Asian Journal of Pharmaceutics

Original Research Articles

ANALYSIS OF FORMULATION EFFECTS IN THE DISSOLUTION OF KETOPROFEN PELLETS

SAINI V*, AHUJA N., SHARMA D. K., AND GUPTA V. B.

Department of Pharmaceutics, B. R. Nahata Collage OF Pharmacy, BRNSS ContracT Research Center. Mandsaur. M.P. 458001, INDIA
E-mail: singhvipins31@rediffmail.com

ABSTRACT

In this work the effects of citric acid and two common fillers, lactose (soluble) and tricalcium phosphate (insoluble) are examined on the release profiles from pellets, using ketoprofen as a model drug with pH-dependent solubility. Also studies were conducted on dependence of these profiles on the specific surface area, bulk density, apparent density, porosity and porosity parameters (pore size distribution, total pore surface area, mean pore diameter and pore shape), as determined by mercury intrusion porosimetry. Pellets were prepared by the extrusion-spheronization method. Four different formulations were considered: two ternary mixtures of ketoprofen (I), lactose (L) or tricalcium phosphate (P) and microcel (M) in the relative proportions 2:3:5 (ILM or IPM) and two four-component mixtures of the same components plus 5% citric acid (C) in the relative proportions 2:2.5:0.5:5 (CILM or CIPM). Pellets with high porosity and total pore surface area but small median pore diameter (tricalcium phosphate pellets—IPM) are found to produce similar dissolution results to those of low porosity and low total pore surface area, but having a high median pore diameter (lactose pellets—ILM), irrespective of the solubility of excipients. Addition of citric acid causes a delay in the initial dissolution for both formulations. During dissolution, however, citric acid reduces the median pore diameter of lactose-based pellets. In contrast, in tricalcium phosphate/citric acid pellets (CIPM), this parameter increases considerably during dissolution, when compared to the IPM formulation. These findings may justify the contrasting dissolution behaviors of CIPM and CILM (lactose/citric acid) pellets, after their common behavior in the initial stages, and show that porosity and its related parameters, along with physical properties of excipients such as solubility, density and specific surface area, are helpful to predict pellet behavior in drug release profiles.

Keywords: Pellets, fillers. dissolution, release profile

INTRODUCTION

Extrusion-spheronization technology has been adopted by the pharmaceutical industry for production of pellets, Factors that mostly influence pellet production have been studied and found to be re-formulation parameters, irrespective of the solid dosage form, influence both the process and the quality of the final product. The presence of soluble or insoluble fillers or organic acids as pH adjusters has already been identified as factors, which can modulate drug release.

In particular, the morphology of pellets and total structure can change with any variation in formulation or in materials properties, affecting quality parameters such as porosity and surface roughness. These properties are considered to have a great influence on coating, flow and packing during capsule filling or tabletting. Porosity and pore structure can also provide relevant information for predicting the disintegration, dissolution, and adsorption and diffusion behavior of drugs. Recent studies have shown that porosity parameters, such as pore size distribution, total pore surface area, mean pore diameter and pore shape of pellets formulated with an insoluble drug, correlate with drug release. The aim of our work was to study the effect of formulation variables (using soluble and insoluble fillers and citric acid) on drug release and their relation to specific surface area, bulk density, apparent density, porosity and porosity parameters. Ketoprofen was used as a model drug, which has a pH-dependent solubility (1).

MATERIALS AND METHODS

Swiss Medicare Pvt. Ltd. Sri Ganganager Rajasthan, India, gifted. Microcrystalline cellulose, lactose, monohydrate and tricalcium phosphate. Ketoprofen was gifted by Hetero Lab Mumbai, India

Sodium hydroxide and potassium dihydrogenophosphate, was procoured from BRN College of Pharmacy, work was done on Fluid Bed Dryer at Mecneil Pharma. (H.P.) All other ingredients were of analytical grade.

Preparation of Pellets

Pellets were prepared by the extrusion-spheronization method. Four different formulations were considered: two ternary mixtures of ketoprofen (I), lactose (L) or tricalcium phosphate (P) and microcel (M) in the relative proportions 2:3:5 (ILM or IPM) and two four-component mixtures of the same components plus 5% citric acid (C) in the relative proportions 2:2.5:0.5:5 (CILM or CIPM). Dematerialized water, 65% in volume to weight of dry matter (v/w), was used as the wetting liquid. The powders were mixed for 5 min before the water was added. Masses were extruded in an extruder with cylinders, fitted with a die of 1mm diameter. The extrudate was spheronized in a spheronizer with 250mm diameter at 1020 rpm for 4 min (2).

The pellets obtained were dried in a fluidized bed dryer, for 10 min at 50^0 C. Pellets were then submitted to sieve analysis using a set of British Standard sieves following a v2 progression from 500 to 2000 μm of mesh diameter, and a mechanical sieve shaker, during 10 min. Pellets characterization, for each formulation, was performed on the size range of 1000–1400 μm.

Characterization of Pellets

Crushing Strength

Strength testing was performed in 20 pellets of each formulation with an available radial force apparatus.

Density And Porosity

Bulk and apparent densities, porosity (4), together with porosity parameters, such as the mean pore diameter, total pore volume, pore size distributions and pores shapes, were determined before, during (t = 15 min), and after dissolution (t = 480 min) using a qualified mercury porosimeter. The method is based on the intrusion of mercury under pressure into the sample pores and is quantified using the adapted Washburn equation

$$D = \frac{4\gamma\cos\theta}{P} \qquad (1)$$

Where D is the pore diameter, ? is the surface tension of mercury (485 dyn/cm), ? is the contact angle (130.) and P is the pressure (.2–30,000 psia). From the above equation, a relationship between pore diameter and pore volume of a porous material can be obtained by measuring the apparent volumes. The total pore surface area (S) is given by

$$S = \frac{\int_0^{Vtot} P\, dV}{\gamma |\cos\theta|} \qquad (2)$$

Where P is the pressure, V is the intruded volume of mercury and Vtot is the total intruded volume of mercury.

In vitro Dissolution Studies

Dissolution was conducted in a USP (Method 1, rotating basket) apparatus, at a speed of 100 rpm, in 6 × 900 ml of dissolution media (phosphate buffer at pH 7.2 ± 0.05), maintained at 37 ± 0.5 .C, using an automated assembly which consisted of a Fujitsu Ergo Proe PC, with UV-1601PC software, a peristaltic pump a UV spectrophotometer. The released ketoprofen absorbance was recorded automatically at 264 nm every 5 min for 8 h. The test was carried out in triplicate and a total of 18 dissolution curves were obtained for each formulation.

Mean dissolution times (MDT) at different time points were determined from mean profiles obtained from these 18 curves, as described previously. In the original reference, variances of dissolution times are also included. Tests conducted with pellets in which the active substance is absent have shown no absorption in the wavelength considered. After 480 min of dissolution, pellets were dried under vacuum at 50 .C and weighed to determine the percentage of weight loss.

RESULTS

Specific Surface Area, Densities And Porosity

The specific area, apparent density and solubility of excipients are shown in Table 1. Tricalcium phosphate, used as insoluble filler, presents a significantly higher value for the specific surface area than the other materials and is also characterized by the highest apparent den-

sity of all powders used. These properties are reflected, as expected, in the physical characteristics of the pellets obtained (Table 2). In fact, specific surface area and apparent density of the IPM and CIPM pellets are higher than of those with lactose, indicating that they offer a larger contact surface with the surroundings. This explains their higher porosity values, with a 5 to 10 times smaller median pore diameter and a smaller pellet crushing strength than those containing lactose. This larger contact surface is also shown by the lower bulk density values in the IPM and CIPM pellets (6-8)

The Effects Of Citric Acid

During dissolution testing, there is the possibility of an acidic micro-environment existing inside and in the closer vicinity of the pellets, inspite of the presence of the buffer in the bulk solution, making ketoprofen dissolution difficult and promoting a delay in its release, since ketoprofen is an acidic drug (pKa 4.4). The modeling of the role of citric acid can also be shown through its influence on porosity parameters. In fact, specific surface area values for formulations containing citric acid are lower than those for the correspondent formulations in

Table 1. Physical characteristics of ketoprofen and excipients

Raw materials	Specific surface area	Apparent density at	Solubilit
ketoprofen		1.118 ± 0.001	6.5
Monohydrate lactose	0.24–0.25	1.542 ± 0.002	215.98
Tricalcium phosphate	70–80	2.985 ± 0.003	0.01
Citric acid		1.57 ± 0.001	>1000
Microcel PH 101	1.06–1.12	1.580 ± 0.001	0.0

Table 2: physical properties of Pellet

Properties	ILM	CILM	IPM	CIPM
Crushing strength (N)	6.66 ± 1.08	9.80 ± 1.57	3.53 ± 0.78	5.10 ± 1.08
Specific surface area (m2 g.1)	0.47 ± 0.01	0.33	15.77	10.76
Bulk density (g cm.3)	1.19 ± 0.01	1.32	1.19	1.26
Apparent density (g cm.3)	1.44 ± 0.01	1.51	1.70	1.61
Porosity (%)	17.78 ± 0.55	13.10	29.78	24.28
Total pore surface area (m2 g.1)	7.91 ± 0.37	7.72	25.97	20.45
Median pore diameter (µm)	1.11 ± 0.02	0.54	0.10	0.10

Table 3: Pellet physical properties 15 minutes of dissolution

Properties	ILM		CILM	IPM	CIPM
Bulk density (g cm.3)	0.87		1.03	1.12	1.07
Apparent density (g cm.3)	1.38		1.40	1.70	1.64
Porosity (%)	36.87		26.87	34.23	34.48
Total pore surface area (m2 g.1)	11.45		12.4	27.97	24.18
Median pore diameter (µm)	1.93		1.18	0.18	0.60
MDT (min)	5.96		7.58	5.92	6.86

Table 4: Pellet physical properties after complete dissolution (480 min)

Properties	ILM	CILM	IPM	CIPM
Bulk density (g cm.3)	0.76	0.83	1.07	1.06
Apparent density (g cm.3)	1.31	1.32	1.77	1.74
Porosity (%)	42.04	37	39.59	39.27
Total pore surface area (m2 g.1)	13.28	15.23	33.62	29.47
Median pore diameter (μm)	2.62	1.76	0.21	1.43
MDT (min)	60	93	64	46
Weight loss after dissolution testing (%)	50.52 ± 0.54	50.21 ± 0.4	20.66 ± 0.49	25.67 ± 0.29

The corresponding MDT values and final weight losses are also presented.

the absence of this excipient. Bulk density values are higher, lessening the penetration of the dissolution medium in the pellet, and also favoring the above-mentioned acidic micro-environment (5).

CONCLUSIONS

Pellets with the soluble filler lactose and pellets containing the insoluble filler tricalcium phosphate have produced similar in vitro release profiles of the model drug ketoprofen On the other hand, when 5% of fillers were replaced by citric acid, we have witnessed different dissolution behaviors, i.e., in lactose pellets citric acid induced a drug release delay, while in tricalcium phosphate pellets a delay was noticed only during the first 15 min, with this formulation being the first to reach complete dissolution.

Porosity and porosity parameters, such as total pore surface area, mean pore diameter, pores size distribution and pores shape, contribute to explain this findings and, along with excipients physical properties as solubility, density and specific surface area, can help predicting drug release profiles of multi-unit dosage forms.

Tricalcium phosphate containing pellets prove to be smoother, due to their high porosity values and low pore sizes, which is a useful property to consider for subsequent technological treatment.

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