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Covid- 19 Management: A Comprehensive Review Of Sars-Cov-2 And The Potential Of Buccal In-Situ Gel As A Novel Drug Delivery Approach

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ABSTRACT

COVID-19 is a contagious viral disease caused by SARS-CoV-2 and is associated with respiratory complications ranging from mild to severe illness. Although antiviral drugs are available, conventional dosage forms show limitations such as poor bioavailability and frequent dosing. Buccal in-situ gel is a novel drug delivery system that transforms from sol to gel under physiological conditions. This system provides prolonged drug release, improved bioavailability, and better patient compliance. The present work reviews COVID-19, its treatment strategies, and the potential application of buccal in-situ gel as an effective drug delivery approach.

KEYWORDS: COVID-19; SARS-CoV-2; Buccal in-situ gel, Patient compliance, Antiviral treatment

1.1 INTRODUCTION OF COVID-19 VIRUS [1]

The human body is exposed to a variety of infectious microorganisms, such as viruses, bacteria, fungi, protozoa, and helminths, which cause tissue damage through different can manipulate the host-cell machinery in a unique way and continuously evolve to survive and prosper in all species. COVID-19 is the disease caused by a new coronavirus called SARS-CoV-2. The case reporting is based on the SARS- CoV-2 antigen testing by Real-Time Reverse Transcription Polymerase Chain Reaction (RT-qPCR) or by Rapid Antigen Test (RAT).

A pandemic novel coronavirus was named as ‘‘Corona Virus Disease 2019’’ (2019-nCoV) by World Health Organization (WHO) in Geneva, Switzerland. As its RNA pattern is closer to SARS, the 2019 Coronavirus is renamed as SARS CoV- 2pandemic. It belongs to the subfamily Orthocoronavirinae inside the family Coronaviridae, order Nidovirales, and the realm Riboviria. A two-dimensional view of Corona beneath a transmission electron microscopy reveals characteristic look of ‘‘paying homage to a crown’’ around the virions. This leads to naming the virus ‘‘Corona’ ’meaning ‘‘crown’’ or ‘‘halo’’ in Latin.

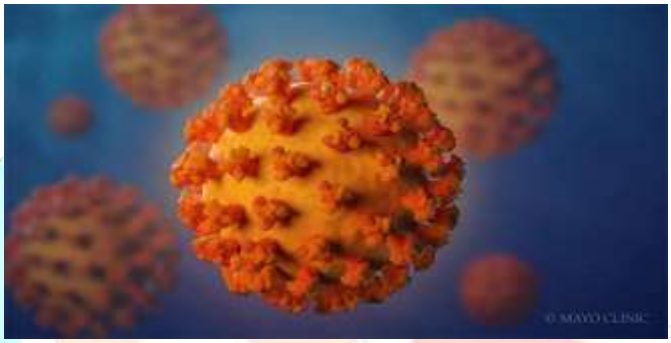

Fig 1.1: COVID-19 VIRUS

1.1.1 Causes of coronavirus [2]

The virus primarily spreads through the following means:

- **Airborne transmission:** Breathing in air that contains COVID-19 particles or having these particles land directly on the mouth, nose, or eyes.
- **Direct contact:** Touching the mouth, nose, or eyes with hands that have the virus on them, either through direct contact with an infected person or by touching contaminated surfaces.
- **Person-to-person transmission:** When an infected individual breathes, speaks, coughs, sneezes, or sings, they release particles containing the virus into the surrounding environment.

1.1.2 Sign and symptoms of Coronavirus [3]

People may only have a few symptoms or none. People who have no symptoms but test positive for COVID-19 are called asymptomatic.

People who go on to have symptoms are considered presymptomatic. Both groups can still spread COVID-19 to others.

Other symptoms include:

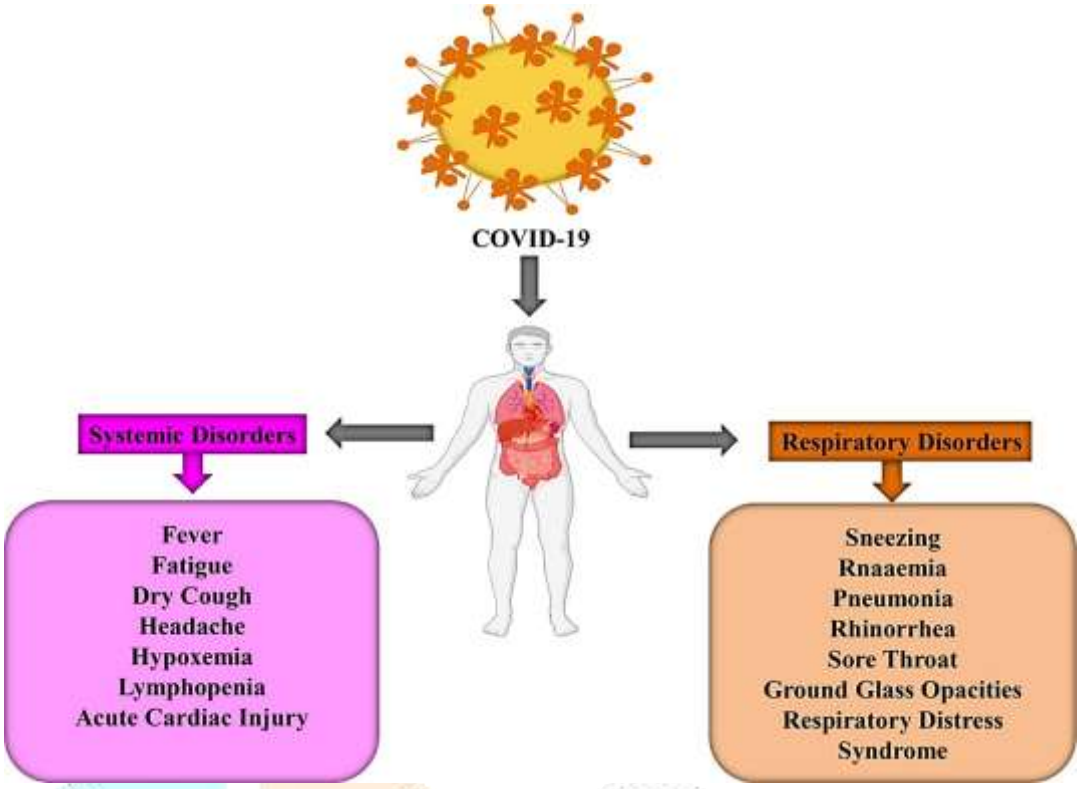

Fig 1.2: Symptoms of COVID-19

1.1.3 COVID-19 Variants [4]

While there are multiple versions of Covid-19 Variants, particular ones are most notable due to their infection rate/mortality rate. Here are the top versions.

Omicron Variant

This version was originally seen in South Africa. On 30 th November 2021, the SIG team under the U.S. Government declared the variant as a variant of concern. Compared to its predecessors, the omicron virus is considered the most dangerous.

WHO reports state that the virus is extremely contagious, highly mutated, and spread fast via contact. It holds more than 50 mutations, and 30 of them exist in the spike protein of the virus. Therefore, it can potentially infect vaccinated individuals as well.

Delta Variant

This variant was first visible in India, starting its spread over the region around October 2020. This was a dominant strain that rapidly spread throughout the region, affecting a lot of victims.

This variant's mortality rate is high and is considered one of the most dangerous covid variants. The common symptoms include difficulty in breathing, loss of taste or smell, drop in oxygen levels in the body, and more.

Gamma Variant

This started in Brazil in November 2020 and was classified as a variant of concern (VOC) in January 2021. The transmissibility rate here was 2.2 times more and affected mostly elderly individuals and adults.

MU Variant

This Covid variant was noticed in Colombia initially, starting its spread in January 2021. There were worrisome mutations noticeable in the virus' spike protein. However, its effect is less risky than Omicron.

1.1.4 Pathophysiology of covid-19 [5]

The pathophysiology of COVID-19 is a complex, multi-system process involving viral invasion, an imbalanced host immune response, inflammation, and blood clotting abnormalities.

The infection with the SARS-CoV-2 virus can range from asymptomatic to severe and life-threatening, particularly in high-risk individuals.

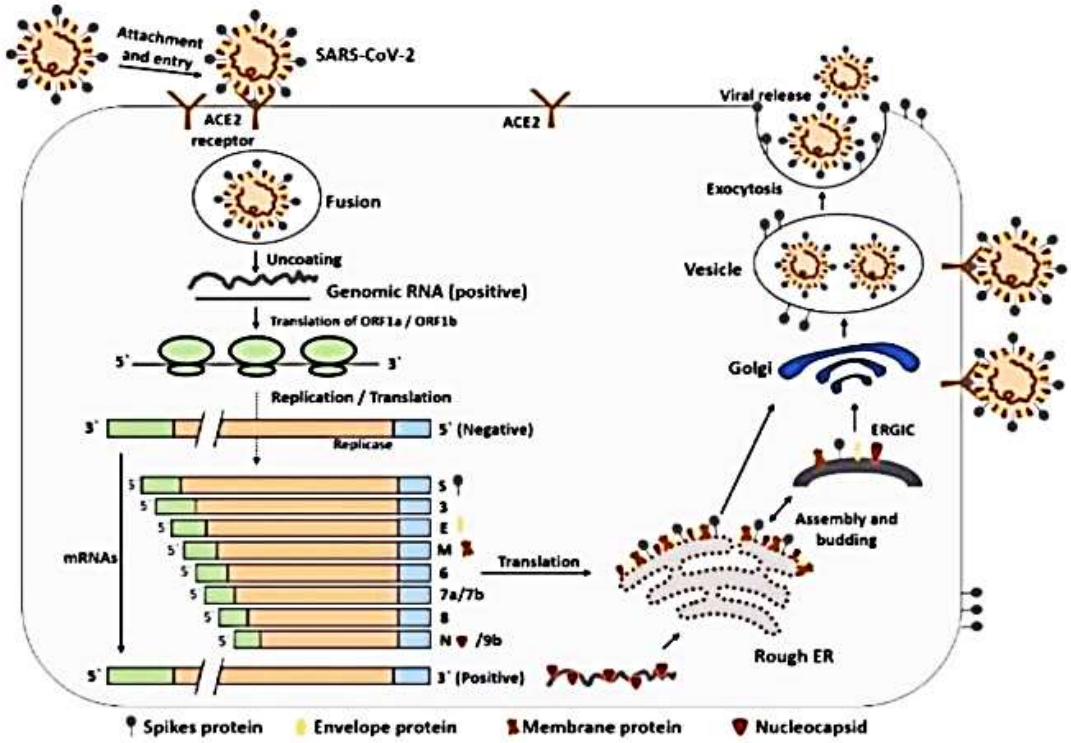

Fig 1.3: Pathophysiology of COVID-19

1.1.5 Treatment [6]

Primary treatment

- For mild case of COVID-19, healthcare provider may advise the patient to treat their symptoms at home with supportive care.
- Over-the-counter analgesic and antipyretic agents, such as ibuprofen or acetaminophen, may be administered to alleviate fever and Body aches.
- It is important to regularly monitor oxygen saturation levels, particularly in individuals at increased risk of developing severe illness.
- Prevent transmission by wearing a mask around others, washing their hands frequently, and not sharing personal items.

Antiviral medications for high-risk individuals

Paxlovid (Nirmatrelvir/Ritonavir): The preferred oral pill for adults and children (12+) at high risk of severe illness. It must be started within 5 days of symptoms.

Veklury (Remdesivir): An intravenous (IV) treatment for hospitalized and high-risk non-hospitalized patients (adults and children). Outpatient treatment typically involves a 3-day course.

Lagevrio (Molnupiravir): An oral pill authorized for adults (18+) when other treatments like Paxlovid or Remdesivir are unavailable or inappropriate. It must be started within 5 days.

Treatment for severe illness

- Patients who are very ill and require hospitalization may receive advanced treatments under the care of a medical professional.
- Supplemental oxygen or mechanical ventilation for breathing support.
- Corticosteroids, such as dexamethasone, to reduce excessive inflammation in the lungs.
- Immunomodulatory, including baricitinib (Olumiant) or tocilizumab (Actemra), for patients with high levels of inflammation.
- Convalescent plasma, from the blood of recovered individuals, may be used for immunocompromised.

1.2 INTRODUCTION OF BUCCAL *IN-SITU* GEL [7]

A buccal in situ gel is a drug delivery formulation designed to be administered in the mouth (on the buccal mucosa, i.e. the inner cheek or related oral lining), in a fluid (sol) form, which then transforms into a gel at the site of application, under physiological conditions (e.g. temperature, pH, or presence of ions).

Such systems combine the advantages of easy application (since the formulation starts as a liquid or low-viscosity sol) and improved retention (once gelled) on the buccal mucosa. They use polymers that respond to triggers in the oral environment to form a gel network that stays in place and releases the active drug locally or systemically.

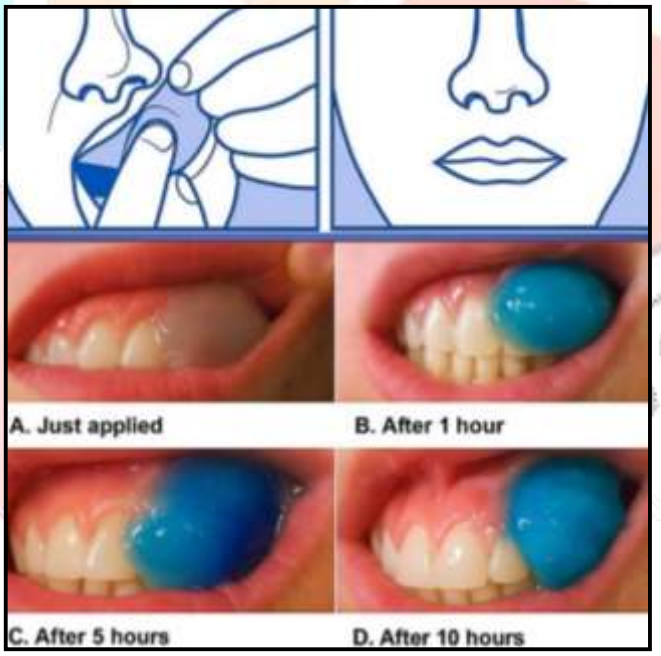

Fig 1.4: Buccal delivery system showing application and retention over time

1.2.1 Advantages of *In-situ* gelling system [8,9]

- It helps to extended or prolonged release of drugs.
- It Can be administered to unconscious patient
- It allows more patient comfort and compliance
- It offers more bio-availability
- Patients who are unconscious might be given *in situ* gel.
- It can reduce drug toxicity and dosage frequency.

1.2.2 Disadvantages of *In-situ* gelling system

- The drug in sol form is more prone to degradation.
- Consumption of food and beverages may be limited for a few hours after taking the medication
- Chances of stability problems due to chemical degradation.
- Only a small dose of the drug can be given and requires a high level of fluid.

1.2.3 Basic components of *In-situ* gel [10]

Sr. no.	Ingredients
1	Drug
2	Thermosensitive polymer
3	pH activated polymer
4	Ion activated polymer
5	Mucoadhesive polymer
6	Preservative agent
7	Isotonic agent

Table 1.1 Basic components of *in situ* gel

1.2.4 Approaches [11]

There are some several Approaches used to obtain an in-situ gelation system.

Temperature triggered in-situ gel: Temperature is the most widely used stimulus in in-situ gelling formulation for environmentally responsive polymer systems. Both in vitro and in vivo, the temperature change that is employed is simple to regulate and apply. Body warmth causes gelation in this system; external heat is not necessary. These hydrogels are liquid at normal temperature (20–25°C), but when they come into contact with bodily fluids (35–37°C), the temperature rises and causes them to gel. Three different kinds of temperature-induced systems exist. They are both positively and negatively thermosensitive, such as poly (nisopropylacrylamide) and thermally reversible polyacrylic acid.

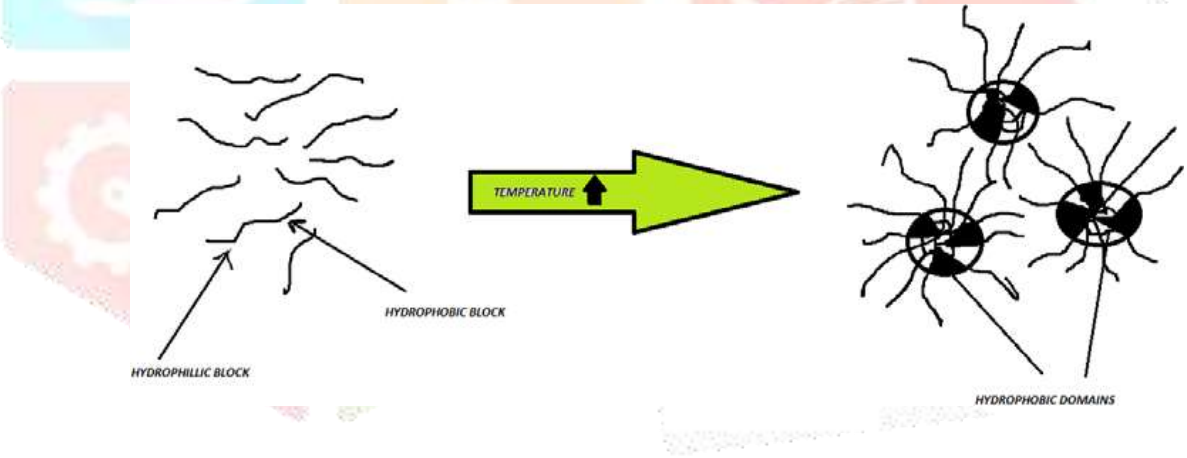

Fig 1.5: Mechanism of temperature sensitive in-situ gelling system

pH-Triggered in-situ gel: In this system, pH variations cause gel formation. This technique uses pH-responsive or pH-sensitive polymers. These polymers have basic or acidic groups that react to variations in the natural pH by releasing or receiving proteins, which subsequently break down and release the medication. Although polyacrylic acid (PAA)-based polymers are also useful, many pH-sensitive polymers are based on carbopol, carbomer, or variants. Polyelectrolytes are the many polymers of ionizable groups. The presence of poly electrolytes in the formulation raise the pH outside, which causes the hydrogel to enlarge and create in situ gel.

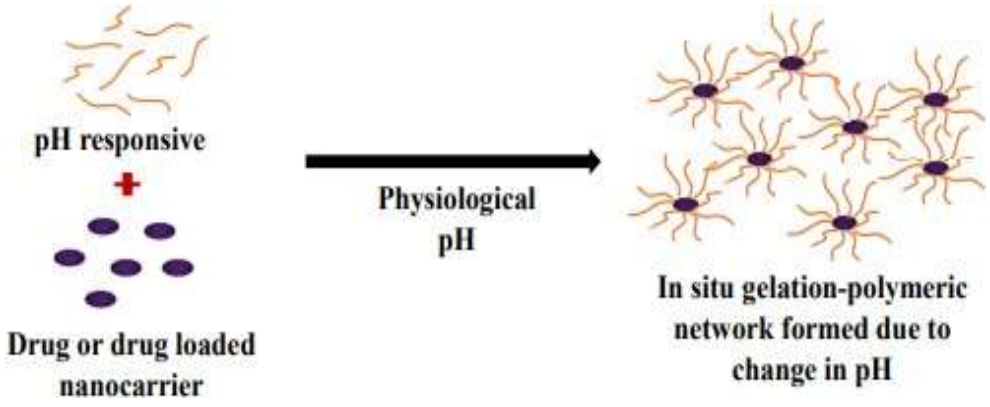

Fig 1.6: pH-sensitive in situ gel

Ion activated in-situ gelation: With this approach, a shift in the ionic strength causes the injected solution to gel. The osmotic gradient across the gel's surface is thought to be the determining factor in the gelation rate. Gelrite or gellan gum, hyaluronic acid, alginates, and other polymers exhibit osmotically driven gelation. Monovalent or divalent ions like Na + and Ca+ cause the sol-gel transition process. A few other elements have an impact on the phase transition are the polysaccharide concentration, the preparation temperature, and the type and concentration of cations. Gelrite was chosen to create the in-situ gel.

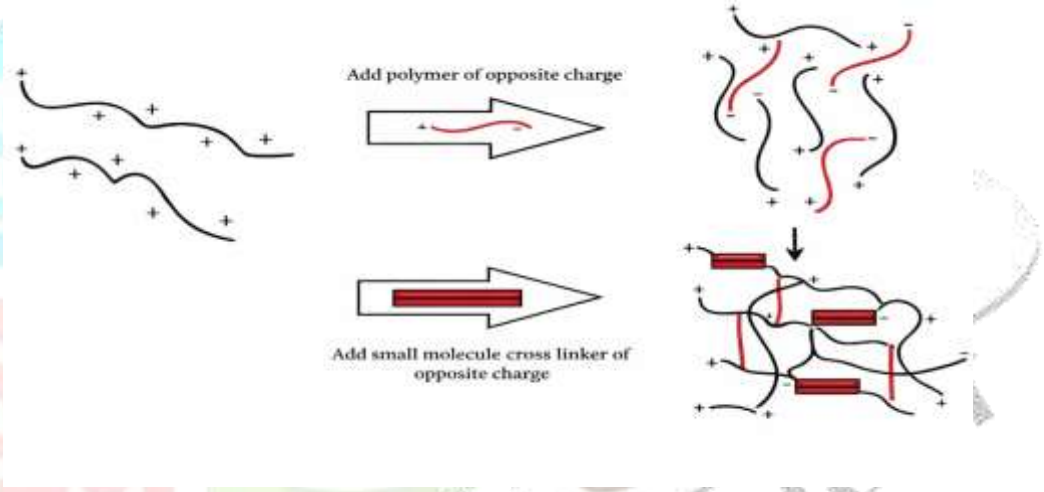

Fig 1.7: Ion-sensitive in situ gel

1.2.5 Polymers use for preparation of in situ gel [11]

Pectin: The cell walls of terrestrial plants include pectin, an anionic polysaccharide hydrogel, also called as poly (1,4-galacturonic acid). In recent years, it has gained attention from the biomedical community despite its historical use as a gelling agent in the food business. When it comes to biodegradation, pectin aerogels outperform wheat starch, which is the industry standard.

Xyloglucan: Xyloglucan (XG), a neutral polysaccharide, has been the focus of numerous investigations due to its mucoadhesivity, and other novel XG-based formulations have made it to the clinical trial stage, proving its advantageous effects as a mucosal protector. By adhering to mucosal membranes, XG forms physical barriers that prevent the spread of bacteria, allergies, and undesirable species. The FDA has approved XG, a non-ionic polysaccharide that is thought to be fully biocompatible and biodegradable, as a food additive and as a medicine delivery excipient.

Poloxamer 188: A hydrophobic chain of polypropylene oxide (PPO) in the middle and two hydrophilic chains of polyethylene oxide (PEO) on either side make up Poloxamer 188 (P188), a non-ionic triblock copolymer.

Poloxamer 407: Poloxamers are composed of two hydrophilic blocks of polyethylene oxide (PEO) along with tri block co polymerson either side of a hydrophobic polypropylene oxide (PPO) centre block. Among

these copolymers, poloxamer 407 is a non-ionic surfactant that exhibits reversible gelation characteristics above a specific temperature and polymer concentration.

Carbopol 934P: Carbopol 934P is a crosslinked polyacrylic acid polymer with a high molecular weight. In pharmaceutical formulations, it is a frequently utilized excipient, especially for topical and oral applications. Because of its high viscosity Because of its mucoadhesive qualities, carbopol 934P can be used in formulations meant for mucosal application.

1.2.6 Methods using for in-situ gel preparation [12]

Cold Method: Curcumin's carbopol–poloxamer gel was made using the cold technique. Here Curcumin is active pharmaceutical ingredients. Using a magnetic stirrer, carbopol P934 (1% w/v) was first dissolved in deionized water. After the solution had completely dissolved, it was chilled in an ice bath before gradually adding 30% w/v Pluronic F127 while stirring constantly. The liquid was refrigerated at 4 °C for 24 hours in order to guarantee full soaking and eliminate any trapped air bubbles. Curcumin powder, either 1% or 2% w/w, or curcumin that had been dissolved in a suitable amount of PEG400 (140 mg/ml) or ethanol (100 mg/ml) was gradually added to the prepared polymer solution while being stirred in an ice bath. After Each sample was then put into an amber bottle and kept in a refrigerator. The formulation for the in-situ gel that contained Curcumin dissolved in ethanol was placed on stirrer overnight to allow the ethanol to evaporate before being stored in a refrigerator.

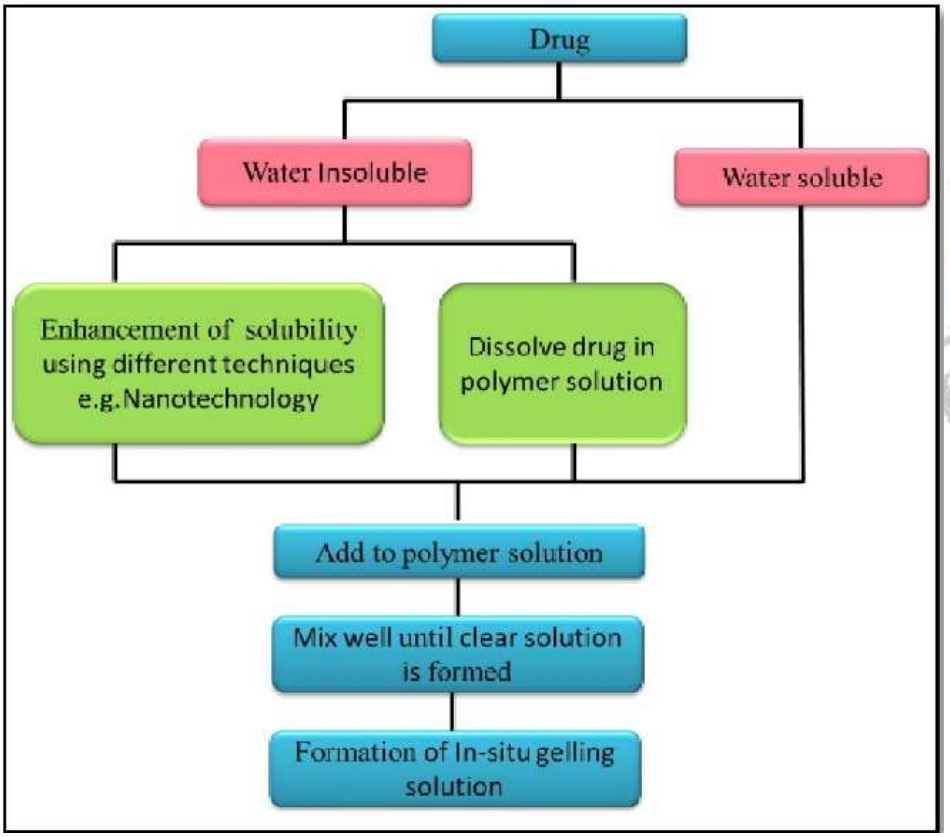

Fig 1.8: General Method of In-situ Preparation

1.2.7 Applications of *In-situ* gel [13,14]

These In situ polymeric systems can be categorized as shown in the following sections based on the mode of administration.

Ocular drug delivery system: The unique properties of the ocular cavity and its effective clearance mechanism make ocular administration of the drug a difficult target with low therapeutic response. New generation ophthalmic formulations are tasked with improving the availability of drugs administered by the ocular route and thus improving their therapeutic efficacy. This can be achieved by using in-situ gelling formulations that increase pre-corneal retention time and achieve optimal drug concentrations at the target site. Following topical application, gel formation in the conjunctival cul-de-sac provides

sustained release of the loaded drug to ensure long-term therapeutic effects, reduce dosing regimens, and thus improve patient compliance.

Nasal drug delivery system:

The nasal cavity has emerged as an attractive route for multi-site targeting for the administration of a wide variety of drugs, from small compounds to biopolymers such as peptides, proteins, and vaccines.

The nasal route is a natural choice for topical administration of drugs aimed at treating local disorders affecting the nose and sinuses, such as allergic or infectious rhinitis, sinusitis, nasal sinusitis, and nasal sinus lesions. Also, the nasal mucosa represents a non-invasive alternative route for the systemic delivery of drugs with low bioavailability. The highly vascularized nasal epithelium has been utilized to achieve rapid absorption of drugs that normally undergo extensive first-pass metabolism and/or gastric degradation after oral administration.

Buccal drug delivery system:

Over the last decade, administration of the intraoral in-situ gelation system has been used primarily for the topical treatment of oral mucositis, controlling pain, regulating the inflammatory response, enhancing the wound healing process, and treating bacterial infections. It has emerged as a valuable strategy to prevent fungal infections. Some pathological conditions are generally characterized by thinning of the oral epithelium leading to mucosal inflammation and ulceration, mainly associated with severe pain and bleeding.

Rectal and vaginal drug delivery system:

The rectal route may be used to deliver many types of drugs that are formulated as liquid, semisolid (ointments, creams and foams) and solid dosage forms (suppositories). Acetaminophen an anti-inflammatory drug formulated as rectal in situ gel by using polycarbophil and poloxamer F188 and poloxamer 407 as synthetic polymer forming in situ gelling liquid suppository which is considered as a synthetic polymer forming *Insitu* gelling liquid suppository which is considered as an effective method shows enhance bioavailability.

Intravesical drug delivery system:

In-situ gelling formulations have attracted some interest as an ideal topical and sustained delivery system for chemotherapeutic agents. After intertumoral or peritumour injection, such a system, in the sol state before administration, turns into a hydrogel in response to a particular stimulus and releases the drug locally in a controlled manner. Increased drug levels at the target site (tumour) maximize anticancer activity and at the same time minimize systemic toxicity.

1.2.9 Evaluation and Characterization of *In-situ* gel [15]

1.Clarity:

Visual assessment under excellent lighting with a black and white backdrop will be used to assess the clarity of the image

2.Measurement of pH:

The pH of each prepared batch will be determined using a pH meter that will be calibrated with standard buffers having pH values of 4 and 7, in accordance with the stated protocol.

3.Gel strength:

The gel strength will be measured using a rheometer. The gel formulation is prepared in a beaker according to the specific gelling mechanism (such as temperature-, pH-, or ion-induced gelation). After gel formation, a probe is allowed to penetrate slowly into the gel at a constant speed. The force (load) required for the probe to penetrate a specific distance or the time taken for the probe to sink a fixed depth is recorded as a measure of gel strength.

4.Rheological studies:

Brookfield Viscometer will be used to study the rheological properties of the in-situ gel. Temperature will be maintained above 40°C. The spindle speed will be increased from 0.3 to 100 rpm to note viscosity, shear rate, and shear stress. All readings will be taken in triplicate.

5. In Vitro Diffusion Cell:

A buccal diffusion cell made of glass will be used. A dialysis membrane (mol. wt. 12,000–14,000 kDa) will be fitted and the surface area will be maintained at 0.785 cm^2. The acceptor chamber will be filled with 20 ml diffusion media. The donor compartment will contain the gel with drug. At predefined intervals, samples will be withdrawn, and the same volume of media will be replaced. The drug concentra tion will be analysed spectrophotometrically using a calibration curve.

6.Drug Content:

The gel will be weighed and diluted properly, then its absorbance will be measured using a UV/Vis spectrophotometer. A standard solution of known concentration will be prepared, and its absorbance will be compared to calculate the drug content.

Conclusion

COVID-19 is a highly infectious viral disease caused by SARS-CoV-2 and has created a major global health burden. Although several antiviral drugs are available, conventional dosage forms have limitations such as low bioavailability and poor patient compliance. Buccal in-situ gel drug delivery systems offer improved drug retention, controlled release, and enhanced bioavailability. These systems are easy to administer and provide better patient comfort. Hence, buccal in-situ gels represent a promising and effective approach for the management of COVID-19 and other diseases.

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