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PREFORMULATION STUDIES OF DROTAVERINE HCL: AN INTEGRAL PART OF FORMULATION DESIGN

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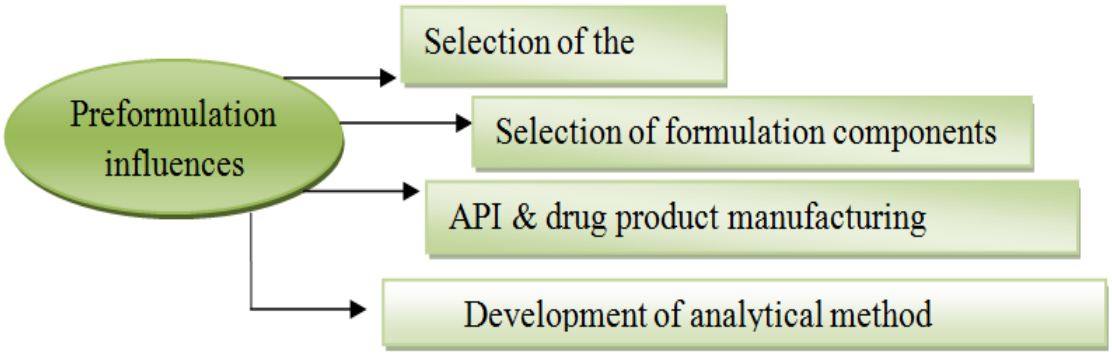
ABSTRACT
Preformulation study is a part which is initiated once the new molecule is seeded. In a broader way, it deals with studies of physical, chemical, analytical, and pharmaceutical properties related to molecule and provides idea about suitable modification in molecule to show a better performance. Preformulation parameters study can be linked to generation of effective, safer, stable, and reliable pharmaceutical formulation. Drotaverine, a selective phosphodiesterase (PDE) isoenzyme IV inhibitor. It has been found to be useful in spastic and motility disorders of the smooth muscle in adult. In the present works overall objective of preformulation studies of Drotaverine HCl is to generate information useful in developing stable and Bioavailable dosage forms.

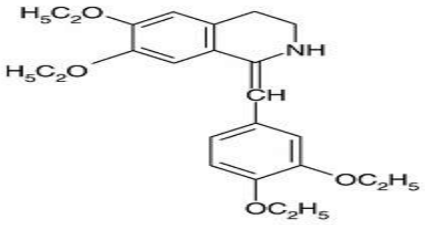
KEYWORDS: Preformulation study, Drotaverine HCl, Solubility & Analytical methods.

INTRODUCTION

Preformulation study is the primary step in the rational development of dosage forms of a drug substance. The study includes an investigation of physical and chemical properties of a drug substance alone and with combined with excepient. The general objective of preformulation testing is to generate information helpful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico-mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials.[1] These studies should spotlight on those physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form. A systematic understanding of these properties may eventually provide a rational for formulation design, or support the need for molecular modification.[8] The aim of this study was to determine some of the physicochemical properties such as solubility, melting point, pKa, dissolution, assay development, stability in solution etc.[2-3]



Drotaverine hydrochloride, 1-[(3, 4-diethoxy phenyl) methylene]-6, 7-diethoxy-1, 2, 3, 4-tetra hydroisoquinolene is an analogue of papaverine.[4] It is phosphodiesterase IV enzyme inhibitor and acts as an antispasmodic agent, specific for smooth muscle spasm and pain, used to reduce excessive labor pain.[5] Drotaverine hydrochloride is official in Polish Pharmacopoeia.[6]

Drug (Drotaverine hydrochloride) description[7]	
IUPAC Name	(*Z*)-1-(3,4-diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline
Structure	
Molecular formula	C24H31NO4. HCl
Molecular Weight	433.97
Description	Light yellow or slightly greenish yellow crystalline powder, almost odourless
Solubility	Sparingly soluble in water, soluble in ethanol(96%), freely soluble in chloroform, slightly soluble in acetone, practically insoluble in petroleum ether.
Therapeutic category	Antispasmodic

In the present works an attempt was made to study preformulation parameters of Drotaverine HCl which helps to generate information useful in developing stable and Bioavailable dosage forms.

MATERIAL AND METHODOLOGY

Procurement of Drug: Drug (Drotaverine hydrochloride) was obtained as a gift sample from Provizer Pharmaceutical, Surat.

Organoleptic properties

Organoleptic properties of the drug sample were studied by visual inspection.

Preformulation studies[8-9]

Identification of Drug

Melting Point Determination

To determine the m.p. of drug powder, it was filled in a capillary tube with one end open and the other end closed and then the capillary was placed in a digital melting point apparatus.

Solubility

The solubility of Drotaverine HCl was determined in different solvent systems and buffers. An excess quantity of the drug was mixed with 10 ml of each solvent in screw capped glass tubes and shaken on constant water bath shaker for 24 hours at 25 ℃. The solutions were examined physically for the absence or presence of drug.

Partition coefficient

About 50mg of drug was dissolved in 50ml of distilled water and n-octanol separately and both the solution was mixed together by using wrist watch shaker for 30 min. Then the solution was kept in a separating funnel until two phases separated. The aqueous phase was then filtered through the filter paper and was diluted 100 times. The absorbance of both the solutions was taken at 234nm by using UV spectrophotometer. The concentration of drug was determined with the help of standard curve and partition coefficient was determined by following formula:

$$\text{Partition coefficient} = \frac{\text{Concentration of drug in organic phase}}{\text{Concentration of drug in aqueous phase}}$$

FTIR spectroscopy studies

FTIR (ATR Bruker, Germany) were used. The IR spectrum was obtained by scanning it in the range 4000-500nm and compared with the reference pharmacopoeia (IP-2014).

Analytical Method

UV spectroscopy was selected as the suitable analytical method for estimation of the drug.

Standard Stock Solution

The standard stock solutions of Drotaverine HCl was prepared by dissolving accurately weighed 100 mg of drug in 100 ml of distilled water in two 100 ml volumetric flasks to get a concentration of 1000 µg/mL. The Solution was diluted with distilled water, to get a concentration of 100 µg/mL, and was kept as the stock solutions.

Determination of λmax

1 ml of standard stock solution of Drotaverine HCl was taken in 10 ml standard volumetric flask diluted to 10 ml with distilled water to get the concentration of 10 µg/ml. The absorbance of resulting solution was measured against respective blank solution (distilled water) in the UV region of 200-400 nm, which shows maximum absorbance at 234 nm.

Preparation of calibration curve

From the standard stock solution of Drotaverine HCl, appropriate aliquots were pipette out in to 10 mL volumetric flasks and dilutions were made with distilled water to obtain working standard solutions of concentrations from 1-12 µg/mL. Nine different concentrations were prepared in the range of 1-12 µg/mL and the absorbance were measured at 234 nm against solvent (water) blank and the absorbance values were noted. The obtained absorbance values are plotted.

Assay of Drotaverine hydrochloride

Accurately 10 mg of drug was weighed and transferred into a 100 ml volumetric flask, dissolved by swirling with 50 ml of water and then solution was made up to the mark with water. Ten ml of the resulting solution was diluted to 100 ml in another volumetric flask, and the absorbance of the final solution was measured at 234 nm against distilled water.

Table 1: Organoleptic Characteristics.

S.No.	Characteristics	Results
1.	Appearance	Pale Yellow Crystalline Solid
2.	Melting Point	211-213 ºC
3.	Solubility	Sparingly soluble in water, soluble in ethanol(96%), freely soluble in chloroform
4.	Partition coefficient	7.10

Determination of λmax

The absorption spectral analysis shows the λ_{max} of Drotaverine HCl at 234 nm**.**

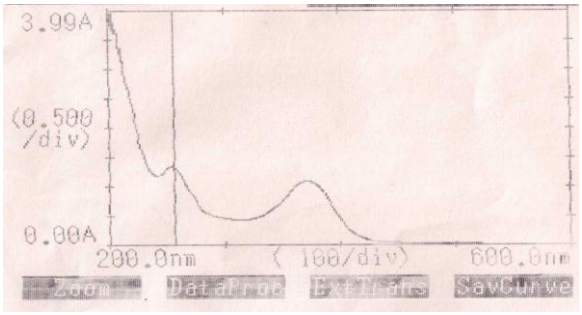


Fig. 1: λmax determination.

Table 2: Results of Calibration Curve at 234 nm for Drotaverine Hydrochloride.

S.No	Concentration (µg / ml)	Absorbance at 234nm
1	1	0.043
2	2	0.072
3	3	0.108
4	4	0.148
5	5	0.182
6	6	0.218
7	8	0.299
8	10	0.376
9	12	0.461

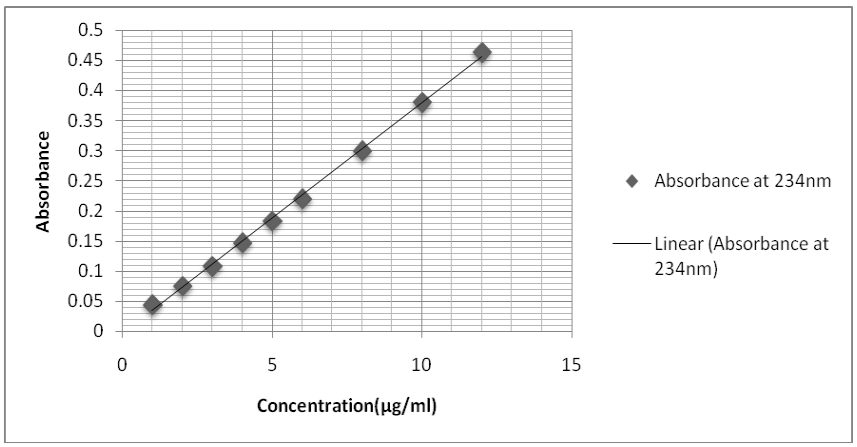


Fig. 2: Calibration curve of Drotaverine HCl in Distilled water.

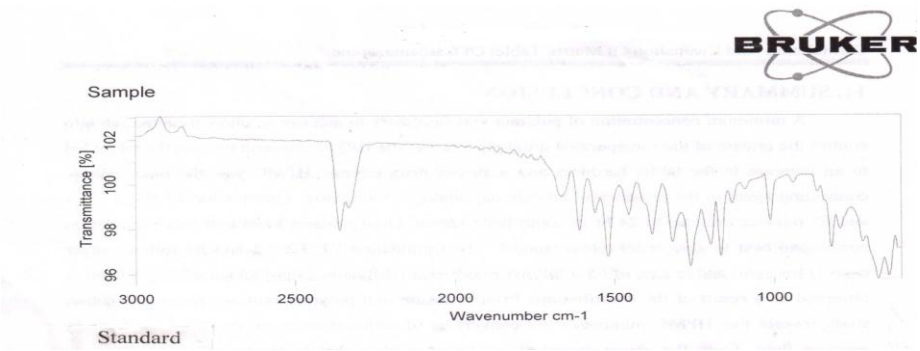


Fig 3: IR spectra of standard drotavetrin HCl.

Table 3: Interpretation of IR spectrums.

Sample	Obtained peak values(cm^{-1})	Theoretical frequency(cm^{1})[15-16]	Functional group
Drotaverine HCl	3468.20	3500-3100	Secondary Amines (-NH) Str
	3068.13	3150-3000	Aromaticity
	3012.35	3000-2850	Methyl (-CH_3) Str.
	1608.58	1650-1550	Aromaticity(Benzene overtones)
	1082.45	1350-1000	Amine (C-N) Str.
	1008.67	1100-1000	C-O ethoxy

RESULTS AND DISCUSSION

The overall objective of the present work was to investigate preformulation studies of Drotaverine HCl is to generate information useful in developing stable and Bioavailable dosage forms. Various organoleptic characteristics were tabulated in table 1. The partition coefficient of rutin was found 7.10, which confirm the lipophilicity of the drug. The analytical method for determination of drug was UV spectroscopy. The absorption spectral analysis showed the λ_{max} of Drotaverine HCl at 234 nm (Fig.1). The calibration curve was obtained for a series of concentration in the range of 1-12 µ g/mL. It was found to be linear and hence, suitable for the estimation of the drug, as shown in the table 2 & fig 2. The FTIR spectrum, there was no variation in the Drotaverine HCl peaks from the standard spectrum of IP 2014(fig 2). The result was tabulated in table 2.

CONCLUSION

The preformulation phase is a vital phase in establishing the properties of drug that will allow suitable risk assessment for development. Usually it begins during the lead optimization phase, continues through predomination, and on into the early phases of development. Hence, it is imperative that preformulation should be performed as carefully as possible to facilitate rational decisions to be made. The preformulation study of Drotaverine HCl is to generate information useful in developing stable and Bioavailable dosage forms.

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