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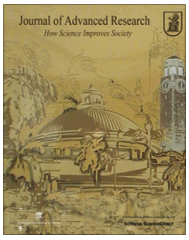

ORIGINAL ARTICLE

Feasibility of optimizing trimetazidine dihydrochloride release from controlled porosity osmotic pump tablets of directly compressed cores

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ABSTRACT

The aim of this study was to develop and optimize Trimetazidine dihydrochloride (TM) controlled porosity osmotic pump (CPOP) tablets of directly compressed cores. A 2^3 full factorial design was used to study the influence of three factors namely: PEG400 (10% and 25% based on coating polymer weight), coating level (10% and 20% of tablet core weight) and hole diameter (0 "no hole" and 1 mm). Other variables such as tablet cores, coating mixture of ethylcellulose (4%) and dibutylphthalate (2%) in 95% ethanol and pan coating conditions were kept constant. The responses studied (Y_i) were cumulative percentage released after 2 h ($Q\%_{2h}$), 6 h ($Q\%_{6h}$), 12 h ($Q\%_{12h}$) and regression coefficient of release data fitted to zero order equation (RSQ_{zero}), for Y_1, Y_2, Y_3, and Y_4, respectively. Polynomial equations were used to study the influence of different factors on each response individually. Response surface methodology and multiple response optimization were used to search for an optimized formula. Response variables for the optimized formula were restricted to $10\% \leqslant Y_1 \leqslant 20\%$, $40\% \leqslant Y_2 \leqslant 60\%$, $80\% \leqslant Y_3 \leqslant 100\%$, and $Y_4 > 0.9$. The statistical analysis of the results revealed that PEG400 had positive effects on Q%2h, Q%6h and Q%12h, hole diameter had positive effects on all responses and coating level had positive effect on $Q\%_{6h}$, $Q\%_{12h}$ and negative effect on RSQ_{zero}. Full three factor interaction (3FI) equations were used for representation of all responses except $Q\%_{2h}$ which was represented by reduced (3FI) equation. Upon exploring the experimental space, no formula in the tested range could satisfy the required constraints. Thus, direct compression of TM cores was not suitable for formation of CPOP tablets. Preliminary trials of CPOP tablets with wet granulated cores were promising with an intact membrane for 12 h and high RSQ_{zero}. Further improvement of these formulations to optimize TM release will be done in further studies.

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Introduction

Controlled drug delivery has taken an important position in pharmaceutical development due to improving the tolerability and patient compliance with prescribed dosing regimens [1]. Despite the extensive use of polymer-based systems,

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alternatives have been developed to decrease the influence of the different physiological factors affected by food intake and patient age [2]. Osmotic drug delivery systems use osmotic pressure as an energy source and driving force for delivery of drugs. Presence of food, pH, and other physiological factors may affect drug release from most controlled release systems (matrices and reservoirs), whereas drug release from oral osmotic systems is independent of these factors to a large extent [3].

The controlled porosity osmotic pump tablets (CPOP tablets) concept was developed by many researchers as an oral drug delivery system [4,5]. This CPOP tablet is a spray-coated tablet with a semipermeable membrane coat containing leachable pore former materials [6]. In this system, the drug, after dissolution in the core, is released from the osmotic pump tablet by hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created by an osmotic agent, the drug itself or a tablet component, after water is imbibed across the semipermeable membrane [7].

Trimetazidine dihydrochloride (TM) is a metabolic antiischemic drug which improves myocardial and muscles glucose utilization [8]. It is used in the prophylaxis against and management of angina pectoris, in cases of ischemia of neurosensorial tissues and also in Meniere's disease [9]. It is rapidly absorbed, and its half-life is relatively short ($t_{1/2}$ = 6.0 ± 1.4 h) [9]. Being a freely water soluble drug, it will be a challenging task to formulate it in a controlled release drug delivery system. The direct compression technique was used to prepare the tablet cores.

Direct Compression of tablets is the easiest way of processing tablets. It includes the main steps of powder blending, lubrication, and compaction. As there is no granulation step to improve the flow and compaction of ingredients, it is usually necessary to use excipients specifically designed for direct compression and engineered to provide the necessary flow and compaction properties [10].

2^3 factorial design was adopted in this study. Factorial designs are of the most efficient designs for experiments involving the study of the effects of two or more factors. By a factorial design, we mean that in each complete trial or replication of the experiment, all possible combinations of the levels of the factors are investigated [11]. Optimization technique based on a response surface methodology (RSM) using polynomial equations [12,13] enables the navigation of the experimental space and finding the optimized formula with predetermined constraints for multiple factors. This optimization technique will be used to search for the optimal TM zero order extended-release formulation for a period of 12 h.

The aim of this study was to answer the question: Can TM release be optimized from CPOP tablets of directly compressed cores?

Material and methods

Materials

Trimetazidine dihydrochloride, Sharon Bio-Medicine, India; spray dried lactose, Molkerei MEGGLE Wasserburg GmbH & Co., KG, Germany; microcrystalline cellulose (avicel PH-102), F M C Biopolymer, Ireland and PEG400, BASF Fine Chemicals, Switzerland, were kind gift samples from Global Napi Pharmaceuticals Company. Magnesium stearate, Witco Corp, USA. Ethylcellulose, viscosity of 5% solution in toluene/ethanol 80:20 is 100 cP, extent of labeling: 49% ethoxyl, Sigma–Aldrich Chemie, Steinhiem, Germany. Dibutylphthalate, Sigma–Aldrich Company, St. Louis, USA. All other chemicals were of the analytical grade and used as received.

Experimental design for CPOP tablets of directly compressed cores

Three independent variables expected to have pronounced effects on the osmotic release of TM from CPOP tablets of directly compressed cores were investigated [14]. Each factor was studied at two levels; hence, a 2^3 full factorial design was applied [11]. The levels of these parameters vary widely in different researches of osmotic formulations. These specific levels were chosen based on the wide ranges used in other studies and on preliminary trials for formation of continuous coat. Other variables such as tablet cores, other coating components, and coating conditions were kept constant. The independent variables (factors) and their respective levels investigated together with the dependent variables (responses) and their constraints are shown in Table 1. These dependent variables constraints were used for obtaining a desirable drug release as described in literature [13,15]. These required constraints choice was based on the desired zero order release profile. The cumulative percentage of drug released was considered to be 0% at 0 h, and the ideal drug release was supposed to be 90% in 12 h. Therefore, the equation of zero order release is $F(\%) = 7.5\ t$ where $F(\%)$ is the cumulative percentage released of drug, and t is the release time in hours [16]. Substitution with the required times for responses (2, 6, and 12 h) yielded the results of (15%, 45%, and 90%, respectively). The constraints were set by giving a range for each response around its calculated value. Setting the Y_2 between 40% and 60% was to allow for about 50% of the drug to be released after half the release period. Y_4 (which is the regression coefficient of release data fitted to zero order release equation) was chosen to be maximized to ensure fitting of the release data to zero order release kinetics.

The preparation of the tablets according to suggested trials as well as the release studies were done in random order. Each combination was performed twice in two separate replicates giving a total of sixteen runs. The trials listed in standard order [11] are shown in Table 2.

Preparation of tablet cores

Tablet cores of 300 mg each were prepared. Each tablet core contained: 35 mg TM, 131 mg spray dried lactose, 131 mg microcrystalline cellulose (avicel PH-102), and 3 mg magnesium stearate.

Aliquots corresponding to 125 g powder blend (passed through sieve #40) except magnesium stearate were geometrically mixed in a plastic bag. Finally, magnesium stearate was passed through sieve #60 and added to the previous blend just before tabletting.

The bulk density of the powder blend containing magnesium stearate was determined using a tapped density tester (Erweka Type: SVM202, Erweka, Germany). The lift height was