Poster Session 3 – Pharmaceutics

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Study of interactions between polyvinylpyrrolidone and paracetamol

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There are some reports in pharmaceutical literature in which the interactions between polyvynilpyrrolidone (PVP) and various pharmaceutical agents in solid state or in aqueous solution have been investigated (Tros-De-Ilarduya et al 1998; Van-Den-Mooter et al 1998). The objectives of this study was firstly to investigate the effect of PVP on the aqueous solubility of paracetamol and, secondly, to predict the possible interactions between PVP and paracetamol.

Samples of paracetamol (2.5 g) were dispersed in 100 mL water or aqueous solutions containing 0.5, 1, 2, 4 and 8% w/v PVP k30 (Kollidone 30) and were shaken. The concentration of paracetamol in solutions was determined by spectophotometery at 244 nm after 24 h. The binding affinity between paracetamol and PVP in aqueous solution was investigated using dialysis. Aqueous solutions of paracetamol (1×10^{-2} M) containing 0, 4 or 8% w/v of PVP were poured into dialysis tubes with a molecular weight cut-off of 12 000 daltons. These tubes were immersed into the USP dissolution flasks containing 1000 mL distilled water and solutions were stirred at 50 rev min^{-1}. The amounts of paracetamol released from dialysis tube were determined specrophotometrically at 244 nm, every 60 min for up to 15 h. The same experiment was also carried out for theophylline as a control study. It has been reported that there is no binding affinity between PVP and theophylline (Horn & Ditter 1982; Ziller & Rupprecht 1990). The amount of theophylline released from dialysis tube was determined spectrophometrically at 272 nm. The infrared spectra of untreated paracetamol, PVP, and the 1:2 paracetamol/PVP co-precipitate were obtained using a Perkin Elmer FTIR 1600 spectrophotometer.

It was shown that PVP has a major effect on the solubility of paracetamol. The solubility at 25C increased from 14.3 mg mL^{-1} in absence of PVP, to 19.7 mg mL^{-1} in presence of 4% w/v PVP, and to 26.7 mg mL^{-1} in presence of 8% w/v PVP. These results indicate that the solubility of paracetamol in presence of 8% w/v PVP increased more than 1.87 times. The results of dialysis studies revealed that PVP has a retardant action on the diffusion of paracetamol from the dialysis tube, while the diffusion of theophylline through the dialysis tube was not affected by PVP. These results suggested that there was a potential for bonding between PVP and paracetamol. The results also revealed that the nature of interaction between PVP and paracetamol was physical and reversible, and there was no strong binding between PVP and paracetamol. The IR studies of paracetamol/PVP co-precipitate proved that paracetamol and PVP interact via hydrogen bonding. This is expected as PVP contains a recurring carboxyl group, which allows it to hydrogen bond with hydroxyl group of paracetamol.

This study revealed that the aqueous solubility of paracetamol in the presence of PVP increased. This was attributed to formation of a water-soluble complex between PVP and paracetamol. Dialysis studies confirmed the potential of binding between PVP and paracetamol in their aqueous solutions. Infrared spectroscopy indicated that the mechanism of interaction between PVP and paracetamol is via hydrogen bonding.

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The effect of plasticizer type and concentration on characteristics of ethylcellulose matrices prepared by solid dispersion technique

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It has been shown that preparation of a solid dispersion (SD) system using a solvent evaporation method is a valuable technique in the production of inert matrices (Pignatello et al 2001). Investigating the effect of plasticizer type and concentration on drug release from coated sustained-release formulations have been the focus of much research activity (Hutchings & Saker 1994; Saettone et al 1995). The objective of this study was to investigate the effect of plasticizer type and concentration on the release of diclofenac sodium from ethylcellulose (EC) matrices prepared by SD technique.

To prepare SD systems, wieghed amounts of drug and polymer (1:3) were dissolved separately in minimum amount of ethanol. The required amount of each plastisizer (3% or 5% with respect to polymer weight), namely diethylphtalate (DEP), oleic acid (OA) or polyethylenglycol 400 (PEG400), was added to the olymer solution. Then the polymeric soultion was added to the drug solution and stirred. The resulting solution was oven dried at 50°C. The dried thin films were ground and passed through a 120-μm sieve. Flat-faced tablets (10 mm in diameter) of the SD systems, equivalent to 100 mg diclofenac sodium, were compressed on an instrumented single-punch tableting machine at 10 kN compaction force. The crushing strengths of the matrices were measured using a hardness tester 24 h after compaction. Dissolution tests were carried out in a USP dissolution apparatus I. The release profiles of matrices in 1000 mL phosphate buffer pH 6.8 at a rotation speed of 100 rev min^{-1} and at 37 ± 0.5°C were determined by spectrophotometry at 275 nm.

The results showed that drug release was sustained over an 8-h period of dissolution testing for matrices without any plasticizer. Incorporation of plasticizers affected the drug release profile and crushing strengths of the matrices. The effect was dependent on plasticizer type. Addition of 3% DEP increased the crushing strength from 10 ± 0.5 kg for matrices without any plasticizer to 12 ± 0.8 kg for matrices containing DEP and consequently decreased drug release rate. OA decreased the crushing strengths of matrices to 8.5 ± 0.2 kg and consequently increased drug release rate. PEG 400 increased the crushing strengths of matrices to 11.2 ± 0.5 kg but drug release was increased because of the water solubility of this plasticizer. Increasing the plasticizer concentration to 5% did not significantly ($P > 0.05$) affect the crushing strengths of matrices compared with those containing 3% plasticizer. The crushing strengths were 11.5 ± 0.2, 8.2 ± 0.7 and 11.0 ± 0.6 kg for matrices containing 5% DEP, OA or PEG400, respectively. Drug release profiles were also not greatly affected by plasticizer concentration.

This study has shown that incorporation of a plasticizer into the SD system of EC and drug affected crushing strengths of matrices and drug release profiles. The effect was dependent on plasticizer type.

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Formulation and in-vitro evaluation of sustained-release captopril matrix tablets

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Captopril, an angiotensin-converting enzyme inhibitor (ACEI), has an excellent clinical effectiveness in the treatment of hypertension and congestive heart failure (CHF). Up to now, various attempts have been made to make a sustained-release drug delivery system of captopril. One of these systems is known as the

hydrodynamically balanced system. Such a system is useful for drugs well absorbed in the proximal gastrointestinal tract or for drugs that degrade in the intestinal fluid (Khan et al 2000). The aim of this study was to design, formulate and evaluate the in-vitro releasing pattern of floating and bioadhesive sustained-release captopril matrix tablets, with emphasis on using yellow beeswax in the formulations.

Captopril, batch no 492440897 (EGIS, Hungary), HPMC K100M, batch no. MM94120602K (Colorcon, UK), Carbopol batch no BC14074 (Hercules, UK) and yellow beeswax (Merck, Germany) were used. The method of Chan et al (1994) was used for the degradation study of captopril in aqueous solution. Standard convex tablets of 8 mm diameter (300 mg) were made containing 50 mg captopril, and different amounts of HPMC K100M, yellow beeswax, lactose and magnesium stearate by dry granulation method. In-vitro dissolution was carried out in 900 mL HCl 0.1 N, at 37 ± 0.5°C using the USP apparatus I (rotating basket) at 50 rev min^{-1}.

Investigation of the stability of captopril solutions with various concentrations indicated that these solutions are stable in the conditions of the dissolution test (HCl 0.1 N, at 37 ± 0.5°C) regardless of air and light, and there is no need to add an antioxidant agent to the dissolution medium. Among the different tablet formulations which were made, the formulation known as D3 (containing 30% yellow beeswax, 30% HPMC, 16% carbopol and 5% magnesium stearate) showed a suitable releasing pattern and a high production efficiency. During the dissolution test these tablets remained floating.

In the progress of this investigation it was proved that there is a direct relation between tablet hardness and granule production efficiency with the P/W ratio (ratio of powders used in granulation (P) to wax content (W)). On the other hand, it was indicated that there is a reverse relation between buoyancy time of tablets and their hardness.

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Preparation and characterization of albumin microspheres encapsulated with propranolol hydrochloride

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Albumin microspheres (AMS) have received wide attention in recent years due to their specificity, biodegradability, desirable release characteristics and biocompatibility. Propranolol hydrochloride (PLH) is a widely used beta-blocker drug in the treatment of angina pectoris, high blood pressure and migraine prophylaxis. The need for controlled systemic delivery of PLH by some convenient delivery system is well established (Gallo & Gupta 1989).

In this study, PLH-loaded AMS were prepared by a modification in the method described by Karunakar & Singh (1994). Briefly, 30 mL of cottonseed oil was mixed with 10 mL of petroleum ether and stirred for 10 min using a magnetic stirrer at 1000 rev min^{-1} as the oil phase. PLH (4% w/w) was dissolved in bovine serum albumin (BSA) solution (5% w/w) as the aqueous phase. The two phases were mixed together in the presence of a surfactant to form the initial emulsion. This emulsion was then added drop-wise to a known volume of preheated cottonseed oil while stirring on a magnet stirrer at 1000 rev min^{-1} to denature and solidify the AMS. The microspheres were then centrifuged, dried in a vacuum desiccator and refrigerated for further testing.

The microspheres were studied for size distribution using an optical microscope equipped with a micrometer, drug loading by complete dissolution of AMS in acetic acid and analysis of PLH content by a spectrophotometric method. To find out how much of the drug attached to the surface of AMS, a known weight of microspheres was suspended in distilled water and centrifuged at 5000 rev min^{-1} for 15 min and the supernatant was assayed for PLH content as mentioned above. In-vitro release rate of PLH from AMS was determined by using a USP dissolution apparatus and bioadhesive properties using the method described earlier by Ranga Rao & Buri (1989).

The results showed that the prepared AMS had mean diameters in the range 1-25 μm of which more than 50%were below 5 μm. The drug content was found to be 90% w/w with the surface drug being around 25% of the total amount of incorporated drug. Also AMS were noted to possess a good bioadhesion such that about 70% of microspheres remained adherent on the surface mucosa of rat jejunum. The drug release from AMS was shown to be mainly controlled by diffusion and it was found that the release of drug from microspheres exhibited a high initial release (burst effect), followed by a more gradual terminal release. The amount of drug released from microspheres after 12 h was about 70%.

It can be concluded that PLH-loaded AMS manufactured by heat denaturation method can be used as a controlled delivery system for PLH and due to their proper size and good bioadhesive properties, this system can be administered via nasal route which would eliminate the high first-pass metabolism of PLH occurs in the oral route.

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Development of fragile carrier particles in dry powder inhalation

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The purpose of α-lactose monohydrate as a carrier, is to limit the adhesive properties of the active. This is achieved as a consequence of the active preferentially adhering to the carrier surface, ideally preventing segregation but allowing detachment during inhalation (Dunbar et al 1998). To improve detachment and thus performance, a disintegrating surface would be expected to be beneficial. Though this would be difficult with lactose crystals, it is possibly feasible with granules.

Four batches of granules were prepared, on a 1-kg scale, from micronised lactose using a Gral mixer. Batches 1, 2 and 3 were granulated with a 5%w/w lactose solution and batch 4 with ethanol. Modifications were made to the process, to purposefully alter granule strength (Table 1). The granule mixture was screened through a 1-mm screen before drying.

Table 1 Process modifications

Batch	Granulation	Drying
1	4 min	Oven
2	4 min	Fluid bed
3	3 min	Fluid bed
4	3 min	Oven

For comparison, fractions of 200–500 μm were prepared by screening with a sieve shaker (Retsch). The granule strength was compared using the repeat impact machine (Beekman 2000), and the robustness during processing by laser light diffraction (Malvern mastersizer) with a propanol-2 dispersant, following 10 min blending in a tumble mixer (Turbula T2C). Each granule batch was blended as described with di-sodium cromoglicate (DSCG) (1.8% w/w) and deposition studies performed in-vitro, on the twin stage impinger with the Novolizer device (Sofotec) at 60 L min^{-1} for 4 s. The DSCG reaching stage 2 was considered to be the fine particle fraction (%FPF). The lactose on stage 2 was quantified by mixing product solution from stage 2 with anthrone solution (anthrone 0.1% w/w in sulphuric acid) at a ratio 1:2, followed by UV analysis at 625 nm.

The quantity of undamaged crystals after 320 s was 77% for batch 1 and 3% for batch 4. Ranking the batches from strongest to weakest produced the sequence 1 > 2 > 3 > 4. Though the strength varied considerably, laser light diffraction showed that all the batches had sufficient robustness for processing. However, the

anthrone test showed an increasing amount of lactose on stage 2 in relation to granule strength, with values of 1, 5, 9 and 24% for batches 1, 2, 3 and 4, respectively. The granules showed a degree of disintegration, dependent on the strength, which influenced deposition with %FPF of 29.1, 45.8, 51.6 and 61%, respectively, for batches 1, 2, 3 and 4. Therefore, fragile carrier particles must promote active detachment from the carrier. The benefit being an increased amount of active being available for deposition.

These systems can potentially provide more choice in the objective of achieving high and constant deposition in delivering actives to the lungs.

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An assessment of the precipitation potential from intravenous formulations

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Formulations intended for intravenous administration must be free from particulate contamination. This can arise from a variety of sources, including the precipitation of low-solubility active compounds when a solubilised formulation is diluted in the bloodstream after injection. The most common method of increasing the solubility of poorly soluble injectable drugs is by the inclusion of an organic water-miscible cosolvent in the formulation. Cosolvents are reportedly used in 10% of FDA-approved parenteral products.

A more recent approach to improving the solubility of poorly soluble drugs is the use of excipients that physically interact with the active compound by mechanisms such as complexation or micellisation, thus maintaining the compound in a more lipophilic environment. Products containing modified cyclodextrin derivatives, particularly hydroxypropyl-β-cyclodextrin are now reaching the market.

The objective of this study was to develop a dynamic in-vitro precipitation model and use it to compare the potential for model insoluble test compounds to precipitate from traditional cosolvent formulations and formulations containing more novel solubilising agents. Phenytoin sodium and an AstraZeneca development compound X were used as model compounds

The dynamic in-vitro precipiation model used in these studies was based on that developed by Yalkowsky & Valvani (1977). Essentially, the test formulation is 'injected' into simulated blood, which is continuously pumped through the flow cell of a UV spectrophotometer. The absorbance at 540 nm is monitored to detect light scattering due to precipitation. Experimental parameters, such as tubing length and the composition of the simulated blood were investigated and optimised.

The phenytoin sodium formulations shown in Table 1 were prepared at a concentration of 5 mg mL^{-1} and also as saturated solutions. These were 'injected' into the system at a flow rate of 10 mL min^{-1}. The investigation was repeated with saturated solutions of compound X.

Table 1 Precipitation from intravenous formulations, measured by UV absorbance at 540 nm

Vehicle	Average absorbance reading		
	Phenytoin sodium solution 5 mg mL^{-1}	Saturated phenytoin sodium solution	Saturated compound X
40% Dma	0.25	0.5[a]	0.4
40% PEG 400	1.2	1.0	0.3
10% Cyclodextrin	0.001	0.4	0
PEG 400:Ethanol	0.4	1.0	0.2
1% Solutol	0	0.02	0

[a]A saturated solution was not obtained in 40% DMA due to the extremely high solubility in this vehicle

Phenytoin showed a greater tendency to precipitate from 5 mg mL^{-1} formulations containing cosolvents than from the cyclodextrin or Solutol formulations. When saturated solutions were evaluated, a similar trend was observed. Compound X also showed a greater tendency to precipitate from the cosolvent formulations. These data suggest that solubilisers that physically interact with the active ingredient may be preferable to cosolvents, even if the compound solubility is greater in the cosolvent formulation. From a manufacturing standpoint the absence of organic solvents in these formulations is also preferable.

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Surface characterisation of inhalation microparticles: physical and chemical analysis

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Two examples of the application of surface analysis to inhalation microparticles are presented. Levels of adhesion between drug and carrier particles are of critical importance in determining the fine particle yield from dry powder inhalers. Here, Atomic force microscopy (AFM) is used to characterise the interaction forces between an active ingredient (micronised salbutamol particles), lactose carrier and a fluoropolymer (PTFE, used to coat inhaler canisters). In addition, the ability to map the interaction between an active ingredient and a lactose carrier particle is demonstrated. A second example highlights the need to chemically characterise the surface of inhaler components. TOF-SIMS is employed to chemically map an inhaler active ingredient with high sensitivity, revealing the presence of a surface contaminant.

AFM can be utilised to measure the degree and nature of interactions between the inhaler components. This is achieved by attaching the particle of interest to an AFM cantilever, and obtaining force distance curves. Such interaction data can be used to calculate adhesion forces between the immobilised drug microparticle and the substrates of interest. To achieve statistical accuracy at least 100 measurements were recorded for a given tip, and averaged to provide an adhesion measurement. In addition, to allow for variations caused by the geometry of the drug particle, three different tips were employed. The results indicate that a consistent ranking of adhesion of the order salbutamol–lactose > salbutamol–salbutamol > salbutamol–PTFE.

In addition to these localised measurements, a force volume map was obtained between a salbutamol functionalised tip and a large lactose carrier particle. Here, spatial variations in adhesion are observed which may correlate to the known existence of active sites for active particle absorption.

TOF-SIMS characterisation of inhaler microparticles enables chemical characterisation. The total ion image displays the morphology and distribution of the inhaler microparticles. A single particle was selected, and mass spectra were extracted. This data revealed the presence of a surface contaminant (Irgafos 168) in addition to the active ingredient. Retrospective data analysis was used to obtain maps of both the active ingredient and the surface contaminant. From these images the contaminant was shown to be is randomly distributed across the particle surface.

In summary, AFM allows ranking of the interactions between the components, at a single particle level. In this case, the ranking of adhesion obtained (lactose > salbutamol > PTFE) indicates that it is favourable for salbutamol aggregates to disperse onto a lactose carrier in a dry powder inhaler system. Furthermore, it was possible to obtain spatial maps of the variations of adhesion of an active particle across a carrier. These measurements may also be performed with controlled humidity, or under a solution environment. As an example of chemical characterisation, TOF-SIMS is used to image the microparticle composition, and in this case reveals the presence and distribution of a surface contaminant.

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Candidal adherence to novel silicones

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Candida albicans is a harmless commensal of the digestive system, vaginal tract and the oral cavity. However, candiduria, although extremely rare in healthy patients, is common in hospitalised patients. *C. albicans* is the causative organism in more than 50% of cases (Sobel 1999). In 5–15% of patients with symptomatic fungal urinary tract infection, funguria is accompanied by fungemia (Krcmery et al 1999). *C. albicans* is a dimorphic organism capable of existing in a blastospore phase and a pseudomycelial phase. It is this latter form that is thought to facilitate adherence, colonisation and subsequent tissue invasion. The increasing use of indwelling urinary catheters presents an interface for candidal colonisation in the urinary tract. This study investigated candidal adherence to novel silicone biomaterials and the activity of antifungal drug-incorporated silicones. All materials manufactured have the ability to produce a lubricious and renewable surface, mimicking the mucosal epithelium of the urinary tract.

Silicones were produced by mixing silicone base with a crosslinking agent, catalysed by a tin catalyst. A control silicone was produced using a Tetra(propoxy)silane crosslinker and the novel silicone using a high molecular weight silane. All materials were cured over a period of 2 min at 80°C. Antifungal materials were produced by the incorporation of antifungal drug into the silicone mixture before curing.

Candidal adherence was investigated using *C. albicans* isolated from microbial biofilm. Silicone discs were suspended in yeast culture (approx. 5×10^6 cfu mL^{-1}) in shaking conditions (100 rev min^{-1}, 37°C). After 4 h the samples were washed to remove non-adherent candida. Adherent candida were dislodged by mild sonication and vortexing and plated onto sabourand dextrose agar. Colony forming units were enumerated after an incubation period of 24–48 h at 37°C.

To examine antifungal materials seeded plates of *C. albicans* (approx. 1×10^5 cfu mL^{-1}) were prepared and a silicone disc containing antifungal drug added to the surface of the agar. Following a period of incubation (24 h, 37°C) zones of inhibition were measured. The disc was transferred to fresh seeded plates on subsequent days to examine the persistence of antifungal activity.

Table 1 Adherence to silicone

Material	Adherence (cfu mL^{-1})
Control silicone	$7.98 \times 10^3 \pm 5.10 \times 10^3$
Novel silicone	$9.32 \times 10^2 \pm 7.95 \times 10^2$

Novel silicones show an approximate nine-fold decrease in *C. albicans* adherence after a four-hour period of contact ($p < 0.05$). Antifungal silicones maintained persistence of activity for up to 7 transfers on fresh seeded plates, producing zones of inhibition greater than at least 15mm on each transfer. In conclusion, a novel silicone has been produced which shows superior resistance to candidal adherence than control silicone and that can produce antifungal materials that demonstrate persistence of antifungal activity.

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Use of experimental design to investigate critical parameters for a dry powder inhaler (Ultrahaler) product

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During the development of drug products, critical parameters affecting product performance need to be identified. Early identification of critical experimental parameters that affect product performance is key for successful and timely product development. Use of experimental design provides a tool to support this requirement.

To optimize the performance of a new chemical entity (NCE) delivered by the Ultrahaler, three parameters, lactose grade, fill weight and vibration amplitude (process parameter) were investigated using the experimental design. The product displayed a gradual reduction in the weight of product emitted throughout the device life; which is un-desirable. The product fill weights of 2.20 g and 1.29 g will deliver 120 and 60 actuations per device, respectively. The target for the commercial product is to deliver 120 actuations.

A full factorial design of the three critical parameters at two levels was prepared as shown in Table 1. Ultrahalers were manufactured as listed in the matrix.

Table 1 Experimental design matrix and results

Experiment number	Lactose grade in blend	Fill weight (g)	Vibration amplitude (G)	Mean Δ EW (mg)
1 & 2	Type A	1.29	8.5 & 3.0	0.25
3 & 4	Type A	2.20	8.5 & 3.0	−2.59
5 & 6	Type B	1.29	8.5 & 3.0	0.77
7 & 8	Type B	2.20	8.5 & 3.0	−0.30

Product performance was assessed by determination of the emitted weight through device life, for 6 devices per experiment, at a flow rate of 60 L min^{-1}. The change in emitted weight through device life (Δ EW) was calculated. The aerodynamic particle size distribution (PSD) was determined, using the Andersen Cascade Impactor, from 9 actuations, taken from 3 devices from experiments 3 and 7. The PSD was measured as different lactose grades can effect drug particle distribution (Ellison et al 2001).

The mean Δ EW results in Table 1 demonstrate that 2.20 g fill weight Ultrahalers, containing type B lactose blend display a lower reduction in emitted weight throughout device life than those with type A lactose. Ultrahalers of 1.29 g fill weight indicate marginal increase in mean Δ EW through life and their performance based on lactose grade is not significantly different ($P = 0.0954$). The mean aerodynamic PSD for Ultrahalers containing type A lactose and type B lactose blends were 38.5 % and 40.0 %, respectively and the difference was not significant ($P = 0.3538$). The vibration amplitude did not have a significant effect on product performance ($P = 0.5485$).

In conclusion, the parameters selected were, lactose type B, fill weight of 2.20 g and vibration amplitude of 8.5 G to deliver a product with 120 actuations. These results demonstrate that application of the experimental design concept facilitates logical evaluation of critical parameters, to resolve issues and provide direction during development.

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