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Research Article

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Unravelling Pharmaceutical formulations of *1-(1-methylethylamino)-3-(1-naphthyloxy) propan-2-ol* (Propranolol)

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Introduction

Propranololis a sympatholytic non-selective beta-adrenergic blocking agent widely used in clinical practice for the treatment of cardiac arrhythmia, hypertension and angina pectoris, dysfunctional labour and anxiety.Sympatholytics are used to treat hypertension, anxiety and panic. Propranolol is used to treat high blood pressure, abnormal heart rhythms, heart disease, heart pain (angina), pheochromocytoma (tumor on a small gland near the kidneys), and certain types of tremor. It is also used to prevent angina (chest pain) and migraine headaches. Propranolol is also used to improve survival after a heart attack. It works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure (Murillo-Pulgarin et al., 1998)

Propranolol inhibits the sympathetic nervous system by blocking the beta receptors on the nerves of the sympathetic system. Since stimulation of the sympathetic nervous system is responsible for increasing the rate with which the heart beats, by blocking the action of these nerves. Propranolol reduces the heart rate and is useful in treating abnormally rapid heart rhythms. Monitoring of propranolol in biological fluids is important not only in clinical practice but also in the field of doping control. Propranolol is subjected to extensive and highly variable hepatic first-pass metabolism following oral administration, with a bioavailability of between 15% and 23%. Prolonged release formulations may reduce the dosing frequency, but the bioavailability of propranolol from these formulations is only 40%–60% of that from a conventional tablet. This has been attributed to the slower absorption in the gastrointestinal tract coupled with an extensive first-pass effect (Charles et al., 1979 and Saravanan et al., 2012)

Materials and Methods

Preparation of Propranolol Stock Solution

About 10mg of Propranolol was accurately weighed and transferred into 10ml volumetric flask containing methanol. The solution was sonicated for five minutes and then the volume was made up with a further quantity of diluent (50:50% v/v of methanol:MilliQwater) to get 1mg/ml (approximately). The concentration of the stock solution is calculated accounting for its potency. The solution is labeled appropriately and then stored in the refrigerator below $8^{o}C$.

Preparation of Internal Standard (Tramadol) Stock Solution

10mg of the internal standard drug Tramadolwas weighed accurately and was dissolved in few ml of methanol. Then it was mixed well using ultrasonic sonicator, make the solution up to mark in a 10ml volumetric flask and then it was filtered through membrane filter paper. A concentration of approximately 1mg/ml Tramadol solution was obtained. The concentration of the stock solution is calculated accounting for its potency and the actual

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amount weighed. The solution is labeled appropriately and then stored in the refrigerator below 8°C.

The ESI-MS is optimized in a view to develop a sensitive and reproducible method for the determination of Propronolol in Human Plasma. In the ESI process the molecules are subjected to a high degree of induced polarization by the application of Ion spray voltage which is usually a magnitude of 3000 – 5500 V. Depending on the polarity of the ion spray voltage the molecule undergoes protonation or de-protonation to form an ion. Conceptually, acidic molecules are electron pair acceptors and therefore ionize in the negative ion mode. Similarly basic molecules tend to ionize in positive ion mode. In the current method positive ion mode is chosen for the ion spray voltage because it resulted in higher response.

Although Propronololand internal standard are highly non-polar and are suitable for extraction using the liquid-liquid extraction technique, it appeared that the –OH groups of both the drug and internal standard can be better entrapped in the bonded phase of solid phase extraction cartridge when Solid phase extraction (SPE) is used. Initial experiments were performed by using non-polar solvents like t-butyl methyl ether, dichloromethane and diethyl ether. Compared to the liquid-liquid extraction, SPE proved to improve the recovery and a better matrix clean up during the extraction. SPE was therefore finalized using the OASIS HLB 30mg/1cc cartridges.

Initial experiments employing conventional flow rates of 0.5-0.7 ml/min resulted in optimal retention times for Propronolol. The run time of analysis is approximately 2.5 minutes when an Inertsil ODS reverse phase column (50 X 4.6 mm id, C18, 5 micron) is used. Also the organic composition of the mobile phase is kept at 90% v/v. The column temperature is maintained at ambient. At the reported flow rate, peak shape was acceptable. There was no interference in the drug and internal standard, from the extracted blank. Acetate buffer and formate buffers were initially used for the experiment. 5mM Ammonium acetate buffer resulted in better ionization response. Since the noise effects in solid phase extraction (SPE) method are almost removed, we have done the final analysis using SPE technique.A summary of the optimized chromatographic conditions.

Results and Discussion

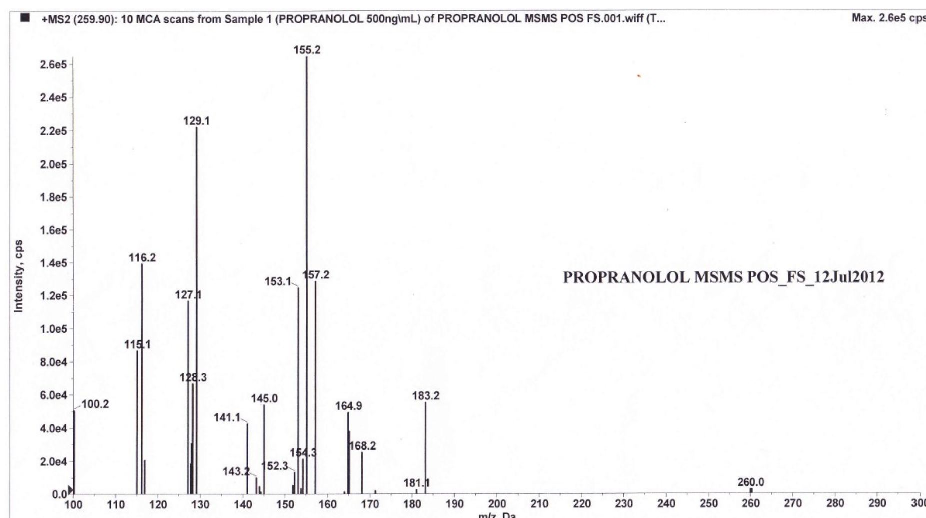

Fig 1 Mass spectra of Propranolol for parent ion and product

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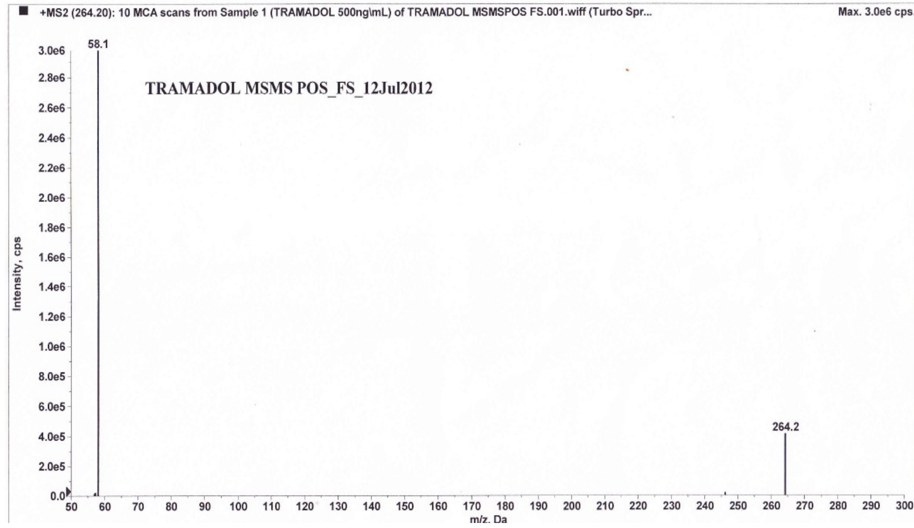

Fig 2 Mass spectra of Tramadol for parent ion and product ion

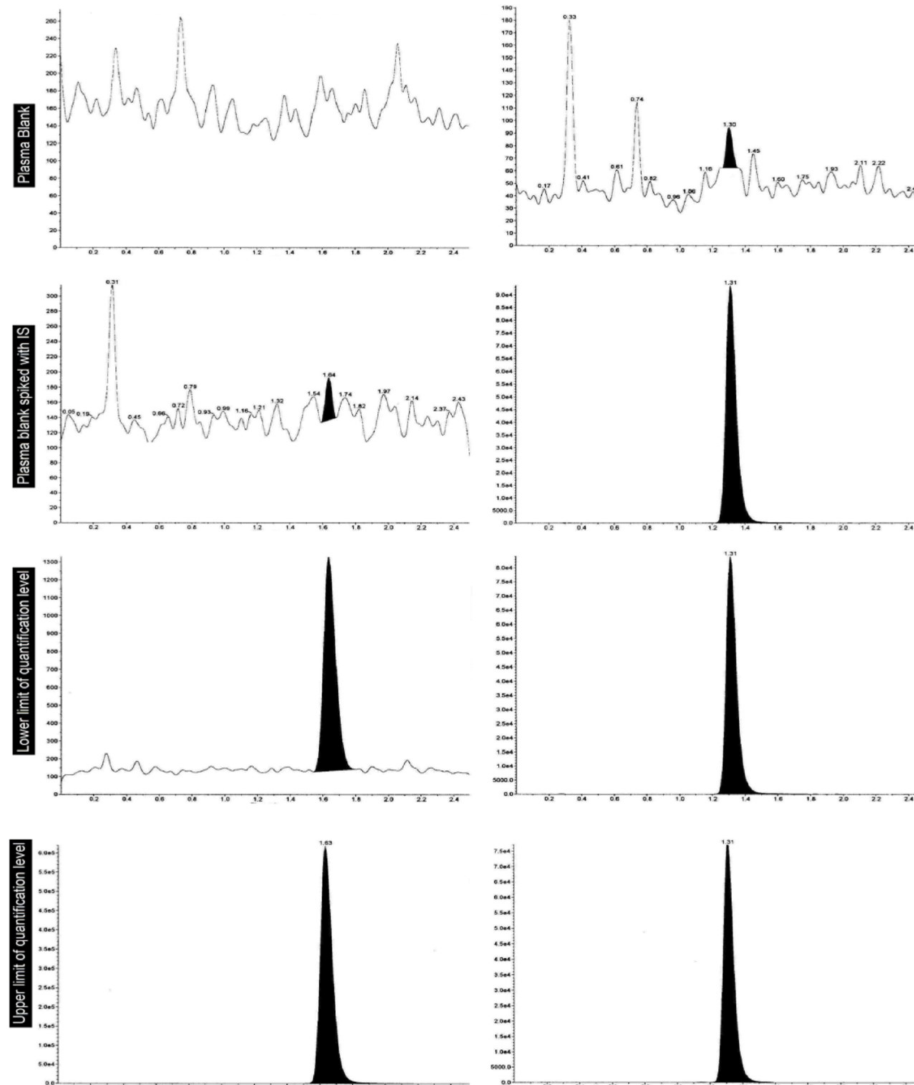

Fig 3 Representative chromatograms of Blank, Zero blank, LQC and HQC

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Data acquisition and processing

The chromatograms were obtained and data was processed by the peak area ratio method using the Analyst 1.4.2 software. The concentrations of the unknown samples were calculated from the following equation of the regression analysis of the spiked plasma calibration graph using $1/X^2$ as weighting factor.

$$Y = m X + C$$

Where, X = concentration of analyte/ concentration of internal standard

Y = area of analyte/ area of Internal standard (area ratio)
m = Slope of the calibration curve
C = Y- intercept value

The present method describes the development and validation of HPLC-mass spectrometric method for the estimation of Propranolol a sympatholytic non-selective beta blocker used to treat hypertension, anxiety and panic in human plasma. Tramadol was used as internal standard for the developed method. In the present study 5mM Ammonium acetate buffer solution and acetonitrile in the ratio of 10:90 v/v was used as eluting mobile phase that gave good separation and sensitivity. The method was successfully used to detect Propranolol with high accuracy. The optimized mass parameters. Retention times of Propranolol and Tramadol were found to be 1.31 minutes and 1.63 minutes respectively. The analysis was completed with shortest run time of 2.5 minutes. The method was validated to evaluate the linearity, precision, accuracy and recovery of the drug.

Specificity was investigated by analyzing six drug-free bottled plasma and volunteer samples for interference of endogenous compounds. The standard curve was obtained through analysis of calibration plot of peak area ratio of standard drug with internal standard versus the corresponding drug concentrations. Linearity of the standard curve was evaluated using least-squares linear regression analysis with weighting $1/ X^2$. The method shows Linearity within the concentration range of 1.000 to 402.171µg/ml for Propranolol. The correlation coefficient (r) ranged from 0.9955 to 0.9975. Table 3.13 shows the Linearity results obtained for Propranolol.

The precision of the assay was measured by the percent coefficient of variation over the concentration range of LLOQC, LQC, MQC and HQC samples respectively during the course of validation. %CV was found to be 1.72 for HQC, 2.82 for MQC, 5.29 for LQC and 3.29 for LLOQ QC (Table 3.15). The intraday and interday precision was less than 10% in each QC level. Accuracy was determined from each QC samples was within ±5%. Results obtained for precision indicates that the method was precise and accurate.

The recovery comparison samples of Propranolol were compared against extracted samples of LQC, MQC and HQC. The mean overall recovery of Propranolol was 65.83% and 82.12% for Tramadol.

Short Term Stability of Drugswere carried out for 8hours by injecting six injections of prepared stock dilutions of Propranolol sample concentration kept at room temperature against the dilution kept in refrigerator. The % Stability was found to be 99.87and 98.97 % for propranolol and tramadol respectively. Long Term Stock Solution Stability was determined by freshly prepared stock solutions were stored in a refrigerator below 10°C (stability samples) for 8 days. The percent stabilities were found to be 101.17 and100.53 for Propranolol and Tramadol respectively. The stability in human plasma was determined for three freeze-thaw cycles. Six injections of LQC and HQC were analyzed after undergoing three freeze thaw cycles. The freeze-thaw quality control samples were quantified against the freshly spiked calibration curve standards. The freeze thaw cycles were carried out in duplicate. The percent nominal ranged from 99.24 % and 104.23 % at low and high concentrations respectively.

The objective of this work was to develop a simple, cost effective rugged and a high throughput method for estimation of Propranolol in human plasma. The method consists of a simple sample pretreatment by liquid-liquid extraction to give consistent and reproducible recoveries of Propranolol. The run time is 2.5 minutes suggests high throughput of the proposed method, which helps in maintaining the efficiency and the lifetime of the column. Moreover, the limit of quantification is low enough to monitor Propranolol concentration in study with good intra and inter-assay reproducibility (%CV) for use in quality controls.

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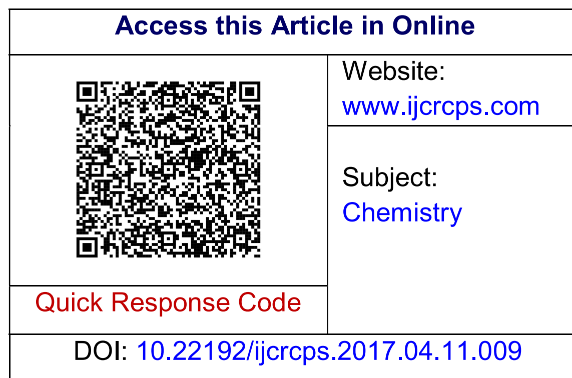

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