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Research

Kinetic analysis of drug release from Nateglinide-loaded ethyl cellulose nanoparticles for oral delivery

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Abstract

With the objective to achieve sustained drug release, especially for the oral delivery and thereby to reduce the side effects of administration of conventional dosage form, Nateglinide (NTG)-loaded Ethyl cellulose (EC) nanoparticles have been formulated. These polymeric nanoparticles have been developed by solvent evaporation method and were subjected to *in-vitro* drug release analysis up to 12 hrs. The formulation demonstrated favourable *in-vitro* sustained release characteristics. Experimental *in-vitro* release data were substituted with available mathematical models to establish the mechanism of release of nateglinide and was found to follow Korsmeyer-Peppas release mechanism of diffusion from the polymeric matrix.

Keywords: Korsmeyer-Peppas, Nateglinide, Oral delivery, Polymeric nanoparticles, Release kinetics, Sustained release.

INTRODUCTION

In the recent past, substantial scientific and technological advancements have been made in the research and development of rate controlled oral drug delivery systems to counter the shortcomings of physiological adversities of conventional drugs and its administration.[1] The rate controlled oral drug delivery system has given impetus to significant advancements in the pharmaceutical engineering, of novel dosage forms such as nanoparticles, which are solid colloidal polymeric carriers in nano scale.[2, 3] These nanoparticles offer great advantages right from helping to increase the stability of drugs, proteins and up to sustained drug release properties. Several attempts have been made, towards developing polymeric nanoparticles as potential drug delivery devices. In addition, polymeric nanoparticles have been found to be extremely effective in sustained and

targeted drug release, and time controlled drug delivery system notwithstanding the fact that the administration is oral.[4]

Diabetes is a major and growing public health problem throughout the world and is associated with increased mortality, so, the current exercise is focused towards anti-diabetic treatments. Nateglinide, an oral hypoglycemic agent is chosen as the drug candidate for polymeric nanoparticle carrier system. As far as the specific properties of the nateglinide are concerned, though it possesses phenomenal anti-diabetic properties, the half-life of the drug is 1.5 hrs for which frequent administration is needed which will ultimately lead to patient compliance.

Nano drug delivery system enclosed anti-diabetic drug, may improve the therapeutic efficacy of the drug and also the polymer coating releases the drug in a predetermined controlled manner for a prolonged duration. Thus the nano formulation of nateglinide makes it available for oral delivery and as well as minimizes the patient compliance. Many biodegradable polymers have major advantage since; they do not require removal after application. Ethyl cellulose is one of the most important candidates for biomedical materials because of its biocompatibility and its relatively stronger mechanical properties.

Recently many studies are focused on safety issues of manufactured nanomaterials to minimize or eliminate their nanotoxicity before they are being widely used.[5-8] Compared to microparticles, the nanoparticles, due to their nanoscale and comparatively larger surface area may interact with biological systems in a more efficient manner. They may be beneficial but sometimes might produce severe toxicity too.[9] Because of the nano size and larger surface area of the nano substances, it is directly correlated to many essential characteristics like surface properties, chemical reactivity, physical absorption ability and permeability through cell membranes.

These factors strongly dominate nanotoxicological behaviour *in-vivo*.[10] The present investigation is carried out to develop and evaluate a stable nanoparticle based biodegradable delivery system using ethyl cellulose as polymer, which would deliver nateglinide, an anti-diabetic drug, at a sustained rate for a prolonged period of time.

MATERIALS AND METHODS

Materials

Nateglinide was procured as a gift sample from Glanmark Pharmaceutics Ltd, Mumbai. Ethyl cellulose was received from Hi-media Laboratories, Mumbai. Polyvinyl alcohol, Methanol and Acetone were purchased from S.D. Fine Chemicals Ltd. (Mumbai, India). All other chemicals and solvents were of analytical grade.

Preparation of nateglinide nanoparticles

The optimized NTG-loaded EC nanoparticles were prepared by the solvent evaporation method. Briefly, weighed 30 mg of NTG 150 mg of EC were dissolved in 40 ml mixture of methanol with acetone in 1:2 ratio using a vortex shaker (to mix small vials of liquid) to form homogeneous organic phase of NTG and EC. This solution was added drop by drop into the 60 ml of 1 % aqueous phase of polyvinyl alcohol using mechanical stirrer at 1000 rpm for 2 hrs to prepare nano-suspension and thoroughly evaporate the organic phase followed by magnetic stirring for 2 hrs under atmospheric pressure at room temperature. The solution was centrifuged at 15,000 rpm for 15 minutes to form the emulsion. After centrifugation the supernatant was excreted and the pellets obtained were washed by using the same volume of distilled water as of the supernatant and again centrifuged at 15,000 rpm for 5 min. The precipitate was washed thrice with distilled water and finally freeze-dried to get the powdered nanoparticles.[11, 12] The nanoparticles were prepared in triplicate to get the reproducibility and reliability. These nanoparticles were characterized by fixing the experimental assay conditions based on the pre-conducted preliminary experimental results, carried out in our previous studies.

Selection of chromatographic method for Nateglinide

Nateglinide estimation was carried out by RP-HPLC based on the reported method by Madhavi *et al.,* 2008.[13] An isocratic reverse phase high pressure liquid chromatographic (RP-HPLC) with Shimadzu LC-20AD PLC pump and a SPD-M20A photo diode array (PDA) detector were used. Separation was carried out on a Phenomenex C18 column (particle size 5 µm; 150 × 4.6 mm i.d) using ACN: 10 mM Sodium di-hydrogen phosphate (NaH_2PO_4) buffer solution [phosphate-buffered solution (PBS); adjusted to pH 3.0 with H_3PO_4] (50:50, v/v). The flow rate was 1.0 mL/min at 27° C and the detection was monitored at a wavelength of 210 nm. The injection volume was 20 µL. Acetonitrile was used as diluent.

The *in-vitro* release study

The *in-vitro* release of marketed formulation and NTG-loaded EC nanoparticles were carried out using dialysis bag diffusion method. Briefly, 2 mg samples are dispersed in 2 mL of PBS pH 7.4 and were kept in a

dialysis bag (cellulose acetate membrane with molecular weight cut-off value of 10,000) and tightly closed. The dialysis bag was immersed in the compartment containing 50 ml of dissolution medium (phosphate buffer solution pH 7.4), which was stirred in a water bath shaker at 100 rpm and maintained at 37 ± 0.5° C. At predetermined time intervals the requisite quantity (1 mL) of sample were withdrawn and analysed by RP-HPLC method. Equal quantity of fresh releasing media was added to maintain the definite volume.[14]

Evaluation of *in-vitro* release kinetics

In order to investigate the mechanism of release, the data were analysed with the following mathematical models: Zero order kinetic Eq. (1), Higuchi kinetic Eq. (2), Hixson-Crowell kinetic Eq. (3) and Korsmeyer-Peppas model Eq. (4).

$Q_t = K_o t$ ----- (1)

$Q_t = k_H t^{1/2}$ ----- (2)

$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t$ ----- (3)

with Q_t is the total amount of drug released after time t (%), Q_0 the initial amount of drug (%), k_0 the zero-order release rate constant (% h−1), k_H the rate constant obtained according to the Higuchi equation (% h−1/2), and k_{HC} is the rate constant obtained according to the Hixson-Crowell equation (% h^{-1}).

$M_t / M_\alpha = K_p t^n$ ----- (4)

Where M_t /M is the fraction of the drug release at time t, K_p is the rate constant and "n" is the release exponent. The value of "n" is used to characterize different release mechanisms and is calculated from the slope of the plot of log of fraction of drug released (M_t /M) vs. log of time.[15]

RESULTS AND DISCUSSION

The *in-vitro* release study of optimized NTG-loaded EC nanoparticles nanoparticle

The percentage of drug release from NTG-loaded EC nanoparticles was studied as a function of time in *in-vitro* condition. The drug release study was performed by using dialysis bag diffusion method. The percentage amount of drug released from NTG-loaded EC nanoparticles formulations was depicted in Fig. 1. The formulation (up to 86.21 % in 12 hrs) shows a significant and sustained release of nateglinide in nanoparticle form as compared to the marketed formulation. About 93.42 % of the drug was released from marketed formulation after 1.5 hrs. Thus, it is evident that nanoparticles have a small initial burst and sustained release from the polymer.

The sustained release nature is thought to be mainly because of the 1:5 ratio of polymer and that of the drug. Entrapment efficiency 72.19 % obtained was expected due to the ratio 1:5 again.

The release of drug from the polymer matrix was carried out by diffusion. Ethyl cellulose is widely used to control the dissolution rate of drugs from sustained release preparations. Ethyl cellulose possess plastic and hydrophobic property, drug particles present in the surface of matrix is initially released into the surrounding media generating many pores and cracks which facilitate further release of drug and EC did not change its drug retaining activity due to the change of pH. The increase in drug content in the particles influence the absolute release profiles of the drug, in such a way that, it increases the induction period and the cumulative amount of drug released at any given point of time. The drug content which is closer to the surface of the nanoparticle is responsible for an increased initial burst and the drug in the core of nanoparticles is responsible for a prolonged drug release from the polymer.[16]

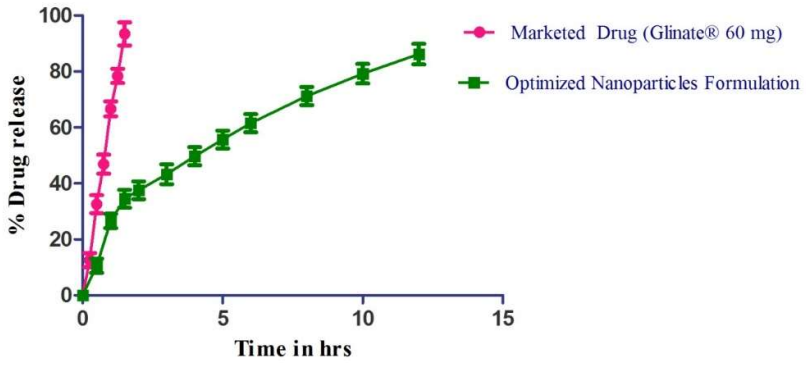


Fig 1: Comparative cumulative percentage drug release plot for Nateglinide marketed immediate release tablets (Glinate® 60 mg) and NTG-loaded EC nanoparticles

***In-vitro* release kinetics study**

The optimized formulation was subjected to mathematical model fitting to assess the kinetics of drug release (Table 1). The correlation coefficient value r^2 is taken in to account to decide upon the relevance of the model/curve fit which will best describe the extent of fit. According to these values the release kinetics of nateglinide from nanoparticles fits Korsmeyer-Peppas release.

To explain the mechanism of drug release, Korsemeyer-Peppas equation, $M_t/M=K_p t_n$ (where M_t/M is a fraction of drug released at time t, kp is the release rate constant and n is the release exponent) was applied, and good linearity was observed. In order to obtain n from $M_t/M=K_p t_n$, *in-vitro* drug release data were plotted as log cumulative percentage drug release versus log time.[15] The release profile of the optimised formulation according to Korsmeyer-Peppas fit, the release of the drug is decided upon the diffusion of the polymeric matrix and the drug release is governed by a variation fick's law of diffusion (n>0.4). The factors which control this are diffusion coefficient and permeability co efficient of the polymer at a constant temperature. The prepared optimized formulation releases the drug by a diffusion process which releases the drug from the polymeric matrix based upon the extent diffusion, erosion of polymeric matrix and subsequent domain separation of drug due to diffusion might also be a possibility.

The Figure 2a shows the cumulative amount of drug release vs. time, for zero order kinetics. Figure 2b, Higuchi model describes the release of drugs from an insoluble matrix as a square root of time dependant process, based on Fickian diffusion.[17, 18] The release constant was calculated from the slope of the appropriate plots and the regression co-efficient (r^2) was determined.

The data were also plotted in accordance with the Hixson-Crowell cube root law which indicates the progressive dissolution of the matrix as a function of time[19] and are shown in Figure 2c. To explain the mechanism of drug release, Korsemeyer-Peppas equation has been applied (cumulative percentage drug release in log scale vs. time) and a linearity (r^2=0.990) was observed. The results are plotted in graphical form in Figure 2d and the results are tabulated in Table 1. In this nateglinide nanoparticle preparation, the *in-vitro* release kinetics was best explained by Korsmeyer-Peppas, as the plots showed the highest linearity (r^2=0.990) followed by Higuchi equation (r^2=0.976) followed by Hixson-Crowell (r^2=0.912), followed Zero order by (r^2=0.902).

Table 1: Release Kinetics data of nateglinide nanoparticles

Equation	Zero order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas
r^2	0.902	0.976	0.912	0.990

From these results we can conclude that the release of nateglinide from the nanoparticle matrix is by Korsemyer-Peppas with release rate based on its diffusion from the polymer matrix.

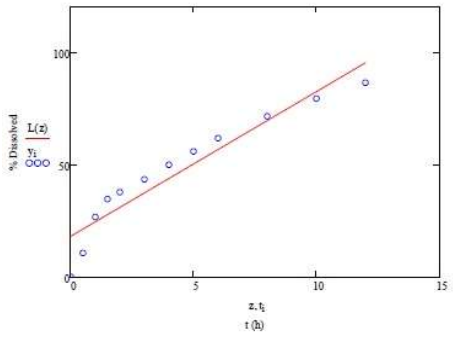


Fig. 2a: Zero order

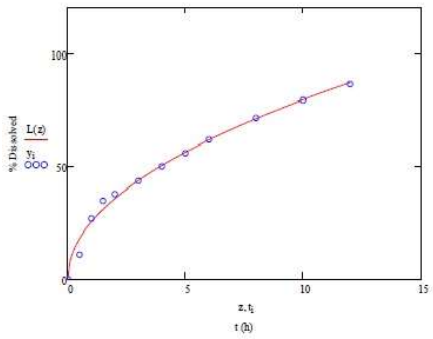
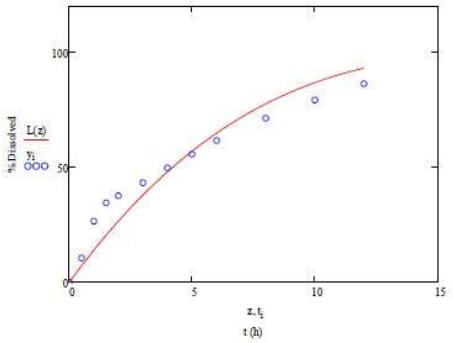
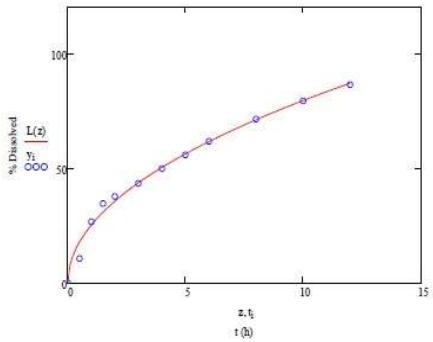


Fig. 2b: Higuchi model





CONCLUSION

NTG-loaded EC nanoparticles were successfully formulated by solvent evaporation method. Investigation on preparation and *in-vitro* release of polymeric nanoparticle was carried out and performance of the formulation was evaluated. The proposed NTG-loaded EC nanoparticles illustrate an effective way, to sustained drug release. On applying the drug release data to various kinetic models, Nateglinide was best fitted with Korsemyer-Peppas indicating uniform distribution of drug over the nanoparticles. The developed nanoparticles are safer and are the need of the hour for pharmaceutical industry as an alternative drug delivery system for the treatments of diabetes.

REFERENCES

1. Sunil KJ, Awasthi AM, Jain NK and Agarwal GP. Calcium silicate based microspheres of repaglinide for gastro retentive floating drug delivery: preparation and *in-vitro* characterization. Journal of Controlled Release. 2005; 107: 300-309.
2. Soppimath KS, Kulkarni AR and Aminabhavi TM. Development of hollow microspheres as floating controlled-release systems for cardiovascular drugs: Preparation and release characteristics. Drug Development and Industrial Pharmacy. 2001; 27: 507-515.
3. Govender T, Stolnik S, Martin CG, Illum L, Stanley SD. PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water soluble drug. Journal of Controlled Release. 1999; 57: 171-185.
4. Bala I, Hariharan S and Kumar MN. PLGA nanoparticles in drug delivery the state of art. Critical review in Therapeutic Drug Carrier System. 2004; 21: 387-482.
5. Nimase PK, Gali Vidyasagar, Suryawanshi DM and Bathe RS. Nanotechnology and diabetes. International Journal of Advances in Pharmaceutics. 2013; 2(4): 40-44.
6. Gupta J, Rajpoot A, Soni R and Sharma P. Formulation development and characterization of oral hypoglycemic agent loaded solid lipid nanoparticles. International Journal of Biopharmaceutical & Toxicological Research. 2012; 2(1): 251-256.
7. Desai J, Alexander K and Riga A. Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. International Journal of Pharmaceutics. 2006; 308:115-123.

8. Wiesner MR, Lowry GV, Alvarez P, Dionysiou D and Biswas P. Assessing the risks of manufactured nanomaterials. Environmental Science and Technology. 2006; 40: 4336-4345.
9. Piao FW and Zhu W. Effect of lead on thyroid function and morphology in pregnant rat. Chinese Journal of Industrial Hygiene and Occupational Disease. 1991; 9: 210-215.
10. Zhao YL, Meng H, Chen Z, Zhao F and Chai ZF. "Dependence of nanotoxicity on nanoscale characteristics and strategies for reducing and eliminating nanotoxicity," in Nanotoxicology, Zhao YL and Nalwa HS (Eds.), American Scientific Publishers, Stevenson Ranch, California, 2007; 265-280.
11. Shelesh Jain and Swarnlata Saraf. Influence of processing variables and *in-vitro* characterization of glipizide loaded biodegradable nanoparticles. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2009; 3: 113-117.
12. Dhanalekshmi UM, Poovi G, Kishore N and Neelakanta Reddy P. *In-vitro* characterization and *in-vivo* toxicity study of repaglinide loaded poly (methyl methacrylate) nanoparticles. International Journal of Pharmaceutics. 2010; 396: 194-203.
13. Madhavi A, Reddy GS, Suryanarayana MV and Naidu A. Development of a new analytical method for determination of related components in nateglinide. Chromatographia. 2008; 67: 639-645.
14. Mohammad Kaleemuddin and Prathima Srinivas. Lyophilized oral sustained release polymeric nanoparticles of nateglinide. AAPS PharmSciTec. 2013; 14(1): 78-85.
15. Costa P and Lobo JMS. Modelling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences. 2001; 13: 123-133.
16. Dhanalekshmi UM, Poovi G, Neelakanta Reddy P. *In-vitro* observation of repaglinide engineered polymeric nanoparticles. Digest Journal of Nanomaterials and Biostructures. 2012; 7(1): 1-18.
17. Sood A and Pachangnula R. Drug release evaluation of dilitizem CR preparations. International journal of pharmaceutics.1998; 175: 95-107.
18. Hamid A, Merchant Harris M, Shoaib, Jaweria Tazeen and Rabia Yousuf. Once daily formulation and *in-vitro* evaluation of cefopodoxime using hydroxypropyl methylcellulose: A technical note. AAPS PharmSciTech. 2006; 7(3): 1-6.
19. Jaleh Varshosaz J, Tavakoli N and Kheirolahi F. Use of hydrophilic natural gums in formulation of sustained release matrix tablets of Tramadol hydrochloride. AAPS PharmSciTech. 2006; 7(1): 1-7.