Short Communication

Exploring the potential of polacrilin potassium as a novel superdisintegrant in microcrystalline cellulose based pellets prepared by extrusion-spheronization

Abstract

Polacrilin potassium (PP), an ion exchange resin, was used as a superdisintegrant to improve the dissolution of rifampicin, from microcrystalline cellulose (MCC) based pellets prepared by extrusion-spheronization. Production of fast release pellets by extrusion-spheronization using MCC is a complicated process. In the present study, pellets were prepared containing 50% w/w rifampicin (BCS class II drug) and 40% w/w MCC as extrusion-spheronization aid. Different levels of PP and lactose ratio investigated were 0:10, 2:8, 4:6, 6:4, 8:2, and 10:0. Pellets were evaluated for yield, size, size distribution, shape, porosity, friability, residual moisture, and dissolution efficiency (DE) at 30 minutes. Incorporation of this novel superdisintegrant had no adverse effect on the mechanical and micromeritic characteristics of pellets. All the batches of pellets showed high yields', ~90%; narrow particle size distribution; aspect ratio, 1.0-1.1; friability, <1%; and porosity, 45.51-49.84%. Dissolution profiles were compared using model-independent approaches; DE and similarity factor, f_2. Addition of Polacrilin results in significant improvement in the DE of rifampicin. The dissolution profiles were significantly different from the dissolution profile of pellets formulated without PP. This preliminary study indicates that PP can serve as an effective superdisintegrant in MCC pellets prepared by extrusion-spheronization.

Key words:
Extrusion-spheronization, pellets, rifampicin

Introduction

Microcrystalline cellulose (MCC) is the extrusion–spheronization aid of choice, because it provides good binding properties, which in turn imparts cohesiveness required for the wet extrusion. MCC-based pellets produced through extrusion–spheronization are spherical with low friability, high density, and smooth surface.[1] Despite the wide applicability of MCC in several cases, it cannot be used for the production of pellets through extrusion–spheronization. Some drugs may get adsorbed to MCC, thereby altering their dissolution pattern.[2] Drugs like ranitidine decompose in the presence of MCC.[1] Furthermore, non-disintegration of the pellets results in slow and incomplete dissolution of poorly water soluble drugs from MCC-based pellets prepared by extrusion–spheronization.[3] Thus, the production of fast release pellets by extrusion-spheronization using MCC can be complicated. Furthermore, the lack of disintegration can be more serious issue for poorly soluble drugs, enteric-coated pellets, and colon-targeted drug delivery system.[4]

The search is still ongoing to find an alternative to MCC or use of water-soluble fillers/surface active agents/use of cosolvent/superdisintegrant which can overcome the negative properties of MCC without affecting its positive properties required for pelletization.[5,6] Some alternative extrusion aids like barium sulfate, glyceryl monostearate, pectinic acid, polyethylene oxide with methoxypolyethylene glycol, and carrageenan have been suggested in the literature.[7] Furthermore, use of hydroalcoholic granulating

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liquids have been tried for disintegrating pellets, however, has resulted in pellets with low mechanical strength.[4] On the other hand, the inclusion of superdisintegrants has received relatively little attention.[8-10] In gist, the available information does not allow drawing of any inference about the performance of functionality of disintegrants in MCC-based pellets.

Polacrilin potassium (PP), polymethacrylic acid, weak cation-exchange resin, is a commercially available tablet superdisintegrant[11]; however, its use in pellets is not yet reported. Thus, the objective of this study was to evaluate the functionality of PP as a disintegrating agent in MCC-based pellets prepared by extrusion-spheronization. The working hypothesis was that PP has remarkably high water uptake capacity, approximately 150%, thereby helping disintegration of the pellets.

Rifampicin (BCS Class-II) was selected as a model drug for the current study. Poor wettability of rifampicin results in slow and incomplete dissolution and hence does not meet United States Pharmacopeia (USP) specification (not less than 75 [Q] within 45 minutes).[12]

Materials and Methods

Preparation of pellets

Rifampicin pellets containing MCC (Avicel® PH 101, Signet Chemical Corporation, India), PP, and lactose (Lactose (India) Ltd., India) were prepared using a gravity-fed cylinder extruder (R. R. enterprises, India), extruding at a constant speed of 125 rpm, through a roller die having holes of 1 mm in diameter and 4 mm in length. The extrudates were rounded for 10 minutes at 700 rpm in a spheronizer (R. R. Enterprises, India) equipped with a rotating plate of regular crosshatch geometry and dried in the fluidized bed dryer (Nero-Aeromatic, Switzerland) at 45°C for 20 minutes. Rifampicin (TwiLight Litaka Pharmaceuticals Pvt. Ltd., India) was used at a concentration of 50% w/w and purified water was used as granulation liquid. MCC was used at 40% w/w, while different levels of PP/lactose ratio, 0:10, 2:8, 4:6, 6:4, 8:2, and 10:0 were investigated.

Characterization of pellets

Usable yield (% theoretical)

The size distribution of pellets was determined by sieving using standard set of sieves (600-2360 μm) on a sieve shaker (Electromagnetic sieve shaker, EMS-8, Electrolab, India) for 5 minutes at a frequency of 50 Hz with an amplitude of 1 mm. The fraction of pellets, 700-1200 μm, was considered as the usable yield.[6]

Pellet size

Particle size for each batch was determined using Laser Light Scattering system (Malvern Mastersizer 2000, Malvern Instruments, Malvern, UK). All the measurements were carried out in triplicate and 50th percentile diameter of the cumulative particle size distribution was considered as mean pellet size.[13]

Determination of the shape using image analysis

For shape analysis, the images were captured using a stereomicroscope (Leica S4E, Leica, Germany). The captured images were analyzed using Image analysis software (AnalySIS®, Soft Imaging system, v. 5.2, Münster, Germany). Ratio was calculated for the characterization of the shape.[14]

Abrasion resistance

The abrasion resistance was analyzed using Roche friabilator (Veego instruments corporation, India). A pre-weighed sample (approximately 6 g) taken from the usable yield fraction was placed in a friabilator along with 25 steel spheres, each 2 mm in diameter. After 100 revolutions at 25 rpm, the mass retained on the sieve (1190 μm) was weighed and the abrasion resistance was calculated as the percentage loss of mass between initial and final weights of each pellet batch.[6] Each batch was analyzed in triplicate.

Porosity

The apparent pellet density was determined using a Helium Pycnometer (SmartPycno 30, Smart Instruments, India) and effective pellet density was obtained from mercury porosimeter. The porosity was calculated using effective and theoretical pellet density values.[15]

Residual moisture

The residual water content of the pellets after drying was determined by USP Method A,[16] using Karl Fischer titrator (Systronics Universal titrator 353, India). Each batch was analyzed in triplicate.

Dissolution studies

Dissolution study was carried out in 0.1N HCl in USP dissolution apparatus I (Hanson Research Corporation, Chatsworth, CA). Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.[17] released was estimated by validated dual-wavelength spectrophotometric method which can estimate rifampicin in presence of its hydrolysis product 3-formylrifamycin SV, since analytical method specified in USP is not separative for these two components.[18] of data was done using PCP Disso v2.8 software, India.

Results and Discussion

Evaluation of pellets showed that extrusion-spheronization capacity of MCC is not affected by addition of PP. High usable yield of pellets ~90% in the nominal size fraction (700-1200 μm) was obtained with low production of dust [Table 1].

Table 1: Characteristics of MCC-based rifampicin pellets containing polacrilin potassium as superdisintegrant

Ratio of PP:lactose	Usable yield (%)*	Aspect ratio†	Mean pellet size (mm)	Span	Porosity (%)*	Residual moisture (%)*	DE_{30} (%)	f_2‡
0:10	89.12±2.1	1.04±0.063	1.147	0.619	45.51±1.21	2.98±0.012	24.84	–
2:8	87.63±1.7	1.09±0.057	1.032	0.514	46.14±1.67	3.12±0.024	36.03	45
4:6	91.21±1.6	1.10±0.048	1.081	0.488	46.98±1.75	3.09±0.026	41.00	39.2
6:4	92.82±2.1	1.03±0.042	1.079	0.620	49.84±1.29	3.37±0.019	57.07	26.8
8:2	88.91±1.8	1.05±0.034	1.036	0.582	48.75±1.33	3.32±0.028	56.33	25.8
10:0	90.06±1.7	1.11±0.029	1.102	0.529	48.89±1.98	3.13±0.029	56.23	25.9

*Mean of three determinations±S.D; †Mean of 50 determinations±S.D.; f_2 was calculated by comparing the dissolution profiles of all the batches containing polacrilin potassium (PP) vs dissolution profile of batch without PP (0:10) as a reference

The quality of the pellets was assessed using Aspect ratio and Span as the indicators of pellet shape and size polydispersity, respectively. An aspect ratio lower or equal to 1.1 is considered good for pharmaceutical pellets. The mean pellet size and aspect ratio for all the batches varied from 1.032 to 1.147 mm and 1.03 to 1.11, respectively. Low span values of experimental batches (<0.62) indicated narrow size distribution and also followed Gaussian distribution [Table 1, Figure 1].

Pellet porosity, an important characteristic, critically affects the friability of the pellets and was found to increase from 45.51% (0:10) to 49.84% (6:4) on addition of PP [Table 1]. However, further rise in the load of PP has not affected the porosity of the pellets. All the batches showed sufficiently high mechanical strength (friability <1%), indicating that addition of PP has not significantly affected the mechanical strength of the pellets.

Despite the different superdisintegrant concentrations used, there was no significant difference in the residual moisture of dried pellets [Table 1].

In general, single-point dissolution test does not characterize the dosage form completely and therefore, the dissolution profile comparison is recommended. It should be noted that pure rifampicin powder floats on the surface thus resulting in the poor wettability. This characteristic property is suspected to be the major reason for the slow and incomplete dissolution of rifampicin products.[12] Drug release profiles [Figure 2] showed that all PP-based pellets released more than 30% rifampicin in less than 20 minutes. This is significantly faster than the MCC-based pellets in which only 20% drug was released. This can be attributed to the ability of PP to disintegrate pellets in dissolution media, thereby increasing surface area available for dissolution. Rifampicin pellet batches containing PP≥6% w/w showed more than 75% drug dissolution in 45 minutes [Figure 2].

The extent of dissolution was compared using DE_{30}, a model-independent parameter.[16] On incorporation of PP, DE_{30} of rifampicin from MCC-based pellets was improved from 24.83% to 57.07% [Figure 3, Table 1]. Significant increase in DE_{30} was observed till 6% PP level; however, further rise

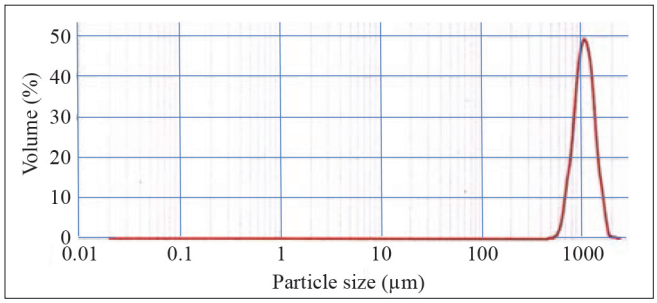

Figure 1: Particle size distribution determined by Malvern Mastersizer for MCC-based rifampicin pellets containing PP:Lactose (6:4)

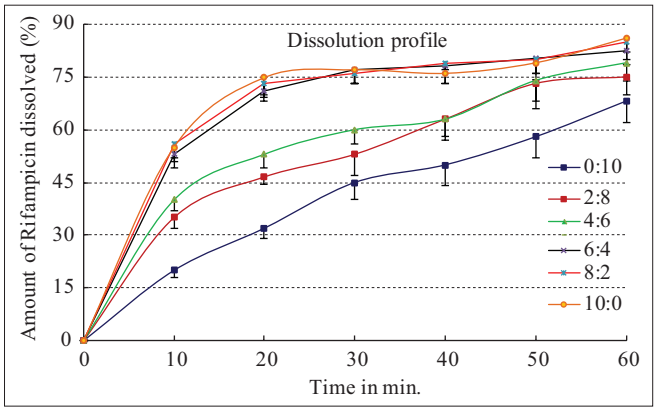

Figure 2: Dissolution profiles of MCC-based rifampicin pellets with various proportions of PP:Lactose

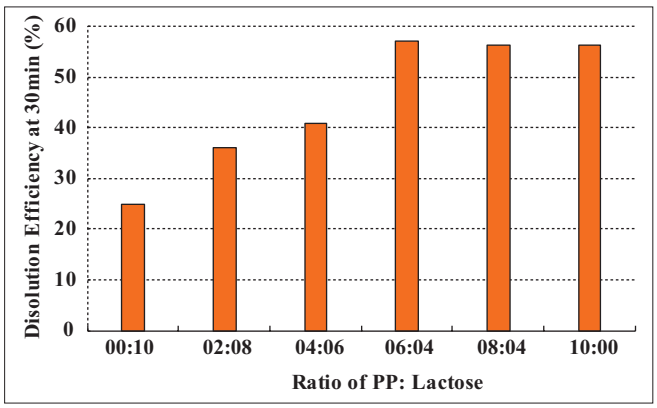

Figure 3: Dissolution efficiency at 30 minutes (DE_{30}) for rifampicin pellets with various proportions of PP:Lactose

in concentration of PP has not shown any improvement [Figure 3]. Similarity factor (f_2) was calculated by comparing the dissolution profiles of PP containing batches with the dissolution profile of the reference batch of pellets without PP (0:10). Resultant f_2 values less than 40 indicate significant difference in the release pattern on addition of PP [Table 1]. However, inter-batch f_2 values for batches having PP at 6, 8 and 10% w/w were greater than 78.5%, indicating similarity in the release profile. Therefore, it can be concluded that the addition of PP at a level of 6% w/w in MCC-based pellets prepared by extrusion-spheronization provides significant improvement in dissolution of rifampicin.

Conclusion

In conclusion, our study indicates that PP retains its functionality as a superdisintegrant even after wet extrusion under high pressure. Incorporation of PP does not show any adverse effect on the extrusion-spheronization capacity of MCC, yet causing disintegration of pellets on wetting in a dissolution media. Efficiency of PP as a disintegrating agent was found to be high since even the formulations containing only 6% w/w of PP resulted in significant improvement in drug release in dissolution medium without rendering pellets mechanically weaker. This study provides the rationale for the use of PP as a potential superdisintegrant in MCC-based pellets prepared by extrusion-spheronization.

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