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Formulation of Controlled Release Levodopa and Carbidopa Matrix Tablets: Influence of Some Hydrophilic Polymers on the Release Rate and *InVitro* Evaluation

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Abstract

This work aims at investigating different types and levels of hydrophilic matrix agents, including Hydroxy Propyl Methyl Cellulose K15M (HPMC K15M), Hydroxy Propyl Methyl Cellulose K4M (HPMC K4M) and Carbopol 974P, in an attempt to formulate controlled release matrix tablets containing 200 mg of levodopa (LD) and 50 mg of carbidopa (CD). The tablets were prepared by direct compression. Majority of the matrix tablets that contained less than 7.5 % of the polymer disintegrated prematurely. Polymers, HPMC K15M and Carbopol 974P produced the desired drug release at 10 % concentration whereas HPMC K4M at 20 % concentration of the tablet weight. The prepared matrix tablets were evaluated for weight variation, hardness, friability, drug content and in vitro drug release studies. From the *in vitro* release studies of the prepared formulations, one formula was optimized from each polymer. HPMC K15M and Carbopol 974P based tablet formulations showed high release retarding efficiency. Matrix tablets produced with Carbopol 974P showed sticking and weight variation problems. All the formulations showed linear release profiles (r^2=0.96) and sustained the release of levodopa and carbidopa over 8–12 h. The release profiles of levodopa and carbidopa from the selected formulations are close to zero order and follow diffusion dependent release. The prepared matrix tablets produced from the optimized formulations were compared with standard commercial tablets (SYNDOPA). The similarity factor (*f2* value*)* was calculated for all these formulations and found to be above 50. Irrespective of the polymer type and its concentration, the prepared hydrophilic matrix tablets showed non-Fickian (anomalous) release, coupled diffusion and polymer matrix relaxation as the values of release exponent (n) are in between 0.5 and 0.89. Finally it was clear that it is possible to design a formulation with any of the above three polymers giving the desired drug release profile suggesting that HPMC K15M and HPMC K4M are good candidates for preparing controlled release matrix tablets of levodopa and carbidopa.

Keywords: levodopa, carbidopa, HPMC K15M, HPMC K4M, Carbopol 974P, controlled release tablets

1. Introduction

A typical controlled release system is designed to provide constant or nearly constant

drug levels in plasma with reduced dose, frequency of administration and fluctuations in plasma concentrations via slow release over an extended period of time (1). A matrix device consists of drug dispersed homogenously throughout a polymer matrix. Two major types of materials are used in the preparation of matrix devices (2), which include hydrophobic carriers like glyceryl tristearate, fatty alcohols, fatty acids, waxes; carnaubawax, methylmetha crylate, polyvinyl chloride, polyethylene, ethylcellulose and hydrophilic polymers like, sodium carboxymethylcellulose, hydroxypropy lmethylcellulose, sodium alginate, xanthan gum, polyethylene oxide and carbopols.

Matrix systems offer several advantages relative to other extended release dosage forms like easy to manufacture, versatile, effective, low cost and can be made to release high molecular weight compounds (3). Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release.

Levodopa and Carbidopa are used to treat Parkinson's disease (4). Parkinson's disease is believed to be related to low levels of a chemical called dopamine in the brain. Levodopa is turned into dopamine in the body. If levodopa alone is administered, readily undergoes peripheral decarboxylation by DOPA decarboxylase, as a result it loses its lipophilicity and can not cross the blood brain barrier (5). If it is administered in combination with Carbidopa, Carbidopa prevents the peripheral decarboxylation of levodopa so it retains its lipophilicity.

The objective of investigation is to develop levodopa and carbidopa using hydrophilic matrices, HPMC K15M, HPMC K4M and Carbopol 974P. The developed formulations were evaluated for weight variation, hardness, friability and in vitro release studies.

2. Experimental

2.1. Materials

Levodopa and Carbidopa were obtained from Venkar labs, Hyderabad. Polymers HPMC K4M and HPMC K15M were obtained from Colorcon limited, U.K. Carbopol 974P was obtained from IPS chemical company, Mumbai. All other chemicals were of analytical grade and were used as such.

2.2. Methods

2.2.1. Drug excipient compatibility

The simple physical mixtures of Levodopa and Carbidopa drugs with all the polymers and other excipients used in the formulations were taken in glass vials and observed every week to make sure that there is no drug-excipient interaction.

2.2.2. Micromeritics

Static angle of repose, compressibility index, Hausner ratio, poured (or fluff) bulk and tapped bulk densities were determined according to the fixed funnel and freestanding cone method reported by Raghuram et al.(6).

2.2.3. Preparation of tablets:

Formulations DK15:1-4, DK: 1-5, DC: 1-4 were prepared using HPMC K15M, HPMC K4M and Carbopol 974P respectively by direct compression (7, 8). Microcrystalline cellulose was used as the filler. Magnesium stearate, talc and aerosil were used as lubricant and glidant respectively. All the ingredients were weighed and sifted through 40 mesh except the brilliant

blue colour which is passed through 100 mesh. Then all the ingredients were mixed in a poly bag for 10 min. Now the blend is compressed into tablets with 12mm flat circular shaped punches. The composition of the tablets prepared under various trials with HPMC K4M, HPMC K15M and Carbopol 974P were given in the table 1**.**

Formulated tablets weighed 400 mg and measured 1.20 cm in diameter. All the formulation ingredients, except the lubricant and glidant, were mixed in a plastic container and shaken by hand for about 10–15 min. The lubricant and glidant were added to the powder mixture and mixed for another 2–3 min by hand. The tablets were compressed on a rotary tablet machine (Cadmech) fitted with flat faced 1.20 cm punch and die sets and compressed.

2.2.4. Dissolution studies

All the tablets prepared were subjected to dissolution studies using Labindia Dissolution test apparatus (Modified USP type II) equipped with an auto sampler and fraction collector for collection and replenishment of samples and dissolution medium respectively. Dissolution medium used is pH 4.0 acetate buffer. Temperature and rpm are 37 ± 0.5 ° C and 50 respectively. Samples were taken at intervals 1, 2, 4, 6 and 12 hrs and analysed for levodopa and carbidopa by HPLC at 280nm.

2.2.5. Chromatographic apparatus and conditions

Chromatographic separation of levodopa and carbidopa was performed on a Shimadzu HPLC System (Japan) equipped with UV-Visible detector using C8 column (Phenomenex 150 x 4.6mmm I.D., 5µ particle size). The mobile phase used was phosphate buffer pH 3.4. Standard solution and dissolution samples were analyzed at 280 nm using a UV detector. The mobile phase was pumped at a flow rate of 1.0 ml/min with an injector valve fitted to a 20 µl volume sample loop.

2.2.6. Release Kinetics (9).

Different kinetic equations (zero-order, first-order, and Higuchi's equation) were applied to interpret the release rate of the drug from matrix systems. The best fit with higher correlation ($r^2 > 0.98$) was found with Higuchi's equation for all the formulations. Two factors, however, diminish the applicability of Higuchi's equation to matrix systems. This model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix.

Therefore, the dissolution data were also fitted according to the well-known exponential Korsmeyer-Peppas equation (10), which is often used to describe drug release behaviour from polymeric systems:

$$M_t / M_8 = kt^n$$

M_t / M_8 is the fraction of drug release at time t, and k is the kinetic constant; n is the release exponent (indicating the general operating release mechanism). n value between 0.43 and 0.5 indicates Fickian (case I) diffusion-mediated release. Non-Fickian (anomalous) release, coupled diffusion, and polymer matrix relaxation occurs if $0.5 < n < 0.89$, purely matrix relaxation or erosion-mediated release occurs for $n = 1$ (zero-order kinetics), and super case II type of release occurs for $n > 0.89$ (11).

2.2.7. The optimized formulations in triplicate were prepared and kept for stability studies at 2-8^{o}C, 25±2^{0}C/60±5% RH, 40±2^{0}C/75±5% RH and in photostability chambers. The drug content in the tablets was determined after 30 and 60 days.

3. Results and discussion

3.1. Drug excipient interaction study

The results of drug excipient interaction study clearly indicated that there is no drug excipient interaction at 25° C but at 40° C after 3 weeks levodopa developed slight brown colour in all the vials where it is present. So levodopa is found to be unstable at 40° C if it is kept for prolonged period. Therefore it is better to store the formulations containing levodopa at a temperature of about 25° C.

3.2. Micromeritics

The various micromeritic properties like Bulk Density, Tapped Density, Compressibility index (%), Angle of repose and Hausner Ratio were determined for both the drugs and are given in the table 2**.** The compressibility index, Hausner ratio and angle of repose indicated poor flow characteristics. So it was improved by inclusion of suitable amounts of lubricants and glidants.

3.3. Weight variation, hardness and friability

The prepared tablets were subjected to hardness, friability, weight variation, drug content and dissolution and the results are given in the table 3 and all these results were found to be in the permissible limits.

3.4. Dissolution studies

The release profiles of both the levodopa and carbidopa in all the formulations are very close to each other. The drugs were releasing for 12 hrs and follow near zero order release. The drug release rate from HPMC K15M, HPMC K4M and Carbopol 974P based matrix tablets decreased with the increase in the polymer level. This effect might be ascribed to an increase in the extent of gel formation in the diffusion layer (12).

The results of *in vitro* release from HPMC K15M matrix tablets were shown in figures 1 a-b. All the formulations except DK15-4 release less than 70% of drug with in12 hrs due to higher concentration of polymer. The formulation DK15-4 released more than 95% of the drug in 12 hrs. However at various time intervals the cumulative % drug release is very close to zero order. Hence the formulation DK15-4 was selected as optimized formulation.

The results of *in vitro* release from HPMC K4M matrix tablets were shown in figures 2 a-b. Formulations DK4-1 and DK4-2 released less than 85% of drug with in12 hrs due to higher concentration of polymer. The formulations DK4-4 and DK4-5 released more than 95% of the drug within 8 hrs due to lower concentration of polymer. The formulation DK4-3 exhibited a release profile close to first order with a drug release more than 95% within 12 hrs. Hence this DK4-3 was considered as the optimized formulation. According to figures 2a-b, HPMC K4M-based matrices exhibited significantly lower drug release-retarding efficiency than the HPMC K15M and Carbopol 974P. These results might be attributed to the relatively low swellability and rapid dilution and erosion of the diffusion gel layer (13).

The results of *in vitro* release from Carbopol 974P matrix tablets were shown in figures 3 a-b. All the formulations except DC-4 released less than 75% of drug within12 hrs due to higher concentration of polymer. The formulation DC-4 released more than 95% of the drug within 12 hrs. The formulation DC-4 showed a cumulative % drug release close to zero order. Hence the DC-4 formula was found to be optimized.

3.5. Determination of *in vitro* release of drug from marketed formulation.

Marketed LDCD CR formulations (SYNDOPA 200+50) are subjected to dissolution studies using Labindia dissolution test apparatus and cumulative % drug release was depicted in the figures 4 a-b. Because of the nature of measurement, f1 was described as difference factor, and f2 as similarity factor. A f2 value of 50 or greater (50-100) ensures sameness or equivalence of the two curves and, thus, the performance of the two products. *f1 & f2* values were calculated for all the optimized formulations and are given in the table 4.

3.6. Release kinetics

The values of release exponent (n) and correlation coefficients (R^2) of all the optimized formulations are given in the table 5. Upon comparison of correlation co-efficient values (R^2) of all the optimized formulations, it was indicated that the release profiles of Levodopa and Carbidopa are close to zero order in the case of HPMC K15M and Carbopol 974P where as first order in case of HPMC K4M. Irrespective of the polymer type and its concentration, the prepared hydrophilic matrix tablets showed non-Fickian (anomalous) release, coupled diffusion and polymer matrix relaxation as the values of release exponent (n) are in between 0.5 and 0.89.

3.7. Stability studies

The drug content remained same in the formulations stored at 2-8^{o}C, 25 ^{o}C/60 RH but small difference in levodopa level was found in the formulations stored at 40 ^{o}C/75 RH. Apart from this a small difference in carbidopa level was also found in the formulations stored in photostability chambers. These results might be attributed to the temperature sensitivity of the levodopa and photosensitivity of the carbidopa.

4. Conclusions:

The drug release from all matrix tablets showed a polymer concentration dependent retardation effect and a non-Fickian (anomalous) release. Though the dissolution profiles of all the optimized formulations were close to the zero order, DC-4 was not considered to be advantageous as the Carbopol 974 used in this formulation posed sticking and weight variation problems as it picks up water very quickly. DK15-4 and DK4-3 were found to be advantageous due to their method of formulation i.e. direct compression which was very easy, feasible, fast and economical. No significant difference in the drug content between initial and the formulations stored at 25 ° C but a small difference was found between initial and formulations stored at 40° C and in photostability chambers. Therefore it is recommended that these formulations should be stored at 25 ° C and protected from light.

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