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Research Article

Polysaccharide-based Controlled Release Mucoadhesive Drug Delivery System for Pain Management

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ABSTRACT

Mucoadhesion is one of the most extensively studied methods for the administration of medication for faster onset of action with enhanced bioavailability. Present investigation was concerned with developing and characterizing a controlled-release muco-adhesive drug delivery system for the tramadol hydrochloride (TRD) to extend the duration of analgesia for patients suffering from acute to chronic pain. Formulations were made using the solvent casting technique, incorporating natural polymers like guar gum, xanthum gum and chitosan in conjunction with hydroxy propyl methyl cellulose (HPMC) to modify the drug release. Fourier transform infrared (FTIR) spectroscopy validated the compatibility of film components and subjected to physicochemical evaluation parameters and *ex-vivo* drug diffusion study. Optimized formulation was tested for analgesic efficacy *in-vivo* to determine extent of their suitability in therapeutic use. All the prepared formulations exhibited superior pharmaceutical qualities with respect to drug content, folding endurance, swelling index and mucoadhesion time. In *ex-vivo* drug diffusion study, all the films displayed a controlled release lasting longer than eight hours. Formulations containing chitosan in combination with HPMC (F6) showed better controlled drug release over other combinations. The formulation F6 bring out remarkable *in-vivo* analgesic efficacy with 58.10% analgesia in contrast to the standard (61.16%). It was deduced that tramadol hydrochloride mucoadhesive films were found to be an effective treatment for moderate to severe pain with a quick onset and a lengthy half-life.

Introduction

Mucoadhesive controlled delivery method for medication is very advantageous, since it provides a controlled drug release for extended periods and targets the medication to a certain area of the body. The prolonged duration of drug residency in the body in turn prolongs its duration of action. This approach can be employed across various routes such as respiratory, gastrointestinal, ocular, buccal, nasal, urethral, rectal, and vaginal, providing both local and systemic effects at a gradual, predetermined rate. Notably, this method offers distinct benefits compared to conventional dosage forms like mouthwashes, oral gels, and lozenges.[1] When considering oral administration, targeting the buccal cavity proves advantageous due to its ease of use, potential for minimizing drug deterioration in the biological fluid, and avoidance of hepatic metabolism.[2] Direct application of oral mucoadhesive formulations to affected mucosal regions demonstrates promise in maintaining effective drug concentrations and exerting control over these levels for extended durations, thereby potentially reducing the need for frequent applications and optimizing treatment efficacy.[3] Various synthetic and natural adhesive polymers have been explored for formulating formulations that interact with mucosal surfaces, with a preference for natural polymers due to their biocompatibility and biodegradability.[4] This study utilizes natural mucoadhesive polymers such as chitosan, guar gum, xanthan gum, and HPMC, which effectively adhere to mucosal tissues, thereby prolonging drug action in the targeted area.

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An opioid analgesic called tramadol hydrochloride (TRD) used to treat mild to severe pain by inhibiting the serotonin-norepinephrine reuptake receptor. It shows the beginning of its effect after about one hour of oral administration. It acts centrally and useful for moderate to severe pain relief.[5] Various formulations containing tramadol HCl are available on the market in liquid, semi-solid, and solid forms. TRD belongs to BCS type-I (having High solubility & high permeability) and shows fast diffusion through the mucosal membrane to reach the systemic circulation. The bioavailability of the drug is less than 70% upon giving orally, with a half-life of approximately 6 hours, necessitating frequent dosing to maintain continuous pain relief.[6] While potent NSAIDs, opioid analgesics, semi-synthetic opioids, and neuroleptic analgesics are typically effective in managing post-operative pain, there are instances, particularly immediately after surgery, where even these strong analgesics may prove inadequate. Following the subsiding of the effects of general anesthetics, typically within 6 to 12 hours post-surgery, patients often experience severe pain that may be difficult to manage. Consequently, this research was undertaken to investigate the possibilities and the determination of the total efficacy of the topical delivery, as topical drug delivery is increasingly considered an option.[7] Considering the pharmacokinetics and physicochemical properties of the drug, it was assumed that the drug can be formulated as a mucoadhesive system.[8]

The current study aimed to create and assess a novel tramadol HCl mucoadhesive film for extended analgesia and to improve the formulation characteristics by incorporating the analgesic agent with different mucoadhesive polymers. The development of a controlled-release medication that could deliver the drug at a preprogrammed rate will prolong its action in the body by affecting its elimination. Consequently, formulations were developed using the solvent casting technique to produce thin films, which were assessed as formulations with the aim of enhancing therapeutic effectiveness, potency, and bioavailability while also decreasing dosing frequency and enhancing adaptability.

Materials and Methods

Materials

TRD was purchased from Ralington Pharma LLP (India) Ahmedabad, Gujarat. Chitosan, HPMC E5 and other polymers have been purchased from Yarrow Chem. Pvt. Ltd, India. Guar gum, xanthum gum, PEG400 and ethanol were bought from Loba Chemie Pharmaceutical Pvt. Ltd. The remaining substances and reagents/chemicals used were of analytical grade.

Methods: Mucoadhesive Film Preparation

The details of all formulations (F1-F9) are presented in Table 1, which were prepared using the solvent casting method. Precisely measured amounts of polymer(s) (Guar Gum, Chitosan, Xanthan Gum) were combined with the appropriate quantity of distilled water under stirring using a mechanical stirrer, followed by the addition and thorough mixing of the drug. The polymer was dissolved in ethanol and added to drug-polymer solution with stirring to obtain a uniform dispersion, followed by the addition of plasticizer PEG400. The resulting system was stirred for 30 minutes, set aside to remove air bubbles, casted, and kept for air drying for a full day. Dried formulations were cut into 2x2 cm^2 pieces for further evaluation.

Evaluation

The formulations were assessed for their physical properties like appearance and texture by applying on the skin.

Weight uniformity of patch

Three formulations from each batch were individually weighed, and the weight (average) was calculated.

Thickness of patch

Screw gauze was used to measure thickness of the film with a minimum count (0.01 mm) at 3 different locations, and the average thickness was recorded.[9]

Folding endurance of patch

Flexibility of formulations was quantified as folding endurance, deduced by repetitively doubling over a short

Table 1: Formulation table

Formulation Ingredients	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Tramadol HCl(%)	55.5	50.0	45.5	55.6	50.0	45.5	55.6	55.6	45.5
HPMC (%)	33.3	30.0	27.3	33.3	30.0	27.3	33.3	33.3	27.3
Guar gum (%)	11.1	20.0	27.3	-	-	-	-	-	-
Chitosan (%)	-	-	-	11.1	20.0	27.3	-	-	-
Xanthum gum (%)	-	-	-	-	-	-	11.1	22.2	27.2
PEG 400 (%)	2	2	2	2	2	2	2	2	2
Acetic acid (%)	-	-	-	1	1	1	-	-	-
Ethanol (ml)	10	10	10	10	10	10	10	10	10
Distill water (mL)	10	10	10	10	10	10	10	10	10

strip of the formulation (appx 2 x 2 cm^2) at the same point until it fractured. The number knew the folding endurance value, the patch could be doubled over at the same place without breaking.[10]

Swelling index of patch

This study was conducted to assess the water uptake or hydration level of the selected polymer used in film fabrication. Pre-weighed formulations were placed in Petri dishes, and 10 mL of phosphate buffer pH 6.8 was introduced. The change in weight resulting from water absorption and patch swelling over 6 hours was recorded at regular intervals, and the % swelling ratio was computed using the designated equation.[11]

$$\text{Swelling ratio } (\%) = \frac{W_t - W_0}{W_0} \times 100$$

where, W_t – weight/area of the swollen patch after time t and
W_o – weight/area of original patch at zero time.

pH of patch

Surface pH of formulations was determined after their swelling in phosphate buffer 6.8 for about 2 hours using a pH meter placed on the surface, and mean value of three readings was recorded.[12]

Drug content uniformity

Drug content uniformity was assessed by dissolving a patch (2x2cm^2 size), containing tramadol HCl in 50 mL of phosphate buffer (pH 6.8) with agitation. The solution was filtered to eliminate any insoluble residual matter, and 1-mL of this filtrate was further diluted to 10 mL with phosphate buffer (pH 6.8). The absorbance was measured at the λ_{max} of 271.1 nm using a UV-visible spectrophotometer. This experiment was conducted in triplicate for formulations from all formulations (F1-F9).[13]

Ex-vivo mucoadhesion time

The *ex-vivo m*ucoadhesive time was evaluated using a modified disintegration apparatus (USP) version. The media consisted of 800 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C. A 2 cm section of porcine buccal tissue was used to attach an adhesive (cyanoacrylate glue) on a rectangular glass piece. The formulation was hydrated on one side with phosphate buffer (pH 6.8), and subsequently, the wet surface was exposed to the mucosal membrane. This set up was then fixed vertically, allowing for vertical up-down movement and complete immersion. The total time taken for the formulation to fully erode or separate from the mucosa was observed and recorded (n = 3).[14]

Ex-vivo drug diffusion study

The drug diffusion study was conducted utilizing Franz diffusion cell employing freshly obtained goat buccal mucosa as the barrier membrane. The membrane was dipped in phosphate buffer (pH 6.8) for 30 minutes and then positioned between the receptor and donor compartments. Phosphate buffer (pH 6.8), totaling 20 mL, was added to the receptor compartment, which was maintained at 37 ± 0.5°C with hydrodynamics set using a magnetic stirrer. A single film measuring 2 x 2 cm^2, previously moistened with a few drops of phosphate buffer (pH 6.8), was placed in the donor compartment. Samples were collected at regular intervals of 1-minute for 8 hours and replaced with an equal volume of buffer. Percentage of drug diffused was evaluated using UV spectrophotometer at λ_{max} of 271.1 nm.[15]

In-vivo analgesic activity

The study was performed according to IAEC guidelines. The experimental animals were kept in separate cages and allowed for food at regular intervals with water. Male albino rats were divided into three groups, with six rats in each group. The control group received blank (non-medicated) films, the test group received tramadol HCl medicated formulation (50 µg•kg–1 body mass), and the third group was administered Marketed tramadol HCl formulation. A 0.6% (v/v) acetic acid solution (10 $mL.kg^{-1}$) was injected intra-peritoneally three hours following treatment. The total number of "writhes" induced by chemical pain (such as stomach constriction, trunk turning, and hind leg extension) was recorded for 20 minutes. Analgesic activity was quantified as the percentage reduction in writhes compared to the control group.[16]

RESULTS

Preformulation Study

λ_{max} determination

UV absorption spectra of tramadol hydrochloride in phosphate buffer pH 6.8 &7.4 showed λ_{max} at about 271.10 nm, as in Fig. 1.

FTIR study

- *FTIR spectrum*

Fourier-transform infrared spectroscopy (FTIR) identified the structure of tramadol HCl. The characteristics peaks of pure drug tramadol HCl were showed in infrared spectra, which can be used to identify its structure as in Fig. 2.

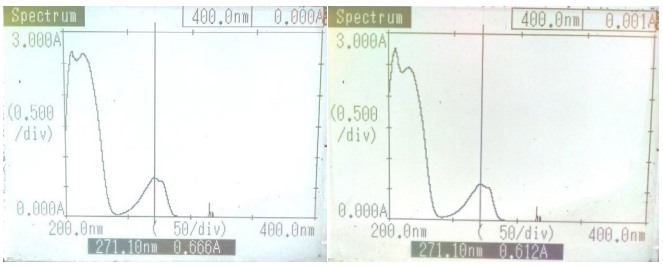

Fig. 1: UV absorption spectrum of tramadol HCl in buffer (pH 6.8 & 7.4)

Characteristic peaks observed in pure drug FTIR spectra were shown in Table 2.

Drug-excipient compatibility study

The drug-excipient compatibility studies were conducted using FTIR spectroscopy by comparing characteristic peaks present in drug spectra with the peaks present in spectra obtained from drug and polymers combination. No interactions were observed as shown in Table 2 and Fig. 3.

Evaluation of Formulations

Weight variation, surface pH, thickness, drug content uniformity and folding endurance

The results of the evaluated parameters are shown in Table 3. The average weight of formulations (F1-F9) ranged from 125 to 147 mg with very less difference in the weight among each patch. Thicknesses for all the formulations were found within the range of 0.49 ± 0.08 mm to 0.58 ± 0.01 mm. All formulations showed a surface pH in the range of 5.73 to 6.46. The folding endurance provides a measure of the patch's mechanical strength.[17] The formulations' folding endurance for was found in the range of 213.33 ± 3.51 to 269.66 ± 2.08.

Swelling index and ex-vivo mucoadhesion time

The initial hydration and swelling are crucial functional attributes that significantly impact mucoadhesion and drug release. The average swelling index and *ex-vivo*

Table 2: FTIR spectrum of Tramadol HCl

Sample	*Obtained peak values (cm^{-1})*	*Theoretical frequency(cm^{1})*	*Functional group*
Tramadol HCl	3301	3500–3100	O-H stretching
	1577	1550–1600	C=C stretching
	2928	2960–2850	Methyl (-CH) stretching
	1241	900–1300	C-O stretching
	1288	1000–1410	Amine C-N stretching
	981	800–1200	C-C (Benzene ring)

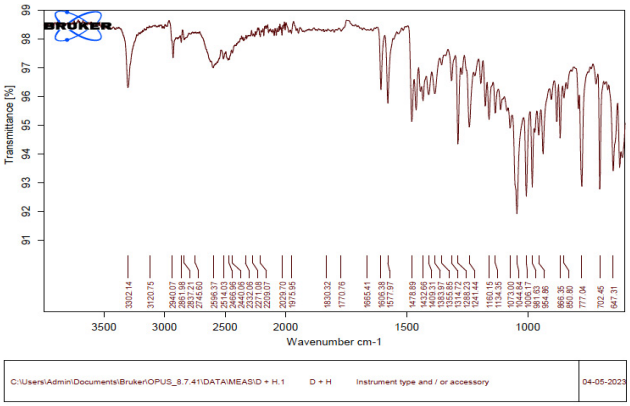

Fig. 2: FT-IR Spectra of tramadol HCl

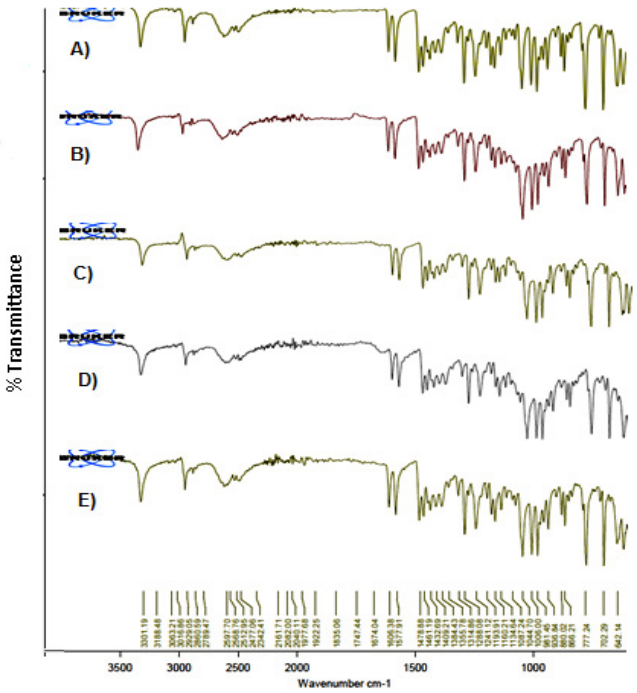

Fig. 3: Fourier transform infrared spectroscopy (FTIR) spectra of: A) Pure Drug, B) Drug + HPMC, C) Drug + Guar Gum, D) Drug + Chitosan, E) Drug + Xanthum Gum

Table 3: Results for dosage form evaluation

Formulation	*Average weight (mg)*	*Thickness (mm)*	*Folding endurance*	*Surface pH*	*Drug content uniformity%*
F1	134.7 ± 1.15	0.55 ± 0.05	213.3 ± 3.51	6.33 ± 0.05	94.4 ± 0.27
F2	137.7 ± 1.27	0.56 ± 0.07	236.0 ± 1.00	6.16 ± 0.05	90.1 ± 0.07
F3	143.3 ± 1.05	0.57 ± 0.06	246.7 ± 3.51	5.82 ± 0.11	93.4 ± 0.11
F4	133.3 ± 1.25	0.53 ± 0.08	243.3 ± 2.08	6.46 ± 0.05	95.0 ± 0.40
F5	128.7 ± 1.15	0.56 ± 0.05	257.3 ± 4.50	6.29 ± 0.35	92.3 ± 0.49
F6	125.0 ± 0.56	0.58 ± 0.01	269.7 ± 2.08	6.12 ± 0.37	98.5 ± 0.07
F7	127.7 ± 1.52	0.49 ± 0.08	223.3 ± 2.64	6.15 ± 0.26	97.8 ± 0.80
F8	145.7 ± 1.32	0.53 ± 0.05	238.0 ± 1.95	5.94 ± 0.15	93.9 ± 0.11
F9	147.7 ± 0.87	0.56 ± 0.04	256.7 ± 2.00	5.73 ± 0.20	96.9 ± 0.81

Value- ± s.d

Table 4: Results of swelling index & *ex-vivo* mucoadhesion time

Formulation	*Swelling index*	*Ex-vivo mucoadhesion time (in hrs)*
F1	42.57	3.23
F2	38.20	3.56
F3	35.15	3.34
F4	36.32	4.05
F5	33.76	4.61
F6	30.05	5.43
F7	38.00	4.65
F8	35.45	4.97
F9	32.57	5.34

Table 5: *In-vivo* analgesic activity of mucoadhesive formulation

Drug	*Oral dose*[a] *($\mu g \cdot kg^{-1}$)*	*Analgesic activity*	
		No. of reactions[b]	*Analgesia%*
Control (without drug)	–	74 ± 4	–
Pure drug (standard)	10	28 ± 1[c]	62.16
F6 (Formulation)	20	31 ± 2[c]	58.10

a = Dose equimolar to drug as per the drug content.
b = Mean ± sem, n = 6.
c = $p < 0.05$ vs. control.

mucoadhesion time are detailed in Table 4. Swelling index and *ex-vivo* mucoadhesion time for formulations (F1-F9) were shown in Figs 4 and 5. The film exhibited a swelling index ranging from 30.05 to 42.57%, while the *ex-vivo* mucoadhesion time varied between 3 to 5 hours, based on the polymer used under experimental conditions.

- *Ex-vivo drug release study*

Regarding the *ex-vivo* drug release study, the release of tramadol hydrochloride through goat buccal mucosa was investigated using a Franz diffusion assembly with a 20 mL capacity. The percentage cumulative drug release over time for different formulations from F1 to F9 is depicted in Fig. 6. An observed trend indicated a decrease in drug release from 92.61 to 72.86% with an increase in polymer concentration in formulations from F1 to F9.

- *In-vivo analgesic activity*

Formulation F6 was subjected to study of *in-vivo* analgesic activity which exhibited significant analgesia (58.10%) as compared to standard which showed 62.16% of analgesia (Table 5).

Discussion

Mucoadhesion stands out as one of the extensively explored strategies for delivering drugs, aiming for rapid onset of action and enhanced bioavailability. The buccal mucosa is highly perfused and thus can deliver drugs directly to blood.[18] In the present study a combination of polymers were taken and the effects of the incorporation

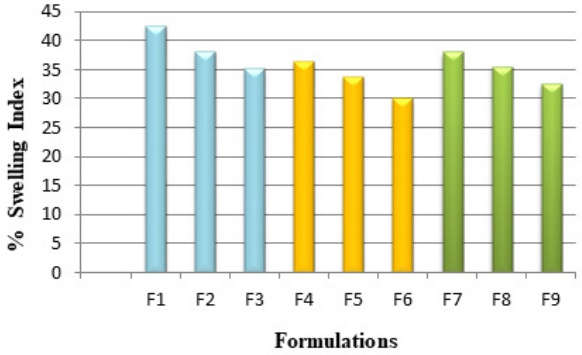

Fig. 4: Swelling index (after six hrs.) of formulations (F1-F9)

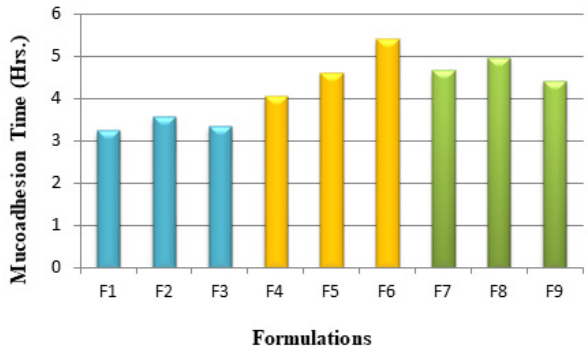

Fig. 5: *Ex-vivo* mucoadhesion time of formulations (F1-F9)

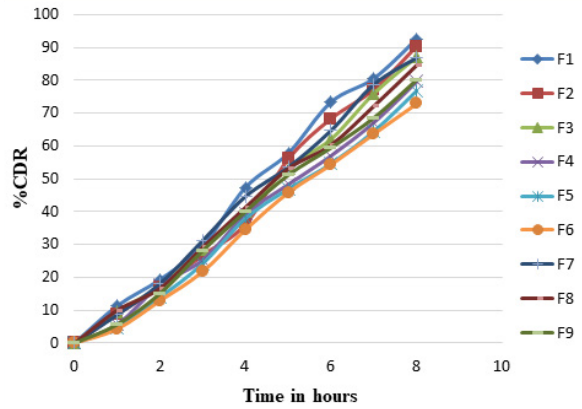

Fig. 6: %Cumulative drug release of different formulations F1-F9

of polysaccharides in combination was done. Different batches were formulated using varied composition of polymers and evaluated.

The FTIR analysis of the drug showed all the identical peaks of the drug and no additional, thus confirming the purity and identity. The primary concern when using a combination of polymers is probable interaction, which may cause alteration in the free drug availability and incompatibilities. The FTIR study shows no structural change or any chemical reaction of drug with the polymers used.

Upon application of mucoadhesive formulations, usually it is observed that the formation of skin folds may cause damage to the integrity of the formulation. The folding

endurance test also confirms the formulation's strength during its storage and handling. The folding endurance value was found to be highest for formulation F6 and the lowest for formulation F1. It was observed that when the polymer amount increases folding endurance increased which may be due to the increased gel structure and improved strength.

For formulations, the initial hydration and swelling are crucial functional traits that greatly impact medication release and mucoadhesion. Swelling characteristics of the formulations were checked for more than 6 hours. The studied polymers' observed hydration or saturation capacity ranked as follows: Guar gum > Xanthan gum > Chitosan.

The results from the mucoadhesion study revealed that formulation F6, characterized by a high concentration of chitosan, exhibited the longest mucoadhesion time compared to the other formulations. Conversely, F1 demonstrated the shortest mucoadhesion time, potentially attributable to the hydrophilic properties of guar gum that loose the bond strength from the buccal mucosa as the hydration of guar gum decreases with added ingredients which are hydrophilic in nature as chitosan. Though guar gum is a much more effective thickening agent that helps to keep large particles in the mix, xanthum gum tends to help starches trap more air and exhibit better swelling. Chitosan is more structured and stable than xanthum gum and enhances swelling dynamics. Chitosan is cationic in nature and when used along with other hydrophilic polymers, helps to create stronger bonds with mucosa.

The swelling characteristics of polymers play a critical role in determining the mucoadhesive properties of polymeric formulations, as patch swelling is crucial for initiating contact with the mucosal surface.[19] Furthermore, the dissolution and release of drugs from polymeric formulations are significantly influenced by their degree of hydration and swelling. An increase in polymer amount in the formulations results in decreased pore size due to increase in viscosity introduced by the polymers, water penetration within the network is ultimately restricted, thereby limiting the swelling of the patch.[20] The bond strength increases with a certain level of hydration until a threshold is reached, beyond which excessive hydration leads to a sudden decline in adhesive quality due to unraveling at the interface between the polymer and mucosal tissue.[21] Mucoadhesion is usually affected by the level of H-bonding especially with moieties having carboxylic, hydroxylic or amino groups. This is evident from the varying level of mucoadhesive characteristics shown by different polymers in formulations F1, F6 and F9 (Table 4).

Ex-vivo drug release showed the following behavior of polymers in the order: Guar gum >Xanthum gum > Chitosan. Above observations proves The rate of drug release is contingent upon the type and concentration of the polymers employed. This observation can be attributed to the hydrophilic polymer's capacity to absorb water molecules, escalating the swelling percentage.[22] No significant drug release was observed in any formulation until polymers start to swell. The presence of polymers in high concentrations increases its viscosity and reduces the porous network, causing a reduction in hydration rate and/or entery of solvent molecules into the system.[23] The hydrophilic polymers have polar groups in their structure that affect the amount of inter cross linking and bonding with water molecules. Consequently, this resulted in a decrease in the dissolution rate of the drug from the film matrices, thereby reducing the diffusion of the drug. Based on the comparative study among all nine formulations, Batch F6 showed uniform thickness, good folding endurance, good *ex-vivo* mucoadhesion time, and best control drug release. So, batch F6 was found to be superior to the other batches and was selected as an optimized formulation.

Formulation F6 exhibited remarkable analgesic efficacy in comparison to the standard oral mucoadhesive gel of Tramadol HCl, displaying a rapid onset of action. Therefore, not only can rapid onset of action be achieved, but prolonged release, as indicated by the *ex-vivo* release data, with the aforementioned optimized formulation, can also be achieved. Also the analgesic effect of chitosan may be credited to its capacity to absorb Bradykinin and absorption of proton ions released in the inflammatory site.[24]

Conclusion

Muco-adhesive drug delivery system shows improved local drug concentration by being longer at the absorption site, which also increases the passage of drugs to systemic circulation. The studies show that combining guar gum with cellulosic polymer enhances surface wetting and better water penetration and hence, offering a desired controlled release. At the same time, incorporating chitosan enhances swelling characteristics and improves drug release profile. The formulations could be useful for better therapeutic drug delivery of the analgesic agent for prolonged duration. The preliminary findings also suggest significant control of drug release. Long time characterization of formulation is required to strengthen the controlled release data. The research work may also be pivotal in understanding and using a combination of polymers for other drugs.

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