Powder Technology 218 (2012) 51–56

Contents lists available at SciVerse ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Evaluating retardation and physicochemical properties of co-ground mixture of Na- diclofenac with magnesium stearate

Yousef Javadzadeh [a,*], Khosro Adibkia [b,*], Zahra Bozorgmehr [b], Siavash Dastmalchi [c]

[a] Drug Applied Research Center and Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[b] Drug Applied Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran
[c] Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz 51664, Iran

ARTICLE INFO

Article history:
Received 12 June 2011
Received in revised form 19 November 2011
Accepted 23 November 2011
Available online 3 December 2011

Keywords:
Dissolution rate
Na-diclofenac
Magnesium stearate
Co-grinding
Crystallinity

ABSTRACT

It is suggested here that co-grinding of drug with a hydrophobic carrier has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. In the present study Na-diclofenac was co-ground with magnesium stearate. Various concentrations of magnesium stearate were used to investigate the effect of carrier concentration on drug release. Dissolution test was carried out at pH **7**.2 for determining of drug dissolution rate from prepared formulations. The release rate of drug from co-ground samples was compared to that of from physical mixture formulations. X-ray crystallography, DSC and FT-IR were used to investigate the formation of any complex between drug and carrier or any crystallinity changes during the manufacturing process. The results showed that all co-ground samples demonstrated slower release rates than their physical mixture counterparts in the ratios higher than 1:0.5 (drug: carrier). Decreased dissolution rate was observed with increasing of magnesium stearate concentration. This could be due to the presence of more hydrophobic particles, magnesium stearate, around the drug particles at high concentrations. XRPD, DSC and FT-IR studied ruled out any significant interaction between drug and carrier, only a minor crystallinity change was observed during the process. Kinetically, release pattern of drug fitted best to Higuchi model. Then co-grinding of water soluble drugs such as Na-diclofenac with hydrophobic carrier such as magnesium stearate could be used as an appropriate approach to retard drug release and thereby production of sustained release systems.

1. Introduction

Diclofenac sodium (Na-diclofenac), a potent non-steroidal anti-inflammatory drug with pronounced analgesic properties, is used in the long term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Its biological half-life has been reported as 1–2 h. Gastrointestinal side effects such as bleeding, ulceration or perforation of intestinal wall are commonly seen [1]. Due to short biological half life and associated adverse effects, it is considered as an ideal candidate for controlled drug delivery in order to achieve improved therapeutic efficacy and patient compliance.

Development of sustained release oral dosage forms is beneficial for optimal therapy in terms of efficacy, safety and patient compliance. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval [2–3]. There are several techniques for preparation of sustained release formulations, among which control of drug dissolution is one of the best and most successful methods due to its simplicity and low cost [4]. To achieve this aim, several methods have been developed such as preparation of salt form of drug, coating with special materials and incorporation of drugs into hydrophobic carriers [4–5].

Cogrinding is widely performed for reducing the particle size of powdered poorly water-soluble drugs with the aim of enhancing their dissolution rates and, consequently, their bioavailability [6–8]. Cogrinding is a process where an active substance and a hydrophilic or hydrophobic carrier in powder form are dry-coground in a mill. Several literatures reported the considerable effect of cogrinding with polymers on the dissolution properties and bioavailability of crystalline drugs [9–12]. Magnesium stearate is an additive that is most frequently used as a lubricant. Magnesium stearate is capable of forming films on other tablet excipients during prolonged mixing, leading to a prolonged drug liberation time, a decrease in hardness, and an increase in disintegration time. It is hydrophobic, and there are many reports in the literature concerning its adverse effect on dissolution rates [13]. There is little information in literature showing that cogrinding of magnesium stearate with drug can be employed as a tool to produce efficient sustained release formulations [8]. Therefore, in the present study, an attempt was made to explore the

* Corresponding authors at: Faculty of Pharmacy, Tabriz University of Medical Sciences, Daneshgah Street, Tabriz, Iran. Tel.: +98 411 3341315; fax: +98 411 3344798.
E-mail addresses: javadzadehy@yahoo.com, javadzadehy@tbzmed.ac.ir (Y. Javadzadeh), adibkia@tbzmed.ac.ir (K. Adibkia).

0032-5910/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.powtec.2011.11.037

use of ball mill (grinding technique) as a tool to sustain the drug release from binary mixtures of Na diclofenac-magnesium stearate. The solid state of binary mixture of drug–magnesium stearate before and after milling was also studied.

2. Methods and materials

2.1. Materials

Na-diclofenac was provided by Zahravi Co. (Tabriz, Iran). Magnesium stearate (Merck, Germany), sodium hydroxide (Merck, Germany), potassium dihydrogen phosphate (Merck, Germany), hydrochloric acid (Merck, Germany), and potassium brimide (Merck, Germany) were used.

2.2. Methods

2.2.1. Spectrophotometeric analysis

The spectrophotometeric analysis of all Na-diclofenac samples in aqueous solutions (pH 7.2) was performed at 275 nm (UV/visible spectrophotometer, Shimadzu-120, Japan). Standard curves were constructed by serially diluting an aqueous stock solution of the drug (at pH 7.2) to obtain concentrations in the range of 2.5–60 μg/ml. Each sample was analyzed in triplicate.

2.2.2. Preparation of solid dispersion and physical mixture formulations

Pure Na-diclofenac powder and magnesium stearate with different ratios (1:0.5, 1:1, 1:2, 1:3, 1:4 and 1:5) were poured into the chamber (made of stainless steel) of the ball mill (Fritsch, Germany) such that all formulations contained 10 g total powder. Stainless steel balls were added in the ball mill chamber so that the total volume of powder mixture and balls equaled one third the volume of the ball mill chamber. The powder mixture was then ground at 360 rpm for 120 min. The samples were collected, labeled, and stored in glass vial before use.

For comparison purposes, the physical mixtures of drug/magnesium stearate were prepared by simply mixing the drug powder and magnesium stearate powder with the same ratios that have been used for coground formulations in the turbular blender (Erweka, Germany). The samples were collected, labeled, and stored in glass vial before use.

2.2.3. Dissolution studies

The in vitro dissolution tests were performed on the USP dissolution apparatus 2 (paddle method) (Erweka, DPT6R, Germany), using 900 ml dissolution medium (pH 7.2) prepared according with a rotation speed of 100 rpm. The amount of Na-diclofenac was 25 mg in all formulations. The dissolution tests for all formulations were run for 8 h at 37 °C. Samples were collected at suitable time intervals. Five milliliters of aliquot was removed from each dissolution vessel and filtered through a 0.45 μm filter (Millipore Corp., Bedford, MA, USA). The same amount of fresh dissolution fluid was added to replace the amount withdrawn. The samples were then analyzed at 275 nm by UV/visible spectrophotometer. The mean of 3 determinations was used to calculate the drug release from each of the formulation.

– The in vitro release profiles of prepared formulations were compared using similarity factors, f_2, as defined by the following equation [14].

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t-T_t)\right]^{-0.5}\times 100\right\}.$$

Where n is number of time points at which% dissolved was determined, R_t is the %dissolved of one formulation at a given time point, and T_t is the %dissolved of the formulation to be compared at the same time point. The similarity factor fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. An f_2 above 50 indicates that the two profiles are similar.

2.2.4. X-ray powder diffraction (XRPD)

X-ray diffractometery of drug, carrier, solid dispersions and physical mixtures were performed using Siemens diffractometer (Siemens, D5000-Germany). The cross section of samples was exposed to X-ray radiation (Cu Kα) with wavelength of 1.5406 Å. The rate of the scanning was 0.6°/min. Samples, ground into powders with an agate mortar and pestle, were measured on a low background quartz plate in an aluminum holder.

2.2.5. Differential scanning calorimetry (DSC)

Thermograms of the samples (Na-diclofenac, carriers and solid dispersions and physical mixtures) were recorded on a DSC-60 (Shimadzu, Japan). Samples (3–5 mg) were placed in aluminum pans and the lids were crimped using a Shimadzu crimper. Thermal behavior of the samples was investigated under nitrogen gas at scanning rate of 20 °C/min, covering a temperature range of 30–350 °C. The instrument was calibrated with an indium standard.

2.2.6. Fourier transform infrared spectroscopy (FTIR)

Drug, carrier, solid dispersion and physical mixture powders were analyzed by FTIR to evaluate potential interactions. The samples were prepared by weighing approximately 5 mg of the material for analysis, homogenously dispersing in dried KBr in a mortar and pestle, and compressing the powder under vacuum with a compression force of 15 t using a 10 mm diameter round flat face punch for 10 s to produce a pellet compacts. The sample was placed in the IR light path and the IR spectra were recorded (Shimadzu 4300, Japan) from 600 to 4000 cm^{-1} in transmission mode.

2.2.7. Kinetics

To clarify the mechanism of release, the in vitro release profiles were fitted to 10 kinetic models which have been represented in Table 1.

The accuracy and prediction ability of the models were compared by calculation of squared correlation coefficients (RSQ) and absolute percent error (E) for each set as well as overall mean percent error (OE) for all sets.

2.2.8. Statistical analysis

All the data were statistically analyzed by analysis of variance or Tukey's multiple comparison test. Results are quoted as significant where $p<0.05$.

Table 1
Kinetic models used for analysis of Na-diclofenac release data (drug-carrier ratio of 1:2).

No.	Model name	Model	RSQ	E
1	Zero order	$F = k_0 t$	0.953	2.1
2	First order	$\ln(1-F) = -k_f t$	0.988	0.91
3	Higuchi	$F = k_H\sqrt{t}$	0.994	0.63
4	Power law	$\ln F = \ln k_p + p\ln t$	0.990	1.41
5	Hixson-Crowell	$1-\sqrt[3]{1-F} = k_3 t$	0.980	1.32
6	Square root of mass	$1-\sqrt{1-F} = k_2 t$	0.974	1.52
7	Three seconds root of mass	$1-\sqrt[3]{(1-F)^2} = k_{\frac{2}{3}} t$	0.968	1.71
8	Weibull	$\ln[-\ln(1-F)] = -â\ln t_d + â\ln t$	0.974	1.75
9	Linear probability	$Z = Z_0 + qt$	0.974	1.51
10	Log–probability	$Z = Z_{0'} + q'\ln t$	0.963	2.11

Parameters of models 1–10 were obtained by linear regression. F and $F\infty$ denote fraction of drug released up to time t and end of the release experiment, respectively. k_0, k_f, k_H, p, k_P, $k_{1/3}$, $k_{1/2}$, $k_{2/3}$, t_d, β, j, Z_0, $Z_{0'}$, q, q′, n, m and b are parameters of the models. Z and Z′ are probits of fraction of drug released at any time.