Spray Dried Excipient Base: A Novel Technique for the Formulation of Orally Disintegrating Tablets

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Received May 13, 2005; accepted September 16, 2005

Orally disintegrating tablets (ODT) are gaining popularity over conventional tablets due to their convenience in administration and suitability for patients having dysphagia. Moreover no water is required for swallowing the tablets and hence suitable for geriatric, pediatric and traveling patients. The purpose of this study is to assess the suitability of spray dried excipient base in the formulation of ODTs of Valdecoxib (low aqueous solubility) and Metoclopramide (high aqueous solubility). Spray dried excipient base was prepared using Scientech spray drier. Super disintegrants (such as Ac-Di-Sol, Kollidon CL, sodium starch glycolate), diluent (mannitol) alongwith sweetening agent (aspartame) were used in the formulation of tablets. The tablets were evaluated for hardness, friability, water absorption ratio, disintegration time (DT) and *in vitro* drug release. Using the same excipients, the tablets were prepared by direct compression and were evaluated in the similar way. Maximum drug release and minimum DT were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique.

Key words orally disintegrating tablet; superdisintegrant; spray dried excipients base; Valdecoxib; Metoclopramide

Recent advances in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for the administration.[1] Difficulty in swallowing (*i.e.* dysphagia) is experienced by patients such as pediatric, geriatric, bedridden, disabled and mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of noncompliance and ineffective therapy.[2] To improve the quality of life and treatment compliance of such patients fast disintegrating or orally disintegrating tablets (ODT) dosage form is a better alternative for oral medication.[3] ODTs are the solid dosage form containing medicinal substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilitate swallowing.[4] ODTs can be prepared by different methods as direct compression, freeze-drying, spray drying, sublimation and wet granulation method.[5]

The aim of this study was to formulate ODTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water. To achieve this goal, spray dried excipient base was used for the formulation of tablets. Attempts were made to enhance dissolution rate alongwith faster disintegration using superdisintegrants like Ac-Di-Sol,[6] sodium starch glycolate[7] (SSG) and Kollidon CL[8] in the formulation of tablets. Two model drugs, one with good aqueous solubility (Metoclopramide HCL) and another with poor aqueous solubility (Valdecoxib), were selected for the studies. Metoclopramide[9] (an antiemetic) is used in the motion sickness and is beneficial to the traveling patients who may have no access to water at the time of taking medication. Valdecoxib[10] (COX-2 selective) is used in rheumatoid arthritis and osteoarthritis associated with elderly patients.

Experimental

Materials The drugs Valdecoxib and Metoclopramide were obtained as gift sample from Aarti Drugs Limited, Tarapur and Pharma Health Pvt Ltd., Hisar respectively. Directly compressible mannitol (PARTECK^{TM} M, EM Industries, Germany). Sodium starch glycolate (SSG, Avebe, Netherlands). Kollidon CL (1-ethenyl-2-pyrrolidinone homopolymer, BASF Corporation, U.S.A.) and Ac-Di-Sol (Croscarmellose Sodium, FMC Europe NV) were obtained as gift sample from Panacea Biotech Ltd., India. All other chemicals/solvents used were of analytical grade.

Direct Compression Directly compressible mannitol, micro crystalline cellulose (MCC) and superdisintegrants like Ac-Di-Sol, SSG and Kollidon CL were mixed uniformly after passing through sieve #120. The drug Valdecoxib/Metoclopramide was added to the above mixture with magnesium stearate (St-Mg) (0.1%) and compressed into tablets using single punch R & D tablet machine (8 mm punch diameter) to produce biconvex tablets weighing 200 mg each. The formulations (D1 to D6) are shown in Table 1.

Compression Using Spray Dried Excipient Base Mannitol (solubility 20 g/100 ml) was dissolved in water using sonicator and requisite quantity of other ingredients *viz*. MCC, superdisintegrants and aspartame (Table 2) were added resulting in formation of a suspension. The suspension was spray dried in SMST Scientech Spray Drier (outer temperature 105—110 °C, inner temperature 260—270 °C and pressure of 2 lb/cm^2) to obtain solid mass of excipient base which was passed through sieve #120. The drug was added to spray dried excipients bases of varying compositions (B1, B2, B3, Table 2). The bases B1, B2 and B3 contained 5% Ac-Di-Sol, SSG and Kollidon CL respectively alongwith 10% MCC, 0.2% aspartame and 84.8% mannitol. Magnesium stearate (0.1%) was added as lubricant. Various formulations (F1—F6) of ODTs were prepared (Table 3). Single punch R & D tablet machine (8 mm punch diameter) was used to produce biconvex tablets weighing 200 mg each.

Measurement of Angle of Repose Angle of repose was measured for the mixture before compression, as to observe the flow properties of a powder. The method employed a funnel secured with its tip at a given height, (H) above the graph paper placed on horizontal surface. Powder was poured through the funnel until the apex of conical pile touched the tip of funnel and the angle of repose was calculated using the formula, $\tan \alpha = H/R$ where α is the angle of repose and R is the radius of conical pile.

Hardness Hardness of the tablets was measured using Monsanto hardness tester.

Friability Friability of the tablets was determined using Roche friabilitor at 25 rpm/min for 4 min. The tablets were weighed and loss in weight (%) was calculated.

Wetting Time and Water Absorption Ratio Wetting time and water absorption ratio was determined by the method described by Bi *et al.*[11] A piece of tissue paper folded twice was placed in small culture dish (i.d. = 6.5 cm) containing 6 ml of water, a tablet was put on the paper and the time for complete wetting was measured. The wetted tablet was again weighed. Water absorption ratio, R, was calculated using the formula;

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Table 1. Formulations of Tablets by Direct Compression Method

Formulations	Drug (mg)	MCC (mg)	Mannitol (mg)	Ac-Di-Sol (mg)	SSG (mg)	Kollidon CL (mg)	Aspartame (mg)	St-Mg (mg)
Valdecoxib								
D1	10	20	159.4	10	—	—	0.4	0.2
D2	10	20	159.4	—	10	—	0.4	0.2
D3	10	20	159.4	—	—	10	0.4	0.2
Metoclopramide								
D4	10	20	159.4	10	—	—	0.4	0.2
D5	10	20	159.4	—	10	—	0.4	0.2
D6	10	20	159.4	—	—	10	0.4	0.2

Table 2. Formulation of Spray Dried Excipient Base

Batch No.	Disintegrants (5%) (g)	MCC (g)	Mannitol (g)	Aspartame (g)	Total (g)
B1 (Ac-Di-Sol)	2.5	5	42.4	0.1	50
B2 (SSG)	2.5	5	42.4	0.1	50
B3 (Kollidon CL)	2.5	5	42.4	0.1	50

Table 3. Formulations of Orally Disintegrating Tablets of Valdecoxib and Metoclopramide Using Spray Dried Excipients Base

Ingredients	F1	F2	F3	F4	F5	F6
Drug (mg)						
Valdecoxib	10	10	10	—	—	—
Metoclopramide	—	—	—	10	10	10
Excipient base (mg)						
B1	189.8	—	—	189.8	—	—
B2	—	189.8	—	—	189.8	—
B3	—	—	189.8	—	—	189.8
Magnesium stearate (mg)	0.2	0.2	0.2	0.2	0.2	0.2

F1—F3: Formulations containing Valdecoxib and super disintegrant Ac-Di-Sol, SSG and Kollidon CL respectively. F4—F6: Formulations containing Metoclopramide and super disintegrant Ac-Di-Sol, SSG and Kollidon CL respectively.

$$R = 100(Wa - Wb)/Wb$$

Where *Wb* and *Wa* are the weight before and after water absorption.

Measurement of Disintegration Time Disintegration time was determined using USP disintegration test apparatus without disk for six tablets. The 1000 ml of distilled water at 37±1 °C was used as test fluid at the rate of 30±2 cycles/min.

Measurement of *in Vitro* Drug Release *In vitro* drug release was determined using USP apparatus XXIV (Paddle assembly) at 50 rpm maintained at 37±5 °C in 900 ml of distilled water as dissolution media. Percent drug release was determined by taking an aliquot of 5 ml at different time intervals, filtered through Whatmann filter paper and was assayed at 247 nm for Valdecoxib and at 308 nm for Metoclopramide. An equal volume of fresh dissolution medium was replaced to maintain the original volume. The dissolution studies were carried out in triplicate.

Scanning Electron Microscopy (SEM) The SEM analysis was carried out using a scanning electron microscope (Leo, 435 VP, U.K.). Prior to examination, samples were mounted on an aluminum stub using a double sided adhesive tape and thereafter making it electrically conductive by coating with a thin layer of gold (approximately 20 nm) in vacuum. The scanning electron microscope was operated at an acceleration voltage of 15 kV.

Results and Discussion

Flow properties of the powder can be judged from the angle of repose. The angle of repose <30° indicates free flowing material and >40° with poor flow properties.[12] Values for angle of repose for spray dried excipient base was found in the range of 23.17 to 33.85° showing that the base was free flowing and can be used for direct compression method. The angle of repose for the three different superdisintegrants was observed in the order: Kollidon CL>SSG> Ac-Di-Sol and the spray dried excipient base showed lower angle of repose (better flow properties) than the excipient alone (Table 4), which is probably due to increased sphericity of spray dried excipient base,[13,14] which was further supported by scanning electron micrographs (Figs. 1, 2). The prepared tablets were evaluated for physical parameters such as weight variation, hardness and friability (Table 5). Percent weight variation was observed between 1.1 and 4.5; well within the acceptable limit for uncoated tablets as per USP. Since mechanical integrity is of paramount importance in successful formulation of ODTs, hence the hardness of tablets were determined and were found to be in the range of 3—4 kg. Friability was observed between 0.70—0.77%, which were below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. Wetting time and water absorption ratio were determined using the method described by Bi *et al.*[11] (results shown in Table 5). It was observed that formulations F2 and F5 containing sodium starch glycolate had higher water absorption ratio (60.52, 67.71 respectively) and take more time (60, 52 s respectively) for wetting of tablets (Table 5). Wetting is closely related to the inner structure of the tablets and the hydrophilicity of the excipients. SSG shows its disintegrant effect by the mechanism

Table 4. Angle of Repose of the Mixed Powders, Disintegration Time and *in Vitro* Dissolution Parameters of ODT Formed from Spray Dried Excipient Base and Direct Compression Method

Formulations	Angle of repose (°)	DT (s)	$PD_{2\,min}$ [a)]	$PD_{5\,min}$ [a)]	$PD_{10\,min}$ [a)]	$RDR_{5\,min}$	$DE_{10\,min}$
F1	27.07±0.22	35±2.0	75.92±0.4	87.92±0.23	95.33±0.20	15.34	60.77
F2	31.59±0.12	55±1.1	77.86±0.8	89.67±0.52	100.18±0.60	15.64	62.93
F3	33.85±0.33	17±1.0	93.87±0.2	96.83±0.60	100.65±0.70	16.84	68.37
F4	23.17±0.23	30±3.0	88.98±0.3	92.73±0.34	97.70±0.67	16.18	64.29
F5	27.65±0.12	45±1.5	93.03±0.6	96.57±0.38	100.09±0.67	16.85	67.49
F6	31.59±0.45	15±1.0	98.53±0.5	100.19±0.1	101.24±0.18	17.48	70.37
D1	30.54±0.24	41±0.5	54.20±0.2	56.20±0.21	58.44±0.21	9.8	27.91
D2	32.42±0.26	65±2.6	58.48±0.1	61.48±0.28	64.68±0.18	10.72	30.78
D3	34.65±0.43	27±1.0	64.22±0.25	68.12±0.81	70.43±0.24	11.95	32.79
D4	32.31±0.36	35±1.6	75.45±0.48	79.11±0.11	82.12±0.38	13.80	39.26
D5	33.72±0.13	50±3.2	80.78±0.56	85.26±0.32	89.16±0.78	14.87	42.06
D6	34.46±0.27	22±1.7	86.28±0.8	89.90±0.33	93.74±0.82	15.68	44.63

a) $n=3$. F1—F3: Formulations containing Valdecoxib and super disintegrant Ac-Di-Sol, SSG and Kollidon CL respectively. F4—F6: Formulations containing Metoclopramide and super disintegrant Ac-Di-Sol, SSG and Kollidon CL respectively. RDR is the relative dissolution rate in 5 min in comparison to pure drug, DE is the dissolution efficacy, PD is the percent drug dissolution.

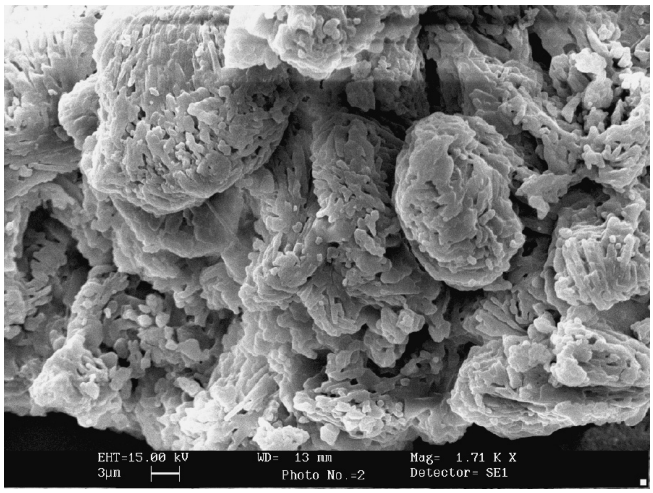

Fig. 1. SEM Photomicrograph of Spray Dried Excipient Base (B3)

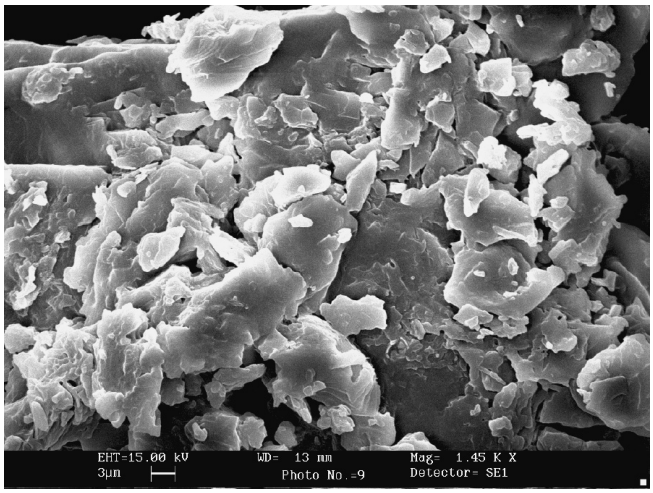

Fig. 2. SEM Photomicrograph of Direct Compression Base (D3)

Table 5. Physical Parameters of Valdecoxib and Metoclopramide ODTs Prepared by Spray Drying Method

Parameters	F1	F2	F3	F4	F5	F6
Weight variation (%)[a)]	2.5±0.56	2.7±0.11	3.2±0.43	4.5±0.22	3.1±0.34	1.1±0.53
Hardness (kg/cm^2)[a)]	3.5±0.11	3.3±0.21	3.2±0.12	3.6±0.11	3.3±0.21	3.1±0.33
Friability (%)[b)]	0.77±0.26	0.72±0.32	0.75±0.02	0.77±0.01	0.70±0.30	0.76±0.25
Wetting time (s)[c)]	37±1.5	60±1.3	20±2.0	33±3.1	52±2.8	19±1.6
Water absorption ratio (R)[c)]	51.46±1.1	60.52±1.5	57.83±0.9	56.48±0.8	67.71±1.2	63.52±1.1

a) $n=10$, *b*) $n=3$, *c*) $n=6$. F1—F3: Formulations containing Valdecoxib and super disintegrant Ac-Di-Sol, SSG and Kollidon CL respectively. F4—F6: Formulations containing Metoclopramide and super disintegrant Ac-Di-Sol, SSG and Kollidon CL respectively.

of "swelling". Formulations F3 and F6 containing Kollidon CL exhibited its disintegrant effect by "wicking" action. Increased porosity provides pathways for the penetration of fluids into tablets resulting in "wicking" through capillary action causing faster disintegration of tablets[15,16] (Table 4). Formulations containing Kollidon CL (crosslinked polyvinyl pyrrolidine), showed less wetting time (20, 19 s) and water absorption ratio (57.83, 63.52) between SSG and Ac-Di-Sol (F3 and F6, Table 5). Ac-Di-Sol (crosslinked sodium carboxymethyl cellulose) shows its disintegrant action by wicking (due to its fibrous structure) and swelling with minimum gelling. It has intermediate wetting time (37, 33 s) and minimum water absorption ratio (51.46, 56.48) respectively for both drugs (F1 and F4, Table 5). Amongst the drugs (Valdecoxib and Metoclopramide), more hydrophilic drug (Metoclopramide) shows higher absorption ratio and less wetting time than poorly water soluble drug (Valdecoxib).

As the DT is of much importance in the formulation of ODTs, it was tried to keep the DT less than 1 min. The disintegration time (DT) was found in the range of 15 to 55 s (Table 4) for the tablets with spray dried excipient base (F1 to F6) and 22 to 65 s for the tablets prepared by direct compression (D1 to D6). The tablets made by direct compression took more time to disintegrate than the tablets made with spray drying method (Table 4). DT was observed in the order Kollidon CL<Ac-Di-Sol<SSG (Table 4). Minimum DT was

observed in all the formulations containing Kollidon CL as disintegrant formed either by direct compression or spray drying method. It was also observed that tablets with the least wetting time (observed with the tablets made with spray dried excipient base) also had the minimum disintegration time. Showing a strong correlation between disintegration time and wetting time ($r^2=0.9773$).

In vitro drug dissolution studies showed the maximum drug release of 93.87% and 98.53% with the tablets made from spray dried excipient base containing Kollidon CL as superdisintegrant, (Table 4) with Valdecoxib and Metoclopramide respectively. Relative dissolution rate at 5 min ($RDR_{5\,min}$) of the tablets made from spray dried excipient base was higher (15.34 to 17.48) when compared to the pure drug, than the tablets made by direct compression (9.8 to 15.68) using the same excipients. The effect was more significant with Kollidon CL as superdisintegrant. Dissolution efficiency (DE)[17] is defined as the area under dissolution curve up to the time (t) was expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{dissolution efficiency (DE)} = \left(\frac{\int_0^t y \times dt}{y100 \times t} \right) \times 100$$

The dissolution efficiency can have a range depending upon the time interval selected. In any case, a constant time intervals should be chosen for comparison. In the present investigation, $DE_{10\,min}$ values were calculated from the dissolution data of each product and used for comparison. $DE_{10\,min}$ was maximum (70.37 in 10 min) for water-soluble drug (Metoclopramide) with excipient base using Kollidon CL as superdisintegrant. In comparison to direct compression tablets containing the same ingredients, a faster drug release was observed from the tablets made from spray dried excipient base which might be attributed to increased porosity in the spray dried excipient base.[13,14]

Conclusion

It was concluded that spray dried excipient base using Kollidon CL as superdisintegrant was a better technique for the formulation of orally disintegrating tablets, due to better flow property and enhanced dissolution in comparison to the tablets made by direct compression method. The method had similar application to both types of drugs (low aqueous solubility/high aqueous solubility) and thus versatile in applications.

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