PreformulationStudiesOfVareniclineforFormulationandDevelopmentofanOrallyDisintegratingFilm

Comment [اشرف1]: The word is added at the end of the title(In vitro)

Abstract

Objective: The main objective of pre-formulation study is to develop the stable, elegant, safe andeffective drug delivery system by establishing drug kinetic profile, formulation compatibility withdifferentexcipientsand physico-chemicalparametersof new drug molecules. This could providekey evidence for implementing formulation design or requirement of the molecular alteration. So, inthepresentstudypreformulationstudieswereperformedonVarenicline(VAR)toassessitssuitability fororalformulation.VAR acts as a partialnicotinereceptor agonistsimilar tocytisine. It isapartialagonist and blocksalpha-4-beta-2 nicotinicacetylcholinereceptorsubtypes. Throughpartial agonism, VAR inhibits dopaminergic activation produced by smoking and decreases thecravingandwithdrawalsyndromethatoccurswithcessationattempts.Itpreventsnicotinestimulationofthemesolimbicdopamine systemassociatedwithnicotineaddiction.

Comment [اشرف2]: The treatment was not used on living organisms (in vivo), but all research was done in the vitro

Methods: TheauthenticityofVARwasestablishedbyDSCandFTIRspectra.AUVspectrophotometricmethodwasemployedfordeterminationofVARinbulkandactivepharmaceuticalingredient(API).

Comment [اشرف3]: Change the abbreviations to the detailed name

Results: TheauthenticityofVARwasestablishedbyDSCandFTIRspectra.AUVspectrophotometricmethodwasemployedfordeterminationofVARinbulkAPI(activepharmaceutical ingredient). The UV method was linear within the range of 5-40 µg/ml. The proposedmethodology is robust which can be concluded from the lower % CV values of intraday and inter dayvariability.Thehigherregressioncoefficientvalue(0.999)indicatesthemethodologyisrobust.

Conclusions: Theoutcomeofthephysico-chemicalexperimentsofdrugmoleculeindicatessuitability of oral route. Additionally, at different conditions like solid as well as liquid state, the drugmoleculewasobservedstable.

Keywords:Preformulation,Varenicline,Oralformulation,orallydisintegratingFilm,Stability

Inroduction

Comment [اشرف4]: Introduction

oral cavity is about 100cm2. The oral mucosal surface is constantly washed by the saliva (daily turn

The self-effacing tablet, and its alter ego, the two-piece hard gelatin capsule, remains at the forefront. Drug delivery through oral route offers many in terms of oral dosage form. The oral cavity has some important significant interest in the development of modified features, such as: low enzymatic activity; it easily releases oral dosage forms because oral delivery accessed facilitating the administration and the market holds approximately 52% of the market.Oral cavity, although highly vascularized area;allowing drug substances to enter to systemic circulation. Some commonly associated problems with oral cavity are where the drugs are directly permeable in the systemic circulation leading to hepatic first pass metabolism resulting into poor oral bioavailability [1]. Administration of drugs while minimizing the risk of chocking involves formulation of Fast dissolving or quick dissolving dosage forms.[2]Partial loss of active ingredients due to tablet leads to dosage inaccuracy and drug therapy properties and They undergo overdosing or ine□ciency [1,2].

Many patients find it difficult to swallow tablets and of the patient within a minute, without the need of hard gelatin capsules and do not take their drinking water where they release the active medicines as prescribed. Difficulty in swallowing or pharmaceutical ingredient, problem of dysphagia is seen to affect nearly 35% general population. Other groups, are the mentally ill. A fast dissolving film dissolves disabled, uncooperative patient and reduced liquid rapidly than other conventional dosage forms [3]. These films are less friable and easy to carry and may be associated with number of medical conditions dosage form compared to commercialized orally who may has generated tremendous business interest experience problems in swallowing solid dosage because of their potential to provide line extension in forms,

disintegrating tablets, which need special packing [4-5].

Likewise, a single dose of strip can be carried easily and may improve patient compliance and generate business. Certain biochemical and physiological aspects of individual drug without requiring the secondary absorption and metabolism, many drugs, cannot be given through this route of administration [8-11]. It is very important to address the delivered effectively through the conventional oral poor stability of liquid dosage forms, especially the route, because after administration are subjected to aqueous formulations.[6-7]

Delivery of any drug requires a stable dosage form pre-systemic clearance extensively in liver, which often leads to a lack of significant correlation to achieve optimum efficacy. For the development of between membrane permeability, absorption, and dosage forms, study of fundamental properties of drug molecule is required. [8-9]

Preformulation is a group of studies that focus on the physicochemical properties of a new drug and the development of a dosage form. Transmucosal routes of drug has intrinsic chemical and physical properties which delivery (i.e., the mucosal linings of the nasal, has been consider before development of rectal, vaginal, ocular, and oral cavities) offer pharmaceutical formulation. This property provides distinct advantages over peroral administration for the framework for drugs combination with systemic effect. Among the various transmucosal pharmaceutical ingredients in the fabrication of routes, oral mucosa has an excellent accessibility, dosage form. Objective of preformulation study is to an expanse of smooth muscle. The total area of the develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish. This article explains some properties and techniques for preformulationevaluation parameters of varenicline tartrate for oral film[10]. Preformulation is the first step in the rational formulation of an active pharmaceutical ingredient (API). It is an investigation of the physicochemical properties of the drug substance, alone and in combination with excipients. Varenicline (VRC), 6,7,8,9-tetrahydro-6,10-methano-6H- pyrazino(2,3- h) benzazepine (VAR) is a relatively novel agent that is a centrally acting a potent and selective partial agonist for α4β2 nicotinic acetylcholine receptors, has been used for smoking cessation treatment.1 It was shown to modify the dependence-related behavioral effects of nicotine. Literature depicted that varenicline showed significant benefit over NRT in measures of craving and withdrawal by decreasing the urge to smoke, negative effect and restlessness. [11]

The aim of the present work was to perform preformulation studies to inform development of

orodispersible film of Varenicline tartrate for the purpose of determining the physical chemical characteristics with possible interactions with excipients. [12]

Materials and Methods

2.1. Materials

Varenicline API was obtained as a gift sample from Torrent Pharmaceuticals, India. Methanol, Ethanol, Ethyl Acetate, Dichloro methane (DCM) were obtained as a gift sample from Final Limited, India. Chemicals and solvents used were of high-performance liquid chromatography (HPLC) grade. Freshly prepared distilled water was used throughout the study.

2.2Drug Identification

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

2.3Determination of Thermodynamic Solubility

Solubility study of drug was performed using different solvents such as methanol, ethanol, dimethyl sulfoxide, ethyl acetate, Dichloromethane (DCM) and N-Methyl-2- Pyrrolidone. Samples were shaken on a rotary shaker at 37ºC for 24 hours. The two phases are then separated by filtration [6]. Amount of solute in supernatant is then determined using UV spectrophotometric analysis at the corresponding λmax of each solvent.

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

The physical stability of VAR with polymer was evaluated at 25□ and 60% relative humidity (RH). Additionally, the samples were also closed in vials and stored in refrigerator (2–8□). The

samples were removed after 30 days.

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

The FTIR analysis was used for qualitative estimation and identification of functional group present in the compound. VAR was mixed with each of the components at an appropriate ratio; equivalent to that used in formulation process. Each mixture was stored in USP type-1 glass vial at 25°C±5°C, 60±5% RH (relative humidity) for one month. FTIR spectroscopy, Shimadzu, Model 8400, Japan, was used to study the compatibility of pure drug and other preparation composites, by KBr pellet method and scanned from 4000 to 400 cm-1.

2.5.2. **Differential Scanning Calorimetry (DSC) [15]**

DSC is the thermal analysis method by which we can measure the interaction of drug with polymer. The thermal analysis of Drug, Polymer(Kollicoat IR), physical mixture of Drug and polymer was performed by using 3-5 mg of samples in a standard thermal aluminum pan with a can measure the interaction of drug with polymer. The thermal analysis of Drug, PLGA, physical mixture of Drug and Polymer was performed by using 3-5 mg of samples in astandard thermal aluminum pan with a comparable lid and heated from 0 to 300°C at a 10°C/min heating rate in Mettler toledo 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.

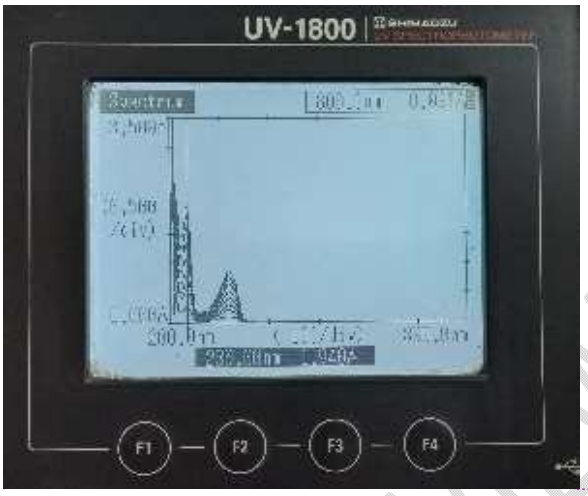

Fig.1.UVspectraofVARinmethanolat236nmand319nmλ-max

3.1.3. Drug identification by FTIR

Results found in FT-IR spectra and Characteristic peaks of VAR drug founds similar to reference FT-IR spectra of VAR drug. The characteristic absorption peaks of VAR in FT-IR spectra is shown in Fig. 2 and the functional groups responsible for characteristic peaks of VAR are mentioned in Table 1.

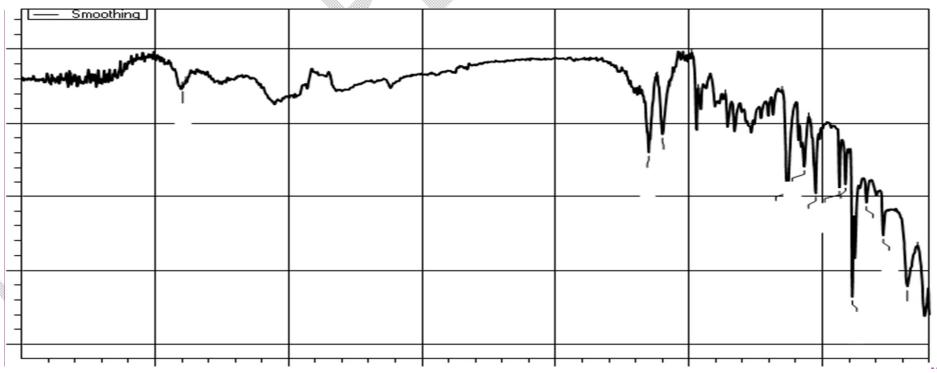

Fig. 2. Fourier transform-infrared spectrum of

VAR Table 1. Stretching bending of

Varenicline

Peak at wave number (cm-1)	Interpretation

Comment [اشـرف5]: Picture is not clear

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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

DSC thermogram of VAR is shown in Fig. 4 which shows sharp melting peak at 196.23□ (195-197□). The melting point determined by capillary method was found at 195-197°C. This confirms the authenticity of drug sample. There were no any additional peaks which further confirms stable characteristics of drug.

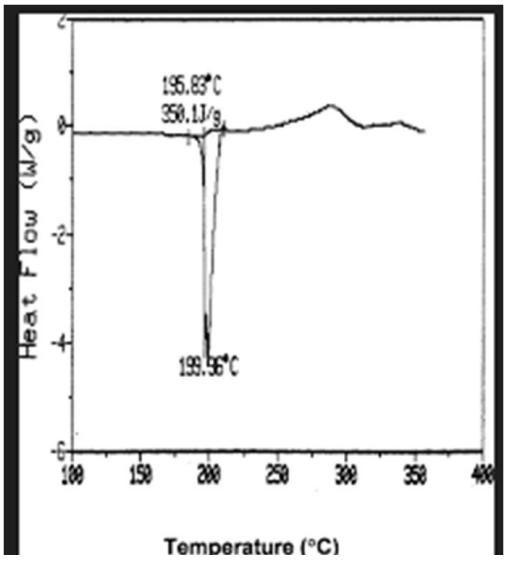

Fig. 3. Differential Scanning Calorimetry (DSC) of Varenicline

3.2. Determination of Thermodynamic Solubility

Varenicline is a freely soluble in water, soluble in dimethyl formamide and N-Methyl-2-Pyrrolidone, sparingly soluble in dichloromethane, very slightly soluble in methanol, ethanol and ethyl acetate. The solubility of drug in various solvents is shown in the Table 2.

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

The development of spectrophotometry methods for the determination of drugs has been increased considerably in recent years because of their importance in pharmaceutical analysis. Based on the experimental data the standard calibration curves were plotted. The regression analysis showed very good correlation (r^2=0.9999) in acetonitrile. These solutions obeyed Beer-Lambert's law and the linearity was found in concentration range of 2-8 µg/ml in acetonitrile. The standard curve of VAR is shown in Fig. 4.

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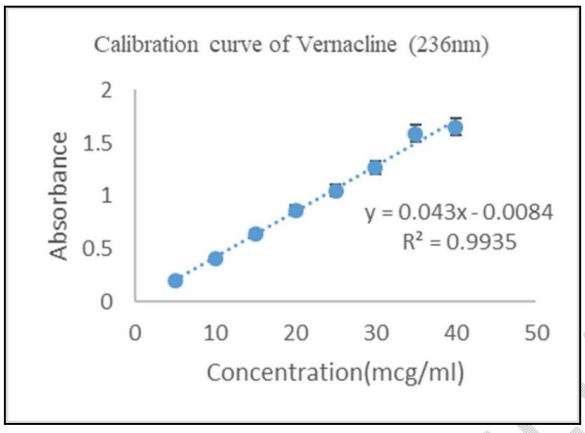

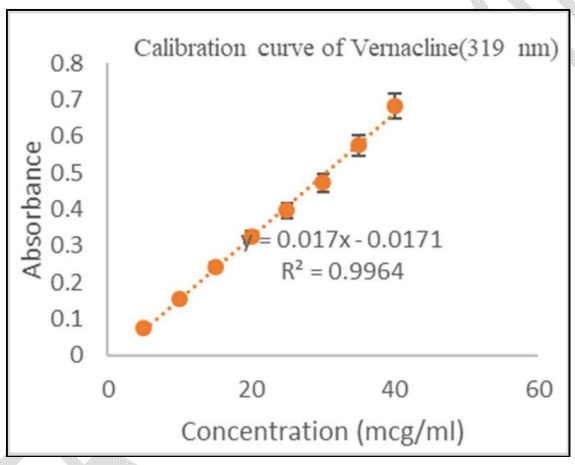

Fig. 4. Standard curve of Varenicline in Methanol

3.4. Drug-Polymer Compatibility Study

The characteristic absorption peaks of VAR in FT-IR spectra as shown in Fig. 3 proves stable and pure drug profile. Further, stability of VAR has been also assessed at various temperatures, moisture, light and oxidation condition. The results obtained from stability study under preformulation exhibited stable characteristics of drug at different storage conditions which are shown in Table 3.

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 FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug Varenicline and in the physical mixture which confirms the absence of chemical interaction between drug and polymers. The FT-IR spectra of physical mixture in initial condition and after 1- m o n t h study are shown in Fig. 5 and 6 respectively and the functional groups responsible for characteristic peaks are mentioned in Table 4

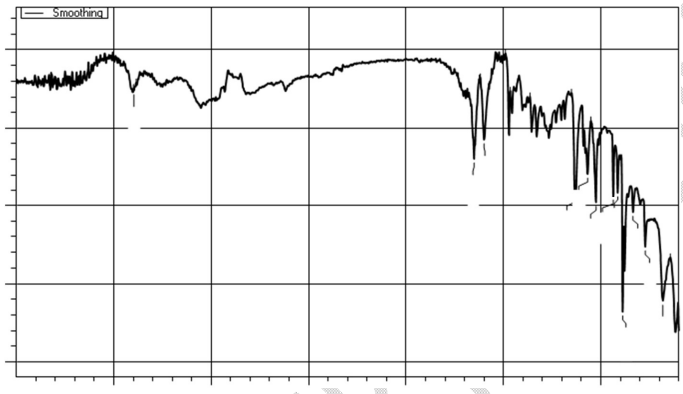

Fig. 5. Fourier transform-infrared spectrum of Varenicline-Polymer mixture (Initial)

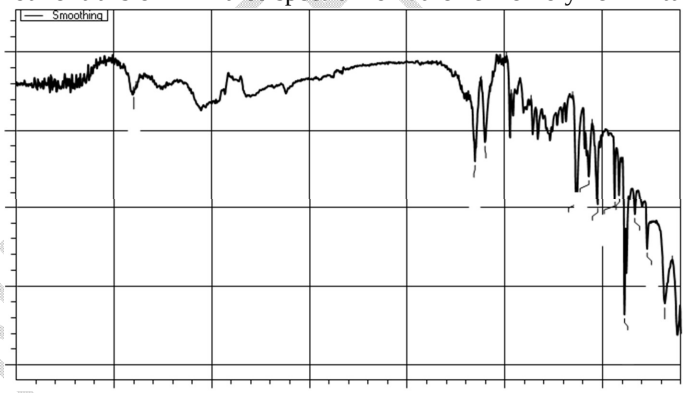

Fig. 6. Fourier transform-infrared spectrum of Varenicline-Polymer mixture (1 Month, 25℃/60%RH)

Table 4. Compatibility of Varenicline-Polymer mixture by FTIR

Varenicline	Varenicline + Polymer	Varenicline + Polymer	Interpretation

(API)	mixture (Initial)	mixture (1 M 25°C/60% RH)	
X (cm-1)	X (cm-1)	X (cm-1)	
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

3.4.2 Differential Scanning Calorimetry (DSC)

DSC thermogram of VAR and polymer mixture showed that there is no change observed in the endothermic peak of drug and polymer in physical mixture at initial condition and after 1 month, which confirms the absence of chemical interaction between drug and polymers as shown in Fig. 7 and 8 respectively.

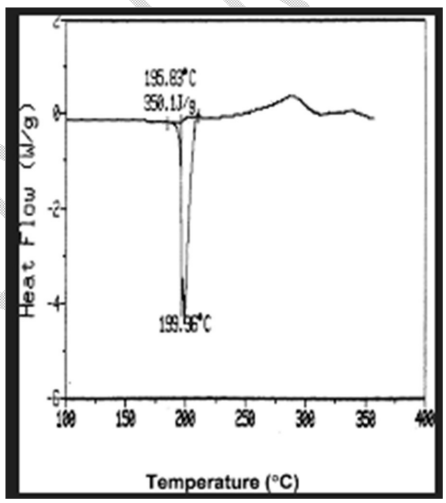

Fig.7. Differential Scanning Calorimetry (DSC) of Varenicline-Polymer mixture (Initial)

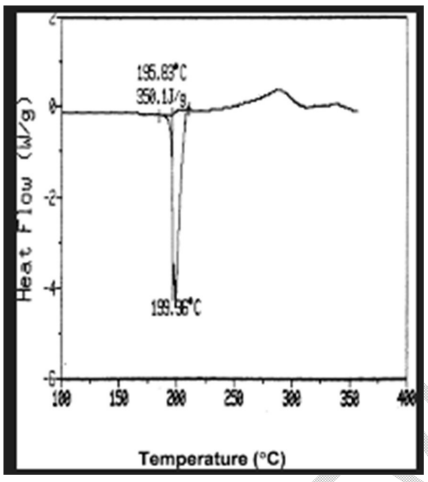

Fig. 8. Differential Scanning Calorimetry (DSC) of Varenicline-Polymer mixture (1 Month, 25□/60%RH)

Discussion

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Conclusion

From the results of the different preformulation studies, it can be concluded that VAR is suitable for formulation of orally disintegrating film. The results of UV, FT-IR and DSC suggested the drug is authentic. The UV method showed good correlation indicating they can be used for quantification of drug in bulk and in vitro studies. The solubility study of drug suggested that it is soluble in aqueous media suggesting its suitability for fast release formulation. Stability study under preformulation studies revealed stable characteristics of drug confirming final stability of formulation.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

REFERENCES

Comment [اشـرف10]: 1-Please check the sources and write them in full with the names of the researchers, and make sure of the research years for all research
2-The sources need more recent research, if any, for the previous five years, i.e. from 2018 to 2023

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