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Formulation and Evaluation of Gel Forming Ocular Minitablets Containing Piroxicam

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aims: The purpose of this *in vitro* and *ex vivo* study was to prepare and characterise ocular minitablets of piroxicam based on different polymeric matrices and to evaluate their potential to provide prolonged and controlled drug release to ocular tissues after surface administration.
Study Design: Experimental study and ex-vivo study.
Place and Duration of Study: School of Pharmacy, University of East Anglia, Norwich, Norfolk, UK, between July 2011 and March 2012.
Methodology: A range of placebo minitablet formulations were prepared based on pharmaceutically-acceptable polymers of differing chemical and physical properties. These were evaluated using standard physical and visual imaging methods. A subset of placebo formulations was chosen to prepare medicated minitablets containing 5 %w/w piroxicam as a model drug. Three different *in vitro* methodologies were used to assess drug release from the minitablets. An *ex vivo* porcine ocular method was used to assess likely tissue distribution of the drug after surface ocular administration of the minitablets.
Results: Minitablets were successfully produced from all formulations. The *in vitro* drug release profile was dependent on the chemistry of the polymer used, its hydration and swelling behaviour and to some extent, the methodology used for assessing the drug

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release profile. The *ex vivo* studies in porcine eyes suggested that the drug disposition was inversely related to the hydration and swelling behaviour of the polymer. Minitablets containing piroxicam based on Pluronic F127 showed the highest posterior segment ocular bioavailability of the formulations studied in the *ex vivo* model. Conversely, the more highly swelling minitablet formulations showed higher anterior segment bioavailability.

Conclusions: Ocular minitablets containing 5 %w/w piroxicam were successfully produced from a range of polymer matrices. *In vitro* release was shown to be dependent on the physical and chemical properties of the polymers used as the basis of the minitablets. Posterior segment deposition in an *ex vivo* model was greatest in the formulation which showed limited hydration and swelling behaviour in a simulated ocular environment.

Keywords: Ocular; minitablets; piroxicam; HPMC; Na-CMC; pluronic F127; dissolution.

1. INTRODUCTION

Eye disorders, particularly posterior segment diseases, are difficult to treat as the eye is usually regarded by patients as being sensitive and there may be unwillingness on their part to use some of the more invasive treatments available. Understandably, therefore, topical application of drugs to the eye is the most popular route of drug administration for the treatment of ocular diseases, with simple aqueous eyedrops being the most common formulation used. However, eyedrops suffer from the disadvantage of the rapid drainage from the ocular surface and hence poor bioavailability in all ocular tissues, but particularly in the posterior segment. Frequent instillation of eye drops is often required to maintain the drug at its therapeutic level over the time period required for treatment. Maximising ocular absorption by the frequent application of highly concentrated solutions has been reported to lead to toxic side effects and damage to the ocular cellular system (Topalkara et al., 2000).

Various ocular formulations have been developed in an effort to overcome the issues with conventional eyedrop formulations described above. Ideally, an ocular formulation should have the following characteristics: 1) be applied once a day only, to maximise patient compliance; 2) be applied to the surface of the eye, to maximise ease of application and hence improve patient compliance; 3) provide sustained and therapeutic levels of the drug at the desired sites, to maximise effectiveness; 4) not interfere with vision, be otherwise pharmacologically inert and be biocompatible and 5) be pharmaceutically elegant and be easy to prepare, sterilise and store.

Ocular drug delivery systems previously studied include liposomes, niosomes, nanoparticles and Chemical Delivery Systems (CDS) or pro-drugs.

Liposomes have the advantage that they can potentially carry both hydrophilic and lipophilic drugs, but the disadvantages of high cost, low drug loading capacity, physical and chemical instability and high temperature sensitivity leading to problems during sterilization (Drulis-Kawa and Dorotkiewicz-Jach, 2010).

Niosomes are similar to liposomes, but prepared by using non-ionic surfactants (the lipids in liposomes have ionic headgroups. They have been reported as a possible approach in

ophthalmic delivery systems but, it was found that the entrapment efficiency of the prepared niosomes are highly affected by the type of surfactant, cholesterol and the method of preparation (Guinedi et al., 2005).

Nanoparticles are polymeric colloidal particles, ranging in size from 10 nm to 1 µm, in which the drug is entrapped. They may be classified into nanocapsules, defined as small capsules with a central cavity surrounded by a polymeric membrane and nanospheres, which are solid spheres, composed of the polymer and drug. Chitosan nanoparticles have been proved to deliver the drug only to external ocular tissues but not to internal tissues (De Campos et al., 2001). In addition solid liquid nanoparticles have been developed as a good carrier in ocular delivery, it was found to produce a higher drug bioavilability in the aqueous humor relative to the used eye drops of the same doses (Cavalli et al., 2002).

Chemical Delivery Systems (CDS) or Pro-drugs are therapeutically inactive forms of the drug, which are metabolised after administration to the active drug. Their disadvantages include reliance on the chemical transformation being the same in all patients. Water soluble pro-drug of cyclosporine A has been developed and it was rapidly transferred into stable cyclosporine A upon contact with tears (Lallemand et al., 2005).

However most of all these previously discussed systems provided more prolong sustained drug release of improved ocular availability. Unfortunately, they are very expensive, need special complicated techniques for manufacturing and faced by the patients' inconveniency after their application; some of them need special applicator or a surgery like in case of implantable systems.

Ocular minitablets are a relatively new innovation in the treatment of ocular disease. These are extremely small tablets, approximately 2 mm in diameter and with an average weight of 5 to 7 mg. They may be easily inserted inside the cul de sac of the eye without irritation. Depending on their chemical nature, they may gel in the presence of ocular fluid, or the tablet matrix dissolves, thus providing drug release. Ocular minitablets have the advantages of conventional and well-understood manufacturing techniques, low cost and predictable behaviour. Weyenberg et al. (2006) prepared ocular minitablets based on drum dried waxy maize starch which found to be very promising formulation with no irritation and prolonged drug release for at least 12 hours. Ocular minitblets were also reported to be generally well tolerated by patients (Weyenberg et al., 2004). In another study, ocular minitablets prepared from a mixture of drum dried waxy maize starch and carbopol 974 were succeeded to prolong the drug release to anterior eye segment up to 9 hours compared to the polymer suspension, with a good mucoadhesion property and patient acceptability (Ceulemans et al., 2001).

In this present study, the potential of a range of polymers to form minitablets appropriate for ocular use has been investigated. Several polymers were studied as the matrix base, some conventional such as hydroxypropyl methylcellulose (HPMC), which have been used previously for ocular formulations and some pharmaceutically-acceptable polymers, which have not previously been used for ocular drug delivery, such as xanthan gum and gellan gum. The model drug used was piroxicam, which is used as a non-steroidal anti-inflammatory drug (NSAID) for a range of ocular inflammatory conditions (e.g. Scuderi et al., 2003). In addition, it was proved that piroxicam eye drops when combined with antibiotic eye drops for treatment of acute hemorrhagic conjunctivitis, it showed decrease in treatment time, fast recovery of all disease symptoms and complete treatment of all symptoms compared to using the antibiotic eye drops alone (Kosrirukvongs, 1997). Placebo minitablets

have been prepared and characterised physically, from which a range of medicated mini-tablets was selected and analysed by a variety of *in vitro* techniques for drug release. Finally, an *ex vivo* study examined the deposition of drug from the medicated minitablet formulations.

2. METHODOLOGY

2.1 Materials

Hydroxypropyl methylcellulose K4M (HPMC) was obtained from The DOW Chemical Company, USA. Sodium carboxymethylcellulose (Na-CMC) was obtained from Fluka Chemie GmbH, Germany. Ethyl cellulose (EC) was obtained from Hercules, UK. Microcrystalline cellulose (MCC), polyethylene glycol (PEG) 6000 and PEG 20,000 were obtained from Clariant GmbH, Germany. Gellan gum (Gelrite) was obtained from CP Kelco, USA and xanthan gum (Xanthural 180) from CP Kelco, UK. Chitosan high density, Pluronic F88, Pluronic F127, lactose monohydrate, magnesium stearate, sodium chloride, calcium chloride dihydrates and sodium bicarbonate were obtained from Sigma Aldrich, UK. Piroxicam was obtained from Gattefossé, France. Minisart syringe filters 0.22 µm were obtained from Sartorius Stedim Biotech GmbH, Germany. Polycarbonate membrane of pore size 400 nm and diameter 15 mm were supplied by Harvard Apparatus, USA. Porcine eyes were (kindly donated from a local abattoir, H.G. Blake Costessey Ltd., UK), from pigs which had been slaughtered under standard UK legislation for food-producing animals. Dulbecco´ s Modified Eagle´s Medium (DMEM) and penicillin streptomycin (PS) solution were obtained from GIBCO, UK. Methanol HPLC grade, sodium dihydrogen orthophosphate dehydrate and sodium hydroxide were obtained from Fisher Scientific Ltd., UK. Deionised water was produced from an Elga still (Elga, UK).

2.2 Experimental

2.2.1 Preparation of minitablets

Placebo minitablets were prepared using various polymers as described below, with a polymer loading of 74% w/w in all cases. Lactose monohydrate at 25% w/w loading was used here to provide mechanical strength to the tablets, as preliminary experiments on "pure" polymer with only lubricant added had shown that the tablets formed were insufficiently robust in some cases. Magnesium stearate was used as a lubricant for all formulations at a level of 1% w/w. The ingredients were ground and passed through a 500 µm sieve prior to mixing. The powder mixture was then compressed on a Piccola rotary tablet press (Riva, Argentina) fitted with 2 mm normal concave dies. The tablet press parameters were kept constant so as to explore the inherent variability between the formulations. However the compression force used was 1 ± 0.2 kN for all placebo formulations except for MCC, gelrite, xanthan gum and chitosan, it was 0.5 ± 0.1 kN.

The polymer components of the placebo formulations were as follows: FP1 HPMC, FP2 Na-CMC, FP3 EC, FP4 MCC, FP5 PEG 20,000, FP6 Gellan gum, FP7 Xanthan gum, FP8 Chitosan high density, FP9 PEG 6,000, FP10 Pluronic F88, FP11 Pluronic F127 (24%) and Xanthan gum (50%) and FP12 Pluronic F127.

Also, medicated minitablets containing piroxicam 5% w/w were prepared in a similar manner, using seven polymer formulations, selected based on the results on the placebo batches.

The polymer and lubricant levels were kept the same at 74 %w/w and 1 %w/w, respectively, with the lactose monohydrate content being reduced to 20 %w/w. The polymer components of the medicated formulations were as follows: FM1 HPMC, FM2 Na-CMC, FM3 PEG 20,000, FM4 Gellan gum, FM5 Xanthan gum, FM6 Pluronic F127 (24%) and Xanthan gum (50 %) and FM7 Pluronic F127.

2.2.2 Physical characterization

The minitablets were evaluated physically using the following tests.

2.2.2.1 Determination of average weight and weight uniformity

The British Pharmacopoeia (BP) 2012 method for weight uniformity was followed. Twenty tablets of each formulation were accurately weighed individually. The mean and standard deviation of the weight for each batch was calculated, as was the percentage weight deviation of each individually weighed tablet from the mean.

2.2.2.2 Determination of minitablets dimensions by optical microscopy

To measure the diameters and heights of minitablets accurately, an optical microscopy (Leica DM 2500P, UK) was used. The dimensions of ten minitablets of each formulation were measured and the means and standard deviations were calculated.

2.2.2.3 Determination of crushing strength

The radial crushing strength of the minitablets (n=10 per batch) was determined using a texture analyser (TA.XT2 Plus Texture Analyser, Stable Microsystems, UK) following the general method outlined by Choonara et al. (2006). The experimental details are as follows: 11 mm diameter cylindrical Perspex probe, pre-test speed 1 mm/s, test speed 0.1 mm/, post-test speed 1 mm/s, compression distance 1 mm, trigger force 0.05 N. The maximal force measured was derived from the force-distance diagram and used to calculate the tensile strength via the Pitt equation for bi-convex tablets (Pitt et al., 1988), Equation 1 below.

$$\sigma_t = \frac{10\,F}{\pi D^2}\,[(2.84\,H/D) - (0.126\,H/W) + (3.15\,W/D) + 0.01]^{-1} \qquad \text{Eq. 1}$$

where: σ_t = tensile strength, F = crushing force, D = diameter, H = thickness (total height) and W = waist height.

2.2.2.4 Determination of friability test

Friability was determined using a modified BP 2012 method, similar to that used by (Weyenberg et al., 2003). The experiment was performed in friability tester (Erweka GmbH, Germany).

Ten minitablets were weighed as a unit. They were then placed in the drum of the friability tester and rotated for 100 revolutions (25 rpm for 4 minutes). The tablets were removed, checked for appearance and re-weighed as a unit. The friability was calculated using Equation 2.

$$F (\%) = 100 \times (P - P') / P \quad \text{Eq. 2}$$

Where P = initial weight of 10 minitablets and P´= final weight of 10 minitablets. The test was repeated three times for each formulation.

2.2.2.5 Water uptake and swelling test.

Individual minitablets were weighed accurately and then placed precisely on the upper side of a filter membrane using a forceps; the filter membrane was connected on its lower surface to a reservoir containing freshly prepared STF pH 7.4 in order to mimic the eye conditions. After predetermined time intervals each minitablet was removed carefully, reweighed and replaced on the membrane. The swelling index (SI) was calculated according to equation 3.

$$SI = (Mw - Md) / Md \quad \text{Eq. 3}$$

Where; Mw is weight of the swelling minitablet, Md is the initial weight of the dry minitablets. SI of 1 indicates that the minitablets have doubled in weight (Weyenberg et al., 2003). The experiment was continued until the minitablets either achieved constant weight or disintegrated. The hydration time was defined as the point at which the minitablets reached maximal hydration. Ten repeats were performed for each formulation.

2.2.2.6 Surface characterisation using SEM

The surface structure of the minitablets was evaluated using scanning electron microscopy (SEM), performed using a JEOL JSM 5900 LV system (JEOL, Japan), mounted with a tungsten filament with an acceleration voltage of 5–20kV. The samples were mounted onto stubs using double-sided tape and were gold coated to a thickness of circa 15 nm by a Polaron SC7640 sputter gold coater (Quorum Technologies). The imaging process was performed in a high vacuum environment

2.2.3 In vitro release study using rotating glass vials method

Each minitablet was accurately weighed and transferred to a glass vial containing 1.00 mL of STF pH 7.4. To avoid water evaporation, the vials were covered with caps or parafilm membrane. Then all vials were placed in an oscillating incubator, thermostatically set at 32 ± 1ºC and rotating at 25 rpm. During the experiment, aliquots of 100 µL were withdrawn at pre-determined time intervals. The samples were diluted with 10%v/v ethanol/STF solutions and the concentration of piroxicam determined spectrophotometrically at 355 nm against a standard calibration curve previously constructed in the same solvent system. The percentage released at each time interval was expressed as a fraction of the total amount released after 8 hours. The experiment was repeated three times for each formulation.

2.2.4 In vitro permeation study using standard Franz diffusion system

A 6-cell jacketed Franz diffusion cell apparatus (Perme Gear, USA) was used for these experiments. The receptor chamber was loaded with 5 mL of STF pH 7.4, the polycarbonate membrane or sclera (as used) was carefully placed on the surface of the receptor phase, ensuring complete contact and then the donor chamber was placed on top and clamped in position. The temperature in the cells was maintained at 32ºC using a circulating water bath. One minitablet was accurately weighed and placed carefully on the membrane or sclera in each cell, then wetted by two drops of STF. To prevent water evaporation, the top of the

donor chamber was sealed with triple layers of parafilm. Samples of 300 µL were taken at predetermined time intervals from the receptor phase through the sampling port and replaced with fresh medium. Piroxicam content in the extracted phase was determined spectrophotometrically at 355 nm, against a standard calibration curve constructed in the same medium.

2.2.4.1 Diffusion through synthetic membrane

In this case, a 400 nm polycarbonate membrane (Harvard Apparatus, USA) was used as the diffusion barrier, with the membrane having been soaked overnight in STF pH 7.4 prior to being used. The experiment was continued for 8 hours, and repeated three times per each formulation.

2.2.4.2 Diffusion through porcine sclera

Here, a porcine scleral membrane was used as the diffusion barrier. Pig eyes were provided by the local abattoir, from pigs which were being processed under standard UK regulations for food-producing animals. The pigs were slaughtered and eyes were removed immediately without further treatment. The eyes were stored on ice, transported to the laboratory within 30 minutes and used within 6 hours post-mortem. The porcine eyes were dissected as follows: firstly removal of all muscles and connective tissues from the bulbus surface, and then the eye was cut parallel to the limbus behind the iris-lens-diaphragm arc. Both the anterior segment and vitreous humor were removed. The eye cup was cut transversely along the vein and the retinal pigment epithelium (RPE)/choroids carefully removed from the sclera). Finally, the sclera was washed with distilled water.

The cleaned sclera was cut into disks fitting the Franz cell size, and the scleral disks were soaked overnight in STF pH 7.4 to ensure complete saturation of membrane by the dissolution medium prior to starting the experiment. In this case, the experiment was conducted for 24 hours and repeated a total of three times per sample.

2.2.5 Kinetic analysis of *In vitro* drug release and diffusion

Kinetic analysis was applied to all three *in vitro* drug release and diffusion profiles. The mean values of the percentage drug detected in the exterior or receptor phase, up to the timepoint of maximal release, was fitted to the first order equation and the Korsmeyer-Peppas equation, equations 4 and 5 respectively (Korsmeyer et al., 1983).

$$\frac{M_t}{M\infty} = 1 - \exp(-kt) \qquad \text{Eq. 4}$$

$$\frac{M_t}{M\infty} = kt^n \qquad \text{Eq. 5}$$

Where, M_t is the amount of drug released at time t, $M\infty$ is the amount of drug released at infinite time (i.e. effectively the total content of the drug in the formulation), k is the release constant and n is the release exponent.

2.2.6 Ex- vivo study

This study was performed to assess the likely ocular distribution of piroxicam from minitablets applied to the surface of the eye. Porcine eyes were used as a model of the human situation. Three formulations were selected, based on their in vitro release profiles: FM1 (based on HPMC), FM2 (based on Na-CMC) and FM7 (based on Pluronic F127).

2.2.6.1 Preparation of porcine eyes for minitablets application

The porcine eyes were received as described above. Excess tissue was trimmed from the eyes and they were then soaked in DMEM / PS 1% solution for one hour at 32ºC to disinfect the surface. Two medicated minitablets from each selected formulation were placed on the eye surface, then covered by the conjunctiva in order to retain them in place throughout the experiment and to mimic as much as possible the normal therapeutic position. The eyes were then incubated at 32ºC for 3, 6, 9 and 12 hours. After each time interval, the eyes were removed from incubator, the minitablets removed from the eyes and the eyes immediately flash frozen with liquid nitrogen. The frozen eyes were then either dissected immediately or stored at -80ºC prior to dissection. For each minitablet formulation tested; six eyes were used at each time point.

2.2.6.2 Dissection of eyes and quantitative determination of piroxicam in different ocular tissues

The frozen eyes were left to be thawed for about 10 minutes at room temperature before dissection. The eyes were cut transversely across the cornea to separate the eye into two halves. Then the half was immediately dissected into the following seven tissues: lens, cornea, vitreous, retina, choroid / RPE, sclera, and conjunctiva. Each tissue was separated and weighted accurately. Piroxicam was extracted from each ocular tissue by the addition of 3 ml methanol HPLC grade, and shaking at 250 rpm for at least 3 hours at room temperature (Glunchedi et al., 2000). All samples were centrifuged at 5000 rpm for 10 minutes and then filtered through 0.22 µm Minisert filter (Sartorius Sedim Biotech, GmbH, Germany), with the piroxicam concentration in the filtrates being ascertained using the following reverse-phase HPLC method, based on that of Basan et al. (2001).

A Hypersil ODS C_{18} column with average particle size 5 µm, length 25 cm and internal diameter 4.6 mm was used. The mobile phase was composed of 60%v/v phosphate buffer pH 7.0 : 40%v/v methanol; the aqueous phosphate buffer solution (0.05 M) was prepared by dissolving sodium dihydrogen orthophosphate dihydrate in de-ionized water and adjusting the pH to 7.0 with1 N Na OH. The mobile phase was filtered through a 0.45 µm filter and degassed with nitrogen. HPLC experimental conditions were as follows: the flow rate was maintained at 1 mL/minute, the sample injection volume was 10 µL, the temperature was 20 ± 1ºC, the total run time 10 minutes and the piroxicam was detected using UV detection at 357 nm.

2.2.6.3 Pharmacokinetic analysis

The drug distribution profiles were analysed in terms of C_{max}, the maximum concentration in individual ocular tissues after incubation for certain time periods and T_{max}, the incubation time at which C_{max} was observed.

3. RESULTS AND DISCUSSION

3.1 Physical Characterization of Placebo Minitablets

The results of physical properties including average weights, dimensions, crushing force, friability percentage, swelling index and total hydration time of all prepared placebo minitablets are shown in Table 1.

3.1.1 Weight and weight variation

The minitablets ranged in weight from a mean of 3.2 ± 0.10 mg for FP4 (based on MCC) to a mean of 7.2 ± 0.08 mg for FP7 (based on xanthum gum). All formulations easily complied with the BP 2012 specifications for weight variability of <10% deviation from the mean for individual samples.

3.1.2 Dimensions by optical microscopy

Fig. 1 shows example optical microscope images of the minitablets, indicating measurement of the diameter and thickness. All diameters were around 2 mm with insignificant variation, as would be expected as this was the constraining dimension of the die. The thickness of the minitablets varied from 1.15 ± 0.035 mm for FP4 (based on MCC) to 1.94 ± 0.036 mm for FP7 (based on xanthum gum). There was a general trend of increasing thickness with increasing weight across all twelve placebo batches (r = 0.909).

3.1.3 Crushing strength

The values of crushing strength ranged from 2.4 ± 0.2 N for FP6 (based on gellan gum) to 8.9 ± 0.7 N for FP3 (based on EC). The calculated tensile strength values generally followed the trend seen for the crushing strength, with values ranging from 0.62 MPa for FP6 (based on gellan gum) to 2.19 MPa for FP3 (based on EC). There was no relationship between either crushing strength or tensile strength and any other measured parameter.

3.1.4 Friability

The lowest friability measured was 0.03 % for FP12 (based on Pluronic F127) and nine other formulations showed friability values which passed the BP 2012 specifications of < 1% weight loss. Two formulations showed higher friability values: FP2 (based on Na-CMC) showed a weight loss of 2.05% and FP8 (based on high density chitosan) showed a weight loss of 2.34%. There was no relationship between friability and any other physical parameter but generally, most prepared minitablets are not too soft and hard enough to resist the breaking during the normal handling and insertion. It should not be very hard as well in order to minimize eye irritation and foreign body sensation.

Table 1. Physical evaluation of the placebo minitablets

Formulation code	Mean compression force (kN)	Weight (mg) mean±SD	Thickness (µm) mean ±SD)	Diameter (µm) mean ±SD	Crushing strength (N) mean±SD	Tensile strength (MPa)	Friability (%) mean±SD	Swelling index	Hydration time (h)
FP 1	1.0	4.77±0.14	1582±33	2025.6±19.3	5.70±0.2	1.22	0.79±0.1	1.7±0.2	4
FP 2	1.2	4.58±0.24	1395.3±8	2044.0±23.0	2.80±0.7	0.71	2.05±0.2	4.3±0.4	4
FP 3	1.0	3.73±0.26	1417.6±43	2010.6±16.1	8.90±0.7	2.19	0.22±0.04	DNS	N/A
FP 4	0.5	3.20±0.10	1149±35	1999.3±22.1	6.16±0.4	1.95	0.27±0.08	Dis.	N/A
FP 5	1.2	5.95±0.12	1658±14	1991.6±9.0	3.86±0.0	0.72	0.62±0.4	DNS	N/A
FP 6	0.6	4.23±0.11	1329.3±7.5	2037.6±3.7	2.4±0.2	0.62	0.31±0.2	6.1±0.1	0.5
FP 7	0.5	7.22±0.08	1939.3±36	2037.3±25.4	7.13±0.5	1.16	0.32±0.3	2.6±0.3	2
FP 8	0.4	6.61±0.14	1848.6±94	2004.3±28.4	7.93±0.7	1.36	2.34±0.2	Dis.	N/A
FP 9	1.3	5.26±0.06	1534.6±24	1997.0±13.5	8.83±0.3	1.83	0.75±0.1	DNS	N/A
FP 10	1.0	5.46±0.14	1713±56	2017.6±26.0	4.53±0.2	0.86	0.37±0.09	DNS	N/A
FP 11	1.1	6.01±0.19	1701.3±42	2003.3±0.5	5.36±0.1	1.00	0.54±0.02	3.7±0.4	3
FP 12	0.9	5.70±0.12	1746.0±32	1985.0±23.3	4.66±0.05	0.86	0.03±0.02	0.7±0.06	3

N/A = not applicable; DNS = did not swell; Dis. = disintegrated

a) FP4 b) FP 8

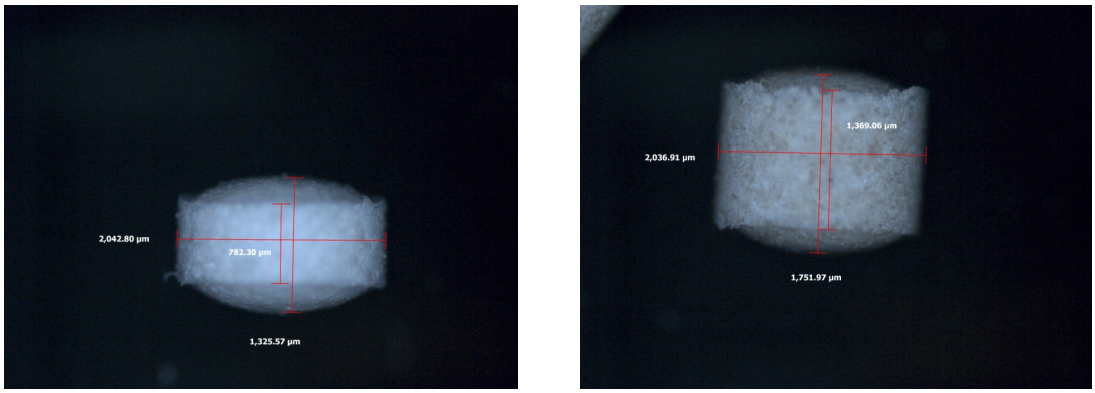


Fig. 1. Example optical microscope photographs showing the dimensional analysis of the placebo minitablets: a) FP4 (based on MCC) and b) FP8 (based on Chitosan high density)

3.1.5 Surface characterization using SEM

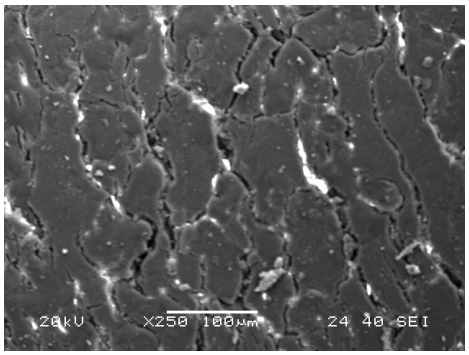
Representative SEM images for the placebo minitablets are shown in Fig. 2, showing some differences in the surface structure. For example, FP12 (based on Pluronic F127) showed a very smooth surface, whereas FP6 (based on gellan gum) showed a very rough surface. Minitablets composed primarily of EC (FP3) showed deep channels in their surface structure, but those based on xanthan gum (FP) presented only shallow channels.

3.1.6 Water uptake and swelling index

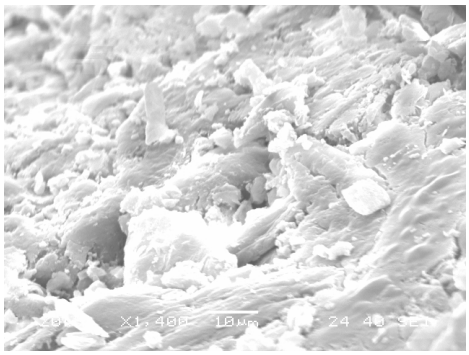
A range of hydration and swelling behaviour was observed, as indicated in Table 1. Minitablets based on EC, PEG and Pluronic F88 (FP3, FP5, FP9 and FP10) did not show any difference in weight over the 4 hour time period of the study. Minitablets based on MCC and chitosan (FP4 and FP8) disintegrated quickly on hydration, rather than swelling. The remaining six minitablet formulations all absorbed water, forming a "gelatinous" layer around the surface of the minitablet and swelling, but were still recognisably intact at the end of the 4 hour test period. Gellan gum-based minitablets (FP6) swelled quickly, giving maximum hydration (SI = 6.1 ± 0.1) over the first 30 minutes, which was then maintained across the test period. The other formulations showed more gradual hydration behaviour, as indicated in Fig. 3. There was an indication that some erosion of the much hydrated minitablets, particularly FP6, had occurred at the end of the experiment.

Minitablets could be ordered according to hydration and water uptake as follow; gelrite > Na-CMC > pluronic F127, xanthan and pluronic F127 > xanthan > HPMC > pluronic F127. This may be explained according to the chemical nature of the polymer used, for example Na-CMC is a hydrophilic anionic polymer which is capable of creating high osmotic pressure leading to higher hydration property, in contrast to non- ionic cellulose derivative polymers as HPMC which is carrying lower hydration character (Rowe et al., 2009).

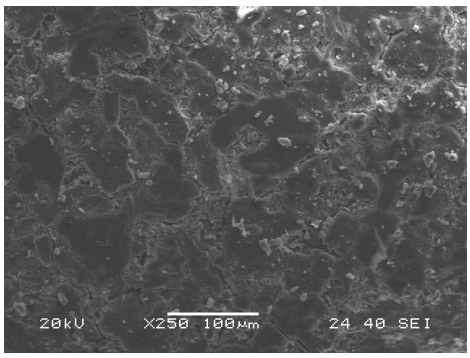
a) FP3



b) FP6



c) FP7



d) FP12

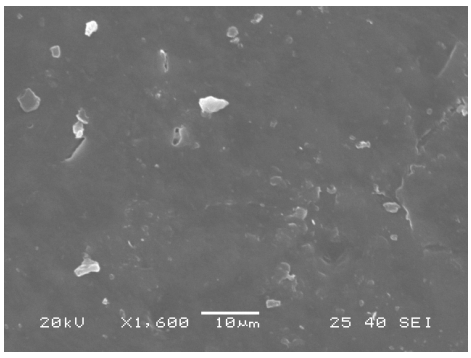


Fig. 2. Example SEM images showing the surface of the placebo minitablets: a) FP3 (based on EC), b) FP6 (based on gellan gum), FP7 (based on xanthan gum) and d) FP12 (based on Pluronic F127)

3.1.7 General discussion on physical properties of placebo minitablets

Minitablets were successfully produced from all placebo formulations, with all batches passing the BP weight uniformity test. A range of physical properties were observed in the minitablets, with the only relationship between the measured parameters being a general trend towards increased thickness with increasing minitablet weight. The surface roughness of the minitablets varied, from the extremely smooth FP12 (based on Pluronic F127) to the very rough FP6 (based on gellan gum). These two formulations also showed extremes of swelling behaviour, with SI values of 0.7 ± 0.1 and 6.1 ± 0.1, respectively, suggesting that these two parameters may be related. However, EC-based minitablets (FP3) showed some surface irregularities, but did not swell during the hydration studies, whereas FP7 minitablets based on xanthan gum swelled to a far greater extent (SI = 2.6 ± 0.3) although their surfaces showed greater irregularities than those of FP3. No relationship was found between the measured compression force and the physical parameters measured; indeed, FP12 and FP6 with their very different behaviour displayed the same low compression force. The most important factor would seem, therefore, to be the chemical nature of the polymers used.

From the results of the placebo minitablet studies, a range of formulations were chosen to be studied in the medicated form. Those which disintegrated quickly in the presence of STF were discounted (FP4 and FP8) as being unlikely to provide good residence time in the eye once inserted. Of the non-swelling formulations (FP3, FP5, FP9 and FP10) only FP5 (based on PEG 20,000) was chosen to be studied further, as a "control" to the swelling formulations. All other formulations were studied further as they exhibited a wide range of swelling behaviour.

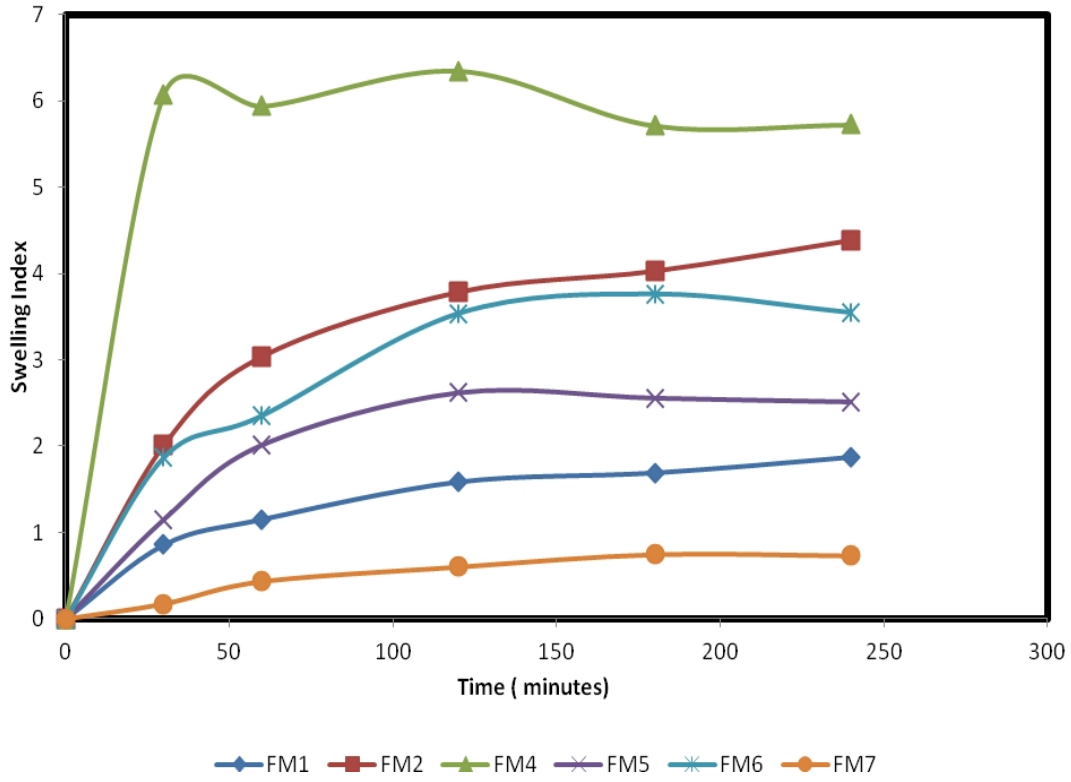


Fig. 3. Swelling behaviour of placebo minitablets over time

3.2 Physical Characterisation of Medicated Minitablets

The medicated minitablets were assessed physically using the same techniques as the placebo minitablets, with the results being shown in Table 2 and some selected SEM images in Fig. 4. The presence of the drug had little effect on the behaviour of the minitablets, as can be seen by comparison of Tables 1 and 2.

Table 2. Physical evaluation of the medicated minitablets

Formulation code	Mean compression force (kN)	Weight (mg) mean±SD	Thickness (µm) mean ±SD)	Diameter (µm) mean ±SD	Crushing strength (N) mean±SD	Friability (%) mean±SD	Swelling index	Hydration time (h)
FM1	0.8	4.3±0.09	1552±13	2006.6±12.3	5.50±0.2	0.16±0.1	1.7±0.2	4
FM2	1.1	4.45±0.2	1415.3±7	2045.0±34.0	2.80±0.7	2.05±0.07	4.3±0.4	4
FM3	0.9	5.3±0.1	1627.6±33	2010.6±16.1	3.90±0.6	0.60±0.1	DNS	N/A
FM4	0.6	4.2±0.05	1249±15	1999.3±32.1	2.16±0.4	0.27±0.08	6.1 ±0.05	0.5
FM5	0.4	7.2±0.12	1958±24	2188.0±9.0	7.86±0.0	0.62±0.4	2.7±0.1	2
FM6	1.2	6.2±0.07	1729.3±9.5	2037.6±3.7	5.4±0.2	0.91±0.2	3.5±0.1	3
FM7	0.9	5.3±0.04	1739.3±26	2056.3±15.4	4.13±0.5	0.16±0.2	0.7±0.04	3

N/A = not applicable; DNS = did not swell

a) FM6 b) FM2

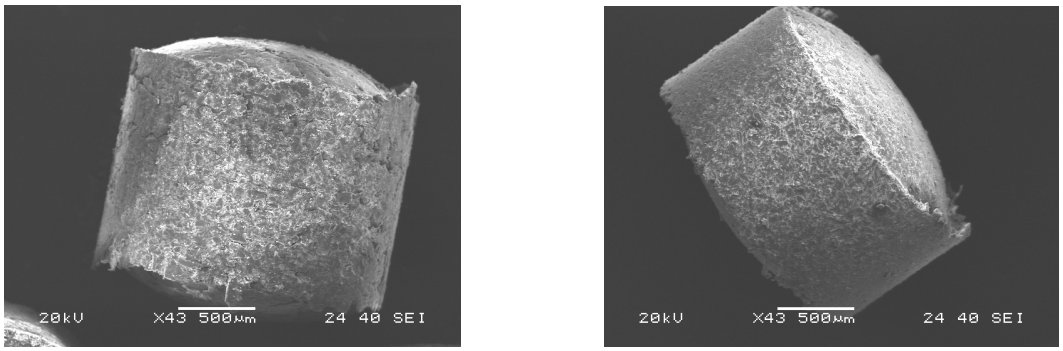


Fig. 4. Example SEM images of the medicated minitablets: a) FM 6 (based on Pluronic F127 and Xanthan gum), b) FM2 (based on Na-CMC)

3.3 *In vitro* Release Study Using Rotating Glass Vials Method

The piroxicam release curves from different minitablets formulations were illustrated in Fig. 5. The minitablet formulations could be assigned to three broad groups based on their drug release profiles using the rotating vials method: FM2, FM3, FM4 and FM7; FM1 and FM6; and FM5. The fastest rate of drug release was from FM3 (based on PEG 20,000) minitablets, with > 80% of the drug being released within 30 minutes and maximal release being observed after 2 hours. FM4 (based on gellan gume) showed slightly lower drug dissolution than FM3 at 30 minutes and 1 hour, but maximal release was also observed at 2 hours. Minitablets of FM7 (based on Pluronic F127) and FM2 (based on Na-CMC) also showed reasonably fast drug dissolution, with maximal drug release being observed by 3 hours. On the other hand, FM5 minitablets (based on xanthan gum) showed a prolonged drug release profile, with only 18% of piroxicam being released after 30 minutes and 73% after 5 hours. FM1 minitablets (based on HPMC) and FM6 minitablets (based on the Pluronic F127: xanthan gum combination) showed profiles intermediate between these two extremes, with maximal release being observed by 6 hours.

As a result, we can arrange the formulations regarding to release time from fast release to prolonged release as follow: FM3 > FM4 > FM7 > FM2 > FM6 > FM1 > FM5. This observed differences in piroxicam release rate between different minitablets matrices containing different polymers may be explained on the base of differences in water hydration and swelling parameters as well as erosion behaviour of different gelled minitablets upon immersion in dissolution medium.

From the previously obtained swelling test results of different polymers matrices, gelrite showed very fast and good hydration property in STF which may be the reason of the fastest drug release profile compared to others. While xanthan which posses one of the lowest swelling index value, gave the slowest, prolongest drug release profile. So, to a large extent, there was a highly significant relationship between the swelling characters of each polymer matrix used in the minitablets preparation and the drug release profile from the minitablets.

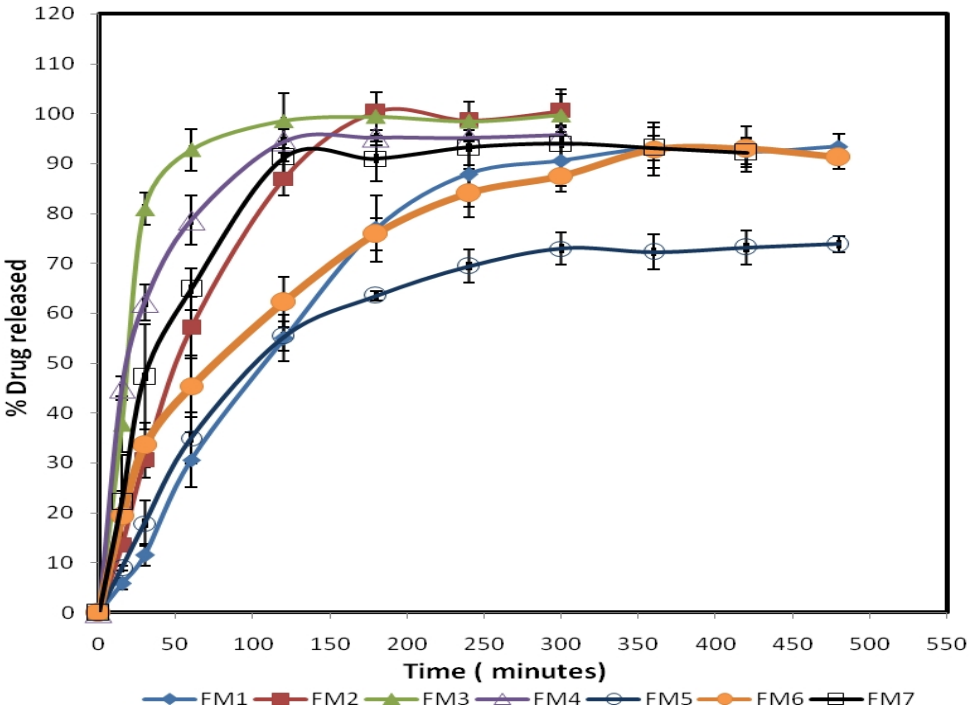


Fig. 5. In-vitro release profiles of piroxicam from medicated minitablets using rotating vial method

As a general trend for most of the tested polymers tried, the higher the swelling, the faster the drug release and vice versa. This is attributed to the fact that the drug release process from polymer matrices described by 2 phenomenons; first, the swelling phenomena of matrix resulted in transfer from glassy state into rubbery state. Second is the dissolution phenomenon of the formed mass to release the drug into dissolution medium. This was in accordance with Mortazavi et al., 2010 who studied the dissolution rate profiles of ciprofloxacin from different minitablets, and proved that there was a relationship between the drug release and extent of the water uptake, the greater the amount of water uptake, the higher the amount of the drug released.

Also, all formulations showed a prolonged release, about 8h, the results obtained could be explained on bases of the differences between the polymers chemistry and the different processes that affect their erosion/degradation to release the drug. It was reported by many researchers that, the release of the drug from gel matrix determined by the gel organization structure (polymer type), gel strength (polymer concentration), diffusion capability, and by the polymer swelling and erosion process. In most cases the drug release mechanism from minitablets is controlled by diffusion from the gel-forming minitablets (Michailova et al., 2000).

3.4 *In Vitro* Drug Release and Diffusion Study Using the Franz Cell Diffusion System with Different Barriers

The release profiles using the Franz cell fitted with a 400 nm polycabonate membrane and porcine sclera are presented in Figs. 6 and 7 respectively. The results from the Franz diffusion cell experiments with the synthetic membrane are broadly similar to those seen with the rotating vials method, in terms of the rank order of behaviour of the formulations. The time course of the drug release profiles is slower for the Franz cell experiments, reflecting the different exposure of the minitablets to the dissolution fluid in the two methods and the necessity for the drug to diffuse through the membrane into the receptor chamber in the Franz diffusion cell studies, rather than to be just released into the external aqueous phase as in the rotating vials method. Diffusion of the piroxicam through the porcine sclera was much slower than through the polycarbonate membrance and a lag period was observed at the earlier time points, relating to the speed at which the piroxicam initially traversed the scleral membrane. However, the rank order of the formulations was similar with both membranes, with the only substantial change being seen with FM7.

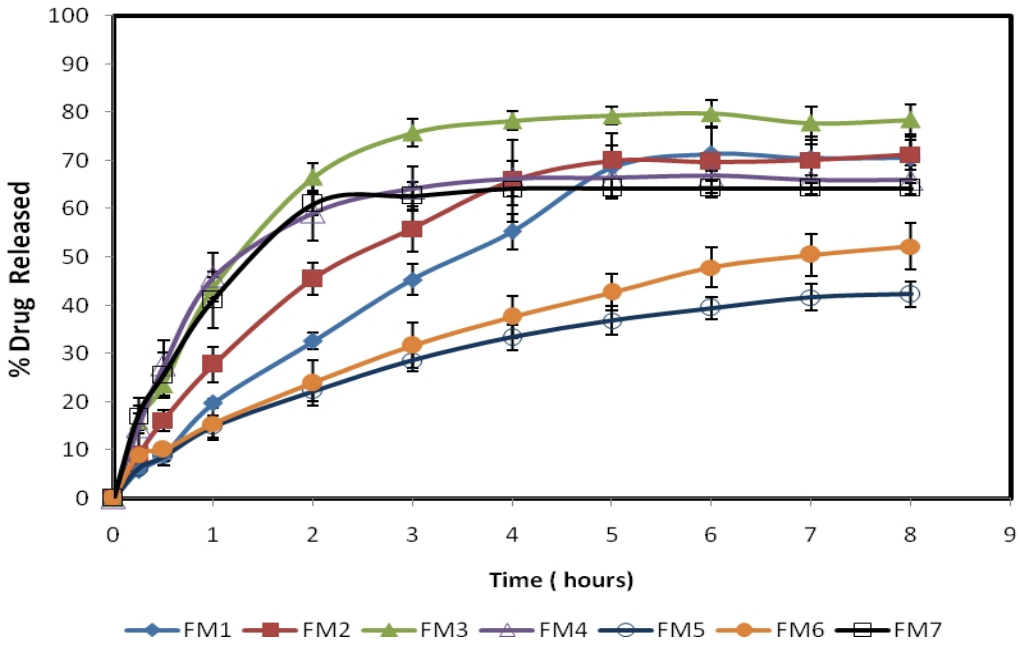


Fig. 6. In-vitro release profiles of piroxicam from medicated minitablets using Franz cell and polycarbonate membrane

Porcine sclera was proved to be considered a good model for the human sclera for in vitro permeation experiments. It has the advantages of having the same histology and collagen bundle organization as the human sclera (Nicoli et al., 2009). Another very important mert is the large surface area of the sclera which has been estimated to be about 17-times larger than that of the cornea (Geroski and Edelhauser, 2001). Also, many researchers evaluated the role of the sclera as a barrier that augments to design new drug delivery strategies for posterior segment of the eye as Ranata et al., 2010. In addition, Jansook et al. (2010) studied the effect of cyclodextrin complexation of dexamethasone on the drug delivery through the sclera.

From the results of the in vitro drug release and diffusion studies, three medicated minitablet formulations showing different release and diffusion profiles were chosen to take forward into the *ex vivo* ocular study. FM1 and FM2, based on HPMC and Na-CMC respectively, were swelling tablets and FM7, based on Pluronic F127, was a non-swelling formulation.

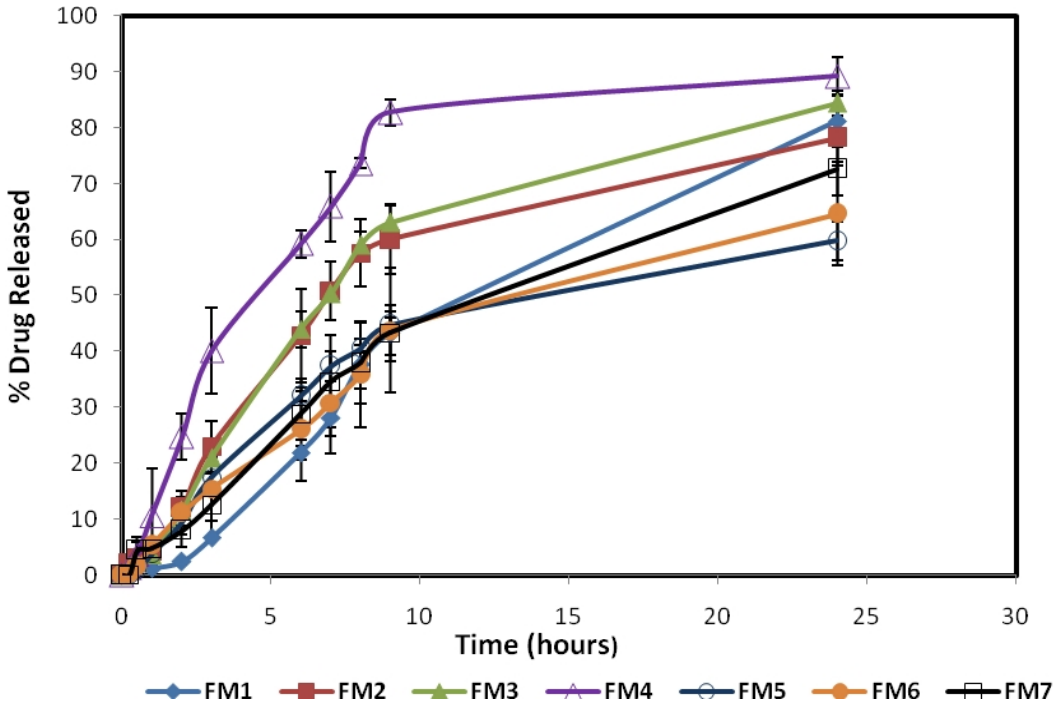


Fig. 7. In-vitro release profiles of piroxicam from medicated minitablets using Franz cell and porcine scleral membrane

3.5 Kinetic Analysis of the *In vitro* Drug Release and Diffusion Studies

Visual observation of the profiles shown in Fig. 5 suggests that the drug release from the tablets in the rotating vials experiment follows first order kinetics. This is borne out by examination of the mathematical data shown in Table 3. In most cases, the fit to the first order model is acceptable and in some cases, excellent, with $r^2 > 0.995$. The Korsmeyer-Peppas analysis was performed to assess the relative contribution of diffusion and erosion to the drug release profile, but as can be seen, in all cases did not provide any additional analytical benefit compared to the more straight-forward first order kinetic analysis.

Similar analysis was performed for the Franz diffusion cell experiments, with the results shown in Tables 4 and 5 for the polycarbonate membrane and the scleral membrane studies, respectively. Again, a first order kinetic profile was observed, with the Korsmeyer-Peppas analysis not providing additional information. However, for the scleral studies, a lag period was observed for some formulations before drug was detectable in the receptor compartment: FM1 (based on HPMC) had a lag period of 2.2 hours, FM2 (Based on Na-CMC) showed a lag period of 1.1 hours and FM3 (based on PEG 20,000) exhibited a lag period of 1.3 hours. All other minitablet formulations gave measureable quantities of drug in the receptor phase even at the earliest time points.

Interestingly, the results from the rotating vials method were generally predictive of the results from the Franz diffusion cells fitted with the polycarbonate membrane, in that a plot of the relative k values gave a linear correlation coefficient of 0.9065, whereas they were not predictive of the results from the scleral studies, even when the lag period was taken into account. It could be argued that as the rotating vials method is simple, straightforward and requires little specialist equipment, it is the best method to use in a screening exercise, such as was conducted here, in order to establish rank order behaviour of formulations.

Table 3. Kinetic fitting parameters for piroxicam release from minitablets using the rotating glass vials method

Formulation	First - order		Korshmeyer-Peppas		
	k (min^{-1})	r^2	k (min^{-1})	n	r^2
FM1	0.0086	0.9897	0.395	1.014	0.9868
FM2	0.0187	0.9991	1.758	0.808	0.9676
FM3	0.0332	0.9559	7.231	0.685	0.8605
FM4	0.0217	0.9989	17.799	0.356	0.9838
FM5	0.0049	0.9666	1.366	0.747	0.9695
FM6	0.0067	0.9957	6.035	0.478	0.9802
FM7	0.0204	0.9910	4.247	0.657	0.9509

K_0: release rate constant; R : Correlation coefficient

Table 4. Kinetic fitting parameters for piroxicam release from minitablets using the Franz diffusion cell fitted with the polycarbonate membrane

Formulation	First - order		Korshmeyer-Peppas		
	k (h^{-1})	r^2	k (h^{-1})	n	r^2
FM1	0.2153	0.9910	17.861	0.8401	0.9948
FM2	0.2587	0.9968	25.960	0.7193	0.9939
FM3	0.5350	0.9980	39.783	0.6595	0.9871
FM4	0.4125	0.9601	38.424	0.5927	0.9495
FM5	0.0915	0.9896	14.194	0.6024	0.996
FM6	0.0981	0.9978	16.901	0.5565	0.9862
FM7	0.4316	0.9920	40.096	0.6194	0.9986

K_0: release rate constant; R : Correlation coefficient

Table 5. Kinetic fitting parameters for piroxicam release from minitablets using the Franz diffusion cell fitted with the porcine scleral membrane

Formulation	First - order		Korshmeyer-Peppas		
	k (h^{-1})	r^2	k (h^{-1})	n	r^2
FM1	0.0762	0.9961	1.192	1.8979	0.9939
FM2	0.1096	0.9939	1.287	1.1997	0.9832
FM3	0.1213	0.9939	1.322	1.2702	0.9874
FM4	0.1643	0.9941	1.460	1.1348	0.9495
FM5	0.0688	0.9988	1.172	1.1096	0.9878
FM6	0.0542	0.9949	1.133	0.9095	0.9936
FM7	0.0551	0.9923	1.135	1.0459	0.9924

K_0: release rate constant; R: Correlation coefficient

3.6 Ex vivo Drug Release and Distribution Study

A summary of the data from the ex vivo study is shown in Table 6, with the maximum piroxicam concentration (C_{max}) in each of the tissues and the timepoint at which this was observed (T_{max}) being displayed. The time-concentration profiles for selected tissues are shown in Fig. 8. Data are expressed as ng of piroxicam per mg of tissue (equivalent to µg/g).

Table 6. C_{max} and T_{max} values for piroxicam in ocular tissues after surface administration of various minitablets containing piroxicam

Tissue	FM1		FM2		FM7	
	*C_{max}	**T_{max}	*C_{max}	**T_{max}	*C_{max}	**T_{max}
Lens	10.95	9	7.47	6	36.28	6
Cornea	134.49	9	101.35	6	81.56	6
Vitreous	2.46	9	1.72	6	16.2	6
Retina	115.1	3	11.18	3	245.57	6
Choroid/ RPE	41.6	3	32.1	6	75.2	6
sclera	58.59	3	46.46	12	68.28	6
Conjunctiva	121.27	3	29.16	6	154.58	6
Total ocular availability	414.9	3	201.6	6	677.7	6

**C_{max}: maximum piroxicam concentration expressed as ng per g of dissected tissue;*
***T_{max}: maximum peak time expressed in hours.*

Some differences in the profiles between minitablet formulations were observed FM1 (based on HPMC) showed a peak concentration in the sclera (58.59 µg/g) and conjunctiva (121.27 µg/g) at 3 hours incubation, after which the concentrations in these tissues decreased. This may be expected as these are the tissues that are in closest proximity to the minitablets application site. The highest total concentration of piroxicam from FM1 was observed in the cornea at 134.49 µg/g at 9 hours, with a roughly linear increase in concentration in this tissue over the 9 hour period. Significant levels of piroxicam were found in the retina (115.1 µg/g) and choroids/RPE (41.6 µg/g), indicating that the drug was being released from the minitablet and diffusing across the scleral membrane into the posterior ocular section. FM2 (based on Na-CMC) showed a slightly different profile, with a lower total amount of drug being released into the ocular tissues. Indeed, only limited quantities of piroxicam were detected in the retina (11.18 µg/g at 3 hours) compared to those seen with both the other formulations. FM7 (based on Pluronic F127) provided the highest piroxicam concentrations in all ocular tissues except the cornea, with a predominance of drug being found in the posterior section, e.g. 245.57 µg/g in the retina at 6 hours incubation.

3.7 General Discussion

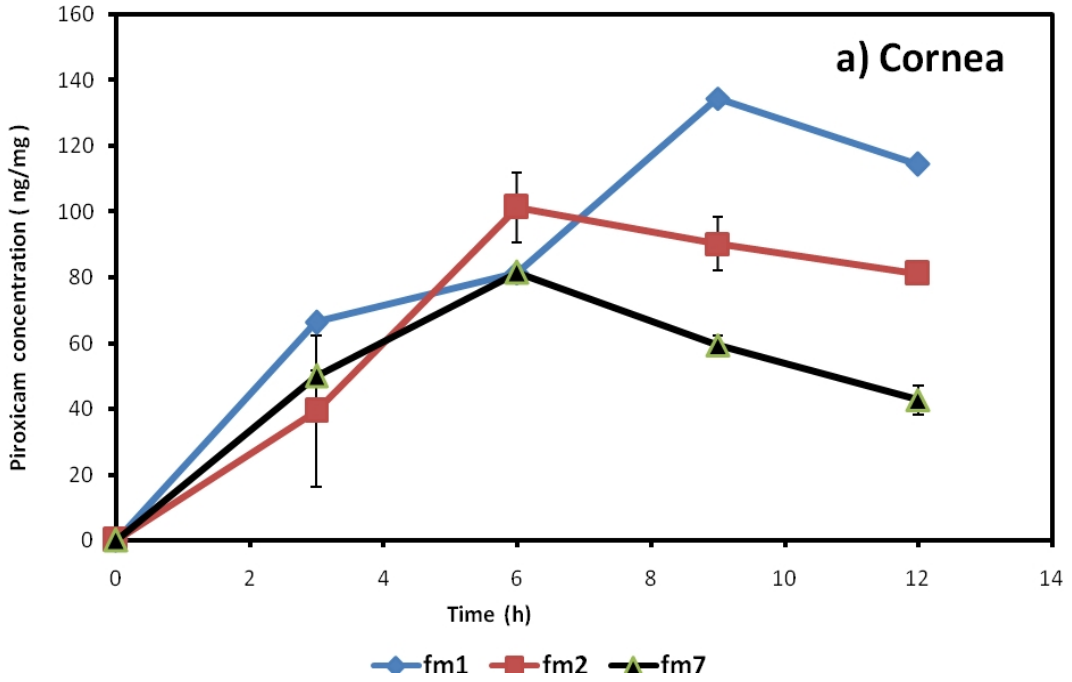
The results of the *ex vivo* drug release and disposition studies contrast to some extent the data from the *in vitro* studies. FM7 minitablets (based on Pluronic F127) showed the fastest drug release and movement in two of the three *in vivo* assessments and would therefore be expected to show the fastest rate of release of drug in the *ex vivo* studies and to exhibit C_{max} at the earliest studied timepoint of 3 hours, but the highest tissue concentrations were all seen at the 6 hour timepoint. However, the one "non-matching" *in vitro* methodology was the Franz cell fitted with the scleral membrane, which may be expected to be the most representative of the biological system and hence support the *ex vivo* findings. FM7 had the highest total drug release of all formulations studied *ex vivo*. FM1 (based on HPMC) showed

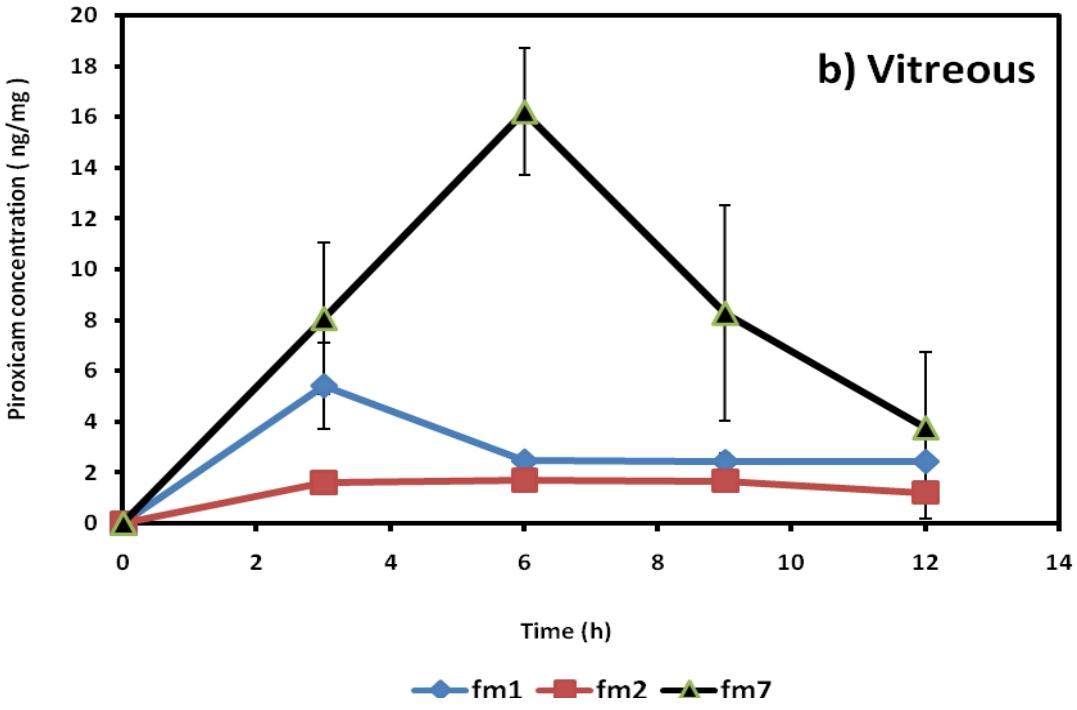
the lowest rate of drug release in all three *in vitro* studies, but a mixed release profile in the *ex vivo* assessment, in that the tissues closest to the application site showed T_{max} at 3 hours, whereas the more distal sites showed T_{max} at 9 hours. It showed an intermediate level of total drug release in the *ex vivo* studies. The final formulation studied in the *ex vivo* studies, FM2 (based on Na-CMC), showed the lowest total drug release in the *ex vivo* analysis and intermediate speed, with most T_{max} values being 6 hours, but intermediate or fastest release in the *in vitro* assessments, and in all three *in vitro* cases showed faster drug release than FM1.

These variations may be explained by examining the physical behaviour of the minitablets and the mechanics of the dissolution and disposition tests. The rotating vials dissolution method exposes the minitablet to fluid across its entire surface and may be expected to lead to hydration of the polymer across all surfaces, not just one face as is the case in the swelling studies and the Franz diffusion cell studies. This is likely to lead to enhanced drug dissolution in the rotating vials method. Any differences would be likely to be seen more with formulations which swell slowly or not very extensively, whereas formulations which swell quickly and extensively may not show such a difference between the methods. This may, at least in part, explain the differences in dissolution profiles observed with FM7 (based on Pluronic F127), which did not hydrate quickly or to any large extent, as the maximum SI of 0.7 ± 0.1 was achieved after 3 hours exposure to STF in the swelling studies, but showed fast release in the rotating vials method. The rate of polymer hydration and the extent of swelling are also related to the aqueous solubility of the polymer and the porosity of the matrix, so subtle differences in these factors will also have an effect on the drug dissolution profile. For example, the solubility of Na-CMC is greater than that of HPMC, so FM2 is likely to swell more and faster than FM1.

The barrier than the sclera presents to the diffusion of the drug should, in theory, be the same whatever the formulation that is applied to it and therefore a similar lag period should be observed for all minitablet formulations. However, this was not the case with the Franz diffusion cell experiment, whereby only FM1, FM2 and FM7 showed significant lag periods, suggesting that the other formulations released the drug molecules sufficiently quickly in order to be able to penetrate the barrier and be detectable in the receptor phase at early sampling timepoints. In the ex vivo studies, however, the lag period may account for why all the formulations showed T_{max} in the posterior segment to be 6 hours.

The *ex vivo* study is a relatively simple method of assessing the likely distribution of the drug after ocular administration and has the extremely large advantage of not requiring live animals for experimentation: the eyes from pigs slaughtered for food are normally not extracted and are treated as waste material in the UK. However, care must be taken with the interpretation of these results (and indeed any results from a biological system). It is not possible to assess the movement of drug through any one individual eye over time, as the analysis is necessarily destructive, hence the eyes tested at 3 hours are not those tested at 6 hours, and so on. There is therefore an inherent potential variability in the behaviour of each eye sample. The eyes were sourced from pigs being sent to the abattoir for food, so exact control over age pre-mortem is impossible; experience shows, however, that the pigs are generally 6 months old at slaughter. Additionally, the biological environment is subtly different post-mortem to ante-mortem: there is no movement of fluid in the vitreous humour or blood flow to the retina post-mortem, so drug clearance is not taken into account in the *ex vivo* studies. Having taken these caveats into consideration, there is still merit in the *ex vivo* studies as they can be used as screening studies prior to moving into an *in vivo* phase of drug development.


a) Cornea
Piroxicam concentration (ng/mg)
160
140
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (h)
fm1
fm2
fm7


b) Vitreous
Piroxicam concentration (ng/mg)
20
18
16
14
12
10
8
6
4
2
0
0
2
4
6
8
10
12
14
Time (h)
fm1
fm2
fm7

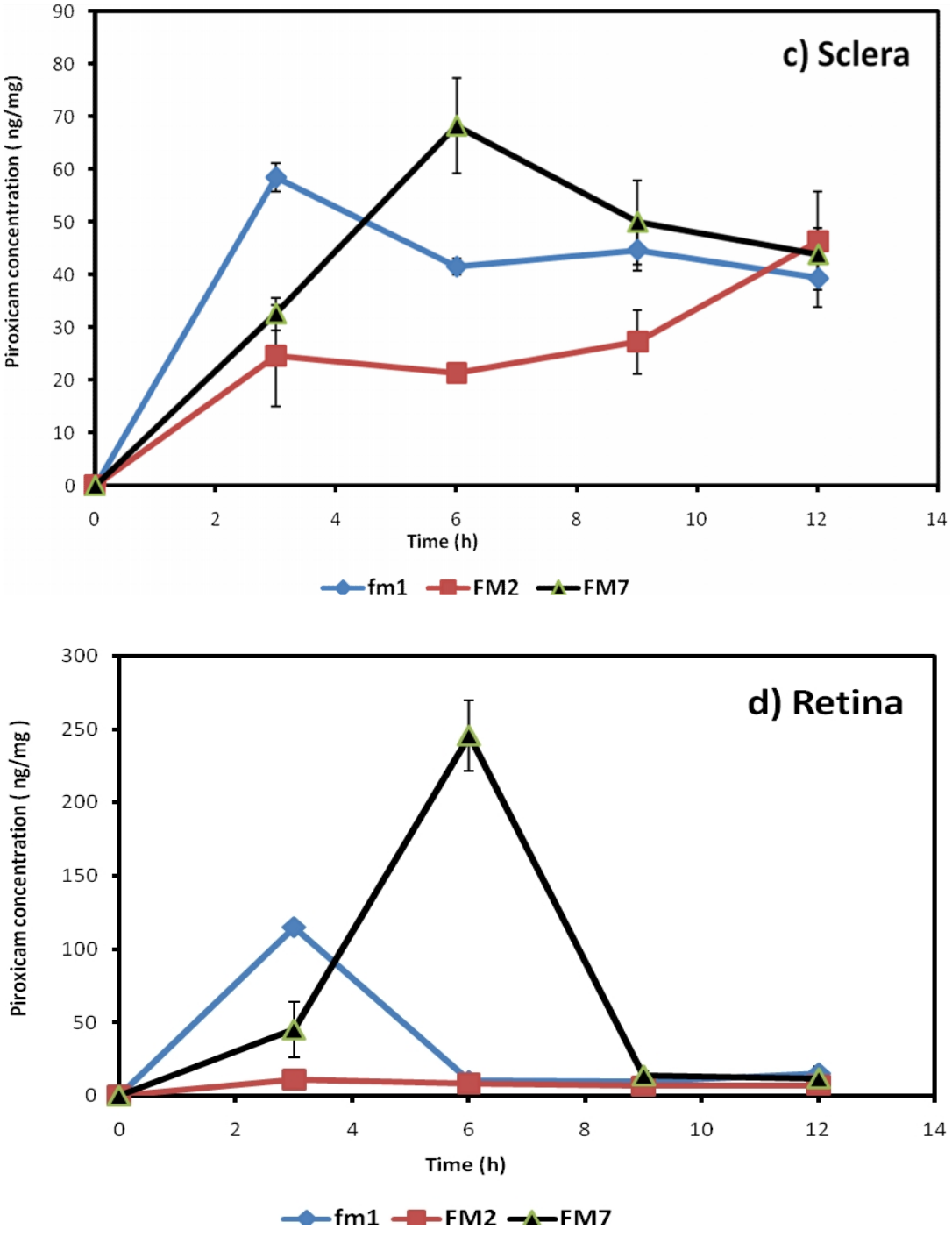


Fig. 8. The time course of piroxicam concentration in selected ocular tissues after surface administration of medicated minitablets: a) cornea, b) vitreous, c) sclera, d) retina

Of the formulations studied here in the *ex vivo* experiment, two were swelling and one was essentially non-swelling. The essentially non-swelling formulation (FM7) was found to give the highest ocular bioavailability of the drug of the three minitablet formulations, in particular in the posterior segment. It is possible that this is related to the mucoadhesiveness of the polymers used and to the levels of hydration expected in the biological situation. Andrews et al. (2009) studied the relationship between hydration and mucoadhesion of various polymers and concluded that there was an optimum level of hydration for mucoadhesion: sufficient hydration was required to expand the polymer and to allow interaction with the mucins present in the biological sample, whereas too much hydration resulted in a product which was too slippery to be entirely adherent to the tissue. Applying this to the current situation, the highly hydrated minitablets may be considered to be less bio-adherent than the less hydrated ones, resulting overall in a lower posterior segment bioavailability, but conversely a higher anterior segment bioavailability with a faster distribution to these tissues. This concurs with the observed results.

As a result, polymers of high swelling index (Na-CMC > HPMC > Pluronic F127) expected to have lower adhesion property to eye surface and hence lower penetration character to posterior segment. Acheampong et al., 2002, found that topical application of [14C] brimonidine was higher in pigmented ocular tissues, including the iris, ciliary body and chord/retina. Also significant amounts were also found in the vitreous and optic nerve head. The absorption, retention, and activity of drugs applied topically to the eye can be affected by binding with ocular melanin (Zane et al., 1990).

So, these results confirmed that the prepared minitablets can be used as a simple sustained release ocular dosage form to deliver the piroxicam into the posterior eye segment. This is very important to treat the inflammatory disorder in these tissues in this segment especially the retina. In contrast to the other conventional ocular drug delivery systems like eye drops which showing poor bioavailability of the drug to posterior eye segment due to, rapid drainage, tear production turnover and short contact time.

Previous studies reported the possibility of the delivery of drugs to posterior segment tissues (including posterior sclera, vitreous, retina, choroid/RPE and optic nerve) after topical application. This drug penetration was through 2 pathways; first across the cornea, then to aqueous humor, and anterior chamber. Second pathway is through conjunctiva, sclera, then to ciliary body, and posterior chamber (Schoenwald, 1993).

4. CONCLUSION

This study investigated the use of a range of polymers as matrices for minitablets for insertion into the ocular cul-de-sac. All formulations allowed successful production of placebo minitablets and following analysis of a variety of physical properties of the placebo minitablets, a range of seven medicated minitablet formulations containing 5%w/w piroxicam were prepared and analysed.

Drug release from the minitablet formulations was studied using three *in vitro* methods and one *ex vivo* method. Of the *in vitro* methods used, the rotating vials method was the simplest to perform and gave good and swift discrimination between formulations. The *ex vivo* method highlighted the importance of understanding the chemical nature of the polymer matrix and its likely behaviour in the biological milieu.

The results presented here suggest that minitablets based on Na-CMC and HPMC show swifter and greater hydration than those based on Pluronic F127, but that the Pluronic F127-based tablets provided greater posterior-segment bioavailability of the model drug than the other two formulations. Hence the posterior segment bioavailability is inversely related to the swelling index of the formulations. However, the rate of penetration of drug into the anterior segments may be greater with the faster hydrating formulations.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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