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Study of Formulation Development and Evaluation of Hydrogel based Mucoadhesive Sustained Release Drug Delivery System of Antifungal Drugs

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ABSTRACT - Recent advancements in the inhalable, injectables, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug administration has been the preferred route for the drug delivery. There are sure components like poor medication solvency or retention, quick digestion system, high change in the medication plasma level and variability in quick and encouraged impact, which assuming imperative part in unsuitable in vivo results that has headed to the disappointment of the routine conveyance framework. The most recent decade, the new measurement has accomplished by oral medication conveyance by utilizing lipid as a transporter for conveying inadequately water solvent, lipophilic medications. Oral medication organization is the favored and most normal course for medication conveyance. A few focal points connected with it incorporate, tolerant consistence, effortless and workable for pharmaceutical toward oneself. In correlation to parenteral conveyance, malady transmission has been stifled by it along with the lessened cost and understanding consistence. Flexible and controlled dosing schedule has also allowed. It is mainly convenient for chronic therapy.

Keywords:- Drug delivery; Mucoadhesion; Oropharyngeal Candidiasis complexation; Transdermal; Parenteral; Trasmucosal

I. Introduction

Drug conveyance alludes to methodologies, details, innovations, and frameworks for transporting a pharmaceutical compound in the body as expected to securely accomplish its craved remedial impact. It may include logical site-focusing inside the body, or it may include encouraging systemic pharmacokinetics; regardless, it is normally concerned with both amount and term of medication vicinity. Drug conveyance is regularly approached by means of a drug's concoction definition; however it might likewise include restorative gadgets or medication gadget mix items. Drug conveyance is an idea intensely coordinated with measurement structure and course of organization, the last frequently actually being viewed as a component of the definition. Drug conveyance innovations alter medication discharge profile, assimilation, appropriation and disposal for the profit of enhancing item viability and wellbeing, and in addition quiet comfort and consistence. Medication discharge is from: dispersion, debasement, swelling, and fondness based systems.

II. Literature survey: Drug Delivery Research on ECN

Moustafa et al, 2006, examined the in vitro helplessness of parasitic life forms to β -cyclodextrin edifices with the ECN and ciclopirox olamine by utilizing laser nephelometry. The antimycotic impact of the edifices against *Candida albicans* DSM 11225 and *Candida krusei* ATCC 6258 species was dead set

utilizing this strategy. A quick restraint and actually slaughtering of both growths was watched just over specific convergences of complex went somewhere around 12.5 and 100 µg/ml for β - cyclodextrin—ECN complex, while for the perplexing with β -cyclodextrin—ciclopirox olamine the extent was somewhere around 150 and 400 µg/ml. The change of solvency of both antimycotic specialists in phosphate cushion arrangement was seen by complexation with β -cyclodextrin.

Sauna et al, 2007 planned Solid lipid nanoparticles of ECN arranged by O/w high-shear homogenization strategy utilizing distinctive proportions of lipid and medication (5:1 and 10:1). After fuse of robust lipid nanoparticles into hydrogels, rheological estimations were performed and ex vivo drug saturation tests were completed utilizing porcine stratum corneum. Utilizing tape stripping technique, in-vivo examination of percutaneous maintenance of ECN as a limit of utilization time and formation of gels was carried out. High shear homogenization system realized a tolerable method for arrangement of ECN strong lipid nanoparticles. Ex vivo tests exhibited that strong lipid nanoparticles could control the medicine release through the stratum corneum; the release rate rely on the lipid content on the nanoparticles. In vivo studies exhibited that robust lipid nanoparticles advanced a fast entrance of ECN through the stratum corneum following 1 hour and enhanced the dispersion of the medication in the deeper skin layers following 3 hour of use contrasted and the reference gel.

Ahmad et al, 2008, exhibited the capability of ECN and moxifloxacin separately against tuberculosis brought on by multidrug safe and idle Mycobacterium tuberculosis. In this study, poly-(dl-lactide-co-glycolide) nanoparticles typified ECN and moxifloxacin were assessed against murine tuberculosis (drug defenseless) keeping in mind the end goal to create a more intense regimen for tuberculosis. Poly (dl-lactide-co-glycolide) nanoparticles were arranged by the numerous emulsion and dissolvable dissipation procedure and were directed orally to mice. A solitary oral dosage of PLG nanoparticles brought about restorative medication focuses in plasma for up to 5 days (ECN) or 4 days (moxifloxacin), whilst in the organs (lungs, liver and spleen) it was dependent upon 6 days. In M. tuberculosis contaminated mice, eight oral measurements of the detailing regulated week by week were discovered to be equipotent to 56 dosages (moxifloxacin controlled day by day) or 112 measurements (ECN directed twice day by day) of free medications. Besides, the mix of moxifloxacin +ecn turned out to be essentially useful contrasted and individual medications. Expansion of rifampicin to this mix brought about aggregate bacterial freedom from the organs of mice in 8 weeks. Poly (dl-lactide-co-glycolide) nanoparticles seem to have the potential for irregular treatment of tuberculosis and mix of moxifloxacin, ECN and rifampicin is the most powerful.

Passerini et al, 2009, examined the suitability of the shower hardening procedure to deliver robust lipid microparticles for topical organization and to study the skin pervasion of ECN from contrasted and strong lipid nanoparticles. Solid lipid microparticles had atom sizes of 18-45 micron, while hearty lipid nanoparticles showed a mean distance across of 130-270 nm. The epitome effectiveness was 80-100%. Saturation profiles of ECN were impacted by both molecule size (huge contrast until 9 hour) and the measure of lipid. The results affirm the handiness of strong lipid nanoparticles as transporters for topical organization and recommend the capability of robust lipid microparticles for the ECN conveyance of medications to the skin.

Albertini et al, 2009, scrutinized mucoadhesive microparticles for creative vaginal conveyance frameworks of ECN ready to upgrade the medication antifungal movement. Seven separate plans were arranged by splash coagulating: a lipid-hydrophilic network (Gelucire 53/10) was utilized as transporter and a few mucoadhesive polymers, for example, chitosan, sodium carboxymethylcellulose and poloxamers (Lutrol F68 and F 127) were included. The antifungal action of the microparticles against a strain of *Candida albicans* ATCC 10231 was explored. Both poloxamers essentially ($p < 0.01$) enhanced the dissolvability and in vitro bioavailability of the low solvency drug and the mucoadhesive quality. Poloxamers/Gelucire based microparticles showed a hindrance impact on the *C. albicans* development, proposing their utilization as a compelling treatment for vaginal candidiasis, with potential for diminished organization recurrence. The results exhibited that shower coagulating engineering can be viewed as a novel and dissolvable free approach for the generation of mucoadhesive microparticles for the vaginal conveyance of ECN.

Current endeavors in the territory of medication conveyance incorporate the advancement of focused on conveyance in which the medication is just dynamic in the target zone of the body (for instance, in harmful tissues) and managed discharge details in which the medication is discharged over a time of time in a controlled way from a plan. With a specific end goal to attain to effective focused on conveyance, the composed framework must keep away from the host's protection instruments and flow to its expected site of activity.

Oral and oropharyngeal candidiasis is a crafty, irresistible condition brought on by a pervasive, saprophytic parasite of the class *Candida*, the most well-known of which is *Candida albicans*. Physician endorsed medication information have demonstrated a wonderful increment in the recurrence of the sickness amid the most recent two decades. Parasitic sharp contaminations, including oral and oropharyngeal candidiasis, are significant reason for horribleness and mortality in tumor patients. Numerous elements can incline a patient to oral and oropharyngeal candidiasis, the most huge of which is the contamination connected with AIDS immunosuppression. General crippling, poor oral cleanliness, badly fitted dentures are a portion of the other inclining variables in charge of the reason for Candidiasis in the oral cavity. Likewise, those people burdened with xerostomia, diabetes mellitus, patients accepting chemotherapy are high hazard for sharp contagious diseases. Mucoadhesion has gotten to be an intriguing theme for exploration in the course of the most recent two decades, for its capability to advance limited medication conveyance, by holding dose structures at the site of activity or systemic conveyance, by holding a detailing in private contact with the ingestion site. mucoadhesive definitions are generally arranged with mucoadhesive polymers. Original mucoadhesive polymers will be hydrophilic in nature, having constrained solvency in different solvents, structuring high gooey fluid in water and pH delicate. These attributes present critical difficulties in the definition improvement of mucoadhesive definitions.

Drug conveyance frameworks that can definitely control the discharge rate of medication to particular body locales have a colossal potential in the medicinal services world. The most recent two decades in the pharmaceutical business have seen an avant-grade connection in the field of polymers and material science, bringing about the improvement of different novel medication conveyance frameworks. Research and mechanical progressions in medication conveyance have prompted usage of more extensive courses for medication organization. Notwithstanding, oral medication conveyance for systemic and nearby impacts still remains the course of decision for medication organization. Peroral organization of medications has notable impediments, for example, hepatic first pass digestion system and enzymatic debasement inside the GI tract, that deny oral organization of specific classes of medications particularly peptides and proteins. Hence, other absorptive mucosae are considered as potential destinations for medication organization.

The idea of bioadhesion includes the coupling of a common/ manufactured bioadhesive polymer to natural substrate, for example, bodily fluid layers and epithelium. Transmucosal course of medication conveyance (for instance - the mucosal covering of nasal, rectal, vaginal, visual and oral depression) offer unique points of interest over peroral organization. Oral mucosal medication conveyance offers a few focal points

Prolongation of the home time of measurements structure at site of retention:-

- As residence time increased, there is enhanced absorption and therapeutic efficacy of drug and improving drug bioavailability.
- Provides rapid drug transport to systemic circulation and avoids degradation by first pass hepatic metabolism.
- Accessibility is excellent and acidic degradation of drug is prevented.

These factors make the oral mucosal cavity a very attractive and feasible site for drug delivery. The oral cavity has been used as a site for local and systemic drug delivery.

Advantages of Buccal Drug Delivery Include

prolongation of the living arrangement time of the measurements structure at the site of retention. As the living arrangement time is expanded, there is upgraded retention and remedial viability of the medication. Fast retention in light of the fact that of tremendous blood supply and great blood stream rates.

- Bioavailability will be expanded due to first pass digestion system shirking.
- Acidic corruption of the medication in gut is forestalled.
- improved tolerant consistence ease of drug organization.
- Mucosal surface gives, quicker onset of activity.
- when the dry measurements structures will be in contact with surfaces with a flimsy bodily fluid layer, such as a buccal mucoadhesive film, two steps are required to secure the Mucoadhesive bond, viz. A contact and a solidification stage.
- mucoadhesion can be characterized as the capacity of manufactured or natural macromolecules to stick to mucosal tissues such as mucosa of eyes, nose, oral, digestive system, rectum and vagina. Mucoadhesion IS considered happening in three major stages: wetting, interpenetration and mechanical interlocking between bodily fluid and polymer. The quality of mucoadhesion is influenced by different components such as sub-atomic mass of polymers, contact time with bodily fluid, swelling rate of the Polymer.

III. Aim and Objective of the our work

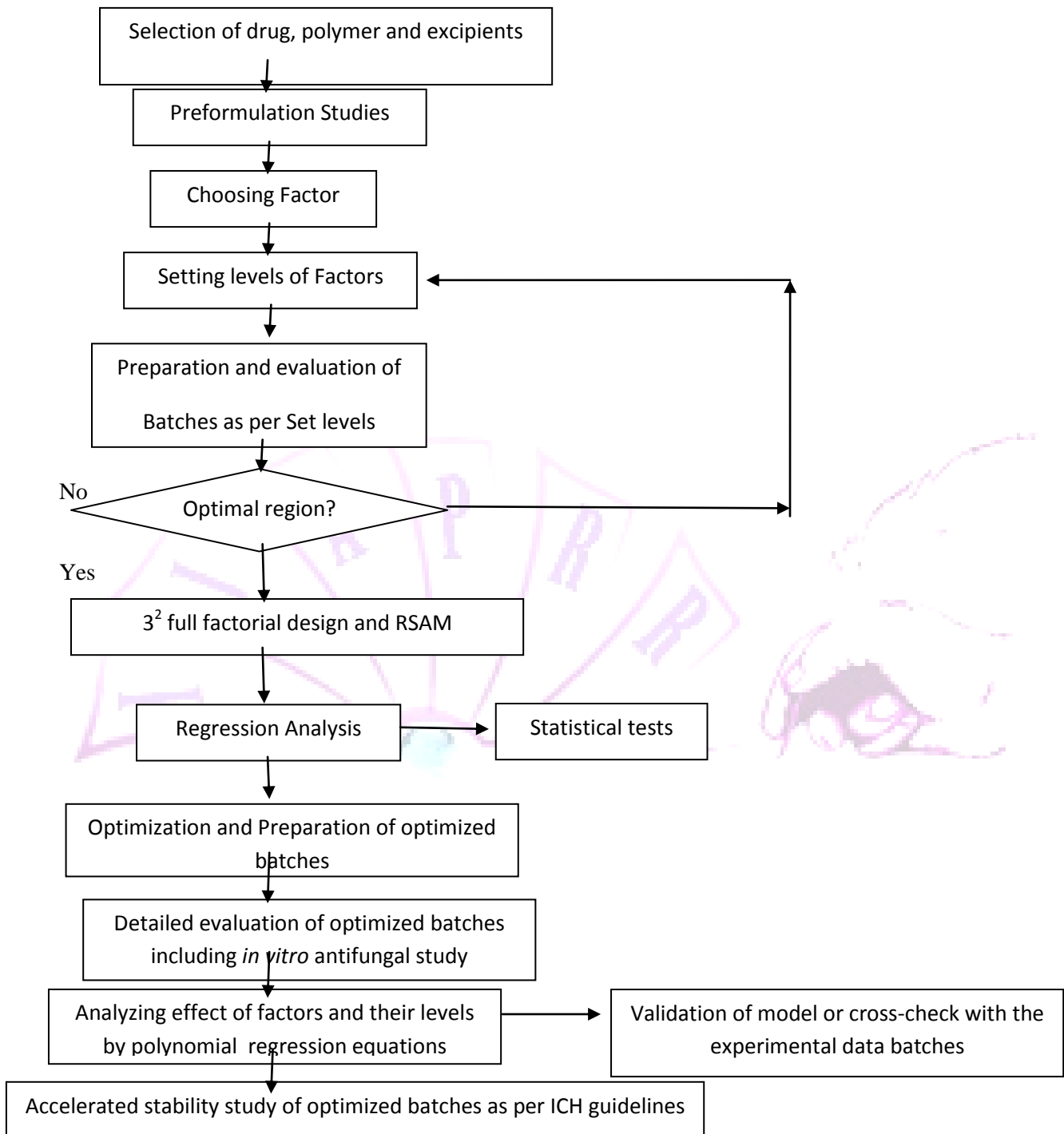
The rationale of the proposed work is to formulate, develop and evaluate Hydrogel based mucoadhesive sustained release drug delivery system of Econazole Nitrate (a potent imidazole antifungal) (ECN) and Nystatin (a polyene antifungal antibiotic) (NYS), potent anti-candidal agents. Hydrogel based mucoadhesive property of the mucoadhesive hydrogel film (MHF) ensure the biocompatibility and increase the retention time whereas sustained release part of the system decrease the frequency of application of the delivery system. So all the problems discussed above with the therapy of oral and oropharyngeal candidiasis can be solved

In the light of the above cited objectives and background (preamble), the principal objective of work is to formulate mucoadhesive films containing small dose of antifungal drugs like Econazole, Miconazole, Nystatin, Fluconazole or Itraconazole etc for topical treatment of oral candidiasis to ensure satisfactory drug level in the mouth for prolonged duration of time and to reduce side effects and possibility of drug interaction encountered during systemic therapy. The prepared formulations would be evaluated through in vitro and in-vivo antifungal activity on *Candida Albicans*

- To select drugs, polymers and excipients.
- To study the preformulation factors including drug-drug, drug-polymer and polymer-polymer interaction and to decide the polymers and other excipients.
- To develop the analytical methods of the drugs in the selected media.
- To decide and set independent variables and their degrees and dependent variables as per the 3² full factorial design.

Our Proposed Flow Chart

Flow Chart of Plan of Work and Experimental Design



Experimental design and formulation protocols

full factorial design was applied as follows

Freezing/Thawing method

Table 1.1 Batch codes and coded values of factor X_1 and factor X_2 of the MHFs prepared by Freezing/Thaw method

Batch Code (With ECN)	Batch Code (With NYS)	Factor X_1	Factor X_2	Y_1 to Y_4
EF1	NF1	-1	-1	
EF2	NF2	-1	0	
EF3	NF3	-1	+1	
EF4	NF4	0	-1	
EF5	NF5	0	0	
EF6	NF6	0	+1	
EF7	NF7	+1	-1	
EF8	NF8	+1	0	
EF9	NF9	+1	+1	

Table 1.2 Coded values and actual values of factor X_1 and factor X_2 of the MHFs by Freezing/Thaw method

Coded values	Actual values	
	Factor X_1	Factor X_2
-1	10	4
0	15	6
+1	20	8

Where, X_1 - Concentration of PVA (% w/v of initial gel)

X_2 - Number of Freeze/Thaw cycles

Y_1 - Time required for 50 % drug release.

Y_2 - Percent of drug Release at 8th hour.

Y_3 - 'k' of Zero order equation.

Y_4 - 'n' of Peppas equation.

X_1 and X_2 are Independent variables

Y_1 , Y_2 , Y_3 and Y_4 are Dependent variables

Table 1.3 Formula for optimization of MHFs of ECN prepared by Freezing/Thawing method

Ingredient	Formulation Batch Codes								
	EF1	EF2	EF3	EF4	EF5	EF6	EF7	EF8	EF9
Econazole Nitrate (mg per MHF)	80	80	80	80	80	80	80	80	80
PVA(%w/v of initial gel)	10	10	10	15	15	15	20	20	20
PEG400 (%v/v initial of gel)	5	5	5	5	5	5	5	5	5
Ethanol (%v/v of initial gel but <1% in the MHF due to evaporation)	3	3	3	3	3	3	3	3	3
No. of freezing/Thaw cycles (not ingredient but important process variable)	4	4	4	6	6	6	8	8	8

Table 1.4 Formula for optimization of MHFs of NYS prepared by Freezing/Thawing method

Ingredient	Formulation Batch Codes								
	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9
Nystatin (mg per MHF)	80	80	80	80	80	80	80	80	80
PVA(%w/v of initial gel)	10	10	10	15	15	15	20	20	20
PEG400 (%v/v initial of gel)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Tween 80 (% v/v of initial gel)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
No. of freezing/Thaw cycles (not ingredient but important process variable)	4	4	4	6	6	6	8	8	8

Copolymerization with Gelatin

Table 1.5 Batch codes and coded values of factor X1 and prepared by Copolymerization with Gelatin method.

Batch Code (With ECN)	Batch Code (With NYS)	Factor X ₁	Factor X ₂	Y ₁ to Y ₄

EG1	NG1	-1	-1
EG2	NG2	-1	0
EG3	NG3	-1	+1
EG4	NG4	0	-1
EG5	NG5	0	0
EG6	NG6	0	+1
EG7	NG7	+1	-1
EG8	NG8	+1	0
EG9	NG9	-1	-1

Table 1.6 Coded values and actual values of factor X1 and factor X2 of the MHFs by Copolymerization with Gelatin method.

Coded values	Actual values	
	Factor X1	Factor X2
-1	10	1.5
0	15	2.5
+1	20	3.5

Where,

X₁ - Concentration of PVA (% w/v of initial gel)

X₂ - Concentration of Gelatin (% w/v of initial gel)

Y₁ - Time required for 50 % drug release.

Y₂ - Percent of drug Release at 8th hour.

Y₃ - 'k' of Zero order equation.

Y₄ - 'n' of Peppas equation.

X₁ and X₂ are Independent variables

Y₁, Y₂, Y₃ and Y₄ are Dependent variables

Table 1.7 Formula for optimization of MHFs of ECN prepared by Copolymerization with Gelatin method.

Ingredient	Formulation Batch Codes								
	EG1	EG2	EG3	EG4	EG5	EG6	EG7	EG8	EG9
Econazole Nitrate (mg per MHF)	80	80	80	80	80	80	80	80	80
PVA(% w/v of initial gel)	10	10	10	15	15	15	20	20	20

Gelatin (% w/v of initial gel)	1.5	2.5	3.5	1.5	2.5	3.5	1.5	2.5	3.5
PEG400 (%v/v initial of gel)	5	5	5	5	5	5	5	5	5
Ethanol (%v/v of initial gel but <1% in the MHF due to evaporation)	3	3	3	3	3	3	3	3	3

Table 1.8 Formula for optimization of MHFs of NYS prepared by Copolymerization with Gelatin method.

Ingredient	Formulation Batch Codes								
	NG1	NG2	NG3	NG4	NG5	NG6	NG7	NG8	NG9
Nystatin (mg per MHF)	80	80	80	80	80	80	80	80	80
PVA(%w/v of initial gel)	10	10	10	15	15	15	20	20	20
Gelatin (% w/v of initial gel)	1.5	2.5	3.5	1.5	2.5	3.5	1.5	2.5	3.5
PEG400 (%v/v initial of gel)	5	5	5	5	5	5	5	5	5
Ethanol (%v/v of initial gel but <1% in the MHF due to evaporation)	3	3	3	3	3	3	3	3	3

IV. Conclusion

We discuss traditional polymer networks to find other innovative drug transport systems. A significant part of the advancement of novel materials in controlled discharge buccal cement drug conveyance is concentrating on the arrangement and utilization of responsive polymeric framework utilizing copolymer with alluring hydrophilic/hydrophobic cooperation, piece or unite copolymers, complexation systems reacting through hydrogen or ionic holding and new biodegradable polymers particularly from common palatable sources. At the current worldwide situation, researchers are discovering approaches to create buccal glue frameworks through different methodologies to enhance the bioavailability of orally less/wasteful medications by controlling the plan systems like consideration of pH modifiers, chemical inhibitors, saturation improves and so forth. Novel buccal glue conveyance framework, where the medication conveyance is steered towards buccal mucosa by securing the nearby environment is likewise picking up investment. Presently strong measurement structures, fluids and gels connected to oral pit are monetarily effective.

Present neighborhood treatment by ordinary measurements structures is awkward and similarly inadequate. This may be because of their wastefulness in keeping up the salivary amassings of the medication over the MIC for the delayed time of time, which might thus be because of the diluent impact of salivation emissions coupled with the purifying activity of the oral musculature. The present study is an attempt to develop mucoadhesive hydrogel films of drugs which could deliver the drugs locally in the oral cavity at concentration above MIC for a prolonged period of time

V. Future Work

The main impediment to the use of many hydrophilic macromolecular drugs as potential therapeutic agents is their inadequate and erratic oral absorption. The moderately late development of recombinant DNA examination and present day engineered and biotechnological strategies permit the organic chemist and scientific expert to deliver unlimited amounts of assortment of peptides and proteins having better pharmacological adequacy. On the other hand, remedial capability of these mixes lies in our

capacity to outline and accomplish powerful and stable conveyance frameworks. The future test of pharmaceutical researchers won't just be polypeptide cloning and amalgamation, additionally to create compelling non-parenteral conveyance of in place proteins and peptides to the systemic dissemination. Buccal pervasion can be enhanced by utilizing different classes of transmucosal and transdermal entrance enhancers, for example, bile salts, surfactants, unsaturated fats and subsidiaries, chelators and cyclodextrins.

The future heading of buccal glue drug conveyance lies in immunization definitions and conveyance of little proteins/peptides. Microparticulate bioadhesive frameworks are especially intriguing as they offer security to restorative elements and additionally the upgraded retention that result from expanded contact time gave by the bioadhesive segment. Energizing difficulties stay to impact the bioavailability of medications over the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa. Successfully developing these novel formulations requires assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials.

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