Journal of Pharmaceutical Research International

Volume 35, Issue 17, Page 31-40, 2023; Article no.JPRI.101964
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Preformulation Studies of Varenicline for Formulation and Development of a Novel Orally Disintegrating Film

Prakruti Amin [a,b++*] and Manish Patel [c]

[a] Gujarat Technological University, Ahmedabad, Gujarat, India
[b] Department of Pharmaceutics, Kadi Sarva Vishwavidyalaya, K. B. Institute of Pharmaceutical Education and Research, Gandhinagar, Gujarat, India.
[c] Department of Pharmaceutics, L. M. College of Pharmacy, Gujarat Technological University, Ahmedabad, Gujarat, India.

Authors' contributions

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

Article Information

DOI: 10.9734/JPRI/2023/v35i177388

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/101964

Original Research Article

Received: 25/04/2023
Accepted: 27/06/2023
Published: 07/07/2023

ABSTRACT

Objective: The major goal of pre-formulation research is to create a drug delivery system that is stable, elegant, safe, and effective by determining the drug's kinetic profile, the formulation's compatibility with various excipients, and the physico-chemical characteristics of new drug molecules. This could offer crucial support for executing formulation design or the need for the molecular change. Therefore, in the current study, studies on Varenicline (VAR)'s appropriateness for oral formulation were conducted. Similar to cytisine, VAR functions as a partial nicotine receptor agonist. It blocks alpha-4-beta-2 nicotinic acetylcholine receptor subtypes and is a partial agonist. Through partial agonism, VAR reduces the urge and withdrawal symptoms associated with quitting efforts by inhibiting the dopaminergic activation brought on by smoking. It stops nicotine from stimulating the mesolimbic dopamine pathway, which is linked to nicotine addiction.

[++] PhD Scholar;
**Corresponding author: E-mail: praktutiamin@gmail.com;*

Methods: The authenticity of VAR was established by DSC and FTIR spectra. A UV spectrophotometric method was employed for determination of VAR in bulk and active pharmaceutical ingredient (API).
Results: The authenticity of VAR was established by DSC and FTIR spectra. For the determination of VAR in bulk API (active pharmaceutical ingredient), a UV spectrophotometric approach was used. In the concentration range of 5–40 g/ml, the UV technique was linear. The lower% CV values of intraday and interday variability indicate the proposed methodology's robustness. The higher regression coefficient value(0.999) indicates the methodology is robust.
Conclusions: The outcome of the physico-chemical experiments of drug molecule indicates suitability of oral route. Additionally, at different conditions like solid as well as liquid state, the drugmoleculewasobservedstable.

Keywords: Preformulation; varenicline; oralformulation; orallydisintegrating film; stability.

1. INTRODUCTION

The mouth cavity is approximately 100 cm2 in size. The surface of the oral mucosa is cleansed repeatedly by saliva (on a daily basis, in this case).

Many options are available for oral dosage forms when a drug is administered through the oral route. The oral cavity has several essential major interests in the development of modified features, such as low enzymatic activity; it easily releases oral dosage forms because oral delivery accessed aiding the administration; and the market holds approximately 52% of the market. These are only some of the features.Oral cavity, although being a highly vascularized area, permits pharmacological compounds to enter the circulation of the body as a whole. Problems that are typically connected with the oral cavity include instances in which medications are immediately permeable in the systemic circulation, which results in hepatic first-pass metabolism and poor oral bioavailability [1]. Formulation of fast-dissolving or quick-dissolving dosage forms is required for the administration of medications while simultaneously reducing the risk of choking [2]. They go through overdosing or inefficiency owing to the partial loss of active substances that occurs due to the tablet. This is because the tablet causes the dosage to be inaccurate as well as the drug therapy qualities.

Many patients have trouble swallowing tablets, and most of them do not take their hard gelatin capsules or their drinking water, which is where the active ingredients in their medications are supposed to be released, as directed by their doctors. The problem of dysphagia, which can manifest as trouble swallowing or the ingestion of pharmacological components, is estimated to impact close to 35 percent of the general population. The mentally ill are a separate category altogether. A patient who is unable to cooperate and has less liquid in their body can be treated more quickly with a fast-dissolving film than with other traditional dose forms [3]. These films are less prone to breaking and easier to transport, and they may be associated with a greater number of medical conditions as a dosage form compared to commercialised orally who may has generated tremendous interest from the business community experience difficulties in swallowing solid dosage because of their potential to provide line extension in forms.Pills that dissolve in the mouth but require specialized packaging [4-5].

In a similar vein, a single dose of strip medication is not only easy to transport but also has the potential to boost patient compliance and bring in revenue. Numerous medications are unable to be administered in this manner because it does not allow for the necessary secondary absorption and metabolism [6-9]. This is due to certain biochemical and physiological features of the individual drug. It is very important to address the poor stability of liquid dosage forms, especially the route, because after administration are subjected to aqueous formulations. This issue must be addressed in order for the drug to be successfully supplied through the normal oral route [10,11].

When it comes to delivery of any drug, a steady dosage form is required prior to considerable clearance in the liver. This frequently results in a lack of significant correlation, which is necessary to ensure maximum efficacy. The study of the fundamental features of the drug molecule is necessary because it is necessary for the development of between membrane permeability, absorption, and dose forms [6,7].

The term "preformulation" refers to a series of research that concentrate on the physicochemical qualities of a novel medicine as well as the development of a dosage form for that drug. Transmucosal routes of drug administration (i.e., the mucosal linings of the nasal, vaginal, ocular, and oral cavities) offer pharmacological formulation because of the drug's inherent chemical and physical qualities. These routes were considered before the advent of rectal, vaginal, ocular, and oral cavities. This trait confers specific advantages over peroral administration for the framework of pharmacological combinations with a systemic effect, as the advantages pertain to the framework. Oral mucosa has a great accessibility and dosage form compared to the other transmucosal medicinal substances used in the production of routes. The preformulation study hopes to achieve an expanse of smooth muscle as its goal. The total surface area of the develop the elegant, stable, effective, and safe dosage form by establishing the kinetic rate profile, compatibility with the other substances, and establish. This article discusses certain characteristics and methods for evaluating preformulation parameters of varenicline tartrate for oral film [8]. An active pharmaceutical ingredient (API) must first go through the process of preformulation before it can be rationally formulated. An research into the physicochemical qualities of the drug ingredient, both on its own and in combination with excipients, is what this step entails. Varenicline (VRC), 6,7,8,9-tetrahydro-6,10-methano-6H- pyrazino(2,3- h) Benzazepine (VAR) is a relatively new medication that has been utilised for the treatment of smoking cessation. It is a centrally acting a strong and selective partial agonist for 42 nicotinic acetylcholine receptors.1 It was demonstrated that it modifies the effects that nicotine has on behaviours connected to dependency. According to the published research, varenicline shown a significantly greater benefit than NRT in terms of measures of craving and withdrawal. This was accomplished by reducing feelings of temptation to smoke, negative effect, and restlessness [9].

The purpose of the current work was to do preformulation experiments to inform creation of an orodispersible film of varenicline tartrate for the purpose of establishing the physical chemical features with possible interactions with excipients. These studies were intended to inform development of the film [12].

2. MATERIALS AND METHODS

2.1 Materials

We were given a free sample of varenicline active pharmaceutical ingredient (API) from Torrent Pharmaceuticals in India. Methanol, ethyl acetate, ethanol, and dichloro methane (DCM) were all presented to us by Final Limited, India, in the form of a free sample. All of the chemicals and solvents that were utilised were of an HPLC (high-performance liquid chromatography) quality. Throughout the course of the experiment, freshly made distilled water was utilised.

2.2 Drug Identification

The drug identification was performed by organoleptic properties, melting point, UV, HPLC, FTIR and DSC.

2.3 Determination of Thermodynamic Solubility

Several solvents, including methanol, ethanol, dimethyl sulfoxide, ethyl acetate, dichloromethane (DCM), and N-Methyl-2-Pyrrolidone, were used to examine the drug's solubility. Samples were shaken for 24 hours at 37°C on a rotary shaker. Filtration is then used to separate the two stages [10]. Then, using UV spectrophotometric analysis at the corresponding max of each solvent, the amount of solute in the supernatant is determined.

2.4 Analytical Preformulation

Analysis of VAR by UV spectrophotometry method [13].

Standard stock solutions of VAR was prepared in water and scanned spectrophotometrically over the range of 200–400nm with double beam spectrophotometer (Shimadzu UV spectrophotometer, 240 j/PC, Japan), against the respective blank, to determine wave length of maximum absorbance (λmax).

A stock solution containing 1000 µg/ml VAR was prepared by dissolving 25 mg VAR in 5 ml of water in a 25 ml of volumetric flask and volume was made upto 25 ml with the water. From these stock solutions, suitable aliquots were taken and diluted using appropriate solvent to get dilutions of 5-40 µg/ml. The determinations were conducted in triplicate and studied for three days to check intra and inter day variations.

Calibration curve was constructed at concentrations range 2-8 µg/ml. Absorbance of each solution was measured at the wavelength of 236nm and 319nm. Calibration curve was constructed for VAR by plotting absorbance versus concentration at 236 nm and 319 nm wavelength. The determination was conducted in triplicate.

2.5 Drug-Polymer Compatibility Study

At 25°C and 60% relative humidity (RH), the physical stability of VAR with polymer was assessed. The samples were also sealed in vials and kept in a refrigerator (2–8°C). After 30 days, the samples were eliminated.

2.5.1 Fourier transform-infrared (FTIR) study [14]

The functional groups present in the molecule were qualitatively estimated and identified using the FTIR analysis. VAR was combined with each of the ingredients in the formulation procedure at the proper ratio. Each mixture was kept in a USP type-1 glass vial for a month at a temperature of 25°C to 5°C and a relative humidity of 60% to 5%. The compatibility of pure drugs and various preparation composites was investigated using FTIR spectroscopy, Shimadzu, Model 8400, Japan, and the KBr pellet method, scanning from 4000 to 400 cm-1.

2.5.2 Differential Scanning Calorimetry (DSC) [15]

The thermal analysis technique known as DSC allows us to measure how a medication interacts with a polymer. 3-5 mg of samples were used in a typical thermal aluminium pan with a can measure the interaction of the drug with the polymer to perform the thermal analysis of the drug, polymer (Kollicoat IR), and physical mixing of the drug and polymer. A conventional thermal aluminium pan with a lid of a similar size and 3-5 mg of samples were used for the thermal analysis of drugs, PLGA, and physical mixtures of drugs and polymers in the Mettlertoledo DSC (METTLER TOLEDO, Switzerland).

3. RESULTS AND DISCUSSION

3.1 Drug Identification

3.1.1 Organoleptic properties and melting point

VAR is odorless and almost white powder which is sticky in nature. The melting point of drug was in the range 195–197°C.

3.1.2 Drug identification by UV

The identification of drugs has been increased considerably in recent years by use of maximum absorbance because of their importance in pharmaceutical analysis. The maximum absorbance of VAR in methanol was found at 236 nm and 319nm as depicted in Fig. 1 which was similar to literature of VAR. This indicates that the received active pharmaceutical ingredient is authentic [16].

3.1.3 Drug identification by FTIR

Results in FT-IR spectra were discovered, together with characteristic peaks of the VAR medication that matched reference FT-IR spectra. In FT-IR spectra, the typical absorption peaks of VAR are depicted in Fig. 2, and Table 1 lists the functional groups that produce these peaks.

Table 1. Stretching bending of varenicline

Peak at wave number (cm-1)	Interpretation
3368.77, 3288	N-H stretch (Secondary amine)
2931.94	C-H stretch (aliphatic)
1704.93	C=O stretch
1670.95	N-C=O stretch
1345.42	O=S=O

3.1.4 Drug identification by DSC

Fig. 4 shows DSC thermogram of the VAR exhibits a significant melting peak at 195 and 197 degrees Celsius. The melting point was discovered to be between 195 and 197°C using the capillary technique. This supports the validity of the drug sample. There were no subsequent peaks, which further supports the drug's steady properties.

3.2 Determination of Thermodynamic Solubility

Varenicline is very faintly soluble in methanol, ethanol, and ethyl acetate, sparingly soluble in dichloromethane, easily soluble in water, soluble in dimethyl formamide, and soluble in N-Methyl-2- Pyrrolidone. Table 2 displays the drug's solubility in several solvents.

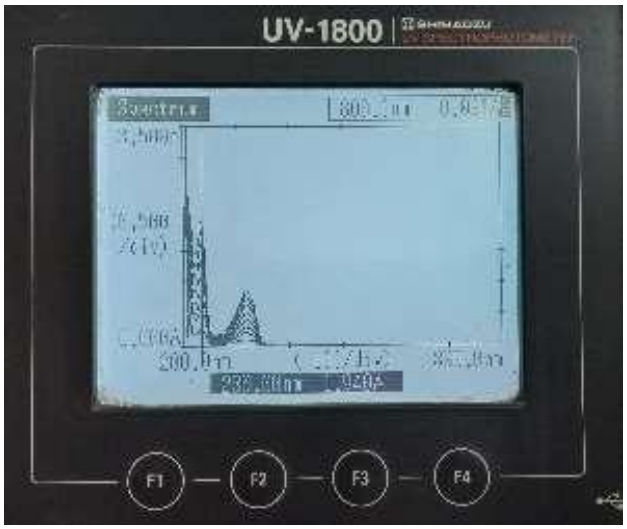

Fig. 1. UVspectraofVARinmethanolat236nmand319nmλ-max

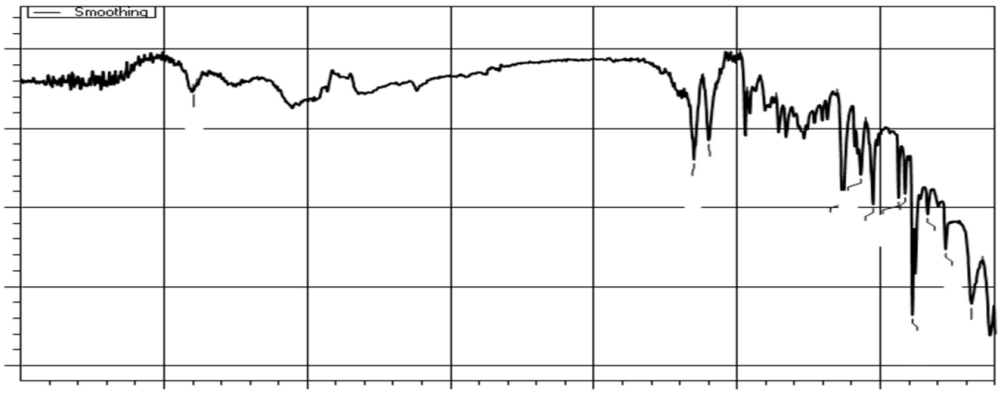

Fig. 2. Fourier transform-infrared spectrum of varenicline

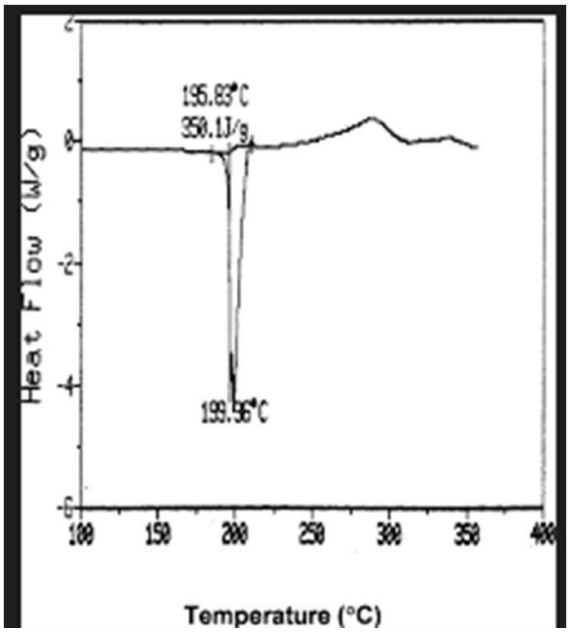

Fig. 3. Differential Scanning Calorimetry (DSC) of Varenicline

Table 2. Solubility parameters of different solvents

Solvents	Solubility (mg/mL)
Methanol	3.4±0.15
Ethanol	3.9±0.15
Water	29.8±2.85
Ethyl Acetate	1.0±0.05
Dichloromethane (DCM)	5.0±0.25
N-Methyl-2-Pyrrolidone	50.0±2.5

3.3 Analytical Preformulation

3.3.1 Analysis of VAR by UV spectrophotometry method

Due to their significance in pharmaceutical analysis, the development of spectrophotometry methods for drug determination has significantly increased in recent years. The standard calibration curves were plotted based on the experimental data. The regression study in acetonitrile revealed a very strong association (r2=0.9999). The linearity was discovered in the concentration range of 2-8 g/ml in acetonitrile, and these solutions followed Beer-Lambert's law. In Fig. 4, the VAR standard curve is displayed.

3.4 Drug-Polymer Compatibility Study

As demonstrated in Fig. 3, the typical absorption peaks of VAR in FT-IR spectra demonstrate a stable and clean pharmacological profile. Additionally, the VAR's stability has been tested in various temperature, moisture, light, and oxidation conditions. The findings from the preformulation stability study revealed stable drug properties under various storage circumstances, which are displayed in Table 3.

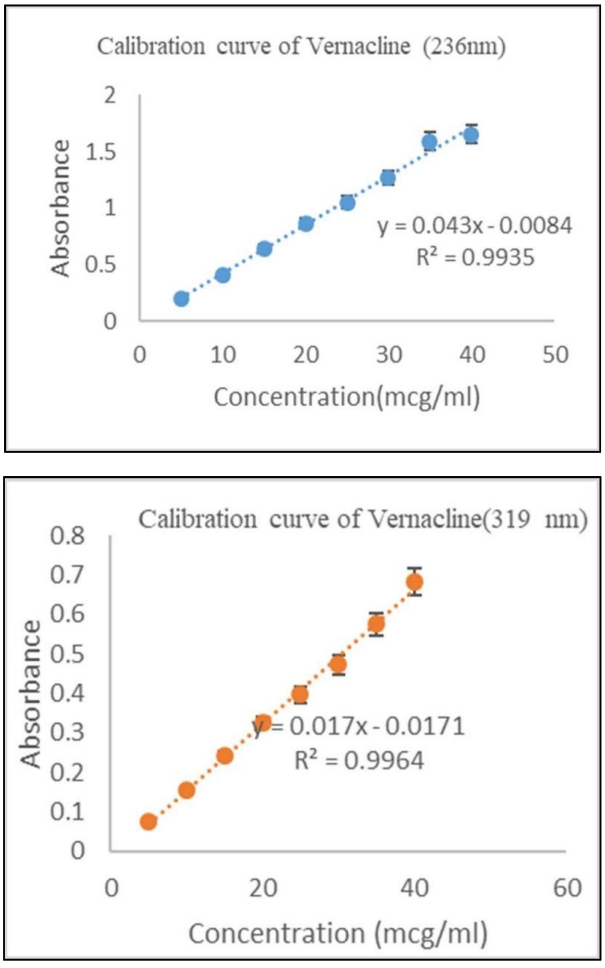

Fig. 4. Standard curve of Varenicline in Methanol

Table 3. Drug stability under preformulation study at different conditions

Sl. No.	Influencing Factor	Test sample	Packing material	Storage condition	Storage times (weeks)	Physical Degradation	Drug content
1	Moisture	Pure drug substance	Open container	25˚C/75 % R.H.	0	No	98.99±0.32
					1	No	98.79±0.29
2	Temperature	Pure drug substance	50 ml glass container with twist-off closure	70˚C	0	No	99±0.74
					2	No	100.43±0.82
					4	No	98.45±0.45
3	Temperature + Moisture	Pure drug substance with absorbed water at 25˚c/75 % RH	50 ml glass container with twist-off closure	70˚C	0	No	99.24±0.34
					2	No	100.23±0.11
					4	No	99.31±0.58
4	Oxidation	1% aqueous solution in 0.35 H_2O_2 solution	25 ml glass flask with glass stopper	50˚C	0	No	99.12±0.63
					1	No	100.66±0.31
					3	No	98.78±0.38
5	Light	Pure drug substance	Open petridish	Xenon lamp	24 hr	No	99.45±0.33
					48 hr	No	101.34±0.68

3.4.1 Fourier transform-infrared (FTIR) study

The results of the FTIR spectral analysis confirmed that there was no chemical interaction between Varenicline and the polymers and that no characteristic peaks of the pure medication Varenicline appeared or vanished in the physical mixture. Figs 5 and 6 depict the FT-IR spectra of a physical combination under initial conditions and after a one-month study, respectively. Table 4 lists the functional groups responsible for the characteristic peaks.

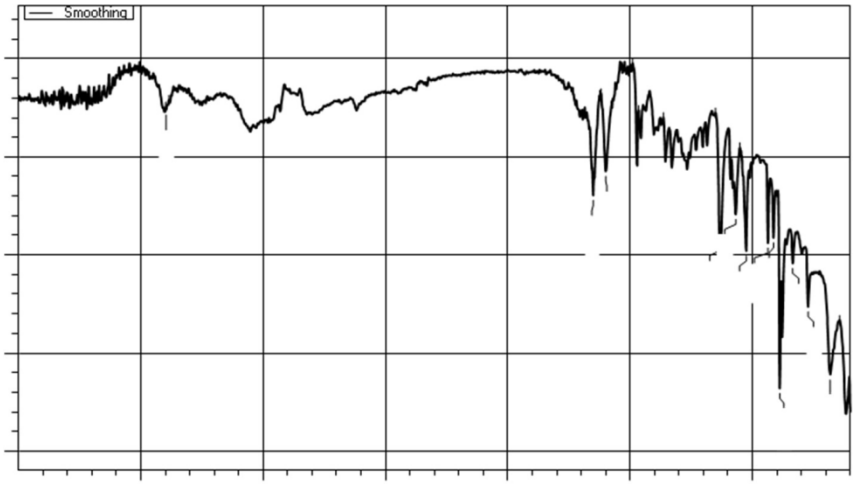

Fig. 5. Fourier transform-infrared spectrum of Varenicline-Polymer mixture (Initial)

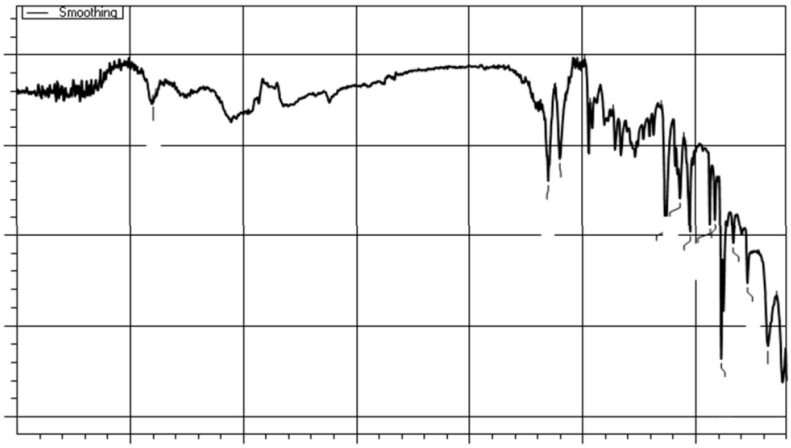

Fig. 6. Fourier transform-infrared spectrum of Varenicline-Polymer mixture (1 Month, 25℃/60%RH)

Table 4. Compatibility of Varenicline-Polymer mixture by FTIR

Varenicline (API) X (cm-1)	Varenicline + Polymer mixture (Initial) X (cm-1)	Varenicline + Polymer mixture (1 M 25°C/60% RH) X (cm-1)	Interpretation
3368.77	3368.82	3368.86	N-H stretch (Secondary amine)
3288	3287.99	3288.03	N-H stretch (Secondary amine)
2931.94	2932.25	2932.18	C-H stretch (aliphatic)
1704.93	1705.25	1705.05	C=O stretch
1670.95	1671.93	1672.87	N-C=O stretch
1345.42	1345.57	1345.46	O=S=O

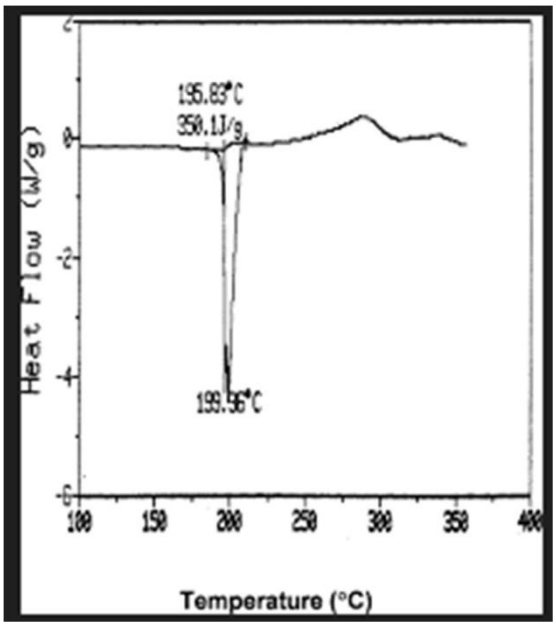

Fig. 7. Differential Scanning Calorimetry (DSC) of Varenicline-Polymer mixture (Initial)

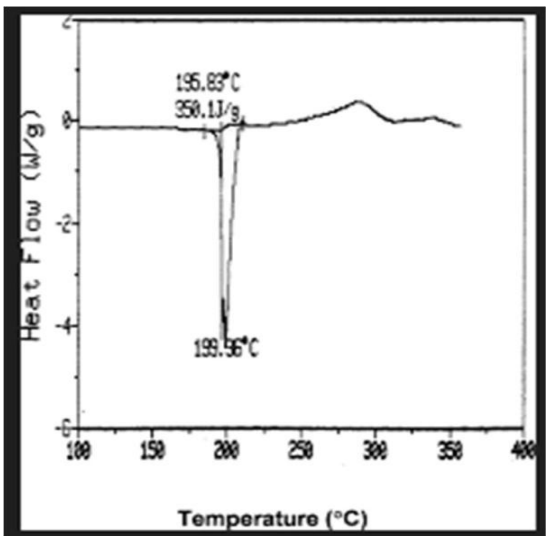

Fig. 8. Differential Scanning Calorimetry (DSC) of Varenicline-Polymer mixture (1 Month, 25℃/60%RH)

3.4.2 Differential Scanning Calorimetry (DSC)

The endothermic peak of the drug and polymer in the physical mixture did not change at the initial condition or after one month, according to the DSC thermogram of the VAR and polymer mixture, which supports the lack of a chemical interaction between the two as shown in Figs. 7 and 8, respectively.

4. CONCLUSION

It is clear from the outcomes of the various preformulation investigations that VAR is a good candidate for formulation of an orally disintegrating film. The UV, FT-IR, and DSC data revealed that the medication is genuine. The UV approach demonstrated good correlation, indicating that it can be applied to *In vitro* and bulk drug quantification research. The drug's solubility analysis revealed that it is soluble in aqueous media, indicating that a fast release formulation might be appropriate. Drug properties that were stable during preformulation investigations were revealed by a stability analysis, indicating the formulation's final stability.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Filipa BA, Claudia S, Jorge FJ, Sergio Coelho S. Oral films: Current status and future perspectives II — Intellectual property, technologies and market needs, J. Control. Release. 2015;206:108–121.
2. Mariagiovanna S, Sven S, WenKai H, Heinz P, Simon G, Massimo B, Amrit P, Mine O. Orodispersible films: Towards drug delivery in special populations, Int. J. Pharm. 2017;523:327–335.
3. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J. Pharm. Sci. 1992;81:1–10.
4. Shojaei AH, Chang RK, Guo X. Systemic drug delivery via the buccal mucosal route.J. Pharm. Technol. 2001;25(6): 70–81.
5. Galey WR, Lonsdale HK, Nacht S. The *In vitro* permeability of skin and buccal mucosa toselected drugs and tritiated water, J. Invest. Dermat.
6. Lam JKW, et al. Oral transmucosal drug delivery for pediatric use, Adv. Drug Deliv. Rev; 2013. Available:http://dx.doi.org/10.1016/j.addr. 2013.08.011
7. Squier CA. The permeability of oral mucosa, Crit. Rev. Oral Biol. Med. 1991; 2:13–32.
8. SatheeshMadhav NV, Semwal R, Semwal DK, Semwal RB. Recent trends in oral transmucosal drug delivery systems: an emphasis on the soft palatal route, Expert Opin. Drug Deliv. 2012;9:629–647.
9. Branca MA. Silvaa,b, Ana Filipa Borgesa, b Cláudia Silvaa, Jorge FJ. Coelhoc Sérgio Simõesa. International Journal of Pharmaceutics. 2015;494(1):537-551.
10. Alok Khunteta, Manish Kumar Gupta, Surendra Kumar Swarnkar. Preformulation studies of rapid dissolving films containing granisetron hydrochloride. Journal of Drug Delivery & Therapeutics. 2019;9(4-A): 511-515
11. Liang AC, Chen LH. Fast dissolving intraoral drug delivery systems. Exp. Opin. Ther. Patents. 2001;11(6):981–986.
12. Borsadia S, O'Halloran D, Osborne JL. Quick dissolving films-a novel approach to drug delivery. Drug Delivery Technology. 2003;3(3).
13. Prabhu SC, Parsekar SD, Shetty A, et al. Review article a review on fast dissolving sublingual films for systemic drug delivery. Int J Pharm ChemSci. 2014;3:501–511.
14. Russo E, Selmin F, Baldassari S, et al. A focus on mucoadhesive polymers and their application in buccal dosage forms. J Drug DelivSciTechnol. 2015;32:113–125
15. Wening K, Breitkreutz J. Oral drug delivery in personalized medicine: unmet needs and novel approaches. Int J Pharm. 2011;404:1–9.
16. Cides LCS. et al. Thermal behaviour, compatibility study and decomposition kinetics of Varenicline under isothermaland non-isothermal conditions. Journal of Thermal Analysis and Calorimetry; 2006.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/101964