RESEARCH ARTICLE

Preparation and Characterization of Instantly-soluble Solid Eye Drop for Glaucomatous Patients

Ahed R. Hameed[1], Athmar Dh H. Al-Shohani[2*]

Department of Pharmaceutics, College of Pharmacy, Mustansiriyah University, Baghdad,10001, Iraq

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ABSTRACT

For the treatment of glaucoma eye drops are chronically used. However, chronic use of preservatives in eye drops cause irritation problem and affects ocular tissues. The aim is to formulate an instant soluble solid eye drop to avoid using preservatives since solid dosage forms do not require preservation.

Ocular mini-tablets of dorzolamide hydrochloride (DZ) and timolol maleate (TM) were prepared by direct compression using different polymers and were evaluated for their physical properties. The release DZ and TM was compared to COSOPT eye drops.

Formulation F2 mini-tablets (which contain DZ, TM, mannitol and microcrystalline cellulose MCC) were chosen as the optimum formula because they had uniform shape and minimum variation in weight 9.69 ± 0.55 mg. Thickness and diameter were 1.38 ± 1.28 and 3.01 ± 0.03 mm, respectively, within the acceptable limits. Hardness and friability were also within the permissable range which were 4.14 ± 0.22 kg/cm^2 for hardness and 0.73% ± 0.05 for friability. The drug content for both DZ and TM were within the acceptable limits and the release had no significant difference ($p > 0.05$) compared to commercial eye drop and the mini-tablets dissolved completely with less than one minute. The FTIR and DSC revealed no interaction between the drugs and excipients used.

Sterilization using gamma radiation was performed to test the animal's mini-tablets. The radiation did not significantly ($p > 0.05$) alter any properties of F2 and no signs of irritation on the animal eye appeared.

In conclusion, instant soluble solid eye drop in the form of mini-tablet was successfully prepared by direct compression method and caused no irritation when tested on animals.

Keywords: Cellulose derivatives, Dorzolamide hydrochloride, Glaucoma, Mannitol, Mini-tablets, Poloxamer, Timolol maleate.

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INTRODUCTION

Glaucoma is a neurodegenerative eye disease and one of the leading causes of blindness worldwide, second only to cataracts, and its prevalence is rising due to an aging population.[1,2] It is linked to elevated intraocular pressure (IOP) which causes damage to the optic nerve.[3,4] Medications in the form of eye drops to reduce IOP are the first line of treatment in the clinic.

However, eye drops have numerous restrictions, from topical to systemic, and preservatives are one of the biggest problems. Chronic exposure of ocular tissues to preservatives may cause damage and irritation, tear film instability, meibomian gland dysfunction, conjunctival inflammation, subconjunctival fibrosis, epithelial damage, and allergic blepharitis, and failure of glaucoma filtration surgery.[5-7] To avoid the problem, preservative-free formulations were produced. Preservative-free containers, single-use vials, and solid ocular medication delivery systems are available. Some techniques are expensive and may raise the burden on patients, as glaucoma medicine is already pricey. Single-use containers are small and hard for seniors to manage. Contamination is a worry if a patient saves extra solution for later use.[8]

Solid ocular dosage forms, in the form of mini-tablets and inserts, require no preservatives and are manufactured in different shapes and sizes. They could be used for extended release or immediate release formulations. An example of FDA approved inserts are Ocusert® and Lacrisert®. Lacrisert® is a rod-shaped, water-soluble cul-de-sac insert for the treatment of dry eye syndrome.[9] Dorzolamide hydrochloride (DZ) and timolol maleate (TM) ocular insert was prepared to utilize

*Author for Correspondence: athmar1978@uomustansiriyah.edu.iq

ethyl cellulose, Eudragit RL100, and Eudragit RS100 using solvent casting process.[10] The insert was developed to extend ocular surface contact time, controlled release, decrease the frequency of administration, and boost therapeutic efficacy.

Mini-tablets are widely researched particularly for glaucoma. TM mucoadhesive sustained release mini-tablets were prepared using ethyl cellulose (100 cps), hydroxylethyl cellulose (300 cps) and carbopol 971P. While timolol instantly soluble solid eye drop using hydroxypropyl cellulose, glycyl-glycine (diglycine), poly(acylic acid sodium salt), Pluronic® F-68 was formulated using freeze drying technique.[11-13]

The aim of this work is to formulate and evaluate a preservative-free instantly soluble solid eye drop for topical ophthalmic drug delivery of DZ and TM maleate as a replacement for eye drop.

MATERIALS AND METHODS

Materials

DZ and TM were kindly supplied from Pioneer Pharmaceutical Company (North, Iraq). Magnesium stearate, mannitol, methylcellulose, carboxyl methyl cellulose and sodium carboxyl methyl cellulose (medium viscosity) were kindly supplied from SDI pharmaceutical company (South, Iraq). Avicel PH102, crosspovidone and polyvinyl pyrrolidone (Thomas Baker laboratory, india). Sodium starch gluconate and hydroxypropyl methylcellulose K15M (15 Cps, Hyperthem, China, India). Hydroxypropyl methylcellulose K4M (Alpha Chemika, India). Hydroxypropyl methylcellulose E5, Poloxamer 407 and Poloxamer 188 (Sigma pharmaceutical company, USA). All other reagents were of analytical grade.

Preparation of DZ and TM Ocular Instant Soluble Solid Eye Drop

Instant soluble solid eye drop was prepared in the form of mini-tablets using direct compression method.[14] In direct compression, 1.13 mg of DZ, 0.35 mg of TM, and different amounts of polymers from Table 1 were weighed and combined for each formula. DZ and TM doses were equivalent to one drop from commercially available COSOPT eye drop. After mixing for 2 minutes, 0.02 mg of magnesium stearate was added. The powder combination was compacted into 3 mm convex mini-tablets using a die of approximately similar size.[15]

Evaluation of the Prepared Ocular Mini-tablets

General Appearance and Dimensions (Diameter and Thickness)

After direct compression, all mini-tablets were visually examined for appearance, surface smoothness, and shape. For the measurement of thickness and diameter, 20 mini-tablets from each formula were randomly picked and measured individually using a digital micrometer screw gauge, then the average was calculated.[16]

Weight Variation Test

For the weight variation test 20 mini-tablets were randomLy selected per formula. Each mini-weight tablet weight was measured and an average of 20 was calculated.[17] USP allows a ± 10% variance in average tablet weights.[18]

Hardness Test

For each formula, 10 mini-tablets were randomly chosen and the hardness for each tablet was measured individually using a hardness tester. The average was then determined.[19,20]

Friability

For the measurement f friability 20 mini-tablets were weighed (P) then placed in the friabilator that rotates for 10 minutes at a rate of 25 rpm. After 10 minutes, the mini-tablets were removed from the friabilator, dusted and weighed (P'). Friability percent was calculated using the following equation:[16,21]

$$\text{Friability}(\%) = 100 \times (1 - P')/P$$

Swelling and Hydration Behavior

The swelling behavior was measured using gravimetric method for each formula at 37°C. Each mini-tablet to be tested was

Table 1: The composition of mini-tablets prepared by direct compression

Amount mg	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*	*F11*	*F12*	*F13*	*F14*	*F15*	*F16*
Mannitol	2	2	2	2	2	2	2	2	2	4.25	2	2	2	2	2	2
MC	6.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MCC	-	6.5	-	-	-	-	-	-	-	-	-	-	-	2.5	-	-
Na CMC	-	-	6.5	-	-	-	-	-	-	-	-	-	-	-	-	-
PVP K30	-	-	-	6.5	-	-	-	-	-	-	-	-	-	-	2.5	
HPMC K 15 M	-	-	-	-	6.5	-	-	-	-	-	-	-	4	4	4	3.25
HPMC K4M	-	-	-	-	-	6.5	-	-	-	-	-	-	-	-	-	-
HPMC E5	-	-	-	-	-	-	6.5	-	-	-	-	-	-	-	-	-
P 407	-	-	-	-	-	-	-	6.5	-	-	-	3.25	-	-	-	3.25
P 188	-	-	-	-	-	-	-	-	6.5	4.25	3.25	-	-	-	-	-
SSG	-	-	-	-	-	-	-	-	-	-	3.25	3.25	2.5	-	-	-

Each formula will contain in addition to the polymers 1.13 mg of DZ, 0.35 mg of TM and 0.02 mg of magnesium stearate so the final weight of the tablet will be 10 mg. methylcellulose (MC), carboxyl methylcellulose (CMC), Microcrystalline cellulose (MCC), sodium carboxy methyl cellulose (Na CMC), sodium starch gluconate (Na St.gly), Polyvinylpyrrolidone K30 (PVP K30), hydroxypropyl methylcellulose k 15 M (HPMC K 15 M,15 cps), hydroxypropyl methylcellulose K4M, (HPMC K 4 M), hydroxypropyl methylcellulose E 5 (HPMC E5), Poloxamer 407 (P 407), Poloxamer 188 (P 188)

weighed and placed in a petri dish filled with 2 mL PBS. At predetermined intervals, the mini-tablet was removed and filter paper was used to remove excess solvent on the surface and then weighed. The process continued until the complete dissolve of the tablet. The swelling index was calculated for each time point using the following equation:[20,22,23]

Swelling Index = (Final weight-Initial weight)/(Initial weight)

Content Uniformity

The uniformity of medication content in mini-tablets was investigated. For each formula, 10 mini-tablets were randomly selected and each one was allowed to dissolve in 10 mL PBS (pH 7.4) at 150 rpm for 24 hours. Then, a sample was taken, filtered and scanned with a UV spectrophotometer to quantify DZ and TM.[24]

Release Study

For the release research, each mini-tablet was placed in a beaker that contains 20 mL pH 7.4 PBS at 37ºC and stirred at 150 rpm. At 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, and 160 minutes, 3 mL aliquot was removed and replaced with PBS. The amount of DZ and TM in each sample was determined using a UV spectrophotometer.[10,24,25] Using the same procedure one drop of commercial eye drop COSOPT was examined.

Choice of the Optimum Formula

The optimum formula was chosen based on the evaluation results and further following test were performed on the optimum formula.

Fourier-transform Infrared Spectroscopy (FTIR) Study

FTIR spectra for DZ, TM, polymers, and optimal formula were studied. A 3 mg of each sample was weighed, compressed into a KBr disc, and scanned at 400–4000 cm^{-1}.[26,27]

Differential Scanning Calorimetry (DSC)

DSC was performed to determine the melting point of DZ, TM, polymers, and F2. In an aluminum pan, 3–4 mg of each medication was weighed and the pan was sealed and heated at a rate of 10ºC/min in the DSC equipment at a temperature range of (10–400ºC).[26,27]

Gamma Sterilization

Cesium-137 (Cs-137) was used for gamma irradiation (0X 840/code: CDRB3796/LD GERMANY). The dosage rate was 24.3468 R/h (0.2435 kGy/h), and the doses were 5 kGy. At room temperature, all experiments were conducted. Mini-tablets of various formulations were sterilized for 15 days to acquire an exact sterilization dose when the strength of radioactive source was 75.26 µCi . Each sterilized mini-tablet was tested for swelling, friability, hardness, drug content, drug release, FTIR, and DSC.[28]

Sterility Test

A rapid sterility test was performed to ensure the sterilization process was effective. Blood media agar was prepared using the (blood agar base oxoid, IVD). Then the mini-tablets placed in the agar and incubated for 48 hours at 35ºC in a sterilized hood. A blood agar without the mini-tablets was also incubated as control and the agars examined at 24 and 48 hours for signs of bacterial or fungal growth.[19]

Ocular Irritation Test

For the best formulation, ocular irritation was tested. Three white albino rabbits weighing 1.5 kg were used in the test. The Iraqi center supplied these rabbits for cancer research and medical inheritance's animal house, Mustansiriyah University, where the study was done. A mini-tablet was inserted in each rabbit right eye, while the left eye served as a control. Redness, swelling, irritation, and discharge were monitored. The monitoring period interval begins at instillation (1, 8, 12 hour).[10,29] The score system in Table 2 was used for evaluation of the experiment.[30,31]

RESULTS AND DISCUSSION

Preparation of Mini-tablets by Direct Compression

Direct compression was utilized to make ocular mini-tablets. All mini-tablets were made without capping, fracturing, or rough surfaces Figure 1.

Evaluation of the Prepared Mini-tablets

Physical Characterization of the Mini-tablets

Mini-tablets weight, thickness, diameter, hardness, and friability results are demonstrated in Table 3. Regarding weight variation, all mini-tablets met weight limitations (± 10%) and thickness and diameter were also appropriate for ocular mini-tablets.[32-34]

Tablet hardness and friability are inversely connected. They ensure tablets can with stand handling, packaging, and storage without breaking.[15,35,36] As it appears in Table 3 the hardness of the mini-tablets varied between (1.88–4.8 kg/cm^2),

Figure 1: Mini-tablets prepared by direct compression compared to regular oral tablet.

Table 2: The scales utilized in the evaluation of the irritation test.

Score	*Irritation description*
0	Absence of any symptoms of inflammation (redness, excessive tearing or swelling)
1	Redness and inflammation of a moderate degree, along with only a few tears.
2	Redness and inflammation of a moderate degree and severe tearing
3	Sever redness, inflammation and tearing

Table 3: Physical properties evaluation of the mini-tablets[36]

F	*Weight (mg)*	*Thickness (mm)*	*Diameter (mm)*	*Hardness (kg/cm²)*	*Friability (%)*	*Drug content (%) DZ*	*Drug Content (%) TM*
F1	10.03 ± 0.7	1.55 ± 0.12	3 ± 0.004	4.8 ± 0.72	0.8 ± 0.06	94.6	97
F2	9.69 ± 0.55	1.38 ± 0.1	3.01 ± 0.03	4.14 ± 0.22	0.73 ± 0.05	97	99
F3	9.00 ± 0.56	1.33 ± 0.04	2.98 ± 0.03	3.34 ± 0.23	14.17 ± 0.6	99	102
F4	9.91 ± 0.77	1.52 ± 0.1	3.01 ± 0.01	4.26 ± 0.23	1.66 ± 0.15	90	94
F5	9.66 ± 0.99	1.42 ± 0.12	2.99 ± 0.01	3.62 ± 0.16	1.8 ± 0.3	96.94	99.3
F6	9.51 ± 0.84	1.45 ± 0.06	3 ± 0.05	3.84 ± 0.21	1.9 ± 0.05	95	90
F7	9.84 ± 0.62	1.34 ± 0.05	3 ± 0.03	3.88 ± 0.22	2.4 ± 0.16	98	93
F8	9.63 ± 0.58	1.38 ± 0.09	2.89 ± 0.23	3.5 ± 0.1	1.2 ± 0.15	94	90.2
F9	9.82 ± 0.44	1.48 ± 0.09	2.96 ± 0.03	3.72 ± 0.22	0.15 ± 0.03	96	93
F10	9.73 ± 0.34	1.32 ± 0.04	2.95 ± 0.3	3.86 ± 0.22	1.97 ± 0.11	99	97
F11	9.97 ± 0.53	1.32 ± 0.07	2.95 ± 0.07	1.88 ± 0.11	3 ± 0.05	97	94
F12	9.92 ± 0.60	1.32 ± 0.13	2.06 ± 0.83	2.64 ± 0.46	3.3 ± 0.2	99.3	92
F13	10.07 ± 0.4	1.51 ± 0.18	2.14 ± 0.57	3.24 ± 0.25	1.3 ± 0.3	99.7	95
F14	9.61 ± 0.48	1.37 ± 0.22	2.14 ± 0.68	3.5 ± 0.5	2 ± 0.5	99.1	94
F15	9.95 ± 0.72	1.42 ± 0.06	2.2 ± 0.807	3.68 ± 0.29	2.25 ± 0.05	99.8	102
F16	10.29 ± 0.7	1.51 ± 0.14	2.9 ± 0.229	3.46 ± 0.25	0.68 ± 0.03	99.6	96

which might be related to the polymers employed in the formulas. Only F11 and F12 were out of range, possibly owing to sodium starch gluconate (SSG) as it may affect the compressibility of the mini-tablets. The sphere-shaped grains of SSG, which is usually used as superdisintegrant, might affect the physical properties of the directly compressed tablets, specifically the hardness and friability.[37–39] For friability only (F1, F2, F9, F16) passed the friability test, which might be due to their composition (MCC, NaCMC, HPMC) as those polymers had the properties of acting as a binder that provided granules with good compressibility, forming tough tablets of moderate strength.[40-42] DZ and TM drug content ranged from 94 to 109%, which meets USP requirements.[18]

Water Uptake and Swelling Behavior

In order for mini-tablets to behave as a drop, they must be soluble as fast as possible and convert to solution. It was noticed that the mini-tablets behaved either as swellable or soluble (erodible) tablets. Swellable means the tablet start to swell and increase in size then dissolve slowly while erodible means the tablet wet without change in size then start to dissolve and the swelling or dissolving behavior of each formula is presented in Table 4 below.

F1, F3, F5, F6, F7, F8, F12, and F16 swell and dissolve in PBS. Smaller swelling time is preferable since solid mini-tablets may irritate ocular tissues if left solid after instillation. Rapid swelling solves the issue. All formulations except F3 had a maximum swelling time of 4 minutes or less. These formulations used swellable natural and semisynthetic fibers, notably NaCMC in F3 which had the highest swelling index.[43,44]

Swelling index is the maximum increase in size after swelling. Low swelling index helps the eye accommodate the tablet without tearing and irritation. Only F1 and F3 showed a swelling index above 1, while the others were low. Swellable mini-tablets F1, F3, F5, F6, F7, F8, F12 and F16 dissolve within 10 minutes, except F1 (16 minutes), while dissolvable mini-tablets F2, F4, F9, F10, F11, F13, F14 and F15 start dissolving within 1-minute which are acceptable to behave as a drop.

Release Study

Formulations with desired dissolving and swelling times were chosen for the release studies to compare with COSOPT®, which comprised DZ and TM. All the formulas tested (F2, F4, F5, F10, F15) show no significant difference ($p > 0.05$) in the release pattern of both drugs compared to commercial eye drops as seen in Figures 2 and 3. All formulae attained maximum drug peak within 10 minutes, except F5, a swellable mini-tablet that needs to swell before dissolving.[45]

Choice of the Optimum Formula

Based on swelling, dissolving, and release data, F2 was chosen as the best formula. F2 is uniformLy shaped and weighs 9.69 ± 0.55 mg. Thickness and diameter were 1.38 ± 0.1 mm and 3.01 ± 0.03 mm, within limitations. Hardness and friability were similarly acceptable at 4.14 ± 0.22 and 0.73 ± 0.05 kg/cm².

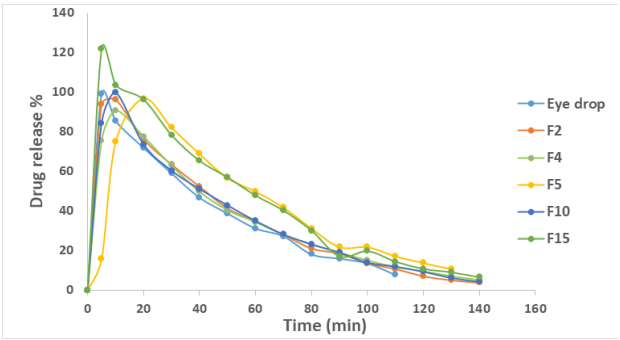

Figure 2: DZ release percent with COSOPT eye drop.

Table 4: Wetting and hydration behavior of the mini-tablets

Formulas (F)	*Type*	*Swelling index*	*Maximum Swelling time (min)*	*Initial dissolving time (min)*	*Complete Dissolving time (min)*
F1	Swellable	1.33	4	5	16
F2	Dissolvable	-	-	0.5	(Dissolve with less than 1 min)
F3	Swellable	1.85	5	6	7
F4	Dissolvable	-	-	0.5	5
F5	Swellable	0.26	1	2	10
F6	Swellable	0.95	3	4	8
F7	Swellable	0.41	2	3	6
F8	Swellable	0.05	1	2	8
F9	Dissolvable	-	-	0.5	5
F10	Dissolvable	-	-	0.5	5
F11	Dissolvable	-	-	0.5	5
F12	Swellable	0.13	1	2	5
F13	Dissolvable	-	-	0.5	(Dissolve with less than 1 min)
F14	Dissolvable	-	-	0.5	(Dissolve with less than 1 min)
F15	Dissolvable	-	-	0.5	4
F16	Swellable	0.07	1	2	5

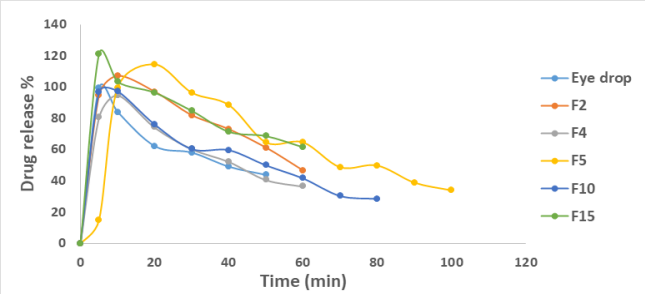

Figure 3: TM release percent with COSOPT eye drop.

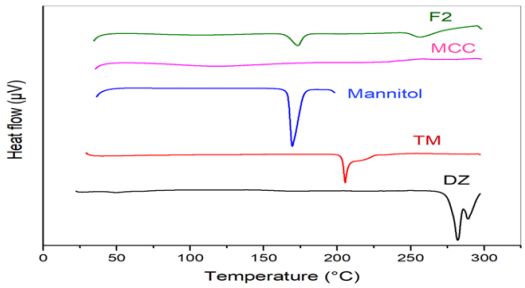

Figure 4: DSC thermograms of DZ, TM, MCC, mannitol and F2.

DZ and TM drug content were within permissible limits, and the release did not differ ($p > 0.05$) from eye drop. FTIR and DSC were performed to further explore this optimum formula; the results are below.

Differential Scanning Calorimetry (DSC) Study[23]

DSC was used to examine the possibility of physical interaction between the formula components. DSC thermogram in Figure 4 shows DZ, TM, and mannitol peaks at 283, 205, and 169.3, respectively; all the peaks are consistent with reported findings. Regarding MCC, a broad endothermic peak (35–120.2°C) followed by another peak at 247–250°C is consistent with reported data.[46]

In the mini-tablet F2 thermogram, DZ and TM were not visible as independent peaks at 283 and 205°C as expected, but as a single wide peak at 242.5–294°C. The wide peak may be due to the conversion of both drugs into amorphous form during tablet grinding. Another possible explanation is polymers used decreased the crystal formation by adsorbing on their surface.[26] Another possible explanation is that the peaks were low and infused with MCC and mannitol because of the low ratio of drugs compared to polymers. Reduced mannitol peak intensity may be related.[47]

FTIR

FTIR spectrum of F2 and its components are demonstrated in Figure 5. The FTIR spectra of pure DZ shows peaks 1155 cm^{-1} for SO2 stretching, 1289 to 1299.55 cm^{-1} for C-N stretching, 1341.75 cm^{-1} for C-H bending vibration, 1535.43 cm^{-1} for N-H bending vibration, 2787.25 cm^{-1} for C-H stretching of alkane, 3044.77 cm^{-1} for NH_2 stretching, and 3370.41 for NH stretching and similar to the references value.[48-50]

Pure TM FTIR spectrum shows the -OH group at 2965.26 and 2852.06 cm^{-1}. A shoulder occurs at 1702 and 1491 cm^{-1},

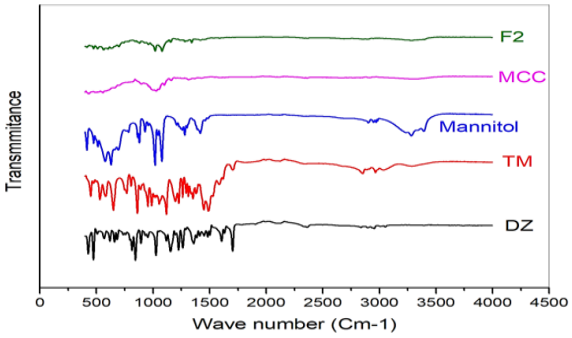

Figure 5: FTIR spectra of DZ, TM, MCC, mannitol and F2.

supporting the molecule -NH group as the absorption source. For the peak at 1449 it represents the NH binding. The drug thiadiazole moiety has a heterocyclic ring structure with multiple C=N absorptions between 2000 to 2500 cm^{-1}. This spectrum is similar to the reference.[51]

Pure mannitol showed O-H stretching vibration maxima between 3400 and 3200 cm^{-1}. C-H stretching vibrations had sharp peaks between 3000 and 2200 cm^{-1}. These peaks' positions and numbers are linked to mannitol's -polymorph, and the numbers match the reference.[52]

Pure MCC FTIR spectra show peak at 1650 cm^{-1} for (-O-tensile vibration of nearby hydrogen atoms). Peaks related to the OH and CH molecules stretching were detected at 3299 and 2916 cm^{-1}, respectively. It also revealed absorption bands at 1428 cm^{-1} for CH_2 stretching and at 1100–1400 cm^{-1} for CH, CH_2, and C-O stretching.[53,54]

The FTIR spectrum of F2 showed that the expected positions for the distinctive absorption bands of N-H stretching and OH stretching was 3285 cm^{-1} and the SO2 stretching was at 1156.5 cm^{-1} for DZ, which is the same for the pure drug, while between 2896–2854.37 cm^{-1} for OH stretching of TM, MCC and mannitol, which is a problem as it is difficult to identify absorption at the range of the O-H stretching for each. The notable peaks at 1017 and 1077 cm^{-1} showed higher intensity in absorbance, indicating a (C-O stretching) bond in TM, mannitol, and MCC, which may or may not be attributable to grinding and amorphization of the medicines. The combined substance's spectrum was the sum of its parts. The results cannot confirmed completely, if there was or not any overlap but we can dismiss the overlap because neither new peaks appear nor typical peaks disappeared.[10,54]

Gamma Sterilization and Sterility Test

Gamma radiation was used to sterilize ocular formulations in the current study. The tablets sterility was tested. Figure 6 shows that sterilization was successful; no bacteria or fungi grew on blood agar after 24 and 72 hours when incubated at 37°C.[26]

Table 5: F2 Characteristics test for the non-sterilized and sterilized mini tablets.

Characteristic test	*F2*	
	Before sterilization	*After sterilization*
Wight variation	9.69 ± 0.55	9.98 ± 0.6
Thickness	1.38 ± 1.28	1.4 ± 0.04
Diameter	3.0095 ± 0.03	3 ± 0.04
Crushing strength	4.14 ± 0.22	4.1 ± 0.15
Friability	0.73 ± 0.05	0.8 ± 0.1
Water uptake	Non-swellable	Non-swellable
Erosion time (min)	0.5	1
Dissolving time (min)	0.5	1
Drug content% DZ	97	98
Drug content% TM	98	99.5

Physical Characterization after Sterilization

Gamma radiation may affect the mini-tablet and drug used. All physical characterization done on the mini-tablets was repeated for the sterilized ones and compared. Table 5 shows that sterilization didn't impact the mini-physical tablet's qualities or medication content ($p>0.05$).[28] Also, Figure 7 illustrated no significant difference ($p>0.05$) in the release pattern of F2 after sterilization for both drugs.

DSC and FTIR Study After Sterilization

DSC thermogram and FTIR Spectra were compared for sterilized and non-sterilized formulation (F2) because if sterilization affected the drug there will be a shift in the peaks observed.[55,56] And as shown in the Figure 8 no difference was

Figure 6: Incubation of the Sterile Mini tablets.

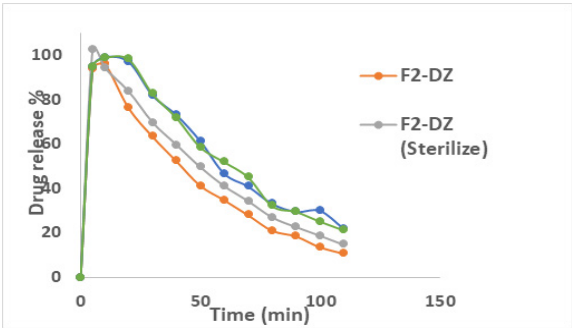

Figure 7: Drug release % of DZ and TM from sterilized and non sterilized ocular mini-tablets.

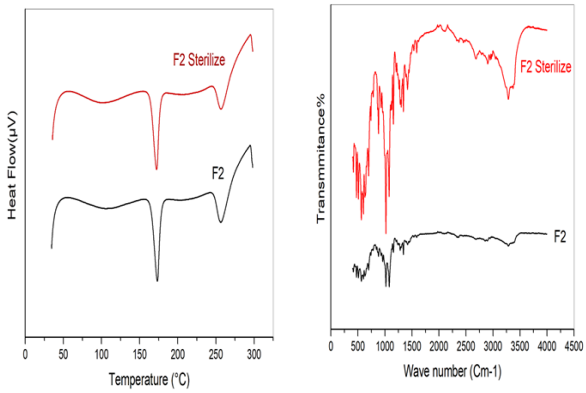

Figure 8: DSC thermograms and FTIR of F2 before and after sterilization.

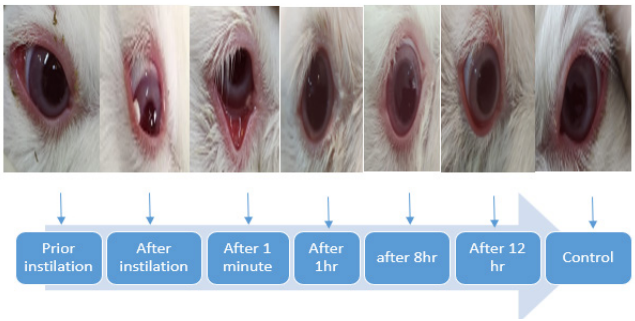

Figure 9: Ocular irritation test on rabbit eye after inserting the mini tablet of the formula F2 sterilize.

observed which indicates that both drugs were not affected by the sterilization process.

Ocular Irritation Test

Because the eye is a sensitive organ, irritation of ocular tissues can produce excessive blinking, severe tearing, redness, and discharge. Rabbits were used for the irritation test. Figure 9 for F2 showed no signs of irritation (redness, tearing, swelling) even after 12 hours of instillation.

CONCLUSION

As an alternative to standard liquid eye drops, a preservative-free mini-tablets of DZ and TM were developed as fast-dissolving solid eye drop. The physical evaluation, swelling-dissolving behavior, drug content and release of DZ and TM demonstrated the achievement of a well-prepared ocular mini-tablet using F2 which contains MCC and mannitol. Also sterilization is critical in ocular formulations and using gamma radiation did not affect the drugs' properties. Preliminary animal studies demonstrated no irritation to rabbit eyes even after 12 hours of instillation. Fast-dissolving mini-tablets are a major improvement in topical ophthalmic delivery due to their rapid dissolving behavior and low cost for production.

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