7].

Mechanisms of in-situ gel formation in plants:

Chlorophyll is a green lipophilic compound which is found in leaves and also in the green stems of plants; it is of five types A, B, C, D and E in which types A and B are mainly found in plants. Type A Chlorophyll is used in oxygenic photosynthesis and it is also essential for photosynthetic organisms to release the chemical energy: it is one of the most important chelates in nature which has the capability of channelling the sunlight energy into chemical energy through photosynthesis.

Several mechanisms of *in-situ* gel formation can be applied in plants. In case of ion activated method, the characteristic of chlorophyll type A is found to satisfy the mechanism of *in-situ* gel since the structure of chlorophyll includes an Mg^{2+} ion at the centre of the chlorin ring. Magnesium plays a major role in the production of chlorophyll and in the plant growth. It has been proven that certain ion sensitive polymers such as Gellan gum, carrageenan, sodium alginate and pectin undergo sol to gel phase transition in the presence of monovalent and divalent cations such as K^+, Mg^{2+}, Ca^{2+}, Na^+ [8, 9]. It is also very well known that calcium which is distributed throughout the plant is an essential plant nutrient and plays an important role in the plant growth, nutrition and in the cell wall deposition. By the formation of cross-links within the pectin polysaccharide matrix, calcium produces strong structural rigidity of the cell wall. Along with the rapid growth of plants, it also strengthens the structural integrity of stems and the quality of fruits that are produced [10, 11].

In case of pH based mechanism, it has been proven that the pH based formulations prepared using pH sensitive polymers such as Carbopol, PEG undergo sol to gel transformation upon increase in pH. The pH of the plants is found to be neutral; when the pH based formulations are developed at a pH within 6, they exist as sol and have the ability to form a gel when it is sprayed over the plants [12]. In case of the pH sensitive polymer Carbopol, the gelling mechanism occurs in the COOH group, the region which is responsible for cross linking. In the case of temperature triggered mechanism, temperature of the environment depends upon the season. But the average temperature of the environment is calculated to be in the range between 25 to 30° C. The mechanisms of *in-situ* gelling systems using different polymers are given in table 1.

From the previous literatures it has been identified that thermosensitive polymers such as Pluronic undergo phase transition from sol to gel when the temperature is raised from cool temperature to the room temperature [13]. In case of temperature sensitive polymer pluronic, the mechanism of gelling is entirely different from cross linking. Here, unimers form micelles which upon increase in temperature form a gel. The gelling mechanisms of the polymers following different mechanisms are given in the fig1. List of drugs that are formulated as *in-situ* gelling systems using different kinds of polymers for sustained release effect are given in table 2.

Applications of in-situ systems:

a. *In-situ* chemical oxidation is a rapidly growing remedial technology which is applied at hazardous waste sites in which a chemical oxidant is introduced into the subsurface which transforms groundwater contaminants into less harmful chemical species [27].
b. *In-situ* conservation of genetic resources preserves both the evolutionary processes and the population that help the population for adaption by managing the organisms in their natural state.

c. In agriculture, *in-situ* conservation technique is the most suitable way for the improvement, maintenance and usage of native or traditional varieties of agricultural crops [28].
d. *In-situ* voltammetric speciation analysis is highly used in aquatic systems which demand the improvement of the voltammetric devices [29].
e. In chemistry, *in-situ* synthesis of chemical intermediates is performed in various processes.
f. *In-situ* recovery or *in-situ* leaching refers to a mining process in which the water is injected underground to dissolve the ore and to bring the uranium impregnated water to the surface for extraction [30].

CONCLUSION

Based on the possibilities of sol to gel phase transition in green leaves and green stems, pesticides can be formulated as polymeric *in-situ* gelling system using ion activated, temperature sensitive and pH triggered mechanisms. It is very well known that *in-situ* gelling polymeric drug delivery systems increase the residence time of the drug in the target site and also the drug efficacy and availability. This also decreases the frequency of administration of the drug. So if pesticides were formulated as *in-situ* gel, it would be beneficial in increasing the crop yield; it would reduce the toxicity level by avoiding frequent spraying of pesticides, avoid run off of chemicals. The most important advantage of formulation of *in-situ* gel of agrochemicals is that it would sustain the active ingredient in the surface of leaves for a longer period whereas conventional pesticide solutions get evaporated leading to incomplete effect of the component.

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