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Design and characterization of aceclofenac and paracetamol spherical crystals and their tableting properties

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ABSTRACT

The objectives of the present research were to prepare directly compressible paracetamol (DCP) by nontypical spherical crystallization technique and spherical crystals of aceclofenac (SCA) by typical spherical crystallization technique. Both spherical crystals were combined and compressed into tablets by direct compression technique. FT-IR and DSC study exhibited no interaction between the drug and the excipients used in the formulation. The Kawakita analysis showed that spherical crystals were less cohesive due to dense nature of particles. Both DCP and SCA showed plastic deformation suggesting improved compressibility. Lower elastic recovery was observed with higher compaction pressure. The Leuenberger analysis showed that maximum crushing strength is reached faster at lower pressures of compression. *In vitro* dissolution study showed that more than 90% paracetamol and aceclofenac were released within 45 and 180 min, respectively. Hence, the combined formulation of SCA and DCP can be used for preparing tablet by direct compression method.

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1. Introduction

Direct tableting is the most desirable and simplest technique of making tablets [1]. However, compressing a high dose drug by direct compression requires good micromeritic properties, such as flowability and compressibility [2]. To thrive in direct compression, the particle modification of a drug is required to impart sufficient flowability and compressibility [3]. Spherical crystallization technique has come into the forefront because of the habit of particles (form, shape, size, surface, etc.), which can be changed by this approach [4]. Spherical crystals exhibit improved secondary characteristics, like flowability and compressibility, so that direct tableting is possible without granulation [5]. Spherical crystals can be obtained by two different techniques, either by typical spherical crystallization technique or nontypical spherical crystallization technique [6, 7]. The nontypical spherical crystallization technique can also be considered as the traditional crystallization process (salting-out, cooling, precipitation, etc.). This process is carried out by controlling the physical and chemical factors [4]. Typical spherical crystallization employs three solvents: one is the drug dissolution medium, i.e., good solvent; another is a medium which partially dissolves the drug and have wetting property, i.e., bridging liquid; and the last one is immiscible with the drug substance, i.e., bad solvent [8]. The two most commonly used typical spherical crystallization techniques are wet spherical agglomeration method (WSA) and quasi-emulsion solvent diffusion method (QESD)[9]. The spherical crystallization technique has already been successfully applied to improve flowability, compressibility [10], solubility, dissolution rate, and bioavailability [11] of drugs.

Paracetamol (*N*-acetyl-*p*-aminophenol) is a high dose nonsteroidal anti-inflammatory drug (NSAID). It is the most widely used antipyretic alone and also in combination with other NSAIDs. Paracetamol exhibits poor compression and elastic deformation characteristics with a high tendency to capping [12]. Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is an orally effective NSAID of the phenyl acetic acid group, which possesses remarkable anti-inflammatory, analgesic, and antipyretic properties. It is used in the treatment of osteoarthritis and inflammatory disease of the joints. It exhibits very slight solubility in water, poor flow, and compression characteristics [13]. Many commercial tablets containing both paracetamol and aceclofenac are available in the market because of better therapeutic benefit. Hence, the objectives of the present research were to prepare directly compressible paracetamol and aceclofenac by the nontypical and the typical spherical crystallization technique, respectively. Finally, both crystals were characterized alone and also in combination. Tableting properties of spherical crystals in combination were compared with granules (wet granulation method).

2. Materials and methods

Aceclofenac and paracetamol were obtained as a gift sample from Mepro Pharmaceuitcals Pvt Ltd, Surendranagar, Gujrat, India. HPMC 50 cPs was obtained as a gratis sample from Colorcon Asia Pvt Ltd, Goa, India. Polyvinyl pyrrolidone (PVP K90) was procured from Sigma

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Table 1
Composition, drug content and percentage yield of directly compressible paracetamol (DCP) and spherical crystals of aceclofenac (SCA).

Composition of directly compressible paracetamol (DCP)	Quantity	Composition of spherical crystals of aceclofenac (SCA)	Quantity
Paracetamol (g)	10	Aceclofenac (g)	2
Ethanol (99.95% V/V) mL	20	Acetone (mL)	8
Polyvinylpyrolidone K90 (0.5% W/V)	100	HPMC 50 cPs (mg)	125
		Dichloromethane (mL)	3
		Distilled water (mL)	250
Evaluation	DCP	SCA	
Drug content (%)	95.44	97.22	
Percentage yield (%)	86.45	90.65	

Aldrich. Ethanol, dichloromethane (DCM), and acetone were procured from LobaChemie, Mumbai, India. All other chemicals used were of analytical grade.

2.1. Experimental methods

2.1.1. Preparation of directly compressible paracetamol (DCP)

Directly compressible paracetamol (DCP) was prepared by nontypical spherical crystallization (NTSC) technique as described in the literature [14, 15]. However, in the present study, the PVP of molecular weight 90,000 (PVPK90) was used in place of the PVP of molecular weight 2000, 10,000, and 50,000. 10 g of paracetamol was taken and dissolved in 20 mL of ethanol (99.5% v/v) and heated up to a temperature of 75 °C, until the drug dissolved completely. Then the temperature was decreased to 65 °C. In another beaker 100 mL of PVP K90 solution (0.5% W/V) at temperature 3 °C was maintained in an ice bath. After the decrease in temperature of the ethanolic solution of paracetamol, it was added to the PVP K90 solution maintained at 3 °C. It was stirred well for 1 min and left undisturbed until the supernatant is clear. At this time, the temperature was maintained below 5 °C. After the production of crystals, it was rapidly filtered out by vacuum filtration. The crystals were then spread on a Petri dish and dried for 24 h at 55 °C in a hot air oven. The composition is shown in Table 1.

2.1.2. Preparation of spherical crystals of aceclofenac (SCA)

Spherical crystals of aceclofenac (SCA) were prepared by wet spherical agglomeration method (WSA). Solvents for the preparation of SCA were chosen according to the literature [3]. Acetone, dichloromethane (DCM), and water were selected as good solvent, bridging liquid and bad solvent, respectively. A solution of aceclofenac in acetone (2 g in 8 mL) was added to a solution of HPMC50 cPs in 3 mL of DCM. Drug was crystallized by adding the above solution to a 500 mL capacity beaker containing 250 mL of distilled water. The mixture was stirred continuously for a period of 0.5 h using a digital mechanical stirrer (Remi, India) at 800 rpm to obtain spherical agglomerates. The agglomerates were separated by filtration and dried at 55 °C in a hot air oven. The composition is shown in Table 1.

2.1.3. Combined formulation of spherical crystals (CFSC)

Spherical crystals of aceclofenac (100 mg equivalent) and directly compressible paracetamol (500 mg equivalent) were taken and mixed with 0.5% of aerosil (glidant), 0.5% talc (lubricant), and 1% of sodium starch glycolate (disintegrant).

2.1.4. Preparation of granules (WG) by wet granulation method

The wet granulation method of massing and screening was used with a batch size of 100 tablets. Granules were prepared for paracetamol (500 mg/tablet) and aceclofenac (100 mg/tablet) in combination, using aqueous binder solution of PVPK90 (5% W/V). The wet mass was passed through sieve no 10 and dried at 80 °C for 1 h. The dried granules were calibrated by passing through sieve no 12. The granules were mixed with 0.5% of aerosil, 0.5% talc, and 1% of sodium starch glycolate (SSG).

2.2. Evaluation of spherical crystals

2.2.1. Yield and drug content

The percentage yield was calculated after drying both DCP and SCA. DCP (equivalent to 500 mg of paracetamol) and SCA (equivalent to 100 mg of aceclofenac) were powdered and extracted with 20 mL of methanol separately. The samples were filtered, diluted suitably and analyzed at 243 nm and 273 nm spectrophotometrically (UV-1800, Shimadzu, Japan) for paracetamol and aceclofenac content respectively.

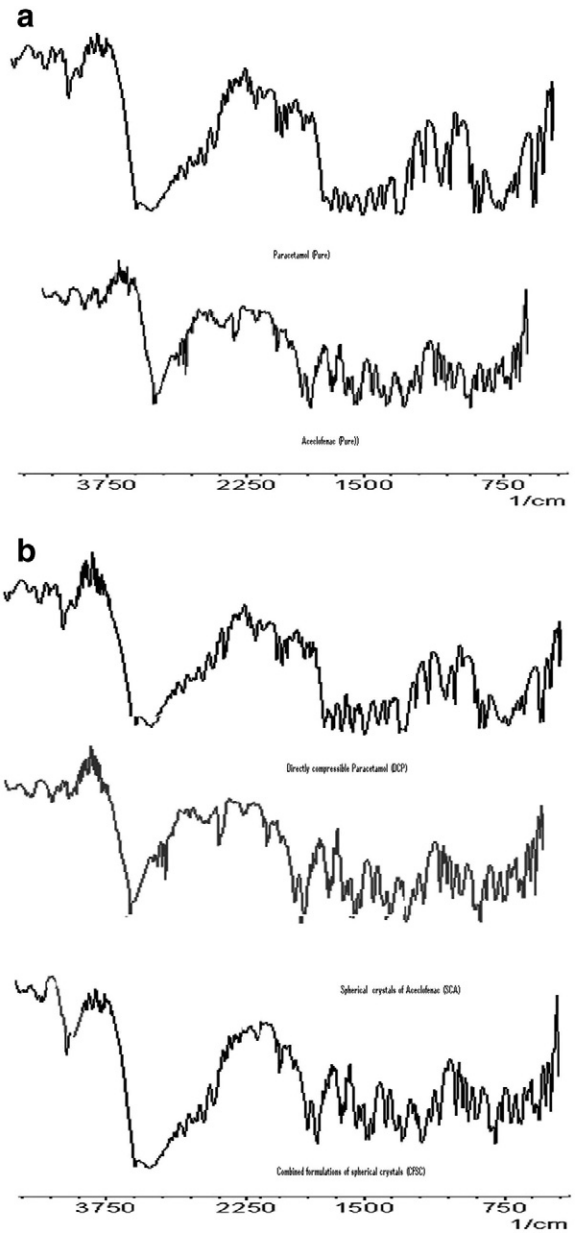

Fig. 1. a: FT-IR spectra of pure paracetamol and aceclofenac. b: FT-IR spectra of DCP, SCA and CFSC.

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