Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 18s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Development and Assessment of an In-Situ Gel for Ocular Drug Administration

Vishal Dubey[1], Akhilesh Pal[2], Rahul Pandey[3], Megha Tiwari[4], Archan Gupta[5]

[1,2 3,4,5] Naraina Vidyapeeth Group of Institutions, Faculty of Pharmacy, Panki, Kanpur.

Cite this paper as: Vishal Dubey, Akhilesh Pal, Rahul Pandey, Megha Tiwari, Archan Gupta, (2025) Development and Assessment of an In-Situ Gel for Ocular Drug Administration. *Journal of Neonatal Surgery*, 14 (18s), 1298-1310.

ABSTRACT

Ophthalmic preparations are specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside the eye (intraocular) or adjacent to it (periocular, e.g., juxta scleral or subtenant), or used in conjunction with an ophthalmic device. The aim of the current study was to create an n-situ gel preparation i.e. sol to gel forming capability that would be able to maintain medication delivery to the eyes for extended time period without loss of drugs. the approach will be effective in treating infectious conditions such bacterial and viral infection, acute and sub-acute conjunctivitis and kerato conjunctivitis. Gellan gum and carbapol 934p were used as polymer in the creation of the gelling system. The various concentration of polymer used in formulation. All formulation were evaluated for clarity, pH, gelation duration, temperature gelling capacity in vitro study. Pre-formulation study of drug (acyclovir)Appearance -Order less Light white crystalline powder as reported in Literature.

1. INTRODUCTION

Ophthalmic preparations are specialized dosage forms designed to be instilled onto the external surface of the eye (topical), administered inside the eye (intraocular) or adjacent to it (periocular, e.g., juxta scleral or subtenant), or used in conjunction with an ophthalmic device [1]. The latter include preparations used in conjunction with surgical implantation (such as an intraocular lens) and dry eye formulations compatible with a punctual appliance (e.g., a punctual plug), and extends to a variety of solutions used in the maintenance of contact lenses [2]. The preparations may have any of several purposes (e.g., therapeutic, prophylactic, or palliative for topically administered agents) but include mechanical, chemical, and biochemical actions of agents used in the care of ocular appliances and tissue prophylaxis during or following surgery [3-7]. Because of the dangers associated with the administration or repetitive administration of intraocular and periocular preparations, their suitability is restricted to therapeutic applications or surgical adjuncts [8-11].
The versatility of dosage forms of ophthalmic preparations allows the clinician to choose the form most suitable for the function desired [12-14]. Therapeutically active formulations can be designed to provide extended action for convenience or for reduction in risk of repetitive administration, improved bioavailability of the agent, or improved delivery to a targeted tissue. The residence of an ocular preparation can range from the few seconds needed for tears to clear an irritating substance; two hours for a gel, a gel-forming solution, or an ointment; to months or years for an intraocular or periocular dosage form. A preparation may be strictly therapeutic or may serve in prophylaxis. The latter includes surgical adjuncts to maintain the health of fragile cells, and postsurgical or post-trauma preparations designed to prevent or reduce the likelihood of infection. Another form of prophylaxis, one for a device, is the antisoiling function provided by some contact lens solutions [15-20].

2. IMPORTANCE OF IN-SITU GELLING SYSTEM:

In-situ gels promote the controlled and sustained release of the drug because of its special 'Sol-Gel transition.' after administration. Because of the sustained release of drug frequency of drug administration and the dose of a drug can be reduced. Accuracy of dosing and controlled release of drugs from in-situ gels results in no drug accumulation and no side effects. Significant increases in bioavailability and reduction in dose of a drug.
The increased residence time of the drug and increased contact of the drug with tissue due to gel formation. Accurate and reproducible doses delivery is possible with in situ gels unlike conventional gel formulations. In-situ gel systems show ease of administration because of their physical form which results in improving patient compliance and comfort [67].

3. APPROACHES OF IN-SITU GEL DRUG DELIVERY

There are three broadly defined mechanisms used for triggering the in-situ gel formation: Physiological stimuli, physical changes in biomaterials, and chemical reactions. In-situ formation based on physical mechanism: Diffusion: Diffusion is the type of physical approach used in in-situ gel formulations. This method involves the release/ diffusion of solvent from a polymer solution to surrounding tissue resulting in Precipitation or Coagulation of polymer matrix. Swelling: In-situ formation can also occur when a material absorbs water from the surrounding environment and expand to occur desired space. In this method, the polymer absorbs surrounding fluids that are present in the exterior environment and swell to release the drug slowly. In-situ formation based on physiological stimuli: Thermally trigged system: Temperature-sensitive hydrogels are probably the foremost commonly studied class of environment-sensitive polymer systems in drug formulation development. The use of polymers, where the transition from sol-gel is caused by increased temperature, is an attractive way to approach in-situ formation. The ideal critical temperature range for such systems is ambient and physiological temperatures, facilitating clinical manipulation and requiring no external heat source other than the body to gel the trigger. The useful system must be adjustable to account for small differences in local temperature that may be encountered on the surface of the skin or the appendages in the oral cavity. There are three main strategies for the formation of temperature-responsive sol-gel polymer systems. For convenience, temperature-sensitive hydrogels are classified into negative heatsensitive, positive heat-sensitive, and heat-reversible gels. Negative temperature-sensitive hydrogels have a low critical solution temperature (LCST) and shrink when heated above the LCST. Polymers with a low critical temperature (LCST) transition between ambient and physiological temperatures are used for this purpose. One of the most widely studied polymers showing useful LCST transitions is poly N-isopropyl acrylamide (PNIPAAm). Positive temperature-sensitive hydrogels have an upper critical solution temperature (UCST) and such hydrogels shrink when cooled below UCST. The polymer network of polyacrylic acid (PAA) and polyacrylamide (PAAm) or poly acrylamide-co-butyl methacrylate has a positive temperature dependence of swelling. These polymers exhibit miscibility gaps at high or low temperatures and have upper or lower critical solution temperatures. pH triggered systems: In these systems solution to gel transition is triggered by pH change. All pH-sensitive polymers contain additional acidic or basic groups that accept or release protons in response to changes in environmental pH. Polymers with many ionizable groups are known as polymer electrolytes. The polyelectrolytes are present in the formulation causes an increase in external pH that leads to swelling of hydrogel that forms in-situ gel. Swelling is dependent upon the external pH and functional group present on the hydrogel. For weakly acidic (anionic) groups hydrogel swelling increases with increasing external pH on the other hand it decreases with weakly basic (cationic) groups. Most anionic pH-sensitive polymers are based on PAA (Carbopol®, carbomer) or its derivatives. Similarly, a low viscosity polyvinylacetal diethylaminoacetate (AEA) solution at pH 4 forms a hydrogel at neutral pH conditions. Drugs prescribed in liquid solutions have some limitations, including limited bioavailability and a tendency to be easily removed by tears. Low pH of the PAA solution was found to damage the surface of the eye before it was neutralized by tears.

4. OBJECTIVES OF RESEARCH

The aim of the current study was to create an n-situ gel preparation i.e.sol to gel forming capability that would be able to maintain medication delivery to the eyes for extended time period without loss of drugs.the approach will be effective in treating infectious conditions such bacterial and viral infection,acute and sub-acute conjunctivitis and kerato conjunctivitis.
To prepare and evaluate in-situ gel gelling capability of various polymeric solution.
To incorporate drug in optimized range of polymeric solutions (based in-situ gelling capability).
To perform evaluation studies of various formulations.

The following goals were established-
Pre-formulation Studies of drug
-Physicochemical properties of drug determined.
1. Lamda max determinbation.
2. Solubility.
3. melting point.
4. IR spectra of pure drug.
5. Development of standard curve for the drug.

Drug Excipient interaction study
IR spectra of Drug excipient compared with IR spectra of pure drug and reference to establish compatibility between drug and excipient.

Formulation Phase
Selection of polymers for formulation.
Optimization of Polymer concentration range

Incorporation of drug in optimized polymeric solution concentration range.
Evaluation of formulated batches.

5. METHODS AND MATERIALS

List of chemicals:

S.no.	Chemicals Required
1.	Gellan gum
2.	Carbopol 934p
3.	Methyl paraben
4.	Sodium chloride
5.	Sodium bicarbonate
6.	Calcium chloride dihydrate
7.	Potassium Chloride

List of Instruments:

S.no.	Instruments Required
1.	pH meter
2.	FTIR
3.	IR
4.	HPLC
5.	Weighing balance
6.	Auroclave
7.	Uv spectroscopy
8.	Melting point

6. DRUG & POLYMER PROFILE

ACYLOVIR

Acyclovir is active against herpes group of virus; H. simplex type 1 is the most sensitive followed by the H. simplex type II> varicella-zoister =Epstein-bar virus; Cytomegalovirus (CMV) is practically not affected .the prototype antiviral agent used to treat various types of herpes infections. Since, acyclovir was the first antiviral to be considered the gold standard for the treatment of herpes infections, all other anti herpes virus medications are compared to it. It is approved for the prophylaxis of herpes genitals.

Synonyms: Acyclovir, Acyclovirum ,Acyclogunosine, Aciclovir, Zovir

Brand Names

Sitavig, Xerese, Zovirax

A. Chemical name: 9 – [(2 hydroxyethoxy) methyl] -9H- guanine 2-amino-1, 9-dihydro-9-[(2- hydroxyethoxy) methyl]-6H-purin-6-one.

B. Structural formula:

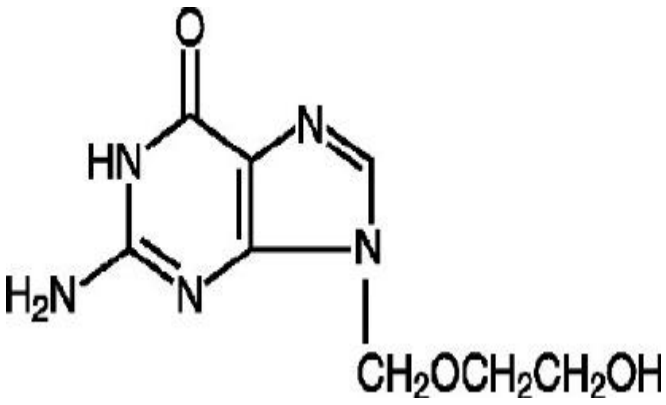
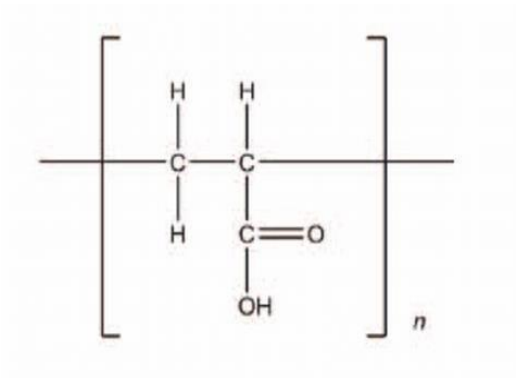


Fig: Structure of Acyclovir

Polymers

Carbopol934p

Synonyms: Acritamer,Acrylic acid polymer,Carbapol ,Carboxy polyethylene , polyacrylic acid ,carboxyvinyl polymer, pemulen, Ultrez.
Functional category: Bio adhesive ,emulsifying agent, release modifying agent, suspending agent, tablet binder, viscosity increasing agent,

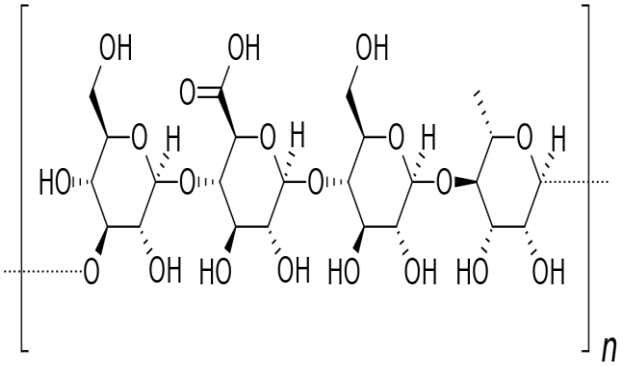


Structure of carbapol934p

Chemical name: Prop-2-enoic acid
Molecular formula:C3H4O2
Molecular weight: About 50000gm
Melting point: Decomposition occurs within 30 min at.260°C
Density:1.4 g/cm cube
Appearance: White to off white, odourless powder.
pH-5.0-70
Applications: Carbopol are mainly used in liquid or semisolid pharmaceutical formulation as suspending or viscosity-increasing agents.
Formulations: Include creams, gel and ointments for use in ophthalmic, rectal and topical preparation, carbopol are also used in cosmetics', therapeutically, carbopol formulations have proved efficacious in improving symptoms.
Solubility: Soluble in water and after neutralization in ethanol (95%) and glycerine. Although they are described as soluble ,carbopol do not dissolve but merely swell to a remarkable extent,since they are three- dimensionally cross likked micro gels .

Gellan gum
A water-soluble anionic polysaccharide called gellan gum is made by the bacterium Sphingomonas elodea (formerly Pseudomonas elodea based on the taxonomic classification at the time of its discovery). [1] The lily plant tissue from a Pennsylvania natural pond was used to find and isolate the gellan-producing bacterium by the former Kelco Division of Merck & Company, Inc. in 1978. It was initially discovered as a replacement gelling agent for agar in solid culture media for the growth of different microorganisms at a much lower use level. [2] Its initial commercial product, which bore the name Gelritegellan gum, was later discovered to be a good agar alternative as a gelling agent in several clinical bacteriological media. [3]

Chemical structure



Gellan gum structure

Molecular formula-Te+
Molecular weight-127.6
Chemical name-Gellan gum
Melting point-No

Melting point of acyclovir-

Melting point equipment was used to determine the melting point of acyclovir. Firstly picked a little capillary tube and sealed one end of it. The material was filled into capillary tubes and allowed to rise to a height of 0.5 cm. The sample-containing capillary tube was then put into the equipment' sample holder. Finally, the melting point range was noticed by thermometer**.**

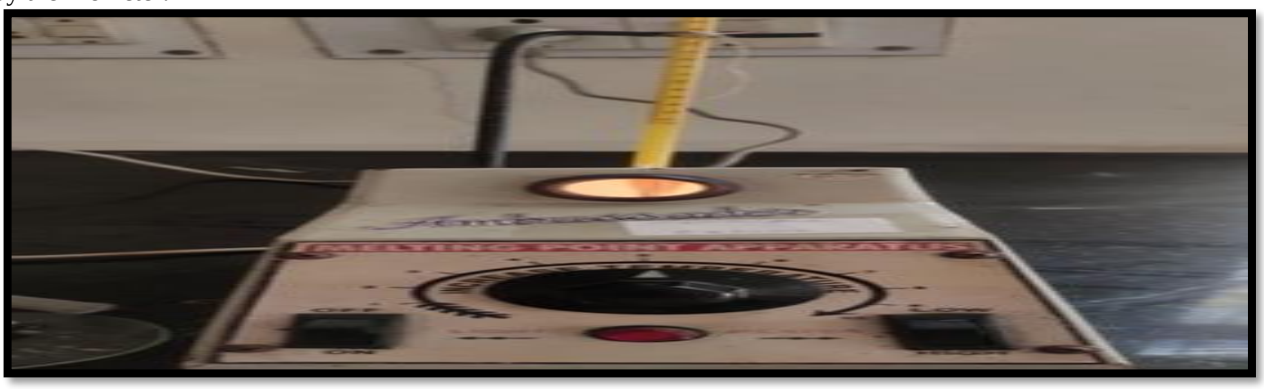


Fig no .1 Ambassador apparatus

Table no1.Melting point

S.no	Properties (drug)	Reported	Observed	Mean
1	Acyclovir	256.5 ℃	258-260℃	259
			257-258℃	
			257-260℃	

Solubility of Acyclovir-

Solubility studies ware done by equilibrium solubility method. According to this method, the pure acyclovir was added to different solvent medium and shaken for 24h.The saturation was confirmed by observation of presence of undissolved material. After centrifugation of the slurry .sample was analysed using UV visible spectrophotometer at lambda 252 nm.

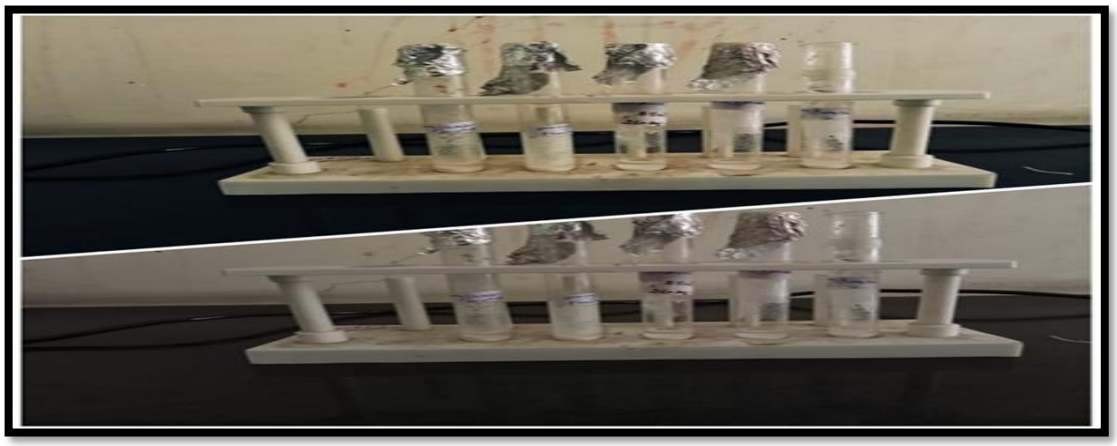


Fig no - Solubility of drug

Table no. Solubility of drug

S.no	Solvent	Volume required (ml)	Solubility
1	Water	6.5ml	Slightly soluble
2	Ethanol	30ml	Insoluble
3	Methanol	6.5ml	Insoluble
4	Phosphate buffer	7.5ml	Soluble

Partition coefficient -

Separating funnel method was used for determination of partition coefficient of acyclovir. This is a classical and most reliable method of log P determinations. Partition coefficient is a measurement of drug. Partition coefficient of acyclovir was taking 50 ml of benzene and 50 ml water. about 5mg of drug added to this solution and was shaken. after shaking the system remained undisbisburbed for 24 hrs. Two layer was separate through Whitman flter, and the amount of acyclovir

solubilised, was determined by measuring the absorbance at 252nm against regent blank through double beam UV spectrometer in both the solution. partition coefficient was determined as ratio of concentration of drug in acyclovir to the concentration of drug in phosphate buffer (pH7.4) and the value were reported as log P.

$$\text{Log P} = \frac{\text{Conc. Of drug in Aq. phase}}{\text{Concentration of drug in Aq. phase}}$$

Log P =Log 10 (partition coefficient)

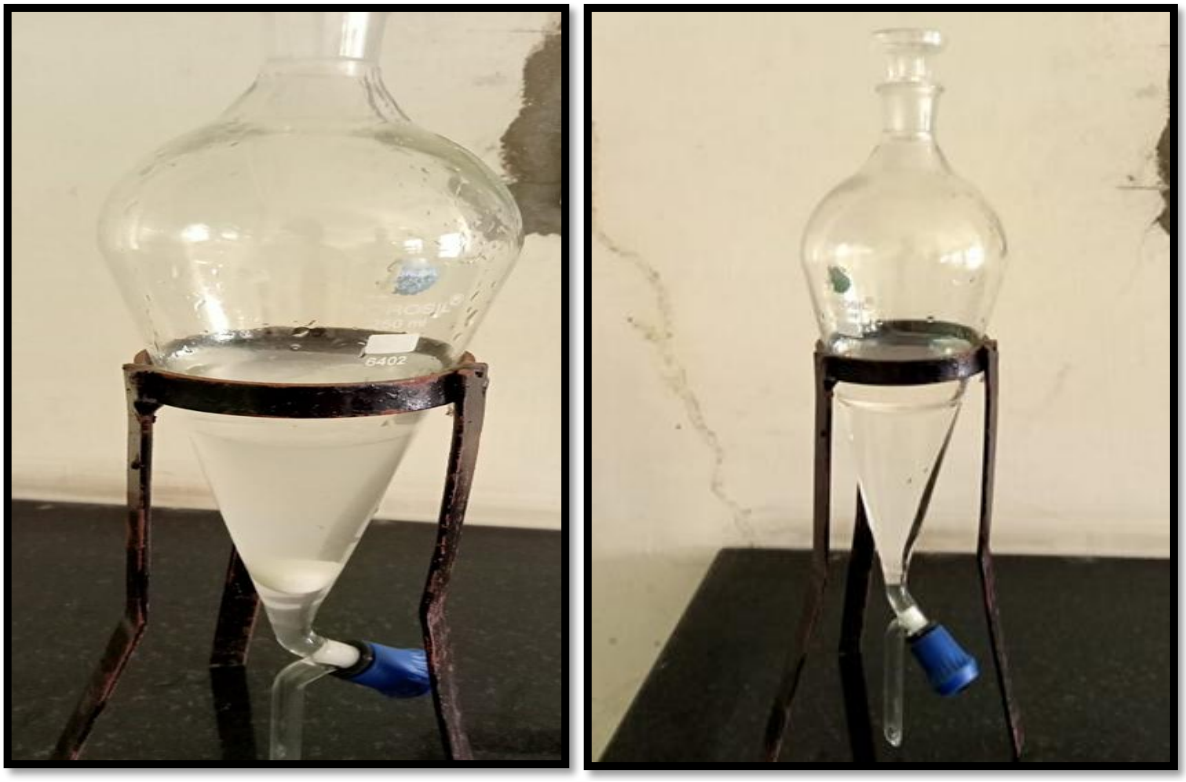


Fig no -Partition coefficient

Preparation of Calibration curves-

Preparation of calibration curve of acyclovir in Distilled water

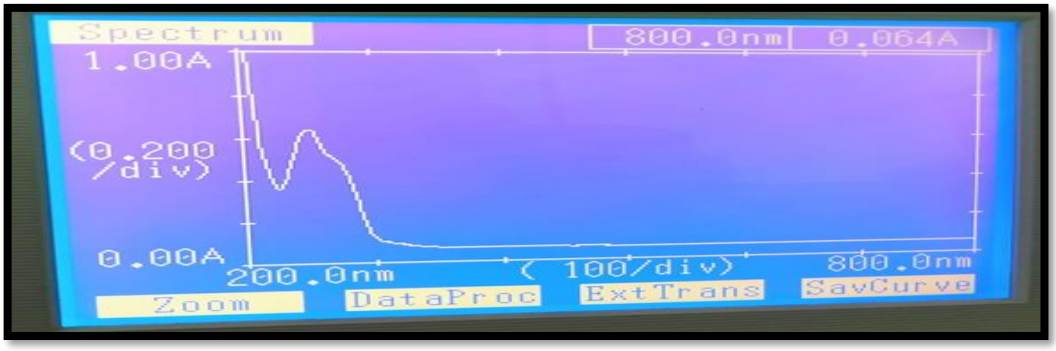
Accurately weighed quantity of acyclovir (10mg) was taken in 100 ml volumetric flask.It was dissolved in an adequate amount of distilled water and the volume was made upto 100 ml to obtain a stock solution of 100µg/ml .From the above stock solution appropriate dilutions were made in distilled water the concentration rang of 2,4,6,8 and 10µg/ml and absorbance was taken at ʎmax 252nm.

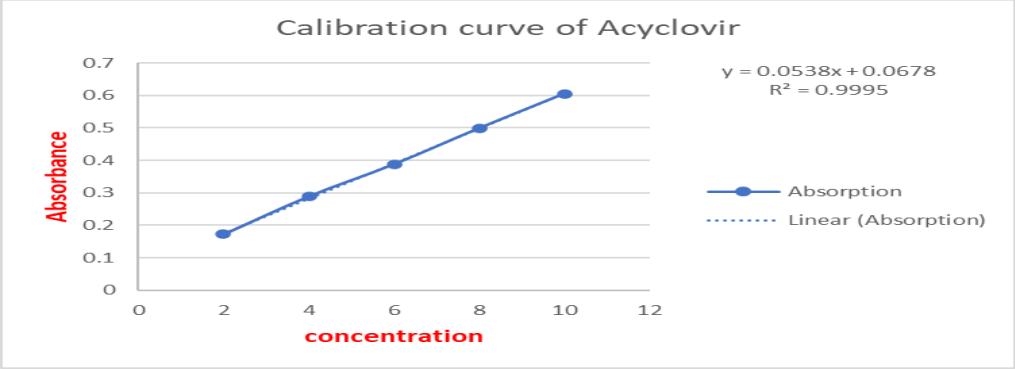
Table no :Acyclovir calibration curve distilled water

S. no	Concentration (µg/ml)	Absorbance(252nm)
1	0.2µg/ml	0.172
2	0.4µg/ml	0.269
3	0.6µg/ml	0.388
4	0.8µg/ml	0.509
5	10µg/ml	0.680

Calibration Curve of drug had to be performed by UV. Spectroscopy

Absorption maxima of Acyclovir were found to be at 252nm.

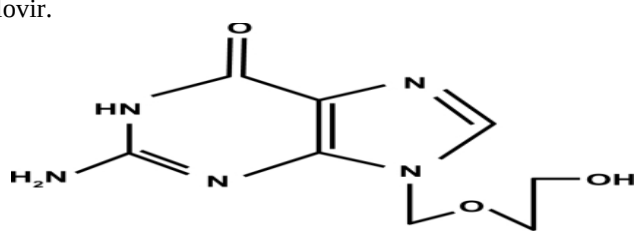




7. FTIR OF ACYCLOVIR-

This study was executed to check the compatibility of API and excipients in the final formulation. The analysis was executed in shimadzu-IR affinity spectrophotometer. The IR spectra of the sample were obtained using Kbr pellet, prepared with hydraulic press with small amount of each sample after careful grinding of each sample with Kbr. The spectral width was 400-4000cm-1

The FT-IR spectrum of the procured sample of the pure acyclovir obtained from shimadzu and was compared with the standard FT-IR spectra of pure acyclovir.



Spectral (FTIR) Analysis of acyclovir-

On comparing the IR spectrum of sample (Acyclovir) and reference spectrum, it was observed that all characteristic peak of drug was found as shown in fig.

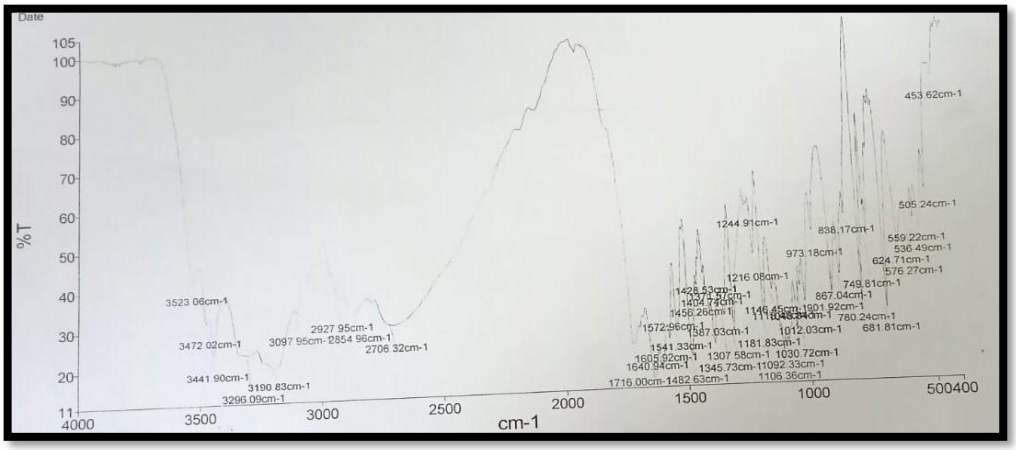


Fig no: FTIR of Acyclovir drug

Result and discussion

Gellan gum and carbapol 934p were used as polymer in the creation of the gelling system. The various concentration of polymer used in formulation .All formulation were evaluated for clarity, pH, gelation duration, temperature gelling capacity in vitro study.

Pre-formulation study of drug (acyclovir)

Appearance -Order less Light white crystalline powder as reported in Literature.

Melting point of acyclovir was determined by open capillary method. The melting point of acyclovir was found to be 258 degree Celsius. The value indicated identity and purity of the drug sample.

Fig- Melting point

S.no.	Reported(°C)	Observed	Mean(°C)
1-	256.5°C	258-260	259°C
2-		257-258	
3-		257-260	

Solubility

Solubility of the sample was found to be 0.1 microgram per ml solubility in different solvent such as water, phosphate buffer, methanol and ethanol.

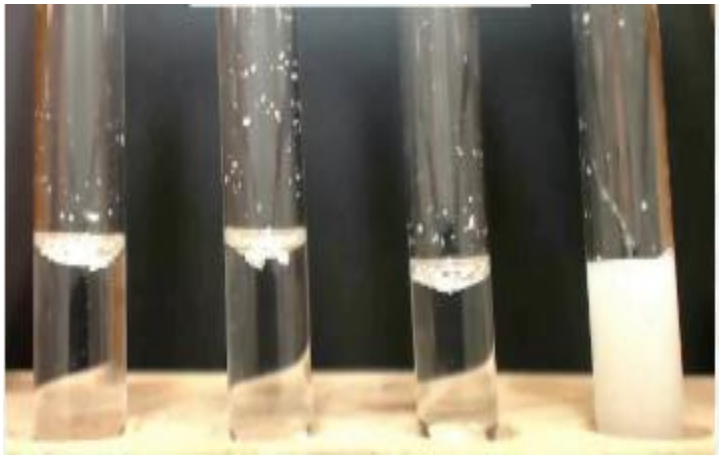


Fig : Solubility

S.no.	Solvent	Volume required (ml)	Solubility
1.	Water	653ml	Slightly soluble
2.	Ethanol	32562ml	Insoluble
3.	Methanol	45367ml	Insoluble
4.	Phosphate buffer	24ml	soluble

Analytical method development for acyclovir by UV visible spectrophotometer

UV Spectroscopy method was developed for the analysis of acyclovir using double beam shimadzu 1700 UV spectroscopy

Identification of drugs by UV spectroscopy

The acyclovir was identified by UV Spectroscopy method. The acyclovir exhibited maximum absorption at 252 respectively. These wavelength were considered as λmax for samples and all the observation by UV spectrophotometer to calculate the amount of drug were taken at this wavelength.

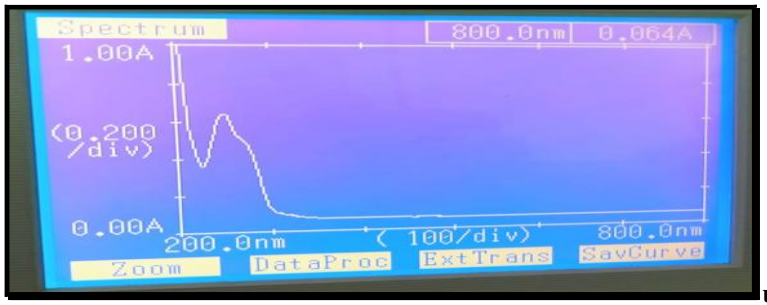
Standard curves of acyclovir

The standard curve of acyclovir was prepared in distilled water and result depicted in table.

The calibration curve was draw for acyclovirin distill water and its shows straight line in range of concentration from 2, 4, 6, 8, & 10 microgram per ml with R^2 value of drugs like 0.9995 respectively , indicating good linearity as shown in figure which follow beer-lambert law in the concentration range 2-10µg.

Table calibration curve of acyclovir in phosphate buffer at 7.4pH

S.no.	Concentration	Absorption at 252nm
1.	**2** µg/ml	**0.172**
2.	**4** µg/ml	**0.289**
3.	**6** µg/ml	**0.388**
4.	**8** µg/ml	**0.499**
5.	**10** µg/ml	**0.605**



ul

Fig:Calibration Curve of drug had to be performed by UV. Spectroscopy

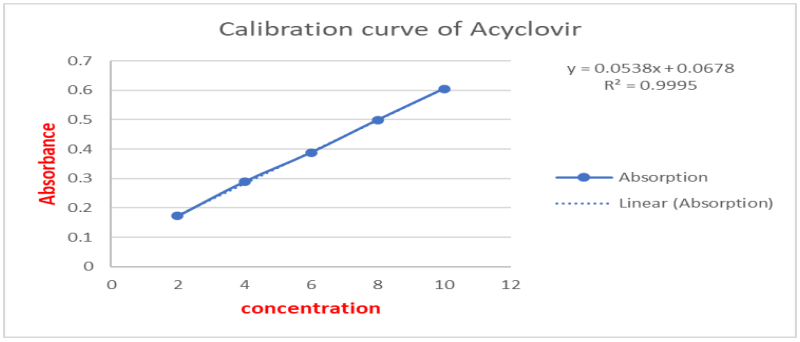


Fig: Calibration curve of acyclovir

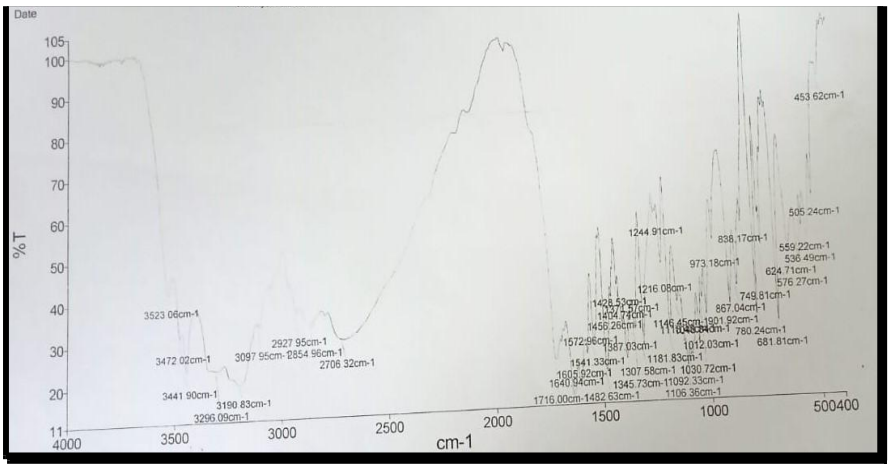


Fig: FTIR Spectra of acyclovir (API)

Table IR characterization of acyclovir

S.no.	Functional group	References Wave no.(cm-1)	Observed wave no.
1.	OH hydroxyl	3500	3523
2.	C=O carbonyl	1695	1640.94
3.	NH2 amino group	3282	3296.09
4.	C=N	1487	1482.63
5.	C-N	1185	1181.83

Table clarity test of various formulations-

Formulation code	colour
F1	White transparent
F2	Off white
F3	White
F4	White
F5	Light white

pH of In-situ gel: the pH of all formulation were determined by pH meter. All formulations were in pH range 6.5-7.4.

Fig : pH

Table pH result of formulated batches-

Formulation code	pH range (Average)
F1	6.5
F2	6.9
F3	7.4
F4	6.6
F5	7.0

Viscosity and rheological studies:

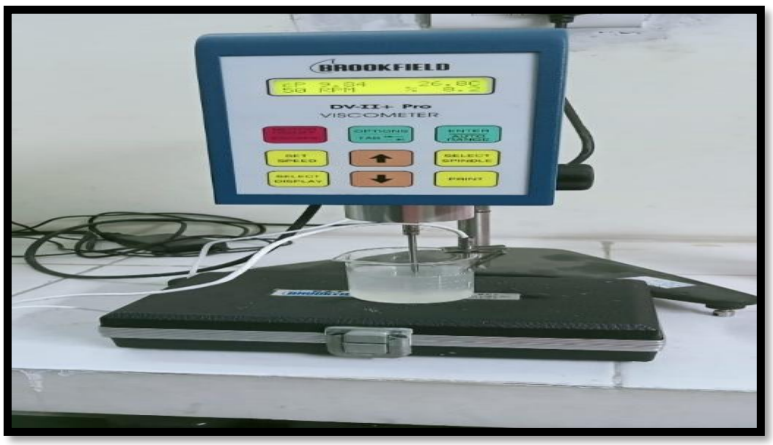


Fig: Image of Brookfield viscometer

Table viscosity of various formulated batches at 35°C.

S.no.	Spindle no.	Rpm 50	Viscosity (°C)
F1	64	50	6.36
F2	64	50	9.98
F3	64	50	13.7
F4	64	50	15.1
F5	64	50	27.0

Time in (min)	F1	F2	F3	F4	F5
5	5.85	4.32	6.41	5.01	5.15
15	12.55	12.13	13.80	11.43	11.84
25	20.21	21.19	23.84	19.09	19.79
35	29.00	32.06	36.11	30.25	30.80
45	39.45	46.84	50.46	44.47	45.02
60	53.53	68.03	70.26	54.50	51.71

8. CONCLUSION

1-pre-formlation studies of Acyclovir revealed that the supplied drug matched all the criteria of drug (API) i.e.. reported literature values (limits) je max (252nm). M.P (2590) Partition coefficient (50ml), Solubility study in various solvents (water-653ml. ethanol-32562ml, methonal-45367, phosphate buffer-24ml)
2. The normal eye drops have very poor bioavailability due to which drug is rapidly washed out from the eye. Such problems can be overcome by modifying the formulation of drug to in-situ gel ophthalmic solutions.
3-FTIR studies showed that all characteristic peaks (OH-3523cm, C-01640.64 cm^2, NH2-3296.0.9 cm^2. C-N-1482.63 cm, C-N-1482 cm) of drugs were found in IR spectra of drug mixture. Therefore, Study revealed there no chemical interaction between drug and selected excipients.
4. Various formulations (In-situ gel) were prepared by using cold method and evaluated for various studies such as pH (ranged,6.2-7.4), viscosity (rang 6.3-27.0°C), clarity (light white to white), drug content uniformity (between 89.01-97.06) and % release (51-71 to 70.26 for 60 min).
5. On the basis of various evaluation studies of Formulation F3 was considered as best batch as it had pH (7.4°C), viscosity (13.7°C), drug content uniformity (97.06%), % release (70.26%).
6. In-situ gel formulation for could be a better approach for eye infection as in-situ gelation of formulation improved duration of action up to 10 hours which was comparatively longer periods than marketed eye drops with reduced number of administration frequency.

REFERENCES

[1] Addo E, Bamiro OA, Siwale R. Anatomy of the eye and common diseases affecting the eye. In: Addo RT, editor. Ocular drug delivery: Advances, challenges and applications. 2016. pp. 11–25. [Google Scholar]

[2] Joseph RR, Venkatraman SS. Drug delivery to the eye: what benefits do nanocarriers offer. Nanomedicine (Lond) 2017;12(6):683–702. doi: 10.2217/nnm-2016-0379. [DOI] [PubMed] [Google Scholar]

[3] Zhu M, Wang J, Li N. A novel thermo-sensitive hydrogel-based on poly(N-isopropylacrylamide)/ hyaluronic acid of ketoconazole for ophthalmic delivery. Artif Cells Nanomed Biotechnol. 2017 doi: 10.1080/21691401.2017.1368024. [DOI] [PubMed] [Google Scholar]

[4] Bisht R, Mandal A, Jaiswal JK, Rupenthal ID. Nanocarrier mediated retinal drug delivery: overcoming ocular barriers to treat posterior eye diseases. WIREs Nanomed Nanobiotechnol. 2018 doi: 10.1002/wnan.1473. [DOI] [PubMed] [Google Scholar]

[5] Makwana SB, Patel VA, Parmar SJ. Development and characterization of in-situ gel for ophthalmic formulation containing ciprofloxacin hydrochloride. Results Pharma Sci. 2016;6:1–6. doi: 10.1016/j.rinphs.2015.06.001. [DOI] [PMC free article] [PubMed] [Google Scholar]

[6] Kaur IP, Smitha R. Penetration enhancers and ocular bioadhesives: two new avenues for ophthalmic drug delivery. Drug Dev Ind Pharm. 2002;28(4):353–369. doi: 10.1081/ddc-120002997. [DOI] [PubMed] [Google Scholar]

[7] Bamiro OA, Ubale RV, Addo RT. Background of Ocular Drug Delivery. In: Addo RT, editor. Ocular drug delivery: Advances, challenges and applications. Springer International Publishing; 2016. pp. 1–9. [Google Scholar]

[8] Kotreka UK, Davis VL, Adeyeye MC. Development of topical ophthalmic in situ gel-forming estradiol delivery system intended for the prevention of age-related cataracts. PLoS One. 2017;12(2) doi: 10.1371/journal.pone.0172306. [DOI] [PMC free article] [PubMed] [Google Scholar]

[9] Ye T, Yuan K, Zhang W. Prodrugs incorporated into nanotechnology-based drug delivery systems for possible improvement in bioavailability of ocular drugs delivery. Asian J Pharmaceut Sci. 2013;8(4):207–217. [Google Scholar]

[10] Liu Y, Liu J, Zhang X, Zhang R, Huang Y, Wu C. In situ gelling gelrite/alginate formulations as vehicles for ophthalmic drug delivery. AAPS PharmSciTech. 2010;11(2):610–620. doi: 10.1208/s12249-010-9413-0. [DOI] [PMC free article] [PubMed] [Google Scholar]

[11] Tan G, Yu S, Pan H. Bioadhesive chitosan-loaded liposomes: a more efficient and higher permeable ocular delivery platform for timolol maleate. Int J Biol Macromol. 2017;94(Pt A):355–363. doi: 10.1016/j.ijbiomac.2016.10.035. [DOI] [PubMed] [Google Scholar]

[12] Addo RT, Yeboah KG, Siwale RC. Formulation and characterization of atropine sulfate in albumin-chitosan microparticles for in vivo ocular drug delivery. J Pharm Sci. 2015;104(5):1677–1690. doi: 10.1002/jps.24380. [DOI] [PubMed] [Google Scholar]

[13] Biswas GR, Majee SB. Niosomes in ocular drug delivery. Eur J Pharmaceut Med Res. 2017;4(7):813–819. [Google Scholar]

[14] Prausnitz MR, Jiang J, Pate SR. 2007. Ocular drug delivery using microneedles; p. 3191. ARVO Annual Meeting. [Google Scholar]

[15] Duan Y, Cai X, Du H, Zhai G. Novel in situ gel systems based on P123/TPGS mixed micelles and gellan gum for ophthalmic delivery of curcumin. Colloids Surf B Biointerfaces. 2015;128:322–330. doi: 10.1016/j.colsurfb.2015.02.007. [DOI] [PubMed] [Google Scholar]

[16] Malavade S. Overview of the ophthalmic system. In: Pathak Y, Sutariya V, Hirani AA, editors. Nano-Biomaterials for ophthalmic drug delivery. Springer International Publishing; 2016. pp. 9–35. [Google Scholar]

[17] Almeida H, Amaral MH, Lobao P, Lobo JM. In situ gelling systems: a strategy to improve the bioavailability of ophthalmic pharmaceutical formulations. Drug Discov Today. 2014;19(4):400–412. doi: 10.1016/j.drudis.2013.10.001. [DOI] [PubMed] [Google Scholar]

[18] Weng Y, Liu J, Jin S, Guo W, Liang X, Hu Z. Nanotechnology-based strategies for treatment of ocular disease. Acta Pharm Sin B. 2017;7(3):281–291. doi: 10.1016/j.apsb.2016.09.001. [DOI] [PMC free article] [PubMed] [Google Scholar]

[19] Huang D, Chen YS, Rupenthal ID. Overcoming ocular drug delivery barriers through the use of physical forces. Adv Drug Deliv Rev. 2017 doi: 10.1016/j.addr.2017.09.008. [DOI] [PubMed] [Google Scholar]

[20] Achouri D, Alhanout K, Piccerelle P, Andrieu V. Recent advances in ocular drug delivery. Drug Dev Ind Pharm. 2013;39(11):1599–1617. doi: 10.3109/03639045.2012.736515. [DOI] [PubMed] [Google Scholar]

[21] Khan N, Aqil M, Imam SS, Ali A. Development and evaluation of a novel in situ gel of sparfloxacin for sustained ocular drug delivery: in vitro and ex vivo characterization. Pharm Dev Technol. 2015;20(6):662–669. doi: 10.3109/10837450.2014.910807. [DOI] [PubMed] [Google Scholar]

[22] Li J, Zhao H, Okeke CI. Comparison of systemic absorption between ofloxacin ophthalmic in situ gels and ofloxacin conventional ophthalmic solutions administration to rabbit eyes by HPLC-MS/MS. Int J Pharm. 2013;450(1-2):104–113. doi: 10.1016/j.ijpharm.2013.04.018. [DOI] [PubMed] [Google Scholar]

[23] Devasani SR, Dev A, Rathod S, Deshmukh G. An overview of in situ gelling systems. Pharmaceut Biolog Evaluat. 2016;3(1):60–69. [Google Scholar]

[24] Cao Y, Zhang C, Shen W, Cheng Z, Yu LL, Ping Q. Poly(N-isopropylacrylamide)-chitosan as thermosensitive in situ gel-forming system for ocular drug delivery. J Control Release. 2007;120(3):186–194. doi: 10.1016/j.jconrel.2007.05.009. [DOI] [PubMed] [Google Scholar]

[25] Sheshala R, Kok YY, Ng JM, Thakur RR, Dua K. In situ gelling ophthalmic drug delivery system: an overview and its applications. Recent Pat Drug Deliv Formul. 2015;9(3):237–248. doi: 10.2174/1872211309666150724101227. [DOI] [PubMed] [Google Scholar]

[26] Laddha UD, Mahajan HS. An insight to ocular in situ gelling systems. Int J Adv Pharmaceut. 2017;06(02):31–40. [Google Scholar]

[27] Wei G, Xu H, Ding PT, Li SM, Zheng JM. Thermosetting gels with modulated gelation temperature for ophthalmic use: the rheological and gamma scintigraphic studies. J Control Release. 2002;83(1):65–74. doi: 10.1016/s0168-3659(02)00175-x. [DOI] [PubMed] [Google Scholar]

[28] Patel N, Nakrani H, Raval M, Navin S. Development of loteprednol etabonate-loaded cationic nanoemulsified in-situ ophthalmic gel for sustained delivery and enhanced ocular bioavailability. Drug Deliv. 2016;23(9):3712–3723. doi: 10.1080/10717544.2016.1223225. [DOI] [PubMed] [Google Scholar]

[29] Klouda L. Thermoresponsive hydrogels in biomedical applications: a seven-year update. Eur J Pharm Biopharm. 2015;97(Pt B):338–349. doi: 10.1016/j.ejpb.2015.05.017. [DOI] [PubMed] [Google Scholar]

[30] Almeida H, Amaral MH, Lobao P. Temperature and pH stimuli-responsive polymers and their applications in controlled and selfregulated drug delivery. J App Pharm Sci. 2012;2(6):1–10. [Google Scholar]

[31] Kamel A.; In vitro and in vivo evaluation of Pluronic F127- based ocular delivery system for timolol maleate; International Journal of Pharmaceutics; 2002; 24 (1): 47–55.

[32] Varshosaz J, Tabbakhian M, Salmani Z; Designing of a Thermo sensitive Chitosan/Poloxamer In Situ Gel for Ocular Delivery of Ciprofloxacin; The Open Drug Delivery Journal; 2008; 2: 61-70.

[33] Saini; In situ gels- a new trends in ophthalmic drug delivery systems, International Journal recent Advanced Pharmaceutical Research; 2015; 5 (3): 285-289.

[34] Peppas NA, Langer R; New challenges in biomaterials; Science; 1994; 263(154): 1715- 1720.

[35] Swapnil S; A Review on polymers used in novel in situ gel formulation for ocular drug delivery and their evaluation; Journal of biological and scientific opinion; 2003; 1(2): 132-137.

[36] Patel N, Rajesh K; ophthalmic in situ gel; Pharmagene; 2014; 1(4): 29-33.

[37] Pandya TP, Modasiya MK., Patel VM; Opthalmic in-situ gelling system; International Journal of Pharmacy & Life sciences ;) 2011; 2(5): 730-738.

[38] Jitendra PK, Sharma A, Banik, Dixit S; A new trend ocular drug delivery system. International. Journal. Of Pharmaceutical. Sciences; 2011; 2(3): 720-744.

[39] Nagyova B, Tiffany JM; Components responsible for the surface tension of human tears; Current Eye Research; 1999; 19(1): 4- 11.

[40] Jain R, Shastri P; Study of ocular drug delivery system using drug loaded liposomes; International. Journal. Of Pharmaceutical. Science Investigation; 2011; 1(1): 234-244.

[41] Abdelbary G; Niosome-Encapsulated Gentamicin for Ophthalmic Controlled Delivery; AAPS Pharm Sci Tech; 2008; 9(3): 740–747.

[42] Taban M, Lowder C, Kaiser Y; Outcome of Fluocinolone acetonide implant reimplantation for chronic non-infectious posterior uveitis; Retina; 2008; 2 (8): 1280–1288.

[43] Vandamme TF, Brobeck L; Poly(amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropic amide; Journal of Control Release; 2005; 102: 23- 38.

[44] Vandamme TF; Micro emulsions as ocular drug delivery systems: recent development and

[45] Al-Sayadi GMH, Verma A, Choudhary Y,Sandal P, Patel P, Singh D, et al. Solid Lipid Nanoparticles (SLNs): Advancements in Modification Strategies Toward Drug Delivery Vehicle. Pharm Nanotechnol. 2023;11(2):138- 54. doi: 10.2174/2211738511666221026163303.

[46]

[47] Vikal A, Maurya R, Bhowmik S, Patel P, Gupta GD, Kurmi BD. From Conventional to Cutting- Edge: A Comprehensive Review on Drug Delivery Systems. Drug Delivery Letters.2024;14:1-18. doi: http://dx.doi.org/10.2174/0122103031304556 240430161553.