Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 4, Issue 4, 2012

Research Article

PHYSICOCHEMICAL CHARACTERIZATION OF SPRAY DRIED FORMULATION CONTAINING AMORPHOUS DRUG

GLORYBEL L PASTRANO[2], EVONE S GHALY[1]

[1,2]School of Pharmacy, Medical Sciences Campus, University of Puerto Rico, P.O.Box 365067, San Juan, PR-00936-5067.
Email: evone.ghaly@upr.edu

Received: 10 July 2012, Revised and Accepted: 21 Aug 2012

ABSTRACT

Zafirlukast is a prescription drug for asthmatic patients. Amorphous zafirlukast is known to convert into the monohydrate form in presence of water or to convert into the crystalline form which has a decreased solubility and bioavailability. The aim of this study is to optimize dissolution and avoid phase transformation of drug, in order to assure drug stability and bioavailability. This research is divided into two stages which are: processing parameters optimization and the effect of excipients on the rate of dissolution, and Zafirlukast amorphous content after spray drying. The selected optimum processing parameters were used in the second stage of this research. The excipient used were lactose fast flow, mannitol, microcrystalline cellulose (Avicel PH-102), and dibasic calcium phosphate (Di-Tab). Drug content, scanning electron microscope (SEM), differential scanning calorimetry (DSC), x-ray diffraction (XRD), and dissolution were performed to determine if there is phase transformation of the drug during processing in the spray dryer or after compression into tablets. The results indicated that formulation composed of lactose as excipient, zafirlukast and SDS at 1:1 ratio, and processed at a flow rate of 10 ml / minute, inlet air temperature of 180^{0}C, and a spray pressure of 0.1 MPa produced particles and tablets of best physico-chemical properties and best drug dissolution (95% in 15 minutes). In conclusion, Spray drying technique is effective in reducing particle size and enhancing the morphology of the particles without inducing phase transformation of the active ingredient from amorphous to crystalline form.

Keywords: Zafirlukast, Spray drying, Physico-chemical properties, Phase transformation.

INTRODUCTION

Spray drying granulation is a unique granulation technique that directly converts liquids into dry granule in a single step[1, 2, 3, 4, 5]. This method removes moisture instantly and converts liquids or suspension into a dry spherical granule. Among the advantages are the speed of forming granules and drying can be a continuous process, and it is suitable for heat and moisture sensitive products. Granules prepared by spray drying technique are spherical, porous, uniform in size with fewer sharp edges than those produced by conventional granulation methods[6, 7, 8, 9]. There are many articles in the literature related to spray drying[10, 11, 12, 13]. However the effect of spray drying on the solid state and phase transformation of the drug is not completely explored.

The drug model selected for this investigation is a synthetic selective peptide leukotriene receptor antagonist (LTRA) named Zafirlukast, which is a prescription drug for asthmatic patients. Amorphous neutral zafirlukast is known to convert to a monohydrate form in the presence of water[14, 15, 16, 17]. The monohydrate has a decreased bioavailability from that of the amorphous form. It has now been found that a crystalline salt of zafirlukast can be isolated following reaction of neutral zafirlukast with strong base. This crystalline salt of zafirlukast has additionally been found to be particularly stable in water. The salt of zafirlukast is stable under both acidic and neutral aqueous conditions. Zafirlukast has three main identified crystal structures: (III) Methanol solvate, (II) Ethanol solvate, and (I) Monohydrate. These three crystal phases are denominated as Form A, Form B, and Form X. They differ in their physicochemical properties, spectroscopy and separation methods. Form A is the relatively stable amorphous form. It is prepared by dehydration of Form B in a vacuum oven for 24 hours at 393 K. It is the desired form since it has good bioavailability. Under high relative humidity and elevated temperatures Form A transforms to Form B. Form B is the unstable crystalline form of zafirlukast hydrate. It is difficult to prepare and keeps it in this form with constant and reproducible water content. Form X is a stable form of crystalline zafirlukast but is relatively low in bioavailability.

Our hypothesis is that Phase transformation of the drug may not take place during spray drying process due to the speed of the process and that increasing particle porosity and that modifying particle shape by the use of spray drying process may enhance the dissolution rate of the drug. The objectives of this investigation are to design and develop an optimum formulation, and to optimize processing parameters in order to produce a stable amorphous form of the drug using spray drying technology. Also, to evaluate the effects of formulation components such as excipient on phase transformation of the drug and physico-chemical property of both granules and the output tablets dosage form.

Different excipient were used such as lactose fast flo, microcrystalline cellulose, mannitol and dibasic calcium phosphate. The DSC, XRD, SEM and other tests were performed in order to determine if there is interaction between the drug and excipient, and also to examine the solid state of the drug and the component of the formulations.

MATERIALS AND METHODS

Zafirlukast, batch number 1500003278, donated by IPR Pharmaceuticals, San Juan, Puerto Rico; Lactose Fast Flo, batch number 3D69030, donated by Bristol Myer, Mayaguez, Puerto Rico; microcrystalline cellulose, Avicel PH102, batch number 1024, FMC Corp, Philadelphia, Pennsylvania USA; dibasic calcium phosphate (DI-TAB), batch number 9017, Rhone-Poulenc, Courbevoie, France; mannitol, batch number 0827K0141, Sigma, Philadelphia USA; sodium dioctyl sulfate, SDS, batch number 17192 KA, Aldrich, Wilmington, USA.

This investigation is sub-divided into two stages. Each stage followed a simple factorial design (p^n), where p is the level and n is the factor.

First Stage: Processing Parameters Optimization (p^n) = 2^3 = 8 experiments

Second Stage: Effect of Excipient (p^n) = 4^1 = 4 experiments

All granules obtained from the two stages were evaluated for physico-chemical properties, drug dissolution and were characterized using X-ray diffraction (XRD), differential scanning calorimetry (DSC) and scanning electron microscope (SEM) to determine if there is phase transformation of the drug during processing

Stage 1: Optimization of processing parameters

In the first stage, the critical processing parameters selected were: spray rate, inlet air temperature, and atomizing pressure, each at

two levels. Optimum parameters for processing were determined in the first stage in order to produce the best formulation in terms of physico-chemical properties such as drug dissolution, granules morphology, and zafirlukast amorphous content.

Preparation of the Physical Mixture

Zafirlukast (19.2 g), SDS (19.2 g) and lactose Fast Flo® (211.6 g) previously passed manually through a #30 mesh, were weighed in an Explorer Pro Ohaus Model EF2102V

Loading Balance and transferred to a container. The solid mixture was mixed in a TurbulaMixer, Type T2C Mixer for 30 minutes.

Slurry Preparation

The physical mixture was transferred to a container containing 500 ml distilled water. The slurry was agitated in magnetic stirrer for 10 minutes.

Preparation of Spray Dried Granule Formulation

This slurry was immediately fed to the spray drying equipment using the processing parameters established in the experimental design as shown in Table 1.

After finishing the spray drying cycle, the product was manually removed from the product compartment. The collected product was passed manually through a #30 mesh, transferred to a plastic bag and left to stabilize overnight.

Stage 2: Effect of excipient

In the second stage, the effect of excipient was evaluated. Factor selected was the type of excipient. Four excipients were selected (mannitol, dibasic calcium phosphate, lactose, and microcrystalline cellulose) at a concentration of 84.62% w/w to test the attribute of excipient on the quality and the performance of both granules and output product. Each excipient was incorporated in the formulation instead of lactose which was uses as excipient in stage 1 of this study. The slurry was processed using the optimum parameters of processing determined in the first stage. Physicochemical properties were evaluated and characterized by XRD, DSC, SEM, and drug dissolution was investigated.

Preparation of the Physical Mixture

Zafirlukast (19.2 g), SDS (19.2 g) and microcrystalline cellulose, mannitol or dibasic calcium phosphate (211.6 g) previously passed manually through a #30 mesh, were weighed in a Explorer Pro Ohaus Model EF2102V Top Loading Balance and transferred to a container. The solid mixture was mixed in a Turbula Type T2C Mixer for 30 minutes.

Slurry Preparation

The same procedure described under stage 1 was followed.

Preparation of Spray Dried Granule Formulations.

The slurry was introduced to the spray drying equipment using the optimum processing parameters established in stage 1 (10 ml/min, 0.1 MPa, and 160^{0}C) and the same steps were followed as described in stage 1.

Compaction

Spray dried granules were compacted into tablets using Manesty B-3B rotary machine equipped with 12/32 inches flat face punches. Target weight was 260 mg $\pm$ 5% and target hardness was 6-7 Kp.

Study of the physical characterization of the formulations

Weight uniformity, thickness and hardness were obtained for 10 tablets from each batch. Mean, range and standard deviation were calculated and are shown in [Table 1].

Drug content

Drug content for all formulations was within the specified limit and are shown in [Table 1].

Dissolution testing

Dissolution testing was performed in a dissolution apparatus 2, Hanson SR8 Plus Model ZT3-2. Dissolution media used was 1% w/v SDS in distilled water. Samples were withdrawn at 15 min, 30 min, 45 min, 60 min, 90 min, 120 min, 180 min, 240 min, and 360 min. Absorbance was determined for each sample using a Beckman Coulter DU 520 UV/Vis Spectrophotometer at a wavelength of 224 nm.

Differential scanning calorimetry (DSC)

Thermograms were obtained for each batch manufactured using Differential Scanning Calorimeter Model DSC 821. Heat content and melting point temperature were determined for each of the reference materials (raw materials and API), physical mixtures and spray dried samples.

X-ray diffraction (XRD)

XRD analyses was performed for the drug alone, physical mixtures and spray dried samples in a Siemens D-5000 X-Ray Diffractometer system equipped with a sealed Copper anode tube (Filters were not used). A Graphite Monochromator and Scintillation counter were used as detector. The collimation slits used were ReS: 0.6mm, DS: 1.0 mm (0.5º), and RaS: 1.0 mm (0.5º). The power used was 45 kV and 40 mA. The normal coupled scan was performed at a scan speed of 0.5 sec/step at a step of 0.02º from a 2Θ angle of 5.0º to 60º.

Scanning Electron Microscopy (SEM)

Morphology of each formulation was obtained using a Scanning Electron Microscope model Phillips 515. Samples were covered with gold using a Sputtering System, Anatech LTD Hummer 6.2. The parameters used for the pictures were 10 µm and approximately 5.49 E2 kV.

RESULTS AND DISCUSSION

Stage 1: Processing parameters optimization

Dissolution testing

In this stage, formulation composed of lactose as a filler, zufirlukast, and sodium dodecyl sulfate as surfactant processed at flow rate of 10 ml/minute, inlet air temperature of 160^{0}C and spray pressure of 0.1 MPa (experiment # 8) showed best physico-chemical properties regarding the shape, solubility and presence of the drug in amorphous state. Even though the percent of drug dissolved for all eight experiments was high. However, percent drug dissolved from experiment 8 (best experiment) was 95% at 15 minutes of testing dissolution. As shown in [Figure 1]. The high dissolution data of all experiments may be due to the fact that all experiments are of the same composition and they contain SDS surfactant as a part of the formulation composition.

Table 1: Processing parameter used in stage 1 for optimizing the process

Experiment	Spray rate (ml/minute)	Inlet air temperature (^{0}C)	Spray pressure (MPA)
001	5	100	0.05
002	10	100	0.05
003	5	160	0.05
004	10	160	0.05
005	5	100	0.1
006	10	100	0.1
007	5	160	0.1
008	10	160	0.1

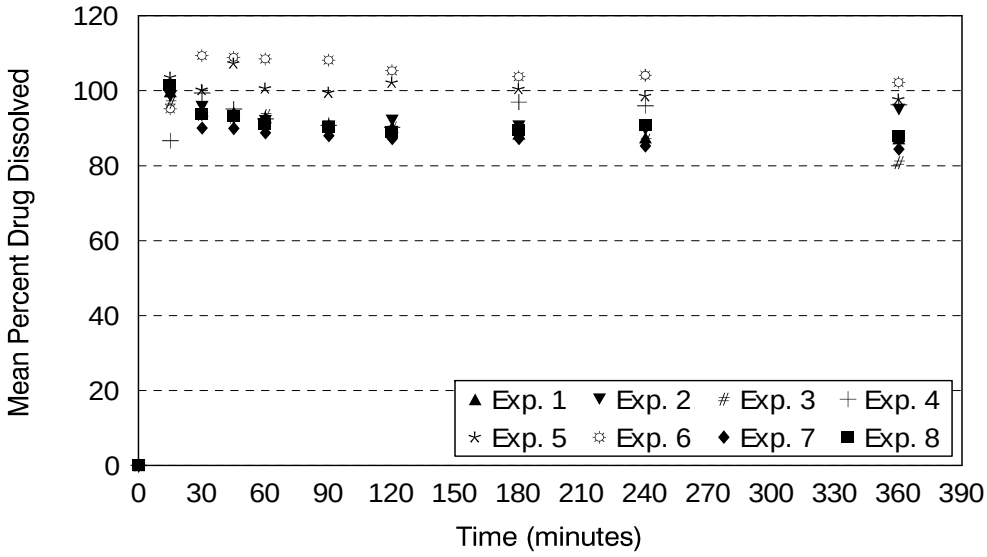


Fig. 1: Dissolution profiles of tablets prepared by compression of spray dried granules prepared under different processing parameters

Differential scanning calorimetry

The differential scanning thermograms of the physical mixture and the spray dried sample of experiment 8 (optimum experiment) showed similar pattern with similar heat content and melting point, indicating that the spray drying process did not induce phase transformation in the active ingredient from amorphous to crystalline [Figure 2].

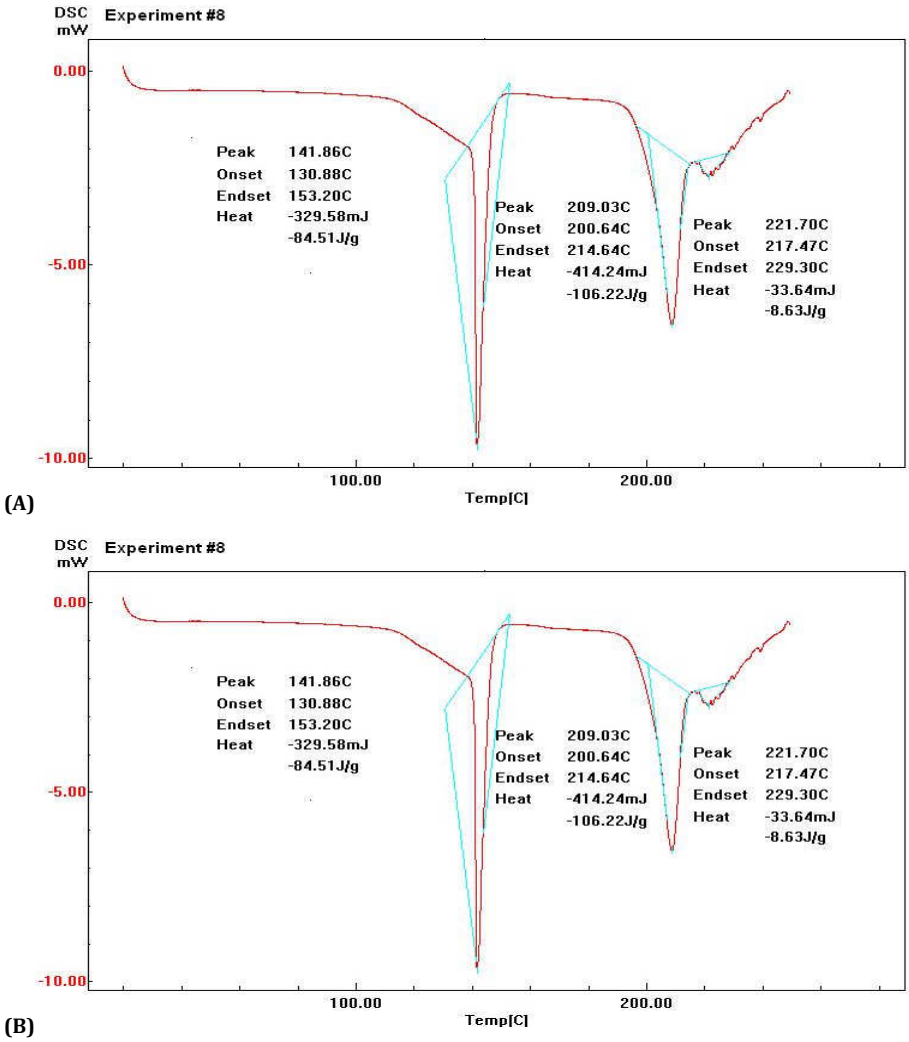
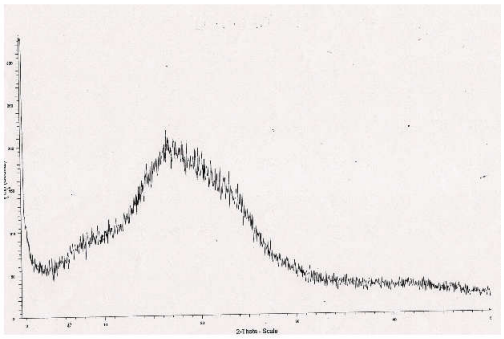


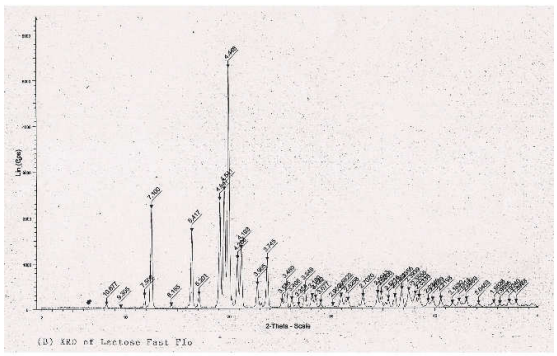
Fig. 2: DSC for physical mixture formulation with lactose (A) DSC for spray dried formulation with lactose B).

X ray diffraction

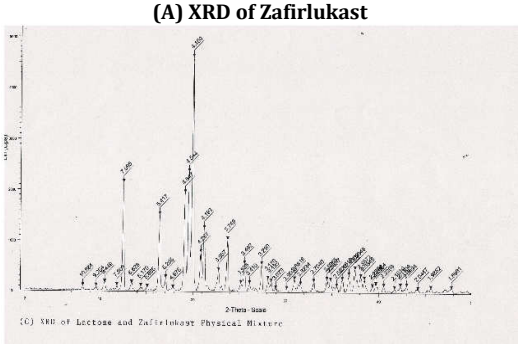
Although the XRD showed that formulation prepared by using lactose and dioctyl sodium sulfosuccinate, processed at optimum processing parameters showed sharp peaks. However those peaks were due to the components of the formulation and not due to any phase transformation of the drug from amorphous to crystalline form as shown in [Figure 3]



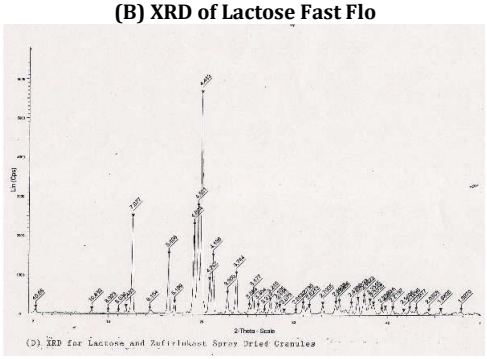
(A) XRD of Zafirlukast



(B) XRD of Lactose Fast Flo



(C) XRD of lactose and Zafirlukast



(D) XRD for lactose and Zafirlukast spray physical mixture dried granules

Fig. 3: (A) XRD of Zafirlukast, (B) XRD of lactose Fast Flo, (C) XRD of lactose and Zafirlukast physical mixture, (D) XRD for lactose and Zafirlukast spray dried granules

Scanning electron microscope

SEM images also confirmed that spray drying process was effective in reducing the size and producing a more spherical shaped particles compared to the physical mixture.

The remaining experiments mentioned before (experiment 1 to 7) showed additional peaks that were not apparent in the XRD of the individual components or the physical mixtures indicating the possibility of the phase transformation of the drug to a crystalline form due to the long time of processing of these formulations.

The shape of the spray dried granules of formulation # 8 was more spherical than its corresponding physical mixture [Figure 4]. However formulations 1 to 7 appear in the SEM images as irregular shape with agglomerates and few micro crystals, suggesting possibility of residual crystallinity due to the long time of processing in the spray dryer compared to experiment # 8.

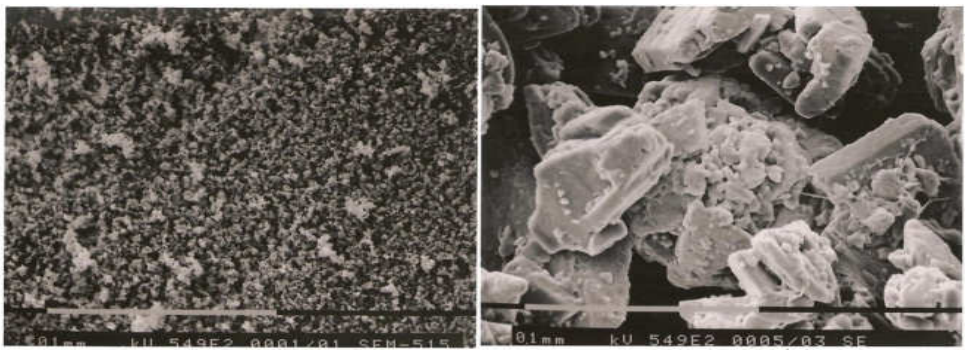
Although the temperature used for drying experiment 8 was high, the flow rate and the spray pressure that were set allowed the granules to be dried rapidly without over heating and the period of drying was short.

The data obtained in stage 1 indicated that the best processing parameters were a flow rate of 10 ml/minute, an inlet temperature of 160ºC, and a spray pressure 0.1MPa. These critical optimum parameters were used in the rest of the zafirlukast

The ANOVA analysis showed significant difference in percent drug dissolved when the spray rate is changed. Also there is an interaction between time and spray rate that affects the percent drug dissolution.

The ANOVA analysis showed significant difference in percent drug dissolved when the inlet air temperature, spray rate, and spray pressure were varied as shown in [Table 2].

Zafirlukast Lactose Fast Flo



Physical mixture-lactose Spray dried formulation with lactose

Fig. 4: Scanning electron photographs for formulations (with lactose)

Table 2: ANOVA Analysis

Source	DF	SS	MS	F	P
1. Effect of processing parameter on drug dissolution					
Inlet air temperature	1	2377.4	2337.4	241.22	0.000
Time	8	214.91	26.86	2.77	0.072
Flow rate	1	3470.54	3470.54	238.34	0.000
Time	8	235.680	29.45	2.02	0.072
Spray pressure	1	41.53	41.537	1.92	0.174
Time	8	205.47	25.6837	1.19	0.334
2. Effect of excipient on drug dissolution					
Excipient	3	1364.64	45488.1	4017.52	0.000
Time	8	72	9.0	0.80	0.607

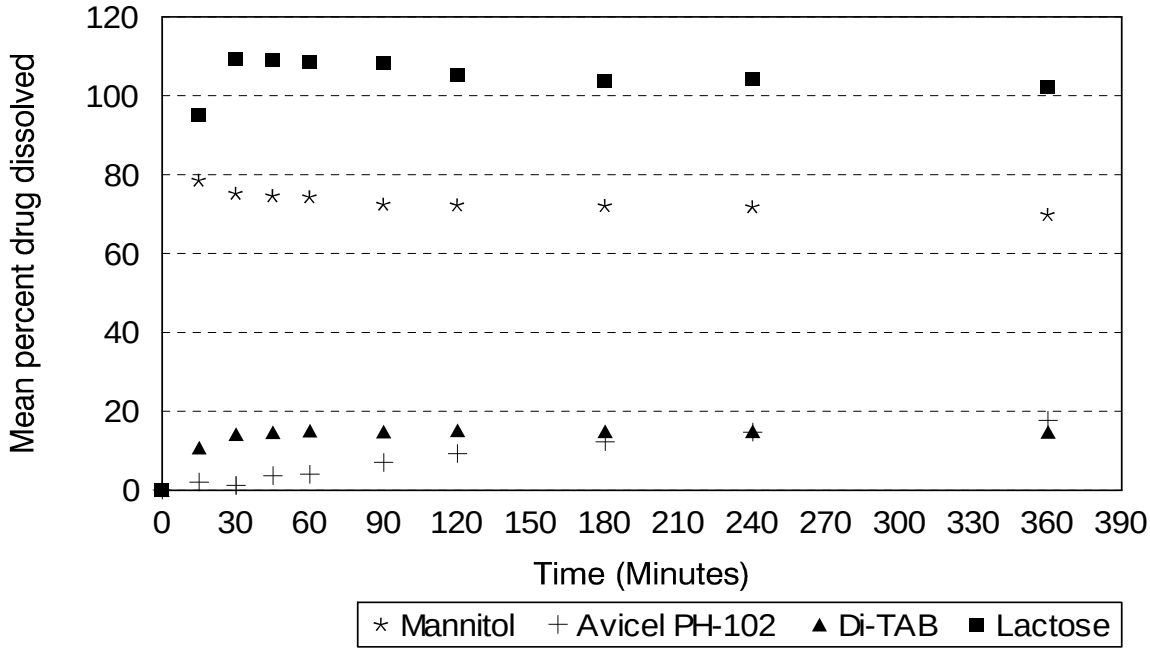
Stage 2: Effect of excipient

In this stage the effect of different type of excipient (lactose, mannitol, microcrystalline cellulose, and dibasic calcium phosphate) on the physico-chemical properties of the granule and the output tablet dosage form was investigated. All formulations were performed under optimum processing parameters (spray rate 10 ml/minute; inlet air temperature 160^0C; spray pressure: 9.1 MPa).

Dissolution testing

The percent drug dissolved at 15 minutes of testing dissolution were: 95%, 11, 2, 78.5% from formulations prepared with lactose, dibasic calcium phosphate, microcrystalline cellulose, and mannitol respectively. [Figure 5].

As indicated in this stage, the best formulation which gives the highest percent drug dissolution was the one prepared with lactose as diluent, SDS as surfactant, zafirlukast and processed by spray dried technology at optimum processing parameters. These data indicated that using different excipient such as mannitol which is hygroscopic, microcrystalline cellulose, and dibasic calcium phosphate which are water insoluble diluents may cause phase transformation of the drug and consequently affect drug dissolution. However, using lactose which is a water soluble excipient appears not to affect the solid state of the drug and maintains the drug in amorphous state. ANOVA analysis ([Table 3] showed that there is significant difference in drug dissolution when different diluents were used. Change in time showed no significant effect on the percent drug dissolved. The interaction between time and diluents affect the percent drug dissolved significantly.



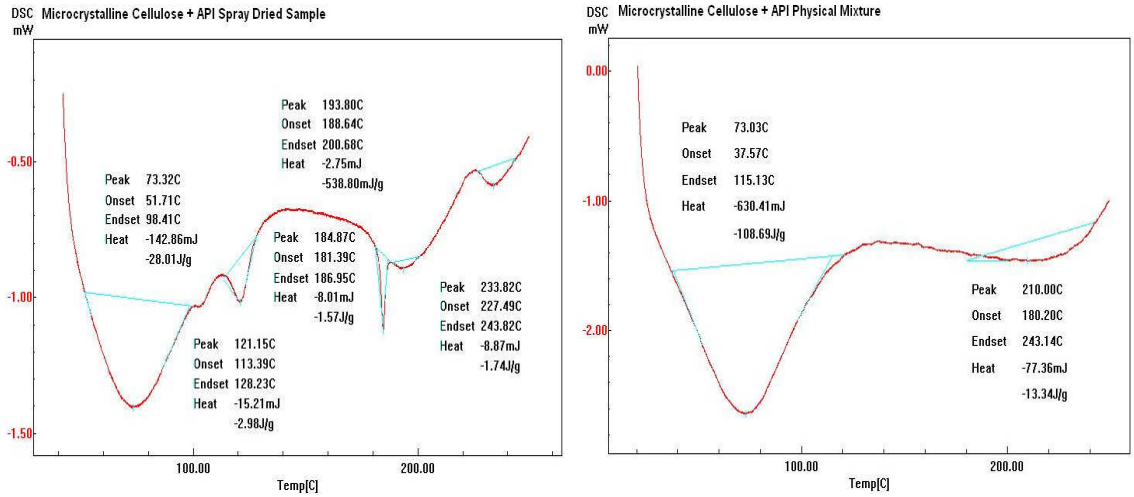
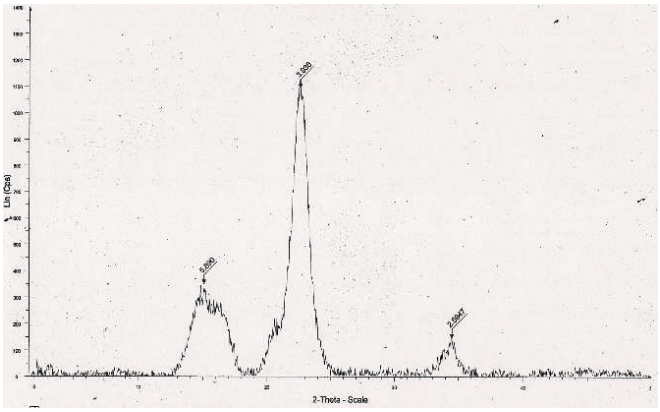


Fig. 5: Effect of type of excipient on dissolution

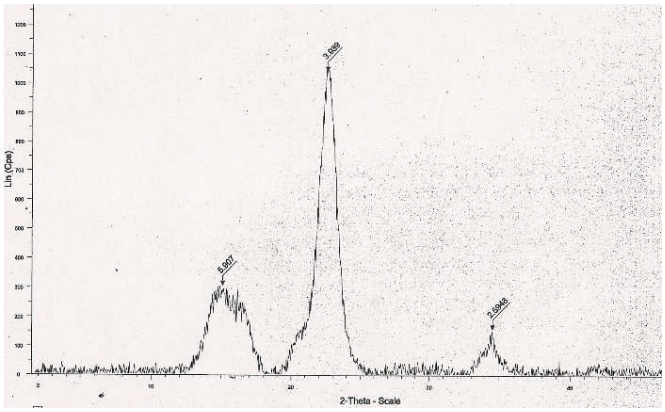
DSC and X-ray diffraction

The DSC thermograms of the spray dried granules prepared by using microcrystalline cellulose were also different from the physical mixture formulations.[Figure 5].

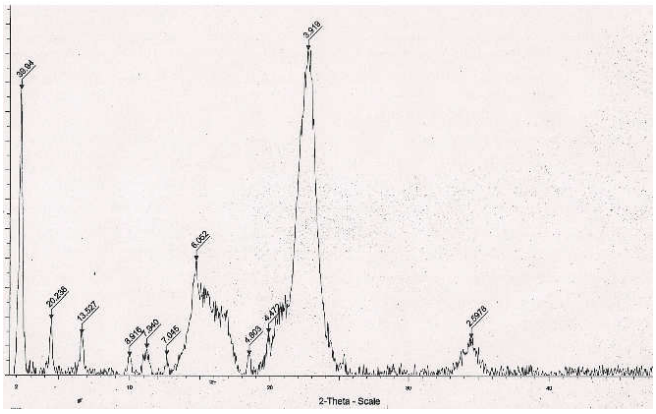
The XRD for spray dried granules prepared by using microcrystalline cellulose as an excipient showed five un-identified peaks that were not in the XRD of the physical mixture or the drug [Figure 6].



A) Microcrystalline cellulose



B) Physical Mixture of microcrystalline cellulose and Zafirlukast



C) Spray dried of microcrystalline cellulose and Zafirlukast

Fig. 6: XRD of microcrystalline cellulose (A); Physical mixture of microcrystalline cellulose and Zafirlukast; (B) Spray dried granules of microcrystalline cellulose and Zafirlukast.

XRD for formulation prepared with mannitol showed crystalline peaks that were not present in any of the individual components (excipient) of the formulation or the drug indicating possibility of phase transformation of the drug.

XRD for spray dried granules prepared with dibasic calcium phosphate showed eight crystalline peaks that were not present in the physical mixture formulation or the drug. These peaks indicate phase transformation of the solid state of the drug.

The differential scanning calorimetry supported these data since the thermograms of the physical mixture formulations and the spray dried granules prepared with dibasic calcium phosphate or mannitol, suggest the possibility of transformation of the solid state of the drug. Dibasic calcium phosphate spray dried formulation XRD showed 8 crystalline peaks that did not appear in the XRD of the excipient or in the physical mixture, which also, suggest phase transformation of the drug.

Scanning electron microscope

The scanning electron microscope photos of spray dried granule formulations prepared with mannitol or dibasic calcium phosphate were spherical and uniform in size than their corresponding physical mixtures. However the spray drying technology did not enhance the shape, porosity or uniformity of particle size of granules prepared by using microcrystalline cellulose compared to its corresponding physical mixture. This may be due to the fact that microcrystalline cellulose is dispersible and not soluble in aqueous fluid containing SDS, and consequently affects percent drug dissolved. Also, the capillary structure of microcrystalline cellulose may lead to non-uniform and large particle size and resulted in entrapment of moisture that probably affect zafirlukast phase transformation to some crystalline form. Dibasic calcium phosphate has a tendency to undergo dehydration making the final product prone to humidity intake from the environment thus causing a phase transformation of zafirlukast.

CONCLUSION

Spray drying technology has potential to maintain the amorphous state of the drug and avoid phase transformation through the use of optimum processing parameter and the optimum formulation composition. The optimum processing parameters found in this study are: spray rate of 10 ml/minute, drying air temperature of 160ºC, and atomizing pressure of 0.1 MPa.

The optimum formulation composition is: zafirlukast (drug) and dioctyl sodium sulfosuccinate (surfactant) at 1:1 ratio, lactose Fast Flo® as diluent using distilled water as liquid to form slurry for spray drying. The DSC and XRD of this formulation compared to the corresponding physical mixture were similar and did not show any additional peaks in the spray dried particles indicating no phase transformation of the solid state of the drug and the drug remains in the amorphous state. Additionally, the percent drug dissolved was within the specification. The scanning electron microscope photos indicated that the particle size of the spray dried particles were spherical and uniform in size.

Other spray dried granules processed under different processing parameters and not under the optimum processing parameters or other formulation of different composition, containing microcrystalline cellulose, dibasic calcium phosphate, and mannitol were not uniform and not spherical in shape. Also the XRD and the DSC showed additional peaks that were not in their corresponding physical mixtures.

ACKNOWLEDGEMENT

This research is entirely funded by Dane O. Kildsig Center for Pharmaceutical Processing Research.

REFERENCES

1. Park J, Park,HU, Chio W, et al. Comparative study of telmisartan tablets prepared via wet granulation and Pritor™ prepared using spray drying method. Acta Pharm Biopharm. 2011; 34:452-458.
2. Dixit M, Kini AG, Kulkami PK. Preparation and characterization of piroxcam by spray drying and spray chilling methods. Res. Pharm. Sci 2010; 5:69-97
3. Ceivera MF, Heinamaki J.de la Paz, et al. Effect s of spray drying on Physiochemical properties of chitosan acid salt. AAPS Pharm. Sci. May 2011.
4. Anshuman A, Mahadik K.R, Paradkar A. Spray-dried amorphous solid dispersions of simvistatin, a low Tg drug: in vitro and in vivo evaluations. Pharm.Res 2005; 22:990-998.
5. Ebihara F, Watano S. Development of a novel granular detergent with an interdispersion particle comprising an anionic surfactant and polymeric polymeric polycarboxalate. Chem.Pharm. Bull2003; 6:743-745
6. Rojas J, Lopez A, Gamboa Y, et al. Assessment of processing polymorphic effect on the powder and tableting properties of microcrystalline cellulose. Che, Pharm.Bull 2011; 59:603-607.
7. Brabakaran J, Ho LSL. Optimization of spray drying conditions for the large-scale preparation of bacillus muringensis var israellensis. Biotechnology & Bioeng 2008;100:103-107.
8. Hamcock, BC, Shamblin SL, Zografi G. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperatures. Pharm Res; 1995; 12:799-806.
9. Vana JK, Dodiya SS, Swaant KK. Cyclosporine located lipid nanoparticles optimization process variables & characterization.Curr Drug Delivery 2011;3:64-69.
10. Chirla DD, Gaves RA, Pamijula S, et al. Spray dried chitosan as a direct compression tableting excipient. Drug Dev Ind Pharm 2009; 36:43-48.
11. Beck-Brocichsitter M, Schweiger C, et al. Characterization of novel spray dried polymeric particles for controlled drug delivery. J Control Release October 29, 2011.
12. Bi R, Shao W, Wang Q, Zhang N. Solid lipid nanoparticles as insulin inhalation carrier for enhanced pulmonary delivery. J Biomed Nanotechnology 2009; 1:84- 92.
13. Kini AG, Dixit M, Kkulkarni PK. Enhancement of solubility and dissolution rate of poorly water soluble drug by spray drying using different grade of chitosan.. Int J Pharm Pharm Sci 2011; 3: 231-235.
14. Spector SL. Management of asthma with Zafirlukast clinical experience and tolerability profile. Drugs 1996; 52:36-48.
15. AstraZeneca. Zafirlukast Solvates. United States Patent Publication, U.S. Provisional Application 2003;Ser. No. 60//516. 797 Nov. 3:1-23.
16. Susid I, Demincan S, Amoz S, Kir S. Optimization, validation, and application of capillary electrophoretic method for the determination of Zafirlukast in pharmaceutical formulations. J Pharm Biomed.Anal 2007; 44:6-22.
17. Sosto I, Amoz S. Electro chemical characteristics of Zafirlukast and its determination in pharmaceutical formulations by volumetric methods. J Pharm Biomed. Anal 2005; 39:535-542.