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Original Article

Advancement and *in vitro* Characterization of an Ocular Gel Containing Chitosomal Encapsulated Drug for Glaucoma Therapy

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ABSTRACT

Background: The most popular and well-designed nano-carriers for drug delivery targeting are liposomes. In order to overcome barriers to cellular and tissue uptake and increase medication bio-distribution to target areas *in vivo*, they have improved medicines for a variety of biomedical applications. **Objectives:** The diffusion method is used to release the medication from liposomes. The major goals of this medication delivery system were to increase contact resistance duration in the eye and bioavailability. **Materials and Methods:** Liposomes were effectively produced by reverse phase evaporation technique and their shape, particle size, drug entrapment efficiency and content were examined. Liposomes were prepared by using drug, egg lecithin, chloroform, and diethyl ether. **Results:** This dosage form bears considerable promise for drug release, according to *in vitro* experiments. As a result, the design of the liposomes revealed virtually spherical vesicles. Up to 88.9% and 92.1%, respectively, of the EE% and DC% were possible. Studies on medication release from liposomes *in vitro* demonstrate that an increase in lipid concentration delays drug release. **Conclusion:** The drug is known as dorzolamide in accordance with the conclusions of the investigations stated above. The medicine is stable in all pH, it was found after the Preformulation experiment was over. The dorzolamide curve was calibrated in analytical experiments using phosphate buffers with pH values of 5.6, 7.4 and 6.8. As a result of the inquiry, it was established that the standard plot may be used in additional analytical studies. Liposome batches show that integration efficiency rose with increasing polymer content. The manufactured liposomes' surface was examined using scanner electron microscopy.

Keywords: Ocular Drug Delivery, Liposomes, Nanoparticles, *In situ* ocular gel, Glaucoma, Dorzolamide Hydrochloride.

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INTRODUCTION

Ophthalmic formulations are sterile in dosage, free of foreign material, and appropriately designed in a form that can be administered to the inner side (intraocular) or the cavity of the eye, or they can be used in conjunction with an ophthalmic treatment device.[1] The eye is a special and vital organ. Since the ocular route is equivalent to other routes and has a particular anatomy that can prevent drug absorption into the deep tissues of the eye, drug delivery by this channel is a very delicate task for researchers. There are many different drug delivery methods for ophthalmic usage, including eye drops, ointments, lotions and suspensions for the eyes, however, these preparations and formulations must be used with caution. Due to their solubility in tears, previously made ophthalmic dose have the potential to lose their viscosity and resistance time in the eye. This issue can be resolved by creating a medication formulation that instantly forms *in situ* gel when injected into the eye cavity. *In situ* gels were created to extend the medication's stay in the eye cavity, improve drug resistance and bioavailability and relieve the eye from repeated doses.[2,3] The delivery methods must preserve certain properties, such as sterility, isotonicity and improved penetration from the eye muscle, in order to control the drug's use in the ocular cavity. Less soluble in tears, less protein binding a simple installation and uninstall process, good rheological characteristics and formulation resistance in the ocular cavity[4-6] Mainly The medication is absorbed into the ocular system through the cornea, which is more efficiently than other routes like scleral and *Maidenhead pericardium* absorption, through which the blood vessel can absorb the drug from the absorption route and finally, general solution of the drug happens in the body. To regulate the drug's use in the ocular cavity, the delivery techniques must maintain specific qualities such as sterility, isotonicity and enhanced penetration from the eye muscle.[7-10] Less protein binding, less solubility in tears, ease of installation and

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removal, good rheological properties and formulation resistance in the ocular cavity. Mainly The drug is absorbed into the ocular system through the cornea, which is more effective than other routes like scleral and Maidenhead pericardium absorption. Afterwards, the drug is generally dissolved in the body.[10-11]

MATERIALS AND METHODS

Dorzolamide Hydrochloride was procured from Century Pharmaceutical Limited. Natural Egg Phospholipid Powder was procured from Vitae Gen Life Sciences, Nagpur. Chitosan was procured from Bangalore Fine Chemicals, Bengaluru, Karnataka.

Method for preparation of liposomes

Liposomes containing the drug were prepared by Reverse phase evaporation technique and the prepared liposomes were then dissolved in a solution containing gelling agents. Different formulations (Formulation F1-F9) of Dorzolamide liposome prepared from different polymers with varying concentration as shown in Table 1.

Evaluation of ocular gel

Physical characteristics

It is important to look into the physical qualities of the prepared formulation. Phase separation, colour, homogeneity and consistency are examined.

FTIR Analysis

FTIR was performed for the conformation of the original drug, polymer and to know polymer and drug interaction. In this test, the sample was weighed and mixed with KBr and placed under a pressure of 100 kg/cm to get pallets. FTIR analysis of the drug (dorzolamide), polymers (chitosan, egg lecithin), and physical mixture of drug-polymer and pellets were recorded. IR Spectra of a) dorzolamide sample b) Egg lecithin c) Physical mixture of drug and polymer d) Chitosan shown in Figure 1.

Preparation of standard curve of dorzolamide hydrochloride in phosphate buffer pH 7.4: The different concentration of drug Dorzolamide 2-12 µg/ml was prepared. Then absorbance of each concentration at λ_{max} 253nm was taken using phosphate buffer ph 7.4 as diluent and the slope, intercept, and correlation coefficient were calculated (Figure 2). Absorbance was taken in triplicate for all the concentration and calculated the standard deviation which is shown in Table 2.

pH determination

The pH of the gel is determined using a pH meter. The procedure involved sticking the electrode tip into the gel and 2 min later, the outcome was recorded. Results of pH for different formulation (F1 to F9) mentioned in Table 3.

Rheological research

The viscosity of the produced formulation is measured using a Brookfield viscometer (Brookfield LV, spindle 64). The spindle of

Table 1: Composition of *in situ* ocular gel containing Dorzolamide liposomes.

Sl. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Dorzolamide Hydrochloride (mg)	20	20	20	20	20	20	20	20	20
2.	Egg lecithin	100	100	150	150	200	250	300	400	500
3.	Chitosan	5	5	7	7	7	10	10	15	15
4.	Diethyl ether	10	10	10	10	10	10	10	10	10
5.	Ethanol	20	20	20	20	20	20	20	20	20
6.	Chloroform	10	10	15	15	15	20	20	20	20
7.	Gellan Gum (mg)	0.5	0.7	-----	0.5	0.7	-------	0.5	0.7	------
8.	Sodium Alginate(mg)	-------	------	0.3	0.5	0.3	------	0.3	0.3	------
9	Poloxamer188 (mg)	-------	-------	-----	-------	-------	18	-------	-------	25
11	Poloxamer407 (mg)	-------	------	------	------	------	-----	18	25	-----
12	HPMC	-------	------	0.4	0.4	0.4	0.5	0.5	0.5	-----
13	Methyl cellulose	-----	0.5	0.5	0.5	------	------	------	0.5	------
14	Buffer solution pH 7.4 (mL)	100	100	100	100	100	------	------	------	------
15	Buffer solution pH 6.5 (mL)	------	------	------	------	------	100	100	------	------
16	Buffer solution pH 4.7 (mL)	------	------	------	------	------	------	------	100	100

the viscometer was allowed to rotate at predetermined rates (100 rpm) while the gel sample was placed within a glass container. The viscosity results are shown in below Table 3.[12-15]

Spreadability and Centrifugation

All the prepared liposomal formulation were evaluated for Spreadability and checked for layer separation by the method of centrifugation. The outcomes shown in Table 3.

Size of the vesicles

The morphology, size, and size distribution of liposomal vesicles were analyzed by field emission scanning electron microscopy (SEM, ZEISS) and Transmission electron microscopy (TEM).[131] SEM and TEM images of formulated liposome (Formulation F5) shown in Figure 3 and Figure 7 respectively.

Swelling index

To test the swelling of ocular gel containing Dorzolamide hydrochloride liposomal formulations as shown in Figure 8, three set of each formulation were weighed and put in a mesh basket and inserted into phosphate buffer saline (PBS) of pH 7.4 maintained at temperature 32 ± 0.5°C at different time intervals (1 hour, 2 hour, 3 hour, 4 hour and 5 hour). The swollen formulation than removed, wiped with lint free tissue to remove excess surface PBS, weighed, and then return back to the same container.
Swelling index was calculated using the following equation:

$$\text{Swelling index} = \frac{Wt - W0}{W0} \times 100$$

Where W0 is the initial weight of the sample and Wt is its weight at time t. Results of swelling index for formulated liposomes (F1 to F9) summarized in Table 4 and comparative chart of time v/s swelling index of different formulation (F1 to F9) shown in Figure 4.

Polydispersity index and Zeta potential

The size and polydispersity index of the different liposomes were obtained from DLS measurements by using a Zeta sizer nano ZS Malvern Instrument. Samples were illuminated with a laser at a fixed detection arrangement of 90° to the center of the cell area and fluctuations in the intensities of the scattered light were analysed. Polydispersity index of formulation F5 shown in Figure 5 and zeta potential of formulation F5 shown in Figure 6.

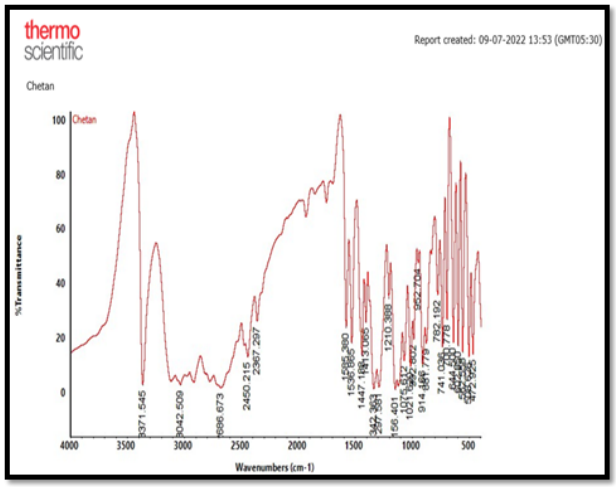
Drug content determination

1 g of gel sample was dissolved in 100 mL of phosphate-saline buffer, pH 7.4 and then sonicated for 2 hr. Before the sonicated mixture was exposed to UV analysis, it was filtered using a 0.45 m Millipore filter.[16-18]

In vitro Release Study

A Franz diffusion cell is used to perform drug release studies. 200 mg of emulgel is evenly distributed across the surface of the egg membrane. Both the chambers of the diffusion cell are sandwiched together by the egg membrane. To solubilize the medication, newly made PBS solution (pH 5.5) is poured into the receptor chamber. The receptor chamber is stirred using a magnetic stirrer. The samples are taken in 1.0 mL aliquots at predetermined intervals. After the proper dilutions, samples are examined using a UV-visible Spectrophotometer to determine their drug content. Cumulative adjustments are made to establish the overall amount of medication released at each time period. The total amount of medication delivered through the egg membrane is then calculated as a function of time.[18-22] Their drug content. Cumulative adjustments are made to establish the overall amount of medication released at each time period. Results of in-vitro drug release summarized in Table 5 and cumulative drug release of dorzolamide hydrochloride from *in situ* ocular gel of different formulation (Formulation F1 to F9) shown in Figure 9.

RESULTS



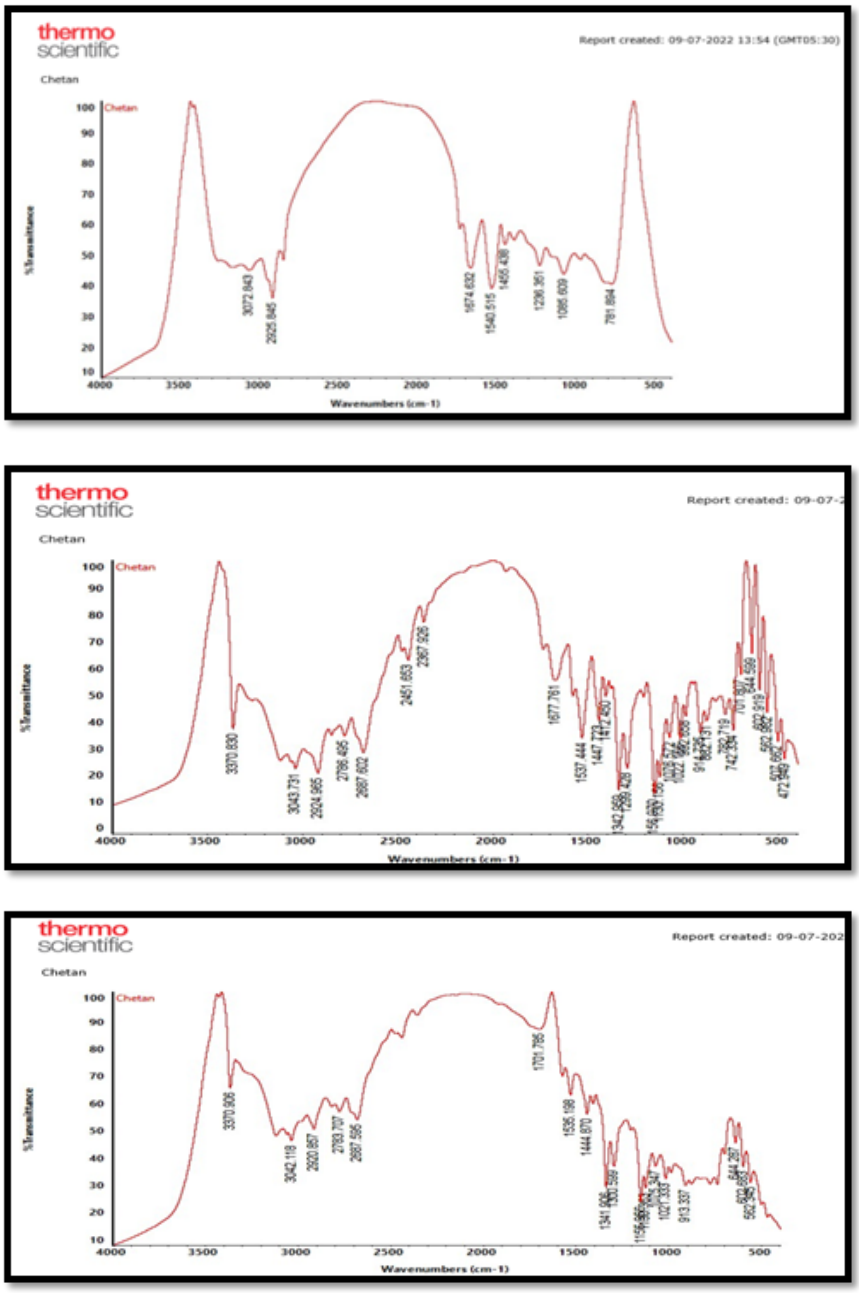


Figure 1: IR Spectra of a) dorzolamide sample b) Egg lecithin c) Physical mixture of drug and polymer d) Chitosan.

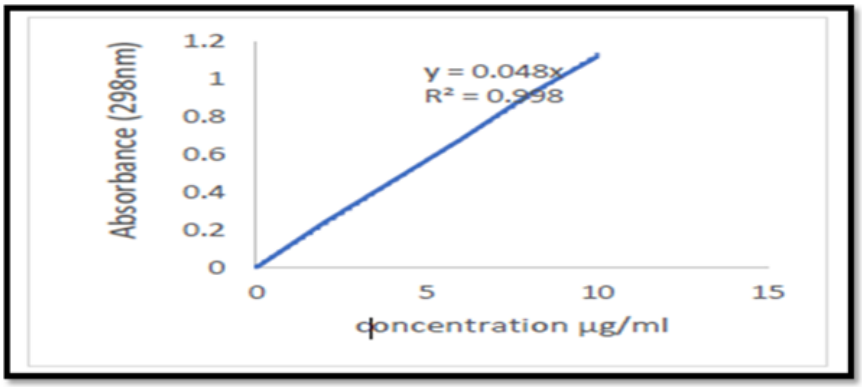


Figure 2: Standard plot of dorzolamide hydrochloride in Phosphate buffer pH 7.4.

Table 2: **Standard curve dorzolamide hydrochloride in phosphate buffer pH 7.4.**

Concentration (µg/mL)	Absorbance (298 nm)
0	0.00
2	0.23
4	0.47
6	0.67
8	0.82
10	1.11

Table 3: **Data for pH, Spreadability, Centrifugation, viscosity.**

Formulation	pH	Spreadability (in cm)	Centrifugation	Viscosity in cps. (Centipoise)
F1	6.80 ± 0.09	7.31±0.03	No separation	21,455 ± 1.6
F2	6.41 ± 0.04	8.2±0.06	No separation	24,576 ± 1.7
F3	6.91 ± 0.03	6.7±0.03	No separation	19,456 ± 1.2
F4	6.75 ± 0.06	7.6±0.03	No separation	22,746 ± 1.3
F5	6.32 ± 0.08	7.9±0.01	No separation	21,776 ± 1.4
F6	6.72 ± 0.03	6.8±0.03	No separation	19,976 ± 1.5
F7	6.73 ± 0.05	7.8±0.02	No separation	23,456 ± 1.7
F8	6.52 ± 0.04	8.3±0.03	No separation	21,786 ± 1.3
F9	6.81 ± 0.06	7.1±0.03	No separation	19,786 ± 1.4

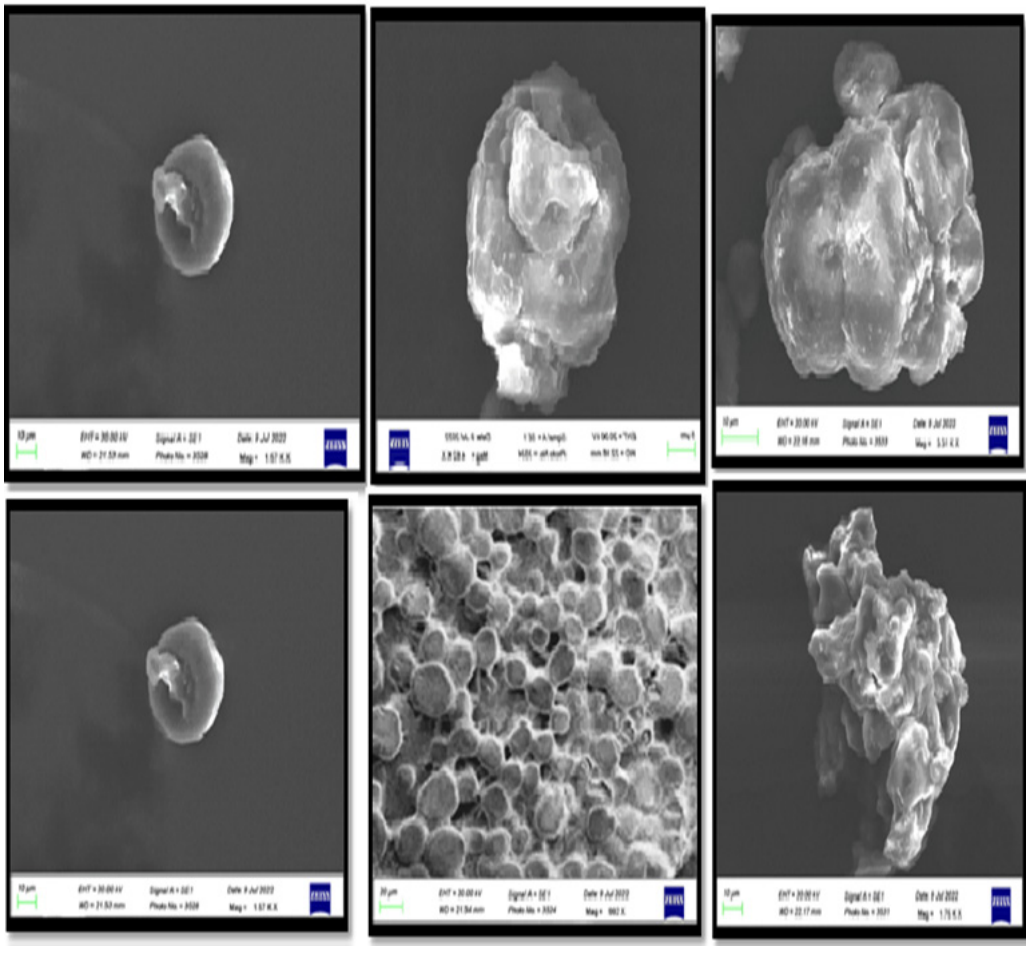


Figure 3: SEM Images of formulated liposomes.

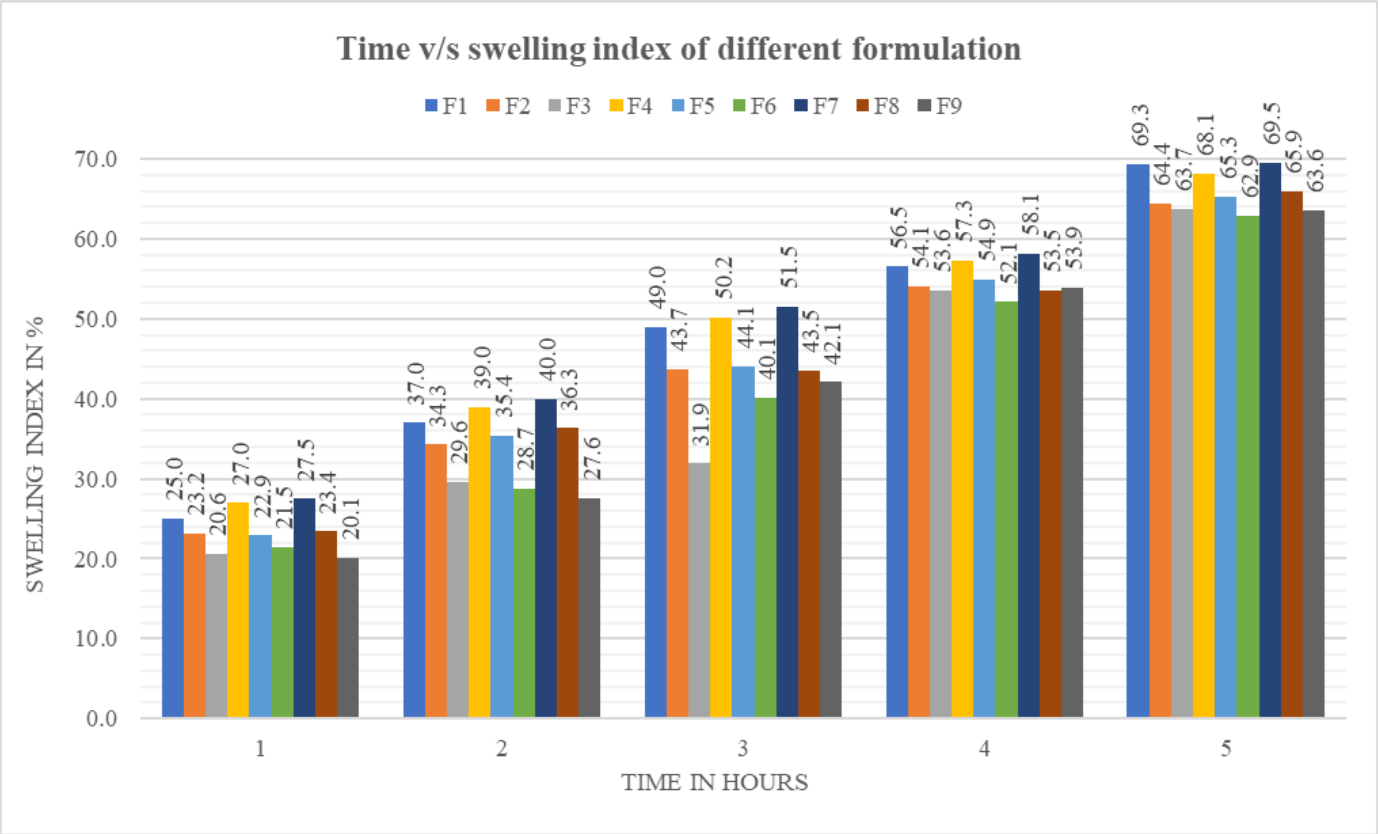


Figure 4: Comparative chart of Time v/s swelling index of different formulation (F1 to F9).

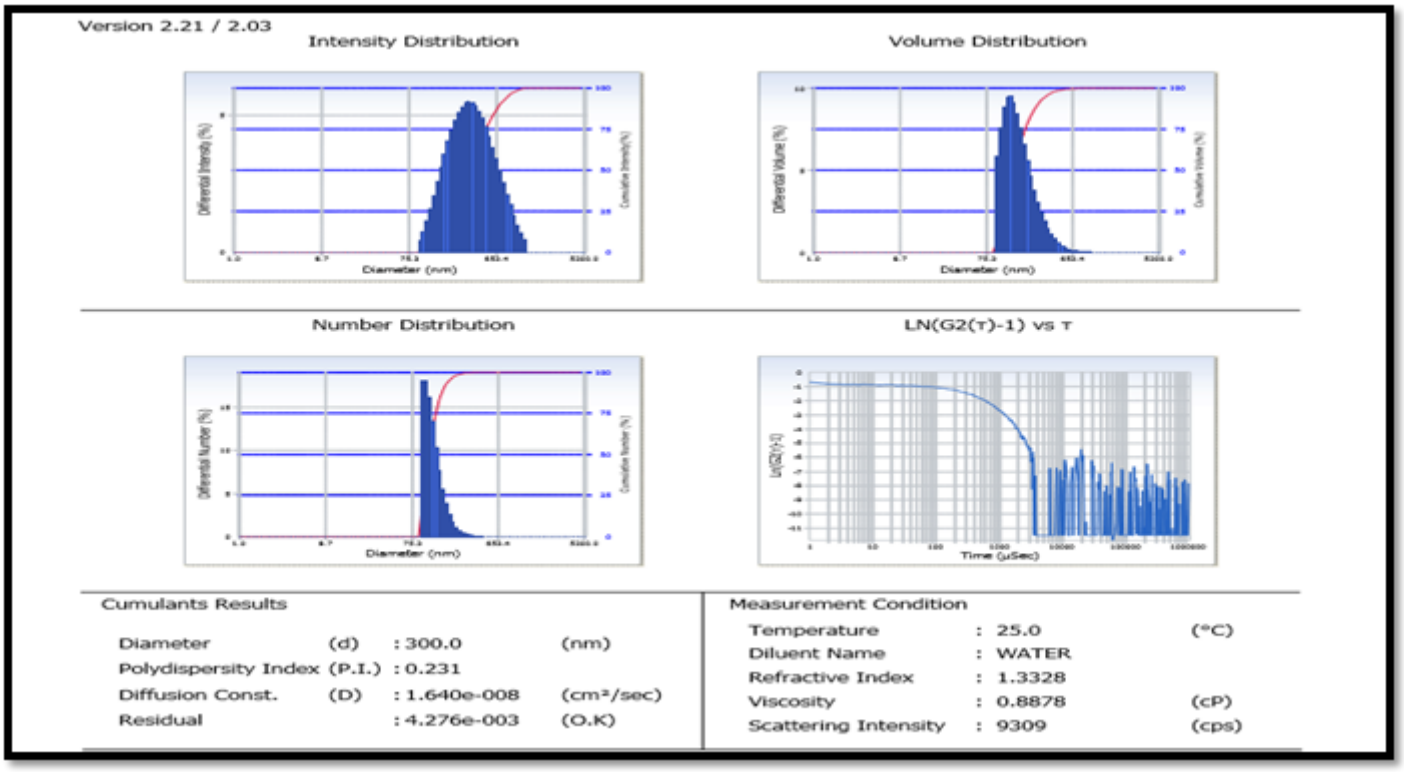


Figure 5: Drug containing liposomes Polydispersity Index .

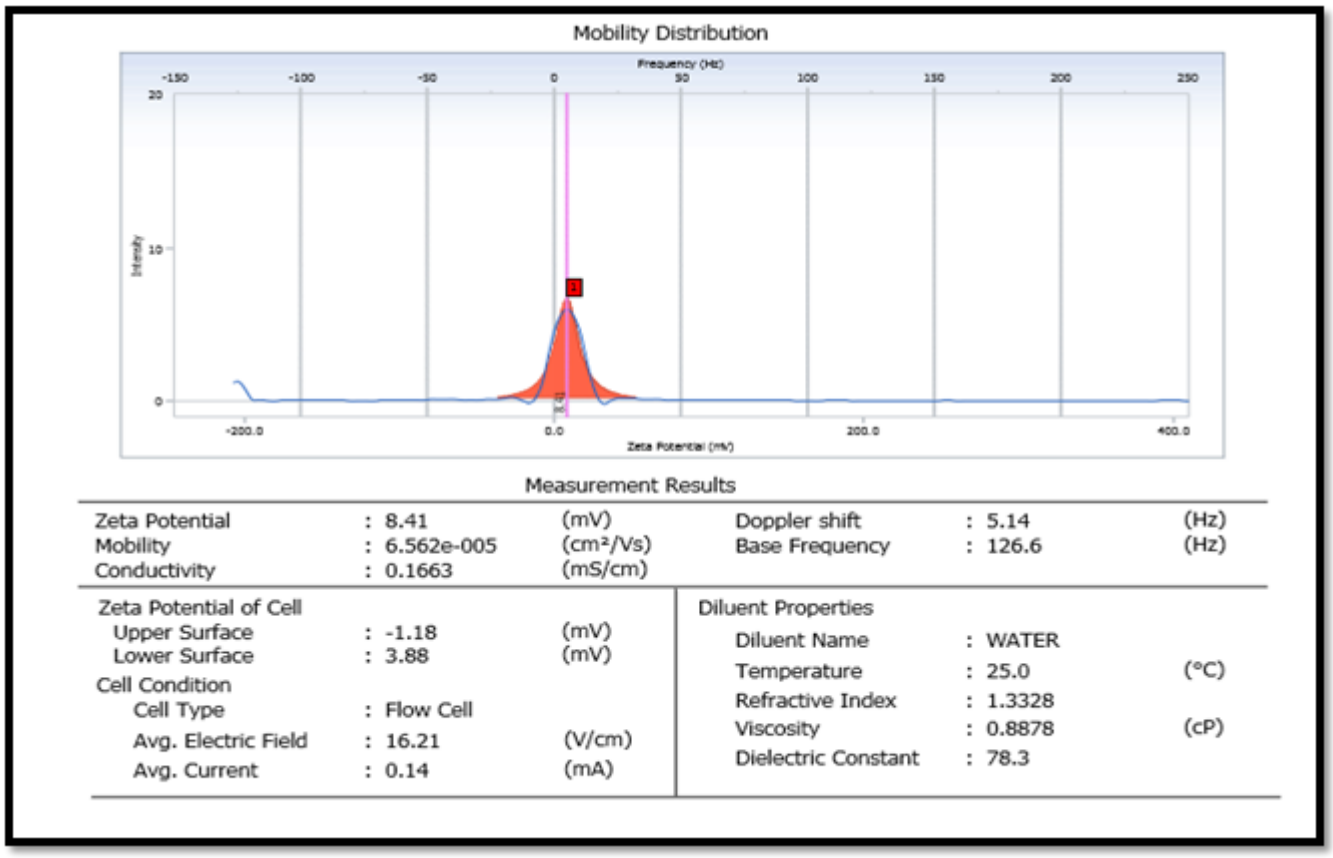


Figure 6: Zeta Potential image of prepared liposome.

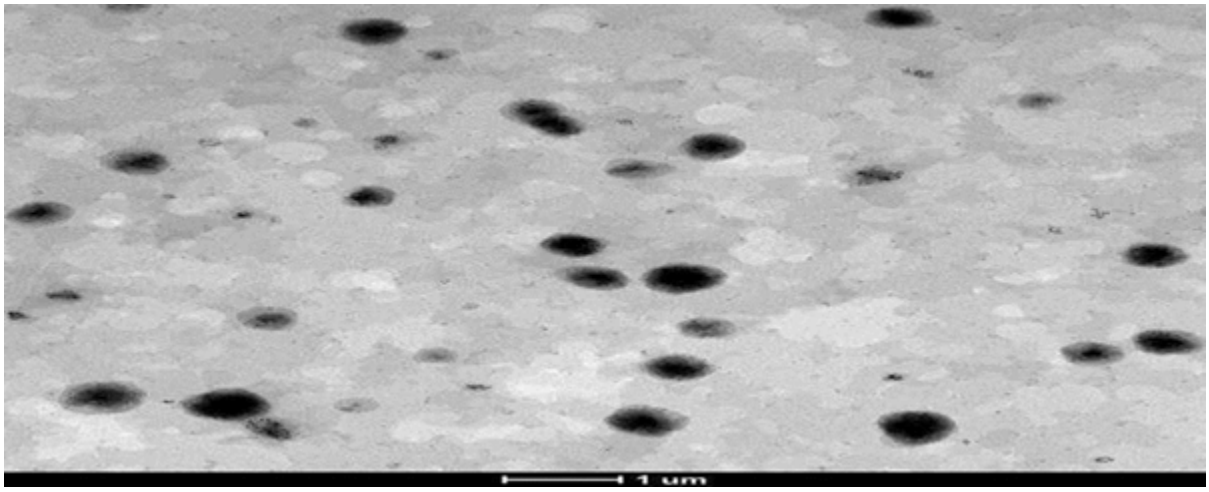


Figure 7: TEM images of prepared Liposomes.

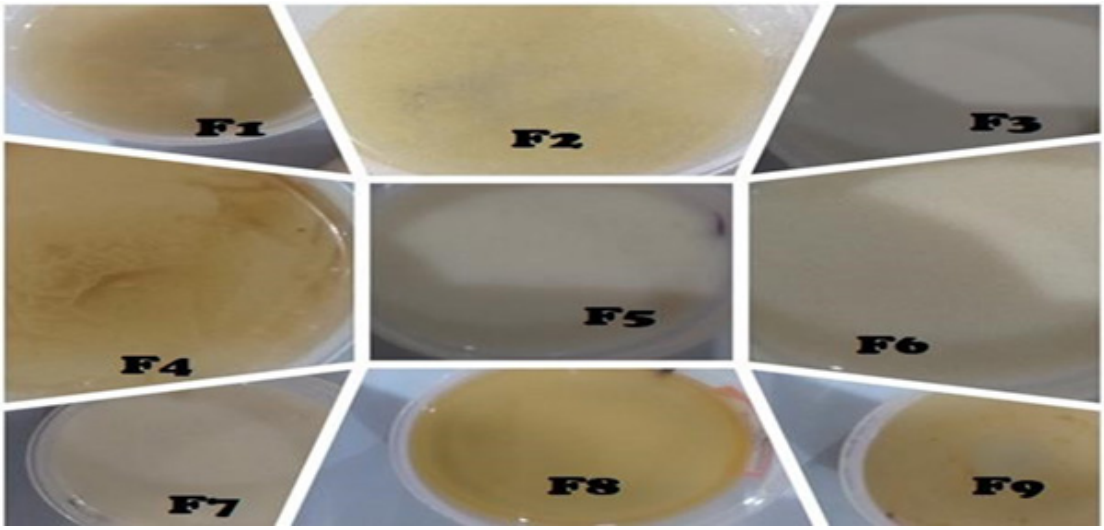


Figure 8: Ocular Gel Containing dorzolamide Liposome.

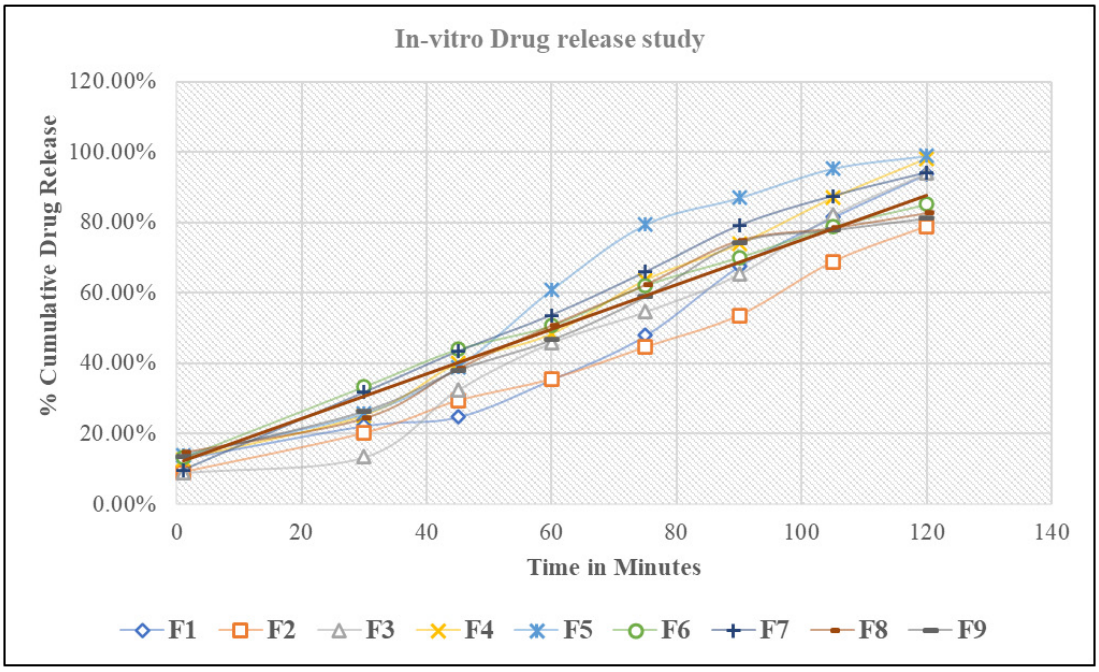
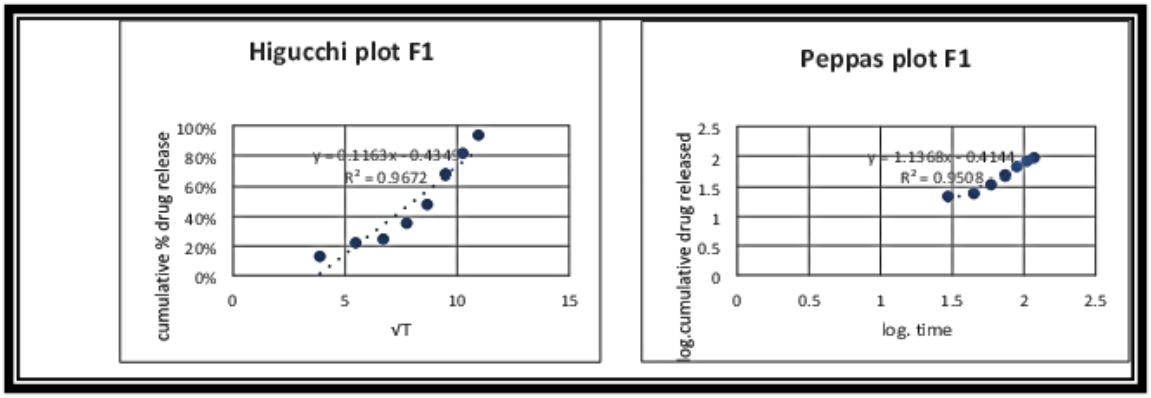
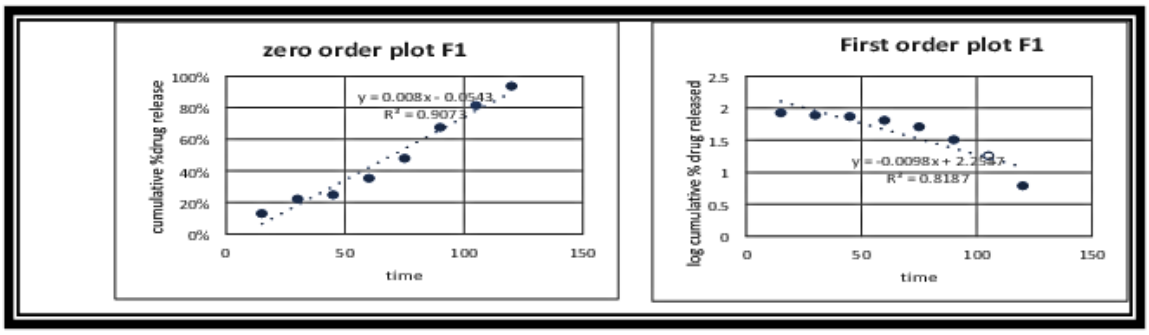


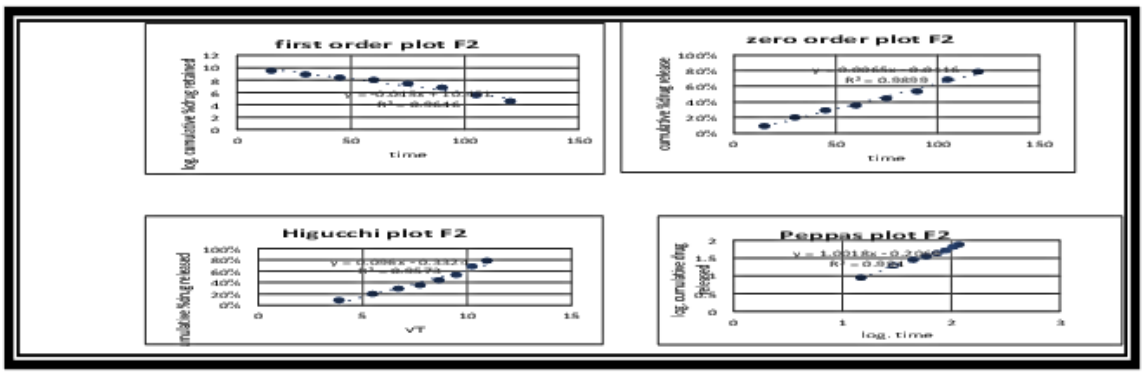
Figure 9: % Cumulative Drug release of Dorzolamide Hydrochloride from *in situ* ocular gel.

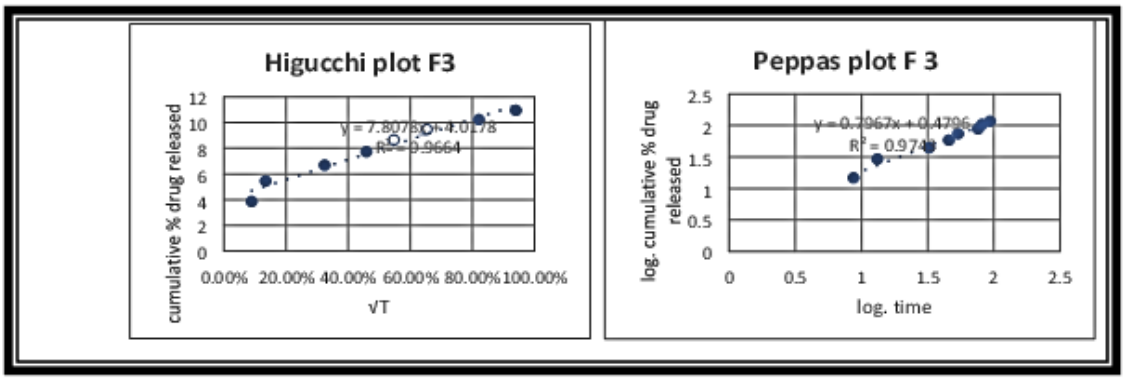
Table 4: Data for swelling index.

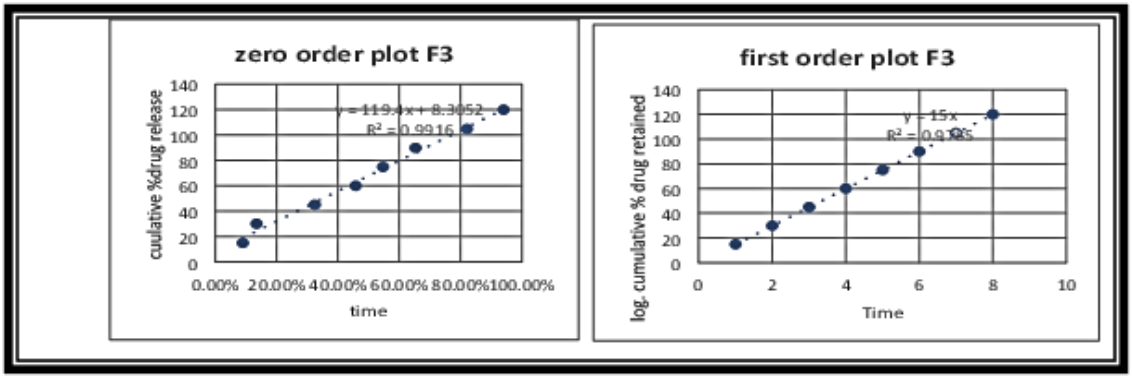
Formulation	1st hr	2nd hr	3rd hr	4th hr	5th hr
F1	±25-0.01%	±37-0.02%	±49-0.01%	±56.5-0.02%	±69.3-0.01%
F2	±23.2-0.02%	±34.3-0.01%	±43.7-0.02%	±54.1-0.01%	±64.4--0.02%
F3	±20.6-0.01%	±29.6-0.03%	±31.9-0.02%	±53.6-0.02%	±63.7-0.01%
F4	±27-0.03%	±39-0.02%	±50.2-0.01%	±57.3-0.04%	±68.1-0.02%
F5	±22.9-0.03%	±35.4-0.04%	±44.1-0.02%	±54.9-0.03%	±65.3-0.01%
F6	±21.5-0.02%	±28.7-0.02%	±40.1-0.02%	±52.1-0.02%	±62.9-0.02%
F7	±27.5-0.01%	±40-0.01%	±51.5-0.02%	±58.1-0.01%	±69.5-0.01%
F8	±23.4-0.02%	±36.3-0.02%	±43.5-0.03%	±53.2-0.02%	±65.9-0.02%
F9	±20.1-0.02%	±27.6-0.01%	±42.1-0.03%	±53.9-0.02%	±63.6-0.02%

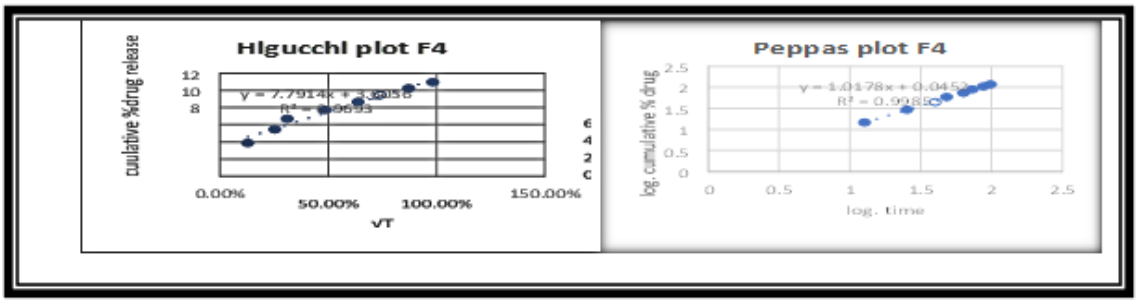

Higucchi plot F1
cumulative % drug release
y = 0.1163x - 0.4345
R² = 0.9672
√T
Peppas plot F1
log.cumulative drug released
y = 1.1368x - 0.4144
R² = 0.9508
log. time

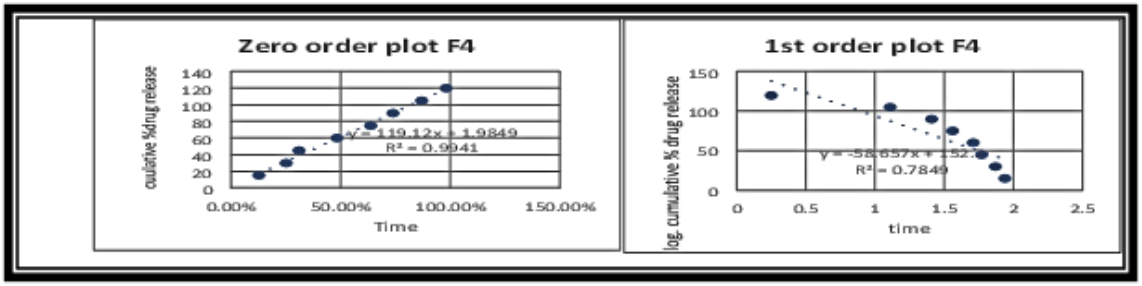

zero order plot F1
cumulative %drug release
y = 0.008x - 0.0543
R² = 0.9073
time
First order plot F1
log cumulative % drug released
y = -0.0098x + 2.2987
R² = 0.8187
time

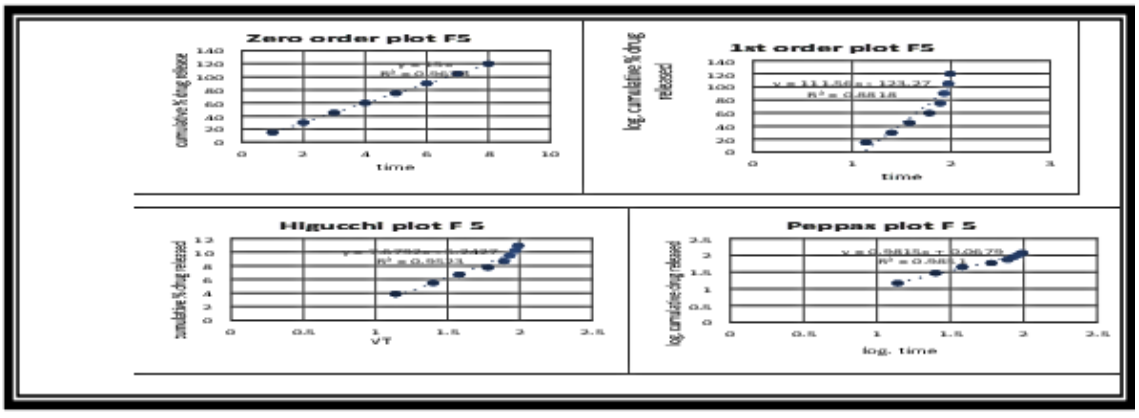

first order plot F2
time
zero order plot F2
time
Higucchi plot F2
√T
Peppas plot F2
log. time

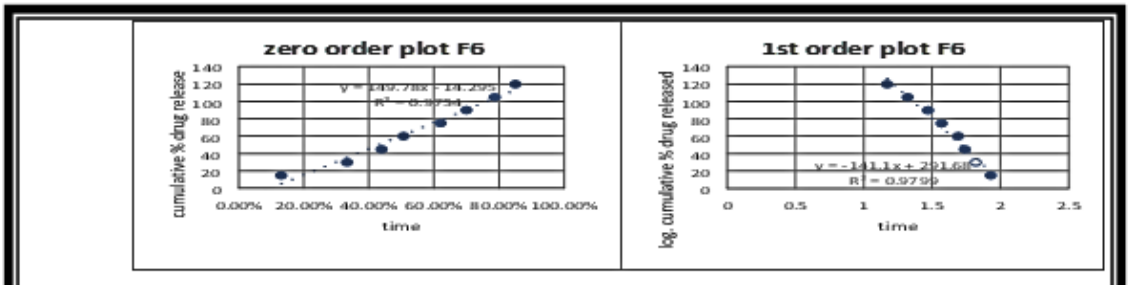

Higucchi plot F3
cumulative % drug released
y = 7.8078x + 4.0178
R² = 0.9664
0.00% 20.00% 40.00% 60.00% 80.00% 100.00%
√T
Peppas plot F 3
log. cumulative % drug released
y = 0.7967x + 0.4796
R² = 0.9748
log. time


zero order plot F3
cuulative %drug release
time
first order plot F3
log. cumulative % drug retained
Time


Higucchi plot F4
cuulative %drug release
VT
Peppas plot F4
log. cumulative % drug
log. time


Zero order plot F4
cuulative %drug release
Time
1st order plot F4
log. cumulative % drug release
time


Zero order plot F5
time
1st order plot F5
time
Higucchi plot F 5
VT
Peppax plot F 5
log. time


zero order plot F6
cumulative % drug release
time
1st order plot F6
log. cumulative % drug released
time

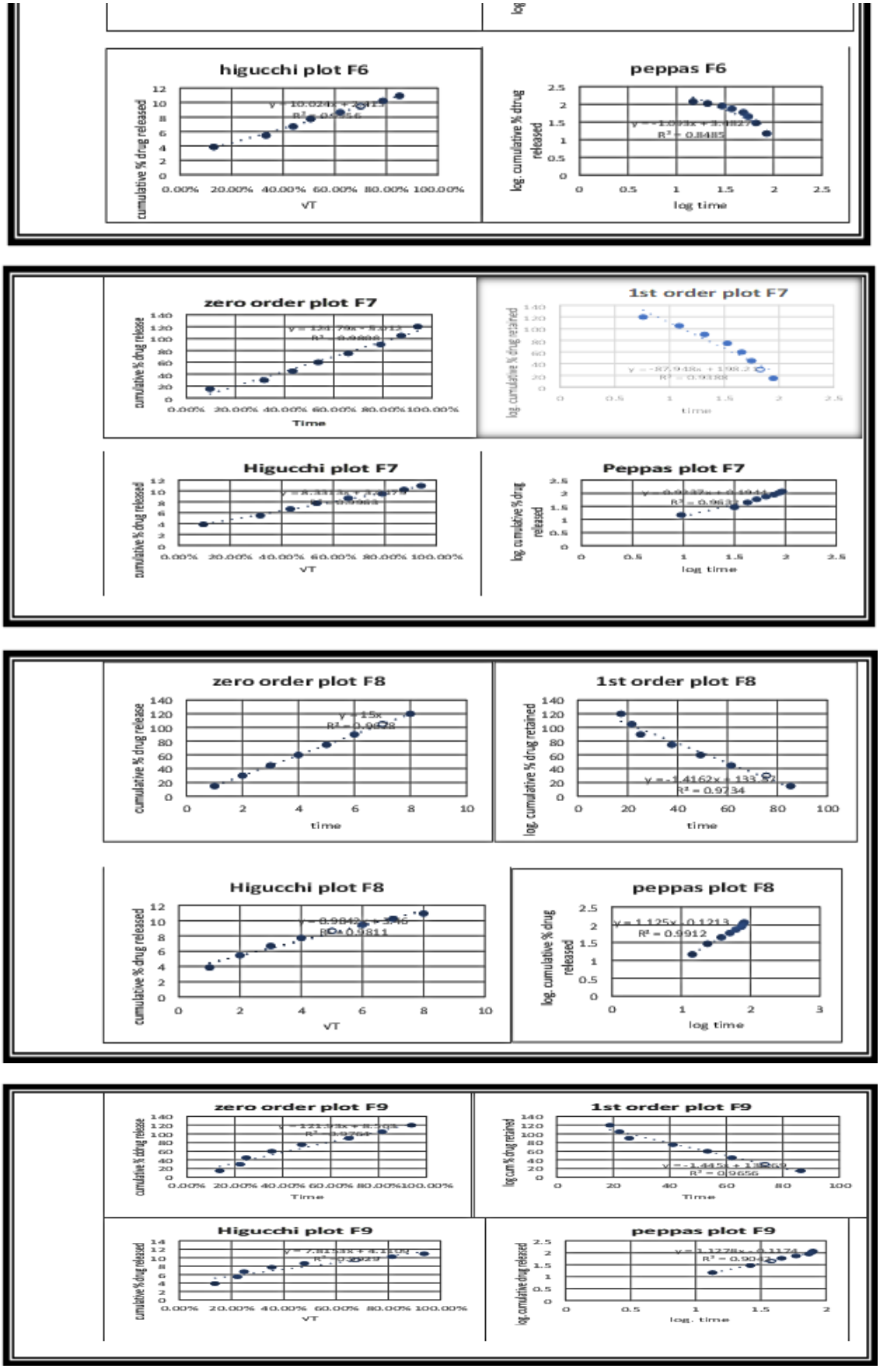


Figure 10: Kinetic drug release study for F1to F9 formulation.

Table 5: *In vitro* drug release study.

Time in min	% Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	12.9%	9.0%	8.92%	12.70%	13.9%	13.11%	9.6%	14.72%	13.4%
30	22.25%	20.15%	13.38%	25.22%	25.65%	33.33%	31.69%	24.44%	26.39%
45	24.76%	29.31%	32.45%	39.96%	38.91%	43.91%	43.32%	38.53%	38.04%
60	35.39%	35.50%	45.85%	48.37%	60.84%	50.66%	53.65%	50.85%	46.64%s
75	47.91%	44.56%	54.68%	63.66%	79.39%	62.06%	65.89%	62.35%	58.89%
90	67.57%	53.59%	65.31%	73.87%	86.98%	70.02%	79.10%	74.88%	74.35%
105	81.46%	68.83%	82.06%	87.03%	95.35%	78.72%	87.50%	78.39%	77.85%
120	93.74%	78.90%	94.02%	98.21%	98.93%	85.09%	94.14%	82.66%	81.18%

Melting point

It was found that the melting point of dorzolamide was 284.4°C.

Analysis of FTIR Spectroscopy

In an IR study, it was discovered that the sample's peaks and the dorzolamide reference spectra from IP had similar peak heights. Similar wavenumber range peaks are visible in the scan as in the reference spectra. It was therefore expected that the sample would be found to be pure dorzolamide and suitable for use in further research.[22-25]

Evaluation of liposomes

Kinetic drug release study for F1 to F 9 formulation.

CONCLUSION

In this study, the potential of liposomes as a drug vehicle for the ophthalmic delivery of dorzolamide was investigated. Nine liposomal formulations have been designed and optimized. Physical characterization revealed that liposomes embedded *in situ* ocular gel are suitable for ocular administration, with an encapsulation efficiency of 90%. The formulations stored at +4°C were stable for two months and greater chemical stability was obtained with the HA coating. Liposomes guarantee a prolonged and gradual release and they improve the residence time of the drug into the eye and also enhance the bioavailability of the drug by enhancing the corneal penetration of the drug.

Finally, the *in vitro* uptake study, conducted with fluorescent liposomes, showed that liposomal formulations increased the absorption at the cellular level and, in particular, at nucleus level, when tested in the corneal and conjunctival cells, with the most marked effect for HA-coated liposomes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

%: Percentage; **EE%:** Percentage entrapment efficiency; **DC%:** Percent Drug Content; **µg:** Microgram; **ml:** Milli litre; **nm:** Nanometer; **FTIR:** Fourier Transform Infra-red; **Kg:** Kilogram; **cm:** Centimeter; **IR:** Infra red; **rpm:** Revolution per minunte; **SEM:** Scanning electron microscopy; **TEM:** Transmission electron microscopy; **PBS:** Phosphate buffer saline; **°C:** Degree Celsius; **v/s:** Versus; **UV:** Ultra violet; **g:** Gram; **µ:** Micron; **hr:** Hour.

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