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Process Optimization and Characterization of Combination Dry Powder for Inhalation: Perspective Approach to Traditional Formulation

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ABSTRACT

The present investigation is focused on to study influence of excipients on physical characteristics of combination dry powder inhaler formulation and to compare it with traditional combination Dry Powder for Inhalation. Formulation contains salmeterol xinafoate (SX) and fluticasone propionate (FP). The formulation was prepared by Spray drying of suspensions obtained by solvent displacement method. The excipients used were α-lactose monohydrate and Poloxamer 188. The powders generated were of a suitable size for inhalation with satisfactory yield. It was found that in optimum concentration with poloxamer 188; lactose gave increased spray drying thermal efficiency. FTIR study showed the close agreement among the spectra of all spray dried formulations and APIs. Effect of excipients was further investigated by different physical characters of spray-dried formulations. The formulation was evaluated for in vitro drug release and in vitro aerosolization study by the modified USP II dissolution apparatus and using an Andersen cascade impactor (ACI). Dissolution study gave immediate drug release profiles. In vitro aerosolisation showed better degree of FPF as compared to marketed formulation containing lactose. The stability study indicated that all the formulations were quite stable at accelerated storage conditions. The results obtained from all observations indicate that in presence of poloxamer.188; lactose was found to be superior over traditional combination dry powder inhaler formulation containing salmeterol xinafoate and fluticasone propionate.

Key Words: Dry Powder for Inhalation, Combination Inhalation Therapy, Long-acting β-2 agonist, Long acting corticosteroid, Pulmonary Drug Delivery.

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INTRODUCTION

A wide variety of agents has been administered to the lung via oral inhalation, for the treatment of diverse disease states[1]. Pulmonary drug delivery has attracted tremendous scientific and biomedical interest in recent years and has progressed considerably within the context of local treatment for lung diseases, by virtue of enhanced local targeting and reduced systemic side effects with the administration of minute drug dosages. Pulmonary tract tends to be considered as very promising and attractive route for the administration of active substances intended to treat local pulmonary (e.g., asthma, chronic obstructive pulmonary disease (COPD), microbial infections) as well as systemic diseases (e.g., diabetes)[2].

DPI consists of drug and carrier particles either mixed or co-precipitated together into dry powder form. Size of drug/dry powder is important and should be near spherical in shape and monodispersed with aerodynamic diameter range of 0.5 to 5 μm[3]. Spray drying is a one-step constructive process that provides greater control over particle size, particle morphology and powder density[4]. It offers an alternative approach to the generation of dry, potentially respirable powders for local pulmonary drug delivery.

Combination inhalation therapy (e.g. a long acting β-2 agonist with inhaled corticosteroid) provides convenience to the patient along with synergistic pharmacological actions, leading to better compliance and therapeutic outcomes in the management of life threatening pulmonary disease[5]. Furthermore, due to the low-dose of both a long-acting β-2 agonist and a long-acting corticosteroid (50–100μg) the co-spray dried or co-precipitated powders cannot be administered without a diluents or bulking agent. Thus, blending with carriers will introduce additional process variables. These shortfalls can potentially be avoided by incorporating crystalline excipients into the co-spray drying solution. Suspensions were prepared by liquid anti-solvent precipitation technique i.e. Solvent displacement method[6, 7].

Currently, lactose is the most commonly used excipient in marketed DPIs (Beclophar®, Flixotide®, Relenza®, Seretide®, Spiriva®, Symbicort®). It has an established safety and stability profile, different manufacturing processes with tight controls over purity and physical properties, is easily available at different grades and is inexpensive. Published inhalation studies in humans have shown no local effects of lactose by inhalation[6]. It has been shown that the crystallinity of lactose plays an important role; having high-energy surfaces, amorphous lactose exhibits strong adhesive interactions with drug particles, leading to low inhalation efficiency. Therefore, α-lactose monohydrate, the crystalline form is most commonly employed as a drug

carrier in DPIs. It has been demonstrated that the presence of Poloxamer 188 in the feed emulsion results in particles with improved dispersibility and a higher fine particle fraction[8].

MATERIALS AND METHODS:

Micronized Salmeterol xinafoate and Fluticasone propionate were donated by Vamsi Labs Ltd., Solapur and Sun pharm. Ind. Ltd., Mumbai respectively. α-lactose monohydrate and Poloxamer 188 were obtained from Research Lab., Mumbai, Potassium dihydrogen phosphate (KH2PO4) and Sodium hydroxide (NaOH) were purchased from Finar chemicals Ltd., Ahmadabad, KBr was obtained from Loba chemicals, Mumbai. Ethanol was supplied by Fisher Scientific LTD. (Loughborough, UK). Water was purified by reverse osmosis (MilliQ, Molsheim, France). All other materials used were of analytical grade. All the chemicals other than listed in materials used were are of Analytical grade. Distilled water used was further filtered through 0.45 µm membrane filter.

Formulation of suspension by anti-solvent method:

Solvent used was Ethanol (95%), antisolvent as Distilled Water, Solvent: Anti-solvent ratio was kept as 30:70. Lactose (500 mg) was used as diluent for each batch. Briefly, the fine drugs were dissolved in ethanol (95%) (S) and sonicated to get the diffusing phase. Excipients were dissolved in distilled water (non-solvent) to obtain dispersing phase. Different concentrations of excipients were added as shown in formulation table 1. Diffusing phase was then added to the dispersing phase i.e. to non-solvent by means of a 18 G 11/2 TW syringe positioned with the needle directly in the medium under continuous stirring for 1 hr at 1200-1500 rpm by using Lab stirrer (Remi-Motors)[9].

Table 1: Formulation components for Batch L series

Formulation	SX:FP	(SX:FP): Poloxamer 188
L1	1:2	1:0.5
L2	1:2	1:1
L3	1:2	1:1.5

Conversion of dispersion (suspension by solvent displacement method) into Dry powder for inhalation by spray drying:

Spray drying using a , LABULTIMA Lab Spray Dryer(LU-222 Advanced Spray Dryer: LABULTIMA, Mumbai) with a co-current 0.7 mm, two fluid nozzle equipped with auto jet deblocking system, was applied in order to retrieve respirable powders in dried state from suspension described above. The inlet and outlet temperatures were 120^0 C and 60^0C respectively. Aspirator speed was of 80 % and Feed pump speed of 10 ml. Suspensions were spray dried with constant stirring with the help of magnetic stirring.

Characterization of dry powder for inhalation (DPI):

Particle size analysis, Percentage yield (%) and drug content:

The particle size and polydispersity of the particles in dried state were determined by (Beckman coulter N4 plus submicron particle size analyzer). Samples were dispersed in water as dispersant medium. Average size and polydispersity index (PDI) is determined[10].The yields of preparation were determined by the weight of the products, spray dried powders, with respect to the weight of the initial drugs and excipients used. The drug content of spray dried powders was determined using UV spectrophotometry. Samples from each batch of spray dried formulation were dissolved in phosphate buffer (pH-7.4): ethanol (95%) in 90:10 proportions and the actual drug content was determined by first-derivative UV Spectrophotometric method. Drug content was calculated from the ratio of actual drug content to total weight of spray dried powders taken for analysis and expressed as a percentage[11].

Fourier transforms infrared spectrometry (FTIR) and Scanning electron microscopy (SEM):

Fourier transform infrared spectrometry (FTIR) spectra were recorded to evaluate the molecular states of pure drugs, excipients, physical mixture and all spray dried formulations. Fourier transform infrared spectrometry (FTIR) of pure drugs: SX and FP; excipients: Lactose and Poloxamer 188 was carried out using a JASCO FTIR-410, JAPAN FTIR Spectrophotomer .The spectra were scanned over wavelength region of 400 to 4000 cm^{-1}, resolution of 4 cm^{-1} and accumulation of 20 scans were used in order to obtain good quality spectra by making a pellet of the sample with KBr[12]. The Surface appearance and shape of the spray dried powders were investigated by scanning electron microscopy. Drug, excipients and all spray dried formulations were mounted onto separate, adhesive coated aluminum pin stubs. Excess powder was removed by tapping the stubs sharply and then gently blowing a jet of particle-free compressed gas across each. The specimen stubs were sputter coated with a thin layer of gold in a JEC-550 Twin coating unit at 10 mA for 4 min using an argon gas purge. The specimens were examined using a scanning electron microscope (SEM, JEOL-JSM-5400)[13].

Differential scanning calorimetry (DSC) and X-Ray powder diffraction study (XRD)

The phase transition of the pure drug, excipients, physical mixture, and all spray dried formulation batches were studied by thermogram obtained by using Differential scanning calorimeter (Dupont 2000, model SDT- 2960, USA). An empty aluminum pan was used as reference. DSC measurements were performed at the heating rate of 10 ^{o}C/min from 25 to 350 ^{o}C using aluminum sealed pan. Sample weight was kept between 5- 10 mg. During the

measurement, the sample cell was purged with nitrogen gas[7]. The crystalline nature of pure drug and all spray dried formulation batches were examined by studying its X-Ray diffraction patterns by using powder X-Ray diffractometer (PW- 3710 BASED). The operating parameters for instrument were Cu filtered K (α) radiations, a voltage of 40 kV, current of 25 mA and receiving slit of 0.2 In. The instrument was operated over 2θ scale. The angular range was 5 to 50^{o} (2θ) and counts were accumulated for 0.8 second at each step[14].

Powder density:

The powder density of all spray dried formulations was determined by pouring a known mass of powder under gravity into a calibrated measuring cylinder and recording the volume occupied by the powder. The tapped density of the spray dried powders was determined by tapped density measurements on the same samples until no further change in the powder volume was observed. Measurements were performed in triplicate[13].

Carr's Index values for each spray-dried powder were derived from poured density and tapped density data, according to given formula. The Carr's Index value gives an indication of powder flow; a value less than 25 % indicates a fluid powder, whereas a value greater than 25 % indicates cohesive powder[15].

Formulation development and in vitro powder aerosolization:

The in vitro aerosolization and deposition properties of DPI blended with different concentrations of excipients are determined using an Andersen cascade impactor (ACI) (Copley Scientific Limited, Nottingham, UK) with a Rotahaler® (Glaxo, UK) device. Experiment is carried out with a preseparator at air flow rates of 30 and 60 L/min. In each experiment, 8mL of the extracting solvent is poured inside the pre-separator. A coating of 1% (w/v) solution of silicon oil in hexane is used on the impaction plates to prevent particle bounce and re-entrainment. Depending upon actual drug content, the representative powder from each batch was filled into hard gelatin capsule (size 3, Capsugel, Germany) manually so that each capsule contained 50 µg SX and 100 µg FP. About 25 mg of L samples of powders were weighed and loaded into size 3 hard gelatin capsule, which were individually installed in a Rotahaler® device[14].

Rotahaler® is used as the inhaler to aerosolize the powder inside the ACI. An actuation time of 4 and 8 s is used for flow rates of 60 and 30 L/min, respectively, for each capsule to completely disperse all the particles. Experimental runs are conducted in triplicate. Particles remaining in the capsule, inhaler and different parts of the ACI are extracted using the same solvent used for the blend homogeneity test mentioned in the earlier section. The solutions are also assayed in a

similar way. Each batch was analyzed in triplicate and the following parameters were used to characterize the deposition profiles of the drug:

- The emitted dose (ED), which was the sum of drug collected from all parts of the ACI
- The fine particle dose (FPD) defined as the amount of drug deposited in the lower stages of the ACI
- The fine particle fraction (FPF) or respirable fraction (RF) calculated as the amount deposited in the lower stage as a percentage of the emitted dose (amount emitted into upper and lower stages excluding the amount remaining in the device). (M.S.Hassan,R.Lau,2010)

In vitro drug release:

The in-vitro drug release of all the spray dried formulations was investigated by dissolution study. An accurately weighed amount of DPI equivalent to 50 µg of SX and 100 µg was added to 700 ml of dissolution medium; Phosphate buffer pH 7.4: Ethanol (95%), in 90:10 proportion and drug release was investigated using the USP rotating paddle dissolution apparatus (Lab India 2000) at 100 rpm and 37 ^{o}C. A percent release study was continued from 5 min. to 3 hrs. The final volume in all cases was 700 ml. The samples were withdrawn from the dissolution medium at various time intervals. 5 ml of sample was diluted to 10 ml with dissolution medium and subjected to UV Spectrophotometric analysis at 214 nm (λmax of SX) and 246 nm (λmax of FP). All the samples were analyzed in triplicate[13].

Stability study:

Short term stability studies:

After the characterizations of physical properties of spray dried powders and drug content, all the formulations batches were kept for 1 month at accelerated stability conditions of temperature and relative humidity 40^{0}C and 75% RH. The choice of appropriate storage condition during accelerated stability study is necessary to predict the long term stability of SX and FP respirable particles. The humidity during storage is also extremely important considering the stability of formulation. Therefore, for the present study, accelerated temperature and relative humidity 40 ± 2^{0} C and 75 ± 5 % RH were selected during stability. Samples were withdrawn after one month and characterized for drug content and stability was predicted[16]. (Pozo-Rodriguez A, 2009)

RESULT AND DISCUSSION:

Particle size, Percentage yield and Drug content.

The particle size of all spray dried formulations was found in the range of 2.43 to 3.62 µm (Table 2).The polydispersity index (PDI) is also an important parameter as it gives an indication about the width of particle size distribution as well as the long-term stability of dispersion. A PDI value of 0.1–0.25 indicates a narrow size distribution whereas a PDI value greater than 0.5 indicates a very broad distribution. The PDI value obtained for all batches of DPI was found to have very broad distribution for L series (Table 2).

Table 2: Particle size of DPI

Batch code	Mean Diameter ± S.D. (µm)	PDI ± S.D.
L1	3.622 ± 0.5006	0.906 ± 0.0552
L2	2.435 ± 0.4156	0.767 ± 0.0412
L3	3.603 ± 0.4648	0.826 ± 0.0435

S.D. - Standard deviation (n=3),
PDI- Mean polydispersity index (n=3)

The observed reasons for the particle size and its distribution pattern are crystalline nature of Lactose because of which degree of conversion of crystalline form of lactose into amorphous was less. Also, based upon the observations; Poloxamer concentration affects the particle size; which indicates that poloxamer 188 acts as a stabilizer in certain amount which will give small particle size. In case of lactose series, poloxamer concentration was found to be optimum up to 1:1(Drug: Poloxamer) proportion, below and beyond this proportion; little increase was found in particle size observations.

Percentage yield and actual drug content are mentioned in the Table 3, which showed as the poloxamer concentration was increased, the yield of the product increased. Presence of poloxamer was found to increase the flow properties of L series which is beneficial during the collection of spray dried particle from cyclone and collector, to increase the percent yield of respirable DPI.

Table 3: Percentage yield (%) and drug content of spray powder powders

Batch Code	% Yield	Theoretical drug Content % (w/w)		Actual drug content % (w/w)			
		SX	FP	SX	± SD	FP	± SD
L1	38.13	2.05	4.10	1.8962	0.0012	3.6955	0.0009
L2	47.98	2.10	4.20	1.9847	0.0011	3.8055	0.0018
L3	60.79	2.15	4.31	2.0061	0.0010	4.3358	0.0022

S.D. - Standard deviation (n=3)

All the formulations showed satisfactory drug loading from 19 mg to 31.5 mg so as to get the appropriate dose containing 50µg of SX and 100µg of FP from the individual respirable DPI.

FTIR spectrometry and Scanning Electron Microscopy (SEM)

As shown in Figure 1 & 2, close agreement between the spectra of all spray dried formulations with FTIR of pure drugs and physical mixture suggested that there were no changes in the structure of SX and FP induced by solvent displacement technique as well as spray drying. The scanning electron micrograph of pure SX (Figure 3-a) showed the powder to be of a crystalline flat material, needle like in structure. Many irregular particles with much fragmentation were observed. The scanning electron micrograph of pure FP (Figure. 3-b) showed the powder to be typical aggregate of amorphous material. Many irregular particles with cluster were observed.

Figure 4 presents SEM micrographs of the DPI containing SX, FP, lactose and poloxamer 188. It shows partial crystalline, prism shaped structure. Morphology showed particles with irregular and broad distribution. Batch L2 and L3 were quite amorphous with pitted surface and shrunken surface than batch L1. The difference in morphological behavior was found because of incorporation of poloxamer which acts as crystal growth inhibitor.

DSC analysis and XRD measurements:

DSC analysis of the SX, FP, Physical mixture and spray dried formulations were performed in order to characterize the physical state of the drug and excipients before and after spray drying are shown in Figure. 5 & 6 which indicates shows DSC scan for SX; an endothermic peak for SX was observed at 127.49^{0}C. Figure 5 (b) shows DSC thermogram of FP indicating endothermic peak 308.55^{0}C which is quite more than its melting range, as it melts with decomposition. Thermogram of Physical mixture L (Figure 5-c) shows indicative broad peak of poloxamer 188 at 61.55^{0}C, sharp endotherm at 126.15^{0}C of SX and at 210.85^{0}C for lactose.

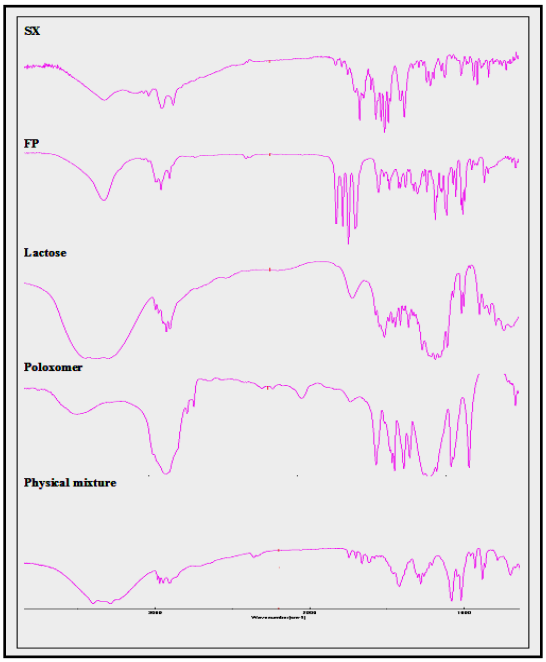


Figure 1: FTIR spectra of SX, FP, Lactose, Poloxamer 188 and physical mixture

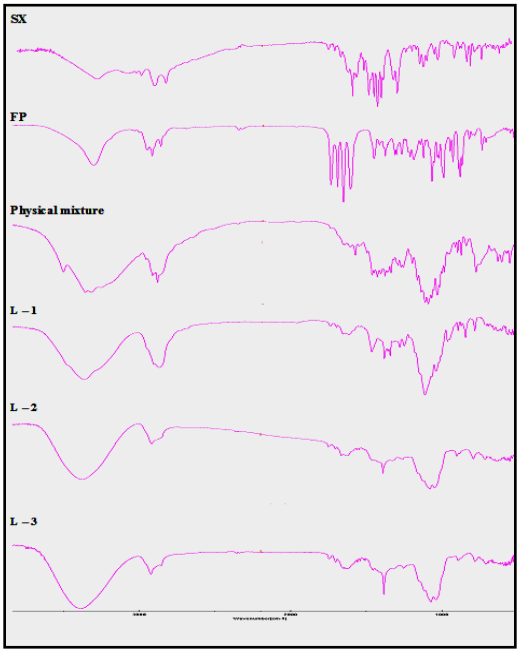


Figure 2: FTIR spectra of SX, FP, physical mixture and L series formulation

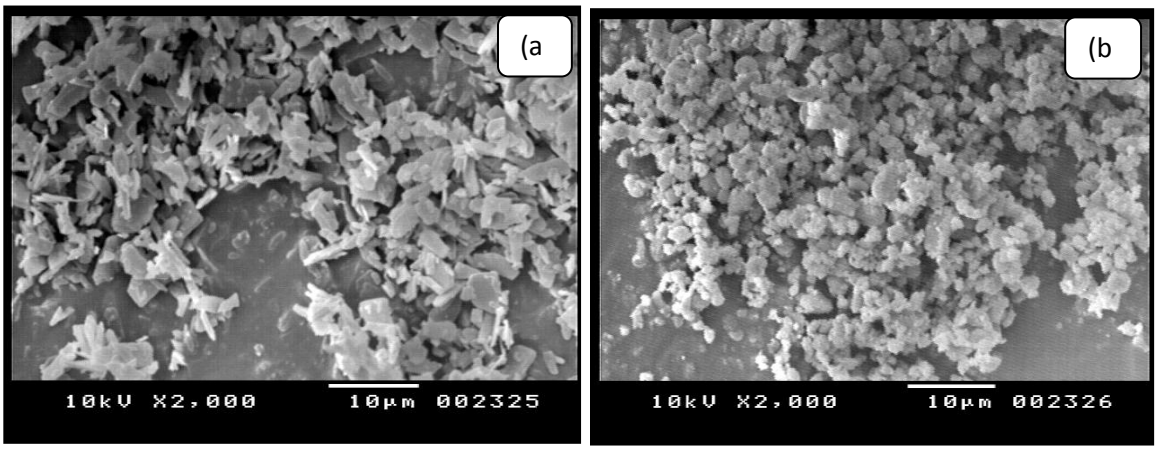


Figure 3: SEM micrograph of: (a) Salmeterol xinafoate (b) Fluticasone propionate

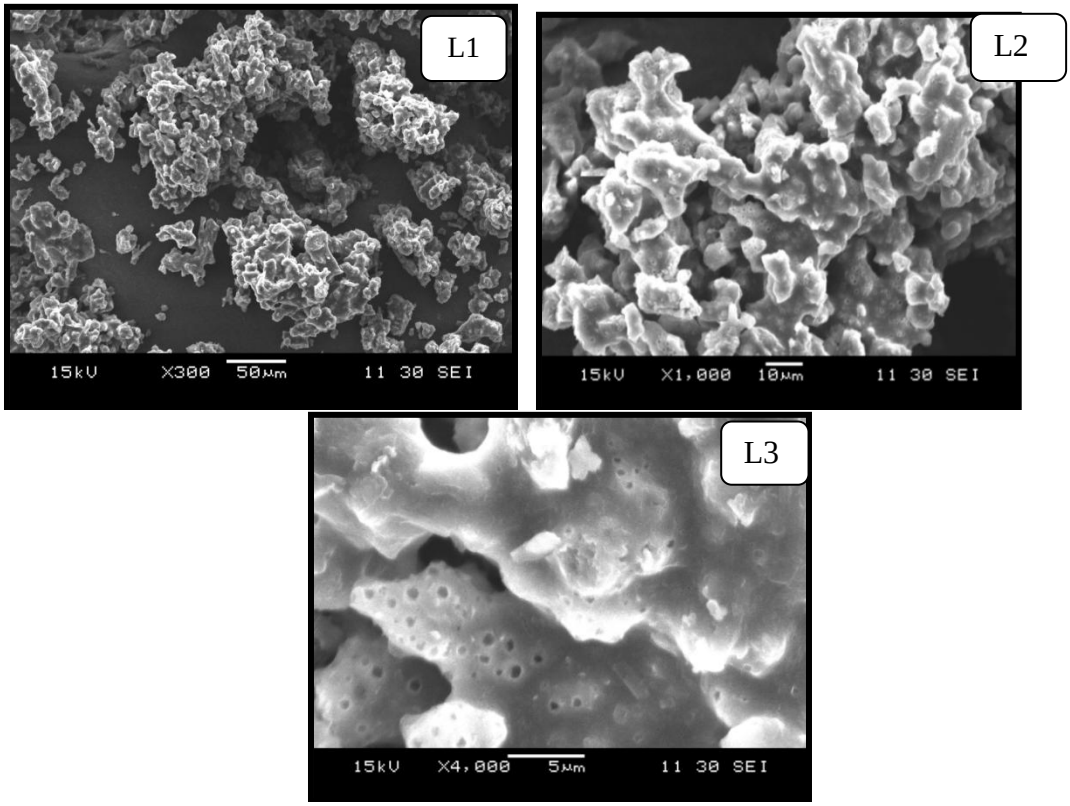
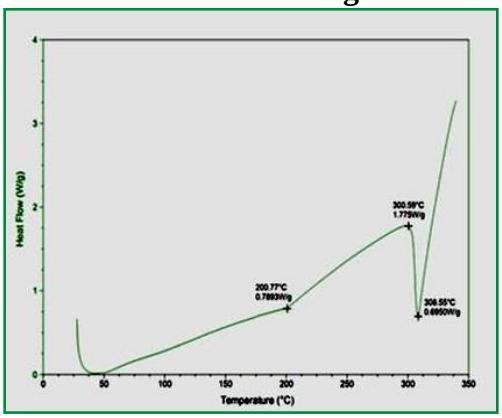
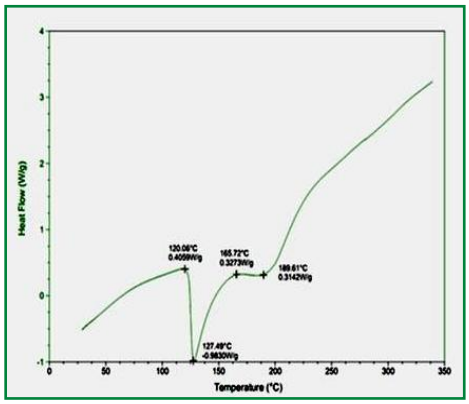


Figure 4: SEM micrographs of L series formulations



(a)



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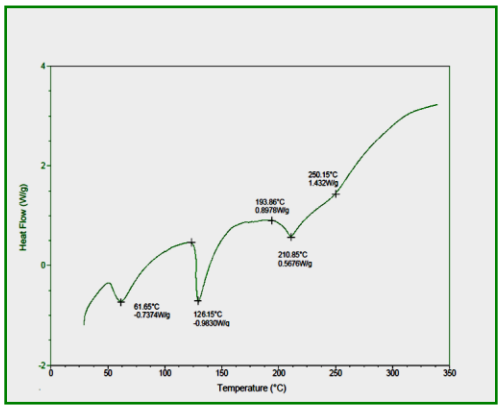
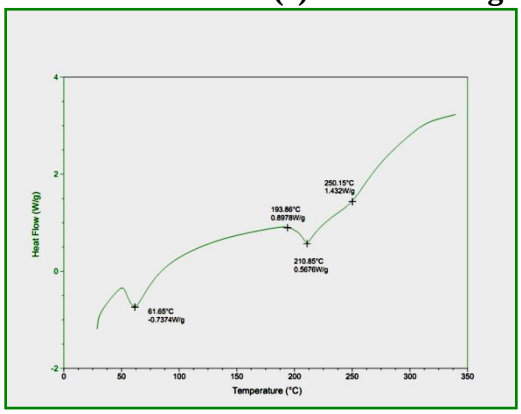
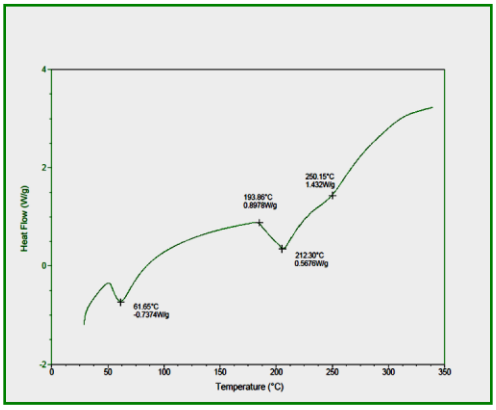


(c)

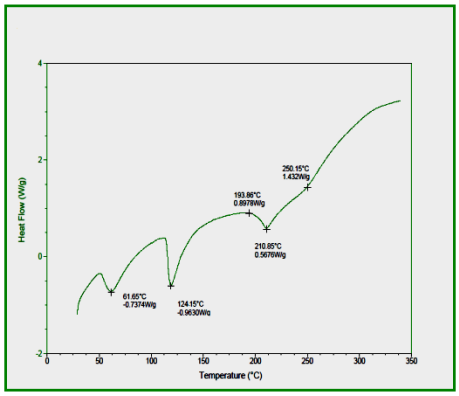
Figure 5: DSC thermogram of: (a) Salmeterol xinafoate (b) Fluticasone propionate (c) DSC thermogram of physical mixture of L series



(a)



(b)



(c)

Figure 6: DSC thermogram of: (a) L1 formulation (b) L2 formulation (c) L3 formulation

Figure 6 (a-c) represents thermogram of L series formulations. All are indicating broad peak of Poloxamer 188 but melting endotherm of SX was found to be shifted towards right side. Also, absence of sharpness of peak indicates the amorphous nature of drug after spray drying. From the observations of all thermograms, DSC measurements revealed a small melting peak of SX in the precipitate, whereas a FP melting peak could not be detected because it melts under

decomposition and therefore, creates no interpretable signal. Also, the lack of endotherm can be concluded that drugs were dispersed inside the matrix of excipients as a solid solution. Since no single DSC curve showed sharp endotherm indicative of melting of crystalline material, the SX, FP and excipients coprecipitate exist as glass solution. Furthermore, flattened, a broad curve indicates amorphous nature of drug after spray drying. Hence, DSC data lead to assumption that coprecipitate is formed.

The crystalline nature of pure drug and all spray dried formulation batches were examined by studying its X-Ray diffraction patterns. Figure 7(a) shows high intensity peaks of SX at 17.3^{o}, 22.2^{o} and 24.6^{o} which confirm that drug is crystalline in nature.

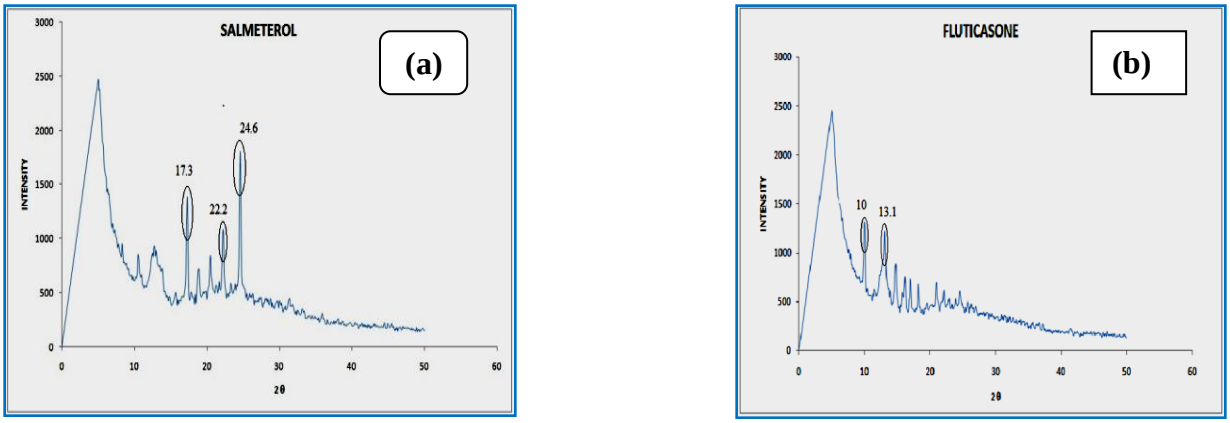


Figure 7: XRD pattern of: (a) salmeterol xinafoate (b) Fluticasone propionate

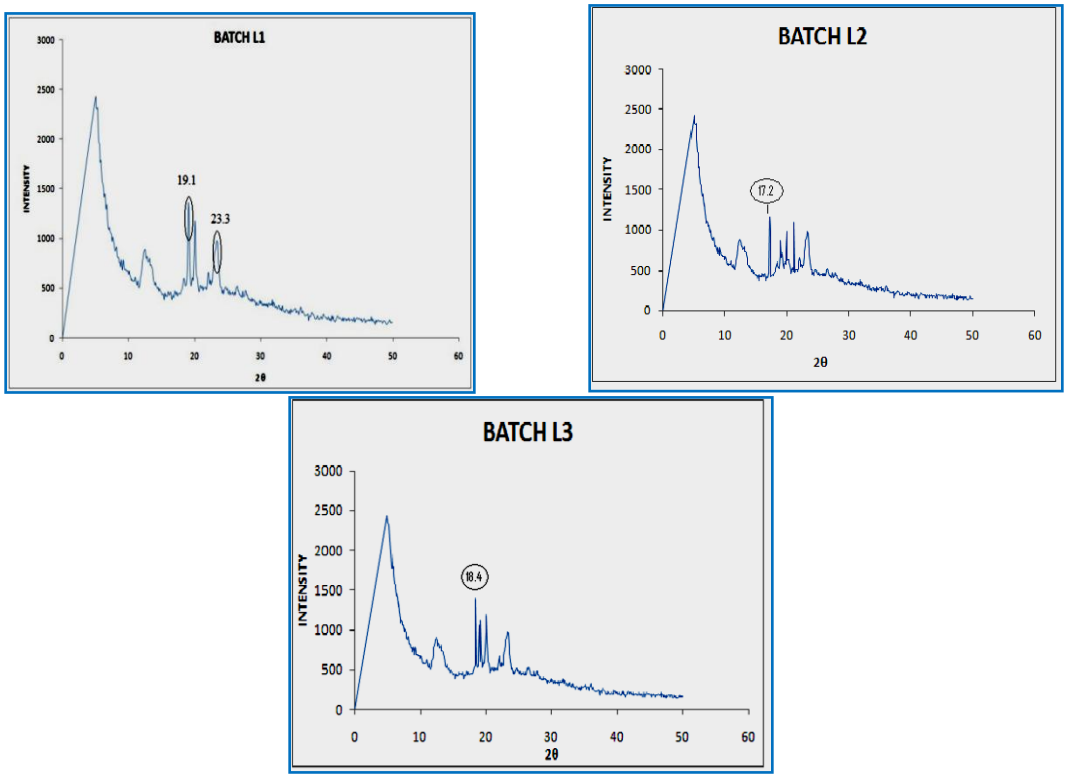


Figure 8: XRD pattern of L series formulations

As shown in Figure 7 (b), XRD pattern of fluticasone indicates the high intensity peaks at 10 and 13.1 which confirm that drug is crystalline in nature, but it seems to be little amorphous or less crystalline than salmeterol in figure 7(a).

Figure 8 shows XRD patterns of L series formulations. From observations, it is clear that degree of crystallinity of pure drugs; SX and FP is reduced and it is shifted towards amorphous nature. L1 formulation tends to be partial crystalline. The probable reason is the effect of stabilizer in reducing surface tension of droplet may have role in conversion of crystalline nature of pure drugs into amorphous one during spray drying process.

XRD pattern of L2 formulation shown in figure suggest further decrease in crystallinity of pure drugs, as peak intensity in L2 is less than that of L1. This data helps in prediction about optimum concentration of stabilizer in the formulation, as concentration of poloxamer is more in L2 than in L1 batch. The XRD pattern of L3 formulation indicates slight crystalline nature as compared to batch L1 and L2.

All spray dried formulations showed less intensive peak confirming that drugs are converted in amorphous nature. Results showed that as the drug to excipient ratio increases upto certain level, crystallinity decreases. Above discussed XRD pattern is due to proper dispersion of drug particle into the excipient matrix. This is in good agreement with previous DSC results. It has been known that transforming the crystalline state to the amorphous state leads to a high energy state and high disorder, resulting in enhancing solubility and dissolution rate.

Powder density:

Powder flow is important in dry powder aerosol formulation for both the filling of gelatin capsules or devices and for subsequent release of drug from the dry powder inhaler. Tapped density of a formulation is associated with good aerosolization; as more porous particles hold better aerodynamic property over solid particles of the same dimensions. Table 4 shows the values for Carr's Index which is used as an indication of powder flow properties.

Table 4: Tapped density, Carr's index and Flowability of spray dried powders

Batch code	Poured density (g/cm^{-3})	Tapped density (g/cm^{-3})	Carr's Index (%)	Flowability
L1	0.2094	0.2417 ± 0.03	13.36	Good
L2	0.4078	0.4392 ± 0.04	7.14	Excellent
L3	0.3088	0.3706 ± 0.03	16.67	Good

Though L series formulations seem to have good and excellent powder flow, tapped density distribution is uneven. The difference in powder flow characteristics was because of excipient

nature in the formulation. This suggests that the lactose gives better flow to spray dried formulation.

In vitro powder aerosolization:

The aerodynamic behavior of the microparticle (DPI) was estimated with Anderson cascade impactor (ACI) making it possible to study the in vitro deposition profile of the representative spray dried formulations. The emitted dose (ED), fine particle dose (FPD), fine particle fraction (FPF) or respirable fraction (RF) of the spray dried powders are displayed in Table 5.

Table 5: In vitro powder aerosolization properties of DPI

Batch code	ED (%)	FPD (µg)	FPF (%)
L1	67.05	47.17	39.29

The amount of drug deposited in the inhaler device and throat regions were 4.2% for L1 spray dried systems. Co-precipitates of fluticasone propionate and salmeterol xinafoate showed a FPF of 22% when formulated with lubricant and 36% with lactose carrier. For the commercial product Seretide®, which is a tertiary mixture of APIs with lactose; FPF of about 20% was found. It is due to low flowability and high adhesiveness of the powder (Westmeier and Steckel, 2008). L series formulation provides an innovative approach for combination formulations at appropriate doses without the need of physical blending.

In vitro drug release:

Currently, no pharmacopoeia methodology exists for the evaluation of the in vitro release rates from respirable dry powders. To study the dissolution pattern of all spray dried formulation, In vitro dissolution study was carried out using USP rotating paddle dissolution apparatus (Lab India 2000). The dissolution medium used was Phosphate buffer (pH 7.4): Ethanol (95%) [17, 18]. The dissolution method used in this study has previously been used in this research area[19].

In formulation L series drug release in the first 45 min was in the range of 97.51% to 99.08 % (Figure 9). An initial burst effect was observed due to the drug located on or near the surface of the microspheres. The pores formed during rapid evaporation of the solvent may also lead to the rapid release of the drug.

The rate of drug release from the formulation depended on the drug to excipient binding while processing, as adhesive force between drug-excipient becomes more than cohesive force between drug molecules themselves. This can be explained by a decreased amount of drug present close to the surface and also by the fact that the amount of uncoated drug decreases with higher excipient concentration. Furthermore, smaller microspheres have a larger surface area exposed to dissolution medium, giving rise to faster drug release. The initial rapid drug release can be

attributed to the formation of solid dispersion of the drug where the drug would have higher solubility and hence dissolution rates.

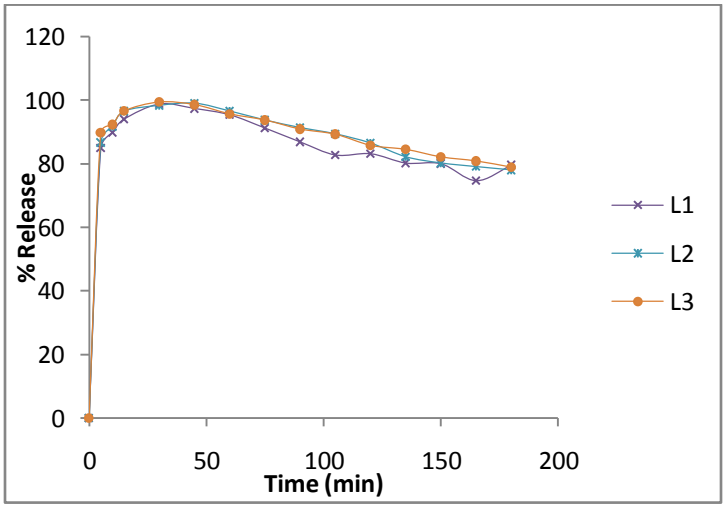


Figure 9: Release profile of L series formulation

Stability study:

The results from drug content study provide an important information regarding stability of spray dried formulation containing SX and FP particles. The result of accelerated stability studies as shown in Table 6 indicated that the selected formulations did not show any physical changes during the study period and the drug content was found to have close agreement with the drug content of formulation before stability study. This indicates that all formulations were quite stable at accelerated storage conditions.

Table 6: Drug content (%w/w) after one month short term stability study

Batch code	Drug content % (w/w)			
	Before stability study		After stability study	
	SX	FP	SX	FP
L1	1.8962	3.6955	1.8912	3.6935
L2	1.9847	3.8055	1.9806	3.8019
L3	2.0061	4.3358	2.0028	4.3338

CONCLUSION:

From the evaluation of different physical characteristics of DPI, it demonstrates that lactose has given combination particle with much better respirable fraction in comparison with marketed formulation. Ethanol was found to have good behavior for both API's among different solvents; as it was expected that the particle size of spray dried particles should be in micrometer range (2-5 µm). Also, the use of excipients is suggested to optimize the flow property and morphological characters of formulations. Formulations containing Lactose and Poloxamer 188 were found to have immediate release in dissolution media. Also, all the formulations were quite stable at

accelerated storage conditions. Thus, it concludes co-spray drying of salmeterol xinafoate and fluticasone along with lactose-poloxamer 188 provided a simple alternative to traditional combination DPI with lactose for effective implementation of combination formulations for inhalation.

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