RESEARCH ARTICLE

Preparation and Evaluation of Ophthalmic Ketorolac Tromethamine Minitablet

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ABSTRACT

Objective: The current research is for improving patient compliance by reducing dosing frequency of ocular ketorolac tromethamine used for allergic conjunctivitis through preparation of minitablet for ocular insertion.

Method: Ocular mini tablet was prepared by direct compression method using xanthan gum, chitosan and carbopol 943P as polymers to prepare the mini tablet for ocular insertion. The mini tablets were evaluated for drug content, weight variation, bioadhesion, water uptake and swelling behavior, in vitro drug release and ocular irritation.

Results: The best formula (F1) containing 1% chitosan gave mini tablets with dimension (3 × 0.7 mm) with satisfactory physical properties and 100% release after 12 hours to be inserted anteriorly.

Conclusion: This work succeeded in preparing ocular mini tablet of ketorolac tromethamine to be inserted anteriorly for the treatment of allergic conjunctivitis. As promising sustained release drug delivery system to be a good alternative for the conventional treatment regimen to improve patient compliance by reducing frequent doses with no irritation.

Keywords: Minitablet, Ketorolac, Ophthalmic.

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INTRODUCTION

In order to treat eye diseases, a systemic and topical drug delivery system may be applied, the latter preferred upon the systemic drug delivery due to less systemic side effects and dosage administration.[1] The applied drugs must overcome many biological barriers topically to reach the targeted site; first one is the dilution of drug molecules on the precorneal tear film. Where the ocular bioavailability is less than 5% due to limiting resident time in the precorneal space (<1-minute) because of the blinking reflex and the rapid renewal rate of lachrymal fluid (2–3 minutes).[2,3] The second one degradation of the drug molecule by metabolic enzymes in the precorneal tear film.[4] The drug needs to retain in the cornea and/or conjunctiva or cross these barriers to the internal layers of the eye. The cornea is the main barrier of access the drug to the inner layers structures of the eye, and the transport of drugs not easy due to the highly organized structure of the corneal epithelium and the hydrophilic stroma.[5] Another barrier is the physicochemical properties on the bioavailability of drugs in the eye. The low molecular weight lipophilic drugs can pass through the corneal epithelium transcellular then drugs stored in the storma and released into aqueous humor as a depot form.[6] Mini ocular tablet have a size range from 1 to 3 mm. It is preferred upon another topical dosage form such as drops, because the conventional ocular dosage forms need frequent dosing to maintain therapeutic drug level that will lead to toxicity and adverse effect as a result of high dosage use, less patient compliance, low bioavailability due to dose loss by lacrimation, blinking fast drainage rate. In addition, mini tablet prioritized upon ointment and gel due to their sticky sensation and blurred vision that caused by viscous vehicles that used to increase the contact time of the drug and the target site at the tear film.[7] Mini tablet inserted in the fornix will stimulate lacrimal gland to secrete fluid that will dissolve it slowly and usually, the ingredient should be water soluble.[8]

Ketorolac tromethamine (KT) is the salt form of ketorolac found as a racemic mixture belonging to the indomethacin group, the levorotatory isomers of KT is two times more effective than dextrorotatory isomers as an anti-inflammatory agent. S-isomers have the most analgesic and COX inhibitory potency of KT.[9] Ketorolac is given in many formulations as oral, intravenous, intramuscular and topical ophthalmic

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dosage form in its salt form for relief of moderate to severe postoperative pain. It's found that having potency in reducing cystoid macular edema and intraocular irritation after lens implantation and cataract extraction—commercially 0.5% KT used to treat wide range of ocular infections like allergic conjunctivitis.[10]

This work aims to prepare mini-tablet of Ketorolac Tromethamine to be applied in the anterior part of the eye to be used as an alternative to the conventional ocular dosage forms to reduce side effects and improve patient compliance.

MATERIALS AND METHODS

Materials

Ketorolac Tromethamine (KT), xanthan gum, chitosan, carbopol 934 (CP 934), spray dried lactose and magnesium stearate.

Methods

Pre-compression Tests

- **Angle of Repose measurement:** Free standing cone and a stainless steel fixed funnel were used in a place 3 cm above the graph paper with height (h) and radius (r). The angle of repose was calculated using this equation:[11]

$$\tan \theta = h/r$$

- **Apparent and Tapped Density Measurement:** Bulk density can be determined by introducing a quantity of measurable weight of each formula to the measurable cylinder and it's calculated by dividing the weight (g) by the volume (mL). Tapping the cylinder until no change in the volume and can be calculated by dividing the weight (g) by the tapped volume.[11]
- **Carr Index and Hausner Ratio Calculation:** These parameters can be calculated by the following equations, respectively:

$$\text{Compressibility index} = [(\text{tapped}–\text{bulk})/\text{tapped}] * 100$$

$$\text{Hausner ratio} = \text{tapped density}/\text{bulk density}$$

Both provide a measure about the flow properties of the powder and its compressibility. Carr index with range from 5–15 and 12–16% provide idea that a powder have excellent and good flow properties respectively, while Hausner ratio indicate good flow properties of powder below 1.25.[13]

- **Preparation of Ketorolac Tromethamin ocular minitablet:** 1% xanthan gum, 1% chitosan and 1% carbopol each one separately were mixed with KT, spray dried lactose and magnesium stearate were mixed properly then compressed into mini tablet by punch specially developed in the lab with diameter 3 mm with compression force range from 2.9–3.2 KPa on each single punch press to give mini-tablet with 3 and 0.7 mm were the diameter and thickness respectively.

Post Compression Evaluation

- **Weight Variation:** Ten tablets selected randomLy from each formulation to be weight and take the average.[14]
- **Content Uniformity:** Dissolve one mini-tablet in 10 mL phosphate buffered saline (PBS). By spectrophotometry the absorbance was measured at 322 nm. Ten individual tablets was used for this test.[15]
- **Measurement of Mini-tablet Dimensions:** The thickness of ten randomLy tablets from each batch was measured by a digital caliper. The diameter was assumed to be constant at 3 mm.[16]
- **Friability**: The drum of a friability tester was used for this test by weighing ten tablets as a unit and placed in this tester then rotated for 100 revolutions at 25 rpm. The tablets re-weighed as a unit to calculate the percent of friability using this equation:[17]

$$F (\%) = (P-P'/p) \times 100$$

P is the initial weight and p' is the weight after rotating in the friability tester.

- **Hardness:** The force required to break the tablet was noted by putting the tablet between a fixed and a moving jaw of hardness test apparatus and the indicator should be adjusted to zero.[18]
- **Moisture Uptake and Swelling Behavior:** One piece of paper tissue was folded twice and placed in a small petri dish containing 4 mL of water. A known weight tablet was placed on the wetted paper and the time needed to complete tablet wetting was recorded. The weight of the wetted tablet was measured to calculate the ratio of moisture uptake (R) according to the following equation: [19]

$$R = \{(Wf – Wi)/Wi\} \times 100\%$$

Wf = tablet weight after water uptake.
Wi = tablet weight before water uptake.

- **Bioadhesion:** A freshly conjunctiva membrane was excised from an adult goat to use as a membrane for the bioadhesion strength test. The conjunctiva's underlying skin was removed and placed in aerated normal saline at 4°C. Before using, the membrane was washed with deionized water and phosphate buffer (PH 7.2, 37°C). A modified two-pan balance was used to determine bioadhesive strength of the tablet (n = 3). The membrane was attached to the upper part of a glass vial full of phosphate buffer (PH7.2). Vial was fixed in a glass beaker center full of simulated tear fluid (PH7.2). The tablet was attached to the lower part of a rubber stopper that fixed to lift of physical balance. Known weight was placed on the other lift of balance just enough to separate the tablet from the conjunctiva membrane surface; bioadhesive strength was measured using this equation:[20]

$$\text{Force of adhesion} = (\text{bioadhesive strength} \times 9.81)/1000.$$

- ***In-vitro* Drug release profile:** *In-vitro* release study of mini-tablets was assessed using a modified franz cell diffusion which its composed of donor and acceptor part separated by dialysis membrane. The minitablet had been placed at the donor site and the franz cell put in a water path at 37°C ± 0.05 and 25 rpm. Each part contain 10 mL of phosphate buffer PH 7.4. 3 mL will be withdrawn at 15, 30, 60 minutes then hourly intervals from donor part and replaced with 3 mL phosphate buffer. The withdrawn sample will be available for reading by spectrophotometry at 322 nm at each time point.[21]

- ***In-vivo* Ocular Irritation Test:** Four rabbits weighing 2 to 2.5 Kg was used to determine the irritation test *in-vivo*. Minitablet was deposit in the lower part of the rabbit's conjunctiva sac's right eye while the left eye let without any treatment as a control. The observation was at intervals 0.25, 0.5, 1, 2, 4, 6, 12, 24, 48 and 72 hours. if there is any changes in the cornea, conjunctiva, iris and secretion in contrast with the control. The scores of the degree of eye irritation was determined as scores according to the modified Draize test[22] as shown in Table 1.

RESULTS AND DISCUSSIONS

Pre-compression Tests

Angle of repose is a classical method to identify the flow property of pharmaceutical powders. Powders containing 1% chitosan and 1% carbopol showed excellent flow (since their values <30°) while 1%xanthan showed good flow (since its value is between 31–35°C). Apparent and tapped density results are shown in (Table 2) and they are within the acceptable limit.[24]

Carr index and Hausner ratio of all the formulas ranged between the excellent and good flow property and within the acceptable limit.[25]

Post Compression Evaluations

Weight Uniformity

The weight of mini-tablets ranged from 6.44–8.16 mg with variation not exceeding 10% for each formulation.

Content Uniformity

Average drug content was 96.18% ± 6.3 and the results of the samples proved homogenous drug distribution.

Measurement of Mini-tablet Dimensions

A thickness test is mandatory due to it has crucial effect on the accuracy of packing of tablets into blisters. However, there are no pharmacopoeial specifications for the thickness of the tablets. The prepared tablets have a diameter 3 and a thickness of 0.7 mm.

Friability

The maximum loss of weight after the test not exceeding 1.0% of the initial weight and agreed with acceptable reported

Table 1: Scores of ocular irritation test[23]

Ocular observation	*Scores*
Cornea	
None	0
Diffusion area, iris can be distinguished	1
Easy distinguishable with translucent area, iris details slightly visible	2
Specular area, iris details not visible, pupil size scarcely visible	3
Opaque cornea, iris not distinguished	4
Iris	
None	0
Markedly depend fold, congestion with moderate to deep swelling , circum cornieal injection, iris still reactive to light.	1
no response to light, hemorrhage, remarkable destruction	2
Conjunctivae Chemosis	
none	0
Any swelling noticed	1
Markedly swelling, lid eversion partially	2
Swelling with about half closed lid	3
Swelling with lid closed more than half	4
Redness	
None	0
Injection of some blood vessels	1
Diffusion, darkened hyperemia, individual vessels not easily to seen.	2
Diffuse with high dense hyperemia.	3
Secretion	
None	0
Any abnormal discharge	1
Discharge leading to wet lids and eye lashes closer to lids.	2
Discharge with remarkable moistening the lid and periorbital areas.	3

data.[26] The following Table 3 showed the post-compression parameters.

Moisture Uptake

The water uptake of mini-tablet depend on the type of polymer used. After 2 hours of study, the swelling index in the following order (Table 4) where carbopol > xanthan > chitosan. It showed that the charged polymer have high extent of water uptake than neutral polymer. This is obviously observed in case of carbopol and xanthan, with perfect correlation with their charge density.

Despite that chitosan is charged polymer, it still showed the lowest swelling index due to the free negative charges of the polyacid or free positive charge of the ammonium group. Chitosan have the swelling ability in acidic and basic media, respectively, while in neutral media, chitosan has no free negative charges of polyacid or free positive charges of the ammonium group so the entry of water will decrease and decrease the swelling index.[27]

Bioadhesion

Macromolecular polymer needed hydration to expand and create sufficient size mesh and also to promote interpenetration processes between mucin and polymer by inducing the mobility of the polymer chain.[27] Due to high swelling index of carbopol,

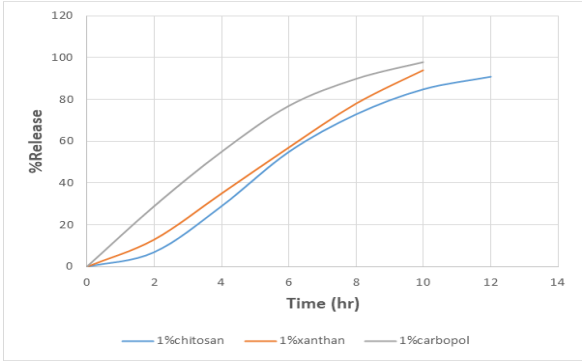

Figure 1: The release profile of ketorolac from the prepared minitablets at pH 7.4, and 37°C.

Table 2: The pre-compression tests results

Formula containing	*Apparent density (g/mL)*	*Tapped density (g/mL)*	*Carr index (%)*	*Hausner ratio*	*Angle of repose (°)*
1%chitosan	0.513	0.576	10.93	1.12	29
1%xanthan	0.532	0.597	10.88	1.12	34
1%carbopol	0.524	0.579	9.49	1.1	29

Table 3: Results of post-compression parameters of all formulations:

Formula containing	*Weight variation (mg)*	*Content uniformity*	*Thickness (mm)*	*Friability (%)*	*Hardness (Kg)*
1%chitosan	7.98	90.79	2.8	0.39	3.9
1%xanthan	6.44	95.45	3.1	0.34	4.1
1%carbopol	6.45	96.09	3.0	0.29	4.5

Table 4: Swelling index of matrix mini-tablets of Ketorolac Tromethamine:

Formula containing	*% of swelling with time in hours*					
	2	*4*	*6*	*8*	*10*	*12*
1%chitosan	26.78	45.74	68.03	91.47	102.64	134.59
1%xanthan	33.24	51.73	73.23	92.18	110.74	139.65
1%carbopol	38.92	54.64	80.29	99.82	126.52	145.84

Table 5: Results of bioadhesion tests.

Formula containing	*Bioadhesion force (N)*
1%chitosan	0.459
1%xanthan	0.387
1%carbopol	1.027

it revealed a great bioadhesive strength (Table 5). One of the polymer characterizations required for mucoadhesion is a strong anionic charge,[28] as shown by the xanthan gum polymer, illustrating good bioadhesion strength. While in case of chitosan, the polymer's structure and cationic nature increase the probability of forming hydrogen and electrostatic bonding with mucin, which explains its good bioadhesive strength.[29]

Drug Release Profile

The type of polymer used in each formula was directly related to the release rate profile. Gel will be formed after hydrophilic polymers come in contact with tear fluid. The hydrated layer's viscosity and thickness depend on the polymer's molecular weight, which determines the rate and the extent of diffusion of KT molecules from the polymer to the liquid tear medium. It also depends on the polymer-polymer interaction and the swelling and erosion of the layer formed.

The faster release profile was observed with carbopol minitablet (Figure 1) due to the biphasic water uptake profile. The drug molecule diffused rapidly through the polymer matrix at the initial phase until the gel layer formed, then slower water uptake led to slower drug release. The property of water uptake and swelling overcome the effect of the viscosity of 1%carbopol on the release rate.[30]

The least release profile showed with 1%chitosan minitablet despite of having low viscosity due to the slow hydration style as agreed with reported data.[31]

The structure of xanthan gum may be attributed to the slow release rate of drug as it's composed of a semi-rigid chain that makes the polymer's viscosity comparatively low.[32]

Ocular Irritation

From this test that following the modified Draize test carried out on rabbit, the total scores of ocular irritation were shown equal to zero at all time during the test up to 72 hours, it was noticed no change in the cornea, iris, conjunctiva and secretion in the eyes treated with the best formula. This result proposes that the formula did not cause irritation in the eye rabbit so it's safe for ocular use.

CONCLUSION

Nowadays, the reduction in dose frequency and increment in patient compliance are the most important goals in many researches. Ketorolac tromethamine ocular mini-tablet using chitosan can be considered as a good drug delivery system to treat allergic conjunctivitis or after ophthalmic surgery as an anti-inflammatory. It offered a prolonged profile of sustained drug release to be given once daily and more preferable than the conventional ketorolac tromethamine 0.4% eye drop formulation, usually given four times daily.

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