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Novel application and spectrophotometric estimation of Melitracen HCl tablet dosage form using Niacinamide as hydrotropic solubilizing agent

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Abstract

Various organic solvents like methanol, chloroform, alcohol, dimethyl formamide; acetonitrile, hexane, acetone and carbon tetrachloride have been employed for solubilization of poorly water-soluble drugs for spectrophotometric estimations. Drawbacks of organic solvents include higher cost, toxicity and error in analysis due to volatility. Attempting to minimize these drawbacks, three new, simple, accurate, environmental friendly, cost effective, safe, sensitive spectrophotometric methods have been developed. The primary objective of the present investigation was to employ these hydrotropic solutions to extract the drugs from their dosage forms, precluding the use of costlier organic solvents. Ultraviolet absorption spectrophotometric method for the estimation of poorly water soluble drugs like Melitracen HCl in pharmaceutical formulations has been developed. Aqueous solubilities of this selected model drugs was to a great extent (28 to 35 fold) in 5.0 M niacinamide solutions**.** The selected λmax for Melitracen HCl were 286.5 nm respectively. The hydrotropic solutions used did not show any absorbance above 306 nm, and therefore, no interference in the estimation was seen. The results of analysis have been validated statistically, and by recovery studies.

Keywords: Hydrotropic Solubilization, Melitracen HCl, niacinamide.

Introduction

Melitracen HCl[1-7] is a white to off White Powder. Amorphous in nature, sensitive to light and moisture. Chemically it 3-(10, 10-dimethyl anthracen-9-ylidene)-N, N-dimethylpropan-1-amine). It is a Tricyclic Antidepressant. And work by inhibiting there-uptake of the neurotransmitters norepinephrine and serotonin by neurons. Tricyclics may also possess an affinity for muscarinic

and histamine H_1 receptors to varying degrees. Although the pharmacologic effect occurs immediately, often the patient's symptoms do not respond for 2 to 4 weeks used in treatment of Trigeminal Neuralgia and severe depression state. A simple, selective, rapid, precise and economical reverse phase HPLC method [8-9] has been developed for the estimation Melitracen Hydrochloride in pharmaceutical dosage forms. However, there is no HPLC method reported for the simultaneous estimation of these drugs in single as well as combined dosage form. Fixed dose containing Melitracen (50 mg is available in the tablet form in the market. The present RP-HPLC method was validated following the ICH guidelines[10-11]. Increasing the aqueous solubility of insoluble and slightly soluble drugs is of major importance. Various techniques have been employed to enhance the aqueous solubility of poorly water soluble drugs. Hydrotropic solubilization is one of them. The term hydrotropy has been used to designate the increase in solubility of various substances in water due to the presence of large amounts of additives. Sodium benzoate, sodium acetate, sodium bicarbonate, sodium chloride, sodium gluconate, thiourea, tri sodium citrate and urea have been employed to enhance the aqueous solubility of many poorly water soluble drugs. Various hydrotropic agents have been used to enhance the aqueous solubility of a large number of drugs[12-27]. Various organic solvents like methanol, chloroform, alcohol, dimethyl formamide and benzene have been employed for the solubilization of poorly water soluble drugs for spectrophotometric estimations. Drawbacks of organic solvents include higher cost, toxicity, pollution, and error, in analysis due to volatility. The primary objective of this study was to employ hydrotropic solubilizing agents for Melitracen HCl to preclude the use of organic solvents.

Materials and Methods

UV Visible spectrophotometer (Shimadzu Model 1601) was employed with spectral bandwidth of 1 nm and wavelength accuracy of 0.3 nm (with automatic wavelength correction with a pair of 1 cm matched quartz cells). All chemicals and solvents used were of analytical grade. Niacinamide was obtained as a gift sample from M/s Alkem Laboratories Ltd., Mumbai. Since niacinamide does not absorb above 286.5 nm and there was more than 35-fold enhancement in solubility of Melitracen HCl in 5.0 M niacinamide solution, it was thought worthwhile to use this hydrotropic solution to extract the drug from fine powder of tablets to carry out spectrophotometric estimation.

Calibration-curve

Accurately weighed 100 mg of Melitracen HCl was solubilized by 50 ml of 5.0 M niacinamide solution in a 100 ml volumetric flask, and distilled water was added to make up the volume. It was necessary to warm on a water bath to accelerate the dissolution process. The standard solutions were diluted with distilled water to obtain various dilutions (5, 10, 15, 20, 25, 30, 35μg/ml). The λmax of Melitracen HCl was found at 286.5 nm. The linear relationship was observed over the range of 5-35 μg/ml. of drug. Absorbances were noted at 300.5 nm against corresponding reagent

Preliminary solubility studies of drugs:

Solubility of Melitracen HCl were determined at 29±1°c. An excess amount of drug was added to screw capped 100 ml glass vials containing different aqueous systems viz. distilled water, buffer of pH 7.5 to 9.5 and hydrotropic solutions. 5.0 M niacinamide solution. The vials were shaken mechanically for 21 hrs at 29±1° in a mechanical shaker. These solutions were allowed to equilibrate for the next 35 hrs, and then centrifuged for 20 minutes at 1850 rpm. The supernatant of each vial was filtered through Whatmann filter paper no. # 41. The filtrates were diluted suitably, and analyzed spectrophotometrically against corresponding solvent blank.

Analysis of the tablet formulations of the drug by proposed method:

Twenty tablets of Melitracen HCl formulation were weighed, and ground to a fine powder. An accurately weighed powder sample equivalent to 50 mg of Melitracen HCl was transferred to a 100 ml volumetric flask. 100 ml of 5.0 M niacinamide solution was added, and the flask was shaken for about 10 min to dissolve the drug, and the volume was made up to the mark with distilled water. The solution was filtered through Whatman filter paper No. # 41. The filtrate was divided into two parts A, and B. Part A was kept at room temperature for 48 hrs to check its chemical stability and precipitation, if any. Part B was diluted appropriately with distilled water, and was analyzed on a UV Spectrophotometer against reagent blank. The drug content of the tablet formulation was then calculated. There was no precipitation in Part A solution after 48 hrs. After 48 hrs (at room temperature), Part A solution was analyzed in the same way as Part B solution.

Recovery Studies

In order to check the accuracy, reproducibility and the precision of the proposed method, recovery studies were conducted. Pre analyzed tablet powder (formulation-I) equivalent to 50 mg of Melitracen HCl was transferred to a 100 ml volumetric flask. Pure Melitracen HCl drug sample (10 mg) was added to the same volumetric flask. Now 40 ml of 5.0 M niacinamide solution was added and the flask was shaken for about 5 min to solubilize the drug. Then volume was made upto the mark with distilled water. Then solution was filtered through Whatman filter paper # 41. The filtrate was diluted with distilled water appropriately and absorbance was noted at 309.5 nm against corresponding reagent blank. Drug content was calculated and % recovery was calculated (Table II). Similar procedure was repeated using 15 mg and 20 mg of pure Melitracen HCl as spiked concentration (in place of 10 mg). Recovery studies using formulation II and III in the same way. The drug contents were determined and % recoveries were estimated (Table II).

Table I: Results of analysis of commercial tablet formulations

Hydrotropic Solution	T F	LC (mg/tab**)**	estimated* (Mean±S.D)	Coeff. of variation	S.E.
5.0M niacinamide	I	50	100.0±0.19	0.65	0.09
5.0M niacinamide	II	50	99.97±0.10	0.39	0.24
5.0M niacinamide	III	50	101.2±0.09	0.53	0.88

*TF- Tablet formulation, LC- Label claim, SE- Standard error, *Mean of three determinations*

Table II: Recovery study for spiked concentration of drugs added to the pre analyzed dosage form

Hydrotropic Solution	T F	AD	Drug Added (spiked mg)	estimated* (Mean±S.D)	Coeff. of variation	S.E.
5.0M niacinamide	I	50	10	100.1±0.11	0.23	0.27
5.0M niacinamide	II	50	15	101.2±0.09	0.43	0.11
5.0M niacinamide	III	50	20	99.89±0.82	0.16	0.21

TF- Tablet formulation, AD- Amount of drug, S.D-Standard deviation, SE- Standard error

Results and Discussion

Results of solubility studies indicated that enhancement in aqueous solubilities of Melitracen HCl in 5.0 M niacinamide solution were more than 28 and 35 folds, respectively as compared to their solubilities in distilled water. Therefore, this solution was employed to extract Melitracen

HCl from the fine powder of tablet formulation. The pH of hydrotropic solutions was ranges from 7.7 to 9.0. Therefore, in order to study the influence of pH on solubilities, buffer solutions of pH 7.7 to 9.0 were made, and the solubilities of all the drugs were determined. This study proves that increase in solubilities of hydrotropic solutions are not due to alteration in pH, but are due to hydrotropic phenomenon. This indicates that the enhancement in the aqueous solubility of Melitracen HCl in 5.0 M hydrotropic solutions was largely due to hydrotropy.Part A solution of drug was kept at room temperature for 48 hrs. There was no precipitation of drug in Part A solutions within 48 hrs. In addition, drug contents of Part A solutions (after 48 h) were same as those of Part B solutions (fresh solutions). This study reveals that the estimations can be done within 48 hrs at least, without having any detrimental effect on drug stability. From Table I, it is evident that there is good agreement between the amounts estimated, and those claimed by the manufacturers. Percent label claims are very close to 100, with low values of standard deviation, % coefficient of variation, and standard error. Accuracy, reproducibility, and precision of the proposed methods, were further confirmed by percent recovery values, which were close to 100 with low values of standard deviation, % coefficient of variation, and standard error (Table I). From this study, it is obvious that there was no interference of hydrotropic solutions in the estimation of Melitracen HCl (λmax 286.5 nm) hydrotropic solutions do not absorb above 306 nm. Because of these reasons, it can be concluded, that a large number of poorly water soluble drugs having λmax above 306 nm, may be tried for estimation by the proposed method, provided that their preliminary solubility studies are conducted to observe the enhancement effect on solubility. Hydrotropic solutions are cheaper than most of the organic solvents and can thus substitute expensive methanol, dimethyl formamide, chloroform and carbon tetrachloride. Drawbacks of organic solvents include toxicity, error due to volatility, pollution, and cost. Thus 5.0 M Hydrotropic solutions may be better substitutes for organic solvents.

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