



FORMULATION DEVELOPMENT AND EVALUATION OF ABACAVIR LOADED POLYMETHACRYLIC ACID NANOPARTICLES

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ABSTRACT

Nanoparticles render a promising drug delivery system of controlled and targeted drug release. These are specially designed to release the drug in the vicinity of target tissue. The aim of this present study was to develop and evaluate polymethacrylic acid nanoparticles containing nanoparticles abacavir in different drug to polymer ratio by nanoprecipitation method. SEM indicates that nanoparticles have a discrete spherical structure without aggregation. The average particle size was accurately found to be 120 ±9 - 403 ±3 nm. The particle size of the nanoparticles was gradually increased with increase in the proportion of polymethacrylic acid polymer. The drug containing nanoparticles was increasing on increasing polymer concentration up to a particular concentration ratio. No difference was observed in the extent of degradation of product during sixty days in which, nanoparticles were stored at various temperatures. FT-IR studies indicated that there were no chemical interaction between drug and polymer and stability of drug. The in-vitro release character from all the drug loaded batches was found to be zero order and rendered sustained release over a period of 24 h. The prepared formulations overcome and breakup the drawbacks and limitations of abacavir sustained release formulations and could possibility be advantageous in terms of increased bioavailability and efficacy of abacavir.

KEYWORDS: Nanoparticles, nanoprecipitation method, polymethacrylic acid, abacavir

INTRODUCTION

During last two decades, considerable attention was given to the development of novel drug delivery system (NDDS)¹. The rationale for control drug delivery is to be alter the pharmacokinetics and pharmacodynamics of drug substance in order to develop the therapeutic efficacy and safety through the use of drug delivery system. Besides more traditional matrix or reservoir drug delivery system, colloidal drug delivery system has profited in popularity. The major colloidal drug delivery system included liposome and polymeric nanoparticles. These systems has been investigated primarily for site specific drug delivery, for controlled drug delivery, and also for the enhancement of dissolution rate as well as bioavailability of poorly water-soluble drugs. The foremost route of administration under investigation are parenteral route, however, other routes such as the oral, ocular, or topical routes are also being investigated frequently. In view of oral drug delivery system microspheres², microcapsule, nanoparticles, liposomes, and niosomes are best options to develop conventional dosage form. Nanoparticles are colloidal polymer particles of a size below the range 1µm³⁻⁴ and hold promise as drug delivery for parenteral, peroral and r vaccines. Due to their wider stability and due to their easiest manufacturing they offer advantages over other colloidal carriers such as liposomes and cell ghosts. They offer advantages like increased and improved bioavailability, site specific drug delivery, sustained release of drug over long period of time, retention of dosage form in entire length of gastrointestinal tract and convenient to patient due to reduction in continuous dosing⁵. Eudragit polymers are series of well known acrylate and methacrylate polymer available in different ionic forms. Eudragit RS 100 is insoluble in aqueous media but it is permeable and has pH- independent release profile. The permeability of Eudragit RS 100 is due to presence of

quaternary ammonium group present in their structure⁶. Abacavir is an nucleoside analog reverse transcriptase inhibitor (NRTI) used to treat harmful HIV and AIDS. It is available under the trade name Ziagen (ViiV Healthcare) and in the combined formulations Trizivir (abacavir, zidovudine and lamivudine) and Kivexa/Epzicom (abacavir and lamivudine). It has been well tolerated, the main side effect is hypersensitivity, this can be severe, and in rare cases, possibility for fatal. Genetic testing can indicating whether an individual will be hypersensitive; over 90% of patients can safely take abacavir. However, in separate study, the risk of heart failure increased by 90%. Viral strains are resistant to zidovudine (AZT) or lamivudine (3TC) are generally sensitive to abacavir, whereas some strains are resistant to AZT and 3TC are not as sensitive to abacavir⁷.

MATERIAL AND METHOD

Abacavir was a gift sample got from ViiV Healthcare Pvt. Ltd. United kingdom. Eudragit RS 100 was obtained from Rohm Pharma., Germany. Dichloromethane was procured from Indian Drug House., Hyderabad. All other chemicals used were of analytical grade.

Preparation of nanoparticles

Nanoparticles consist of abacavir was developed using nanoprecipitation method⁸⁻⁹. Drug dissolved in water, and then to co solvent (acetone) was added into this solution. A co solvent was required in order to make the inner phase more homogeneous. Then polymer and 150 mg of propylene glycol has been dissolved in chloroform, and this solution was added to the drug solution to produce dispersion. The dispersion was added to 10 ml of aqueous ethanol solution (70%). After 5 minutes of proper mixing, the organic solvents were eliminated by evaporation at 35° under normal pressure, nanoparticles were separated by use of cooling centrifuge (10000 rpm for 20 min), supernatant were removed and nanoparticles were washed with water and dried at room

temperature in a desiccator. By follow the above mentioned procedure five other batches of nanoparticles in the ratio of 1:1, 1:2, 1:3, 1:4 and 1:5 were prepared and named F1, F2, F3, F4 and F5 respectively. Particle size, surface morphology and zeta potential. The surface morphology (roundness, smoothness, and formation of aggregates) and particle size was studied by scanning electron microscopy (SEM)¹⁰⁻¹¹. Zeta potential of the best formulation (F4) was determined by zeta potential probe model DT- 300. Drug content was determined by known centrifugation method. The redispersed nanoparticles suspension was centrifuged at 15,000 rpm for 40 min at 25° to separate the free drug in the supernatant. The concentration of abacavir in the supernatant was determined by UV-Vis spectrophotometrical system at 271 nm after using suitable dilution. Fourier Transform Infra-red Spectroscopy (FT-IR) analysis The FT - IR spectra of pure abacavir and Eudragit RS 100 nanoparticles loaded with abacavir was recorded to check drug polymer interaction and stability of drug. In vitro release studies were carried out by dialysis tubes with an artificial membrane. The prepared abacavir nanoparticles and 10 ml of phosphate buffer pH 7.4 added to the dialysis tube and subjected to dialysis by immerse the dialysis tube to the receptor compartment consist of 250 ml of phosphate buffer pH 6.8. The medium in the receptor was agitated continuously utilize a magnetic stirrer at 37±1°. 5ml of sample of receptor compartment has been taken at various intervals of time over a period of 24 h and each and every time fresh buffer was replaced. The amount of drug releasing was determined spectrometrically at 271 nm. Kinetic modeling used in order to understand the kinetic mechanism of drug release, the result of in vitro drug release study of nanoparticles were fitted with various kinetic equation such as zero order¹² (cumulative % release vs. time), first order¹³ (log % drug remaining vs. time), Higuchi's model¹⁴ (cumulative % drug release vs square root of time). r^2 and k values were calculated for the linear curve obtained by regression analysis of the above plots.

Stability study

The stability study has been carried using the batch F4. The stability of drug loaded nanoparticles was evaluated in terms of their drug content¹⁵. The stability of nanoparticles evaluated in PBS (pH 6.8). Nanoparticles formulation was incubated at 5-8° and 37±1° for a period of 60 days. After specified time intervals, the suspension was centrifuged at 15,000 rpm for 1 h, supernatant removed and nanoparticles were dissolved in dichloromethane. After adding of water and separation, the amount of drug was determined by UV-Vis spectrophotometrical method at 271 nm.

RESULT AND DISCUSSION

A abacavir nanoparticle with various proportions of abacavir and Eudragit RS 100 has been prepared by nanoprecipitation method. The scanning electron microphotograph of abacavir nanoparticles is shown in fig.1. This shows that abacavir nanoparticles have a discrete spherical structure without aggregation. The particle size of nanoparticles varied among the developed formulation due to variation in the composition of formulations. Zeta potential of best formulation was determined and it was found + 27 mV due to quaternary ammonium group of Eudragit. Since there was a decrease of surface potential, it should be concluded that a part of drug has been absorbed on the polymeric particles. The drug content has been determined by centrifugation method and it was maximum in formulation F4. The nanoparticles exhibited an increase in drug content with an increased in the polymer

ratio, up to particular concentration (1:4). A decrease in drug quantity was observed after that point due to the saturation capacity of polymer. In FT-IR studies the characteristic peak due to pure abacavir has appeared in the spectra of nanoparticles without any remarkable change in the position. This pointed that there was no chemical interaction between abacavir and Eudragit RS 100. In stability study there was no remarkable change in the drug content. This indicated that formulation was stable in storage medium condition. The in vitro release profile of all formulation is shown in fig.2. The release of abacavir mainly depends on the polymer concentration. The burst release of abacavir from nanoparticles at initial stage resulting from the dissolution of drug crystals on the surface of nanoparticles. On increasing polymer concentration, the release rate of abacavir from nanoparticles declined drastically. The in vitro release data has been applied to various kinetic models to predict the drug release kinetic mechanism. The release constant calculated from the slope of appropriate plots, and the regression coefficient (r^2) was determined. This was found that the in-vitro drug release of nanoparticles was best explained by zero order kinetics for best formulation F4 as the plots shows highest linearity. The correlation coefficient (r^2) was found 0.99 for F4.

CONCLUSION

The method of preparation of nanoparticles of abacavir was found to be simple and reproducible. The slow and constant release of abacavir from nanoparticles maintain constant drug plasma concentration thereby increasing therapeutic efficacy. This study shows that polymethacrylic acid nanoparticles could be a useful carrier for abacavir. The developed formulation overcome and alleviates the drawbacks and limitations of abacavir sustained release formulations.

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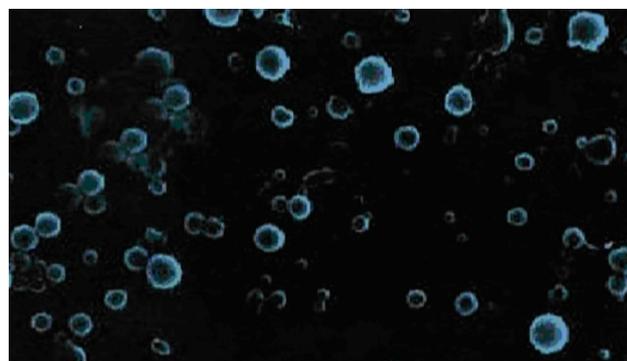
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TABLE 1: Formulation and physicochemical characterization of abacavir nanoparticles

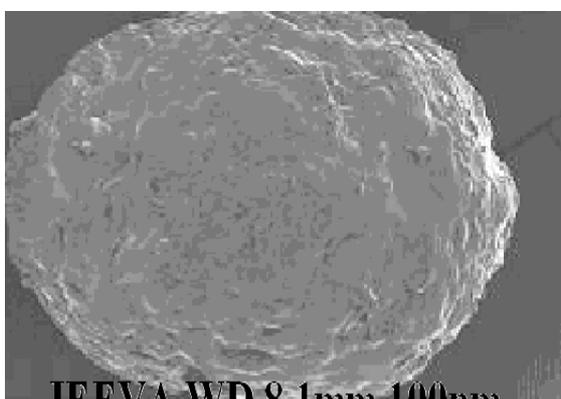
Formulation code	Drug : Polymer ratio	Drug Content* (%)	Particle Size* (nm)
F1	1:1	59.04± 0.02	120 ±9
F2	1:2	65.16±0.02	266±5
F3	1:3	65.06±0.02	288±8
F4	1:4	71.02±0.04	333±4
F5	1:5	59.96 ±0.04	403 ±3

* Average of three preparation ± S.D



JEEVA WD 8.1mm 100 nm
(B) At higher magnification

Fig.1: Scanning electron microphotograph of abacavir hydrochloride nanoparticles (A) (B).



JEEVA WD 8.1mm 100nm
(A) At lower magnification

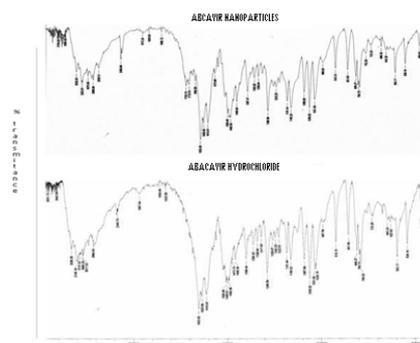


Fig.2: FT-IR spectra of pure abacavir and abacavir loaded nanoparticles formulation (F4)

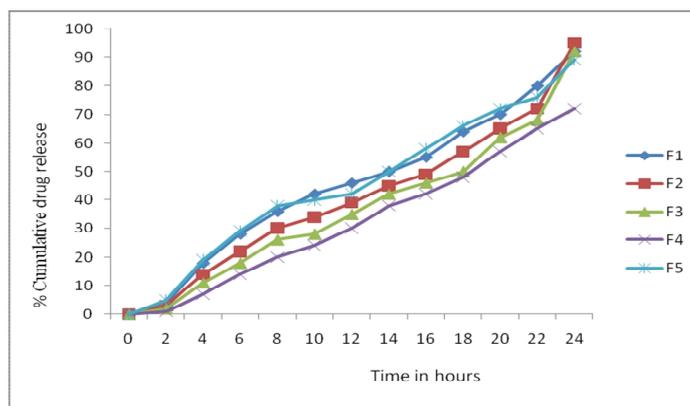


Fig.3: In vitro drug release of abacavir from polymethacrylic acid nanoparticles formulation F1, F2, F3, F4, F5

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