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Development and In-vitro characterization of Eudragit RS100 coated alginate microspore of diclofenac sodium thermosensitive gel for ocular delivery

MOHAMMAD AATIF ,MONIKA BANSAL.
Akal College of Pharmacy and Technical Education

1.Introduction:-

The eye's complex anatomy and protective mechanisms challenge drug delivery. Topical administration offers direct, localized treatment, avoiding systemic side effects. However, barriers like blinking and tear drainage reduce bioavailability. Polymers in formulations can enhance drug retention on corneal tissue, improving therapeutic efficacy.General considerations for the design of ocular drug delivery formulations.

1.1. Rationale of alginate as ocular drug carrier:-

Alginate is a beneficial ocular drug carrier due to its mucoadhesive properties, biocompatibility, and biodegradability. It forms non-covalent linkages with mucin, extending drug residence time and improving bioavailability. Alginate transitions from sol to gel via electrostatic interactions with Ca2+ ions, facilitating in situ gelation. Its ion-sensitive gelation and pH-sensitive swelling enhance drug release in ocular environments.

1.2 Alginate microsphere:-

Alginate's gelling and stabilizing properties make it valuable in various industries, including pharmaceuticals, where it serves as a binder and dissolving agent in tablets. Ca2+ alginate hydrogels are effective for drug and protein delivery and cell encapsulation due to their biocompatibility and mucoadhesion. Challenges with Ca2+ alginate microbeads include stability issues and rapid drug release due to high porosity. Coating alginate microspheres with polymers can enhance drug release profiles and stability. These microspheres are extensively used in drug delivery, with significant research dedicated to improving their applications and efficacy.

1.3 Microspheres preparation:-

The creation of Ca2+ alginate microspheres typically involves dropping an alginate solution into a CaCl2 solution, forming instant hydrogels. Factors like needle diameter, flow rate, and solution concentrations affect microsphere size. To standardize production, tools like electrostatic microbead generators and emulsification methods are employed. Internal gelation using CaCO3 or Ca2+ EDTA solutions enables controlled microsphere formation. Innovative technologies, including T-junction equipment and microfluidic devices, offer precise size and shape control, beneficial for drug delivery and cell encapsulation. Recent advancements include microfluidic systems producing various shapes and size-controlled microbeads using silicon micronozzle arrays and Teflon line arrays, enhancing drug delivery applications.

1.4 Application of Eudragit as ocular drug delivery

Enhancing ocular drug bioavailability is crucial due to significant loss from reflex tearing and nasolacrimal drainage. Initial methods involved adding viscosity-building agents like polyvinyl alcohol and methyl cellulose to prolong drug contact time, but their impact was minimal. Mucoadhesive polymers have since gained attention for their ability to bind to the mucin layer of the eye, increasing drug residence time and local concentration. Eudragit, a copolymer used in ophthalmic treatments, demonstrates strong mucoadhesive properties through electrostatic attraction, hydrophobic interactions, and hydrogen bonding. It enables sustained drug release and forms water-insoluble films with variable permeability, applicable in both ocular and transdermal delivery systems.

2. Drug and excipient profile:-

2.1 Diclofenac sodium [83], Chemical Name: Diclofenac sodium

Molecular Formula: C14H10Cl2NNaO2, Molecular Weight: 318.13g/mol

2.2. Description:-

Diclofenac Sodium, a benzene acetic acid-derived NSAID, inhibits cyclooxygenase (COX) non-selectively and reversibly, blocking the transformation of arachidonic acid into prostaglandin precursors, thus preventing the formation of prostaglandins involved in pain, inflammation, and fever.

2.3. Mechanisms of action:-

Putative mechanisms of action of diclofenac may include inhibition of leukotriene synthesis, Inhibition of phospholipase A2, modulation of free arachidonic acid levels, stimulation of Adenosine triphosphate-sensitive potassium channels via the L-arginine-nitric oxide-cyclic Guanosine monophosphate pathway and centrally mediated and neuropathic mechanisms. OtherEmerging mechanisms of action may include inhibition of peroxisome proliferator activated Receptor-c, reduction in plasma and synovial substance P and interleukin-6 levels, inhibition of The thromboxane-prostanoid receptor and inhibition of acid-sensing ion channels.

2.4 Sodium alginate :-

2.4.1 Empirical Formula and Molecular Weight:-

Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of Polyuronic acids composed of residues of Dmannuronic acid and L-guluronic acid.The block structure and molecular weight of sodium alginate samples have been investigated.

2.5 Eudragit RS100 :-

It is a copolymer of Ethyl acrylate, methyl methacrylate and a low content of methacrylic acid Ester with quaternary ammonium groups. The ammonium groups are present as salts and make The polymers permeable.

3. Review of literature:-

Karmakar et al. (2022) explored alginate-based carriers for ocular drug delivery. Alginate, a GRAS polysaccharide from seaweeds and bacteria, offers ion-sensitive gelation, biodegradability, and mucoadhesiveness. These properties enhance ocular drug bioavailability and reduce dosing frequency, inspiring new strategies in ocular therapeutics.

Velázquez-González et al. (2022) developed acetaminophen-loaded alginate microspheres using a water-in-oil emulsion-solvent evaporation technique. The microspheres, sized 1.4-2.6 µm, exhibited 83% yield, 76% encapsulation efficiency, and 46% moisture loss. They demonstrated sustained drug release for up to 20 days in PBS at pH 7.4 and 37°C.

Cassano et al. (2021) reviewed gel-based drug delivery systems for ophthalmic use, emphasizing their adaptability and potential to enhance drug bioavailability and therapeutic efficacy. These materials, used in therapeutic contact lenses, intravitreal injections, gel eye drops, and in situ gelling formulations, offer prolonged-release, increasing precorneal residence time and reducing dosing frequency.

Wang et al. (2018) developed retinoic acid-loaded alginate microspheres (RA-MS) for slow-release intravitreal treatment. These uniformly spherical microspheres, averaging 95.7 ± 9.6 µm, demonstrated controlled, long-term RA release in vitro and in vivo, with excellent biocompatibility and no inflammation, showing promise for retinal PVR treatment.

Uyen et al. (2019) produced alginate microspheres (AMs) using emulsification/gelation, controlling particle size and distribution. Made from sodium alginate, liquid paraffin, and calcium chloride, the spherical AMs averaged under 65.88 µm. SEM and FTIR confirmed morphology and chemical integrity. AMs demonstrated significant potential for drug delivery systems.

4. Need of the study and Objective:-

4.1 Need of study:-

Ocular drug delivery faces challenges due to strong barriers, leading to low bioavailability. Diclofenac sodium, an FDA-approved NSAID for ocular use, is commonly administered as eye drops with low bioavailability and frequent dosing. Enhancing bioavailability

involves prolonging drug residence time using biocompatible-biodegradable matrices like alginate microspheres. Alginate, a polysaccharide, offers quick ion-inducible gelation and size control, improving drug encapsulation and release. Eudragit (EDU) RS 100, a coating material for controlled drug distribution, provides high bioavailability but faces challenges due to its use of organic solvents. This study aims to prolong diclofenac sodium's ocular residence time by employing Eudragit-coated alginate microspheres in a thermosensitive gel. The microspheres ensure controlled, sustained drug release through ion exchange, diffusion, or polymer breakdown, enhancing bioavailability and reducing dosing frequency. Surface modification with a small amount of EDU RS 100 aims to improve ocular properties while ensuring biocompatibility and safety. This innovative approach addresses the limitations of traditional ocular drug delivery methods, aiming for improved patient compliance and therapeutic efficacy.

4.2 Objective

- To improve the drug loading of diclofenac sodium
- To sustain the release of diclofenac sodium

5. ***Plan of Work:-***

- **Literature survey**
- **Preformulation study of drug**

In this investigation involves the assessment of the Organoleptic properties, melting point Determination, solubility study in different solvents, Preparation of standard calibration curve, FT-IR study of pure drug.

- **Preparation of diclofenac sodium loaded alginate microsphere**
- **Evaluation of diclofenac sodium loaded alginate microsphere**

This step involves the assessment of the various prepared diclofenac sodium loaded alginate Microsphere formulation characterization parameters like Percentage Yield, Drug entrapment Efficiency, percentage drug loading, particle size.

- **Preparation of Eudragit RS 100 coated diclofenac sodium loaded alginate microsphere**
- **Evaluation of Eudragit RS 100 coated diclofenac sodium loaded alginate microsphere**

This step involves the assessment of the various prepared Eudragit RS 100 coated diclofenac Sodium loaded alginate microsphere formulation characterization parameters like Percentage Yield, Drug entrapment efficiency, percentage drug loading, particle size and SEM of selected Formulation.

- **Preparation of Eudragit RS100 coated diclofenac sodium loaded alginate microsphere Thermosensitive gel**
- **Evaluation of Eudragit RS100 coated diclofenac sodium loaded alginate microsphere Thermosensitive gel**

  Appearance, pH, Gelation time, % Drug content, In-vitro drug release study, In-vitro drug Release kinetic study and FTIR of selected formulation.

6. ***Experimental work:-***

6.1 Preparation of diclofenac sodium loaded alginate microsphere

Batches of diclofenac sodium-loaded alginate microspheres were prepared using water-in-oil emulsification. Sodium alginate solution was mixed with diclofenac sodium and emulsified into an oil phase containing surfactant and light liquid paraffin. Cross-linking with calcium chloride induced gelation. The stable emulsion was stirred continuously and then allowed to settle. The microspheres were filtered, washed with n-hexane, and dried at room temperature. The composition of formulations varied by sodium alginate amount, stirring speed, and stirring time, with these parameters assessed for their effect on properties such as percentage yield.

6.2 Preparation of Eudragit RS 100 coated diclofenac sodium loaded microsphere

The coating of diclofenac sodium loaded alginate microspheres was executed using the oil-in-oil Solvent evaporation method. The Eudragit RS 100 coating solution was prepared by solubilizing The weighed amount of Eudragit RS 100 in the 5ml of a mixture of the solvent (Ethanol: acetone 4:1). An accurately weighed amount of the 20mg of aluminum stearate was dispersed in the Coating solution as an anti-sticking agent. An accurately weighed amount of the microsphere was Added to the coating solution under continuous stirring at 100rpm for 10min and labeled asPolymer organic solution. The organic coating solution was emulsified in the beaker containing 50 mL light liquid paraffin and 1%w/v of span 80 under continuous stirring at 800rpm the Stirring was continued for the additional 3hr at room temperature. The emulsion was filtered Using the vacuum pump and washed with 50ml of n-hexane three times to remove the light liquid Paraffin. The coated microsphere was dried at room temperature and stored till further use .

6.3 Preparation of thermosensitive gel containing the coated diclofenac sodium loaded Alginate microsphere

The thermosensitive gel containing the coated diclofenac sodium loaded alginate microsphere Consisting of the poloxamer 407 as gelling agent was prepared employing cold method. Accurate Weighed amount of the poloxamer 407 was added slowly to the beaker containing 10ml of Beaker maintained at 4°C with gentle agitation. The mixture was left at 4°C in refrigerator for Overnight for swelling of the polymer. The coated diclofenac sodium loaded microsphere was Added to the clear, transparent solution under continuous stirring at 100rpm at 4°C in ice bath till a uniform solution was formed. The mixture was stored at 4°C till further use [92,112].Composition of thermosensitive gel containing the coated diclofenac sodium loaded alginate Microsphere.

7. Result and Discussion:-

7.1 Preparation and diclofenac sodium loaded alginate microsphere

The microspheres were prepared by water in oil emulsification with a slight modification Method. In the current set of experiments initial batches were prepared by varying the amount of Sodium alginate followed by the next set of batches were prepared under various stirring speedsAnd stirring times. The prepared diclofenac sodium loaded microsphere was evaluated for their Characterization parameters like physical appearance, percentage drug entrapment, percentage Drug loading, and particle size.

7.2 Evaluation of diclofenac sodium loaded alginate microsphere

7.2.1 Physical Appearance

The prepared microsphere formulations were observed for their physical parameters and Observations were shown in Table 7.3. All prepared formulations appeared uniform and spherical In shape except the formulations DAM1 and DAM9. Both formulations DAM1 and DAM9 both Displayed aggregation of particles.

7.2.2 Percentage yield

The percentage yield of the prepared batches of the diclofenac sodium loaded alginate Microsphere is shown in Table 7.4. The observations attributed the yield was found to be Between 77.809±0.532 to 96.061±0.381. The percentage yield of the microspheres was increasesAs the concentration of sodium alginate increased.

7.2.3 Percentage drug entrapment and percentage drug loading

The study found that drug entrapment efficiency (65.533±0.983% to 99.528±0.903%) and drug loading (1.414±0.018% to 5.958±0.089%) are higher compared to the ionotropic gelation method due to diclofenac sodium's high aqueous solubility. Entrapment increased with higher sodium alginate concentration (up to 91.877±0.602% in batches DAM1 to DMA3), but decreased in DAM4 due to increased medium viscosity.

7.3 Preparation of eudragit-coated diclofenac sodium loaded alginate microsphere Formulation

In the current investigation the eudragit RS 100 polymer was employed as a coating material for The diclofenac sodium loaded alginate microsphere to improve the ocular properties including a High bioavailability in the eye. In the current investigation the coating process was executed Employing the different amounts 400mg, 800mg, and 1200mg of eudragit RS 100 and Investigated the properties of the coated diclofenac sodium loaded alginate microsphere .

7.4 Preparation of the eudragit RS 100 coated diclofenac sodium loaded alginate Microsphere thermosensitive gel

The experiment involved preparing Eudragit RS 100-coated diclofenac sodium-loaded alginate microspheres using thermosensitive gel Poloxamer 407. Poloxamer 407 exhibits reversible thermal characteristics, forming spherical micelles and gelation through hydrophobic interactions upon heating. Microspheres were added to poloxamer solutions at varying concentrations (19%, 20%, 21% w/v). The resulting gel's characterization parameters were thoroughly investigated.

8. Summary :-

The aim of the current study to prolong the residence time of the diclofenac sodium employing The eudragit-coated microsphere containing thermosensitive gel. In the preformulation Investigation, the diclofenac sodium drug appeared white, crystalline, odorless,

and tasteless. The Observed value of melting point for diclofenac sodium was found to be was assessed to be 282.670C±1.154-285.340C±0.578. The UV spectrum of the working solution concentration 10µg/ml in methanol indicated absorption maxima at 283nm. The linearity curve of diclofenac Sodium in methanol was prepared between a concentration range of 2-22µg/ml at 283nm. The Linearity curve equation was observed to be Y = 0.0393x+0.0202 with a regression coefficient Value of 0.999 indicating good linearity and accuracy of the developed method. A solubility study Confirmed that diclofenac sodium shows maximum solubility in the methanol followed by Ethanol solvent. The diclofenac sodium also shows sparingly solubility in the water and Simulated tear fluid. FTIR study confirmed the absence of the interaction between diclofenac Sodium and the excipients used in the preparation of the formulation.

The diclofenac sodium loaded microspheres were prepared by water in oil emulsification with a Slight modification method. In the current set of experiments initial batches were prepared by Varying the amount of sodium alginate followed by the next set of batches were prepared under Various stirring speeds and stirring times. The prepared diclofenac sodium loaded microsphere Was evaluated for their characterization parameters like physical appearance, percentage drug Entrapment, percentage drug loading, and particle size. Among all prepared batches of the Microsphere, the batch DAM8 diclofenac sodium loaded microsphere was spherical and discrete Particles as indicated in optical microscopy and SEM images. The batch DAM8 comprises of Diclofenac sodium 0.1%w/v, sodium alginate 5%w/v, and stirring speed and stirring was Employed during the agitation were 600rpm and 120min. respectively. Batch DAM8 possessesThe percentage yield, percentage drug entrapment, percentage drug lading, and particle size 96.061±0.381%, 99.528±0.903%, 2.427±0.022 and 24.910±0.976µm respectively. The residence Time of the microsphere was increased by coating the microsphere using the eudragit RS 100 Polymer at different concentrations. The percentage yield, percentage drug entrapment, Percentage drug loading, and particle size of the coated microsphere batch E2DAM8 were 97.813±0.420%, 98.706±0.467%, 0.822±0.004% and 45.005±0.290 µm respectively. The coated Microsphere formulation was embedded in a thermosensitive gel carrier employing thepoloxamer 407 gelling agent. The formulation E2DAM8G2 possesses pH 6.484±0.035, gelling Time 12.334±1.527sec, and percentage drug content 99.101±0.640%, The in-vitro drug profile Study using the dialysis membrane formulation E2DAM8G2 showed nearly 96.768±0.510% Release of diclofenac sodium within 12 hours while the aqueous drug solution released diclofenac Sodium 99.059±0.180% with in 2hr. The drug release profile of eudragit RS 100 coated Diclofenac sodium loaded alginate microsphere thermosensitive gel E2DAM8G2 was subjected To various kinetic models like zero, first, Higuchi and Korsmeyer peppas model. The regression Coefficient value was found to be higher than 0.944 for the Korsmeyer–Peppas.

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