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A Research on Gauging of Colon Targeted Drug Delivery of Loperamide HCL with Pectin-Bora Rice Microsphere

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Abstract:- By far, the most widely used method for creating multi partuculate drug delivery systems is microencapsulation. However, this method has significant drawbacks, including non-uniform coating, non-reproducible release kinetics and more importantly, the use of more or less harsh conditions during the formulation process, which restricts the encapsulation of a variety ofsubstances, including proteins, enzymes, live cells, and others. In addition, the regulatory bodies, such as the U.S. FDA, are increasingly limiting the permitted amounts of additional components, such as organic solvents. A method that resolves this issue without the use ofharsh chemicals or high temperatures and on the basis of ionotropic gelation is provided (polyelectrolyte complexation). The significance of ionotropic gelation and its capacity for cross-linking are emphasized in this review.

Purpose: The main objective of this study was to gauge the Hydrogel beads for Colon Targeted Drug Delivery of Loperamide HCL for Treatment of Diarrhea.

Methods: Loperamide HCL laden Bora rice beads were processed by using Ionotropic GelationTechnique method. In this Sodium Alginate is used as Gelating agent polymer and Pectin with Bora Rice as a colon Specific polymer.

Result & Discussion: The microspheres were prepared by using Sodium alginate as a Gelating polymer although we have used yeast also in trial batch but due to insufficient knowledge how yeaststabilizes the microspheres that's why avoided used the yeast in our final microspherepreparation, after that we have used different crosslinking agents the different cross linking agent used are Barium chloride and calcium chloride, which are separate low molecular-weight cross linking agents, were used. The study was conducted on thestability of the microspheres, and finally discovered that the Sodium alginate microspheresare only stable at cold temperatures, i.e. 0-4 degrees Celsius, the main formulation thatis PT-BR microsphere was stable at normal room temperature but very sensitive to increase in temperature.

Conclusion: In conclusion, these study demonstrated that the Pectin-bora rice microsphere are stable at room temperature for longer period of time as compare to yeast containing sodium alginate beads which was only remain stable in 0-4 degree Celsius.The microsphere prepared were spherical in shapes and it is found that the barium chloride cross linked microspheres was similarly stable as the calcium chloride cross linked microspheres.

Keywords:- *Microspheres, beads, sodium alginate, loperamide, microencapsulation, pectin, bora rice.*

I. INTRODUCTION

By far, the most widely used method for creating multipartuculate drug delivery systems is microencapsulation. However, this method has significant drawbacks, including non-uniform coating, non-reproducible release kinetics, and more importantly, the use of more or less harsh conditions during the formulation process, which restricts the encapsulation of a varietyof substances, including proteins, enzymes, live cells, and others. In addition, the regulatory bodies, such as the U.S. FDA, are increasingly limiting the permitted amounts of additional components, such as organic solvents. A method that resolves this issue without the use of harsh chemicals or high temperatures and on the basis of ionotropic gelation is provided (polyelectrolyte complexation). The significance of ionotropic gelation and its capacity for cross-linking are emphasized in this review. Drug targeting is a new drug delivery system that aims to deliver the drug to the target site of action or site of absorption without releasing the drug at any other non-target site [1]. The inherent benefit of this method allows for the delivery of the needed medication at a lower dose and with fewer side effects. A targeted medicine delivery system aims to extend, localize, target, and engage with the sick tissue in a safe manner [2].The colon targeted drug delivery system (CDDS)is highly desirable for local treatment of a variety of bowel diseases. The CDDS technology was designed to avoid the inherent problems associated with pH or time dependent systems. Drug Carrier is factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule [3]. Polysaccharide-based drug delivery techniques that are aimed towards the colonhave an advantage over other techniques. While moving through the GIT, polysaccharides maintain their integrity and stop the

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medication from being released. However, when it comes into touch with colonic fluid, it is exposed to the action of microbes, and as a result, the medicine that was previously confined is released [4].Since natural polymers are essentially polysaccharides, they are both biocompatible and free of side effects. All green plants produce starch as a form of energy storage, and it is particularly prevalent in seeds and subterranean organs. Several starches have been approved for use in pharmaceuticals. These include potato (Solanum tuberosum), wheat (Triticum aestivum), rice (Oryza sativa), and maize (Zea mays) (olanum tuberosum). Two polymers, namely amylose and amylopectin, make up its composition.

- **BORA RICE:** For delivery methods, many natural sources of the polymer have been targeted. Because of intriguing qualities, including being non-toxic, biocompatible, biodegradable, mucoadhesive, and non-immunogenic, Assam Bora Rice Starch appears to be a better alternative. The rice known as Assam Bora, also referred to as Bora Chaul locally, was first brought to Assam, India, from Thailand or Myanmar by Thai-Ahom and is now widely grown throughout Assam. The high amylopectin content (i.e., > 95%) of the starch derived from Assam Bora rice is characterized by a branching waxy polymer that exhibits physical stability and resistance to enzymatic action. In cold water, Assam Bora rice starch hydrates and expands, creating a viscous colloidal dispersion or sol that gives it its bio adhesive properties [6].
- **PECTIN:** Pectin's are non-starchy linear polysaccharides found in abundance in plant cell walls. Pectin was first extracted and isolated in 1820, and the first commercial production of liquid pectin extract was recorded in Germany (1908)., and the process of pectin production spread quickly to the United States [8,9,10]. Pectin has been successfully utilized for a long time in the food and beverage sector as a thickening ingredient, gelling agent, and colloidal stabilizer in various types of goods. Based on its chemistry and gel-forming properties, pectin has been studied for its potential in the pharmaceutical business, analysis, and health care. It has been discovered that big sources, as opposed to multiple natural sources, can provide valuable and high-grade pectin. Pectin has been widely used as a carrier for a wide range of biologically active substances in pharmaceutical preparations and drug formulations [8].
- **LOPERAMIDE HCL:** Loperamide is synthetic piperidine derivative, It is an antidiarrheal resulting from gastroenteritis or inflammatory bowel disease. The effect of loperamide are rapid. Loperamide act on opioid receptors in the intestinal wall with lesser effect on muscarinic receptors. It extracted and metabolized by cytochrome P450 in the liver, it is conjugated in the liver and excreted in the bile. Because of this, loperamide reaches the systemic circulation. Its antidiarrheal action result from direct absorption into gut wall. Just like morphine and other u-receptor agonist. Through its actions on the intestine's circular and longitudinal muscles, loperamide reduces gastrointestinal motility. Its anti-diarrheal effect may in part be brought on by opioid receptor binding in the intestinal mucosa, which reduces gastro-intestinal output. (NCI04). Enterier neurons synthesize and unleash endogenous opioid peptides and alternative neurochemicals, comparable to neurotransmitter and substance P. Endogenous opioids bind to opioid receptors expressed on these neurons to control channel signaling, motility, and balance of fluids and electrolytes.5 Loperamide acts on the mu-opioid receptor expressed on the circular and longitudinal intestinal muscle.1 Receptor binding ends up in the accomplishment of G- protein receptor kinases and therefore the activation of downstream molecular cascades that inhibit enteric nerve activity. By inhibiting the excitability of enteric neurons, loperamide suppresses neurotransmitter release, pre-synaptic and post-synaptic inhibition of transmission of excitant and repressive motor pathways, and secret motor pathways. Loperamide inhibits the discharge of neurotransmitter and prostaglandins, thereby reducing propulsive activity and increasing enteric transit time. Loperamide stimulates the intestinal absorption of water and electrolytes by inhibiting calmodulin. Loperamide will bind to and hyperpolarize submucosal secret motor neurons, promoting dry, laborious stools. Loperamide may be an anti-diarrheal agent that gives symptomatic relief of diarrhea. It decreases bodily function and fluid secretion within the canal tract, delays colonic transit time, and will increase the absorption of fluids and electrolytes from the gastrointestinal tract. Loperamide additionally increases body part tone, reduces daily soiled volume, and increases the body and bulk density of feces. It also increases the tone of the anal sphincter, thereby reducing incontinence and urgency. The onset of action is regarding one hour and also the length of action will be up to a few days. whereas loperamide is a potent mu-opioid receptor agonist, it does not mediate vital analgesic activity at therapeutic and supratherapeutic doses. However, at high doses of loperamide, inhibition of P-glycoprotein-mediated drug outflow may enable loperamide to cross the blood-brain barrier, wherever loperamide can exert central opioid effects and toxicity. At terribly high plasma concentrations, loperamide can interfere with internal organ conduction. as a result of loperamide inhibits the Nat-gated cardiac channels one and ether-a-go-go-related sequence K channels, the drug can prolong the QRS advanced and also the QTc interval, which might cause bodily cavity dysrhythmias, monomorphic and polymorphic ventricular tachycardia, torsade American state pointes, ventricular fibrillation, Brugada syndrome, cardiac arrest, and death [11,12,13].

II. MATERIAL AND METHODS

Loperamide HCL drug was used as Received. Assam Bora Rice was purchased from local villagers of Nagadera district ofJorhat, Assam. Pectin was purchased from Bhosari, Pune- 411039.1The other chemicals used in the study were of analytical grade and used as received. Ionotropic Gelation Technique Simply interacting an ionic polymer with an oppositely charged ion causes ionotropic gelation, which starts the cross-linking process. Contrary to simple monomeric ions, the electro neutrality principle cannot fully account for the interaction of polyanion with

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cations (or polyanion with polycation). The three-dimensional structure and the presence of other groups have an impact on the capacity of cations (or anions) to conjugate with anionic (or cationic) functions, and selectivity is evident. The ionotropic gelation approach can be used to create hydrogel beads using either of two methods. The source of the cross-linking ions varies between these techniques. One of the techniques positions the cross-linker externally, as shown in Fig. In contrast, the alternative technique incorporates the cross-linker ion into the polymer solution as an inactive form, as seen in Fig. Compared to internally cross-linked films, external cross-linking created thinner films with smoother surfaces, better matrix strength, stiffness, and permeability. Additionally, externally cross-linked micro particles were able to encapsulate drugs more effectively and release them more slowly. [14].

A. Formulation of trial batches of Microspheres with Sodium Alginate

The standard ionotropic gelation technique was used for the preparation of the hydrogel beads with slight modification as described below: Aqueous dispersion of sodium alginate is used. Appropriate amount of the model drug Loperamide (2:1 polymer: drug) was dispersed until an uniform dispersion was obtained. The bubble free dispersion was added drop wise, through a disposable syringe (nozzle of 1.0 mm inner diameter) to a 100 ml of a gently agitated solution of the crosslinking agents i.e. [$CaCl_2$ and $BaCl_2$] at room temperature separately as shown in Table 1. The distance of falling of the drops was 5 cm. The gelled particles thus formed were allowed to remain in the crosslinking solution up to different duration of time period. The particles were subsequently washed with purified water, in order to remove CI and excess of Ca* and Ba* ions and separated by filtration. The particles were air dried for 1 hr. and stored in a desiccator at room temperature [15].

B. Formulation of trial batches of Sodium alginate and Yeast Microspheres

The enzyme immobilization technique was used for the preparation of the hydrogel beads with slight modification as described below: Aqueous dispersion of sodium alginate and Yeast is used. Appropriate amount of the model1 drug Loperamide HCL (2:1:2 & 2:1:1 polymer: drug: yeast) was dispersed until a uniform dispersion was obtained. Sodium alginate forms gel (primarily liquid substances that can to varying degrees, behave like solids due to cross-linking) when exposed to divalent cations like calcium or barium. The Barium chloride added to solutions of sodium alginate under goes reaction to form barium alginate, which forms gel. Advantage to enzyme immobilization is that they are more resistant to factors like pH changes and temperature fluctuations.

C. Formulation of Loperamide HCL Laden Pectin- Bora Rice Microspheres

For encapsulation of Loperamide HCI drug in Pectin-Bora rice beads, in an effort to use the largest feasible percentage of bora rice, the microbeads were made using mixtures of pregelatinized bora rice starch and pectin using the micro-orifice ionic gelation process. By autoclaving the aqueous suspension of rice polymer at 121 degrees Celsius for 1 hour. The Pectin (1% w/v) and bora rice gel (4 % w/v) were mixed in the ratio by weight in a ratio so as to have the 2:1 ratio by weight of the bora rice and Pectin by weight in the final blend. In the final blend of the Pectin-bora rice the HPMC and ethyl cellulose were added (1:1) by continuous stirring on magnetic stirrer. 2g of Loperamide HCL was added in prepared gel mixture and vigorously stirred for 1hr. The effervescence free drug polymer mixture was added drop wise, with the help of 10 ml Syringe (Opened Mouth) into a 100ml of gently agitated solution of the Crosslinking Agent Barium chloride (BaC12) at room temperature, the solution was stirred in 250 ml beaker with the help of Mechanical stirrer for an hour, after that the beads are filtered from the solution and kept for drying [16,17].

Table 1: Formulation of trial batches of drug laden with Sodium alginate and Yeast Microsphere

Batch code	Polymer: Drug: Yeast	Cross linking agent	Conc. Of cross linking agent (%w/v)
X1	2:1:1	BaCl2	2
X2	2:1:2	BaCl2	2

III. RESULT AND DISCUSSION

A. Formulation of trial batches of Microspheres with Sodium Alginate

The prepared sodium alginate beads with calcium chloride and barium chloride were spherical in shape, but were not stable at room temperature; they started degrading in a few minutes after the preparation. Our discussion started from here: how to make the microspherestable at least for a few months. We prepared a microsphere a second time and kept it in the refrigerator for observation. The sodium alginate microspheres were discovered to be stable for 20 to 30 days after preparation but only at very cold temperatures.

B. Formulation of trial batches of Sodium alginate and Yeast Microspheres

The stability for a sodium alginate microsphere was for more than 20 days, after which the beads begin to dehydrate, and our next discussion has been started on how to make microspheres stable for more than a month, which we have achieved through enzyme immobilization using yeast. According to a source, the enzyme immobilization makes the microspheres more resistant to factors such as pH changes and temperature fluctuations. So we performed two preparations in which we incorporated yeast in low and high concentrations.

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C. Formulation of LoperamideHCL Laden Pectin- Bora Rice Microspheres

After preparing all the trial batches of sodium alginate microsphere and achieving the desire stability of microspheres we move towards the main preparation i.e., Pectin- bora rice. We have prepared formulation and found that the pectin - bora rice is most stable than the prepared trial batch of sodium alginate.

IV. CONCLUSION

These study demonstrated that the Pectin-bora rice microsphere and Alginate microsphere are stable at cold temperature i.e., 0-4 °C. The microsphere prepared were spherical in shapes and it is found that the barium chloride cross linked microspheres was similarly stable as the calcium chloride cross linked microspheres. The microspheres which contain yeast shows highest stability profile as compare to any other formulation which do not contains yeast. And at the last we found that the pectin -bora rice microsphere has better stability than the trial batch of sodium alginate microspheres.

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