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Research Article

SUSTAINED RELEASE OF SPRAY-DRIED COMBINATION DRY POWDER INHALER FORMULATION FOR PULMONARY DELIVERY

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ABSTRACT

The controlled release of drugs for pulmonary delivery is a research field which has been so far rather unexploited but is currently becoming more attractive. This study investigated the formulation and evaluation of respirable spray-dried combination powders showing the sustained release of two chemically distinct therapeutic agents. Spray dried formulations were produced from 70% v/v aqueous ethanol formulations containing salmeterol xinafoate, fluticasone propionate, leucine as a surfactant and HPMC as a drug release modifier. The aim of this work is to use leucine-HPMC combination as an excipient to impart sustained release profiles to drugs. The influence of leucine-HPMC combination as an excipient on spray drying thermal efficiency and drug release profile was investigated. Also, resultant powders were subjected to physical characterization. Sustained drug release profiles were observed in dissolution tests for both agents; increased HPMC concentration associated with increased duration of drug release. The controlled co-delivery of long acting β-2 agonist and glucocorticoid molecules underlines the capability of spray drying to produce respirable combination particles with sustained release for pulmonary delivery.

Keywords: Salmeterol xinafoate, Fluticasone propionate, HPMC, Leucine, Spray drying.

INTRODUCTION

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. Blending of the active pharmaceutical ingredients (APIs) with lactose carrier particles is commonly used in formulating combination inhalation products[1]. However, the blend performance is highly variable; depending on the amount of fines[2]. The problem when using the traditional polyhaler formulation is the inability to develop sustained release characteristics without an additional step to the micronisation of the components and blending. Therefore long-acting agents such as the long-acting β2 agonist salmeterol are required to achieve the recommended twice day dosing of the current crop of marketed polyhalers). This research aims to produce a long-acting therapy for asthma using the sustained release of spray-dried formulations containing long acting β-2 agonist with inhaled corticosteroid to reduce the dose frequency from twice to only once daily.

The delivery of a highly efficacious long acting β-2 agonist with a corticosteroid to the bronchi, as part of a sustained release formulation, could theoretically simplify dose regimens by reduced frequency of administration, improved patient compliance and reduction of side effects and elimination of a secondary reliever inhaler, and so improve asthma management. Use of a polymer is employed as a rate-limiting factor to achieve sustained drug dissolution. Barriers Associated with the delivery of formulations to the lungs include the geometries and areas of turbulence within the human lung, which require a particulate to be of an aerodynamic size of typically less than 5μm. A further consideration when delivering particulates for controlled delivery is the mucocilliary clearance mechanism of the lung which can move particles from the target bronchioles to the throat at a rate of≤12mm/min. A suitable mucoadhesive polymeric component to any formulation must therefore be considered for sustained release. Further consideration must be taken as to which polymer should be incorporated because foreign high molecular weight additives can be toxic on accumulation in the lung[3].

The addition of various amino acids to formulations for inhalation obtained by spray drying has been demonstrated to significantly improve the in vitro deposition profile of a dry powder. Different studies that include various amino acids have demonstrated that the addition of leucine yields the best results in term of aerosolization. The consensus is that 10–20% (w/w) of leucine in spray-dried solutions of ethanol or water gives optimal aerosolization characteristics of powders containing peptides or sodium cromoglycate. It seems that addition of leucine results in less cohesive particles and a possible decrease in particle size due to the surfactant behavior of leucine, reducing the size of droplets produced during atomization which will give more shrinkage and maximum drying of droplet to get amorphous particle (decrease in particle size).[4].

Spray-drying technology also offers the potential to incorporate a range of excipients into the formulation. It is a one-step constructive process that provides greater control over particle size, particle morphology and powder density[5]. In addition, spray-dried powders that exhibit sustained drug release properties may be generated through the inclusion of drug release modifiers such as hydroxypropyl methylcellulose (HPMC), glyceryl behenate and polylactic acid, chitosan, etc. Also, it was shown that HPMC produce spherical particle during the spray drying process acting as lubricant and dispersion modifier[6]. Leucine-HPMC is the promising excipient combination that can be employed in a wide range of applications, including sustained release preparations.

Co-precipitation or co-spray drying a solution containing two APIs is a potential alternative to produce particles of uniform drug composition. The low FPF was attributed to low flowability and high adhesiveness of the amorphous powder. 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 diluent or bulking agent. Thus, blending with carriers will introduce additional process variables. These shortfalls can potentially be avoided by incorporating a crystalline excipient into the co-spray drying solution. Suspensions were prepared by liquid anti-solvent precipitation technique i.e. Solvent displacement method[2,4].

This novel study demonstrates how spray-dried formulations containing the dispersibility enhancer leucine-HPMC can generate highly respirable powders, which give the simultaneous latent delivery of both a long acting β-2 agonist (salmeterol xinafoate) with inhaled corticosteroid (fluticasone propionate)

MATERIALS AND METHODS

Materials

Micronised Fluticasone propionate and Salmeterol xinafoate were kindly donated by Vamsi Labs Ltd., Solapur and Sun pharm. Ind. Ltd., Mumbai respectively. Pharmaceutical grade l-leucine and hydroxyl

propyl methyl cellulose (HPMC) were procured from Poona chemical Lab., Pune and Research Lab., Mumbai respectively. Potassium dihydrogen phosphate (KH2PO4) and Sodium hydroxide (NaOH) were purchased from Finar chemicals Ltd., Ahmadabad; KBr was obtained from Loba chemicals, Mumbai. Ethanol was purchased by Fisher Scientific LTD. (Loughborough, UK). Purified Water was obtained by reverse osmosis (MilliQ, Molsheim, France). All other materials used were of analytical grade. From this point forward, l-leucine and hydroxy propyl methyl cellulose will be referred to as leucine and HPMC. K-series batches are containing leucine and HPMC as excipients.

Formulation of microsuspension

Microsuspensions were prepared by solvent displacement technique (Liquid anti-solvent precipitation method) according to the formulae given in table-1. Solvent used was Ethanol (95%) and Distilled Water as an Antisolvent. Solvent: Anti-solvent ratio was 30:70.

Briefly, the fine drugs and excipients were dissolved in Solvent: Anti-solvent mixture (30:70) with the aid of sonication. The system is operated under continuous stirring for 1 hr at 1200-1500 rpm by using Lab stirrer (Remi-Motors). For every batch, different concentrations of excipients were added as shown in formulation Table 1.

Conversion of dispersion (microsuspension) into Dry powder for inhalation by spray drying[7]

Spray drying using a ,Lab Spray Dryer (LU-222 Advanced Spray Dryer: LABULTIMA, Mumbai) with a co-current 0.7 mm, two fluid nozzle equipped with autojet deblocking system, was applied in order to retrieve respirable powders in dried state from suspension described above. Suspensions were spray dried with constant stirring with the help of magnetic stirring (Whirlmatic Mega, SPECTRALAB). The conditions used during spray drying were as mentioned in the Table 2. The resultant dry powder was blown through cyclone separator and collected in container. Powders were kept in glass vials and stored in glass vials and stored in desiccator at ambient temperature before use.

Characterization of Dry Powder for Inhalation (DPI)

Particle size analysis, Percentage yield and drug content

The particle size was measured by laser diffraction (HELOS, Sympatec, Germany). The Sample was suspended in double distilled water saturated with both drugs under ultrasonication in an appropriate dilutions and immediately afterwards transferred to a 6 ml cuvette for measurement. For each batch, the measurement was carried out in triplicate using three individual samples[8]. 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 spectrophotometer (JASCO model V-550, JAPAN UV-visible double beam spectrophotometer). Drug loading was calculated from the ratio of actual drug content to total weight of spray dried powders taken for analysis and expressed as a percentage[9].

Fourier transforms infrared spectrometry (FTIR)

Infrared spectroscopy is one of most powerful analytical technique when it comes to the determination of presence of various functional groups involved in making up the molecule. It provides very well accountable spectral data regarding any change in the functional group characteristics of a drug molecule occurring while in the processing of a formulation and after spray drying[10].

Fourier transform infrared spectrometry (FTIR) spectra of pure drugs; salmeterol and fluticasone; physical mixture and all formulations were recorded with a JASCO FTIR-410, JAPAN FTIR Spectrophotomer in order to rule out drug-carrier interaction occurring during the formulation process. 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. The procedure consisted of grinding the sample with KBr in an agate mortar and pestle and compressing the sample in an evacuable KBr die by applying a pressure of 5 tons for 5 min in a hydraulic press, Techno search instrument M-15 KBr press (KBr pellet method). The pellet was placed in the light path and the spectrum was obtained.

Scanning electron microscopy (SEM)

The Surface appearance and shape of the spray dried powders were investigated by scanning electron microscopy. Drugs and all spray dried formulations were mounted onto separate, adhesive coated aluminium 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).The SEM was operated at high vacuum with an accelerating voltage 0f 5-10 kV. Secondary electron images were recorded digitally at higher magnification. Particles surface was determined by examining the microphotographs[11].

Differential scanning calorimetry (DSC)

The phase transition of the pure drug, excipients, 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[2].

X-Ray powder diffraction study (XRD)

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). It was determined whether the obtained formulation after precipitation is a coprecipitate of individual substances or whether it becomes cocrystal. 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[12].

Powder density

The poured 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[3].

Carr's Index values for each spray-dried powder were derived from poured density and tapped density data. The Carr's Index value gives an indication of powder flow; a value less than 25 % indicates a fluid powder[13].

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 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 and 246 nm for salmeterol xinafoate and fluticasone propionate respectively. All the samples were analyzed in triplicate.[3]

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 40^0 C and 75% RH were selected during stability; All study was conducted inside an environmental test chamber (Stability chamber: CHM- 10 S. Remi, Mumbai), capable of maintaining an environment of 10-95% RH (-0.2%RH) at 250C. Samples were withdrawn after one month and characterized for drug content and stability was predicted.[14]

Table 1: Formulation component for Batch LH series

Formulation code	SX: FP	Leucine	HPMC
K1	1:2	850 mg	108 mg
K2	1:2	108 mg	850 mg
K3	1:2	600 mg	130 mg

SX: Salmeterol xinafoate, FP: Fluticasone propionate

Table 2: Spray drying parameters

Parameter	Optimized conditions
Inlet Temperatur	120^{0}C
Outlet Temperature	60^{0}C
Aspirator Speed	80 %
Feed Pump Speed	10 ml
Atomization pressure	20-30 psi
Vacuum (mmWc)	-80 mmWc

Table 3: Particle size of DPI

Batch code	Mean Diameter ± S.D. (µm)	PI ± S.D.
K1	1.225 ± 0.2289	0.205 ± 0.0189
K2	1.057 ± 0.2068	0.124 ± 0.0127
K3	1.555 ± 0.2652	0.408 ± 0.0096

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

Table 4: 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	FP
K1	18.66	2.33	4.66	2.1433 ±0.0008	4.5496±0.0011
K2	21.52	2.33	4.66	2.1449±0.0014	4.5549±0.0006
K3	22.29	2.99	5.98	2.2606±0.0017	4.9706±0.0012

SX: Salmeterol xinafoate, FP: Fluticasone propionate

Table 5: Tapped density, Carr's index and Flowability of spray dried powders

Batch code	K1	K2	K3
Poured density (g/cm^{-3})	0.1840	0.2115	0.2441
Tapped density (g/cm^{-3})	0.2556 ± 0.02	0.2738 ± 0.02	0.3357 ± 0.03
Carr's Index (%)	28.57	20	60
Flowability	Poor, cohesive	Fair	Extremely poor

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
K1	0.2433	0.4496	0.2404	0.4476
K2	0.2549	0.4549	0.2519	0.4518
K3	0.2606	0.4706	0.2602	0.4711

SX: Salmeterol xinafoate, FP: Fluticasone propionate

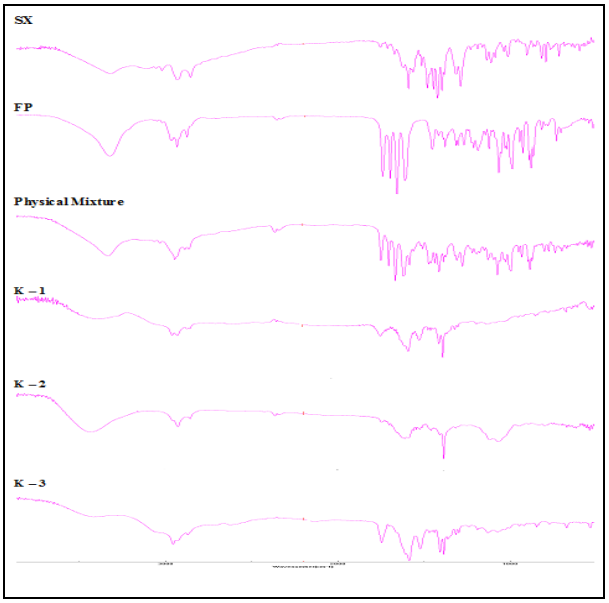


Fig. 1: FTIR spectra of SX, FP, physical mixture, K1, K2 and K3 formulations

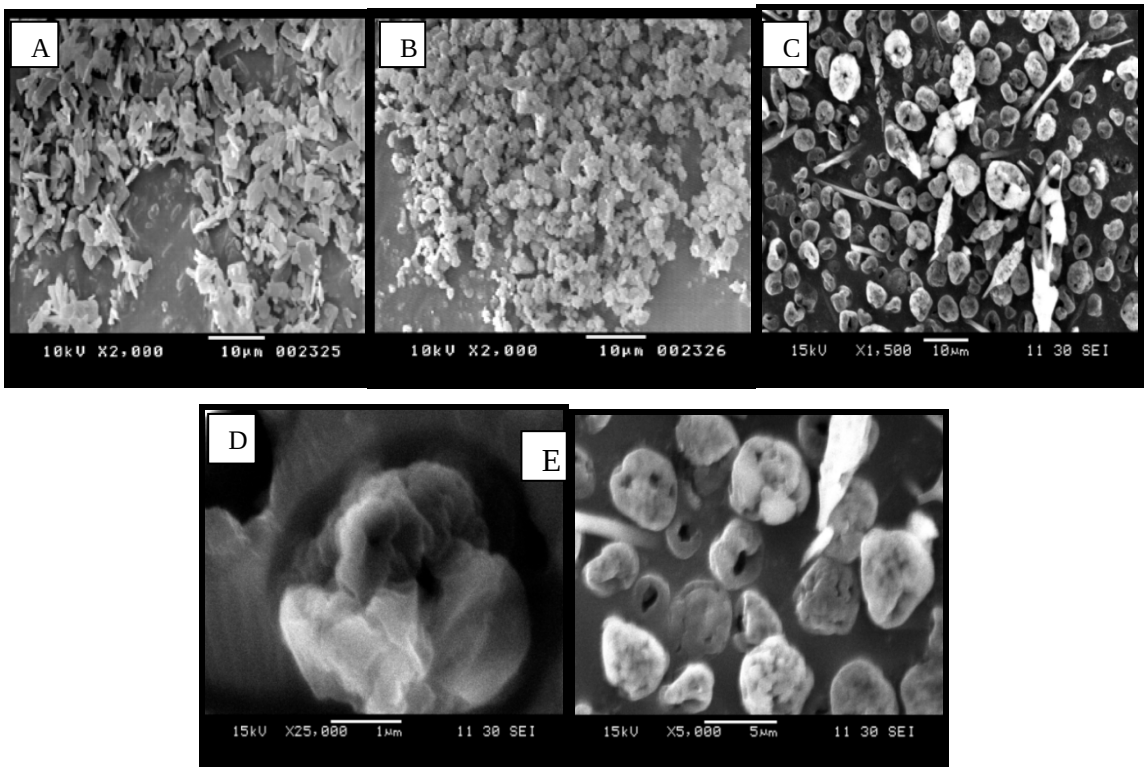
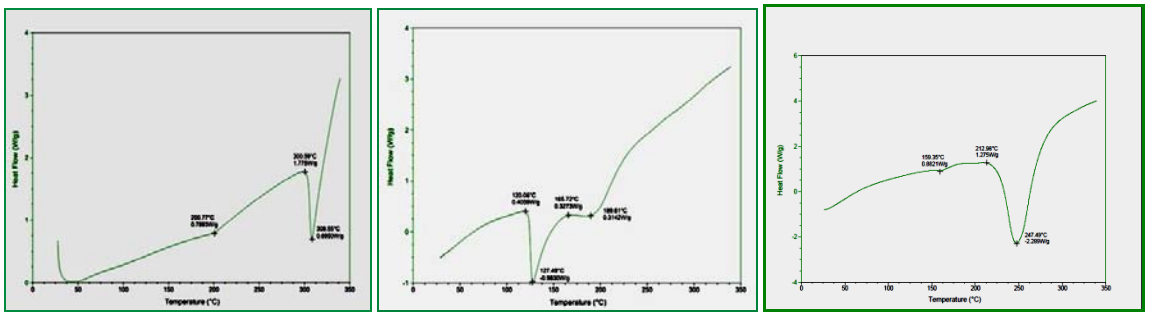
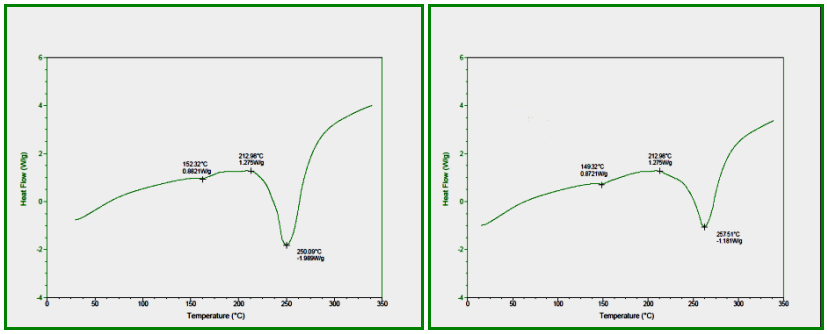


Fig. 2: SEM Micrograph of pure drugs and formulations: A) Salmeterol xinafoate B) Fluticasone propionate C) K1 D) K2 E) K3



(a) **(b)** **(c)**



(d) **(e)**

Fig. 3: DSC thermogram of a) SX b) FP c) K1 d) K2 e) K3 all formulations

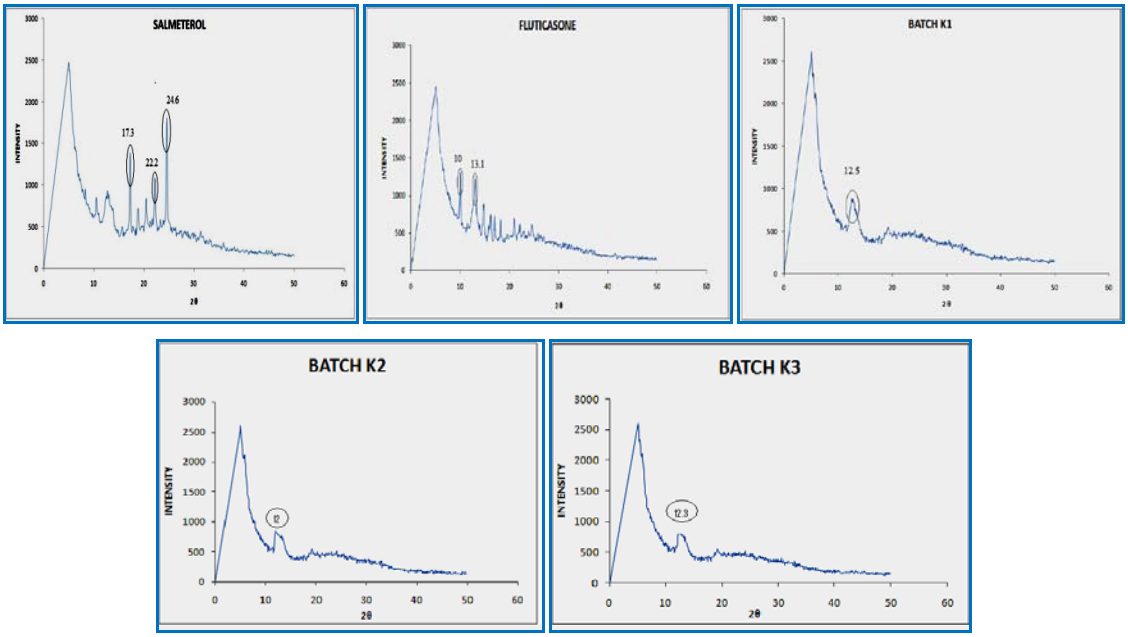


Fig. 4: X-ray diffraction pattern of pure drugs and all formulations

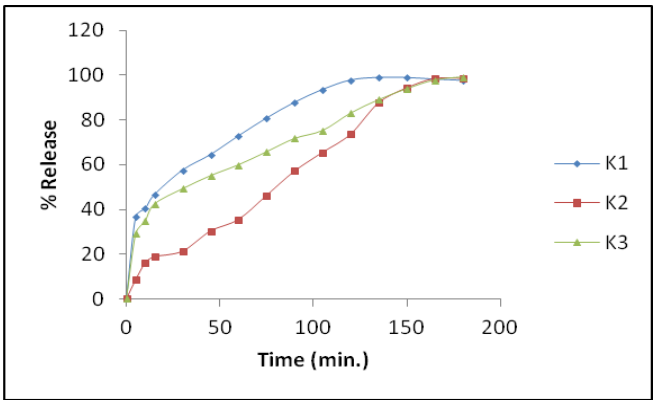


Fig. 5: Release profile of all formulations

RESULT AND DISCUSSION

Particle size, Percentage yield and Drug content

The mean diameter of spray dried powders derived from dispersion containing Leucine- HPMC as an excipient combination is given in Table 3. The polydispersity index (PI) 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 PI value of 0.1–0.25 indicates a narrow size distribution whereas a PI value greater than 0.5 indicates a very broad distribution.[15] The PI value obtained for LH series formulations was found to have quite narrow distribution of particle size.

Presence of Leucine was found to reduce the particle size of contents after spray drying. Narrow particle size distribution was observed

because of Leucine-HPMC combination, as HPMC is used as a good dispersing agent.

Percentage yield and actual drug content are mentioned in the table 4, which showed Leucine-HPMC combination showed low percent yield. The main reason of getting the low product yield of K series is sticky nature of Leucine onto deblocking shaft of spray dryer and other reason is adherence of spray dries particles on to the wall of cyclone chamber which is difficult to collect because of small particle size and poor handling properties of DPI. All the formulations showed satisfactory drug loading from 19 mg to 21 mg so as to get the appropriate dose containing 50µg of SX and 100µg of FP from the individual respirable DPI.

FTIR spectrometry

Fourier transform infrared spectrometry (FTIR) spectra of pure drugs, physical mixture and all formulations are shown in Figure 1. Close agreement between the spectra of all spray dried formulations with FTIR of pure SX and FP suggested that there were no changes in the structure of SX and FP induced by formulation process as well as spray drying.

Scanning electron microscopy

Scanning electron microscopy was used to visualize the particle diameter, structural and surface morphology of the spray dried powders. The scanning electron micrograph of pure SX (Figure 2) 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 showed the powder to be typical aggregate of amorphous material. Many irregular particles with cluster were observed.

The SEM images shown in Figure 2 suggested that the powders formed after spray drying were towards amorphous, partial crystalline in nature; as this was expected, as powders generated through spray-drying are known to be predominantly amorphous in nature. This observation was further confirmed by differential scanning calorimetry and X-ray diffraction study. SEM micrographs of the DPI containing SX, FP, Leucine and HPMC show regular spherical amorphous particles. Morphology showed particles with uniform and narrow particle distribution. Batch K2 and K3 showed little shrunken, protruded amorphous surface with some pitting. Batch K1 and K3 were found to have pitted surface but less shrinkage. The difference in morphological behavior was found because of Leucine; it tends to shrinkage at the particle surface during drying in the chamber and reduction in particle size. Increased concentration of HPMC revealed the hollow and protruded interior structure in batch K2.

DSC analysis

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 excipient before and after spray drying are shown in Figure 3. It was also used to determine the existence of possible interaction between the excipient and drug.

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 endotherms 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 resulting into amorphous nature to spray-dried powder.

XRD measurements

The crystalline nature of pure drug and all spray dried formulation batches were examined by studying its X-Ray diffraction patterns. As shown in figure 4, XRD pattern of fluticasone indicates the high intensity peaks at 10^{o} and 13.1^{o} which confirm that drug is crystalline in nature, but it seems to be little amorphous or less crystalline than salmeterol.

From observations, it seems that degree of crystallinity of pure drugs; SX and FP is reduced; which indicates the role of leucine-HPMC towards degree of crystallinity. It is clear that HPMC is responsible to make the particle fluppy. This gives an idea regarding the optimum concentration of Leucine-HPMC in the formulation. All spray dried formulations showed less intensive peak confirming that drugs are converted in amorphous nature. 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.

In all XRD measurements, the formulation shows a partly crystalline pattern masking the crystalline peaks of pure drugs. Therefore it is assumed that the formulation resulted from coprecipitation.

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 5 shows the values for Carr's Index which is used as an indication of powder flow properties; a value less than 25% indicates a fluid flowing powder, whereas a value greater than 25% indicates cohesive powder characteristics. It is observed that increased concentration of Leucine indicates poor powder flow.

It would, however, be expected that the spray dried material would have better flow properties than that of the micronized material because of its spherical nature, there being fewer points for physical contact. Poor flowability may have been due to differences in the surface energies of the individual components in the formulation. Also, although spherical, the surface area of the spray dried particles was pitted, protruded; increasing the total surface area for contact between the particles[16].

In vitro drug release

Although, several in vitro models for the prediction of respirable fraction and site of deposition in the lung following pulmonary administration (e.g. Twin stage impinge, MSLI, Anderson cascade impactor, Next generation impactor, etc.), there is no readily available in vitro model to predict the rate and extent of drug dissolution in the lung following inhalation. However, for a sustained release DPI, it becomes essential to evaluate the release of an API (SX and FP) molecule from the formulation matrix as a function of time.

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%). The dissolution method used in this study has previously been used in this research area[17].

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.

HPMC sustains the release of the drug. In K series formulation, drug release in the first 45 min was in the range of 30.36 % to 64.48%. The increased density of the Leucine-HPMC matrix results in an increased dissolution path length. This may decrease the overall

drug release from the excipient matrix. From the drug release pattern given in Figure 7, it is clear that as concentration of HPMC increases the drug release and becomes more sustained. K2 formulation gives slow and sustain release of API among K series of formulation.

Stability study

The result of accelerated stability studies as shown in Table 7 suggests, that the 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 .

CONCLUSION

These investigations conclude that it was possible to formulate sustained release spray-dried combination Dry Powder Inhaler formulation for pulmonary delivery. It was found that increased spray-drying thermal efficiency, obtained through the use of a surfactant and correlated with aerosolization properties of a powder. The formulation process resulted in the formation of co-precipitate which was confirmed by SEM, DSC and XRD analysis. The combination particle obtained was found to be of amorphous nature with optimum particle size. As expected, the Leucine-HPMC combination of excipients exhibited sustained release characteristics. Thus, it concludes that a stable Dry powder for inhalation (DPI) formulations containing salmeterol xinafoate and fluticasone propionate as an API showed excellent in vitro performance with sustained release with leucine-HPMC combination as excipients.

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