International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 16, Issue 2, 2024

Original Article

PREFORMULATION STUDIES OF NIOSOMAL GEL CONTAINING DIPIVEFRIN HYDROCHLORIDE FOR ANTIGLAUCOMATIC ACTIVITY

NEERAJ JAIN[1*], ANURAG VERMA[2], NEELAM JAIN[3]

[1,2*]Teerthankar Mahaveer College of Pharmacy, TMU, Moradabad-244102, Uttar Pradesh, India. [3]University Institute of Pharmacy, Oriental University, Indore-452003, Madhya Pradesh, India
*Corresponding author: Neeraj Jain; *Email: jneerajdops@gmail.com

Received: 19 Aug 2023, Revised and Accepted: 13 Dec 2023

ABSTRACT

Objective: The present study was focused on developing and characterizing niosomal gel formulations for ocular controlled delivery of an adrenergic agonist; dipivefrin HCl. In the present study, the pre-formulation studies are showed towards the development of Novel formulation.

Methods: Preformulation studies of drug were carried out for identification (physical appearance, melting point and UV spectrophotometric analysis), solubility profile, lipophilicity (Partition Coefficient), compatibility studies by FTIR and thermal behavior by DSC.

Results: The melting point of dipivefrin HCl was found to be 147.6±3 °C. The log P value was found to be 3.14±0.02, from which it can be interpreted that drug is highly lipophilic in nature. The scanned λ_{max} were found to be 254 nm. No significant changes were found when FTIR spectra of the physical mixture compared with FTIR spectra of pure drug and excipients. This indicates absence of any possible interaction between the drug and excipients which confirms the identity and purity of drug. DSC thermogram of pure drug showed a sharp exothermic peak at 131.202 °C (area=1726.267 mJ, delta H=575.422 J/g), indicating the crystal melting point of the drug.

Conclusion: These results suggest that the dipivefrin HCl serve as suitable candidate for ocular drug delivery system.

Keywords: Dipivefrin hydrochloride, Preformulation, Ocular delivery, Spectrometric analysis, Compatibility

DOI: https://dx.doi.org/10.22159/ijpps.2024v16i2.49174. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps

INTRODUCTION

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form. This could provide important information for formulation design or support the need for molecular modification. Every drug has intrinsic chemical and physical properties, which has been consider before development of pharmaceutical formulation. This property provides the framework for drugs combination with pharmaceutical ingredients in the fabrication of dosage form. Objective of preformulation study is to develop the elegant, stable, effective, and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish physio-chemical parameter of new drug substances. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in the preformulation study. Thus, to ensure optimum condition for a clinically beneficial delivery system, preformulation studies were carried out. A thorough understanding of these properties ultimately provide a rational for formulation design. Characterization of drug and drug excipient compatibility studies were done in this phase to provide a useful support in development of dosage form [1].

Dipivefrin (DV) HCl, a prodrug of epinephrine (EP), is an adrenergic agonist and direct-acting sympathomimetic agent that is used to reduce IOP in patients suffering from chronic open angle glaucoma [2]. This drug acts through decreasing production and increasing the outflow of aqueous humor from the eye [3]. A controlled study proved the usefulness of topically applied DV (0.1%, w/v) over EP (2%, w/v) in reducing the IOP in patients who were intolerant to topically applied EP [4]. In terms of safety, DV is associated with less systemic adverse effects (e. g., cardiovascular side effects) compared to EP, since it is only needed in very small dose. Thus, DV is considered more suitable for ocular application as compared to EP, especially in patients with cardiovascular disorders [5]. In addition to the clinical benefits, DV has favorable physicochemical properties compared to EP. DV has an ideal lipophilicity and diffusivity across the lipophilic ocular dynamic and static barriers due to the esterification of the two hydroxide (-OH) functional groups of EP, yielding dipivaloyl-EP. This chemical modification allows DV to avoid the unfavorable physicochemical and biopharmaceutical characteristics of the EP [6]. Therefore, using DV in an ocular formulation will resolve the lipophilicity issue associated with EP and would provide a site-specific delivery with a 10-fold enhanced therapeutic efficacy compared to EP [7].

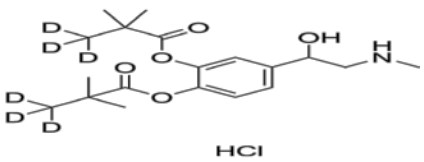

Fig. 1: Chemical structure of dipivefrin HCl

Delivering drugs via the ocular route is challenging due to the immediate tear-turnover rate and corneal impermeability, which restricts the ocular bioavailability of conventional topical eye drops or solutions. Therefore, there is a need for an appropriate ocular delivery system to achieve high trans-corneal permeation sustained and controlled delivery while providing sufficient ocular bioavailability [8]. These problems can be minimized using niosomal vesicular system.

Therefore, the current aim of the study was to investigate some of the important physicochemical properties of dipivefrin HCl, which can help to select subsequent approaches during the development of niosomal gel for ocular use.

Preformulation studies were carried out for identification (physical appearance, melting point and UV spectrophotometric analysis), solubility profile, lipophilicity (n-octanol-water partition-coefficient determination), spectrometric fingerprints and compatibility studies

by FTIR and thermal behavior analysis by DSC. The use of preformulation parameter maximize the chances of getting a formulation which is safe, efficacious, and stable product and at the same time provide optimization of the drug product quality [10].

MATERIALS AND METHODS

The dipivefrin HCl was kindly received as a gift sample by M/s Piramal Enterprises Ltd. (Digwal AP, India). Sorbitan monolaurate (span 20), sorbitan monosterate (span 60), sorbitan monooleate (span 80), cholesterol, locust bean gum and carbopol 934 were procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Isopropanol, methanol, acetone, chloroform, boric acid, sodium hydroxide, sodium bicarbonate, potassium chloride, glacial acetic acid, magnesium, sodium chloride, calcium chloride dehydrate, potassium dihydrogen phosphate and disodium hydrogen phosphate were purchased from were purchased from SD Fine chemicals (Mumbai, India). Double distilled water was used throughout the study.

The polymers used were locust bean gum and carbopol 934. The required quantity of these polymers was weighed and dispersed in a small amount of phosphate buffer saline pH 7.4 to prepare an aqueous dispersion and sterile in hot air oven at 1600 °C for 1 h. The aqueous dispersion was allowed to hydrate for 4-5 h. The pH was adjusted to 6 by addition of triethanolamine solution. The final weight of the gel was adjusted with phosphate buffer saline pH 7.4. Niosomal suspension containing drug was separated from aqueous medium by ultracentrifugation at 15000 rpm at 40 °C and was added gently by vortex in the sterile blank gel under laminar airflow cabinet. The solution was made isotonic with sodium chloride (0.9% w/v). Then, benzalkonium chloride (0.001% v/v) was added as a preservative. The gel was made consistent with glycerin (10% w/v). Vortexing was continued until a homogenous niosomal gel was obtained and the gel was then sonicated to become bubble-free. The prepared gels were filled in amber-colored glass vials refrigerated at 4 to 8 °C.

Characterization of dipivefrine HCl

Organoleptic properties

Organoleptic properties of the dipivefrine HCl was characterized based on appearance, color, odor and taste by visual inspection.

Melting point determination

The melting point of a drug was determined by using digital melting point apparatus (DB-31354, Decibels Instruments, Perfit, India). In this method, a tiny amount of drug was introduced into a small capillary tube, attaching this to the stem of a thermometer centered in a heating bath, heating the bath slowly, and observing the temperatures at which the melting of drug begins and is completed. The melting point was recorded and compared with literature value.

Determination of solubility

Qualitative solubility

Qualitative solubility of dipivefrin HCl in different solvents was determined according to (USP NF, 2007) [11]. Dipivefrin HCl (1 mg) was accurately weighed and transferred into a 10 ml test tube then, it was dissolved in the respective solvents (1 ml each) such as distilled water, phosphate buffer saline (pH 7.4), methanol, ethanol, acetic acid, acetic anhydride and diethyl ether. The solubility (mg/ml) was observed by visual inspection and compared with that available in literature.

Quantitative solubility

Quantitative solubility analysis of drug was done by taking 5 ml of each solvent and drug in gm(s) into the solvent till saturation of solvent. Solutions were filtered and absorbance was recorded using UV spectrophotometer and the concentration of drug dissolved in respective solvents was calculated [12]. Different solvents like distilled water, phosphate buffer saline (pH 7.4) and simulated tear fluid (STF) pH 7.4 were used for the solubility determination. This is done to determine the capacity of the solvent for dissolving the drug in it.

Lipophilicity (Partition coefficient)

The partition coefficient of a chemical compound provides a thermodynamic measure of its hydrophilicity-lipophilicity balance. The partition coefficient of a substance between n-octanol and water is referred to as log $P_{o/w}$, which corresponds to the negative logarithm of the ratio of the concentration of the substance in the aqueous and hydrophobic phases [13]. The partition coefficient of dipivefrin HCl was carried out in water: octanol (1:1) using shake flask procedure.

Method

Before a partition coefficient is determined, the phases of the solvent system were mutually saturated by shaking at the temperature of the experiment. To do this, high-purity analytical grade n-octanol and water were taken into a separating funnel in 1:1 ratio. Then separating funnel was shaked for 30 min. to allow complete mixing and then the funnel was allowed to stand for 24 h to develop two phases which were saturated with each other after that the drug in minimum quantity (not more than 0.01 mol/l) was added to one of the phases and the funnel was again shaked for 30 min and then allow to stand for 1 h after that the amount of drug in both phases (n-octanol and water) was determined spectrophotometrically.

The partition coefficient is a ratio of concentrations of unionized compounds between the two solutions. To measure the partition coefficient of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is unionized. The logarithm of the ratio of the concentrations of unionized solute in the solvents is called log P [14, 15].

$$log\ P_{oct/wat} = log\left(\frac{[solute]_{octanol}}{[solute]_{water}^{un-ionized}}\right)$$

UV-visible spectrophotometric analysis

Determination of λ_{max} of dipivefrin HCl in phosphate buffer solution (pH 7.4)

A standard stock solution of dipivefrin HCl was prepared by dissolving 100 mg of drug in a 100 ml volumetric flask and the volume was made upto 100 ml by using phosphate buffer solution (PBS) of pH 7.4 to get the concentration 1000 µg/ml of standard dipivefrin HCl. From the standard stock solution, 10 ml was pipette out into 100 ml volumetric flask and the volume was made up to 100 ml with PBS of pH 7.4 to get the concentration 100 µg/ml. From this solution, 1 ml was pipette out into 10 ml volumetric flask and the volume was made upto 10 ml with PBS of pH 7.4 to get the concentration 10 µg/ml. Maximum wavelength (λ_{max}) was obtained by scanning the resulting solution (14 µg/ml) in the wavelength region between 200 nm to 400 nm by using UV-VIS spectrophotometer (UV1700 PharmaSpec, Shimadzu, Japan).

Preparation of standard curve of dipivefrin HCl in phosphate buffer solution of pH 7.4

From the above-prepared stock solution, five dilutions were made by using PBS of pH 7.4 which has ultimate concentration 12 µg/ml, 14 µg/ml, 16 µg/ml, 18 µg/ml and 20 µg/ml. Then check the pH of the diluted solutions to confirm that the diluted solutions were ranges in the pH of 7.4. The absorbance was measured at λ_{max} 254 nm by using UV-VIS spectrophotometer.

FTIR spectroscopy

FTIR spectra of the pure drug were obtained using FTIR spectrometer (FTIR-8400S spectrophotometer, Shimadzu, Japan). Sample were ground thoroughly with KBr powder in mortar and pestle, in a weight ratio of 1:100 and then pressed the mixture in dies set in pellet press under a hydraulic pressure of 15 tons for a minute. Release the pressure by rotating the side valve in anticlockwise direction to take of the pellet from the dies set. Then, the pellet was placed in the sample holder and spectral scanning was taken in the wavelength region between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1} and scan speed of 2 mm/sec [16].

Drug excipient compatibility screening by FTIR

FTIR spectra of locust bean gum, carbopol 934 and a physical mixture of locust bean gum: carbopol 934: Dipivefrin HCl in a

weight ratio of 1:1:1 was obtained using FTIR spectrometer (FTIR-8400S spectrophotometer, Shimadzu, Japan). Each sample were ground thoroughly with KBr powder in a weight ratio of 1:100 and then pellets were prepared using a hydraulic pellet press under a hydraulic pressure of 15 tons for a minute. Then, the pellet was placed in the sample holder and spectral scanning were taken in the wavelength region between 4000 and 400 cm^{-1} at a resolution of 4 cm^{-1} and scan speed of 2 mm/sec. IR spectra of the physical mixture was then compared with the IR spectra of pure drug and polymer to find out the evidence of any compatibility [17].

Differential scanning calorimetric (DSC) study

DSC analysis was performed on the pure drug by using Perkin-Elmer instrument (Pyris-1, Osaka, Japan), available at Department of Textile Technology, Indian Institute of Technology, New Delhi, India. Initially, the moisture was removed by heating the samples and then, each sample (about 3-7 mg) was accurately weighed into platinum crucible 40 µl aluminum pan in hermetically sealed condition, where alpha alumina powder used as a reference. Thermograms were recorded from 50 °C to 300 °C at the heating rate of 20 °C/min under a constant flow of an inert nitrogen gas atmosphere with the flow rate of 20 ml/min [18]. The DSC spectra used to find out the exotherm peak position or any change in their position compared with the standard spectra.

RESULTS AND DISCUSSION

Characterization of drug

Organoleptic properties

Organoleptic properties of the drug sample were found to be as given in table 1. The physical properties were found as similar as reported in literature that proves the identity of drug.

Table 1: Organoleptic properties of dipivefrin HCl

Organoleptic properties	Results
Physical form	Slightly hygroscopic crystalline powder
Color	White to off-white
Odor	Odorless
Taste	Tasteless

Melting point determination

The melting point of drug was determined in triplicate and their mean values with standard deviation are shown in table 2. The melting point of dipivefrin HCl was found to be 147.6±3 °C, which corresponds to the literature value of 146°C to 149°C that proves the identity and purity of drug.

Table 2: Melting point of dipivefrin HCl

S. No.	Melting point (°C)	mean±SD (°C)
1	148	147.6±3*
2	149	
3	146	

*Values are mean±SD of data from 3 experiments.

Determination of solubility

Qualitative solubility

The qualitative solubility data of dipivefrin HCl in different solvents at room temperature was shown in table 3.

Qualitative solubility

Results of quantitative solubility data of the drug in different solvents at room temperature was given in table 4.

Table 3: Qualitative solubility of drug in different solvents at 37 °C

S. No.	Solvent (1 ml)	Solubility of the drug (1 mg)
1	Distilled water	Freely soluble
2	Phosphate buffer saline pH 7.4	Freely soluble
3	Methanol	Freely soluble
4	Ethanol	Freely soluble
5	Acetic acid	Freely soluble
6	Acetic anhydride	Sparingly soluble
7	Diethyl Ether	Insoluble

Table 4: Quantitative solubility of drug in different solvents at 37 °C

S. No.	Solvent	Concentration of drug in solvent (mg/ml)
1	Distilled water	2.02
2	PBS pH 7.4	2.13

These results indicated that the available dipivefrin HCl form is freely soluble in water and there is no noticeable difference between the solubility of the dipivefrin HCl form used and the solubility of the reference dipivefrin HCl.

Partition coefficient

The log P value of drug was determined in triplicate and their mean values with standard deviation are shown in table 5. The log P value was found to be 3.14±0.02 and reported value was 3.22 from which it can be interpreted that drug is highly lipophilic in nature. Hence, the corneal epithelium is expected to be the rate-limiting barrier for ocular absorption [19]. This is an incentive to consider niosomes (surfactant/lipid-based system) for the ocular delivery of dipivefrin HCl.

Standard curve of dipivefrin HCl

Determination of λ_{max} of dipivefrin HCl in PBS (pH 7.4)

UV spectrophotometric study was carried out to determine the λ_{max} of dipivefrin HCl in PBS of pH 7.4. λ_{max} of dipivefrin HCl was found to be 254 nm as shown in table 6. The scanned λ_{max} were found to be similar as that of reported λ_{max} (254 nm).

Table 5: Partition coefficient of dipivefrin HCl

S. No.	Log P value	mean±SD
1	3.22	3.14±0.02*
2	3.15	
3	3.07	

*Values are mean±SD of data from 3 experiments.

Preparation of standard curve of dipivefrin HCl in phosphate buffer solution of pH 7.4

The concentration and absorbance data of dipivefrin HCl in PBS of pH 7.4 were given in table 7. This absorbance was plotted on Y-axis against concentration on X-axis that, was shown in fig. 2. The slope and intercept were found to be 0.0213 and 0.0016, respectively.

Table 6: Scanned λ_{max} and absorbance of dipivefrin HCl in PBS (pH 7.4)

S. No.	Strength (µg/ml)	Scanned λ_{max} (nm)	Absorbance
1	14	254	0.313
2	14	254	0.180
3	14	254	0.076

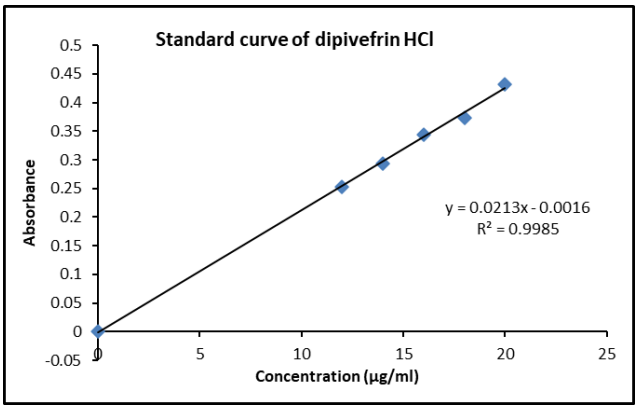

Fig. 2: Standard curve of dipivefrin HCl in PBS pH 7.4

Table 7: Standard curve data of dipivefrin HCl in PBS pH 7.4

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	12	0.252
3	14	0.294
4	16	0.344
5	18	0.373
6	20	0.432

FTIR spectroscopy

FTIR spectra of the pure drug were obtained using FTIR spectrometer (FTIR-8400S spectrophotometer, Shimadzu, Japan) and were presented in fig. 3. The interpretation of FTIR spectra of dipivefrin HCl was shown in table 8. Dipivefrin HCl showed the principle IR peaks at 3217.10 cm^{-1} resulted from N-H stretching, the peak at 1764.75 cm^{-1} resulted from C=O stretching, the peak at 1612.38 cm^{-1} resulted from C=N stretching, the peak at 1552.59 cm^{-1} resulted from N=H bending. All the principal peaks of dipivefrin HCl are present in the spectra, which confirm the purity and identity of drug.

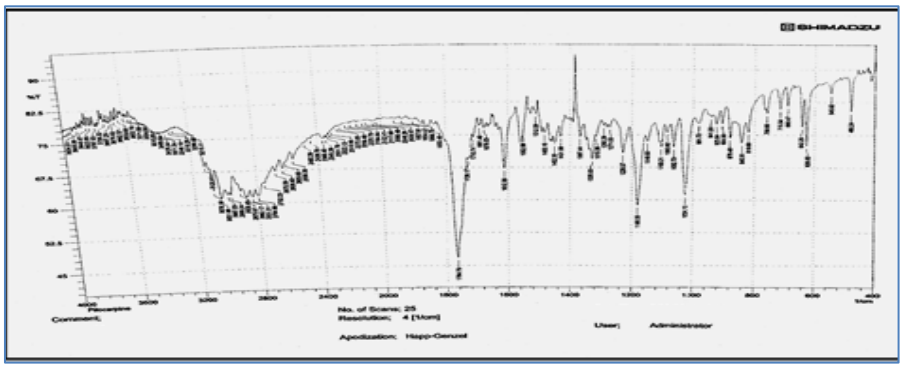

Fig. 3: FTIR spectra of dipivefrin HCl

Table 8: Interpretation of FTIR spectra of dipivefrin HCl

S. No.	Functional group	Reported frequency (cm^{-1})	Observed frequency (cm^{-1})
1	N-H stretching	3400-3250	3217.10
2	C=O stretching	1900-1600	1764.75
3	C=N stretching	1700-1600	1612.38
4	N=H bending	1700-1500	1552.59
5	C-H bend in plane	1500-1300	1483.16
6	C-C stretching	1200-800	1180.35
7	N-H rocking	900-700	759.90
8	C-Cl stretching	800-600	626.82

Drug excipient compatibility screening by FTIR

FTIR spectra of locust bean gum, carbopol 934 and a physical mixture of locust bean gum: carbopol 934: dipivefrin HCl in a weight ratio of 1:1:1 was obtained using FTIR spectrometer (FTIR-8400S spectrophotometer, Shimadzu, Japan) and was presented in fig. 4, fig. 5 and fig. 6 respectively and the interpretation of FTIR spectra was shown in table 8, table 9, table 10 and table 11 respectively.

No significant changes were found when FTIR spectra of the physical mixture compared with FTIR spectra of pure drug and excipients. This indicates absence of any possible interaction between the drug and excipients.

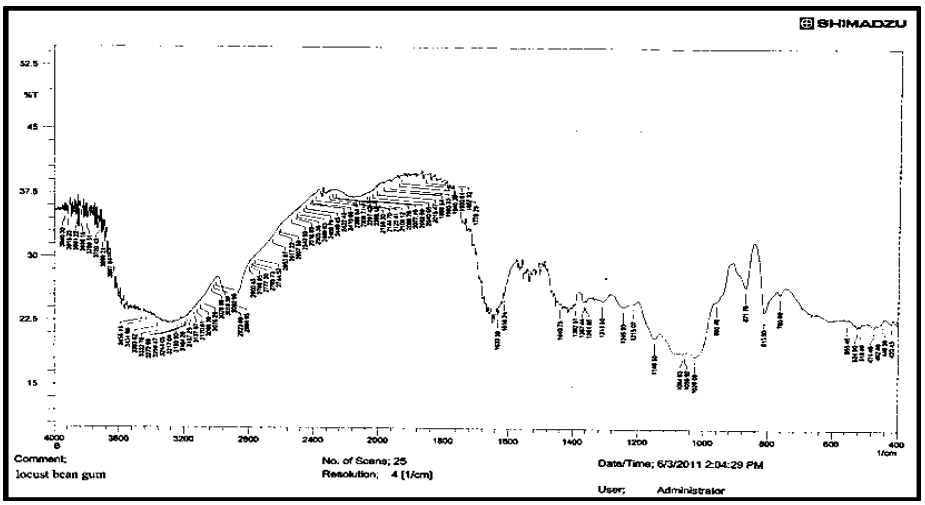

Fig. 4: FTIR spectra of locust bean gum

Table 9: Interpretation of FTIR spectra of locust bean gum

S. No.	Functional group	Reported frequency (cm^{-1})	Observed frequency (cm^{-1})
1	O-H stretching, H-bonded	3500-3200	3458.13
2	C-O-C stretching in ring	1150-1000	1056.92
3	C-H stretching in ring	3330-3000	3272.98
4	C-H stretching	3000-2840	2923.88
5	C-H bending	1470-1450	1440.73

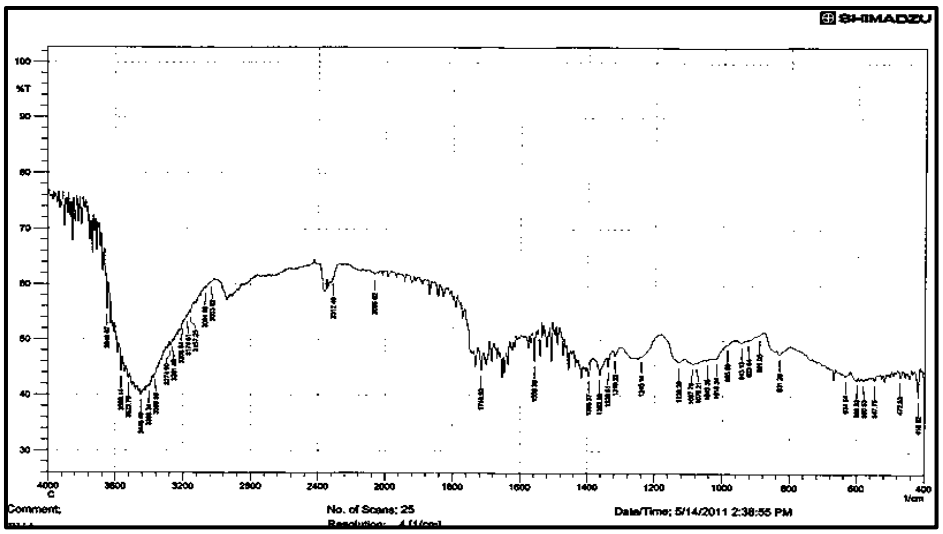

Fig. 5: FTIR spectra of carbopol 934

Table 10: Interpretation of FTIR spectra of carbopol 934

S. No.	Functional group	Reported frequency (cm^{-1})	Observed frequency (cm^{-1})
1	O-H stretching	3640-3610	3640.07
2	C-C stretching	1300-800	1240.14
3	C-H stretching	3000-2840	2894.95
4	C=O stretching	1725-1700	1716.53

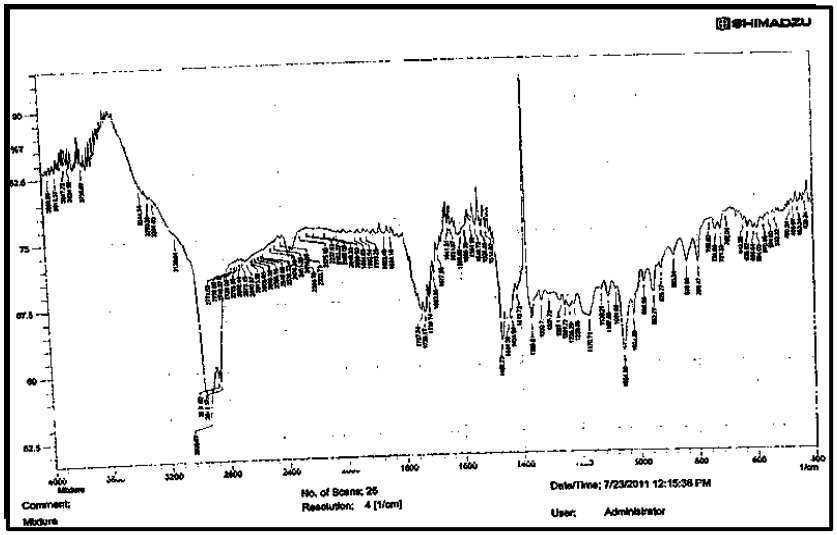

Fig. 6: FTIR spectra of physical mixture

Table 11: Interpretation of FTIR spectra of physical mixture

S. No.	Functional group	Reported frequency (cm^{-1})	Observed frequency (cm^{-1})
1	N-H stretching	3400-3250	3217.10
2	N-H bending	1650-1580	1540.13
3	N-H wagging	910-665	632.26
4	C=N stretching	1700-1600	1677.95
5	C-H stretching	3000-2850	2937.38
6	C-H bending	1470-1450	1427.23
7	Aromatic C=C stretching	1675-1650	1637.45
8	O-H stretching, H-bonded	3500-3200	3400.27
9	C-O-C stretching in ring	1150-1000	1116.71

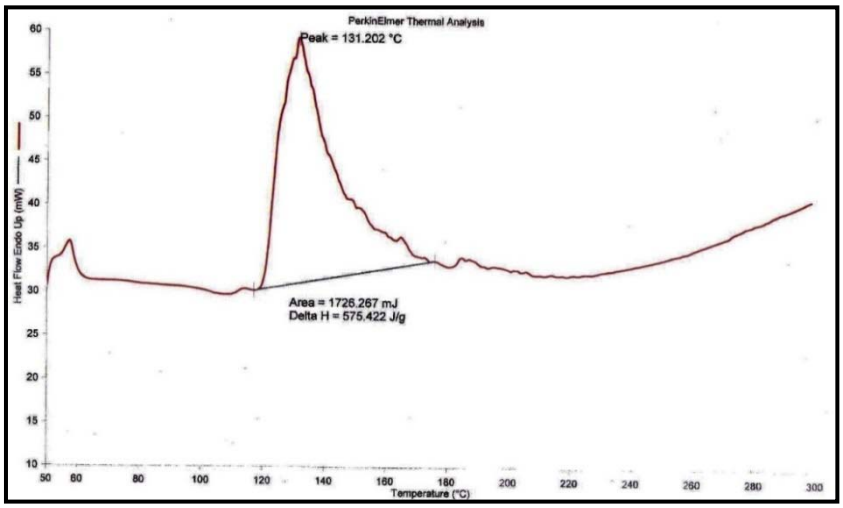

Fig. 7: DSC Themogram tracings of dipivefrin HCl

Differential scanning calorimetric (DSC) study

DSC thermogram tracings of dipivefrin HCl was shown in fig. 7. It showed a sharp exothermic peak at 131.202 °C (area=1726.267 mJ, delta H=575.422 J/g) indicating the crystal melting point of the drug. This result is in contrary to that of the reference melting point of dipivefrin HCl which is 147.6 °C. The marked difference between the observed melting point and the reference one is attributed to crystallization form of the drug.

CONCLUSION

The preformulation parameter such as melting point and UV spectrophotometric analysis, solubility profile, partition-coefficient, spectrometric fingerprints, and compatibility studies by FTIR and thermal behavior analysis by DSC; maximize the chances of getting a formulation which is safe, efficacious, and stable product and at the same time provide optimization of the drug product quality. Based on these studies, it was concluded that the dipivefrin HCl serve as suitable candidate for niosomal gel for ocular use.

ACKNOWLEDGEMENT

The authors are thankful to the Principal of Teerthankar Mahaveer College of Pharmacy, Teerthankar Mahaveer University, Moradabad for their kind support and providing all the necessary facilities and encouragement for successful completion of this work.

FUNDING

Nil

ABBREVIATION

IOP, Intraocular pressure; DV, Dipivefrin; EP, Epinephrine; Log P, Partition coefficient; FTIR, Fourier transform infrared; STF, Simulated Tear Fluid; DSC, Differential scanning colorimetry; UV, Ultraviolet; PBS, Phosphate buffer solution.

AUTHORS CONTRIBUTIONS

The corresponding author, Neeraj Jain performed the experimental works and wrote the manuscript. Neelam Jain assisted in experiments and Anurag Verma supervised the work. All authors discussed the results and contributed to the final manuscript.

CONFLICT OF INTERESTS

The authors report no conflicts of interest.

REFERENCES

1. Chaurasia G. A review on pharmaceutical preformulation studies in formulation and development of new drug molecules. Int J Pharm Sci Res. 2016 Jun 22;7(6):2313-20.
2. 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 Apr 21;19(4):400-12. doi: 10.1016/j.drudis.2013.10.001, PMID 24120893.
3. Anderson JA, Davis WL, Wei CP. Site of ocular hydrolysis of a prodrug, dipivefrin, and a comparison of its ocular metabolism with that of the parent compound, epinephrine. Invest Ophthalmol Vis Sci. 1980 Jul 03;19(7):817-23. PMID 7390729.
4. Yablonski ME, Shin DH, Kolker AE, Kass M, Becker B. Dipivefrin use in patients with intolerance to topically applied epinephrine. Arch Ophthalmol. 1977 Dec 25;95(12):2157-8. doi: 10.1001/archopht.1977.04450120063004, PMID 588107.
5. Blondeau P, Cote M. Cardiovascular effects of epinephrine and dipivefrin in patients using timolol: a single-dose study. Can J Ophthalmol. 1984 Feb 20;19(1):29-32. PMID 6713266.
6. Barot M, Bagui M, Gokulgandhi MR, Mitra AK. Prodrug strategies in ocular drug delivery. Med Chem. 2012 Jul 19;8(4):753-68. doi: 10.2174/157340612801216283, PMID 22530907.
7. Mandell AI, Stentz F, Kitabchi AE. Dipivalyl epinephrine: a new pro-drug in the treatment of glaucoma. Ophthalmology. 1978 Mar 15;85(3):268-75. doi: 10.1016/s0161-6420(78)35668-2, PMID 662280.
8. Alshamsan A, Abul Kalam M, Vakili MR, Binkhathlan Z, Raish M, Ali R. Treatment of endotoxin-induced uveitis by topical application of cyclosporine a-loaded PolyGel™ in rabbit eyes. Int J Pharm. 2019;569:118573. doi: 10.1016/j.ijpharm.2019.118573, PMID 31356955.
9. https://www.pharmaffiliates.com/en/64019-94-9-4-methylamino-acetyl-1-2-phenylene-dipivalate-hydrochloride-pa310951000.html.
10. Tomar S, Singhal T. Preformulation studies of niosomal gel of prednisolone and azithromycin for topical drug delivery system. J Innov Pharm Biol Sci. 2015 Jan 29;2(3):312-21.
11. Jain N, Verma A. Preformulation studies of pilocarpine hydrochloride as niosomal gels for ocular drug delivery. Asian J Pharm Clin Res. 2020 Apr 18;13(6):149-55. doi: 10.22159/ajpcr.2020.v13i6.37523.
12. United States Pharmacopeia. National formulary. The official compendia of standards. United States Pharmacopeial Commission; 2007.
13. Jayanthi B, Madhusudhan S, Mohanta GP, Manna PK. Preformulation, characterisation, designing and formulation of aceclofenac-loaded microparticles. Int J Drug Dev Res. 2012 Jul-Sep;4(3):186-96.
14. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1987.
15. Berthod A, Carda Broch SC. Determination ofliquid–liquid partition coefficients by separation methods. J Chromatogr A. 2004 May 22;1037(1-2):3-14. doi: 10.1016/j.chroma.2004.01.001, PMID 15214657.
16. Jain N, Verma A, Jain N. *In vitro* evaluation of niosomal gel containing pilocarpine hydrochloride for ocular delivery. Lat Am J Pharm. 2020 Mar 28;39(3):431-8.
17. Meylan WM, Howard PH. Atom/fragment contribution method for estimating octanol-water partition coefficients. J Pharm Sci. 1995 Jan 06;84(1):83-92. doi: 10.1002/jps.2600840120, PMID 7714751.
18. Jain N, Banik A, Gupta A. Novel interpenetrating polymer network microspheres of Lepidium sativum and poly(vinyl alcohol) for the controlled release of simvastatin. Int J Pharm Pharm Sci. 2013 Jan 13;5(1):125-30.
19. Jain N, Singh N, Sharma U, Jain N, Dwivedi S. Fabrication and characterization of novel antiulcer drug delivery system: LBG/PVA based interpenetrating polymer network (IPN) mucoadhesive microspheres of famotidine. Lat Am J Pharm. 2021 Dec 19;40(12):2862-72.