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Review Article

COMPARISON OF ANTIBIOTIC PHARMACOKINETICS PROFILE OF OPHTHALMIC *IN SITU* GEL AND CONVENTIONAL PREPARATION IN EYE INFECTION: A REVIEW

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ABSTRACT

This article review was aimed to see a significant comparison of the bioavailability of *in situ* gel preparations compared to conventional preparations in terms of pharmacokinetic profile parameters such as AUC (Area Under Curve), C_{max}, T_{max}, $t½$, *k* (elimination rate constant) and MRT (Mean Residence Time*)*. This article review was conducted by looking for available articles with a different assessment based on original research articles published during 2002–2022. An electronic search was conducted from Pubmed and Google Scholar. A significant increase in bioavailability was produced by *in situ* gel preparations compared to conventional preparations; this happened because the polymer that used improved the drug delivery system to the targets of previous conventional preparations. The *in situ* ophthalmic gel preparations have better bioavailability based on pharmacokinetic profiles compared to conventional preparations.

Keywords: *In situ* gel, Ophthalmic, Fluoroquinolones, Macrolides, Aminoglycosides, Bioavailability, Pharmacokinetic

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INTRODUCTION

Human eye has the natural defense mechanisms to detect the presence of external infection [1-3] Some eyes infection can be medicated by antibiotics. It is considered as the most important treatment in the history of medicine, especially treatment with eye infection [4, 5]. Many of antibiotics groups such as fluoroquinolone (levofloxacin, ofloxacin, moxifloxacin), macrolides (azithromycin), aminoglycoside (tobramycin sulfate) are used for the treatment of several eye infections (6). Most of them are available in the form of various conventional preparation such as eye drops, suspensions, and ointments [6, 7].

Among of those conventional dosage forms, the highlighted eye drops have some disadvantages that lead to poor bioavailability of the drug in the ocular cavity. This can be occurred due to the drainage of the drug by the nasolacrimal duct and the reduction of drug retention time by productive corneal absorption. Many approaches have been conducted to improve the bioavailability in conventional dosage form, one of the efforts was to develop a form of *in situ* gel preparation system [8-12].

In situ system is a polymer solution that undergoes phase transitions from the liquid into gel phase due to some influence of physiological conditions on the eye [13, 14], such as temperature, pH, and electrolytes composition. These physiological terms are the key roles to extend the drug residence time in the eye pre-corneal region; therefore *in situ* dosage form can increase bioavailability [15, 16].

Many eye dosage forms can affect several pharmacokinetic parameters, such as AUC (Area Under Curve), $t_{1/2}$ (half time), C_{max}, and T_{max}. These parameters usually affect the bioavailability of drugs, which is the relative amount of drugs that enter the systemic circulation in certain preparations [17, 18]. Many dosage form has some unique properties that can affect those parameters. Therefore, it is necessary to prove the comparison of some pharmacokinetic profile of *in-situ* gel preparations which is associated with conventional dosage forms. This article review results obtained from research of several literature studies that will be analyzed by descriptive analysis.

MATERIALS AND METHODS

The design of the literature study was conducted by examining the pharmacokinetic profile comparison among antibiotic *in situ* gel and conventional dosage forms. Therefore, it was treated with a further review of the pharmacokinetic parameters from each dosage form (*in situ* gel and conventional). The selected article consists of related *in vivo* studies also pharmacokinetic parameters of antibiotic *in situ* gel and conventional dosage forms. This studies were conducted by looking for available articles, with different assessments based on original research articles published during 2002-2022. An electronic searching was conducted from PubMed and Google Scholar databases from May 2002 until July 2022. Searching strategy involves re-examining selected keywords based on the title Medical Subject "Pharmacokinetics" "*in vivo*" "Antibiotics," "ophthalmic *in situ* gel" "nanoparticles". The search was limited to publication in clinical trials of *in vivo* studies and pharmacokinetic parameters of *in situ* antibiotic gel with conventional preparations. The excluded article was one that did not related to the criteria of the study and not involved an *in vivo* study. The flow chart was used to identify and exclude in this review as depicted in fig. 1.

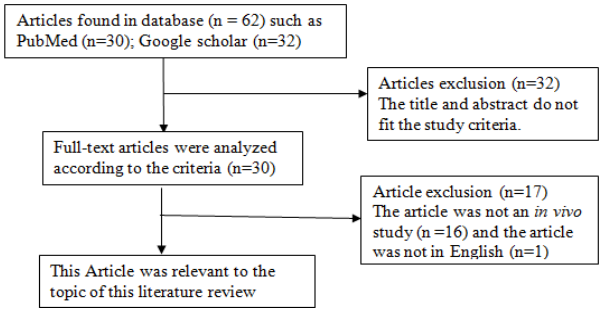

Fig. 1: Schematic diagram of article selection

RESULTS

Table 1: The antibiotics *in situ* gel *in vivo* assay were analyzed by HPLC

Antibiotic	Animals sample	Duration interval (h)	Mobile phase	Types of colom	Wavelength (nm)	Flow rate (ml/min)	Ref.
Levofloxacin	Rabbit	24	85 % Buffer (0.3 % Ammonium acetate, 0.54 % sodium perchlorate, 0.5 % triethyl amine), 15 % acetonitrile	C18	293	1.5	[19]
Besifloxacin	Rabbit	12	N/A	N/A	N/A	N/A	[20]
Azithromycin	Rabbit	12	Acetonitrile, Potassium hydrogen phosphate (15: 85)	C18	210	1	[21]
Ofloxacin	Rabbit	12	Methanol 50 %, Acetic Acid 5 %, Sodium octane sulphate 45 %	C18	290	0.7	[22]
Levofloxacin	Rabbit	12	Acetonitrile, Ammonium acetate perchlorate (20:80)	C18	294	N/A	[23]
Tobramycin Sulphate	Rabbit	24	Methanol, water (60:40)	C18	380	1	[24]
Ofloxacin	Rabbit	24	Methanol, water (50;50)	C18	294	0.45	[25]
Gatifloxacin	Rabbit	8	Acetonitrile, Triethylamine (1:4)	C18	293	1	[26]
Moxifloxacin	Rabbit	8	trifluoroacetic acid, acetonitrile (70:30)	C18	296	0.4	[27]
Tobramycin sulphate	Rabbit	8	Acetonitrile, Monosodium phosphate, disodium phosphate (30:70)	C18	240	1	[28]
Ofloxacin	Rabbit	24	Methanol, Acetonitrile, Acetic acid (3:1:10)	C18	290	0.8	[29]
Moxifloxacin	Rabbit	8	Acetonitrile: potassium dihydrogen ortho phosphate (20: 80)	C18	305	1	[30]

Table 2: Comparison of pharmacokinetic profile among *in situ* gel and conventional solutions

Antibiotics	Polymer	Sample	Pharmacokinetic parameter								Remarks	Ref.
			C_{max} (µg/ml)	T_{max} (h)	$AUC_{(0-t)}$ (h µg/ml)	AUC_{∞}	AUC_{rel}	MRT (h)	t ½ (h)	*k* (h^{-1})		
Levofloxacin	Gellan gum 0.25 % w/v	Aqueous humour	5.56±1.59	4	17.61±3.54	N/A	2.7	8	N/A	N/A	t_{max} ($p<0.05$); AUC_{0-24} ($p<0.0005$), MRT ($p<0.0001$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation.	[19]
	Gellan gum 0,40% w/v	Aqueous humour	4.15±1.95	4	22.66±4.21	N/A	3.5	15	N/A	N/A	t_{max}($p<0.05$), AUC_{0-24} ($p<0,0005$) and MRT ($p<0.0001$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	
	Eye drop preparation	Aqueous humour	3.68±1.69	1	6.41±2.02	N/A	N/A	4	N/A	N/A	N/A	
Besifloxacin	Chitosan 0.5 % w/v+Gellan Gum 0.25 % w/v	Aqueous humour	0.47±0.01	2±0.12	3.20±0.01	3.85± 0.02	12.2	N/A	6.45± 0.14	N/A	N/A	[20]
	Eye drop preparation	Aqueous humour	0.29±0.01	1±0.09	0.84±0.02	0.32± 0.02	N/A	N/A	2.50± 0.21	N/A	N/A	
Azithromycin	Poloxamer 188, poloxamer 407, Carbopol 1% w/v	Aqueous humour	0.39±0.49	N/A	0.52±0.75	N/A	N/A	6.86± 1.25	N/A	N/A	AUC_{0-12} ($p<0.05$); MRT ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[21]
	Eye drop preparation	Aqueous humour	0.39±0.83	N/A	0.29±0.57	N/A	N/A	4.30± 0.97	N/A	N/A	N/A	
Ofloxacin	HPMC 3.6 % w/v, PEG 4% w/v–4000 (WP–0405)	Cornea	19.11	0.5	N/A	39.93	N/A	N/A	2.2	0.321	N/A	[22]
		Aqueous humour	1.84	2	N/A	5.25	N/A	N/A	1.1	0.639		
		Conjuctiva	63.38	0.83	N/A	31.41	N/A	N/A	5.1	0.137		
		Iris calliary body	4.76	0.83	N/A	6.48	N/A	N/A	2.8	0.246		
	Eye drop preparation	Cornea	12.92	0.25	N/A	19,27	N/A	N/A	2.9	0.241	N/A	
		Aqueous humour	0.74	1	N/A	2,05	N/A	N/A	1.0	0.666		
		Conjuctiva	41.20	0.83	N/A	11,01	N/A	N/A	2.9	0.239		
		Iris calliary body	1.42	0.83	N/A	3.56	N/A	N/A	2.4	0.292		
Levofloxacin	Hexanol glycol chitosan 2%	Aqueous humour	3.50±0.30	N/A	11.89±1.46	N/A	N/A	N/A	N/A	N/A	C_{max} ($p<0.05$), AUC_{0-12} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[23]

Antibiotics	Polymer	Sample	Pharmacokinetic parameter								Remarks	Ref.
			C_{max} (µg/ml)	T_{max} (h)	$AUC_{(0-t)}$ (h µg/ml)	AUC_{∞}	AUC_{rel}	MRT (h)	t ½ (h)	k (h^{-1})		
	Eye drop preparation	Aqueous humour	2.24±0.28	N/A	6.18±1.94	N/A	N/A	N/A	N/A	N/A	N/A	
Tobramycin sulfate	Poloxamer 407 17%, Chitosan HCL 0.5 %	Aqueous humour	19.44±2.27	1	269.76±28.23	N/A	N/A	10.66 ±0.13	6.38± 0.15	N/A	C_{max} ($p<0.0001$), AUC_{0-12} ($p<0.0001$), and MRT ($p<0.0001$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[24]
	Eye drop preparation	Aqueous humour	2.25±0.55	2	10.99±3.02	N/A	N/A	3.53± 0.06	1.66± 0.63	N/A	N/A	
Ofloxacin	Carbopol 4 %, HPMC 8%	Aqueous humour	84.04±17.75	0.50	302.08±124.24	N/A	N/A	N/A	N/A	0.21±0.11	AUC_{0-t} ($p<0.05$), C_{max} ($p<0.05$), T_{max} ($p<0.05$) of *in situ* gel were considered as Statistically Significant in terms of eye drop preparation	[25]
	Eye drop preparation	Aqueous humour	55.01±3.26	0.25	146.47±25.57	N/A	N/A	N/A	N/A	0.30±0,05	N/A	
Gatifloxacin	Alginate1.3 %, HMPC 2.6 %	Aqueous humour	0.33±0.06	2.0±0.67	1.43±0.13	N/A	N/A	N/A	N/A	N/A	C_{max} ($p<0.05$), AUC_{0-t} ($p<0.05$), T_{max} ($p<0.1$) of *in situ* gel were considered as statistically Significant in terms of eye drop preparation	[26]
	Eye drop preparation	Aqueous humour	0.11±0.01	0.66± 0.17	0.37±0.03	N/A	N/A	N/A	N/A	N/A	N/A	
Moxifloxacin	Polyox	Aqueous humour	1.164	1.5	4.593	N/A	N/A	N/A	1.98	N/A	AUC_{0-t} ($p<0.05$) of *in situ* gel was considered as statistically Significant in terms of eye drop preparation	
	Sodium alginate	Aqueous humour	1.187	1.5	5.198	N/A	N/A	N/A	2.43	N/A	AUC_{0-t} ($p<0.05$) of *in situ* gel was considered as statistically significant in terms of eye drop preparation	
	Poloxamer	Aqueous humour	1.220	1.5	5.388	N/A	N/A	N/A	2.61	N/A	AUC_{0-t} ($p<0.05$) of *in situ* gel was considered as statistically significant in terms of eye drop preparation	[27]
	MF_9 18% Poloxamer w/v, HPMC K4M 0.5% w/v	Aqueous humour	1.233±0.5	1.75± 0.5	5.453±0.5	N/A	N/A	N/A	2.74± 0.5	N/A	AUC_{0-t} ($p<0.05$) of *in situ* gel was considered as statistically significant in terms of eye drop preparation	
	Eye drop preparation	Aqueous humour	1.076	0.5	1.115	N/A	N/A	N/A	0.39	N/A	N/A	
Tobramycin sulfate	Poloxamer, HPMC K4M	Aqueous humour	4.44±1.23	3.30± 1.63	8.23±25.36	1728.79	N/A	N/A	7.25± 0.2	0.006± 0.002	C_{max} ($p<0.005$), T_{max} ($p<0.005$) AUC_{0-t}($p<0.005$), AUC_{∞} ($p<0.005$), T ½ ($p<0.005$) k ($p<0.005$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[28]
	Eye drop preparation	Aqueous humour	0.47±1.55	0.20± 1.31	0.96±22.27	1.11	N/A	N/A	1.79± 0.35	0.021± 0.014	N/A	
Ofloxacin	Poly (DL-lactide-co-glycolide)	Aqueous humour	21±2.2	1	55.47	N/A	7.94	N/A	N/A	N/A	C_{max} ($p<0.05$), AUC_{0-t} ($p<0.05$), AUC_{rel} ($p<0.05$),t_{max} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
	deacylated gellan gum	Aqueous humour	18±1.1	2	64.41	N/A	9.22	N/A	N/A	N/A	C_{max} ($p<0.05$), AUC_{0-t} ($p<0.05$), AUC_{rel} ($p<0.05$),t_{max} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	
	Poly (DL-lactide-co-glycolide),	Aqueous humour	15.2±1.2	2	82.36	N/A	11.7	N/A	N/A	N/A	C_{max} ($p<0.05$), AUC_{0-t} ($p<0.05$), AUC_{rel} ($P<0.05$) and t_{max}	

Antibiotics	Polymer	Sample	Pharmacokinetic parameter								Remarks	Ref.
			C_{max} (µg/ml)	T_{max} (h)	$AUC_{(0-t)}$ (h µg/ml)	AUC_{∞}	AUC_{rel}	MRT (h)	t ½ (h)	*k* (h^{-1})		
	deacylated gellan gum										(p<0.05) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	
	Eye drop preparation	Aqueous humour	4.68±0.4	1	6.98	N/A	1	N/A	N/A	N/A	N/A	
Moxifloxacin	HPMC 0.5 % Natrium Alginat 0.3 %	Aqueous humour	0.727±56	2	2.881±108	N/A	N/A	N/A	N/A	N/A	C_{max} (p<0.0001), AUC_{0-t} (p<0.0001) and t_{max} (p<0.0001) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[30]
	Eye drop preparation	Aqueous humour	0.503±85	1	0.978±86	N/A	N/A	N/A	N/A	N/A	N/A	

Description: N/A: Not Available, AUC: Area Under Curve, MRT: Mean Residence Time

Table 3: Improvement of C_{max} value of *in situ* gel preparation

Polymer	Improvement Cmax (%)	Remarks	Ref.
Gellan gum	51	N/A	[19]
Gellan Gum	13	N/A	[19]
Gellan Gum, Chitosan	62	N/A	[20]
Poloxamer, Carbopol	0.6	N/A	[21]
HPMC, PEG	148	N/A	[22]
Hexanol glycol chitosan	56	C_{max} (p<0.05) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[23]
Chitosan, Poloxamer	764	C_{max} (p<0.0001) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[24]
Carbopol, HPMC	52	C_{max} (p<0.05) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[25]
Alginate, HPMC	201	C_{max} of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[26]
Polyox	8.1	N/A	[27]
Sodium Alginate	10.3	N/A	[27]
Poloxamer	13.4	N/A	[27]
Poloxamer, HPMC	14.6	N/A	[27]
Poloxamer, HPMC	844	C_{max} (p<0.005) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[28]
Dl-lactide–co-glycolide	348	C_{max} (p<0.05) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
Deacylated gellan gum	284	C_{max} (p<0.05) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
Dl-lactide–co–glycolide, Deacylated gellan gum	224	C_{max} (p<0.05) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
HPMC, Sodium Alginate	44.5	C_{max} (p<0.0001) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[30]

Table 4: Improvement of T_{max} value of *in situ* gel preparations

Polymer	Improvement T_{max} (%)	Remarks	Ref.
Gellan gum	300	t_{max} (p<0.05) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[19]
Gellan Gum	300	t_{max} (p<0.05) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[19]
Gellan Gum, Chitosan	100	N/A	[20]
Poloxamer, Carbopol	0	N/A	[21]
HPMC, PEG	100	N/A	[22]
Hexanol glycol chitosan	50	N/A	[23]
Chitosan, Poloxamer	-50	N/A	[24]
Carbopol, HPMC	116	T_{max} (p<0.05) of *in situ* gel were considered as Statistically Significant in terms of eye drop preparation	[25]
Alginate, HPMC	200	T_{max} (p<0.1) of *in situ* gel were considered as statistically Significant in terms of eye drop preparation	[26]
Polyox	200	N/A	[27]
Sodium Alginate	200	N/A	[27]
Poloxamer	200	N/A	[27]
Poloxamer, HPMC	250	N/A	[27]

Polymer	Improvement T_{max} (%)	Remarks	Ref.
Poloxamer, HPMC	1550	T_{max} ($p<0.005$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[28]
Dl-lactide–co-glycolide	0	T_{max} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
Deacylated gellan gum	100	T_{max} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
Dl-lactide–co–glycolide, Deacylated gellan gum	100	T_{max} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
HPMC, Sodium Alginate	100	T_{max} ($p<0.0001$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[30]

Table 5: Improvement of AUC value of *in situ* gel preparations

Polymer	Improvement AUC (%)	Remarks	Ref.
Gellan gum	174	AUC_{0-24} ($p<0.0005$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[19]
Gellan Gum	253	AUC_{0-24} ($p<0.0005$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[19]
Gellan Gum, Chitosan	281	N/A	[20]
Poloxamer, Carbopol	77	AUC_{0-12} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[21]
HPMC, PEG	N/A	N/A	[22]
Hexanol glycol chitosan	92	AUC_{0-12} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[23]
Chitosan, Poloxamer	2354	AUC_{0-12} ($p<0.0001$), and MRT ($p<0.0001$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[24]
Carbopol, HPMC	106	AUC_{0-t} ($p<0.05$) of *in situ* gel were considered as Statistically Significant in terms of eye drop preparation	[25]
Alginate, HPMC	281	AUC_{0-t} ($p<0.05$) of *in situ* gel were considered as statistically Significant in terms of eye drop preparation	[26]
Polyox	311	AUC_{0-t} ($p<0.05$) of *in situ* gel was considered as statistically significant in terms of eye drop preparation	[27]
Sodium Alginate	366	AUC_{0-t} ($p<0.05$) of *in situ* gel was considered as statistically significant in terms of eye drop preparation	[27]
Poloxamer	366	AUC_{0-t} ($p<0.05$) of *in situ* gel was considered as statistically significant in terms of eye drop preparation	[27]
Poloxamer, HPMC	383	AUC_{0-t} ($p<0.05$) of *in situ* gel was considered as statistically significant in terms of eye drop preparation	[27]
Poloxamer, HPMC	757	AUC_{0-t}($p<0.005$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[28]
Dl-lactide–co-glycolide	694	AUC_{0-t} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
Deacylated gellan gum	822	AUC_{0-t} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
Dl-lactide–co–glycolide, Deacylated gellan gum	1029	AUC_{0-t} ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[29]
HPMC, Sodium Alginate	194	AUC_{0-t} ($p<0.0001$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[30]

Table 6: Improvement of t½ value of *in situ* gel preparations

Polymer	Improvement t½ (%)	Remarks	Ref.
Gellan gum	N/A	N/A	[19]
Gellan Gum	N/A	N/A	[19]
Gellan Gum, Chitosan	158	N/A	[20]
Poloxamer, Carbopol	NA	N/A	[21]
HPMC, PEG	10	N/A	[22]
Hexanol glycol chitosan	N/A	N/A	[23]
Chitosan, Poloxamer	284	N/A	[24]
Carbopol, HPMC	N/A	N/A	[25]
Alginate, HPMC	N/A	N/A	[26]
Polyox	407	N/A	[27]
Sodium Alginate	523	N/A	[27]
Poloxamer	569	N/A	[27]
Poloxamer, HPMC	602	N/A	[27]
Poloxamer, HPMC	305	t½ ($p<0.005$ of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[28]
Dl-lactide–co-glycolide	N/A	N/A	[29]
Deacylate gellan gum	N/A	N/A	[29]
Dl-lactide–co–glycolide, Deacylate gellan gum	N/A	N/A	[29]
HPMC, Sodium Alginate	N/A	N/A	[30]

Table 7: Improvement of *k* value of *in situ* gel preparations

Polymer	Improvement *k* (%)	Remarks	Ref.
Gellan gum	N/A	N/A	[19]
Gellan Gum	N/A	N/A	[19]
Gellan Gum, Chitosan	N/A	N/A	[20]
Poloxamer, Carbopol	N/A	N/A	[21]
HPMC, PEG	-4.05	N/A	[22]
Hexanol glycol chitosan	N/A	N/A	[23]
Chitosan, Poloxamer	N/A	N/A	[24]
Carbopol, HPMC	-27	N/A	[25]
Alginate, HPMC	N/A	N/A	[26]
Polyox	N/A	N/A	[27]
Sodium Alginate	N/A	N/A	[27]
Poloxamer	N/A	N/A	[27]
Poloxamer, HPMC	N/A	N/A	[27]
Poloxamer, HPMC	-71	*k* ($p<0.005$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[28]
Dl-lactide–co-glycolide	N/A	N/A	[29]
Deacylated gellan gum	N/A	N/A	[29]
Dl-lactide–co–glycolide, Deacylate gellan gum	N/A	N/A	[29]
HPMC, Sodium Alginate	N/A	N/A	[30]

Table 8: Improvement of MRT value of *in situ* gel preparations

Polymer	Improvement MRT (%)	Remarks	Ref.
Gellan gum	100	MRT ($p<0.0001$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[19]
Gellan Gum	275	MRT ($p<0.0001$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[19]
Gellan Gum, Chitosan	N/A	N/A	[20]
Poloxamer, Carbopol	59.5	MRT ($p<0.05$) of *in situ* gel were considered as statistically significant in terms of eye drop preparation	[21]
HPMC, PEG	N/A	N/A	[22]
Hexanol glycol chitosan	N/A	N/A	[23]
Chitosan, Poloxamer	201%	N/A	[24]
Carbopol, HPMC	N/A	N/A	[25]
Alginate, HPMC	N/A	N/A	[26]
Polyox	N/A	N/A	[27]
Sodium Alginate	N/A	N/A	[27]
Poloxamer	N/A	N/A	[27]
Poloxamer, HPMC	N/A	N/A	[27]
Poloxamer, HPMC	N/A	N/A	[28]
Dl-lactide–co-glycolide	N/A	N/A	[29]
Deacylated gellan gum	N/A	N/A	[29]
Dl-lactide–co–glycolide, Deacylate gellan gum	N/A	N/A	[29]
HPMC, Sodium Alginate	N/A	N/A	[30]

DISCUSSION

On table 1, rabbit eyes were selected as testing subjects on all antibiotics *in situ* gel *in vivo* studies. Anatomically and physiologically, rabbit eyes define similarity with the human eye [31]. Also the acclimatization and handling of rabbits were easy and did not need much time [32]. Beside of that, the sampling on rabbit *aqueous humour* is fairly easier than other test animals. The *in vivo* samples on all antibiotics *in situ* gel, were analyzed in HPLC (High Performance Liquid Chromatography). One of the strong points for this instrument selection is due to the complex matrix substance of *aqueous humour* sample beside active substance, and capability of HPLC can resulted with perfect separation between those matrix and active drug substance [33]. In HPLC the use of the flow rate determines the ability to separate the components present in the compound; the smaller flow rate the ability to separate each component in the compound the better [34]. The system of column and mobile phase of all the research is a reverse phase system. It defines the terms where the column phase has non-polar property, with a carbon chain of 18 (C_{18}) and the mobile phase has a polar property. This indicates that the antibiotics used in table 1, have polar solubility as the mobile phase has similar polar property. On table 1, the interval sampling used varies with an interval time of 8, 12, and 24 h. The sampling interval aimed to detect the active substance presence duration after initial administration; the interval time and the duration of the test was determined based on the half-life time of each antibiotic.

Cmax describes the highest concentration during drug distribution in blood plasma. tmax was defined as the time to reach Cmax. From table 2, all *in vivo* assays on antibiotics in situ gels show longer Cmax and tmax results than eye drop preparation. It means the *in situ* gel dosage form could retained the contact time of the active substance on the pra-corneal region [35]. The statistically significance of some pharmacokinetic parameters between *in situ* gel and eye drop preparation was shown by Li *et al.*, 2013. The results shown that the C_{max} *in situ* gel of 84.04 µg/ ml and for eye drop preparation of 55.01 µg/ ml. Another significance difference is shown on t_{max} values for *in situ* gel of 0.5 h and eye drop preparation t_{max} values of 0.25 h ($p<0.05$).

Then in the research conducted by Liu *et al.*, 2007 the values of C_{max} and T_{max} for *in situ* gel preparations are 0.33 µg/ml and 2.0 h, while for eye drop preparation, 0.11 and 0.66 h with P value $P<0.05$ for C_{max} and P value 0.1 for T_{max}. From Patel *et al.*, 2015 the C_{max} and T_{max} for *in situ* gel were to 4.4 µg/ ml and 3.3 h and C_{max} and T_{max} for eye drop preparation were 1.23 µg/ml and 0.2 h ($p<0.005$).

Another *in vivo* study by Sayed *et al.*, 2015 was conducted with 3 different types of *in-situ* gel polymers have a value of C_{max} 21 µg/ml, 18 µg/ml and 15.2 µg/ml while eye drop preparation C_{max} value is 4.68 and the t_{max} of all this 2h and the value of T_{max} eye drop preparation 1h ($p<0.05$). A research conducted by Nair *et al.*, 2021 C_{max} and T_{max} *in situ* gel amounted to 0.727 (µg/ml) and 2 h while the value of C_{max} and T_{max} eye drop preparation 0.503(µg/ml) and 1h with p value $P<0.0001$.

C_{max} dan T_{max} parameters of *in situ* gel could be improved from eye drop preparation. This is due to the use of polymeric system that improve drug delivery [36]. From these improvement data from table 3 and table 4. It can be concluded that each polymer has a diverse increase for its pharmacokinetic profile the use of a combination of poloxamer and HPMC polymers in the study of Patel *et al.*, 2015 gave a very significant improvement compared to other polymers.

AUC is a pharmacokinetic parameter that describes the bioavailability of a drug preparation in the blood [36]. In table 2, antibiotics *in situ* gel that have been tested *in vivo* found that the preparation *in situ* gel has a greater AUC value than eye drop preparation significantly. Evidenced by statistical data with P value compared to eye drop preparation as in Nair *et al.*, 2021 with P value<0.0001 with AUC *value in situ* gel of 2881±108 ng h/ml and AUC eye drop preparation value of 978±86 ng h/ml.

Then in the research conducted by Khan *et al.*, 2017 with a P value of 0.0001 with an AUC gel value in situ of 269.76±28.23 and AUC eye drop preparation value of 10.99±3.02 this occurs because the preparation of the gel *in situ* undergoes a change of transition phase solution to gel which is influenced by physiological conditions of the body such as temperature, pH and electrolyte composition in the eye fluid so that this transition causes the time of contact with the cornea to be longer [37]. On one side of the eye has a rapid pre-corneal absorption mechanism; eye drop preparation do not have a longer contact time than gel in situ; therefore the mechanism of pre-corneal absorption can make the level of eye drops preparation drastically reduced compared to in situ gels that have a longer contact time with the cornea of the eye [38]. Based on the study of this review, polymer factors used in *in situ* gels are responsive to changes in temperature, pH and electrolyte composition in eye fluids provide better AUC results than eye drop preparation [35, 36]. From table 5, each polymer has a diverse increase for the AUC value of the use of a combination of polymers (DL-lactide-co-glycolide and deacylate gellan gum) in the study Sayed *et al.*, 2015 gave a significantly greater increase compared to other polymers.

t½ is a pharmacokinetic parameter that describes the times for the concentration of the drug in the blood plasma to be reduced by half of the level of the drug given from the initial dose given [38]. t½ depends on the speed of the elimination constant (*k)* and the value is inversely proportional to the *value of k* from the literature study conducted [38]. From table 6, The value of t½ *in situ* gel preparations is greater than in eye drop preparation, significantly as evidenced by the data analysis. In the study of Patel *et al.*, 2015 with a p value of t½ ($P<0.005$) k ($P<0.005$) with a value of t½ and k in situ gel preparations of 7.25±0.2 and 0.006±0.002 and t values 1/2 and k for eye drop preparation 1.79±0.35 and 0.021±0.014.

The study conducted by Fukaya *et al.*, 2006 on corneal samples obtained inverse results, t½ in situ gel is smaller than eye drop preparation and the value of *k in situ* gel is greater than eye drop preparation; this happens because the gel preparation *in situ* is undergoing phase changes from sol to gel so that when there is the elimination of the drug in pre corneal the concentration of drugs becomes less than eye drop preparation then the value of t½ and the value of *k* becomes inverted at the time of the corneal swab [39].

From table 6 and table 7 this increased data it can be concluded that each polymer has a diverse increase for the t½ value of the use of a combination of Poloxamer and HPMC in the study Nanjwade *et al.*, 2012 gave a significantly greater increase compared to other polymers. Each polymer has a diverse increase for the *k* value of the use of a combination of Poloxamer and HPMC in the study Patel *et al.*, 2015 gave a significantly greater increase compared to other polymers.

Mean Residence Time (MRT) is a pharmacokinetic parameter that describes how long drug molecules can be held at the site of drug absorption. From table 8, obtained a greater MRT value from *the* preparation *in situ* gel compared to eye drop preparation, is significantly evidenced by the data analysis in Khan *et al.*, 2017 with P value $P<0.0001$ with an MRT value of gel *preparation in situ* of 10.66±0.13 and eye drop preparation MRT value of 3.53±0.06.

Then in Cao *et al.*, 2010 with a P value of $P<0.05$ with an MRT gel preparation value *in situ* of 6.86±1.25 and eye drop preparation MRT value of 4.30±0.97 and Bhalerao *et al.*, 2019 with a P value of $P<0.0001$ with a gel *in situ* preparation MRT value of 8 and 15 for 2 preparations with 2 different polymers and eye drop preparation MRT value of 4. This caused the polymer *in situ* gel has hydrophilic properties that can distability eye fluid. It is not easily eliminated to the retention time of the drug becomes longer [38]. From table 8, this increase data it can be concluded that each polymer has a diverse increase for the MRT value of the use of a gellan gum polymer in the study Bhalerao *et al.*, 2019 gave a significantly greater increase compared to other polymers

CONCLUSIONS

In situ gel have better properties compared to eye drop preparation based on several pharmacokinetic profiles such as (AUC, C_{max}, t_{max}, $t_{1/2}$, *k,* MRT) because the polymer that used improved the drug delivery system to the targets. *In situ* gel can be said to be an innovation of drug delivery system that can enhance the bioavailability of antibiotics ophthalmic drug delivery.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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