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PREFORMULATION STUDIES OF TRAMADOL HCL: VITAL PART OF FORMULATION DESIGN

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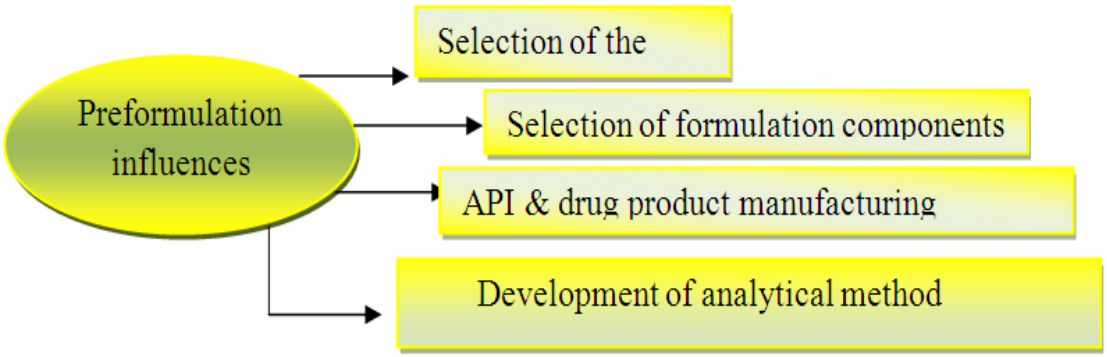
ABSTRACT
Preformulation study is a fraction which is initiated once the new molecule is seeded. In a broader way, it deals with studies of physical, chemical, analytical, and pharmaceutical properties related to molecule and provides idea about suitable modification in molecule to show a better performance. Preformulation parameters study can be linked to generation of effective, safer, stable, and reliable pharmaceutical formulation. Tramadol Hydrochloride is a centrally acting synthetic opioid analgesic. The mode of action is not clear, even though the parent and metabolite of Tramadol binds to μ-opioid receptors and results in weak inhibition and reuptake of nor-epinephrine and serotonin. In the present works overall objective of preformulation studies of Tramadol HCl is to generate information useful in developing stable and Bioavailable dosage forms.

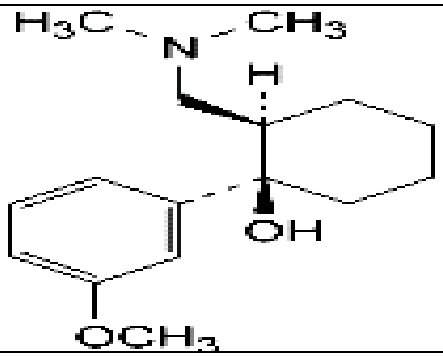
KEYWORDS: Preformulation study, Tramadol HCl, Solubility & Analytical methods.

INTRODUCTION
Preformulation study is the principal 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 aim 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. 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]



Tramadol hydrochloride, (±)cis-2-[(dimethylamino) methyl]-1-(3- methoxyphenyl) cyclohexanol. Hydrochloride.[4] Tramadol Hydrochloride is a centrally acting synthetic opioid analgesic. The mode of action is not clear, even though the parent and M1 metabolite of Tramadol binds to μ opioid receptors and results in weak

inhibition and reuptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-opioid receptors. In several animal tests Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone.[5]

Drug (Tramadol hydrochloride) description[6-7]	
IUPAC Name	(±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol Hydrochloride
Structure	
Molecular formula	$C_{16}H_{25}NO_2$. HCl
Molecular Weight	299.8
Description	White, bitter, crystalline and odorless powder
Solubility	It is readily soluble in water and ethanol
Therapeutic category	Opioid analgesic

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

MATERIAL AND METHODOLOGY

Procurement of Drug: Drug (Tramadol hydrochloride) was obtained as a gift sample from Milton Drugs Pvt. Limited Puducherry.

Organoleptic properties

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

Preformulation studies[8-10]

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 Tramadol 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:

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

Hygroscopicity

Hygroscopic substance absorbs water because of hydrate formation. These type of change in moisture content may greatly influence the parameters like chemical stability, flowability and compatibility. Hygroscopic analysis is done by placing 2mg of drug at two petri dish with a thin powder bed for assure maximum atmospheric exposure. These samples are then exposed to the atmosphere and kept for 48 hrs and then again the powder.

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring perceived blend into a graduated cylinder via a large funnel and measure the volume and weight as is given by.

Bulk density = weight of the blend /bulk volume of the blend

Tapped density

Tapped density is determined by placing a graduated cylinder containing known mass of blends on a mechanical tapper apparatus, which is operated for a fixed number of

taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.
Tapped density =weight of blends/ tapped volume of blends

Carr's index
Carr's index is measured using the values of the bulk density and tapped density. The following equation is used to find the Carr's index

$$CI = \frac{(TD - BD)}{TD} x100$$

Where,
TD – Tapped density
BD – Bulk density

Angle of repose
The manner in which stresses are transmitted through a bed and the beds response to applied stress are reflected in the various angles of friction and repose. The most commonly used of these is angle of repose, which may be determined experimentally by a number of methods. The method used to find the angle of repose is to pour the powder in a conical heap on a level, flat surface and measure the inclined angle with the horizontal pile.

$$\tan\theta = h/r$$
$$\theta = \tan^{-1} h/r$$

Where, h- Height of the heap
r- Radius of the heap.

FTIR spectroscopy studies
FTIR (ATR Bruker, Germany) was 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 Tramadol 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 Tramadol 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 274 nm.

Preparation of calibration curve
100mg of Tramadol Hydrochloride was dissolved in phosphate buffer 7.4 in a 100ml standard flask and filled up to the mark using phosphate buffer 7.4. Serial dilutions were made in phosphate buffer pH 7.4 in order to obtain 10µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml. Absorbance of these solutions were measured at 274nm using UV-Visible Spectrophotometer [Schimadzu 159] and standard graph was plotted.

Table 1: Preformulation Characteristics.

S.No.	Characteristics	Results
1.	Appearance	White, bitter, crystalline
2.	Melting Point	211-213 ºC
3.	Solubility	Sparingly soluble in water, soluble in ethanol(96%), freely soluble in chloroform
4.	Partition coefficient	1.34
5.	Hygroscopicity	(-)ve
6.	Bulk density	0.63±0.02
7.	True density	0.55±0.009
8.	Carr's index	12.2
9.	Angle of repose	38.91±0.4.1

Determination of λmax
The absorption spectral analysis shows the λ_{max} of Tramadol HCl at 274 nm**.**

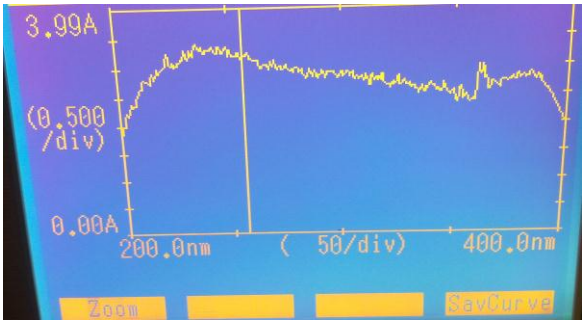


Fig. 1: λmax determination.

Table 2: Standard plot of Tramadol Hydrochloride in phosphate buffer 7.4.

Concentration (µg/ml)	Absorbance at 274 nm
0	0.00
10	0.196
20	0.384
30	0.586
40	0.776
50	0.946

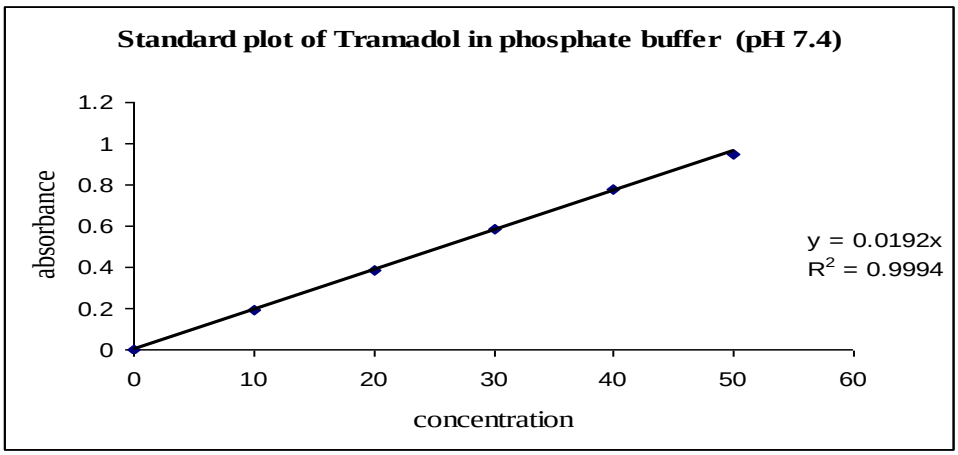


Fig. 2: Standard cuve of Tramadol.

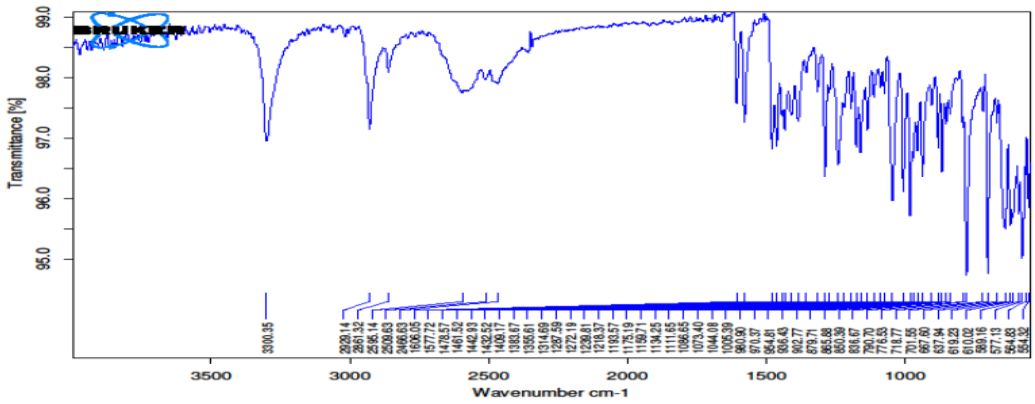


Fig 3: IR spectra of standard Tramadol.

Table 3: Interpretation of IR spectrums.

Sample	Obtained peak values(cm^{-1})	Theoretical frequency(cm^{1})	Functional group
Tramadol HCl	3100	3500-3100	Secondary Amines (-NH) Str
	1462	1450-1600	C=C(S)
	2961	2960-2850	Methyl (-CH) Str.
	938	900-1300	C-O(S)
	1040	1000-1410	Amine C-N(S)
	852	800-1200	C-C(S)

RESULTS AND DISCUSSION

The overall objective of the present work was to investigate preformulation studies of Tramadol HCl is to generate information useful in developing stable and Bioavailable dosage forms. Various Preformulation Characteristics were tabulated in table 1. The partition coefficient of rutin was found 1.34, which confirms the lipophilicity of the drug. The analytical method for determination of drug was UV spectroscopy. The absorption spectral analysis showed the λ_{max} of Tramadol HCl at 274 nm (Fig.1). The calibration curve was obtained for a series of concentration in the range of 10-50 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 Tramadol HCl peaks from the standard spectrum of IP 2014(fig 3). The result was tabulated in table 3.

CONCLUSION

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

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