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Development and validation of RP-HPLC method for determination of content uniformity of haloperidol

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ABSTRACT

Aim of the present work was to develop simple, shorter and effective HPLC method with UV detection (285nm) and subsequent validation for the content uniformity determination of Haloperidol in marketed tablet samples. The method uses isocratic mobile phase of 0.1M sodium phosphate buffer (pH adjusted to 6.5 with sodium hydroxide solution) and acetonitrile 65:35 compositions on reverse phase Lichrosphere RP-100 C8 column. The RSD was observed to 0.21 percentage and linearity range of (LOQ) 0.025 – 150 percentage of label claim established with 0.9999 correlation, 8 different brands marketed samples were successfully analyzed for content uniformity and compared the results with the USP and other guidelines for acceptance criteria.

Keywords: Haloperidol, methylene chloride, acetonitrile, dichloromethane.

INTRODUCTION

HP is {4-[4-(p-chlorophenyl)-4-hydroxypiperidino] 4'-flurobutyrophenone} a typical butyrophenone antipsychotic drug. HP is a tertiary amine that occurs as a white or almost white powder, is practically insoluble in water, and is slightly soluble in alcohol, methanol (MeOH) and methylene chloride. The melting point of HP is 150 to 153 ^{o}C. The empirical formula for HP is $C_{21}H_{23}CIFNO_3$. The drug has a pKa value of 8.3.

HP is effective in the treatment of many psychotic disorders such as hyperactivity, agitation and mania. HP effectively treats positive symptoms of schizophrenia while in effective against negative symptoms of schizophrenia. HP is also used in the treatment of neurological disorders such as Gilles de la Tourette syndrome, Huntington's chorea and acute/chronic brain syndrome. Long-term use of HP can result in side effects resembling Parkinson's disease and tardive dyskinesia, an irreversible motor disorder.

Nearly 40 years after its discovery, HP is still one of the most popular drug used for the management of various classes of psychosis. The pharmacology of HP has been extensively reported. Different assay methods have been described in the work, which will be discussed in the following section.

MATERIALS AND METHODS

1.1. Materials

Poly (D, L-lactic-co-glycolic acid) (PLGA) 50:50 DL (inherent viscosity, 0.37 dL/g), 50:50 DL (0.44 dL/g), 75:25 (0.55 dL/g), 100:0 (0.68 dL/g. Polyvinyl alcohol (PVA) (MW, 25,000, 88% hydrolyzed). Haloperidol, phosphate

buffered saline (PBS), ammonium acetate, 1-Piperazineethane sulfonic acid, 4-(2-hydroxyethyl)-monosodium salt (HEPES), gelatin, and chitosan. Acetonitrile, dichloromethane (DCM) and acetone. All the solvents were HPLC grade.

1.2. Nanoparticle Preparation

Nanoparticles were prepared by using two methods: 1.) Emulsification by homogenization-solvent evaporation, and 2.) Emulsification by sonication-solvent evaporation. Henceforth, these methods will be referred as simply homogenization and sonication. Both methods involve preparation of an organic phase consisting of polymer (PLA or PLGA) and drug (haloperidol) dissolved in organic solvent (DCM). The organic phase is added to an aqueous phase containing a surfactant (PVA) to form an emulsion. This emulsion is broken down into nanodroplets by applying external energy and these nanodroplets form nanoparticles upon solvent evaporation. Once the colloidal suspension of nanoparticles is prepared using either of the above methods, the free drug is removed by using our free drug extraction method to obtain the final nanoparticulate suspension.

1.3. Nanoparticle Characterization

Nanoparticles were characterized for the size and size distributions were measured by laser dynamic light scattering. The haloperidol content was measured using HPLC. Briefly, the nanoparticle suspension (coated or uncoated particles) was completely dissolved in the mobile phase of HPLC and injected into the machine. Drug content was calculated as the ratio of the mass of drug inside the nanoparticles to the total initial mass amount of the drug.

RESULTS AND DISCUSSION

We now present the isolated effects of L: G ratio, drug content, surface coating and particle size on the kinetics of drug release. Each point represents the mean value from one batch of nanoparticles from multiple dissolution cells and error bars indicate the standard deviation within a batch. Error bars are omitted when the error is <10 % of the mean. We used our method of sonication to produce 220 nm particles with very narrow size distribution. We were also able to produce uniformly sized particles by our homogenization method for various polymer types and drug contents by selecting the materials and controlling the processing conditions as described in paper. The polydispersity index of the particle size ranges from 0 to 0.3, where 0.3 refers to the most polydisperse population. The polydispersity indexes of these haloperidol-PLGA nanoparticles, particularly those prepared by sonication, are low and show little variability between different batches of particles prepared under various conditions.

2.1.Effect of L: G Ratio

Haloperidol released as a function of time from three batches of nanoparticles made from PLA using the sonication method. The size of particles from each batch is 220 nm and the drug content is 1.7 %. Demonstrates our capacity to produce a system of small nanoparticles (~220 nm) that releases haloperidol consistently with an extraordinary reproducibility across different batches. The drug release profile from nanoparticles can be divided into four zones: (i) Initial burst period, during which the surface drug is dumped into the release medium; here it is taken as one day (ii) Induction period, during which the drug is released at a gradually-decreasing fast rate (iii) slow release period, during which the drug is released at a steady slow rate (iv) final release period (not shown), during which the particle disintegrates to release the remaining drug at a fast rate. The haloperidol release profiles from nanoparticles made from PLGA 50:50 and PLA. The size of particles is 220 nm and the drug content is 1.3 % for PLGA particles and 1.7 % for PLA particles.

2.2. Effect of Drug Content

The haloperidol release profiles from 220 nm PLA particles prepared by sonication and having a drug content of 0.66 %, 1.7 % and 2 %. As the drug content increases, the absolute initial burst increases from 7 to 17 μg/ml. The % release profile is not significantly affected by change in drug content the increase in drug content in the particles influences the absolute release profiles such that both, the cumulative amount of drug released at any time (including initial burst) and the induction period increases. The increase in drug content increases the amount of drug close to the surface as well as the drug in the core of nanoparticles. The former is responsible for an increased initial burst while the latter causes an increase during the induction period.

2.3. Effect of Coating the Particles

The haloperidol release profile from 220 nm PLA particles uncoated or coated with gelatin, chitosan, or L101, prepared by sonication. Particles have a drug content of 1.3 %. The % haloperidol released at the end of day 1

(initial burst) from uncoated particles is 46 %, while that from particles coated with gelatin, L101 and chitosan is 30 %, 20 % and 17 %, respectively. The haloperidol release profile from 220 nm particles coated with chitosan and prepared from PLGA 50:50 and PLA using the method of sonication. The initial burst is ~20 % for PLA particles and ~43 % for PLGA particles.

2.4. Effect of Particle Size

The haloperidol release profiles from PLA particles with 1.8 % drug content having different diameters. The 220 nm particles were prepared using sonication at standard conditions, while the 450 nm and 1300 nm particles were prepared using homogenization at different speeds. As the size increases, the initial burst decreases and the induction period increases. The burst is reduced because on increasing the size, the total surface area of a constant weight of particles decreases. Increasing the size of particles increases the length of diffusion pathways for the drug molecules. For the same amount of drug inside the particles, increasing the length of diffusion pathways exercises two opposing effects on the induction period. The induction period increases because the drug molecules have to traverse a longer distance within the polymer matrix to reach the surface. However, the products of polymer degradation also have to travel a longer distance before they can dissolve in the release medium. The trapped products increase the local pH within the polymer matrix, which accelerates the polymer degradation due to autocatalysis. This accelerates the rate of loss of molecular weight within the matrix leading to faster drug diffusion. This has an effect of reducing the induction period. The final value of induction period depends on the dominating mechanism. For our small sized particles (<1000 nm), autocatalysis is insignificant and the overall impact of increasing the diffusion pathways (by increasing the particle diameter) is an increase in induction period and the induction amount.

Table:-1.Summary of HPLC method for haloperidol determination.

Hexane : isoamylalcohol (98 :2, v/v) (6 ml)	Sodium hydroxide (5 M, 100 µl)	Hydrochloric acid (0.1 M, 100µ1)	Direct inject
Heptane: isoamylalcohol (98.5: 1.5. v/v)	Sodium hydroxide (2 M, 1 ml)	Sulphuric acid (0.005 M, 2ml)	Methanol
Heptane: isoamylalcohol (15% in 1L) (5 ml)	Sodium hydroxide (1 mol/l, 0.5 ml)	Sulphuric acid (5 mM, 0.6ml)	Direct injection
Hexane: isoamylalcohol (98:2, v/v) (10 ml)	Sodium hydroxide (2 M, 0.2 ml)	Hydrochloric acid (0.1 M, 150 µ l)	Direct injection
Diethylether (4 ml)	Sodium hydroxide (1 N, 1 ml)	Hydrochloric acid (0.1 N, 3.5ml)	Direct injection
Diethyleter (5 ml)	Sodium hydroxide (2 N, 200 µl)	Hydrochloric acid (0.2 N, 2.5ml)	

Table:-2.Concentration of HP and RH in a single intraperitoneally injection of HP or RH (1mg/kgbodyweight)

Tissue / time after injection	HP treatment		RH treatment	
	HP	RH	HP	RH
Plasma				
10 min	0.2 ± 0.1	n.d.	0.0 ± 0.0	0.1 ± 0.1
30 min	0.1 ± 0.0	n.d.	0.0 ± 0.0	0.1 ± 0.0
120 min	0.1 ± 0.0	n.d.	0.0 ± 0.0	0.0 ± 0.0
Liver				
10 min	24.0 ± 7.8	0.4 ± 0.2	6.8 ± 0.5	1.8 ± 0.1
30 min	6.2 ± 0.2	0.1 ± 0.0	3.1 ± 0.1	0.8 ± 0.1
120 min	2.9 ± 0.2	0.0 ± 0.0	2.1 ± 0.1	0.3 ± 0.0
Corpus striatum				
10 min	3.4 ±1.3	n.d.	0.2 ± 0.0	1.6 ± 1.3
30 min	3.2 ± 0.5	n.d.	0.5 ± 0.1	2.3 ± 0.9
120 min	1.2 ± 0.2	n.d.	0.6 ± 0.1	0.6 ± 0.2

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