Characterization and Evaluation of Spray Dried Co-Processed Excipients and Their Application in Solid Dosage Forms

AMELIA AVACHAT* AND V. J. AHIRE[1]

Sinhgad College of Pharmacy, 44/1 Vadgaon (Bk.), Off Sinhgad Road, Pune-411 041, [1]Department of Pharmacy, Faculty of Technology and Engineering, Kalabhavan, M. S. University, Vadodara-390 001, India.

Major challenge for tablet manufacture comes from the powder characteristics of the materials to be compressed. This in turn poses a challenge in achieving greater productivity and better quality product especially on the new generation high-speed machines. Advancement in directly compressible materials has come in the form of co-processed spray dried materials. The present work evaluates and characterizes two spray dried co-processed materials, one comprising of microcrystalline cellulose, colloidal silicon dioxide and cross povidone and the other composed of microcrystalline cellulose, colloidal silicon dioxide and sodium starch glycollate. Prototype tablet formulations were developed with these co-processed materials using actives such as diclofenac sodium, iron polymaltose complex and amoxycillin trihydrate. Their performance was compared vis-à-vis conventionally processed tablet formulations as well as with leading marketed brands. This study revealed that the co-processed materials have excellent flow properties, high compressibility, render low disintegration time to tablets and have better binding properties. These materials can be a good substitute for inert granules, which are normally used in tablet manufacturing.

Major challenge for tablet and capsule manufacturing comes from the flow properties of the materials to be compressed. Poor flow of the materials poses challenges in terms of achieving requisite quality parameters, greater productivity, and in turn, economy. Despite enormous improvements in wet granulation techniques, tablet manufacture by direct compression technique has increased steadily over the years. The major reason for this being, new molecules are more sensitive to moisture, oxidation or heat. It has been reported in a survey conducted in 1992 that direct compression is the preferred method of compression used by a of majority of the manufacturers[1]. Further, use of these "co-processed" excipients in spray-dried form has also given a much-needed impetus to this technology.

The conventional method of wet granulation has inherent drawbacks in terms of achieving batch-to-batch reproducibility and higher productivity, especially in low particle size range. Compared to wet granulation, direct compression requires fewer processing steps, offers simplified validation and results in product with better stability[2]. Tablets consist of active drugs and excipients. A single drug or excipient does not possess all the desired physico-mechanical properties required for the development of robust directly compressed product, which can be scaled up smoothly[3]. Hence, there is a need to have excipients with multiple characteristics built into them such as better flow, low/no moisture sensitivity, superior compressibility and rapid disintegration ability[4].

New combinations of existing excipients are an interesting option for improving the overall characteristics of the material, which is to be compressed. Excipient mixtures prepared by co-processing have improved functionality as compared to simple physical blends[5]. The development of these single bodied excipients known as co-processed excipients has gained importance in the last decade[6]. The compaction properties of mixtures have been reviewed by Fell[7], who concluded that the relationship between the tabletting properties of a mixture could only rarely be predicted from knowledge of the same properties of the individual components[8]. Many co-processed brands of excipients are in use today, which contain a blend of excipients which interact with each other at the sub particle level resulting in a synergy of improved functionality, whereby it can mask the undesirable properties of the individual excipients. Spray drying normally imparts improved flow and compressibility characteristics to excipients.

***For correspondence**

E-mail: amavachat@yahoo.com

The present investigation was aimed at evaluating and characterizing two co-processed spray dried materials comprising of microcrystalline cellulose and other excipients. This co-processed blend consists of individual materials having filler, binder and disintegrant characteristics. Use of such a product also reduces the cost of final formulation. These materials were then used along with different drugs to make tablets by direct compression and compared with the tablets obtained from conventional method of manufacture as well as with marketed preparations.

MATERIALS AND METHODS

Ran Explo-C; consisting of microcrystalline cellulose, colloidal silicon dioxide, crospovidone and Ran Explo-S; consisting of microcrystalline cellulose, colloidal silicon dioxide and sodium starch glycollate; in the spray-dried form were obtained as gift samples from M/S RanQ Pharmaceuticals and Excipients Ltd., Nashik. Diclofenac sodium, iron polymaltose complex and amoxycillin trihydrate were obtained from Noble Drugs, Nashik. Magnesium stearate, talc, starch, mannitol, colloidal silicon dioxide, microcrystalline cellulose and sodium saccharine were obtained as gift samples from Blue Cross Laboratories, Nashik.

Evaluation of physicochemical properties of co-processed materials:

Two directly compressible co-processed materials Ran Explo-C and Ran Explo-S were evaluated for their flow properties (Table 1), like angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner's ratio using well-established methods[9-11]. Angle of repose was determined using reposograph. Bulk density, tapped as well as untapped, was determined using bulk density apparatus and particle size distribution was done by sieve analysis using standard sieves i.e. 40#, 60#, 85# and 120#.

TABLE 1: PHYSICOCHEMICAL PROPERTIES OF THE CO-PROCESSED MATERIALS

Properties	Ran Explo-C	Ran Explo-S
Angle of repose	23.78°	29.12°
Untapped bulk density (g/cc)	0.322	0.277
Tapped bulk density (g/cc)	0.4	0.357
Carr's compressibility index	19.5%	24.4%
Hausner's ratio	1.242	1.288
Sieve analysis	**% weight**	**% weight**
Retained on BSS 30#	0.0	0.0
Retained on BSS 40#	2.0	0.6
Retained on BSS 60#	5.97	4.2
Retained on BSS 85#	10.9	11.59
Retained on BSS 120#	29.47	31.44
Passed through BSS 120#	48.83	50.61

This '#' indicates the sieve used for evaluation of excipients

Development of prototype formulations:

To check the performance of co-processed materials for direct compression some prototype formulations were prepared and comparison was made with conventional formulations. Three different active ingredients viz. amoxycillin, iron polymaltose, diclofenac sodium were chosen for the study due to their specific properties. Amoxycillin is used as dispersible tablets. Due to the high dose requirement and sticky nature of amoxycillin it is difficult to make a formulation with ultra low dispersion time**.** Iron polymaltose has high dose and is highly water-soluble. Due to its high solubility, the tablet disintegrates by erosion and not by explosion. Diclofenac sodium is a low dose product and can be made by direct compression method.

All the formulations were studied for granule properties important for flowability. The compressed tablets were also evaluated for various physical parameters. Formulation details of each product, along with evaluation data are given in Tables 2-7.

Brief manufacturing process for amoxycillin tablets:

Formulation A and B were prepared by blending weighed amounts of amoxycillin (30#) and Ran Explo-C or Ran Explo-S with lubricants, sweeteners and flavours in a tumbling mixer for 15 min. The prepared blend was compressed into tablets using 11.2 mm FFBE punch on a 10 station rotary machine (direct compression).

Formulation C was prepared using the following procedure; weighed amounts of starch and MCC were granulated using starch paste. The cohesive mass was then passed through 10# sieve. The resultant wet granules were subjected to tray drying for one hour at 60°. The dried granules were then passed through 30# sieve. The dummy granules so obtained were blended with amoxycillin (30#), lubricants, sweeteners and flavours. The blend was compressed into tablets using 11.2 mm FFBE punch on a 10 station rotary machine (conventional method, wet granulation). The details of the formulation are given in Table 2.

Brief manufacturing process for iron polymaltose tablets:

Formulation A and B were prepared by blending weighed amounts of iron polymaltose (30#) and Ran Explo-C or Ran Explo-S with the lubricants, sweeteners and flavours in a tumbling mixer for 15 min. The prepared blend was compressed into tablets using 11.2

TABLE 2: FORMULATION OF AMOXYCILLIN TABLETS

Name of the ingredient	Formulation-A (mg /tab)	Formulation-B (mg /tab)	Formulation-C (mg /tab)
Amoxycillin trihydrate (compacted)	289	289	289
Ran Explo-C	201	-	-
Ran Explo-S	-	201	-
Dummy granules	-	-	Present
Starch	-	-	96
Microcrystalline cellulose	-	-	100
Starch for paste	-	-	5
Magnesium stearate	5	5	5
Talc	5	5	5
Flavour mango	10	10	10
Sodium saccharine	10	10	10
Total weight	520	520	520

Formulation A and B are made by direct compression and formulation C is made by conventional method using dummy granules

TABLE 3: FORMULATION OF IRON POLYMALTOSE COMPLEX TABLETS

Name of the ingredient	Formulation-A (mg/tab)	Formulation-B (mg/tab)	Formulation-C (mg/tab)
Iron poly maltose complex (pot: 43%)	232	232	232
Ran Explo-C	246	-	-
Ran Explo-S	-	246	-
Dummy granules	-	-	Present
Mannitol	-		343
Starch for paste	-		18
Sodium starch glycollate	-		20
Magnesium stearate	6	6	6
Talc	6	6	6
Flavour chocolate	10	10	10
Colloidal silicon dioxide	5	5	5
Sodium saccharine	10	10	10
Total weight	515	515	650

Formulation A and B are made by direct compression and formulation C is made by conventional method using dummy granules

TABLE 4: FORMULATION OF DICLOFENAC SODIUM TABLETS

Name of the ingredient	Formulation-A (mg/tab)	Formulation -B (mg/tab)	Formulation-C (mg/tab)
Diclofenac sodium	50	50	50
Ran Explo-C	130	-	-
Ran Explo-S	-	130	-
Microcrystalline cellulose		-	130
Starch for paste	-	-	10
Magnesium stearate	5	5	5
Talc	5	5	5
Total weight	190	190	190

Formulation A and B are made by direct compression and formulation C is made by conventional method

mm FFBE punch on a 10 station rotary machine (direct compression).

Formulation C was prepared as follows; weighed amount of mannitol was granulated using starch paste. The cohesive mass was then passed through 10# sieve. The resultant wet granules were subjected to tray drying for one hour at 60°. The dried granules were then passed through 22# sieve. The dummy granules so obtained were blended with iron polymaltose (30#), lubricants, sweeteners and flavours. The blend was compressed into tablets using 12.5 mm FFBE punch on a 10 station rotary machine (conventional method, wet granulation). The details of the formulation are given in Table 3.

Brief manufacturing process for diclofenac sodium tablets:

Formulation A and B were prepared by blending weighed amounts of diclofenac sodium and Ran Explo-C or Ran Explo-S with the lubricants in a tumbling mixer for 15 min. The prepared blend was compressed into tablets using 8.00 mm FFBE punch on a 10 station rotary machine (direct compression).

Formulation C was prepared as follows. Granules of diclofenac sodium were prepared by wet granulation technique using starch paste after premixing it with microcrystalline cellulose. The granules were dried and sized by passing through 22# sieve. Dried granules were

TABLE 5: PHYSICAL PROPERTIES OF AMOXYCILLIN GRANULES AND TABLETS

Properties of granules/ tablets	Formulation-A	Formulation-B	Formulation-C	Marketed tablets (D)
Angle of repose	25.46°	35.2°	34.75°	––
Untapped bulk density (g/cc)	0.417	0.418	0.538	––
Tapped bulk density (g/cc)	0.566	0.558	0.756	––
Carr's compressibility index	26.28%	25.0%	28.8%	––
Hausner's ratio	1.356	1.33	1.405	––
Sieve analysis	**% weight**	**% weight**	**% weight**	**––**
Retained on BSS 30#	0.19	5.35	2.2	––
Retained on BSS 40#	18.88	17.7	47.71	––
Retained on BSS 60#	26.61	13.08	16.38	––
Retained on BSS 85#	3.82	12.4	9.55	––
Retained on BSS 120#	31.16	34.97	14.02	––
Passed through BSS 120#	18.83	15.36	10.01	––
Tablet diameter (mm)	11.2	11.2	11.2	12.5
Tablet thickness (mm)	4.9	4.2	4.4	3.6
Tablet disintegration time (sec.)	15	50	63	35
Tablet hardness (kg/cm^2)	7-8	7-8	7-8	6-6.5
Tablet friability (%)	0.05	0.1	0.05	0.1
Uniformity of dispersion	Passes	Passes	Passes	Passes
Weight variation (as per IP)	Passes	Passes	Passes	Passes
Tablet dissolution time	Passes	Passes	Passes	Passes

This '#' indicates the sieve used for evaluation of granules

TABLE 6: PHYSICAL PROPERTIES OF IRON POLYMALTOSE COMPLEX GRANULES AND TABLETS

Properties of granules/Tablets	Formulation-A	Formulation-B	Formulation-C	Marketed tablets (D)
Angle of repose	22.5°	32°	21.03°	––
Untapped bulk density (g/cc)	0.56	0.465	0.833	––
Tapped bulk density (g/cc)	0.7	0.588	1.0	––
Carr's compressibility index	25%	20.9%	16.7%	––
Hausner's ratio	1.25	1.264	1.2	––
Sieve analysis	**% weight**	**% weight**	**% weight**	**––**
Retained on BSS 30#	0.64	0.54	17.21	––
Retained on BSS 40#	1.1	1.11	17.6	––
Retained on BSS 60#	0.75	3.16	5.2	––
Retained on BSS 85#	7.23	7.43	2.91	––
Retained on BSS 120#	15.95	18.1	3.97	––
Passed through BSS 120#	72.36	68.01	50.27	––
Tablet diameter (mm)	11.2	11.2	12.5	12.0
Tablet thickness (mm)	3.7	3.7	3.6	5.5
Tablet hardness (kg/cm^2)	7.0	7.5	7.0	6-6.5
Tablet disintegration time (min.)	1.5	4.5	10.0	19
Tablet friability (%)	0.2	0.28	1.2	0.1
Weight variation (as per IP)	Passes	Passes	Passes	Passes
Tablet dissolution time	Passes	Passes	Passes	Passes

This '#' indicates the sieve used for evaluation of granules

then blended with the lubricants. The tablets were compressed using 10-station rotary machine using 8.0-mm FFBE punches. The details of the formulation are given in Table 4.

Evaluation of tablets:

Hardness was determined using Monsanto hardness tester, while friability was done in Roche friabilator. Disintegration test was performed in a disintegration test apparatus (Model: Eectrolab, Mumbai) at 37° in 900 ml water for iron polymaltose and diclofenac sodium tablets. Dispersible tablets of amoxycillin were subjected to disintegration test in water at 25° according to well-established methods[12]. Dissolution studies were carried out using dissolution test apparatus (Model: LabIndia,) using apparatus-1 as per well-established techniques.

RESULTS AND DISCUSSION

Ran Explo-C and Ran Explo-S are very fine free flowing co-processed materials as can be observed from Table 1. The values of Carr's compressibility index between 5-15% indicate excellent flow[13]. Both Ran Explo-C and Ran Explo-S are having a particle size distribution which shows that 90% of the material has particle size less than 60#, indicating the fine nature of the material. Low angle

TABLE 7: PHYSICAL PROPERTIES OF DICLOFENAC SODIUM GRANULES AND TABLETS

Properties of granules/tablets	Formulation-A	Formulation B	Formulation-C	Marketed tablets (D)
Angle of repose	25.6°	29.87°	23.9°	––
Untapped bulk density (g/cc)	0.361	0.365	0.487	––
Tapped bulk density (g/cc)	0.475	0.422	0.66	––
Carr's compressibility index	23.9%	13.4%	26.1%	––
Hausner's ratio	1.314	1.155	1.352	––
Sieve analysis	**% weight**	**% weight**	**% weight**	**––**
Retained on BSS 30#	0.03	0.03	40.5	––
Retained on BSS 40#	1.24	1.73	30.05	––
Retained on BSS 60#	2.91	6.16	6.07	––
Retained on BSS 85#	12.41	10.4	9.25	––
Retained on BSS 120#	31.21	30.2	5.96	––
Passed through BSS 120#	50.96	49.2	11.58	––
Tablet diameter (mm)	8.0	8.0	8.0	8.0
Tablet thickness (mm)	3.1	3.2	2.9	3.0
Tablet hardness (kg/cm^2)	5.0	5.0	5.0	N.A.
Tablet disintegration time (in phosphate buffer, pH 6.8)	36 sec (uncoated tablets)	50 sec (uncoated tablets)	6 min (uncoated tablets)	12 min
Tablet friability (%)	0.06	0.1	0.15	N.A.
Weight variation (as per IP)	Passes	Passes	Passes	Passes
Tablet dissolution time	Passes	Passes	Passes	Passes

This '#' indicates the sieve used for evaluation of granules

of repose (<30°), Hausner's ratio of less than 1.3 and Carr's compressibility index of less than 25% indicate the excellent flow properties of these materials in spite of the fine particle size. This is achieved predominantly because of spray drying process.

One of the objectives of the study was to investigate these spray-dried materials as directly compressible filler-disintegrant-suspending agents by incorporating them with some of the model drugs. Tablets of amoxycillin made by direct compression using Ran Explo-C and Ran Explo-S showed very short disintegration time as compared to the tablets made by conventional method of granulation. Even at the same hardness, disintegration was less, specifically with Ran Explo-C. The tablets also passed uniformity of dispersion test (IP) indicating that it can be conveniently incorporated in dispersible tablets. The marketed preparation had lower hardness but still its disintegration time was comparable with tablets made with Ran Explo-C or Ran Explo-S. The tablets prepared using Ran Explo-C and Ran Explo-S, also had better suspendibility of the drug particles upon disintegration, which is an essential requisite of a dispersible tablet since they have to be administered to pediatric patients without losing the dose in the spoon (Table 5).

Tablets of iron polymaltose made by direct compression with Ran Explo-C and Ran Explo-S showed a drastic reduction in disintegration time as compared to marketed preparation as well to those made in-house by conventional granulation method. It is also indicated that the tablets can be compressed at a lower diameter resulting in a smaller exposed area and still have improved properties. Friability values also indicate better results as compared to conventionally made tablets (Table 6).

Diclofenac sodium tablets showed improved characteristics with respect to disintegration time and friability for the same given hardness of the tablets, as can be observed in Table 7. Prototype formulations thus produced using co-processed materials showed, superior compressibility, excellent binding properties resulting in very low friability, low disintegration time, faster rate of dissolution and a fine dispersion, which was achieved on disintegration of tablets.

Commercially available microcrystalline cellulose (MCC) has the required directly compressible characteristics but it fails to provide the disintegration and suspending properties required specifically for its use in dispersible tablets. Prosolv (Pen West Pharmaceuticals) is a commercially available co- processed excipient comprising of MCC and silicon dioxide having better flow and compressibility but lacking in disintegration ability and suspendibility. As compared to it, the investigated co-processed excipients additionally contain sodium starch glycollate/crospovidone which are proven superdisintegrants. Incorporation of these imparted additional property of disintegrability and suspendibility to the co-processed excipients.

These materials can be an ideal choice for making, tablets containing low dose medicament using direct compression technique, as well as dispersible tablets with low

dispersion time at high tablet hardness and moderate to high drug content. They can also be a good substitute for inert/dummy granules, which are normally used in tablet manufacturing.

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