CHAPTER 5

POWDER PROPERTIES

5.1 INTRODUCTION

Optimization of inhaled therapy is necessary for successful administration via this route. The use of dry powders for inhalation has been the focus of renewed attention for the delivery of conventional pharmaceuticals with the development of new dry powder inhalers. It is these devices together with stable dry powder formulations which may offer the best possibility for the routine delivery of therapeutics including proteins and peptides to and via the respiratory tract. Initially, the challenge is to bring about the size reduction of vulnerable therapeutic agents to produce a particle size distribution suitable for pulmonary deposition, while maintaining activity, together with physical and chemical stability of the molecules. The design of particles for inhalation must take into account the need for small primary particles to obtain deep lung deposition. There is an additional need for control of interparticle interactions to optimize the requirements for good production handling properties, transport/mechanical robustness, physical and chemical stability, and allow for patient handling and fulfill consistency of dose criteria.

The number and variety of factors that govern the complex behavior of pharmaceutical powders hinder the development of predictive methods. However, the complexity may well mask a degree of underlying order that may be defined at some level of scrutiny. A theme of the application of various analytical methods to irregularities in dry powder aerosol morphology, behavior and delivery need to be addressed. The description of irregular particle morphology and powder properties may offer unique insights into the performance of materials intended for use in dry powder inhalers. Various important factors which affect dry powder aerosol delivery have been reported. These include humidity (Forbes et al, 1998; and Young et al, 2003) air flow (Chavan et al, 2000; and Chew et al, 1999), particle size, shape, surface nature, flow and dispersion (Hicky et al, 1997). Influence of particle size, shape and surface nature of ALLP on aerosolization has already been discussed in chapter 4. Hence the scope of present chapter includes study of influence of humidity, airflow rate on aerosolization and flow & dispersion properties of ALLP.

5.2 METHODS

5.2.1 Effect of Humidity on Aerosolization of ALLP

It is widely acknowledged that any interactions between the dry powder formulation for inhalation and the environmental relative humidity may be critical in determining the aerosol performance of the powder (Braun et al, 1996). Moisture adsorption may lead to problems of increasing the adhesive nature of the powder, causing variable particle deaggregation during the generation of the respirable aerosols (Hindle et al, 1996). Aggregate formation may also affect powder flow characteristics and produce problems during dose metering. Solid-state stability issues must also be addressed; water may act to alter the physical and chemical stability of both the active drug and excipient (Oguchi et al, 1996; and Ward et al, 1995).

A comprehensive investigation was undertaken to evaluate the effect of humidity on the aerosolization of ALLP. This study focused on the investigation of drug-drug interactions after relatively long storage times (12 hr) at a variety of specific humidities. The moisture sorption properties of ALLP were investigated by storing 100 mg of each spray dried TB and AMK- ALLP sample in tightly sealed containers, together with different saturated salt solutions for 12 hr. Saturated salt solutions of lithium chloride (11% RH), calcium chloride (29% RH), potassium carbonate (43% RH), sodium permanganate (63% RH) and sodium chloride (75% RH) (Richardson et al, 1955). Phosphorous pentoxide was used to produce a moisture-free environment. Each powder was then weighed accurately and analyzed for total water content (n=3) by Karl Fischer titration (DL38 Volumetric KF Titrator, Mettler-Toledo, Inc., Columbus, USA).

In order to understand the effect of humidity on particle size of ALLP, the particle size was determined by laser diffractometry (Malvern MasterSizer 2000 series, Malvern Instruments, Worcestershire, UK) using the Hydro 2000SM sampling unit. Each sample in sufficient quantity was dispersed in isopropyl alcohol so as to achieve obscuration range between 10-20%. Samples were kept under stirring using a blade stirrer at 1000 rpm to keep particles in suspended form and the measurements were recorded for VMD, which is related to the mass median diameter by the density of the particles.

The aerosolization of ALLP was investigated by an eight stage, nonviable Andersen cascade impactor with a preseparator (Graseby-Andersen, Atlanta, GA, USA) operating at an airflow of 28.3 L/min. The cutt-off aerodynamic diameters of stages 0 to 7 were 9, 5.8, 4.7, 3.3, 2.1, 1.1, 0.7, and 0.4. The impaction plates were pre-coated with a 2% w/v of hydroxypropylmethylcellulose (4000 cps) gel in water to prevent particle bounce and re-entrainment. A size '2'hard gelatin capsule (Universal capsules, Mumbai, India) was filled with 20 mg of powder and aerosolized using Rotahaler (Cipla limited, Mumbai, India). Ten capsules were shot for each impaction with each capsule had air drawn through it for 10 secs. The powder deposited in induction port, preseparator, individual impaction plates, and powder remaining in capsule and inhaler device was recovered by immersing each part in methanol. Fluorescence of each solution due to coumarin (incorporated in the ALLP) was determined using a Shimadzu spectroflourometer RF 540 (Shimadzu corporation, Japan) at λexcitation= 458 nm and λemission= 545 nm. Each measurement was repeated thrice.

ED, FPF and MMADe of spray dried TB-ALLP and AMK was calculated according to USP 27 NF 22. FPF was calculated from ratio of the total mass of powder (R) having particle size below 5 μm to the total mass (ΣA) of powder delivered from the mouthpiece of the inhaler into the apparatus i.e

$$FPF = R/\Sigma A \text{ -------- Equation (5.1)}$$

The cumulative mass of powder less than the stated size of each stage of the Andersen impactor was calculated and plotted on a log probability scale, as percent of total mass recovered in the impactor against the effective cut-off diameter. The MMADe of the particles is defined from this graph as the particle size at which the line crosses the 50% mark.

5.2.2 Effect of Air Flow Rate on Aerosolization of ALLP

The extent of dose delivery to the lung can change because of the variability in inhalation characteristics between patients (Hindle et al, 1995; and Clark et al, 1996). As airflow increases through the inhaler with increasing inspiratory effort, increased emptying and fine particle generation probably results from increased pneumatic entrainment and deaggregation of particle agglomerates (Hickey et al, 1994; and Srichana 1998). Higher inspiratory flow rates, however, increase deposition by impaction in the oropharynx and at airway bifurcations, whereas they reduce deposition by sedimentation and diffusion because of the reduction of particle residence times. Hence, the deposition pattern of drug in the lung and the resulting

efficacy depend in a complex manner on inspiratory flow rate. The purpose of this study is to evaluate the effect of the rate of increase in airflow on powder emptying from DPIs.

The dispersion behavior of spray dried TB and AMK ALLP was accessed by a Rotahaler coupled to eight Anderson stage cascade impactor. Approximately 20 mg of ALLP was filled into size '2'hard gelatin capsule (Universal capsules, Mumbai, India).Immediately after filling the capsule was loaded into the inhaler and the powder was dispersed into the running cascade impactor. A total of 10 capsules for each formulation wad dispersed, mass of powder deposited on each stage was calculated by estimating previously incorporated fluorescent dye coumarin at $\lambda_{excitation}$= 458 nm and $\lambda_{emission}$= 545 nm. Prior to dispersion of ALLP the impaction plates of cascade impactor were pre-coated with a 2% w/v of hydroxypropylmethylcellulose (4000 cps) gel in water to prevent particle bounce and re-entrainment. For each formulation Cascade impactor was operated at airflow of 28.3, 60 and 90 L/min for 10 s, 5 s and 3 s respectively. The cutt-off diameters for various stages at different air flow are shown in Table 5.1. ED, FPF and $MMAD_e$ of ALLP were calculated at each flow rate.

Table 5.1 Stage Cut-off Sizes (μm) for the Andersen Cascade Impactor at Selected Flow Rates

	*Flow rate (L/min)**		
Stage	**28.3**	**60**	**90**
-2	Not used	Not used	8.0
-1	Not used	8.6	6.5
0	9.0	6.5	5.2
1	5.8	4.4	3.5
2	4.7	3.2	2.6
3	3.3	1.9	1.7
4	2.1	1.2	1.0
5	1.1	0.55	0.43
6	0.7	0.26	Not used
7	0.4	Not used	Not used

5.2.3 Particle Flow and Dispersion

Angle of Repose

The pile of powder was carefully built up by dropping the powder material through a funnel tip from height of 2 cm (Carr, 1965). The angle of repose was calculated by inverting tangentially the ratio of height and radius of the formed pile.

Compressibility Index

The compressibility index was determined by tapping the formulation for 500 taps to reach plateau condition (Carr, 1965).

Dispersibility Index

Formulation (10 g) was dropped through a cylinder (length 16.5 cm, internal diameter 5 cm) held 5 cm above a watch glass of 2.5-cm diameter. The dropping point was 7.6 cm above the cylinder from a funnel tip. Dispersibility index was calculated as the relative proportion of material lost to the material dropped (Carr, 1965).

Hausner's Ratio

Hausner's ratio (HR) was determined from the minimum and maximum bulk density values with the tapping method by Equation 5.2

$$HR = \rho_t / \rho_b \text{ --------- Equation (5.2)}$$

Where ρ_t is the maximum bulk density and ρ_b is the minimum bulk density.

Packing Properties of ALLP

The packing properties of the ALLP were determined with the tapping method by means of Kawakita's equation for indicating porosity.

$$1/(\varepsilon_n - \varepsilon_f) = K.n + 1/(\varepsilon_0 - \varepsilon_f) \text{ ---------- Equation (5.3)}$$

Porosity (ε) = 1- (Bulk density/skeletal density)*100%

Where ε_0, ε_n, and ε_f are the porosity of powder bed at the initial, nth, and final tapping, respectively, and n is the number of taps. The constant K is expressed as the packing rate constant. Packing property of carrier lactose (Inhalac 230, d50=100 μm) was also evaluated for comparison purpose.

5.3 RESULTS AND DISCUSSION

In order to understand the effect of humidity on the ALLP, it is important that the particles are characterized in terms of particle size and dispersibility (span value). VMD of spray dried TB and AMK ALLP subjected to varied humidity conditions revealed non significant ($P>0.05$) particle growth at 15-45% RH. However at 60 and 75% RH, marginal increase of VMD was observed, but was well with in the respirable range (Table 5.1), suggests suitability of ALLP for inhalation applications. The 'span' measures the width of the particle size distribution (polydispersity) and small span value indicated narrow particle size distribution. Results shown in Table 5.1 reveal marginal increase in particle size distribution (Polydispersibility) at RH above 60%.

Karl Fischer–obtained moisture equilibrium profiles for spray dried TB and AMK ALLP, as a function of humidity, are presented in Figure 5.1 and are calculated as percentage water in the total mass. Analysis of the Karl Fischer water contents suggested a significant (ANOVA $p<0.05$), positive increase in water content, for both ALLP, as the storage humidity was increased. The water content of both ALLP were dramatically increased (Table 5.1) at storage conditions of 60%RH and above. The high moisture sorption above 60%RH partly may be because of large proportion of hydrogenated soyaphospatidyl choline (>30%w/w) in the formulation. In addition to this, the crystalline nature of both TB and AMK would have further contributed to the high moisture sorption. As discussed in chapter 4.5.1 (DSC thermograms), the crystallinity of both spray dried TB and AMK-ALLP do not altered by manufacturing process. Crystalline drug molecules staked in rods, held together by water molecules, on high humid conditions considerable moisture sorption into the crystal lattice can occur (Paul et al, 2003).

The *in vitro* aerosolization of TB and AMK-ALLP was conducted at 15, 30, 45, 60, and 75% RH by using cascade impactor. The results obtained from the in vitro investigations are shown in Table 5.1. It was observed that the recoverable powder mass for all formulations were with in the range of 95.0 ± 1% of mass of powder filled into capsules. The capsule and device retention was significantly higher ($p < 0.05$) above 60% RH, with respect to humidity conditions of 15-45% RH. The mean percentage delivered dose (ED) falling from 89% at 15% RH to 74% at 75% RH with TB-ALLP and 91% at 15% RH to 73% at 75% RH with AMK-ALLP. The results indicate that 15 and 18% of recoverable dose of TB and AMK-ALLP was retained in

Table 5.2 Effect of varying humidity on properties of ALLP (Mean ± s.d., n=3).

	Humidity (± 2%)	*VMD (μm)*	*Span*	*EMC (%w/w)*	*ED (%)*	*FPF (%)*
TB-ALLP	15	7.147	1.36	2.267	89.25	59.25
		±0.233	±0.005	± 0.229	± 1.61	± 2.76
	30	6.886	1.214	2.83	88.43	61.30
		±0.173	±0.002	± 0.097	± 1.782	± 3.12
	45	7.804	1.532	3.153	87.56	57.88
		±0.224	±0.003	±0.267	±1.884	± 2.54
	60	9.451	2.104	5.446	81.08	52.14
		±0.239	±0.002	± 0.118	±2.45	± 1.57
	75	10.62	2.316	6.207	73.81	44.43
		±0.185	±0.001	± 0.327	± 2.23	± 2.76
AMK-	15	6.668	1.42	2.06	91.42	60.24
ALLP		±0.183	±0.001	± 0.324	± 2.56	± 1.98
	30	6.87	1.307	2.656	90.24	61.76
		±0.268	±0.002	± 0.154	± 2.024	± 3.33
	45	7.247	1.62	3.051	88.48	59.07
		±0.312	±0.001	±0.347	±2.64	± 2.57
	60	8.782	2.247	5.537	83.271	53.04
		±0.320	±0.002	± 0.221	±3.24	± 2.77
	75	10.08	2.42	6.424	73.14	46.22
		±0.204	±0.002	± 0.217	± 2.74	± 3.17

the capsules and/or in the inhaler device at high humidity conditions. The reason for lower emission may be due to formation of agglomerates at high humid conditions. A plot of FPF against humidity, presented in Figure 5.2, suggests a decrease in mean FPF of both ALLP, at 60% and 75% RH, which may be attributed to the large increase (about 3-4% w/w) in moisture uptake above 60% RH. The relationship between increased humidity and decreased aerosolization performance of ALLP most likely is attributed to the hygroscopic nature of the powder, because water is rapidly absorbed into the crystal lattice at a specific humidity until it forms equilibrium with the surrounding environment (Cox et al, 1971). The presence of such a dynamic

equilibrium can only promote the condensation of water between the capillaries of the powder particulates, thus increasing the interparticulate forces while decreasing the aerosolization efficiency.

From the Figures 5.3 and 5.4, it was evident that both ALLP were almost completely dispersed (mean value of 94.26±1.81 and 92.45±2.78 for TB and AMK ALLP respectively) from the Rotahaler at air flow rates of 28.3, 60 and 90 L/min. The amount of powder emptied for both ALLP was similar at all air flow rates. The MMADe of the ALLP were 4-5 μm at air flow rate of 28.3 L/min to 90 L/min (Figure 5.3B and 5.4B), and are larger than theoretical estimates of primary aerodynamic diameters (Table 4.10, chapter 4.0), indicating that the powder aerosols exited the inhaler device as particle aggregates and that increasing the airflow rate created insufficient differences in shearing to profoundly impact on the degree of dispersion of these aggregates. This is advantageous for pulmonary drug delivery because it alleviates the dependence of delivered doses with the breathing pattern of the patient (Hickey et al, 1996 and Niven et al, 1997).

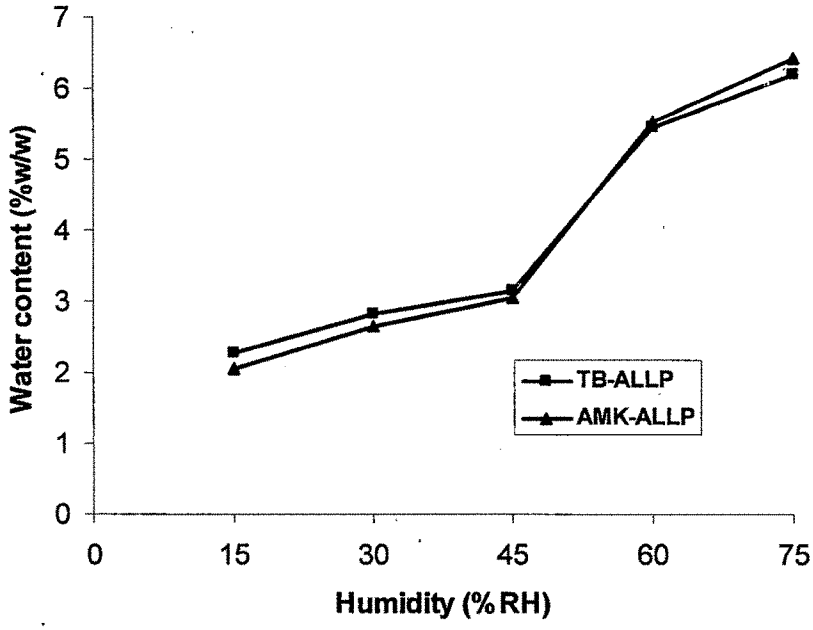


Figure 5.1 **Percentage equilibrium moisture content of the ALLP after storage at different relative humidities (%w/w) (Mean ± s.d., n=3).**

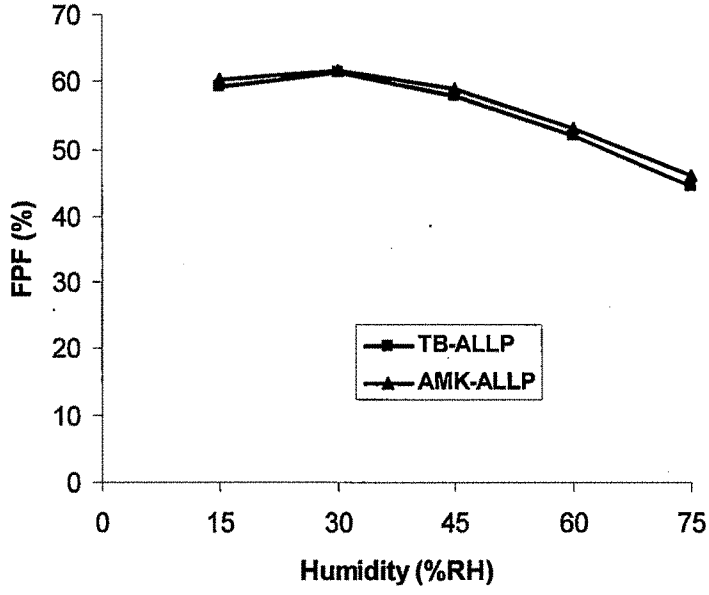
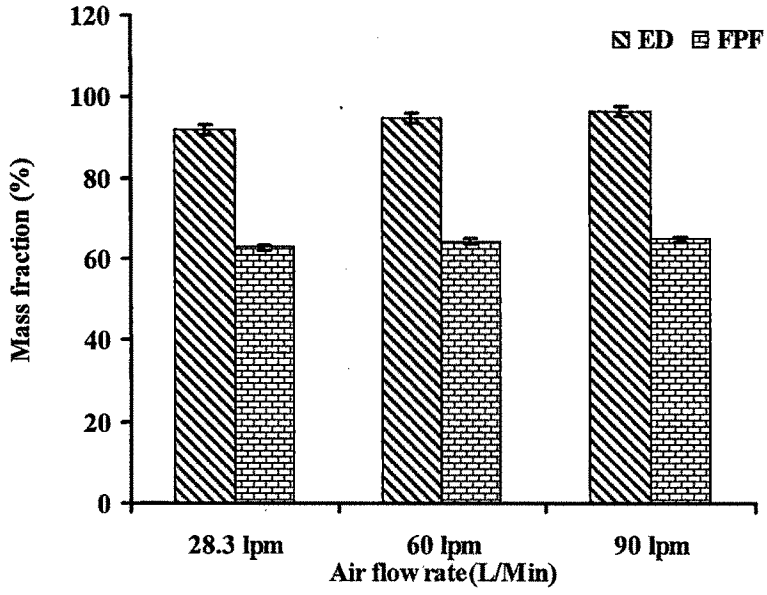
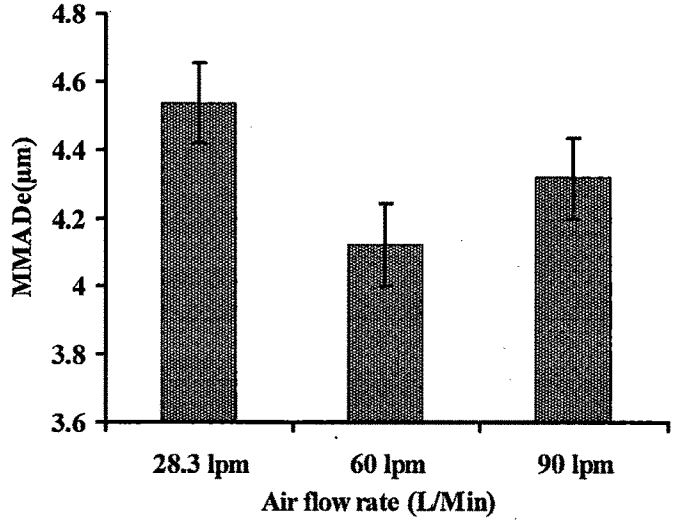


Figure 5.2 **Effect of humidity on the percent FPF (Mean ± s.d., n=3).**

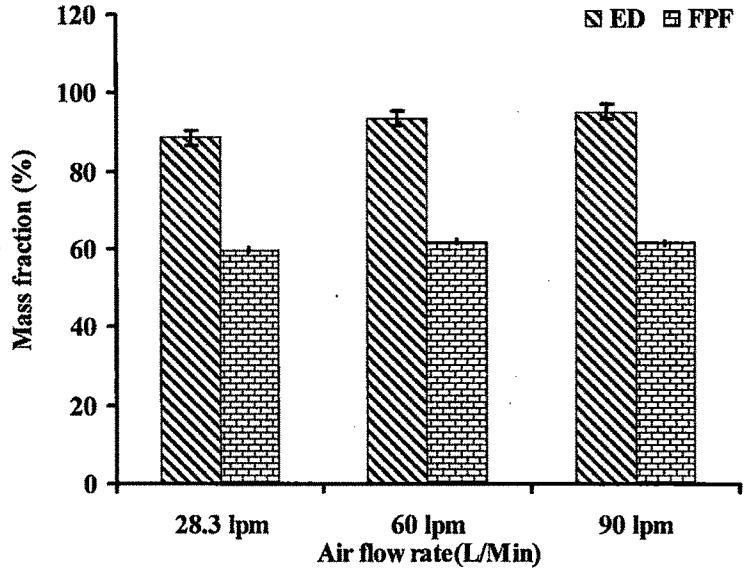


(A)

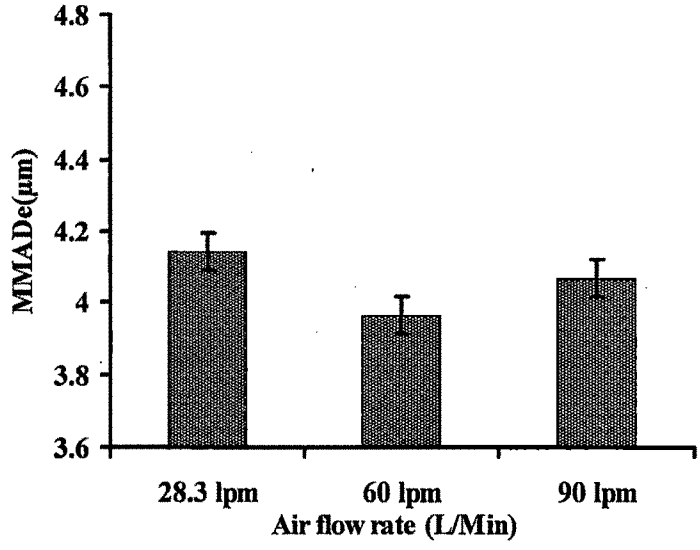


(B)

Figure 5.3 Influence of the airflow on the aerosolization properties of TB-ALLP assessed in cascade impactor (Mean ± s.d., n=3).



(A)



(B)

Figure 5.4 **Influence of the airflow on the aerosolization properties of AMK-ALLP assessed in cascade impactor (Mean ± s.d., n=3).**

Evaluation and control of flow and dispersion (deaggregation) characteristics of the formulation are of critical importance in the development of DPI products. Inter-particle forces that influence flow and dispersion properties are particularly dominant in micronize or microcrystalline powders required for inhalation therapy (< 5μm) (Gonda, 1992; Hickey, 1996). It has been demonstrated that powder adhesion, mediated in part by Van der Waal forces, is directly related to particles < 10 μm (Hickey, 1996). Predictions of powder rheology based on the possible relationship of a number of physicochemical properties are extremely complicated. Hence, flow and dispersion properties like angle of repose, dispersibility index and compressibility index are characterized and controlled.

The angle of repose has been used in several branches of science to characterize the flow properties of solids. Nelson (1955) was the first to use angle of repose measurements to determine the flow properties of pharmaceutical materials. The flowability and floodability expressed by angle of repose (28.2 ± 0.4 and 30.2 ± 0.3), Hausner ratio (1.38±0.01 and 1.26±0.03), dispersibility index (20.7 ± 0.2 and 20.2 ± 0.4), and compressibility index (24.6 ± 2.8 and 23.3 ± 1.8) for TB and AMK-ALLP respectively, falls under the category of good and floodable (Carr, 1965).

Packing processes of the ALLP were determined using the tapping method to evaluate their packing property. Figure 5.5 shows an example of the measured values plotted by Kawakita's equation. There was a linear relationship between '**n**' and **1/(εn-εf)**, and the constant ***K*** was obtained from the slope of this line. Inhalac 230 a carrier lactose, frequently used with DPI, having d_{50}= 100 μm, excellent flow characteristics and good packing property has been used as reference. Table 5.3 shows the constant ***K*** values of Inhalac 230, TB and AMK-ALLP. The constant ***K*** of all three powders is comparable. Good packing properties are also desirable for the handling of dry powder inhalation.

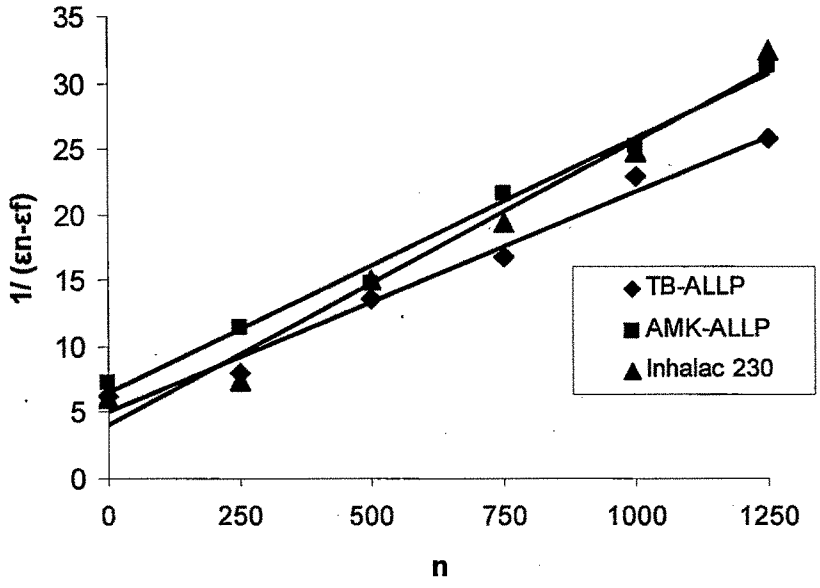


Figure 5.5 **Relationship between $1/(\varepsilon_n-\varepsilon_f)$ and 'n' in Kawakita's Equation.**

Table 5.3 **Results of Flow properties and Constant *K* of Kawakita's Equation (Mean ± s.d., n=3)**

Formulation/sample	*Angle of Repose (°)*	*Compressibility index*	*Dispersibility*	*Hausner's Ratio*	**K**
TB-ALLP	28.2 ± 0.4	24.6 ± 2.8	20.7 ± 0.2	1.38 ±0.01	0.0166 ±0.17
AMK-ALLP	30.2 ± 0.3	23.3 ± 1.8	20.2 ± 0.4	1.26 ±0.03	0.0193 ±0.23
Inhalac 230	--	--	--	--	0.0215 ±0.22

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