

Theoretical Uses of Pramipexole dihydrochloride in Parkinson's Resistance Depression

Samuel Langhorne, Eric Arthur Blair

Department of Psychological Medicine, Rheinfelden, Switzerland.

*Corresponding Author : Samuel Langhorne, Department of Psychology, Reha Rheinfelden, Rheinfelden, Switzerland, E-mail: langorne_samuel32@gmail.edu

Received date: December 05,2017 ;Accepted date : December 14,2017; Published date: December 20,2017.

Citation for this Article: Samuel Langhorne, Jenny Butler, Brian Andrews, Udo Kischka and Thierry Ettlin. Theoretical Uses of Pramipexole hydrochloride in Parkinson's Resistance Depression. J Psychology and Mental Health Care . Doi: 10.31579/2637-8892/019

Copyright : © 2017 Samuel Langhorne. This is an open-access article distributed under the terms of The Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Pramipexole dihydrochloride monohydrate is an antiparkinson's agent which is known as dopamine D2 receptor agonist. It is structurally different from the ergot-derived drugs, e.g. bromocriptine or pergolide. Pramipexole is designated chemically as (S)-2-Amino-4, 5, 6, and 7-tetrahydro-6-(propylamino) benzothiazole and has the molecular formula $C_{10}H_{17}N_3S$. It comes under class I of Biopharmaceutical Classification System. The purpose of this study was to develop and evaluate pramipexole dihydrochloride monohydrate extended release tablets by wet granulation method using different proportions of polymers and binder. Pre-formulation studies were done initially and the results were found to be within the limits. All the mentioned batches were prepared and granules were evaluated for pre-compression parameters such as loss on drying, bulk density, tapped density and compressibility index. Tablets were evaluated for weight variation, thickness, hardness, friability; disintegration time and assay were found to be within the limits. In vitro dissolutions were performed with 0.05M 6.8 PH phosphate buffer and effect of various polymers were explored. Final selection of formulation was based on dissolution profile, from dissolution studies formulation 9 showed 80% drug release within 20 hours, so it will be compared with innovator. Similarity and difference factors which revealed that formulation (F 9) containing HPMC K 200, Eudragit L100 and binder are most successful as it exhibited in vitro drug release that matched with innovator product. In vitro drug release profile reveals that with increased concentration of Eudragit L 100. Accelerated stability studies were performed for the optimized batch which indicated that there were no changes in drug content and in vitro dissolution.

Extended release drug delivery system

The main objective of any drug delivery system is to provide a correct dose of drug at the proper site in the body to achieve results, and then to maintain the desired drug concentration. Since there is increase in cost and compliance involved in the development and marketing of new drug entities, this has forced most of the pharmaceutical industries to focus their attention on the development of extended / controlled / prolonged system.

The extended release dosage forms are becoming popular as these have a number of advantages over conventional dosage form on dose frequencies, less fluctuation in circulating blood levels, increased patient compliance, and more uniform effect.

Extended release system consists of two parts.

- 1) An immediately available dose to establish the blood level concentration quickly.
- 2) An extended release portion or maintenance dose, which contains several times the therapeutic dose for maintaining the achieved blood level concentration. The main concept of controlled / extended drug delivery system is the use of the system and techniques for altering and controlling the absorption, blood levels metabolism, organ distribution and cellular uptake of pharmacologically active agents.

The main aim of the extended or controlled dosage form is to produce an improved therapy by producing a uniform plasma concentration of drug at steady state and by reducing the ratio of maximum and minimum plasma levels. $[C_{max} / C_{min}]$ after each dose. This could be achieved if the release of drug from the dosage form is slow first order or slow zero order absorption of the drug occurs from the gastro intestinal tract.

The term "extended release" is known to have existed in the medical and pharmaceutical literature for many decades.

It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and / or prolonged and its plasma profile is extended in duration. The onset of its pharmacological action is often delayed, and duration of its therapeutic effect is extended.

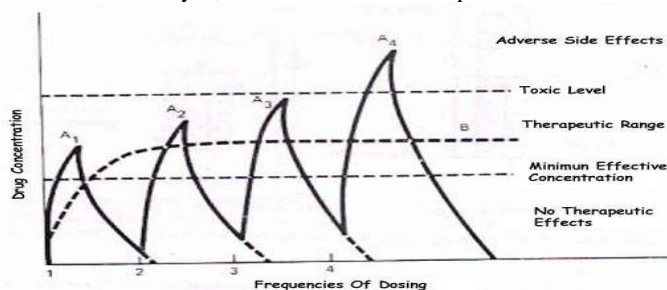


Figure-1: Hypothetical drug concentration profiles in the systemic circulation resulting from the consecutive administration of multiple dose of an immediate release drug delivery system (A1, A2...)

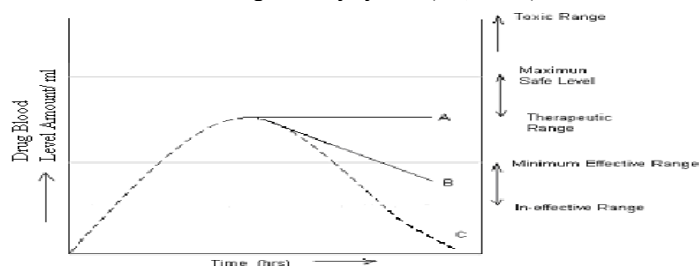


Figure-2: Drug blood levels Versus Time Profiles showing the Relationship between Controlled Release (A), Prolonged Release (B) and Conventional Release (C) Drug Delivery.

Methodology

List of chemicals used with their grades and supplier names

| SI. No | Materials | Source |
|--------|-----------------------------------|---|
| 1 | Pramipexole diHCl monohydrate | A gift sample from Eros Pharma, Bangalore CFL Pharma, Goa |
| 2 | Lactose monohydrate | Kelco Pharma |
| 3 | Microcrystalline cellulose PH 101 | Rohm Pharma. Bombay |
| 4 | Eudragit L 100 | Rohm Pharma. Bombay |
| 5 | HPMC E 3LV | SD Fine Chem., Bombay |
| 6 | Povidone K 90 | SD Fine Chem., Bombay |
| 7 | HPMC K4M | SD Fine Chem., Bombay |
| 8 | HPMC K 200 | SD Fine Chem., Bombay |
| 9 | MCC 112 | SD Fine Chem., Bombay |
| 10 | Aerosil 200 | SD Fine Chem., Bombay |
| 11 | Stearic acid | SD Fine Chem., Bombay |

Preformulation Studies

Drug-Excipients compatibility studies:

Method

Selected excipients were checked for any changes when thoroughly mixed with drug in fixed proportions and checked at various temperatures like 25°C/ 60% RH and 30°C/65% RH and 40°C/75% RH and it was observed that there were no changes in the physical properties namely appearance, colour etc.

Drug uses

All 11 patients with PD and pathological gambling were taking therapeutic doses of a dopamine agonist; 3 of these patients were not treated with levodopa. In 7 patients, pathological gambling developed within 3 months of starting to take or escalating the dose of the agonist; in the other 4 with a longer latency, gambling resolved after the agonist use was discontinued. Pramipexole dihydrochloride was the agonist in 9 of 11 cases in our series and 10 of 17 in the literature (68% in total).

Parkinson disease (PD) is primarily treated by drugs that restore or improve brain dopaminergic neurotransmission. Brain dopamine also plays a central role in the behavioral reward system of both humans and animals, reinforcing a myriad of both productive and counterproductive behaviors. It has been implicated in mediating the reward of gambling behavior.

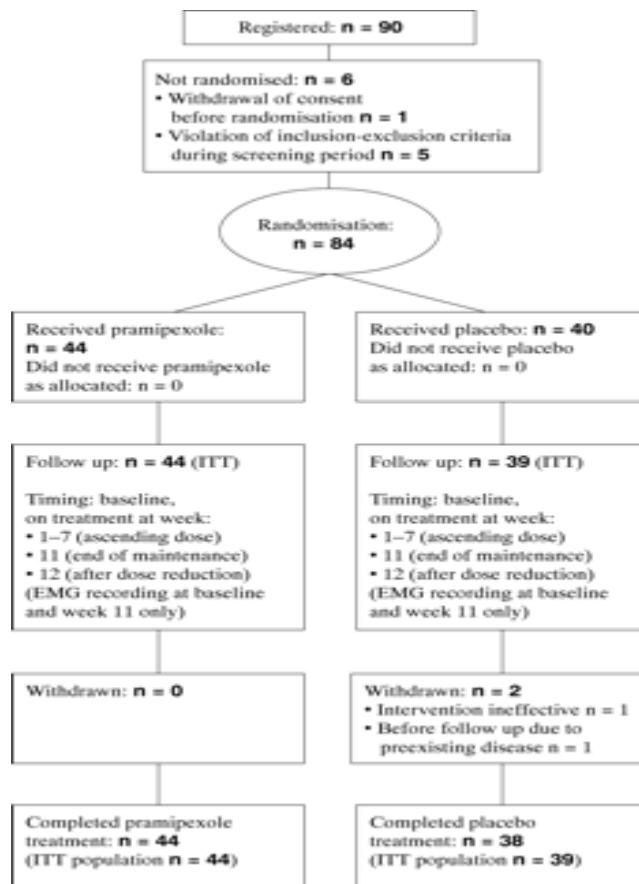
Several recent reports have linked PD dopamine replacement therapy to pathological gambling. Within the last 3 years, 2 of us encountered 11 patients with PD and pathological gambling in our routine neurology practice (movement disorders). The gambling addiction had recently developed and was temporally related to use of dopamine agonist drugs.

Eighty four patients with early or advanced Parkinson's disease and marked, drug resistant tremor under a stable and optimised antiparkinsonian medication were included in a double blind, randomised, placebo controlled, multicentre study and assigned to add on treatment (7 week dose titration interval, 4 week maintenance period) with either pramipexole (n=44) or placebo (n=40) as adjunct. The primary end point was the absolute change in tremor score, defined as the sum of tremor related items (16, 20, 21) of the unified Parkinson's disease rating scale (UPDRS) in "on" periods. Secondary end points included the percentage change in tremor score, the absolute and percentage changes in long term EMG tremor registration, and the change in tremor self rating scales. Safety and tolerability were assessed on the basis of adverse events, laboratory tests, ECG, and vital signs.

Results

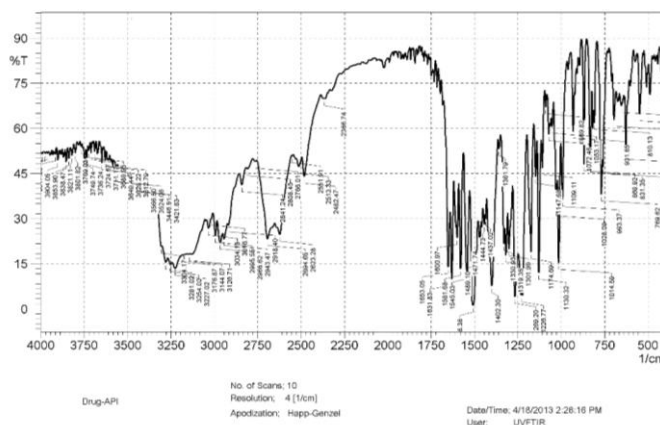
The present study was carried out to formulate and characterize oral extended release tablets of Pramipexole dihydrochloride monohydrate by wet granulation method. The tablets were prepared by using different combination of polymers viz. HPMC K4M, HPMC 3LV, and Eudragit L-100.

Treatment population



Profile of the randomised trial: flow diagram with the progress of the patients throughout the trial.

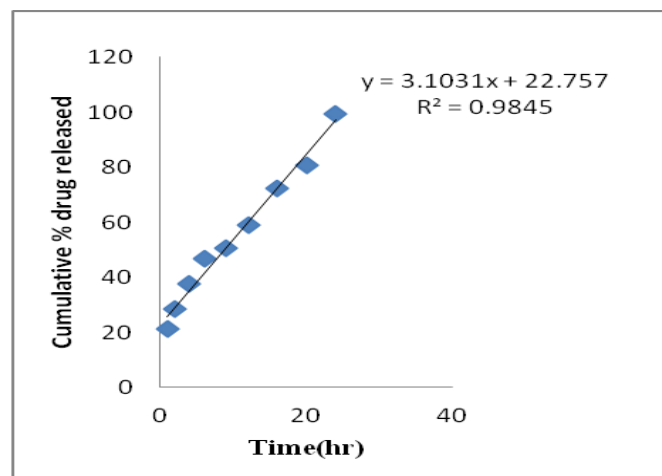
The results are summarized as follows. Similarly FT-IR spectra of Prampexole dihydrochloride monohydrate in combination with polymers are shown in Figures 4 to 8. These peaks were not affected and prominently observed in FT-IR spectra given in Figures 4 to 8. This indicates that there is no interaction between Pramipexole dihydrochloride monohydrate and polymers and the drug was compatible with the formulation components.



FTIR graph of pure drug of Pramipexole dihydrochloride monohydrate

Results of Drug and excipients compatibility study.

| S.No. | Drug and excipients | Ratio | Observation |
|-------|-----------------------------|-------|-------------|
| 1 | API and lactose monohydrate | 1:5 | NCC |
| 2 | API and MCC | 1:5 | NCC |
| 3 | API and Eudragit | 1:5 | NCC |
| 4 | API and HPMC 3LV | 1:5 | NCC |
| 5 | API and HPMC K4M | 1:5 | NCC |



MirapexER fitted in Higuchi model

The conclusions drawn from the present investigation were given below:

Suitable analytical method based on UV-Visible spectrophotometer was developed for Pramipexole dihydrochloride monohydrate λ_{\max} of 260 nm was identified in pH 6.8 Phosphate buffer.

From the FT-IR spectra the interference was verified and found that pramipexole dihydrochloride did not interfere with the excipients used. Procedure to manufacture extended tablets by Wet granulation method was established.

The tablets were evaluated for pharmacopoeial and non-pharmacopoeial (industry specified) tests. Based on the results, F-IX was identified as better formulation amongst all formulations developed for matrix tablets.

Tablets of the formulation F-IX passed all official and unofficial quality control tests.

In vitro release profiles of optimized formulations of pramipexole dihydrochloride monohydrate tablets (F-IX) were found to be similar to that of theoretical drug release profile. The f_1 and f_2 values for the comparison of release of drugs from the formulation F-IX with the theoretical drug release profile were found to be 7, 67 in 6.8 Phosphate buffer.

Pramipexole dihydrochloride monohydrate release from the tablets of F-IX formulation follows zero- order kinetics.

Pramipexole dihydrochloride monohydrate release from the tablets of F-IX formulation follows Higuchi model. Release mechanism of pramipexole dihydrochloride monohydrate from tablets of F-IX formulation follows Diffusion- rate limited mechanism. According Krosmeier-Peppas the mechanism was Anomalous (Non-Fickian) diffusion.

References

1. Juliano RI, Drug Delivery Systems. Oxford University Press, New York.1980.
2. Robinson JR, Sustained and Controlled Drug Delivery System; Marcel Dekker Inc-New York and Basel; 1978.
3. Yie W.Chien Novel Drug Delivery Systems 1992 Marcel Dekker Inc New York 2nd edition: 1-2.
4. Gennaro AR.The Science and Practice of Pharmacy 1995; 19th edition (2): 1662.
5. Peter G Welling, Drug Develop & Ind. Pharma., 9(7),1188,(1983).
6. Robinson JR and Lee HL.Controlled Drug Delivery fundamentals and application 1987; Marcel Dekker Inc New York, 2nd edition: 373.
7. Herbert A, Liberman and Leon Lachman. Pharmaceutical Dosage Forms Tablets; Marcel Dekker Inc New York, Vol.3: 9-10
8. Dahkuri A et al., J.Pharma.Sci. 1978; 67:357.
9. Krishnaiah YSR and Patross.Pharma Times 2001; 33:16-18.
10. Lachman L, Liberman HA and Kanig JL. The theory and practice of industrial Pharmacy 1991; 3rd edition: 296, 299, 430.
11. Bhalla HL and Raj C Piyush. Indian drugs1991; 28(11): 519-522.
12. Brahmkankar DM et al., Cellulose matrices for controlled release of ketorlac tromethamine. Indian drugs 1996; 33(3): 120-123.
13. Bhalla AL et al., Controlled release matrices for ketoprofen. Indian drugs 28(9): 420-422.
14. Baskaran S and Remiz M. Novel approach to zero order drug delivery via hydrogel for diltiazem hydrochloride. Indian J.Pharm.Sci 2002; 64(4): 357-361.
15. Bijaya Ghosh, Chaurasia, Urmi and Nagesh C. Development and In – Vitro Evaluation of once daily formulation of diltiazem hydrochloride. Indian drugs 2001; 38(4): 193-196.
16. Carla Sanchez-Lafuente et al., Development of Sustained release matrix tablets of didanosine containing methacrylic and ethyl cellulose polymers. International Journal of Pharmaceutics 2002;(1-2): 213-221.
17. Di Colo G, Falchi S and Zambito Y. In vitro evaluation of a system for pH Controlled peroral delivery of Metformin.J.Controlled Release 2002; 80:119-128.
18. Gao P and Skoug JW. Swelling of hydroxy propyl methylcellulose matrix tablets .J.Pharmaceutical.sci.1996;(85): 732-740.
19. Hajare AA, More HN and D'souza JI. Design and evaluation of sustained release tablets of Diltiazem Hydrochloride. Indian drugs 2004; 41(3): 175-6.
20. Haririan I, Ghaffari A and Mohammad M.Formulation of controlled release matrix tablets of isosorbide dinitrate. Indian J.of Pharm.Sci.2001; 63(1): 24-9.
21. Kusum Devi and Vijayalaxmi P.Dual Polymer controlled mini MR tablets of glizalide. (This work was presented as a poster during CSPS symposium held in June 2004 in Vancouver, Canada).