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Preformulation Studies of Pralidoxime Chloride for Formulation Development of Microspheres

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ABSTRACT

Microspheres are one of the novel drug delivery system which possess several applications and are made up of assorted polymers. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm range in diameter having a core of drug and entirely outer layers of polymers as coating material. They are made up of polymeric, waxy or other protective materials i.e. biodegradable synthetic polymer and modified natural products such as starches, gums, proteins, fats and waxes. Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form. This couldprovide important information for formulation design or support the need for molecular modification. Every drug has intrinsic chemical and physical properties which has been consider before development of pharmaceutical formulation. This property provides the framework for drugs combination with pharmaceutical ingredients in the fabrication of dosage form. Objective of preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish Physico-chemical parameter of new drug substances. The purpose of the present study was to systematically investigate some of the important physicochemical properties of pralidoxime chloride for preparation of microspheres. The physicochemical properties such as solubility, pKa, dissolution, melting point, assay development, excipient compatibility etc. of pralidoxime chloride was carried out. Before selection of excipients, the Preformulation study of drug pralidoxime is completed for successful formulation of microspheres. The result of Preformulation studies shows good flow properties, excipient compatibility, solubility efficiency and melting point. From this study we concluded that pralidoximewith HPMC and EC can be used to formulate pralidoxime microspheres for modified release.

Keywords: Microspheres, Preformulation, Pralidoxime chloride, Physico-chemical parameter.

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INTRODUCTION

Preformulation evolved in the late 1950s and early 1960s as a result of a shift in emphasis in industrial pharmaceutical product development. It was improvement in analytical methods that spurred the first programs that might bear the name "preformulation". The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass-produced. During the early development of a new drug substance, the synthetic chemist, alone or in co-operation with specialists in other disciplines including preformulation, may record some data which can be appropriately considered as preformulation data. Before starting the preformulation studies we should know the properties of the drug, potency relative to the competitive products and the dosage form, literature search providing stability and decay data, the proposed route of drug administration, literature search regarding the formulation approaches, bioavailability and pharmacokinetics of chemically related drugs. It also includes preliminary investigations and molecular optimization by the drug should be tested to determine the magnitude of each suspected problem area (Step I), if a deficiency is detected, a molecular modification should be done (Step II). To overcome this deficiency molecular modification is done be salts, prodrugs, solvates, polymorphs or even new analogues. The dissolution rate of a salt form of a drug is generally quite different from that of the parent compound. Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve much more readily than do the, respective free acids or bases. For example Ephedrine base is very poorly water soluble molecules that characterized by low solubility and dissolution rates. So, it is modified in the form of the salt Ephedrine HCL that is ionized and offer higher water solubility and dissolution rate. Preformulation commences when a newly synthesized drug shows sufficient pharmacologic promise in animal models to warrants evaluation in man. These studies should focus on those physicochemical properties of the new compound that

could affect drug performance and development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rational for formulation design, or support the need for molecular modification[1]. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000µm range in diameter having a core of drug and entirely outer layers of polymers as coating material. They are made up of polymeric, waxy or other protective materials i.e. biodegradable synthetic polymer and modified natural products such as starches, gums, proteins, fats and waxes[2]. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be achieved by coupling bioadhesion characteristics to microspheres[3]. Microspheres constitute an important part of such particulate drug delivery systems by virtue of their small size and efficient carrier capacity[4]. They have varied applications and are prepared by using various polymers. Mucoadhesive drug delivery system are delivery system which utilizes the property of bioadhesion of certain polymers which become adhesive on hydration and can be used for targeting a drug to a particular region of the body for extended periods of time. Pralidoxime chemically,2-formyl-1-methylpyridinium chloride oxime. It occurs as an odorless, white, nonhygroscopic, crystalline powder which is soluble in water. Stable in air, it melts between 215ºC and 225º C with decomposition. The specific activity of the drug resides in the 2-formyl-1-methylpyridinium ion and is independent of the particular salt employed. The chloride is preferred because of physiologic compatibility, excellent water solubility at all temperatures, and high potency per gram, due to its low molecular weight. Pralidoxime chloride is a cholinesterase reactivator. Pralidoxime (PAM^+, Cl^-, I^- and $CH_3SO_3^-$) was the first oxime antidote for treatment of organophosphate (nerve gas) poisoning[5-8]. PAM and subsequent oximes (obidoxime, TMB-4, HS-6, HI-6 etc.) act through regeneration of the irreversibly inhibited enzyme acetylcholinesterase. Therapy with oximes against organophosphate poisoning must commence immediately after exposure since some organophosphates otherwise may cause permanent damage (ageing) to the enzyme[9]. Since PAM is a quarternary ammonium compound it is poorly and slowly absorbed from the gastrointestinal tract. Together with a rapid renal elimination the oral route will be less useful even for prophylaxis[10-16]. Intramuscular administration shows high availability and rapid absorption. Thus, the parenteral route is the best if not the only way to administer PAM to a poisoned individual[11,13, 15].

MATERIAL AND METHODS

Chemicals and reagents

Pralidoxime chloride was synthesized and taken from DRDE, Gwalior. All the chemicals used in this study were obtained from Hi Media Laboratories Pvt. Ltd. (Mumbai, India), SD Fine-Chem. Ltd. (Mumbai, India) and RANKEM RFCL Ltd.(New Delhi, India). Water was glass-double distilled and further purified from Milli Q water purification system. All the chemicals used in this study were of analytical grade.

Methods

The purpose of Preformulation study was to establish physicochemical parameters of drug, physical characteristics & compatibility with common excipients. Various parameters like melting point, solubility and drug excipients compatibility studies etc. were carried out.

Solubility study

Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1 N HCl, 0.1 N NaOH and phosphate buffer pH 6.8). Shake vigorously and kept for some time. The solubility of the drug in various solvents was determined (at room temperature)[17].

Melting point

It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point. The melting point of the drug was performed by capillary method. In this, drug was filled in the capillary tube sealed at one end to a height of 3 mm from closed end and capillary was introduced into melting point apparatus.The temperature range at which drug melt was noted down.

Determination of Angle of repose andbulk density

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

$$\tan\theta = h/r$$

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

Where, θ is the angle of repose, h is the height, r is the radius.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Determination of partition coefficient

10 mg drug was added in 50 ml of n-Octanol (pre saturated with water) and it was shaked and then 50 ml of distilled water (pre saturated with n- Octanol) was added and was shaked the mixture by mechanical shaker for 24 hours. After 24 hour both phases are separated. Absorbance was taken of both the phases and calculated the concentration in each phases[18] [18].

Partition Coefficient = Drug concentration in Octanol/Drug concentration in water

pH determination

This was done by shaking a 1%w/v dispersion of the sample in water for 5min and the pH determination using a digital pH meter[19].

Drug-excipient compatibility studyby FT-IR Spectroscopy

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic

compound. The region from 400-4000 cm^{-1} called infra-red region. Approx 5 to 10mg of drug was used as ATR techniques, using FT-IR spectrophotometer (Bruker, USA).

Determination of λ_{max} and calibration curve of drug

Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HClsolution in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 0.1 N HCl solution, prepare suitable dilution to make it to a concentration range of 5-25µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (SHIMADZU UV-1800).

RESULTS AND DISCUSSIONS

Solubility of pralidoxime was freely soluble in 0.1 N HCl, methanol, soluble in water, 0.1 N NaOH, slightly soluble in phosphate buffer pH 6.8, ethanol. The melting point of pralidoximewas 212-223°C which is same as documented (215-225°C) and the results of true density, bulk density, angle of repose, pH and partition coefficient was calculated and the results are given in Table 1.λ_{max} of pralidoxime was found to be 294 nm by using U.V. spectrophotometer (SHIMADZU UV-1800)in linearity range 5-25µg/ml Figure1& 2. The FTIR spectrum of pure drug, ethyl cellulose, HPMC and physical mixture were recorded on ATR techniques, using FT-IR spectrophotometer (Bruker, USA).After observing the spectra, it could be concluded that the peak of all the characteristic functional groups of pralidoxime chlorideare intact in pure drug (pralidoxime chloride) and physical mixtures correspondingly. As there was no shifting, deleting and broadening of the peak observed in the spectrum, it was concluded that no chemical interactions occurred Figure 3.

Table 1: Physicochemical properties of Pralidoxime chloride

Parameters	Results
Description	Pralidoxime chloride occurs as an odorless, white, nonhygroscopic, crystalline powder
pH	3.6 ± 0.27
True density (gm/cc)	1.62 ± 0.42
Bulk density (gm/cc)	0.64 ± 0.57
Angle of repose (θ)	28.16 ± 1.15
Partition Coefficient	0.87 ± 0.53

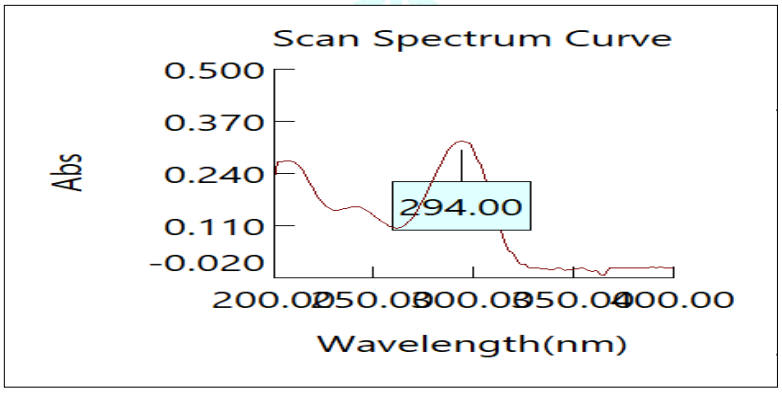


Figure 1: λ_{max} of pralidoxime chloride

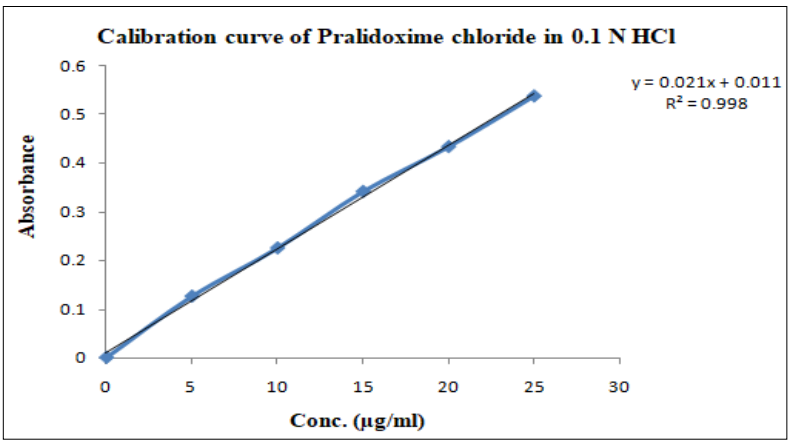
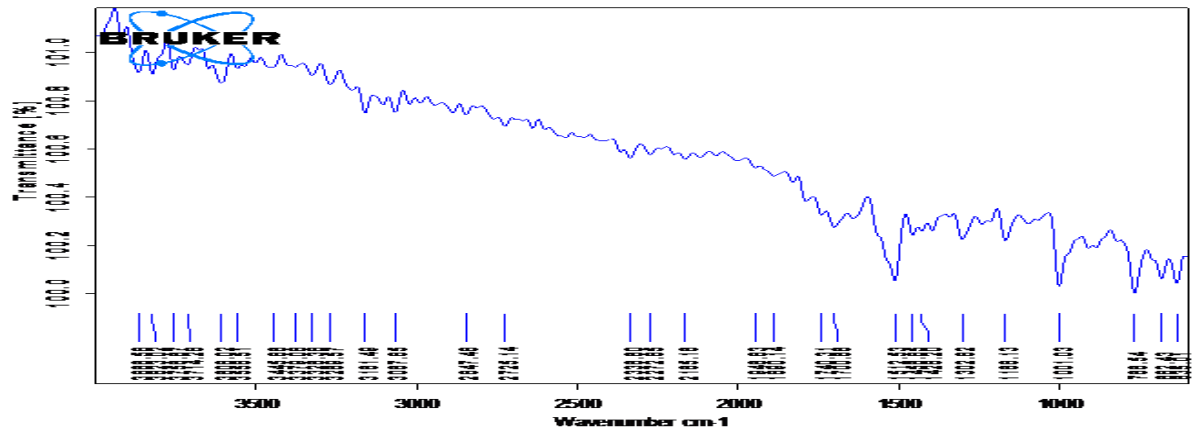
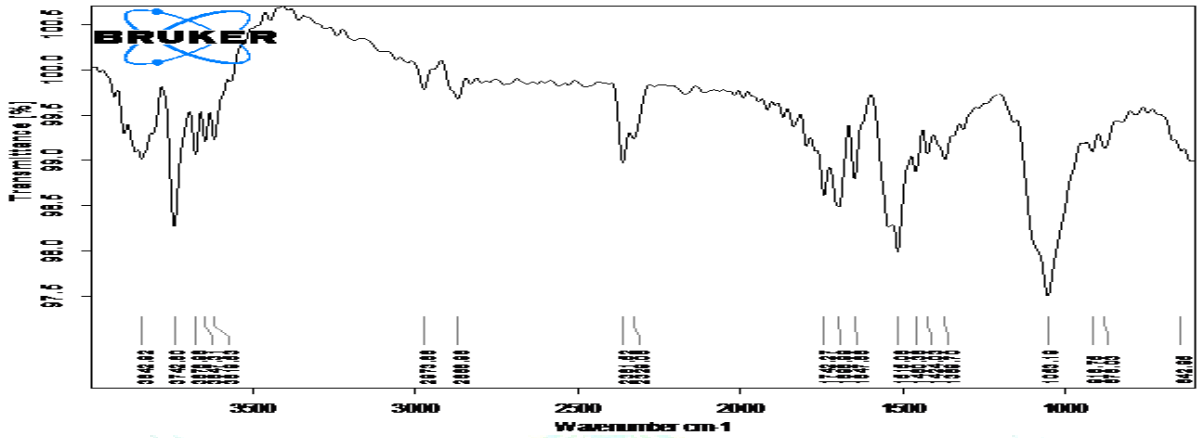


Figure 2: Calibration curve of pralidoxime chloride in 0.1 N HCl at 294nm



(A)



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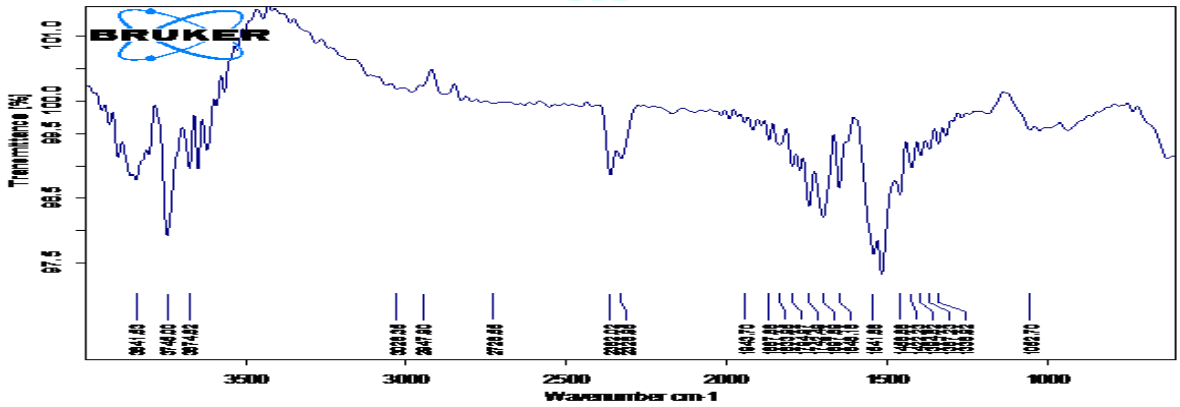
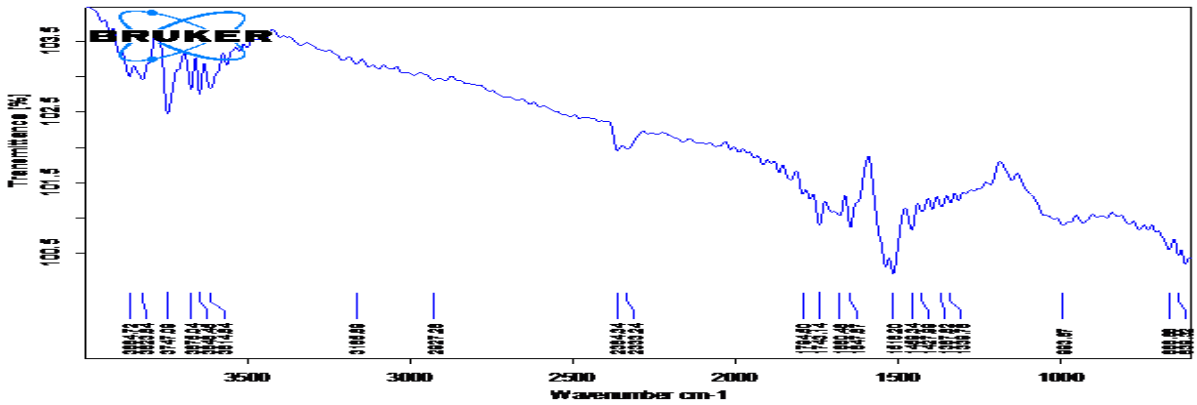


(C)



(D)

Figure 3: FTIR Spectra of Pralidoxime chloride (A), Ethyl cellulose (B), HPMC (C), Pralidoxime chloride+ EC+HPMC (D)

CONCLUSION

In the present work, the preformulation study of Pralidoxime drug was done. Preformulation studies have a significant part to play in anticipating formulation problems and identifying a logical path in both liquid and solid dosage form technology. Preformulation study gives brief idea about the identification (physical appearance, solubility studies, melting point, U Vand IR spectrophotometer spectra, estimation of drugs).This study shows a satisfactory result for all characterization and on the basis of this study we concluded that the drug was suitable for choice of formulation.

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