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Choosing an Appropriate Method for Sustained Release Flurbiprofen Pellet Production

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ABSTRACT

Flurbiprofen is a slightly water soluble, nonsteroidal anti-inflammatory active ingredient with analgesic and antipyretic activity. The purpose of this study was to develop an appropriate pellet production method for pH independent sustained release pellet formulation of flurbiprofen. Flurbiprofen pellets were produced by three different production methods; Suspension Layering, Extrusion Spherization, Rotagranulation. Although the simple and fast processing properties of Extrusion Spheronization and Rotagranulation methods, according to visual control and comparative dissolution profiles, Suspension Layering method was found more suitable for Flurbiprofen SR (Sustained Release) having high drug load for each single dose. Beginning with the spherical core has brought great advantage to Suspension Layering method, since ideal sphericity could not be reached at Extrusion Spheronization and Rotagranulation methods due to limited microcrystalline cellulose amount.

Keywords: Controlled release, Flurbiprofen SR pellet, Pelletization techniques, Suspension Layering, Extrusion Spheronization, Rotagranulation.

INTRODUCTION

Flurbiprofen is a member of the phenyl alkanoic acid derivative group of non-steroidal anti-inflammatory drugs with analgesic and antipyretic activity. Flurbiprofen is a white or slightly yellow crystalline powder. It is slightly soluble in water at pH 7.0 and readily soluble in most polar solvents. The chemical name is [1, 1'-biphenyl]-4-acetic acid, 2-fluoro-alpha-methyl-, (±)-. The molecular weight is 244.26. Its molecular formula is $C_{15}H_{13}FO_2$ and its structural formula shown in Fig. 1.

There are several benefits of using Controlled Release formulations. Controlled Release formulations improve patient compliance by reducing dose frequency and dose reduction, maintaining constant level of drug concentration in blood plasma, reducing toxicity due to overdose and reducing the fluctuation of peak valley concentration. Also, the safety margin of high potency drugs can be increased and thus side-effects or adverse effects can be minimized.

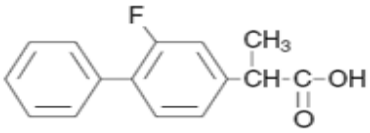

Fig. 1: Structure of Flurbiprofen

Multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The

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release of drug from multiparticles depends on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them.

Multiparticles are less dependent on gastric emptying, resulting in less inter and intra-subject variability in gastrointestinal transit time. Pellets which are a member of multiparticulate systems are agglomerates of fine powders or granules of bulk drugs and excipients. Besides having the advantages of multiparticulate systems, pellets also have important superiorities including very low hygroscopicity, low abrasion, easy to dose, excellent stability, compact structure, high active ingredient content possibility and they are spherical / semi spherical, free flowing, dust free solid units with a narrow size distribution, especially in between 500 and 1500µm diameter. [1-2]

Mostly used pellet production methods are: Extrusion Spheronization Method, Powder Layering Method, Solution/ Suspension Layering Method, Rotagranulation Method, Spray drying/ Spray congealing Method.

Although flurbiprofen is a molecule that is rapidly absorbed from the gastrointestinal tract after oral administration, using sustained release pellets helps to achieve sustained absorption of Flurbiprofen. The objective of the present study is to find the optimum formulation and manufacturing method to obtain homogenous and spherical Flurbiprofen SR pellets for the purpose of achieving the target dissolution profile and particular size distribution. Micropellet production methods dealed within this study are; Suspension Layering Method, Rotagranulation and Extrusion Spheronization Method. Moreover, the effects of different production methods on the spericity of the pellets and the similarity of the dissolution profile with the reference product were investigated.

MATERIAL AND METHODS

Materials

The following chemicals were obtained from commercial suppliers and used as described: Flurbiprofen was obtained from Aesica Pharmaceuticals Limited, Ammonio Methacrylate Copolymers (Eudragit RS 30D and Eudragit RL 30D) were obtained from Degussa, Evonik, Neutral pellets (Cellets 500, Cellulose Microcrystalline) were obtained from IPC Process – Center GmbH & Co, Triethyl citrate was obtained from Jungbuzlauer, Microcrystalline Cellulose was obtained from F.M.C. Biopolymer, Magnesium Stearate was obtained from Peter Greven, Silicon dioxide (Syloid 244FP9) was obtained from Grace Davison and PEG 6000 (Polyethylene glycol 6000) was obtained from Clarient. These excipients were used for the trial productions. Sodium dihydrojen phospate dihydrate, phosphoric acid and acetonitrile were obtained from Merck and were used for analytical purposes.

Dissolution profiles of the trials were compared with the reference product, Cebutid L.P. Flurbiprofene 200 mg with batch number 9009, produced in Rottendorf Pharma Zone Industrielle N°2 Batterie 1000, 59309 Valenciennes Cedex.

Methods

Extrusion Spheronization Method

Extrusion / spheronization is a multistage process for obtaining pellets with uniform size from wet granulates (extrudates).

The method involves the following main steps:

- the dry mixing of the active ingredients and excipients, in order to achieve homogenous powder mixture;
- wet massing, in which the powders are wet mixed to form a sufficiently plastic mass.
- an extrusion stage, in which the wet mass is shaped into cylindrical segments with a uniform diameter (spaghetti-like extrudates);
- the Spheronization stage, in which the small cylinders are rolled into solid spheres (spheroids);
- the drying of the spheroids, in order to achieve the desired final moisture content;
- Dry sizing or sifting (optional), to achieve the desired narrow size distribution.
- Coating (optional) [3]

Rotagranulation Method

The main piece of the Rotagranulation equipment is a rotating disc. Three forces –centrifugal, gravitational and fluidization air- act upon the product from different directions. The rotating disc provides a centrifugal force, which forces the pellets toward the wall of the processing chamber at the periphery of the rotor. Fluidized air provides, via a slit, a vertical force that pushes the particles upwards. As the airflow above the slit relaxes with distance, the particles cascade down towards the bottom of the disc by gravitational force. The sequence is then repeated until the completion of the process. The centrifugal force is a function of the rotational speed of the disc, while the vertical distance the particles traverse depends on air velocity and volume. The combined action of the three forces generates a spiral rope-like material motion and a rapid turnover rate that is responsible for the high efficiency of centrifugal equipment. [4]

Suspension Layering Method

Converting powders to pellets can be achieved by a variety of techniques. Layering a suspension or solution of drug onto a seed material (generally, a coarse crystal or nonpareil) can result in pellets that are uniform in size distribution and generally possess very good surface morphology. These characteristics are especially desirable when the pellets will subsequently be coated for some type of controlled release. [5]

The first step of solution / suspension layering is preparing a solution or suspension containing drug particles and solvents or other application medium.

Solid bridges are formed between the cores and the following layers containing drug substance and coating materials (polymers). Process is finished when desired layer of drug or polymer is formed. [6]

Drug release studies

Drug release studies of the trails were performed in 37°C, 900 mL pH 7.2 phosphate buffer at USP Dissolution Apparatus 2 – Paddle. The solutions taken from the dissolution apparatus were analyzed by Waters UPLC. Chromatographic conditions are given below.

Column: Acquity UPLC BEH™ C_{18}, 2.1 × 50 mm, 1.7µm
Flow rate: 0.6 mL / min.
Wavelength: UV, 263 nm.
Injection volume: 2µL
Column Temperature: 30°C
Tray Temperature: 15°C
Duration: 3 minutes
Mobile Phase: Mobile Phase A (%57) + Mobile Phase B (%43)
Mobile Phase A: Dissolve 3.64 g sodium dihydrogen phosphate dihydrate ($NaH_2PO_4.2H_2O$) in water and dilute with 2000 mL water. Adjust the pH of the solution to 2.35 ± 0.05 with phosphoric acid.
Mobile Phase B: Acetonitrile

RESULTS AND DISCUSSION

The first method used in the trials is Rotagranulation Method. A Fluid Bed Rotor Processing equipment was used with the unit formula given in Table 1.

For granulation solution, some Eudragit RS 30 D was mixed with water and polyethylene glycol 6000 solution in water was added. Flurbiprofen drug substance was mixed with microcrystalline cellulose in granulator and granulation solution was added while the granulator was processing and mixture was mixed for 5 minutes. Processed amount was dried in fluid bed dryer and sieved from 1400µm sieve. And magnesium stearate is mixed up with the pellets.

However similarity factor f2 was found as 56, the appearance of the pellets were not satisfactory. The sphericity of the produced granules was insufficient. Results of the comparative dissolution studies are given in Table 4.

The second method used in the trials is Extrusion Spheronization Method. Unit formulas given in Table 2 were used for the trials.

For granulation solution, some Eudragit RS 30 D was mixed with water and polyethylene glycol 6000 solution was added in water. Flurbiprofen drug substance was mixed with microcrystalline cellulose in high shear mixer and granulation solution was added while the mixer was processing and mixture was mixed for 5 minutes. Wet mass was passed through the extruder to form rods, similar to short strands of spaghetti. The wet extrudate is then processed in the spheronizer to form pellets. Processed amount was dried in fluid bed dryer and sieved from 1400 µm sieve. And magnesium stearate is mixed up with the pellets.

Since the drug percent of the pellets were so high, satisfactory sphericity could not be achieved.

For more sphericity, a new batch trial containing more Microcrystalline Cellulose was planned since Microcrystalline Cellulose amount is the most important parameter for the sphericity.

Same production method with Trial B was used for Trial C. The only difference was the amount of microcrystalline cellulose and ammonia methacrylate copolymer. At the end of this process, the shapes of the pellet were much better than Trial B, because of microcrystalline cellulose amount increased by 30%. Although, the total solid content of each capsule should had been nearly 380 mg and this amount is too much for 0 number capsule capacity, which the reference pellets had been filled with.

Similarity factor f2 was found as 36, since the amount of copolymer was increased and the granulation time was extended both in granulator and extruder. Results of the comparative dissolution studies are given in Table 4.

The third method used in the trials is Suspension Layering Method. A Fluid Bed Dryer equipment was used with the unit formula given in Table 3.

Table 1: Formulation of Trial A produced with Rotagranulation

Ingredients	mg/capsule
Flurbiprofen	200
Microcrystalline Cellulose	94.6
Polyethylene glycol 6000	1.4
Ammonia Methacrylate Copolymer	102.3 (30% aqueous dispersion)
Magnesium stearate	3.3
Total solid content of a capsule	330

Table 2: Formulation of Trial B and Trial C produced with Extrusion Spheronization

	Trail B	Trail C
Ingredients	**mg/capsule**	**mg/capsule**
Flurbiprofen	200	200
Microcrystalline Cellulose	97.9	127
PEG 6000	1.4	1.4
Ammonia Methacrylate Copolymer	102.3 (30 % aqueous dispersion)	154 (30 % aqueous dispersion)
Magnesium stearate	3.3	3.3
Total solid content of a capsule	333.3	377.9

Table 3: Formulation of Trial D produced with Fluid Bed Dryer

	Trail D
Ingredients	**mg/capsule**
Flurbiprofen	200 mg
Neutral pellets	68 mg
Triethyl citrate	11.54 mg
Ammonia Methacrylate Copolymer mix	153 mg (30 % aqueous dispersion)
Silicon dioxide	1.58 mg
Total solid content of a capsule	327 mg

Water was put into a tank containing mechanical mixer and homogenizer, triethyl citrate was added to the tank and mixed. While homogenizer was processing, Flurbiprofen was added by portions. Ammonia

Methacrylate Copolymer mix [Eudragit RL30D: Eudragit RS30D (1:1)] was added to this suspension and is mixed for 2-3 hours without homogenizer, until the foam is dispersed.

Neutral pellets which were between 500-710µm particle size distribution was put in to fluid bed dryer. Pellets were coated by spraying the suspension mix to the placebo pellets in the fluid bed dryer with the help of peristaltic pump.

After coating process, pellets were dried until to the desired moisture level and coated by 10% silicon dioxide (Syloid FP 244) suspension to ensure their stabilization.

To avoid the conjugation of pellets, sieving process was performed after coating.

Similarity factor f2 was found as 84 and the sphericity of the pellets were perfect since the core of the drug is neutral spherical pellets. Results of the comparative dissolution studies are given in Table 4 and Figure 2.

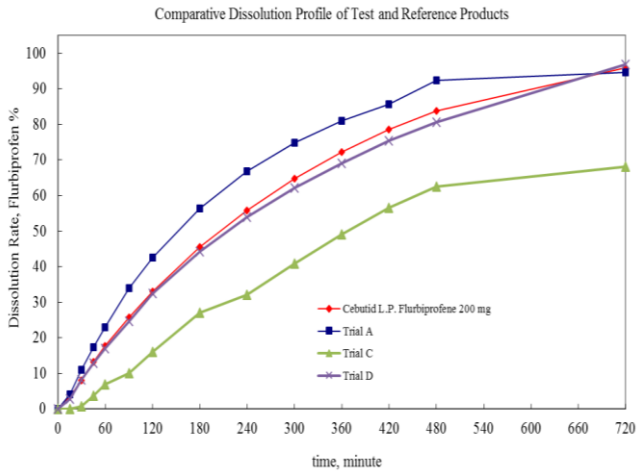

Fig. 2: Comparative dissolution profiles of the original product and the trials

Table 4: Dissolved Flurbiprofen % of the original product and the trials

		Dissolved Flurbiprofen %			
	Limits	**Cebutid L.P. Flurbiprofene 200 mg**	**Trial A**	**Trial C**	**Trial D**
15 min	-	3.5	4.1	0.0	2.8
30 min	-	8.1	11.0	0.8	8.1
45 min	-	13.2	17.3	3.7	12.8
60 min	10-40 %	17.7	23.0	6.9	17.0
90 min	-	25.8	33.9	10.1	24.7
120 min	-	33.1	42.6	16.0	32.5
180 min	-	45.5	56.4	27.1	44.2
240 min	50-80 %	55.8	66.8	32.0	54.0
300 min	-	64.8	74.8	40.9	62.1
360 min	-	72.2	81.0	49.0	69.0
420 min	-	78.6	85.7	56.5	75.3
480 min	Min. 75 %	83.7	92.3	62.6	80.7
720 min	-	95.8	94.7	68.1	96.8
F2		-	56	36	84

Spheronization enhancers are formulation aids that facilitate the production of spherical pellets, mainly during spherinozation and balling. The Spheronization enhancer that has been studied extensively and found to generate spherical pellets routinely is microcrystalline cellulose. The proportion of microcrystalline cellulose in a pellet formulation suitable for Spheronization is determined by the physicochemical properties of both the active ingredient and other excipients and, as such, varies with the composition of the formulation. Since the drug load of a capsule is 200 mg Flurbiprofen and the content of one capsule is nearly 330 mg, limited amount of microcrystalline cellulose could be used for Rotagranulation and Extrusion Spheronization Methods. Since Extrusion Spheronization and Rotagranulation Methods have simple and fast processing properties, due to limited microcrystalline cellulose amount, sphericities of the trials done with these methods were unsatisfactory. [7-21]

Also, comparative dissolution profiles show that, trail D which has been produced with the suspension layering method is similar with the reference product by means of dissolution rate. With extrusion Spheronization method, more trails would have been done as reducing copolymer and water amount to improve the similarity factor f2. Similarly, dissolution rate of the pellets produced with Rotagranulation Method, would have been improved as increasing the copolymer and water amount. Although the dissolution problems could have been solved, due to limited microcrystalline cellulose amount dealing with sphericity problem was not easy.

As a result, according to the dissolution studies and sphericities, it was seen that the suspension layering process is more suitable for the Flurbiprofen 200 mg Sustained Release Capsule, due to its high drug load.

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