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In-Situ Gelling System as Phyto-Medicine for Treatment Gastric Ulcer

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ABSTRACT

The Innovative Novel Approach system can treat histological and critical type of diseases with better screening treatment as compare conventional treatment and also In-situ gel give spark advantages and having the capability to treat with better advance treatment. It can consisting of a higher concentration of drugs with the polymeric system provide the site-specific absorption in conditions like pH, Temperature, Ionic cross-linking, and Enzymatic cross-linking. The dosing frequency is less and given high bioavailability and also reducing the lag time (Drug release pattern) of drug and provide the prolonged-release drug. Histological Gastric Ulcer still represents a major health issue reason gastric ulcer highly affected 10 to 20 years before those with the highest risk there is a need for novel approaches due to under social impact. Gastric ulcer associate with mucosal inflammation due to decrease acid between corpus and antrum transitional zone and also the development in the presence of *Helicobacter pylori* influenced by a variety of host and bacterial factors. *Helicobacter pylori* is a gram-negative bacteria characteristic colonizes on mucosa and surface of the gastric antrum, it can fight off the stomach acid that does reach it which enzyme urease**.** Using Phyto-medicine as an effective therapeutic agent for gastric ulcer it shows more merits than antibiotics. It can single line therapy as compared to antibiotics triple line therapy and reduced adverse drug reaction toxicity and achieve the therapeutic level. The treatment of gastric ulcer is phytomedicine use as *Trachyspermum*. It is also able to fight H. pylori. The In-situ gel entrapment *Trachyspermum* is known as phytopharmaceutical preparation is given the number of better screening with the polymeric condition. It is susceptible to reduce protein and enzyme secretions. In the present study, an attempt has been to prepare a formulation of *Trachyspermum* as an in-situ gel forming drug delivery system for oral delivery prolong release pattern.

INTRODUCTION:

The Imitative Phyto-medicine use of herbs to treat a histological and critical type of disease with given appropriate therapeutic level the same as other pharmaceutical material. It is traditional and scientific uses due to social impact and is also known as phytopharmaceutical. phytotherapeutic agent. It also expresses a secondary product using to better screening treatment. The development of chemical and phytochemical analysis has led to the increasing use of herbal medicine for the treatment of human disease use of specific selective phytoconstituent. In the list under World Health Organization (WHO) above 70-80%, Indian has preferred herbal product and medicine. Phyto-medicine full fill limited effect of other medicine, easy to body acceptance, less toxicity given therapeutic response. The selection criteria are based on phytoconstituents response and various types of activity. It's also standardized clinically tested for a distinct clinical condition. [1] The scientific entity of study is achieved specific site effect or local effect to an active drug as a form of a sustained and extended period. The felicitous design of the dosage regimen is important to execute this goal and the Phyto drug remedy achieved a steady-state blood plasma level that is therapeutically effective and nontoxic for an extended period. The Novel approach In-situ gel having a capability to releasing drug a specific manner with sustained-release introducing due to plasma concentration, the floating in-situ gel has liquid in room temperature but they gel after contact body fluid or charge in pH. These have to characteristic property of temperature depend, pH depend, and cations.[2] The oral drug delivery system has less the dosing frequency reason sustained release pattern of the drug show the slow releasing of a drug molecule within specific manner and the dosing criteria it describes sustained release, sustained action, controlled release, extended action, time-release, depot terms to achieving a steady-state in plasma drug concentration.[3] In-situ gel having floating behavior and show active gastro-retentive form and this formulation help to improve oral prolonged-release that has an absorption window in a particular area of gastrointestinal tract hence such system help to continuously release the drug while reaching the absorption window ensure maximum bioavailability.[4]

GASTRIC ULCER EPIDEMIOLOGY [5, 6, 7, 8,]

PEPTIC ULCER

The Etymology Peptic Ulcer diseases have shown a large variation over the past 150 years the risk factor is high and strong in the case of peptic ulcer ensuring birth cohorts and then declined in an ensuing generation. The higher risk of developing gastric ulcer was born 10-20 years before the highest risk of ulcer, peptic ulcer defines Gastric and Duodenal ulcers known both of them as defect mucosal in a specific diameter at least 0.5cm penetrating through the muscularis mucosa. It occurs in the stomach both long and lesser curvature in particular at the transition from corpus to antrum mucosa and duodenal ulcer usually occur in the duodenal bulb the most effective exposed to gastric acid. Duodenal ulcer are four-time more than gastric ulcer in the age group of 50, it is more in males than women (4:1) and the more common in patients with blood group "O" and associated with increased serum pepsinogen.

Symptoms of Peptic Ulcer

- ✓ The pain epigastrium of pain in early morning
- ✓ Burning pain in the gut is the most common symptom.
- ✓ The pain feels like a dull ache comes and goes for a few days or weeks start 2-3 hr. after a meal comes in the middle of night when stomach empty.
- ✓ Bleeding can also occur prolonged bleeding may cause anemia
- ✓ Feel sick to the stomach
- ✓ Having pain while eating
- ✓ Not feeling like eating

HELICOBACTER PYLORI [9, 10, 11, 12]

The Infective bacteria listed *H. pylori* effective 80% of the population is positive and show larger variation in human health, it shows enough effective in young ages above 35% cases are carried out and also industrialized area generally remains under 40% and is considerably lower children and adolescent that in adults and elderly people. According to WHO (World Health Organization), H. pylori as class "1" carcinogen carcinoma of the stomach, country to

countries about *H. pylori* study carried out 90% of gastric malignancies and is the leading cause of ulcer and cancer-related death in countries its incidence is high. The highest incidence is between 40-60 age of life and is twice more common in men and women. The gastric ulcer is *H. pylori* infection with a marginally factor-like diet irritating food, tobacco, smoke, alcohol, etc. The effective a transmission cases in human of *H. pylori* is unclear but seems to be person to person spread a fecal-oral route. H. pylori are a gram-negative bacterium it is a spiral-shaped organism with a smoother outer coat with four to six bulbous tipped sheathed flagella at one end which helps to penetrate the mucosa and colonized on the surface gastric. *H. pylori* having gene sequences cage allow to bacteria protein to enter the host cell and VacA and Bab2 permit adhesion bacteria to the cell surface. After the fecal-oral transmission and colonized in stomach *H. pylori* are fight the stomach acid that reaches with enzyme urease which counters urea into bicarbonate and ammonia which is a strong base and neutralizes acid and chemical around the *H. pylori*.

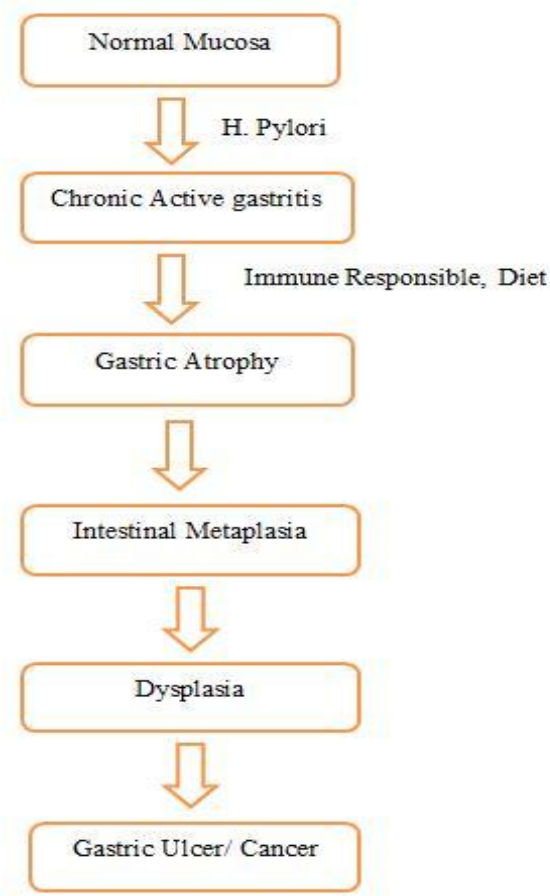

Figure No. 1: *H. pylori* factor in gastric carcinogenesis

Outline of *H. pylori* Infections

- **Step: 1**

✓ Mild diffuse gastritis

✓ No disruption of acid secretion

✓ No clinical outcome

- **Step: 2**

✓ 15% inflammation main in the antrum

✓ Spare acid-producing area of the stomach

✓ Increased gastrin secretion

✓ Increase acid production

✓ Increase risk for peptic ulcer

- **Step: 3**

✓ Inflammation in stomach

✓ Destroy acid-producing glands

✓ Mucosal atrophy

✓ Decreased acid secretion

✓ Intestinal metaplasia

✓ Increased risk for gastric ulcer

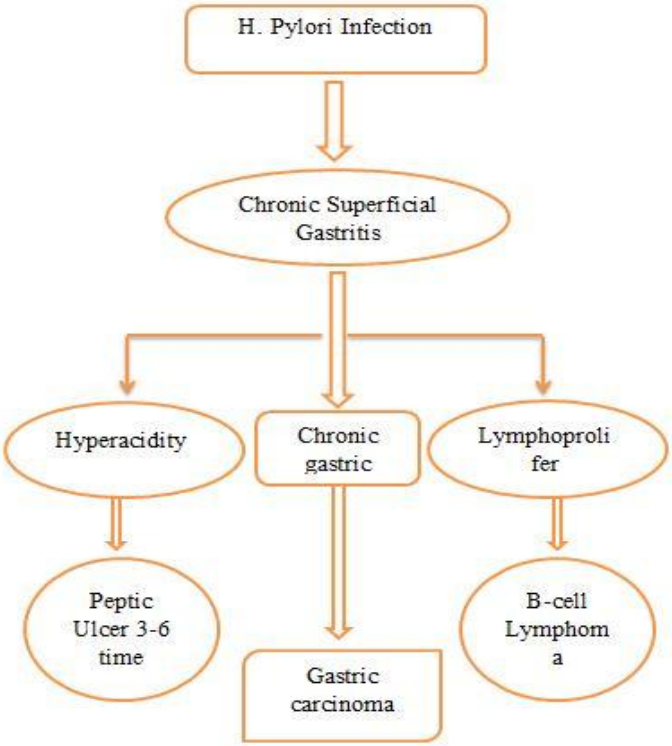

Figure No. 2: Consequences of long-term *Helicobacter pylori* gastritis

Virulence genes factor

***VacA* (Vacuolating Cytotoxin) Is an 88-kDa pore-forming protein**

✓ The toxin Vacuolating A (VacA) is *H. pylori* secreted protein that assembles into oligomers.

✓ The oligomers accumulate into selective channels (anion) that typically define VacA as a pore-forming toxin.

✓ Increase the VacA pores can transcellular penetrability to organic molecules, iron, and nickel within gastric epithelial cells, resulting in redemptive energetic nutrients for *H. pylori* survival.

✓ Gene is involved in the membrane sequence formation, Cytochrome c (cyt c) release from mitochondria to apoptosis, and required to cell membrane receptors,

✓ In lipid membranes toxin inserts to form a hexameric anion-selective, voltage-dependent channel (bicarbonate, urea, and organic anions released, providing substrate for urea hydrolysis and hence protection from gastric acidity).

✓ The VacA inhibits the development of bacterial protein-detecting T-cells and promotes the differentiation of cells into a tolerogenic phenotype.

***CagA* (Cytotoxin-Associated Gene A Product)**

✓ The most lethal *H. pylori* the CagA protein, which transform cells from a columnar epithelial shape to elongated shape, is known as hummingbird phenotype.

✓ One of the host proteins that CagA targets in cells

✓ It is transferred to host cell type IV secretory system.

✓ A syringe-like pilus that penetrates gastric epithelial cells and facilitates the translocation of CagA.

***DupA* (Duodenal Ulcer Promoting)**

✓ Duodenal ulcer promoting (dupA) gene was reported to be associated with duodenal ulcer development.

✓ DupA pathogenesis appears to involve the induction of IL-8 production in the antrum, leading to antrumpre dominant gastritis which is a well-recognized characteristic of duodenal ulcer.

✓ *H. pylori* containing intact DupA induces the IL-12 production in monocytes.

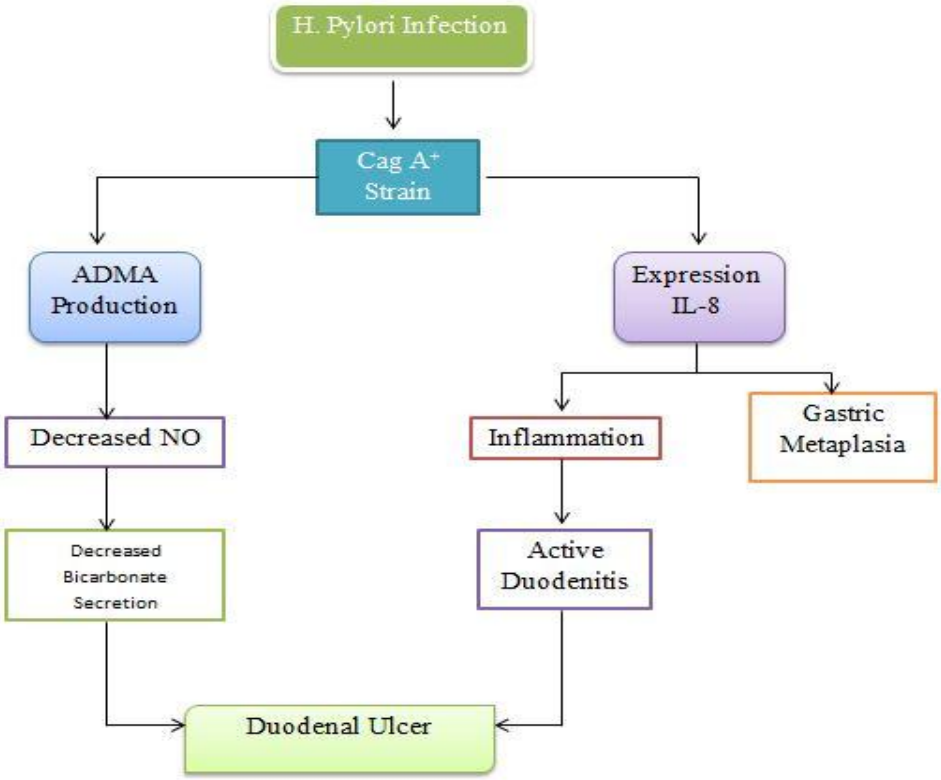

Figure No. 3: *H. pylori* induced duodenal ulcer

H. pylori associated disease

H. pylori approximately 95% of Duodenal Ulcers and 85% of Gastric Ulcer transpire in infection

Table No. 1: *H. pylori* associated disease

Types of Disease	Elucidation
Acute Gastritis	Acute phase of the infection of colonization with H. pylori may be associated with transient nonspecific dyspeptic symptoms such as fullness, nausea and vomiting, and considerable inflammation of both the proximal and distal stomach mucosa and pangastritis. This phase is often associated with hypochlorhydria it is unclear whether his initial colonization can be followed by spontaneous clearance and resolution of gastritis.
Chronic Gastritis	In this condition histological changes observed in biopsies from the stomach when colonization is done become tenacious a close correlation between the level of acid secretion and the distribution of gastritis. Resulting in the counteractive effects of acid on bacterial growth versus those of bacterial growth and associated mucosal inflammation on acid secretion and regulation. *H. pylori* in precise colonize the gastric antrum, few acid-secretory parietal cells are present. This colonization pattern is associated with antrum-predominant gastritis resulting in chronic inactive inflammation and low numbers of superficially colonizing *H. pylori* bacteria. **Chronic Gastritis can be classified as** **Type-A Gastritis:** (Auto-Immune Gastritis):- This type of Gastritis occurred due to the presence of circulatory antibodies. Type A gastritis predominantly involves the body-mucosa **Type-B Gastritis:** The type B gastritis involves the region of antral mucosa and is more common. It is also called hypersecretory gastritis due to excessive Secretions of acid, due to infection with Helicobacter Pylori. **Type AB Gastritis:** It is also called environmental gastritis because several as yet unitified environmental factors have been implicated in its etiopathogenesis. Antral body of the stomach is involved in this type of gastritis. **Chemical Gastritis:** It is also known as reflux gastritis

PHYTO-THERAPEUTIC AGENT [13, 14]

Trachyspermum ammi

Common name: AJWAIN

Botanical name: *Trachyspermum ammi*

Chemical constitute

Ajwain contains many phytoconstituents including carbohydrates, glycosides, saponins, phenolic compounds, volatile oil (thymol, γ-terpinene, para-cymene, and α- and β-pinene), protein, fat, fibre and mineral matter containing calcium, phosphorous, iron and nicotinic acid.

Traditional uses & benefits

- It is used as digestion a side dish of ajwain seeds often accompanies food in the Middle East.
- Abdominal discomfort due to indigestion and an antiseptic.
- They are used in the treatment of influenza, asthma, coughs, colds, colic, diarrhea, cholera, indigestion, edema, rheumatism.
- For relieving flatulence, dyspepsia, and spasmodic disorders
- For removing phlegm
- For bronchial asthma

Applications of Novel delivery based phytomedicine formulation

- ✓ Protection from toxicity
- ✓ Enhance solubility
- ✓ Enhance stability
- ✓ Protection from chemical and physical degradation

- ✓ Improve pharmacological activities
- ✓ Improve bioavailability
- ✓ Sustained released
- ✓ Prolonged released
- ✓ Reached therapeutic level

Merits of Novel Delivery Phyto-medicine

- ✓ Enhanced poor water-soluble phytomedicine
- ✓ Target delivery of phytomedicine
- ✓ The large macromolecule phytomedicine delivery in the intercellular site of action
- ✓ Co-delivery of two or more phytomedicine

***IN-SITU* GEL [15, 16]**

The Avant-garde pharmaceutics dosage system has consist standards of drug delivery as a sustained release to improve the dosing system consisting of the *in-situ* gel having a polymeric delivery system, higher drug-loaded capacity and reduce the dosing frequency of drug increase drug bioavailability and also improvement better screening for reducing the discomfort of patients. The innovative formulation of the in-situ gel depends on environmental factor like temperature modulation, pH change, presence of ions and ultraviolet irradiation from which the drug get released in a sustained and controlled manner and for the gelling system carried out with using various biodegradable polymers it uses for the formulation of in-situ gel include sodium alginate, sodium citrate, gellan gum, alginic acid, xyloglyan, pectin chitosan, etc.

***In-situ* Gel Merits for oral Administration**

- ✓ The capabilities of gel consistency for using polymer behaving according to environment factor
- ✓ Enough concentration of the drug is loaded.

- ✓ Reduce the dosing frequency
- ✓ Reduce the lag time of drug and given sustained release
- ✓ Increase bioavailability of the drug
- ✓ Improved Pharmacokinetics of drug

General Formulation Considered In-situ Gel Polymer [17, 18]

Table No. 2: General Formulation Considered In-situ Gel Polymer

Type of Drug Delivery	**Polymers**
Oral In-situ Gel	Carbopol-934, Chitosan, Gellan gum, Gum karaya, HPMC, Hyaluronic acid esters, MC, Methylpyrrolidinone Chitosan, Pectin, Poloxamer, Pluronic F-127, Sodium-Alginate, Trimethyl Chitosan, Xyloglucan, etc.

Environmental factor for oral In-situ Gelling and Drug Delivery System [19, 20]

Table No. 3: Environmental factor for oral In-situ Gelling and Drug Delivery System

Factors	**Elucidation**
Thermally Trigger System	In this system use of biomaterial transition from sol to gel is triggered by an increase in temperature is an approach in the *in-situ* formulation. The ideal critical temperature range for the system is ambient and physiologic temperature and no external source other than that of body heat is requires triggering gelation. Three main tactics exist in thermoresponsive sol-gel polymeric system. negatively thermosensitive, positively thermosensitive, thermally reversible gels.
pH Trigger System	The system involves external pH increase in the case of weakly acidic group (anionic) but decreases if the polymer contains a weakly basic group (cationic). pH-sensitive polymers contain pendant acidic or basic groups that resulting release protons in response to changes in environmental. The polymers consist of a large number of ionic groups are known as polyelectrolytes.

	Hydrogel swelling and increases as the external pH increases in the case of weakly acidic (anionic) groups, pH. The polymer mixtures sol. at pH 4 and gel at pH 7.4 Mixtures of poly (methacrylic acid) (PMA) and poly (ethylene glycol) (PEG) also has been used as a pH-sensitive system to achieve gelation.
Ionic Cross Linking	The system has taken phase transition in presence of various ions such as k+, Ca^{2+}, $Mg^{2+,}$ Na+. Example: Sodium alginate the free Ca^{2+} entrapped in the polymeric chain. Alginic acid undergoes gelation in the presence of divalent/polyvalent cations e.g. Ca^{2+} due to the interaction with a guluronic acid block in alginate chains.
Enzymatic Cross-Linking	In Enzymatic action, the natural enzyme operates efficiently under the physiological conditions without the need for potentially harmful chemicals such as monomer and initiator.

GASTRO-RETENTIVE BEHAVIOR *IN-SITU* GEL [21, 22, 23]

The *In-situ* gel gastro-retentive formulation expressed in the stomach to improve oral prolonged delivery of active drug it helps to a particular absorption in the gastrointestinal tract. Formulation of behaves presence of stomach acid to sustained release to improve drug bioavailability reduce the dosage frequency and also reduce drug Lag time. *In-situ* formulation behaves under different approaches such as bioadhesive system, swelling, floating, delayed gastric empty.

Gastro-retentive *In-situ* Gel Formulation Factors

- **Fed or Unfed State:** Under the gastro-retentive system migrating myoelectric complexes (MMC) occur every 1.5 to 2 hours MMC sweeps undigested material from the stomach timing of administration of the formulation corresponding with the MMC and gastro-retentive time is short resulting in the fed state, MMC is delayed and GRT is considerably longer.

- **Density:** In the formulation, gastric retention time (GRT) is a function of dosage form floating that is dependent on the density.

➢ **Nature of the meal:** Formulation having polymers of fatty acid salts can change the pattern of the stomach to a fed state resulting in decreasing the gastric emptying rate and prolonging the drug release.

➢ **Posture**: GRT can vary between supine and upright ambulatory states of the patients.

➢ **Size and Shape:** Ideal formulation under 7.5 mm diameter increased GRT with a diameter of 9.9 mm. The dosage form having shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5.

EVALUTION PARAMETTER OF *IN-SITU* GEL [24-28]

Appearance:

Clarity is one of the most important characteristic features of In-situ Gel. Formulations evaluated for clarity by visual observation against a black and white background. Formulations were evaluated for clarity by visual observation against a black and white background.

Drug content:

The drug content in In-situ gel determines by a single-point estimation method. The method is based on the comparison between standard and test.

pH:

The pH determines *in-situ* solutions consisting of drug-using a calibrated digital pH meter at 25°C. All measurements of pH made in triplicate.

***In-Situ* gelling capacity:**

In-situ gelling capacity determines by visual inspection. The formulation has been exposed to the physiological conditions of temperature and pH. Simulated Gastric Fluid (SGF) prepared and warm up to 370ºC. Formulations introduce into SGF in an appropriate ratio Change in consistency of Formulations visually inspect.

Viscosity study:

The viscosity of the in situ gelling solution is determined with a Brookfield viscometer.

***In-vitro* floating study:**

The floating study determines by introducing of 0.1 N HCl in a beaker. Specific measured of solution added to HCl. Time requires for immersed on the surface after adding solution and total floating time measured.

***In-vitro* drug dissolution study:**

The *In-vitro* release studies of drugs from the In-situ gel formulation studied using dissolution testing apparatus USP II.

Stability studies:

Stability is defined as the extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics that it possessed at the time of its manufacture. Stability testing is performed to ensure that drug products retain their fitness for use until the end of their expiration dates.

Storage conditions for Stability Studies according to ICH guidelines

Table No. 4: Storage conditions for Stability Studies according to ICH guidelines

Study	Storage Condition	Minimum Time Period
Long term	25ºC±2ºC, 60%±5%RH Or 30ºC±2ºC, 65%±5%RH	12 Months
Intermediate	30ºC±2ºC, 65%±5%RH	6 Months
Accelerated	40ºC±2ºC, 75%±5%RH	6Months

CONCLUSION

The Novel approach in-situ gel dosage form is a liquid before administration but converts into a gel that floats on gastric contents as it comes in contact with it. Such gel conversions are due to one or more mechanisms such as physiological stimuli (e.g., temperature and pH), physical changes in biomaterials (e.g., diffusion of solvent and swelling), and chemical reactions (e.g., enzymatic, ionic and photoinitiated polymerization). Floating in situ gel drug delivery systems have been used to deliver many drugs which are used either for their systemic or for their local effects in the stomach. *Helicobacter pylori* (H. pylori), one of the

causative agents for bacterial infections in humans is responsible for several gastrointestinal diseases such as gastritis, gastric ulcer. Phyto-medicine is used as traditional and scientific it is helps to treat the gastric ulcer fight to *H. pylori* with reducing protein and enzyme. Therefore to improve its local effects in the stomach and achieve better eradication of H. pylori, certain floating systems developed, including beads, Pellets, and tablets Gastric retention is advantageous for the delivery of drugs with narrow absorption window in the small intestinal region. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment and advantageous for drugs that degrade in the colon. It does have applications also for local drug delivery to the stomach and proximal small intestines. Gastro retentive formulations help to provide better availability of new products with new therapeutic possibilities and substantial benefits to the patients Thus in the present study attempt has been to prepare a formulation of *Trachyspermum ammi* as an in situ gel-forming drug delivery system for oral delivery for suitable prolong release.

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