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NASAL IN-SITU GEL: NOVEL APPROACH FOR THE TREATMENT OF NEUROLOGICAL DISEASE LIKE DEPRESSION

***Vaishnavi N. Ghati, Pankaj R. Dhapke[1], Nilakshi N. Dhoble[1], Nitin Padole[1] and Jagdish R. Baheti[1]**

*Department of Pharmaceutics Kamla Nehru College of Pharmacy, Butibori, Nagpur.
[1]Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur 441108, Maharashtra, India.

***Corresponding Author: Vaishnavi N. Ghati**

Department of Pharmaceutics Kamla Nehru College of Pharmacy, Butibori, Nagpur.

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ABSTRACT

The treatment of neurodegenerative and psychiatric disorders remains a challenge in medical research. Several strategies have been developed over the years, either to overcome the blood-brain barrier or to achieve a safer or faster brain delivery, one of them being intranasal (IN) administration. Many pharmaceuticals are commonly delivered via oral ingestion (e.g., tablets or capsules) or through parenteral injection, especially when substances are susceptible to degradation in the gastric environment or lack absorbability. Nonetheless, these methods present drawbacks, such as challenges associated with swallowing tablets and the need for trained personnel and sterile environments to mitigate contamination risks during parenteral administration. The possibility of direct nose-to-brain transport offers enhanced targeting and reduced systemic side effects. Conventional nasal drug delivery systems, encompassing solutions, suspensions, and ointments, exhibit inherent limitations such as brief retention within the nasal cavity, substantial variability in efficacy, diminished permeability and impracticality in terms of administration. In-situ forming gel drug delivery systems with the capability to circumvent the blood-brain barrier, target specific sites for therapeutic delivery, mitigate peripheral toxicity, and regulate drug release kinetics, have been formulated. The optimal mode of administration for this drug has been achieved through the formulation of mucoadhesive and thermoreversible gel preparation for various pharmaceutical compounds.

KEYWORDS: Conventional, therapeutic delivery, thermoreversible, permeability.

INTRODUCTION

DEPRESSION

The central nervous system (CNS) constitutes a highly intricate component of the human organism, overseeing complex physiological processes. The blood-brain barrier (BBB) represents a primary impediment in the delivery of pharmaceutical agents to the brain.[1] The blood-brain barrier (BBB) is the most important physical barrier in brain drug delivery, being estimated that all macromolecular compounds, and over 98% of low molecular weight drugs, are unable to permeate it, leading to a very low drug bioavailability at the desired target site. Among the strategies to surpass the BBB's low permeability to non-lipophilic drugs, it is possible to consider the bypass offered by the nasal route, commonly called intranasal (IN) delivery.[2] Depression is a multifactorial psychiatric disorder, widely prevalent in the human population, characterized by a deficiency in the availability of neurotransmitter's particularly norepinephrine and serotonin.[3] In order to treat depression, we have to increase the levels of NA and 5-HT.3.[4]

According to the world health organization (WHO), depression is a prevalent mental disorder typified by a despondent mood, diminished interest or pleasure, sentiments of guilt or diminished self-worth, disrupted sleep or appetite patterns, reduced energy levels, and impaired concentration.[5]

Neurological disorder exerts a pervasive impact on a multitude of individuals across the globe. According to the WHO, the prevalence of dementia stands at an estimated 47.5 million people worldwide, with an additional 77 7.7 million new cases being documented annually.[5]

TYPES OF DEPRESSION

Major depressive disorder (MDD) is characterized by a confluence of symptoms that impede functionality in areas such as occupational performance, sleep patterns, dietary habits, and the capacity to derive pleasure from previously enjoyable activities. These incapacitating episodes of depression may manifest singularly, intermittently, or recurrently throughout an individual's lifespan.[6]

Bipolar disorder, colloquially referred to as manic depression, involves cyclic fluctuations in mood, oscillating between states of elevated euphoria (referred to as "high") and periods of depressive ideation (characterized by a "low" emotional state.[7]

Dysthymia: Dysthymia, a variant of depression, is characterized by a milder yet typically more enduring nature in comparison to major depression. It entails persistent (chronic) symptoms that, while not incapacitating, hinder the affected individual from operating at optimal capacity or experiencing a sense of well-being.[7,8]

CAUSE OF DEPRESSION: The primary cause of depression is the disturbances in the monoaminergic i.e. norepinephrine, serotonin, dopamine transmission in brain due to complex interaction of several social, psychological and biological factors. Some other causes are.[9]

- Brain chemistry. There may be a chemical imbalance in parts of the brain that manage mood, thoughts, sleep, appetite, and behaviour in people who have depression.[10]
- Family history. You're at a higher risk for developing depression if you have a family history of depression or another mood disorder.[11]
- Early childhood trauma. Some events affect the way your body reacts to fear and stressful situations.[12]
- Substance use. A history of substance or alcohol misuse can affect your risk.[13]
- Pain. People who feel emotional or chronic physical pain for long periods of time are significantly more likely trusted Source to develop depression.[14]

SYMPTOMS

Sleep disturbance 2. Interest/pleasure reduction 3. Guilt feelings or thoughts of worthlessness 4. Energy changes/fatigue 5. Concentration/attention impairment 6. Appetite/weight changes 7. Psychomotor disturbances 8. Suicidal thoughts 9. Depressed mood.[15]

MECHANISM OF DEPRESSION

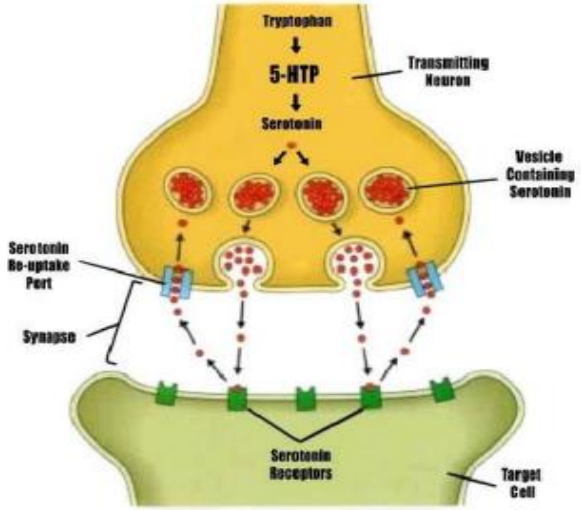

Figure 1: Illustrates the signalling from the presynaptic serotonergic neuron to the postsynaptic neuron mediated by serotonergic neurotransmission.

Serotonin is synthesized from tryptophan released by vesicular transport. The serotonin transporter is located at the presynaptic neuron and mediates reuptake of serotonin from the synaptic cleft. The signal to the postsynaptic neuron is mediated by receptors The pathophysiology of depression has been linked, during the past 50 years, to disturbances in the brain's serotonin (5-HT) and norepinephrine (NE). First proposed to explain how tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) enhanced the neurotransmission of the monoamines, 5-HT and NE, the monoamine hypothesis developed over time. Nevertheless, although elevated concentrations of NE and 5-HT appear within 1-2 days, this theory is unable to explain why it requires antidepressant medication exposure of 2-3 weeks to reduce depression symptoms. As per the desensitisation idea, the delayed start of action of antidepressant therapy may be explained by the desensitisation of the 5-HT- and NE-receptors over prolonged therapy. Insufficient 5-HT and NE are released during depression, according to the dysregulation theory, which integrates the desensitisation and monoamine theories.[16]

TREATMENT[17,18]

Several classes of antidepressant therapy that are currently on the market include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors. Nevertheless, the therapeutic efficacy of these antidepressants is dependent on their continuous prolonged presence at the site of action in brain.

Classes of antidepressants	Examples
Tricyclic and tetracyclic antidepressants (TCAs)	Imipramine, clomipramine, maprotiline, amitriptyline, desipramine,
Reversible inhibitors of monoamine oxidase A (RIMAs)	Moclobemide, tranylcypromine
Serotonin modulators and stimulators (SMS)	Vortioxetine, aripiprazole, cariprazine
Selective serotonin reuptake inhibitors (SSRIs)	Sertraline HCl, Fluoxetine, amitriptyline Citalopram and Escitalopram, Paroxetine Vilazodone
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine, bupropion, Duloxetine Desvenlafaxine Levomilnacipran.
Noradrenergic and specific serotonergic antidepressants (NaSSAs)	Mirtazapine, mianserin

PATHWAYS TO THE CNS AND ADVANTAGES OF INTRANASAL DRUG DELIVERY

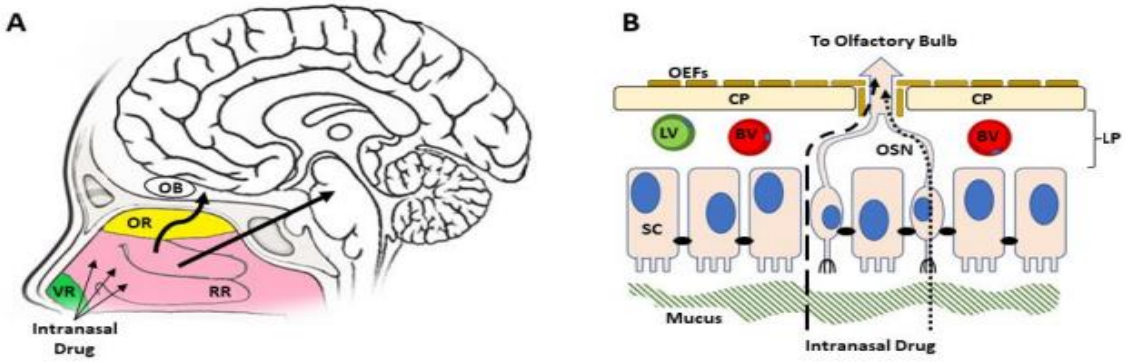

Figure 2: Intranasal drug delivery system.

The nasal cavity constitutes the foremost cephalic segment of the respiratory system, serving the primary functions of conditioning air for the respiratory pathway and facilitating the sense of olfaction.[19] The olfactory region, adjacent to the respiratory region, represents the primary site through which a drug can undergo direct absorption into the brain, eliciting central nervous system effects.[20,21]

In the intracellular mechanism, the olfactory neuron initiates internalization of the molecule through endocytosis, facilitating its uptake. Subsequently, the molecules undergo axonal transport to reach the olfactory bulb and are ultimately released through exocytosis. The extracellular pathway involves drugs traversing intercellular gaps between olfactory neurons in the nasal epithelium, followed by their transport to the olfactory bulb.[22,23]

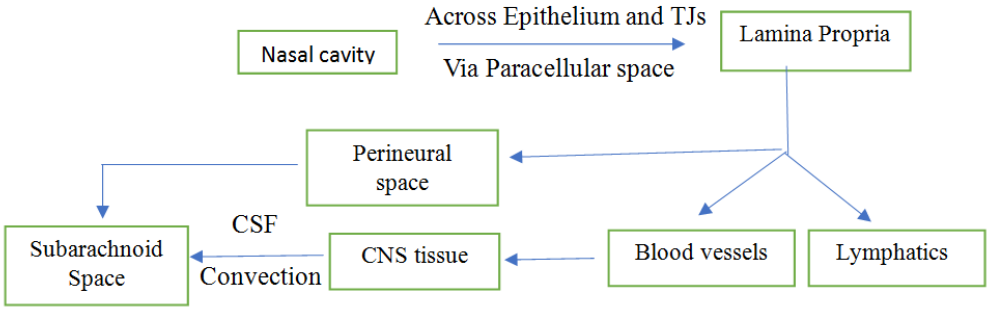

Figure: Flow chart illustrating the key aspects of the extracellular mechanism for transportation to the CNS following intranasal administration.

ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM[24]

- Absorption of drug is rapid via highly vascularised mucosa.
- A sizable nasal mucosal surface area that is available for dosage absorption.
- The action starts quickly.
- Simple to administer and non-invasive.
- Get around the Better Business Bureau.
- The drug's recognised degradation in the GIT is prevented.
- There is no hepatic first pass metabolism.
- Nasal absorption of tiny medicinal compounds is satisfactory.

- Enhanced absorption capacity

IN-SITU GEL: In-situ-based gel formulations are distinguished by their inclination to experience a sol-to-gel transition when introduced into the biological environment. When administered, these gels are initially liquid, but they change phases to become gels in response to external stimuli such as changes in pH, temperature, ion concentration, magnetic field, or biological environment.[3,25,26]

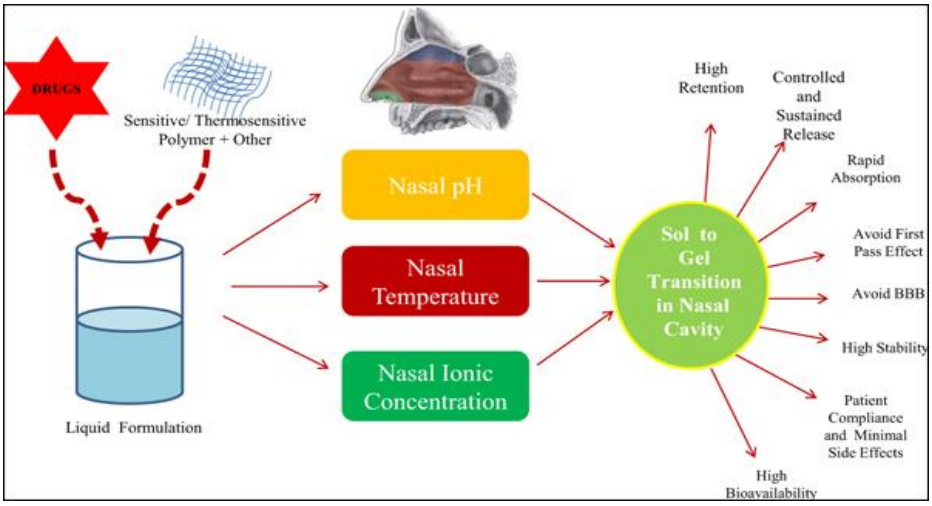

Figure no. 3: Benefits of *in-situ* gel by using thermo, pH, ion sensitive polymer.

APPROACHES

A continuous medication release from an in-situ gel could increase bioavailability and reduce the need for frequent dosage to improve patient adherence. As will be explained below, a variety of trigger mechanisms can cause a phase shift.[27]

1) Temperature-triggered in-situ gel: Poloxamer 407, sometimes referred to as Pluronic F 127, is the main polymer in this class and is widely used in the creation of in-situ nasal gel formulations. Another polymer that reacts to heat and is used to make in-situ nasal gels is chitosan. Phase transition is observed in both polymers at physiological temperatures. Temperature-responsive hydrogels are one of the most well studied environment-responsive polymer systems in drug delivery research. Their popularity is a result of their practicability and controllability, which are shown in both biological and laboratory contexts. Starting at room temperature (25°C), a polymer solution enters the gelation process. It reaches the target site and becomes gelled due to a temperature increase (35–37°C).[28]

2) Ion-triggered in-situ gel: Polymers that can undergo phase transition in the presence of ions are the means by which ions-activated gelation is accomplished. When gellan gum, an anionic polysaccharide, comes into contact with monovalent and divalent cations like Ca2+, Mg2+, K+, and Na+ that are present in nasal secretions, it experiences a phase transition known as the sol-gel transition.[29]

3) pH triggered in-situ gel: Carbopol 934 and carbopol 940 serve as crucial constituents facilitating pH-induced sol-gel conversion of formulations intended for nasal delivery. Changing pH is a common approach to perform sol-to-gel transition for pH-sensitive, water-soluble polymers. They usually undergo phase transition due to the functional groups on the polymers that either accept or donate protons as a result of pH changes in the environment. Chitosan is a cationic polyelectrolyte, whose solutions would exhibit a liquid–gel transition around pH 6.5, when pH changes from slightly acidic to neutral. Increasing the pH will deionize chitosan, thus generating the three-dimensional chitosan network due to physical junctions' hydrogen bonds.[30]

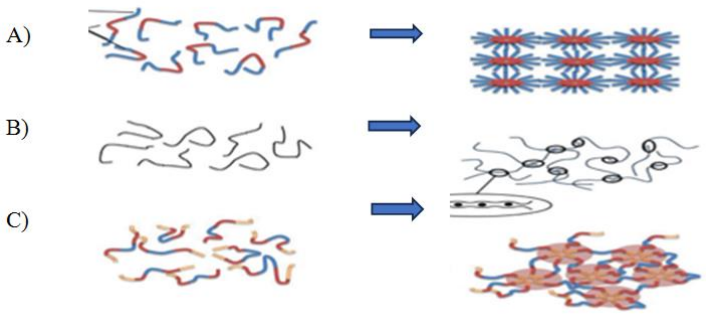

Fig. A) thermosensitive B) pH sensitive C) Ion sensitive.

METHOD OF PREPARATION

There are mainly two types of method to prepare in-situ gel

1) Cold Method: This dispersion contained the thermoreversible polymer (poloxamer), which was dissolved and then left at 4ºC for overnight. The procedure involved using a thermostatic magnetic stirrer set to 30 ºC to dissolve the polymer in water while swirling continuously. The mixture was then stirred while sodium cholate, polyethylene glycol 6000, sodium chloride (which served as a tonifying agent), and benzalkonium chloride (which served as a preservative) were added.[31]

2) Hot Method: Using deionized water to generate a polymeric solution of gellan gum and xanthan gum, the mixture was stirred mechanically for two minutes. Polymeric solutions were treated with preservatives, including mannitol, ethyl paraben, and polyethylene glycol (PEG), and they were then placed in a water bath for a short while. It was then allowed to cool to room temperature. After adding a modest amount of methanol to the drug, it was sonicated. After adding the drug solution, the beaker containing the polymeric mixture was constantly agitated until the drug had dissolved. After the prepared formulation was moved to a sterile glass container and filled to a capacity of 10 millilitres with distilled water, it was kept in a cool location.[32,33]

SOME EXAMPLES OF DRUG THAT IS MAINLY USED AS A ANTIDEPRESSANTS

Drug	Mechanism of action	Important effects	Important indications	Important ADRs
Amitriptyline[34]	NSMRI	Mood enhancing, sedative	Moderate to severe depression (level 3), anxiety disorders, migraine prophylaxis, neuropathic pain, nocturnal enuresis	ADRs result from the increased NE and 5-HT concentrations in the synaptic cleft, antimuscarinic syndrome, orthostatic hypotension.
Citalopram[35]	SSR	Mainly mood lifting	Moderate depression (level 1), anxiety disorders, obsessive compulsive disorders, panic disorders, phobia, post-traumatic stress disorder, phobia, adjunct therapy for schizophrenia.	ADRs result from the increased 5-HT concentration in the synaptic cleft; serotonin syndrome with overdose or when combined with MAOIs
Imipramine[36]	NSMRI	Mood enhancing, motivating, and sedative effects are balanced	Moderate to severe depression (level 3), co-analgesic for severe pain (e.g., tumour pain)	See amitriptyline

MATERIALS UTILISED IN IN-SITU NASAL GEL (POLYMERS)

Different natural and artificial polymers that react to pH, temperature, and ions have been added for the aim of delivering drugs. Some of these have been made available for purchase. Notably, polymers such as poloxamer, chitosan, gellan gum, pectin, carbopol, and xyloglucan are commonly used in nasal administration routes, though not without limits. In the sections that follow, the mechanics behind gel formation and other beneficial properties of these polymers in intranasal delivery are described.[37]

Poloxamer: Pluronic, or poloxamer in technical parlance, is marketed as a thermoresponsive gelling agent and non-ionic surfactant. At 25°C, the concentrated poloxamer solution shows thermoreversible gelation. It is often used in the pharmaceutical industry to create innovative dosage forms because of its unique gelation properties and non-toxic qualities. However, studies suggest that changes in intrinsic micellar behaviour and micelle entanglement at high temperatures may cause gelation. The PPO block becomes dehydrated as a result of the temperature increase causing methyl groups on the side chain to reorient. It also causes the water to be released from the micelle core. All of these elements work together to cause the poloxamer aqueous solution to gel.[38]

Chitosan: Because of its unique properties, chitosan, the only naturally occurring cationic polymer, has been widely used in a variety of applications. Moreover, it is easily prepared into solutions, hydrogels, pastes, films, fibres, and micro/nanoparticles due to its solubility in aqueous media. In addition to its antimicrobial and antioxidant qualities, which make it useful in medicine, chitosan has been shown to selectively chelate ions like iron, copper, cadmium, or magnesium. Notably, chitosan has many benefits and produces safe breakdown products that don't cause inflammation.[39]

Gellan gum: Formerly known as Pseudomonas elodea, the bacteria Sphingomonas elodea secretes gellan gum, a linear anionic polysaccharide. It is composed of 1β-l-rhamnose, 1β-d-glucuronic acid, and 2β-d-glucose in the molar ratio 1:1:2, forming a tetra saccharide repeating unit.47 Acetate and l-glycerate are used to partly esterify the original polysaccharide.48 The degree of acylation

determines how quickly it gels and is triggered by cations. Therapeutic Drug Carrier Systems: Left Critical Reviews TM 418 Acylated gellan, according to Wang et al., creates elastic, translucent, and flexible gels. It can create brittle, rigid, nonelastic gels after deacylated. Gellan gum offers a possible path towards the production of in-situ gels for use in medication delivery and regenerative medicine. Among the many benefits these gels provide are reductions in medication irritation, prolonged retention time of drugs at specific target locations, precise control over drug release kinetics, and ultimately enhancement of drug bioavailability and therapeutic efficacy.[40]

Pectin: pectin is a naturally occurring polysaccharide made up of galacturonic acid methyl esters. The degree of galacturonic acid esterification determines the gelation characteristics of pectin. Gelation cannot be induced by additional ions if the esterified methoxy level exceeds approximately 50%. The hydrophilicity of pectin rises and it becomes more cation-sensitive as the degree of methylation decreases. Since low methoxyl (LM) pectin can gel upon contact with the nasal mucosa without the need for exogenous cations, it is the ideal pectin for use in nadication delivery.

The chainchain interactions described by the egg box mo del provides a better explanation for gelation.

Peptin's mucoadhesive properties are thought to result fr om the creation of secondary chemical connections betw een theSince LM pectin solution can gel upon contact with the nasal mucosa without the need for exogenous cations, it is the preferred option for medication delivery via the nasal mucosa. Pectin forms secondary chemical connections with the following substances to give it its mucoadhesive properties.[41]

Carbopol: Carbopol, a cross-linked polyacrylic acid with a high molecular weight, undergoes a sol-gel transition in aqueous solutions as the pH exceeds its pKa of 5.5. It contains a substantial proportion of carboxyl groups, which exhibit dissociation, leading to the formation of a flexible coil structure under acidic conditions. Upon exposure to an alkaline environment, these carboxyl groups ionize, resulting in the generation of negative charges along the polymer backbone. Electrostatic repulsion causes the expansion of the anionic groups, facilitating the entanglement of polymer chains and subsequent gel formation. Due to its outstanding mucoadhesive properties, Carbopol is widely utilized as a key constituent in gel-based drug delivery systems for various applications including buccal, transdermal, ocular, rectal, and nasal routes.[42]

Xyloglucan: Xyloglucan is a major hemicellulose component present in the cell walls of all vascular plants as well as many dicotyledonous plants. The structure is made up of a backbone chain of (1-4)-β-d-glucan and branches of (1-6)-α-d-xylose, which are partially replaced by (1-2)-β-d-galactoxylose. The precise configuration of xyloglucan exhibits variation among several plant taxa. The most widely used xyloglucan comes from tamarind seeds, which include three different xyloglucan oligomers: octa saccharide, Nona saccharide, and heptasaccharide. Each of these oligomers has a different amount of galactose side chains. Xyloglucan does not display thermoresponsive gelation in water in its natural state. Nevertheless, when heated, the result of β-galactosidase's enzymatic breakdown of xyloglucan exhibits a reversible sol-gel transition.[43]

CONCLUSION

Understanding the biology of major depression is a challenging scientific problem with enormous sociological and clinical relevance. From above study, I have concluded that novel drug delivery system like in-situ gel is effective and shows their prolonged effect on human body due to polymeric property of adherence. For nasal administration it is the most effective way to enhance brain drug delivery system. Hence, we can enhance the bioavailability of particular drug by increasing their adherence. Nasal route is the best route of absorption because it directly corelate with brain. Various polymers are used to show their effects according to pH, temperature, ion.

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