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Fabrication and characterization of new combination ocular insert for the combined delivery of tinidazole and levofloxacin

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ABSTRACT

Bacterial keratitis is one of the widely used infection of the eye and usually treated with antibacterial eye drops. In complicated infection more than one eye drop is needed. Several problems arise from using eye drops such as frequent instillation and low patient compliance. The aim of the research is to formulate an ocular insert that have the ability to delivery two drugs at the same time with sustained release pattern. Several formulations were used utilizing HPMC K15M as the main polymer with polyvinyl pyrrolidone k30, Carbopol 934, sodium carboxymethyl cellulose and Ethyl cellulose as polymer blends, propylene glycol as plasticizer and levofloxacin and tinidazole as antibacterial agents. Different formulation were prepared using solvent casting method and evaluated for their weight variation, thickness, drug content, pH, in-vitro drug release and kinetics. The formula with 1:1 HPMC K15M :Carbopol 934 was chosen as the optimum formula which showed proper physical properties and had the proper strength and mucoadhesion with high swelling index and sustained release of both drugs for around 12 h. When examined in animals no irritation was observed and also the drug remain in ocular tissues for a long period. Levofloxacin and tinidazole were successfully formulated as solid insert and sustained the release of both drugs for around 24 h. The approach of solid insert is promising approach to overcome problems with topical ocular delivery.

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1. Introduction

Bacterial keratitis is one of the common eye infections especially in developing countries. It is caused by different bacterial strains such as staphylococcus aureus. Pseudomonas aeroginosa and streptococcus pneumonia. If untreated it may end with blindness[1]. Instillation of antibiotics eye drops is the common treatment available in the clinic. However, the need for frequent instillation made the adherence to treatment low. Frequent instillation is often required with eye drops due to the low bioavailability following topical formulations[2]. Increasing ocular residence time is an approach used to enhance bioavailability. Once the dosage form remain in contact with ocular tissues the time required to cross the cornea enhanced, the nasolacrimal drainage reduced and consequently the instillation time will be reduced [3]. Different dosage forms have been investigated for this approach such as gels, *in situ* gels, solid lipid particles, polymeric micelles, therapeutic contact lenses, ocular minitablets and inserts [4].

Ocular inserts is an attractive alternative to conventional dosage forms. They are solid or semisolid formulations that are placed at the cul de sac to overcome pre-corneal barriers. Compared to other dosage forms, they are easy to manufacture and scale up, not require preservatives due to their solid nature, shape and dimensions can be controlled, large dose of the drug can be incorporated with the insert and the possibility of combination therapy[5]. Hydrophilic polymers are mainly used for their fabrication such as cellulose polymers, polyvinyl alcohol and polyvinyl pyrrolidone. The release of the drug can be modified through the use of a combination of polymers [6].

Occasionally complex bacterial infections require the use of multiple antibiotics which is an issue when applied as eye drops. An interval of at least 10 min must be placed between each drug and the eye will be exposed to double the amount of

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preservatives. The aim of our research is to formulate two antibiotics (levofloxacin and tinidazole) for simultaneous ocular delivery with no preservative applied by the use of solid ocular inserts approach.

2. Experimental

2.1. Materials

Tinidazole, Levofloxacin, Hydroxy propyl methyl cellulose K15M (HPMC K15M), Polyvinyl pyrrolidone k30 (PVP K30), Carbopol 934, Sodium carboxymethyl cellulose (NaCMC) and Ethyl cellulose (EC) were obtained from Hangzhou Hyper Chemicals Limited, Zhejiang, China. All other ingredients were of analytical grades.

2.2. Fabrication of the solid insert

Solvent casting method was used for the formulation of the solid insert[7]. A combination of HPMC K15M and different polymers (PVP K30, Carbopol 934, EC, NaCMC) were used as seen in Table 1. First HPMC K15M solution was prepared by dissolving the required amount in 4 mL D.W. heated previously to 70–80 °C with vigorous stirring[8]. Each of the remaining polymers were added according to their physical properties. The required amount of PVP K30, 30% (w/w) of propylene glycol as plasticizer, 6 mg of tinidazole and 6 mg of levofloxacin were dissolved in 6 mL cold water and added with continues stirring to the previously prepared solution of HPMC K15M until a clear homogenous solution achieved [9]. The final volume was 10 mL. Similar procedure was used for the addition of Carbopol 934 and NaCMC [10]. Due to the low solubility of EC in water it was first dissolved in 4 mL 98% ethanol followed by the addition of 2 mL D.W. in which propylene glycol and both drugs were dissolved [11]. Then the mixture was added as previously explained. The finished solution was poured into a locally fabricated rectangular glass sheet contains 3 circular glass mould of 1.7 cm diameter and dried in a hot air oven at 40 °C for 8 h. Finally, the circular film of 1 cm diameter was cut and stored in a desiccator for further evaluation. The final weight for each insertTable 2.

2.3. Characterization of the ocular insert

2.3.1. Physical appearance

Formulated ocular inserts were assessed for the physical characters including size, shape, colour and smoothness.

2.3.2. Uniformity of thickness

For each formula 10 inserts were randomly chosen and their thickness was measured using vernier calliper. The standard deviation and mean thickness were measured.

Table 2
Scores evaluation of irritation.

Score	Irritation description
0	No signs of inflammation (redness, excessive tearing or swelling)
1	Mild redness with inflammation and slight tearing
2	Moderate redness with moderate inflammation and excessive tearing
3	Severe redness with severe inflammation and excessive tearing

2.3.3 wt. uniformity

Ocular inserts prepared were evaluated for uniformity of weight. For each formula ten inserts were chosen randomly and weighted individually then the average weight and SD was calculated [12].

2.3.4. Folding endurance

The folding endurance is expressed as the number of folds (number of times the insert is folded at same location) needed to break specimen or create visible cracks. This test is necessary to assess the sample's ability to withstand folding. This may also give an indication of brittleness. The specimen was folded in centre, between the fingers and thumbs, then opened. This was referred as one folding. This procedure was repeated until the insert showed signs of breakage and cracks in the middle of insert. The total folding procedure was termed as folding endurance value[11].

2.3.5. Determination of surface pH

The surface pH of the inserts was measured by first placing the insert in 1 mL DW and allow it to swell for 10 min. After swelling the insert was placed on a pH paper to measure the surface pH and the color was recorded and compared with the standard colour scale[13].

2.3.6. Swelling index percent

The inserts were individually weighed and placed in beakers containing 4 mL distilled water. The films were withdrawn regularly at predetermined time intervals, and any excess water on their surface was removed using filter paper and re-weighted, the swelling index was calculated as following equation:[11]

$$\textbf{Swellingindexpercent} = \frac{\textbf{FinalWeight} - \textbf{Initialweight}}{\textbf{Initialweight}} \textbf{X}100$$

2.3.7. Uniformity of drug content

For the determination of drug content, 3 inserts were randomly taken and evaluated and the mean was calculated. Each insert was allowed to dissolve in 100 mL phosphate buffer pH 7.4 at 37 °C for 24 h. The solution was then filtered through 0.45 μm Whitman filter paper and the filtrate was tested for the drug content using UV–visible spectrophotometer at λ_{max} 317 nm and λ_{max} 288 nm for levofloxacin and tinidazole respectively[11].

Table 1
Composition of each fabricated insert with 1 cm diameter. Each insert will contain 7 mg propylene glycol and 0.7 mg for each drug in addition to the polymer.

Formula code	HPMC K15mg	PVP K30mg	Carbopol 934mg	NaCMCmg	ECmg
F1	23				
F2	17.2	5.8			
F 3	11.5	11.5			
F 4	17.2		5.8		
F 5	11.5		11.5		
F 6	17.2			5.8	
F 7	11.5			11.5	
F 8	17.2				5.8
F 9	11.5				11.5

2.3.8. Ex vivo Bioadhesive study

A freshly excised conjunctiva membrane of an adult sheep was used as a model membrane for the measurement of bioadhesive strength. It was purchased from a local slaughterhouse and kept in isotonic phosphate buffer (pH 7.4, 37 °C) until used. The Bioadhesive strength of the insert (n = 3) was measured on a modified physical balance. The membrane was washed with phosphate buffer pH 7.4 and adhered to the bottom of the Petri dish by cyanoacrylate glue such that the mucosal surface faced upward and the phosphate buffer is added till the buffer reached the surface of the membrane and kept it moist.

The film adhered to the lower side of the glass stopper with cyanoacrylate glue which is hanged from the balance left arm by threads after removing its pan. The two sides of physical balance were made equal before the study, by keeping (1.8) gm weight on the right-hand pan, then this weight was removed from the right-hand pan, which lowered the glass stopper along with the film over the membrane.

The balance was kept in this position for 10 min, a weight was applied to the right pan by pouring water drop by drop into a beaker till complete detachment of the film achieved. The mucoadhesive strength (bioadhesive strength) represented the amount of water added minus the weight of the preload. The force of adhesion and bond strength were calculated from the following equations[14]:

Force of adhesion (N) = Bioadhesive strength × 9.8 / 1000

2.3.9. Tensile strength and percentage elongation

Tensile testing was performed using a texture analyser (Tinius Olsen UK). It was measured according to the standard test method for tensile properties of thin plastic sheeting by the American Society for Testing Materials (ASTM). Insert strip with dimensions (20 × 2) cm and free from air bubbles or physical imperfections, were placed between two clamps, the upper one is moveable and the lowered one is fixed, the test was performed with a head speed of 10 mm/min. with a cell load of 50 kN. Cardboard was taped to the clamp's surface to prevent the film from being cut by the clamp's grooves. During measurement, the strips were pulled by the top clamp till the film broke. The maximum stress applied to a point at which the film specimen breaks is known as tensile strength (TS). It is determined by dividing the maximum load by the original cross-sectional area of the specimen and is expressed in force per unit area (MPa).

Tensile Strength = Force at break (N)/ Cross sectional area (mm2)

For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film. The percentage elongation of the films was then calculated using the formula below: -

$$\%E = Df -- D0/D0 \times 100$$

Where: -

%E = Percentage elongation

D0 = Distance between the tensile grips before the fracture of the film.

Df = Distance between the tensile grips after the fracture of the film [15]

2.3.10. In-Vitro release study

The *in vitro* drug release of Tinidazole and levofloxacin from the prepared inserts was studied using the dialysis bag diffusion technique. A 250 mL beaker, magnetic stirrer and dialysis membrane with molecular cut-off 8000–14000 D were used. The membrane was soaked in PBS (pH 7.4) for 24 h before each experiment and then opened from each side. One end was sealed with elastic rubber, each formulated insert contains (1 mg of each tinidazole and levofloxacin) was inserted inside the membrane. After placing the insert into the membrane, the other end was also sealed with a rubber band. The membrane was then submerged in 100 mL PBS (pH 7.4) and stirred at 100 rpm at 37 ± 0.5 °C. A 5 mL sample was withdrawn from the release medium at a given time interval (0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8,12, and 24 h) and replaced with 5 mL PBS (pH 7.4) to accomplish sink condition. The withdrawn samples were filtered through a 0.22 μm syringe filter and scanned in the UV-spectrophotometer at the λmax of Tinidazole and Levofloxacin (317, 288)nm respectively[16].

2.3.11. In-Vivo release study

The protocol for the study was approved (approval number 205/2017) by animal care committee in the Iraqi national center for drugs control and researches. The optimum formula of the ocular inserts were instilled into one eye of six rabbits at the same time and another eye served as control. The inserts were carefully extracted after 1, 2, 4, 6, 8, and 24 h and analysed for the remaining drug content by UV spectroscopy[17].

2.3.12. Ocular irritation test

To determine the safety of the chosen insert formula, an ocular irritation test was conducted. In this experiment, six white Albino rabbits weighing 1.5 kg were used. The test was performed according to the modified Draize test. Insert (1 cm) was instilled in the lower cul-de-sac of the animal's left eye, and the untreated contralateral left eye was used as a control. To prevent the loss of instilled preparations, the eyelids were gently held together for about 10 s. At 0.25, 0.5, 1, 2, 3, 6, 9, 12, 24 h after installation, each animal was observed for ocular reactions (redness, swollen discharge, iris and corneal lesions)[18]. The following scores were used to assess the irritation (Lallemand et al., 2005). A score of 2 or 3 in any category was considered an indicator of clinically significant irritation[19].

2.3.13. Differential scanning calorimetry

Differential scanning calorimetry analysis (DSC) was performed to examine the change in the thermal behaviour of pure drug, polymer, physical mixture and the selected formula. A 3–4 mg powder sample was packed inside a sealed aluminium pan and heated at a scanning rate of 10 °C/min on a temperature range from 25 °C to 250 °C [20].

2.3.14. Drug release kinetics

The mechanism of drug release was investigated by fitting the drug release data into zero-order, first-order, Higuchi kinetics, and Korsmeyer–Peppas equations. The goodness of fit of drug release was evaluated by the determination coefficient (R2) value [21].

3. 3.Result and discussion

3.1. Physical characterization

All inserts prepared were thin, homogenous, and transparent with visually smooth surface and absence of cracks which indicates proper formulation technique.

3.2. Evaluation parameters

The prepared inserts were evaluated for their thickness, weight variation, drug content, surface pH and folding endurance and the results can be seen in Table 3. Although the thickness of the ocular inserts varied between 0.125 ± 0.05 mm and 0.465 ± 0.07 mm, the

Table 3
Evaluation parameters for the prepared ocular inserts.

Code	Surface pH	Thickness(mm)	Weight uniformity (mg)	Folding endurance	Drug content (%)Tinidazole	Drug content (%)Levofloxacin
F1	7–7.5	0.125 ± 0.05	29.2 ± 0.83	<300	95.55 ± 0.017	96.56 ± 0.0205
F2	7–7.5	0.148 ± 0.04	28.84 ± 0.42	<300	94.44 ± 0.03	95.47 ± 0.025
F3	7–7.5	0.2 ± 0.08	30.65 ± 0.60	<300	97.56 ± 0.012	98.77 ± 0.034
F4	7–7.5	0.26 ± 0.07	27.8 ± 0.83	<300	91.32 ± 0.014	92.56 ± 0.025
F5	7–7.5	0.385 ± 0.05	33.64 ± 0.72	<300	90.58 ± 0.04	91.60 ± 0.077
F6	7–7.5	0.364 ± 0.09	30.9 ± 0.89	<300	92.58 ± 0.035	93.76 ± 0.038
F7	7–7.5	0.465 ± 0.07	33.28 ± 0.85	<300	94.85 ± 0.015	95.97 ± 0.014
F8	7–7.5	0.32 ± 0.02	29.55 ± 0.93	<300	91.30 ± 0.032	95.9 ± 0.046
F9	7–7.5	0.22 ± 0.04	32.66 ± 0.96	<300	90.60 ± 0.055	90.21 ± 0.035

inserts were found to possess uniform thickness within the same batch prepared for each insert.Table 4.

The pH of all the prepared inserts were within the pH of ocular tissues (7.4) so no irritation is expected to occur due to insert application [35–39]. The films were folded manually and the value recorded was more than 300 for all batches, which was considered good, and revealed good film properties. As notices in Table 3 the drug content for both drugs in all the formulations were within the acceptable limits which indicate uniform distribution of drugs through formulation and reproducibility of the method of preparation [12].

3.3. Swelling index

The results of swelling index percent for all the prepared formulation can be seen in Fig. 1. Swelling is important parameter to be considered because solid dosage forms if inserted into the eye irritation will ocular with reflex blinking and excessive tearing. The faster the swell, the less effect observed due to instillation. The highest swelling index was seen in (F4, F5) in which Carbopol was one of the ingredients for formulation. A possible cause is the ionization of carboxylated moiety at the pH environment of the experiment, which led to development of negative charges along the back bone of the polymer. The repulsion of the like charges uncoils the polymer. The counter ion diffuses inside the insert creates an additional osmotic pressure differences across the insert leading to a considerable swelling of the polymer[22].

3.4. Ex vivo Bioadhesive strength

Bioadhesion is an important parameter to increase precorneal residence time and allow more time for the drug to cross ocular tissues. Among all the prepared formulations (F5), which contain high amount of Carbopol, has the highest bioadhesive force and force of adhesion. This is probably due to the formation of strong gel by formation of hydrogen bonding between the gel formed after swelling of the insert and ocular surfaces [14].

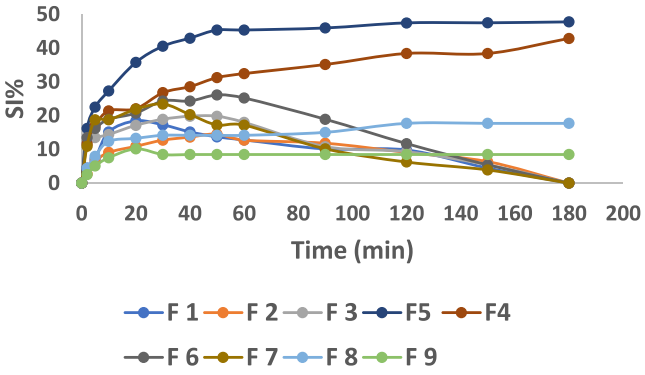

Fig. 1. Swelling index of formulated tinidazole and levofloxacin ocular inserts.

3.5. Mechanical characteristics

The tensile test gives an indication of the strength and elasticity of the patch and reflected by the parameters such as TS and %EB. It is suggested that a suitable insert should have a moderate TS and high %EB to have a soft and tough character [23]. The results for all formulations can be seen in Table 5. The results varied considerably depending on the type and ratio of polymer used. The highest tensile strength value was observed in (F8) that containing a combination of HPMC and EC which reflects the strength and high elasticity of the polymer film. Tough films are hard to be endured by ocular tissues. On the other hand, F5 had low tensile strength with high EB% which is preferable for ocular tissues[24].

3.6. In-Vitro release study

Fig. 2 A and B shows the cumulative percentage of drug released as a function of time for all formulations for both drugs. Burst release was observed in all formulas, except F4 and F5. F1, F2 and F3 showed a complete drug release within 1 hr while F6, F7 and F8 within 2 h. Although F9 extended the release for more than 10 h, it had 70% of the loaded drug released within 2 h which is

Table 4
Bioadhesive strength of prepared tinidazole and levofloxacin ocular inserts.

Formula No.	Bioadhesive strength (g)	Force of adhesion (N)
F1	6.11 ± 2.02	0.05978
F2	5.76 ± 0.57	0.05644
F3	7.1 ± 1.73	0.06958
F4	8.15 ± 1.05	0.07987
F5	71.4 ± 1.45	0.69972
F6	3.3 ± 1.11	0.03234
F7	1.5 ± 0.25	0.0147
F8	15.1 ± 1.95	0.1470
F9	7.1 ± 1.90	0.0695

Table 5
Mechanical characteristics of prepared tinidazole and levofloxacin ocular inserts.

Formula No	Tensile Strength (mpa)	Percentage elongation at the break (EB%)
F 1	0.327	61.8
F 2	1.1	29.9
F 3	1.89	23.2
F 4	5.13	25.5
F 5	0. 4	56.8
F 6	0.607	31.5
F 7	5.13	25.5
F 8	26.7	66.6
F 9	4.31	42.2

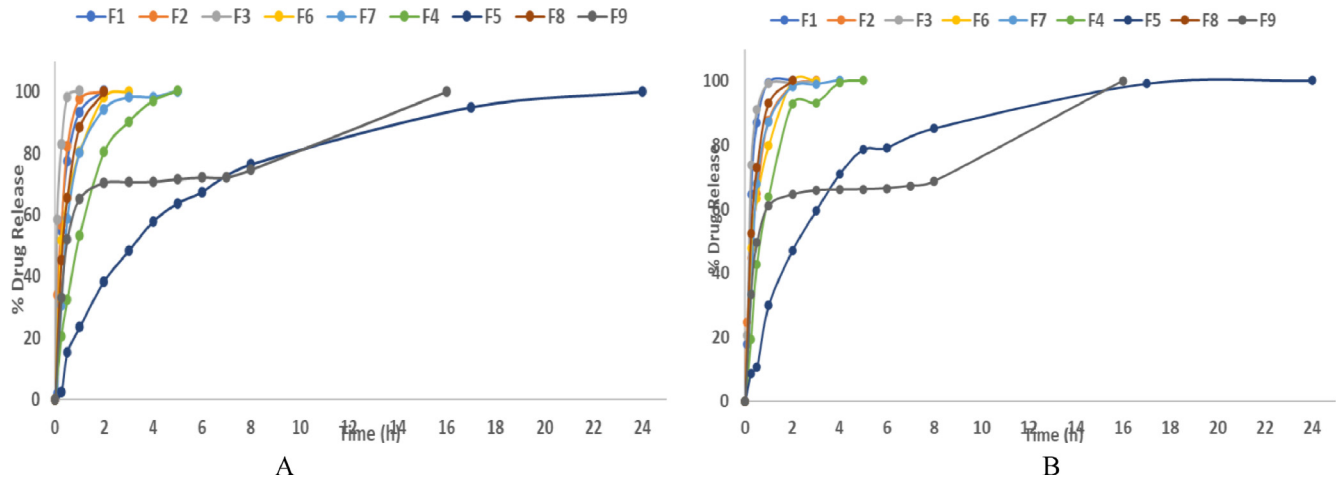

Fig. 2. Percent of drug release from HPMC and HPMC-polymer blend for A) Levofloxacin; B) Tinidazole.

unfavourable for sustained release formulation. Only F5 had no burst release and both drugs sustained for around 24 h[25].

3.7. In- vivo release study

Although all the prepared formulations had proper physical characteristics, the release profile favours the choice of F5 as optimum formula. *In vivo* release of the drug from F5 was studied in rabbit's eyes by measurement of the content of the drug remaining in the ocular inserts at particular time intervals for 24 h and the results can be seen in Fig. 3 [17]**.** For both drugs it was noticed that around 60% of the drug still remain in the insert after 4 h and within 8 h of tinidazole and 20% of levofloxacin still remain in the insert. The results suggested that the insert was successful in increasing precorneal residence time and reduce the frequency of administration.

3.8. Ocular irritation test

To examine whether the present of an insert for a long period may cause irritation to ocular tissues, irritation test was performed and the results can be seen in Fig. 4. No signs of inflammation in the right eye (redness, tearing or swelling) after 1 hr and for the next 12 h from the first insert installation, which indicates that it is not irritant to the eye and the score is 0 [17].

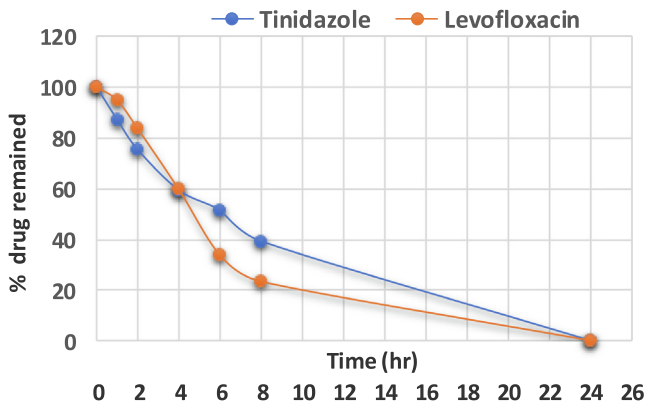

Fig. 3. drug remaining vs. time for optimized formulation at different time intervals.

3.9. Differential scanning calorimetry

Solvent casting method was used for the insert formulation and mixing more than one polymer with two drugs followed by drying may change the nature of the drug. To confirm any changes in crystallinity of the drugs used, DCS was performed and the results can be seen in Fig. 5. Both tinidazole and levofloxacin had a sharp endothermic peak at 126 °C and 105 °C respectively when examined alone[26 27]. It was stated that the thermal analysis of HPMC exhibits an endothermic effect above 100 °C[28].Finally the thermogram of Carbopol showed an endotherm between 50 and 100 ○C [29].

However, the drug peak intensity is lower than that observed in the pure drug DSC curve; this may be elucidated by the interaction between Drugs (Tinidazole, Levofloxacin) and polymers (HPMC, Carpobol) in the DSC pan during ramping. As the polymer starts to melt at a temperature lower than the drug's melting point, the drug may interact with the molted polymer, and by the time when the temperature reaches the melting point of the drug, a small amount of drug has already been solubilized into the moulted polymer and thus give rise of lower peak intensity[30]. The drug's peak is absent in the formula DSC curve, meaning the drug had transformed into amorphous state [31,32].

3.10. Analysis of drug release kinetics

In-vitro release data were fitted to various mathematical models such as zero order, first order and Higuchi Moreover, analysis of experimental data according to Korsmeyer-Peppas model with explanation of the release exponent values (n) leads to better understanding the mechanism of release from ocular insert. For tinidazole the kinetic results can be seen in table 6 and all the formulations followed 1st order model for release, with the exception of F1, F6, F9 which followed Higuchi model. While for levofloxacin, all formulas prepared followed 1st order model table 7. This indicates that the release of the drugs from each insert depends on concentration of the drug remaining in the insert.

These differences may be due to the fact that the precise determination of the mechanism of drug release from matrix is complex, especially when there is more than one polymer as a matrix, the performance of the hydrophilic matrices as a prolong drug release system is dependent on the hydration properties of the polymer chains, gel forming properties and relaxation of polymer chains when the fluid gets into the matrix [3334].

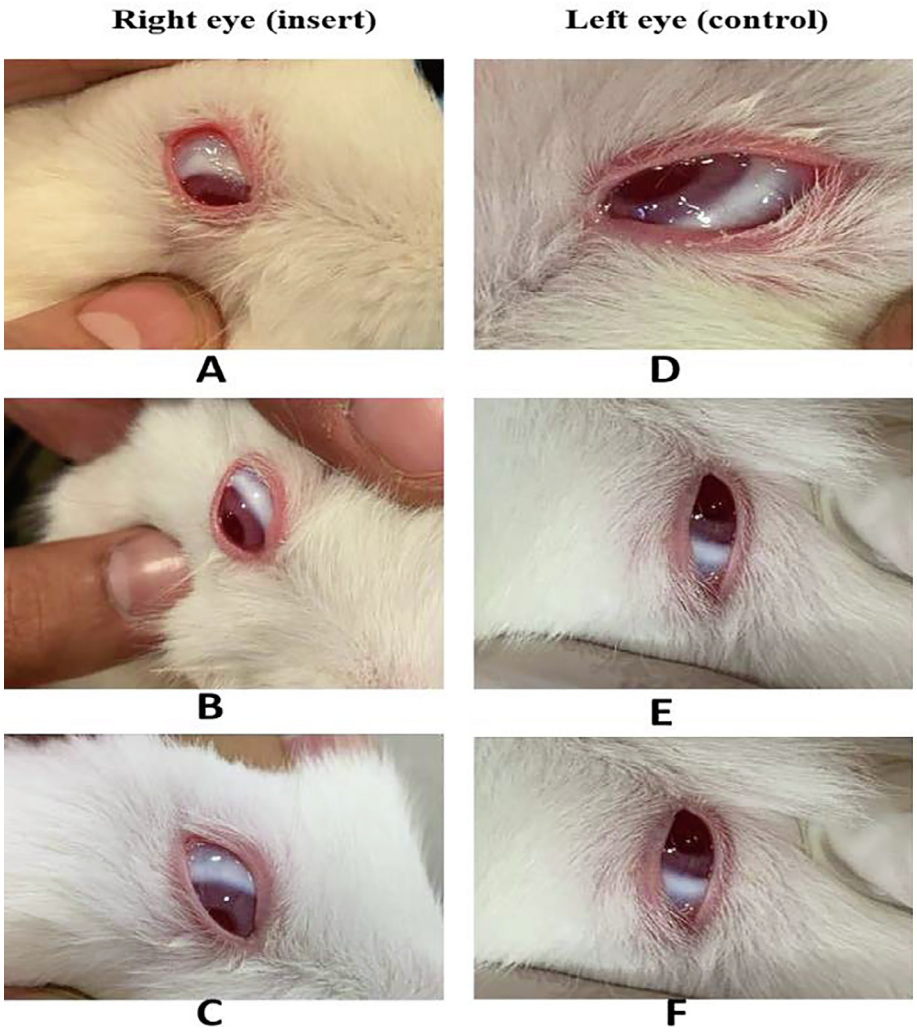

Fig. 4. Ocular irritation test in which the insert was placed in the right eye and the left eye was a control. Picture A and D after 1 hr; B and E after 6 h; C and F after 12 h.

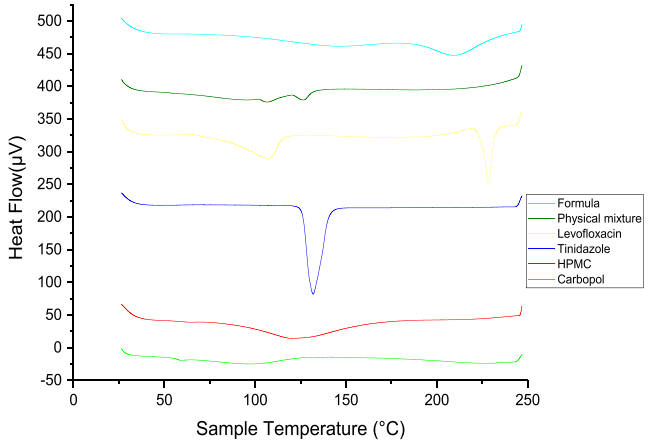

Fig. 5. Differential scanning calorimetry of pure drugs, polymers, physical mixture and optimum formula F5.

4. Conclusion

One of the main problems associated with treatment of bacterial infections of the eye is multiple application of eye drops. The rapid elimination of eye drops require hourly instillation which decrease patient compliance. To overcome the problem the concept of solid insert was used to deliver two antibiotics at the same time. Formulations using different polymers were prepared and based on physical characterization formulation with 1:1 HPMC K15M :Carbopol 934 was the optimum formula that had the proper strength and mucoadhesion with high swelling index and sustained release for around 12 h. When examined in animals no irritation was observed and also the drug remain in ocular tissues for a long period. Levofloxacin and tinidazole were successfully formulated as solid insert and sustained the release of both drugs for around 24 h. The approach of solid insert is promising approach to overcome problems with topical ocular delivery.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 6
Release Kinetic of Tinidazole ocular inserts.

Formula TINIDAZOLE	Zero order R^2	First order K_0	Higuchi R^2	Kores Meyer K_{1ST}	R^2	K_{HC}	R^2	K KROS-MAYER	RELEASE EXPONENT
F1	0.8452	0.4447	0.9206	−0.0127	0.9332	8.1802	0.9343	5.676	0.5836
F2	0.7401	0.3873	0.9493	−0.0116	0.8867	6.7929	0.9474	14.635	0.4014
F3	0.4007	0.2875	0.6165	−0.0106	0.5737	5.5129	0.6997	17.40	0.3899
F4	0.7535	0.254	0.9165	−0.0075	0.8777	5.8557	0.8984	6.211	0.5215
F5	0.6133	0.057	0.9312	−0.0016	0.8311	2.8142	0.8944	2.243	0.5832
F6	0.84	0.3068	0.6632	−0.0137	0.9299	5.6507	0.9701	21.61	0.309
F7	0.6138	0.2308	0.8785	−0.0084	0.7125	4.1393	0.8025	16.66	0.355
F8	0.7866	0.4115	0.9941	−0.016	0.886	6.6031	0.9337	23.631	0.3161
F9	0.7777	0.0511	0.7878	−0.0016	0.8047	1.7735	0.8161	23.812	0.1886

Table 7
Release Kinetic of Levofloxacin ocular inserts.

Formula Levofloxacin	Zero order R^2	First order K_0	Higuchi R^2	Kores Meyer K_{1ST}	R^2	K_{HC}	R^2	K KROS-MAYER	RELEASE EXPONENT
F1	0.8611	0.4424	0.9723	−0.0122	0.9445	8.1097	0.9551	6.106	0.5659
F2	0.7821	0.3664	0.9768	−0.0115	0.8897	6.8414	0.923	11.948	0.434
F3	0.6504	0.3361	0.8082	−0.0152	0.7718	5.5364	0.8533	31.593	0.2584
F4	0.8676	0.2755	0.9918	−0.0066	0.9566	6.1803	0.9729	5.223	0.5415
F5	0.7477	0.0604	0.9959	−0.0013	0.9257	2.8516	0.856	1.007	0.6979
F6	0.8593	0.2827	0.9501	−0.0111	0.9435	5.1861	0.9794	25.398	0.2745
F7	0.6573	0.1952	0.9288	−0.0064	0.7977	4.5945	0.848	15.059	0.3579
F8	0.8443	0.4822	0.9982	−0.0167	0.9287	7.6476	0.957	16.834	0.3864
F9	0.7037	0.0497	0.8169	−0.0016	0.7904	1.7984	0.8158	24.210	0.1969

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