Review Article
CODEN (USA): IJPLCP

ISSN: 0976-7126
Pophalkar & Karole, 12(1):57-63, 2021

International Journal of Pharmacy & Life Sciences
Open Access to Researcher

Review on Formulation and Development of Controlled Porosity Osmotic Tablet of Repaglinide

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Article info

Received: 28/12/2020

Revised: 16/01/2021

Accepted: 28/01/2021

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www.ijplsjournal.com

Abstract

The porous osmotic pump based drug delivery system for excellent controlled release of drug for 24 hrs. The porous osmotic pump contains pore forming water soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an in situ formation of a microporous structure. The porous osmotic pump delivery from this system is not influenced by the different physiological factors. The present review is concerned with the patent study of drug release through controlled porous osmotic pump. This patent review is useful in knowledge of controlled porous osmotic pump for its application. The aim of the present investigation was to formulate and characterize nanocrystal formulation of Repaglinide for diabetes therapy. Formulation was done by high pressure homogenization. HPH pressure and cycles range were screened by preliminary batches (T1 and T2). 5, 8, and 10 cycles and 500 to 1500 bar pressure range had kept for further investigation.

Taguchi design was used to optimize type of polymer, % polymer concentration, number of cycles, and HPH pressure for nanocrystal formulation. Formulations were characterized for particle size, zeta potential, and *in vitro* drug release. Optimized formulation (NC 3) showed particle size of 187 nm, zeta potential of −29.4 mv, and % drug release of 80.58% and it was used for further study. Data analysis proved significant effects of factors on responses. Polydispersity index (PDI) Analysis of optimized formulation was found to be 0.248. SEM showed nanocrystal aggregation of drug, may be due to water removal process. DSC showed slight change in crystallinity, may be due to the presence of PEG 4000. Stability study was carried out for 3 months. It indicated no significant change in particle size and zeta potential. However, further studies in higher animals and human being need to be performed before this formulation can be commercially exploited.

Keywords: Microporous, Investigation, Nanocrystal Aggregation, Polydispersity

Introduction

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS).[1]Conventional drug delivery systems have no control over the drug release and effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations; hence once-daily controlled release preparation is often desirable. Drug release from oral controlled release dosage forms may be affected by pH, gastrointestinal motility, and presence of food in the gastrointestinal tract.[2]

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ISSN: 0976-7126
Pophalkar & Karole, 12(1):57-63, 2021

One practical approach with a potential to overcome the abovesaid disadvantages is the osmotic drug delivery system, [3, 4] wherein drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis.

The osmotic drug delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane that has an orifice drilled on it by means of a laser beam or mechanical drill.[5]

To obviate the need for complicated laser drilling, tablets coated with a membrane of controlled porosity have been described. These membranes consist of a leachable material which dissolves upon contact with water, leaving behind the pores through which the drug solution is pumped out. However, due to the relatively low permeability of the dense coatings, osmotic delivery of drugs with moderate to low solubility is limited.[6, 7]

Repaglinideis a non-steroidal agent with powerful analgesic and low anti-inflammatory activity, widely used in the management of both moderate and severe pain. Although oral bioavailability of ketorolac was reported to be 90% with very low hepatic first-pass elimination, the biological half-life of 4–6 hours requires frequent administration to maintain the therapeutic effect. The long-term use of currently available dosage forms of ketorolac may result in gastrointestinal ulceration and acute renal failure.[8]

In the present investigation, an attempt will be made to design a simplified controlled porosity osmotic system of ketorolac and development of sustained release tablet dosage, which is expected to improve patient compliance due to reduced frequency; [9] it also eliminates the need for complicated and expensive laser drilling and maintain continuous therapeutic concentration.

Regular medication conveyance framework gives a quick arrival of medication which doesn't control the medication discharge and furthermore not keep up powerful focus at target site for long time period. Thus to maintain a strategic distance from the defects there is improvement of different controlled medication conveyance framework. Among these osmotic medications conveyance system (ODDS) uses the osmotic weight standard and makes conveyance of medication portion in an advanced way and keeps up drug fixation inside the helpful window and furthermore it limits poisonous impact. Chances discharges drug at a fixed pace of control that isn't rely upon the pH and thermodynamics of disintegration medium. The arrival of medication through ODDS follows zero request energy. The delivering of medication from osmotic framework relying on different definition factors, for example, osmotic weight of center parts, solubility,size of the conveyance opening and nature of the rate controlling film. Controlled porosity osmotic siphon (CPOP) contains drug, osmogensexcipients for example idle substances in center and a covering of semipermeable layer with water solvent added substances. In CPOP water solvent added substances break up at whatever points it interacts with water, bringing about an in-situ detailing of a microporous film.

Numerous imaginative techniques have been produced for acquiring controlled medication discharge. From the commonsense view point, controlled porosity osmotic tablet is perhaps the best methodologies for creating controlled delivery dose structure.

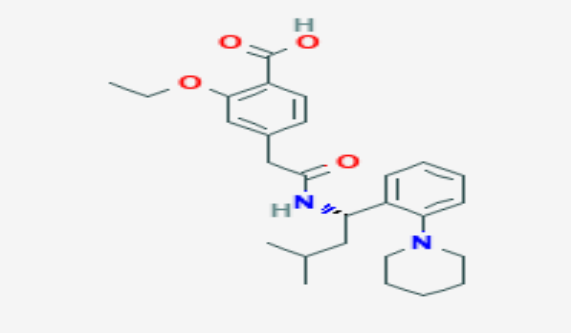
Mechanism of drug release:

Subsequent to interacting with water, water solvent added substances present in the covering disintegrates and it brings about an in situ plan of a micro porous layer as appeared in Figure1. The arrival of medication happens through these micro porous channels.

Drug Profile:

Repaglinide:

Repaglinides is an oral antihyperglycemic operator utilized for the treatement of non-insulin subordinate diabetes mellitus (NIDDM). It has a place with the meglitinide class of short-acting insulin secretagogues, which act by official to cells of the pancreas to animate insulin discharge.



ISSN: 0976-7126
Pophalkar & Karole, 12(1):57-63, 2021

Molecular Fomula: C27H36N2O4
Molecular Weight: 452.6 g/mol
Melting point: 130-131 oC
Half life: 1 hour

Mechanism of action:

Repaglinide brings down the blood glucose by animating the arrival of insulin from the beta islet cells of the pancreas. It accomplishes this by shutting ATP-subordinate potassium diverts in the film of the beta cells. This depolarizes the beta cells, Opening the beta cells calcium channels and the subsequent calcium inundation incites insulin secretion.

Methods

Procurement of drug and excipients

Repaglinide is a nonsulfonylurea; oral hypoglycemic agent used in the treatment of type 2 diabetes mellitus and was the first of the meglitinide analogs to be marketed. It stimulates insulin secretion and is intended for administration before meals in order to improve early phase meal-induced insulin secretion, the loss of which is widely acknowledged as an important event in the natural history of type 2 diabetes mellitus. When taken before meals, it induces a rapid insulin response to the meal. Due to the drug's short half-life, there is a lower risk of hypoglycaemia if a patient misses a meal compared to the sulfonylureas. Its action on the beta-cell also appears to be glucose-dependent, and it does not stimulate insulin secretion in the absence of glucose. The reduced risk of hypoglycemia and consequent more flexible eating patterns may offer important therapeutic advantages. Repaglinide may be used alone or in combination with metformin or the glitazones that increase the action of insulin.[10]

Characterization of drug and excipients.

Solubility Stud

An appropriate amount of Repaglinide was dissolved in a beaker by continuously adding the suitable solvents. The solvents screening was conducted in water, methanol, chloroform, and acetone. The solvents were added in a pipette in aliquots of 0.2 mL applying magnetic stirring until complete dissolution of drug. The solubility was calculated in mg/mL. Once an approximate solubility was found, the saturation solubility was determined, after which the mixture was stirred on a magnetic stirrer at 80 rpm for 24 hr and then filtered, and the content of dissolved drug was analyzedspectrophotometrically at 243 nm.

Production of Nanocrystal Formulations

Nanocrystal formulations were prepared by high pressure homogenization. The optimum combination of four independent variables, such as type of polymer, % polymer concentration, number of cycles, and pressure of HPH, were at three levels by Taguchi orthogonal experimental design to achieve optimum particle size, zeta potential, and in vitro drug release.

High Pressure Homogenization Method

Repaglinide loaded nanocrystal was prepared by high pressure homogenization method. Stabilizer was dissolved in 50 mL of distilled water to obtain aqueous surfactant solution and drug is separately dissolved in acetone. Then, drug solution is added into aqueous surfactant solution under high speed homogenizer at 10,000 rpm for 15 min. to obtain coarse suspension. Then, this coarse suspension was subjected to high pressure homogenizer at varying pressures and cycles. Samples were withdrawn after the size reduction step for size distribution analysis. Then, this nanocrystal dispersion was lyophilized to obtain the nanocrystal.[11]

Evaluation of Osmotic tablet

Drug Excipients Compatibility Study

FTIR spectroscopy was carried out to further elucidate the interaction With Repaglinide polymer. Repaglinide and polymers were mixed with KBr and pressed (1 tone) into the pellets to carry out spectra by applying sufficient pressure with precaution to avoid moisture.[12]

Measurement of Particle Size

Particle Size and size distribution of the particles in the formulation were determined with a zetasizernanoseries ZS. The sample for particle size analysis was added to a small dispersion unit called a cuvette. Average values were calculated from three batches of each sample. The diameters reported were calculated using volume distribution.[13]

Zeta Potential

Zeta potential of the formulation was determined with a zetasizernanoseries ZS. The sample for particle size analysis was added to the small dispersion unit called a cuvette. Average values were calculated from three batches of each sample.[14]

In Vitro Drug Release

Dialysis bag diffusion technique was used to study in vitro release of drug from the prepared nanocrystal formulation. The 5 mL of formulation was placed in the dialysis bag HiMedia, molecular weight cut off 110 Dalton, sealed, and immersed into a 250 mL beaker containing 200 mL of the release media 0.1 N HCl which was maintained at °C (stirred at 500 rpm) on magnetic stirrer (Remi instruments, India). Aliquots of 5 mL were withdrawn at predetermined time intervals (5, 15, 30, 45, 60, 90, 120, 150, and 180 min) and immediately restored with the same volume of fresh media maintained at the same temperature. The drug was analyzedspectrophotometrically using 0.1 N HCl as a blank.[15]

Polydispersity Index

PDI analysis of the formulation were determined with a zetasizernanoseries ZS. The samples for PDI analysis were added to the small sample dispersion unit called as a cuvette. Average values were calculated from three batches of each sample.[16]

Scanning Electron Microscop

Scanning electron microscopy was used to check the morphological evaluation of drug nanocrystals. For SEM, the sample were glued and mounted on metal sample plate. The sample plate was gold plated with sputter coater using electrical potential of 2 kv at 25 mv for 10 min. The samples were examined under scanning electron microscope.[12]

Stability Study of the Formulation

The stability study of the formulation was carried out using three different temperature conditions according to ICH stability guideline Q1A R2: 5°C ± 3°C (refrigerator), 30°C ± 2°C/65% ± 5% RH (Ambient conditions), and 40°C ± 2°C/75% ± 5% RH (Stability Chamber). The nanocrystal formulation was stored in sealed vials and physical stability of the nanocrystal formulation was evaluated after 3 months. The particle size and zeta potential were measured by the Malvern Zetasizer.[12]

Angle of repose θ

The angle of repose was determined bythe funnel method. The accurately weighed powder blendwas taken in a funnel. The height of the funnel was adjustedin such a way that the tip of the funnel just touched the apexof the heap of the powder blend. The blends were allowed toflow freely onto the surface. The diameter of thepowder cone was measured. Angle of repose is calculatedusing the following equation:

$\tan \theta = h/r$ (1)

$\theta = \tan^{-1}(h/r)$ (2)

Where **θ** is the angle of repose, h is the height of heap in cmand r is the radius of the circular support (cone) in cm.

Bulk density (eb)

Bulk density is determined by pouring thegranules into a graduated cylinder of bulk density apparatus(Sisco, India). The bulk volume (Vb) and mass (m) of thegranules is determined. The bulk density is calculated by
using the following formula.

$Eb = m / vb$

Thickness

The thickness of individual tablets is measured byusing verniercaliperMitutoyo Corp., Japan) which gives theaccurate measurement of thickness in mm. The limit of thethickness deviation of each tablet is ± 5%.

Measurement of coat thickness

After dissolution the filmwas isolated from the tablets and dried at 40°C for 1 hr.Thickness was measured by using electronic digital calipers(Mitutoyo Corp., Japan) and mean values were taken.

Hardness

The hardness of tablets can be determined byusing Monsanto hardness tester (Sisco, India) and measuredin terms of kg/cm2.

Friability

Friability of tablets was performed in a Rochefriabilator (Sisco, India). Twenty tablets of known weight (W0)were de-dusted in plastic chamber of friabilator for a fixedtime of 25 rpm for 4 minutes and weighed again of weight(W). The percentage of friability was calculated using the
following equation.

$$\% \text{ Friability} = F = \left(1 - \frac{W}{W_0}\right) \times 100$$

Where, W0 and W are the weight of the tablets before andafter the test respectively.[17]

Effect of pH

In order to study the effect of pH of release medium inthe drug release of optimized formulation, the *in vitro* releasestudy was carried

ISSN: 0976-7126
Pophalkar & Karole, 12(1):57-63, 2021

in dissolution media having different pHmedia. Dissolution can be carried in 900 ml of 0.1 N HCl, pH6.8 phosphate buffer and pH 7.4 phosphate buffer in USPtype II dissolution apparatus in 75 rpm. The temperature wasmaintained at 37 ± 0.5°C. The release was studied atpredetermined time intervals.[18]

Effect of agitation intensity

To study the effect of agitation intensity on drug release,optimized formulation was subjected to dissolution at variousrotation speeds. Dissolution was carried out in USP-II (Paddle)at 50, 100 and 150 rpm. The samples were withdrawn atpredetermined intervals and analyzed by UV spectrometer.[19]

Scanning Electron Microscopy (SEM)

In order to observe the mechanism of drug release fromthe developed formulations surface coated tablets before andafter dissolution studies was examined using scanningelectron microscope. Scans were taken at an excitationvoltage (KV) in SEM fitted with ion sputtering device.[20]

Effect of osmogen concentration

To check the effect of osmogen concentration on drugrelease formulations were prepared with differentconcentration of osmotic agents and all other parameters oftablet kept constant. The drug release was compared with thedifferent osmogen concentration of formulated batches byusing USP-II dissolution apparatus.[21]

Effect of pore former concentration

Different concentrations of pore former were used insemi permeable membrane formation. In order to comparethe effect of pore former on *in vitro* release profile as well asnumber of formation of micropores were compared.[22]

Effect of membrane thickness

Tablets with varying coating thicknesses were preparedto demonstrate the effect of coating thickness on drugrelease. The drug release rate was measured using 0.1 N HCland phosphate buffer pH 6.8 as a dissolution medium.[23]

Effect of osmotic pressure

To increase the osmotic pressure of the release mediapre-equilibrated to 37°C ± 1°C temperature and osmoticallyeffective solute mannitol was added to produce 30 atm, 60atmand 90 atm respectively. The drug release rate was testedand compared for various dosage forms.[24]

Summary

Repaglinide shows very low solubility and poor bioavailability. Considering the drawbacks of conventional dosage form, nanocrystal formulation was thought to provide required delivery. The main objective of this project was to develop a nanocrystal formulation for Repaglinide for the treatment of diabetes that is capable of efficient delivery of loaded drug. Nanocrystal formulation of Repaglinide will give the required release of drug through oral route. To achieve this objective, by using Taguchi experimental design, nanocrystal formulations of Repaglinide were prepared by high pressure homogenization method. While preparing it, the effect of various formulation variables like the type of polymer, % polymer concentration, number of cycles, and high pressure homogenization pressure on the particle size, zeta potential, and *in vitro* drug release was evaluated. Optimized batch NC 3 was found to have the required particle size, zeta potential, and Polydispersity Index. Particle size of nm, zeta potential of − mv, and PDI of were obtained. Scanning electron microscopy (SEM) image of lyophilized formulation shows the formation of nanocrystalline drug particles. Nearly identical sharp melting point peak in DSC thermograms shows that there is slight physical change in crystalline form in the formulation which may be due to the presence of PEG 4000. Finally, stability studies were carried out at three conditions for 3 months. The final formulation was also examined for the particle size and zeta potential. The particle size of the optimized formulation was tested after 3 months and also zeta potential was determined in three different conditions. Results show that there is no more variation in particle size and zeta potential so the formulation is stable.

Conclusion

The present study was an attempt to formulate nanocrystals of poorly water soluble drug, Repaglinide, having low bioavailability. The objective was to increase the dissolution of drug and to improve the patient compliance. The nanocrystal formulation of Repaglinide with the smaller particle size can be effectively produced by the high pressure homogenization method. The nanosizing approach enhanced the *in vitro* drug release of the Repaglinide. Repaglinide was

successfully entrapped within the polymer with high efficiency. Thus, nanocrystal approach may be a promising carrier for Repaglinide and other class II drugs.

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Cite this article as:
Pophalkar P. B. and Karole S. (2021). Review on Formulation and Development of Controlled Porosity Osmotic Tablet of Repaglinide, *Int. J. of Pharm. & Life Sci.*, 12(1): 57-63.

Source of Support: Nil
Conflict of Interest: Not declared
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