Pharmaceutical Technology

203
Effect of ageing on drug release from poloxamer solid dispersions

A. Kattige and G. Rowley[1]

Department of Pharmacy and Pharmacology, University of Bath, Bath BA2 7AY and [1]10 Greystoke Avenue, Ashbrooke, Sunderland SR2 9DX, UK A.Kattige@yahoo.co.uk

The use of solid dispersions to increase the dissolution rate of drugs with poor aqueous solubility is well documented (Okonogi et al 1997). However, the commercial application of solid dispersion technology is limited and there are very few marketed preparations, probably due to stability (Markovich et al 1997) and processing problems. In a solid dispersion, the drug may be present as an unstable polymorph, amorphous state or molecularly dispersed. Thus decrease in dissolution rate on storage could be due to crystallization of the drug, drug particulate coarsening or structural changes in the carrier, and consequently the behaviour of drug/carrier solid dispersions on storage should be investigated. The aim of this study was to investigate the effect of ageing of poloxamer solid dispersions on storage at 25°C using isoniazid as a model drug with low polymer solubility. 10% w/w isoniazid/poloxamer (Synperonics F38, F68, F88) solid dispersions were prepared by mixing under vacuum at 70°C and filled (70°C) into hard gelatin capsules (size 1) using the Hibar capsule filler. Dissolution tests were performed 2 hours after preparation and after 7 days, 1, 3 and 6 months storage at 25°C. Using BP dissolution apparatus I with basket stirring rate of 100 rpm, the drug concentration in solution was determined spectrophotometrically at 262 nm. 10% w/w isoniazid/poloxamer solid dispersions exhibited good capsule filling properties and disperse phase uniformity at 70°C. In addition, the solid dispersions stored for up to 6 months at 25°C exhibited no significant difference ($P > 0.05$) between mean $T_{50\%}$ values ($n = 6$) for isoniazid dissolution (Table 1). The majority of the drug was a particulate dispersion and consequently there was no significant crystallization of the drug on ageing due to the low (1.8% w/w) drug solubility in the poloxamer melt. The initial $T_{50\%}$ values for F38, F68 and F88 isoniazid formulations were 15, 31 and 40 minutes respectively and since the particle size distribution of isoniazid within the three poloxamers remained similar, the reduction in drug release was attributed to a reduced dissolution rate of carrier with increased molecular weight F88 > F68 > F38. It was concluded that the solid dispersions formed a stable system with unchanged drug dissolution rate for up to 6 months, confirming the suitability of poloxamers as thermosoftened carriers for liquid-fill hard gelatin capsules. Furthermore, the results indicate that the structure of the polymer/particulate dispersion can play a significant role in controlling the release of drug from the semi-solid matrix and is a function of the poloxamer molecular weight.

Table 1 $T_{50\%}$ of isoniazid from 10%w/w isoniazid/poloxamer dispersions (n = 6)

	Mean $T_{50\%}$ (% cv) (min)		
	F38	F 68	F88
2 hours	15 (7.5)	31 (3.2)	40 (2.5)
7 days	15 (9.9)	31 (7.3)	40 (2.5)
1 month	16 (10.8)	34 (2.9)	39 (2.6)
3 months	14 (6.5)	33 (4.6)	42 (1.4)
6 months	12 (4.6)	34 (1.7)	41 (2.8)

Markovich, R. J. et al (1997) *Pharm Biomed Anal*. **16**: 661–673
Okonogi, S. et al (1997) *Int. J. Pharm*. **156**: 175–180

204
Formulation studies on a type III fibronectin domain pair

P. Pereira, P. Gellert and C. F. van der Walle

Pharmaceutical Sciences, University of Strathclyde, 27 Taylor St, Glasgow, UK chris.walle@strath.ac.uk

Physical and chemical instability of proteins during formulation remains a major obstacle in the achievement of an acceptable shelf life and maintenance of biological activity. Here, we evaluate the affect of stabilisers and pH on the central cell binding domain of fibronectin (FN), a β-sandwich domain pair belonging to the immunoglobulin structural superfamily, in the liquid and solid states. Specifically, the protein is a mutant of the 9^{th}-10^{th} FN type III domains (termed $^{9-10}$FIII-P), in which a Leu^{1408} is substituted for Pro, which increases conformational stability and biological activity (Van der Walle et al 2002). The stabilisers added, sucrose and PEG 6000, were chosen as representative of protein lyoprotectants and cryoprotectants, respectively (Wang 1999, 2000). We investigated the affect of pH on $^{9-10}$FIII-P conformational stability to thermal denaturation and aggreagation. Conformational stability of $^{9-10}$FIII-P to thermal denaturation was monitored by differential scanning calorimetry (DSC) in the liquid state and circular dichroism (CD). Protein concentrations were kept between 0.05 ± 0.012 mM at pH values of 4, 7, 8 and 10. Sucrose was added at concentrations of 0.05, 0.28 and 0.5 M, and PEG 6000 at 1, 3 and 5% (w/v). DSC scans were performed over a temperature range of 20–80°C (at 60°C/h) and the reversibility of thermal denaturation evaluated by relating the shape of the peak of heat capacity curve to the van't Hoff enthalpy. Protein refolding was only observed at pH 4, irrespective of sucrose or PEG addition, suggesting that that pH plays a dominant role in maintaining conformational stability. At pH 4, increasing concentrations of sucrose increased the melting temperature (Tm) of $^{9-10}$FIII-P from 59.44 to 62.09°C, although partial loss of protein conformation was found on repeated heat-cool cycles. Increasing concentrations of PEG decreased the Tm suggesting that PEG should be avoided in liquid formulation of $^{9-10}$FIII-P. CD analysis of $^{9-10}$FIII-P secondary structure carried out at pH 4 in the absence of sucrose, for temperatures ranging from 4 to 79°C, showed a loss of antiparallel β-sheet structure while increasing other non-classified structure at temperatures above 54°C, the structural changes being irreversible. The same CD analysis but in the presence of 0.5 M sucrose, showed that $^{9-10}$FIII-P maintained antiparallel β-sheet structure up to 64°C, although some structural loss was observed on repeated heat-cool cycles. The CD data therefore corroborated the DSC data, showing that sucrose maintained $^{9-10}$FIII-P conformation during thermal denaturation. Studies were also made to evaluate the same formulation variables on $^{9-10}$FIII-P stability on the solid state. DSC analysis of $^{9-10}$FIII-P in solution below 0°C gave a glass transition temperature for the frozen liquid (Tg') of −52°C, typical of other proteins. Lyophilisation of $^{9-10}$FIII-P in the presence and absence of sucrose and PEG, followed by rehydration and testing of biological activity via inhibition of cell spreading analysis, showed that biological activity was equivalent to non-lyophilised $^{9-10}$FIII-P. This suggests that the immunoglobulin β-sandwich fold of $^{9-10}$FIII-P is conformationally stable to stresses experience during the freezing and drying.

Van der Walle, C. F. et al (2002) *Protein Engineering* **15**: 1021–1024
Wang, W. (2000) *Int. J. Pharm*. **203**: 1–60
Wang, W. (1999) *Int. J. Pharm*. **185**: 129–188

205
Electrostatic charge measurement in formulation and process design

K. G. Pitt, H. Watanabe[1] and M. Ghadiri[1]

Merck Sharp and Dohme, Hertford Road, Hoddesdon, Herts EN11 9BU and [1]Institute of Particle Science and Engineering, University of Leeds, LS2 9JT, UK kendal_pitt @merck.com

Table 1 Triboelectric series: material versus stainless steel

Material	Charge (nC/g)
Drug A	+4
Drug C	± 0
Microcrystalline cellulose (MCC)	+1
Drug B	−4
Lactose monohydrate	−5

Powder handling forms an important part of the production of oral pharmaceutical solid dosage forms such as tablets and capsules. Pharmaceutical processing has a number of powder handling operations, such as milling, sieving and powder transfer by gravity or by pneumatic conveying. During these powder handling operations the particles will make frequent contact with other particles and with equipment surfaces. Hence during any of these operations there is ample opportunity for electrostatic charge generation to occur due to this triboelectrification, which can subsequently cause a number of problems. This can manifest itself in processing difficulties such as powder transfer problems in conveying or in end product quality for example poor content uniformity or poor tablet weight uniformity. However, these charging effects of pharmaceutical powders can also be exploited to assist in product design. For example, selection of excipients or carriers that charge negatively compared with a positively charged drug can be used to produce extremely stable low dose ordered mixtures for tablet compression or capsule filling. In the work described here particle charge measuring equipment (Watanabe et al 2005) was designed to record the size and polarity of charge on processed powders and pellets. The electrostatic charging potential of excipients and Active Pharmaceutical Ingredients (API) was measured against typical pharmaceutical surfaces such as stainless steel. This enabled the differing charging potentials of the materials to be ranked so as to construct a triboelectric series for these powders. See example in Table 1. The API for this study were specifically selected as they had also been formulated as binary capsule mixtures of drug and excipients. Hence formulation and processing characteristics were known such as flowability and content uniformity. In addition scanning electron microscope (SEM) images were taken of the binary mixtures as well of the API and excipients alone. The triboelectric series was able to predict and characterise the particle interactions seen under SEM and in processing. For example oppositely charging particles (Drug A and Lactose Monohydrate) attracted one another and formed stable ordered mixtures resulting in capsule formulations with low content uniformity of 2% RSD. Similarly charging particles (Drug B with Lactose Monohydrate) repelled one another resulting in capsule formulations with a high content uniformity of 6% RSD. The size of the charging is also important in characterising the particle interactions. For example Drug C and MCC had low or zero charges and did not form any strong association or repulsions resulting in a random mixture with a low content uniformity of 2% RSD. In addition the equipment was used to measure the charging potential developed during pellet coating and packaging of capsules thereby assisting in characterisation of these processes.

Watanabe, H. et al (2005) *Powders and grains 2005*. Stuttgart, 1257–1261

206
The generation of spherical crystalline particles via a novel particle engineering process

C. Pitchayajittipong, J. Shur and R. Price

Pharmaceutical Surface Science Research Group, Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, UK R.Price@bath.ac.uk

Active pharmaceutical ingredients used in many solid pharmaceutical dosage forms require processing to achieve defined physicochemical properties, to ensure the development of stable and efficacious formulations. Mechanical milling remains the most widely employed technique in the pharmaceutical industry for obtaining the required particle size characteristics of drug and excipient materials. This method employs a vast amount of energy to induce particle attrition to reduce particle size, but can also lead to disorder of the surface physico-mechanical properties of crystalline materials, with the formation of thermodynamically unstable domains on the particle surface (Buckton 1997). The production of mesoscopic crystalline drug particles with defined size, shape and morphology via a novel particle engineering strategy (the solution atomisation and crystallisation by sonication (SACS) process) shows great promise in developing robust crystalline particles for solid-dosage forms (Kaerger & Price 2004). The SACS process consists of defined stages, which begins with generation of aerosol droplets of a suitable solution of the drug, with defined droplet size distribution using an appropriate atomiser. Follow-

ing atomisation, the carrier solvent evaporates, resulting in the formation of highly supersaturated droplets, which are then collected in a crystallisation vessel containing an anti-solvent of the drug. The final step is the application of ultrasonic energy to induce homogeneous nucleation and crystal growth. In this study, a 2^n factorial experimental design was implemented, to investigate the affect of using different carrier solvents and varying separation distance between the atomiser and collection vessel on the percentage yield, particle size distribution and crystallinity of SACS produced materials. Briefly, solutions of budesonide were prepared in either acetone or ethanol, which were atomised at varying lengths from the collection vessel. Scanning electron micrographs revealed that the SACS produced particles were spherical in shape, which suggests the formation of particles on crystallisation of the supersaturated aerosol droplets. Results suggest that the type of carrier solvent employed had a significant affect ($P < 0.05$) on percentage yield, where on using ethanol the percentage yield was significantly lower in comparison to yields obtained when using acetone. There were no significant second-order interactions between separation distance and carrier solvent on percentage yield. However, second-order interaction between type of carrier solvent and separation distance between atomiser and collection vessel significantly ($P < 0.05$) affected the particle size of SACS produced budesonide. Centre-points used in the study confirmed that these interactions followed a linear relationship. Therefore, by employing an appropriate carrier solvent, the separation distance may be varied to achieve particles with defined size. DSC thermograms of SACS budesonide particles from both acetone and ethanol at all separation distances showed the same endothermic transition at approximately 260°C, which corresponds to the melting point of the crystalline solid, suggesting that the particles were predominantly crystalline. The study highlights the potential benefit of the SACS process in producing crystalline particles of defined morphology and size, which may be manipulated to suit various solid-dosage forms.

Buckton, G. (1997) *Adv. Drug Deliv. Rev*. **26**: 17–27
Kaerger, J. S., Price, R. (2004) *Pharm. Res*. **21**: 372–381

207
Preparation of IgG coated microcrystals using a novel three-line continuous flow coprecipitation system

J. Partridge, J. Vos, C. Lyle and B. D. Moore

Xstalbio, University Avenue, Glasgow and [1]University of Strathclyde, Cathedral Street, Glasgow, UK b.d.moore@strath.ac.uk

The production of protein-coated microcrystals (PCMC) can be achieved in the laboratory via a simple batch precipitation process. We have explored the use of continuous flow coprecipitation with the aim of obtaining a manufacturing process better suited to scale-up. Bovine IgG (Lampire Biological Lab, Pipersville, USA) and valine, were coprecipitated into propan-2-ol using both two-line and three-line strategies, to produce IgG-valine PCMC. In the two-line system, IgG and valine were pre-blended in a single vessel prior to coprecipitation. In the three-line system, the IgG and valine were introduced independently from separate vessels; in which the pH of each solution could be controlled independently. Subsequently, IgG and valine were coprecipitated by rapid mixing into excess propan-2-ol. After coprecipitation the product was harvested by filtration and air-dried. The various PCMCs samples were reconstituted into buffer, and the relative amounts of soluble bovine IgG bound to the crystals determined. A clear advantage of using the three-line system is that the protein solution can be held under different storage conditions from the excipient. This includes temperature, pH, buffer constituents and stabilizers. For the experiment with IgG a theoretical protein loading of 7.5% w/w was expected. After reconstitution it was demonstrated that the two-line system produces PCMCs with 6.6% w/w of soluble IgG (88% IgG recovery), while the three-line system produced PCMCs that retained 7.7% w/w of soluble IgG (103% IgG recovery). These results show that for bovine IgG a three-line coprecipitation strategy can provide significant improvements over the two-line strategy. In this case it produces PCMCs that contain ~12% more soluble IgG. The reason for the improvement is thought to arise from the better control the three-line system offers over the protonation state of IgG during the coprecipitation process. Bovine IgG PCMCs were produced using two-line and three-line continuous flow coprecipitation strategies. It was demonstrated that for this protein the three-line system produces a superior PCMC formulation.

208
The use of a novel polyamine based amphiphilic polymer to enhance the aqueous solubility of hydrophobic drugs

M. Perry and W. P. Cheng

School of Pharmacy, The Robert Gordon University, Schoolhill, Aberdeen, AB10 1FR, UK w.p.cheng@rgu.ac.uk

Table 1 Griseofulvin recovery analysed by a UV Spectrophotometer

Polymer concn (mg mL^{-1})	Griseofulvin recovered (μg mL^{-1}) at polymer:drug weightratio of				
	1:2	1:1	2:1	5:1	10:1
1	55.1 ± 1.3	36.3 ± 0.8	20.3 ± 0.7	25.1 ± 3.4	40.1 ± 0.7
2	251.5 ± 1.6	184.1 ± 2.2	130.8 ± 3.2	102.7 ± 0.6	77.6 ± 1.2

Ata are means ± s.d., n = 3.

Hydrophobic drugs present a challenge to the pharmaceutical industry as poor aqueous solubility hinders the drugs to be given intravenously and also limits oral drug bioavailability. Traditional technologies such as cyclodextrin, organic solvents, low molecular weight surfactants and emulsions have been utilised to improve drug aqueous solubility (Cheng et al 2006). Today, the use of amphiphilic polymers as drug carriers for poorly soluble drugs has gained much attention because of the diversity, versatility and biocompatibility of these polymers. We reported previously on the synthesis of a new polyallylamine (PAA) based amphiphilic polymer and its ability to form nano self-assemblies that can encapsulate hydrophobic probes in aqueous media (Perry & Cheng 2006). Here, we set out to investigate the potential of this amphiphilic polymer in solubilising a model hydrophobic drug. The PAA amphiphile was synthesised and characterised as previously described (Perry & Cheng 2006). The modified 15 kDa PAA consists of 5 mol% cholesteryl groups and 45 mol% quaternary ammonium moieties. Solubilisation studies were carried out using griseofulvin, a hydrophobic drug. Self-assembled polymer aggregates were prepared by probe sonication in distilled water. Drug loading was then achieved by probe sonicating the drugs in the presence of polymer aggregates in distilled water. Polymer-drug solutions with varying polymer:drug weight ratios were prepared (Table 1). The solutions were then filtered (0.45 μm) and the filtrates were dissolved in methanol and subsequently analysed using a UV-visible spectrophotometer. The aqueous solubility of griseofulvin was determined by sonicating excess drugs in distilled water. The solution was then filtered and analysed as described earlier. A griseofulvin calibration curve was prepared using various standard solutions (1–30 μgmL^{-1}, $R^2 = 0.993$). The best formulation was sized with a photon correlation spectroscopy. All filtered polymer-drug solutions gave rise to clear, micellar liquids. At low polymer concentration 1 mg mL^{-1}, the aqueous solubility of griseofulvin did not increase compared with the intrinsic solubility (48.3 ± 1.0 μg mL^{-1}). As anticipated, at higher polymer concentration 3 mg mL^{-1}, an increase in the drug solubility was observed at all polymer: drug weight ratios indicating the incorporation of griseofulvin in the polymer aggregates (Table 1). The drug loading concentration is also a paramount factor in determining the level of drug incorporation, where an increase in drug recovery was detected at higher drug loading concentrations (Table 1). At polymer concentration 3 mg mL^{-1}, the maximum drug encapsulation was achieved at polymer: drug weight ratio of 1:2, which produced a clear micellar solution with a particle size of 124 nm. In conclusion, the novel PAA based amphiphilic polymer is able to improve the solubility of griseofulvin up to 5-fold demonstrating its potential as a new drug delivery system for hydrophobic drugs. Further investigations using higher polymer concentrations will be carried out to determine the maximum solubilising capacity of the polymer.

Cheng, W. P. et al (2006) *Biomacromolecules*. In press
Perry, M., Cheng, W. P. (2006) *Proceedings of 33rd CRS Annual Meeting*. Submitted

209
Preparation and evaluation of new co-processed directly compressible excipient of lactose and colloidal silicon dioxide

N. K. Yadav, D. C. Bhatt, R. Dass and N. K. Langyan[1]

Depatment of Pharmaceutical Sciences, Guru Jambheshwar University, Hisar, Haryana and [1]Jubilant Organosys Ltd. R & D center Noida, Utter Pradesh, India nk.yadav@yahoo.co.in

Impalpable Lactose (Pharmatose 200 M) is used as diluent only for wet granulation process, because of its poor flow properties. Colloidal silicon dioxide (Aerosil 200) used as glidant in low concentration to increase the flow of powder blend. Spray drying is a suitable method for preparation of co-processed excipients. Until now co-processed excipient of Lactose and Aerosil is not available. Preparation of a new co-processed excipient, with the use of spray drying process suitable for direct compression. Evaluation of the flow property associated with new co-processed excipi-

Table 1 Comparison of different parameters

Excipients	Carr's Index	Hausner Ratio	Angle of Repose
DCL-11	16.8	1.51	34.2
Pharmtose 200 M	36.95	1.62	47.22
Physical mixture of Pharmtose and Aerosil	38.55	1.68	43.07
Co-processed Excipient	15.2	1.35	33.5

ent by comparing with other different grades of Lactose using suitable parameters. Different concentrations of Lactose monohydrate (Pharmatose 200M, DMV Pharma) and Aerosil 200 (Degussa) were taken. Spray drying of two above said excipients were taken in lab scale Spray Dryer (Labultima, LU-222) by dissolving the Pharmatose 200M in the purified water at 50–55°C and Aerosil 200 was dispersed in it with the help of magnetic stirrer. The spray drying parameters were adjusted in term of flow and compression of the product. The inlet temperature was maintained at 120°C, aspirator was fixed at –140 mm of WC. The feed pump speed was at 5 rpm, with a nozzle diameter of 2.0 mm and outlet temperature was 55°C. Dummy tablets were prepared using 16 station rotary tableting machine. Plain lactose monohydrate, its physical mixture with Aerosil and spray dried product of lactose and Aerosil were characterized on the basis of following parameters. Particle size distribution by Malvern (Mastersizer 2000, U. K); Compressibility Index; Hausner Ratio; Loss on drying; Angle of Repose; Time of flow and effect of addition of lubricant to time of flow; Bulk and Tapped density by USP specification apparatus; Confirmation of polymorphism by polarized light microscope (Leica, Germany); DSC; X-RD. The results of different parameter obtained from plain lactose, its physical mixture with Aerosil and spray-dried product were compared in Table 1. Particle size distribution of spray-dried product is narrower than the physical mixture. Dummy tablets from co-processed excipient, plain lactose and its physical mixture were prepared by keeping whole parameters constant. The values for crushing strength were 11, 8 and 8.5 kps, respectively. The values for disintegration time were 60, 45 and 50 s, respectively. DSC study revealed that no chemical interaction between Lactose and Aerosil. X-RD pattern signifies the presence of some amorphous form of Lactose. From the above study it was concluded that flow properties of the spray-dried product is good as compared with other non-processed excipients and suitable for direct compression. Reduced Compressibility index and Hausner ratio signifies better flow of the product. Presence of small amount of amorphous form revealed the higher compressibility and faster dissolution. Best results were obtained using 1:0.1 ratio of Lactose and Aerosil.

210
Mechanical and release behavior of ibuprofen pellets based on Eudragit RL plasticised with triethylcitrate

F. Sadeghi, M. R. Abbaspour, F. Tayarani and H. Afrasiabi Garekani

School of Pharmacy and Pharmaceutical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran fatemehsadeghi@yahoo.com

In our previous study we showed that ibuprofen pellets with different drug loadings could be successfully prepared using Eudragit RS and/or RL polymers along with Avicel in their formulation (Abbaspour et al 2005). In this study the possibility of replacing Avicel with rate retarding polymer of Eudragit RL in production of ibuprofen pellets with 60% drug loading and its influence on mechanical and release properties of pellets were evaluated. In addition the effect of inclusion of plasticizer in pellet formulation and curing of the pellets on these properties were also studied. Pellets containing 60% ibuprofen, 2% PVP (as binder) and 38% excipient (Avicel and/or Eudragit RL) were prepared using extrusion spheronization process. The percent of Eudragit RL in formulation was 7.6, 15.2, 22.8, 30.4 and 38%. For those pellets containing 22.8, 30.4 or 38% Eudragit RL, 1% w/w triethylcitrate based on Eudragit content was added as plasticizer to aid process of extrusion spheronization. The resulted pellets were evaluated for their size distribution, crushing strength, elastic modulus and drug release rate. The effect of curing of the pellets at 60°C for 24 h was also investigated on these properties. It was shown that increasing amount of Eudragit RL in pellet formulation resulted in extrudates which did not have suitable consistency. In formulations with 22.8, 30.4 and 38% Eudragit RL proper extrudates were not formed. Addition of plasticizer into formulations containing 22.8 and 30.4% Eudragit RL facilitates the process of extrusion spheronization and proper extrudates were formed. However formulation with 38% Eudragit RL and no Avicel did not form extrudates even in presence of plasticizer. Increase in amount of Eudragit RL resulted in decrease in crushing strength and elastic modulus of pellets. Pellet behavior under the compression force was changed due to plasticizer addition so that pellets containing plasticizer showed plastic deformation. The presence of plasticizer also decreased the elastic modulus of the pellets. Crushing strength and elastic modulus of pellets containing more than 7.6% Eudragit RL increased after curing. This effect was attributed to the coalescence of polymer chains following curing. The mean dissolution time of pellets decreased slightly with increasing Eudragit RL in pellet formulation. However, plasticizer addition prolonged the mean dissolution time. Curing dramatically increased the MDT of pellets containing Eudragit RL. In conclusion, replacement of Avicel with Eudragit RL in pellet formulation changed the mechanical properties of the pellets but did not profoundly affect drug release rate from uncured pellets. Curing of pellets containing Eudragit RL caused dramatic changes in mechanical behaviour of the pellets and decreased drug release rate. Presence of plasticizer facilitated the process of extrusion spheronization, affected mechanical properties of the pellets and decreased the release rate of drug from uncured pellets but did not have any effect on release rate of drug from cured pellets.

Abbaspour, M. R. et al (2005) *Int. J. Pharm.* **303**: 88–94

211
Ion exchange resins: improving palatability without compromising bioequivalence

T. B. Ernest, D. P. Elder, L. G. Martini[1] M. Roberts[2] and J. L. Ford[2]

GlaxoSmithKline Research & Development, Ware, Hertfordshire, SG12 0DP, [2]GlaxoSmithKline Research & Development, Harlow, Essex, CM19 5AW and [3]School of Pharmacy and Chemistry, Liverpool John Moores University, Liverpool, L3 3AF, UK terry.b.ernest@gsk.com

Oral aqueous solutions or suspensions are the most common types of dosage form used for paediatric and geriatric patients. Appropriate drug substance palatability is required to help ensure patient compliance. Ion exchange resins may be used for taste masking ionisable drugs (Hughes 2004; Sohi et al 2004; Elder 2005). Two types of exchange resin, Amberlite IRP69 and Amberlite IRP88 have been evaluated to assess the impact of the drug-resin complex on the bioavailability of a hydrochloride salt of a novel heterocyclic amine. The drug substance is extremely bitter tasting, has an aqueous solubility of 4.9 mg/mL, pK_a of 9.9 and is ionised across the physiological pH range. Amberlite IRP69 is a strong cation exchange resin comprising a sulphonic acid moiety ($pK_a < 1$) bound to a styrene/divinylbenzene copolymer. Amberlite IRP88 resin comprises a carboxylic acid moiety ($pK_a \sim 4$) bound to a polymethacrylic acid/divinylbenzene copolymer. Two in-vivo experiments were conducted to determine the effect of exchange resin type on the bioavailablity of the drug-resin suspension compared with a tablet. Study 1 compared a standard suspension prepared using Amberlite IRP69 with a tablet. Study 2 compared a standard suspension prepared using Amberlite IRP88 at two drug:resin ratios, with a tablet. All formulations contained 20 mg of drug substance. Table 1 shows a significantly reduced C_{max} and $AUC_{0\text{-inf}}$ for the Amberlite IRP69 drug-resin suspension compared to the reference tablet. This is due to the basic drug binding very strongly to the strong cation exchange resin. In Study 2, in-vivo data was comparable between the Amberlite IRP88 suspension and the tablet. Data for the standard suspension containing a drug:resin ratio of 1:2 was most comparable with the tablet. Finally, a third study was undertaken using clinical doses (Table 2) where the data demonstrate bioequivalence in accordance with regulatory guidelines. Weak ion exchange resins can be used to form drug resin suspensions that overcome the problems of poor drug palatability without compromising bioavailability.

Table 1 In-vivo data comparing a suspension using a strong exchange resin and a suspension using a weak exchange resin, with a conventional tablet

Mean PK parameter	Study 1 (n = 8)		Study 2		
	Tablet	Suspn	Tablet (n = 6)	Suspn (1:1) (n = 3)	Suspn (1:2) (n = 5)
C_{max} (ng/mL)	14.36 (8.72)	7.14 (4.59)	10.89 (8.24)	8.48 (7.86)	9.36 (7.25)
T_{max} (h)	6.52 (0.91)	7.74 (1.67)	6.11 (2.67)	5.33 (2.18)	5.11 (1.69)
$AUC_{0\text{-inf}}$ (ng.h/ml)	346 (266)	180 (164)	247 (266)	179 (164)	181 (164)
T(h)	16.1 (6.1)	13.9 (5.2)	17.6 (6.1)	22.6 (5.2)	16.3 (5.2)

Standard deviation is shown in brackets.

Table 2 In-vivo data comparing Amberlite IRP88 drug-resin suspension (drug: resin ratio 1:2) with a reference tablet formulation in a regulatory bioequivalence study at clinical dose of 30 mg

PK Parameter (n = 47)	Tablet (T)	Suspension (S)	Ratio of point estimates (S/T)
Mean C_{max} (ng/mL)	40.68 (23.17)	42.16 (24.59)	1.01
Median T_{max} (h)	6.0 (range 2.0–18.0)	4.0 (range 0.0–14.0)	—
Mean AUC_{0-24} (ng.hour/mL)	677.7 (441.2)	736.2 (462.2)	1.08
Mean C_{min} (ng/mL)	24.29 (19.03)	26.43 (18.65)	—

Standard deviation is shown in brackets

Elder, D. P. (2005) *J. Chem. Education*. **82**: 575
Hughes, L. (2004) *Business Briefing: Pharmagenerics* 2004
Sohi, H. et al (2004) *Drug Dev. Ind. Pharm*. **30**: 429–448

212
Prediction of dry powder dispersion performance from blending studies using budesonide as model drug

I. Y. Saleem and H. D. C. Smyth

Advanced Drug Delivery Lab, College of Pharmacy, University of New Mexico, Albuquerque, USA ImSaleem@Salud.unm.edu

Pharmaceutical Dry Powder Inhaler (DPI) formulations are binary mixtures of drug (1–5 μm) and carrier particles (~50–150 μm) in the size range which are subject to a multitude of interparticulate forces. This type of formulation is termed an interactive mixture due to the ability of carrier particles to modulate the interactive forces between drug particles. Understanding and being able to predict interparticulate forces in these systems is a major focus of research that could lead to the ability to predict DPI performance. The approach presented here is to investigate interparticulate forces in DPI formulations by studying dynamic powder mixing phenomena. Milled (VMD 70.23 μm) and Spraydried lactose (VMD 69.83 μm) (Lactose New Zealand) carrier particles were prepared using optimized sieving methods (sieve fraction between 63 μm and 90 μm). Particle size characteristics were determined using a Sympatec Helos laser diffraction instrument (Sympatec GmbH, Germany) and a JEOL 5800LV Scanning Electron Microscope operated in low pressure mode. Blending studies were performed by initially preblending 20 mg of micronized budesonide (Spectrum Chemicals and Laboratory Products, USA) with 1 g of sieved Lactose (Spraydried n = 3, milled n = 3) by geometric dilution in a glass vial (6 ml). The preblended powders were blended using an orbital blender (Turbula mixer, WAB, Switzerland) at 42 rpm and evaluated (n = 4) at multiple time points up to 30 min for sample variance. Dispersion and powder aerosolisation performance was determined from cascade impaction studies using a Next Generation Impactor (NGI) (MSP, USA) as per USP/NF guidelines (USP 26, 2003). Budesonide content was analysed using a validated HPLC method (Gupta et al 2006) to determine blending uniformity and to quantify the drug deposition patterns within the NGI, with the fine particle fraction (FPF) determined as the fraction of deposited drug less than 5 μm aerodynamic diameter. Generally, blend uniformity improved as a function of time. At 30 min the uniformity (% coefficient of variance) of the blends was less than 10% (Spray-dried 1.99%, Milled 5.57%). A mixing rate constant was derived from logarithmic decay functions fitted to the data. Spraydried lactose had a higher rate constant than milled blends, indicating a shorter time to an optimally blended state. This can be related to different balances of cohesive and adhesive interactions between drug and carrier particles (milled and spraydried systems). More rapid blending indicates stronger carrier-drug forces that result in more efficient coating of carrier particles with micronized drug. Dispersion and powder aerosolisation studies also indicated strong carrier drug interaction with spraydried lactose resulting in FPF and FPD (FPF 5.23 ± 2.1, FPD 15.40 ± 5.7) being significantly less than ($P < 0.05$) milled lactose (FPF 15.73 ± 2.5, FPD 41.34 ± 5.8). Spraydried lactose blends resulted in majority of drug being deposited in throat and preseparator which would be associated with higher drug-carrier interparticulate forces. These observations indicate rapid mixing rates to reach blend uniformity result in poorer dispersion performance. These studies investigate the dynamics of blending as a predictor of DPI performance related to interparticulate forces. Our results indicate the rate of convergence to blend uniformity during powder blending may be used as a predictor of the powder performance in a passive DPI system.

Gupta, M. et al (2006) *J. Pharm. Biomed. Anal*. **40**: 423–428
USP 26-NF 21. United States Pharmacopeia. Rockville, MD: United States Pharmacopeial Convention; 2003: 2105–2123

213
Use of poloxamers in the formulation of innovative oral solid dosage forms

T. Laverty, D. Jones and G. Andrews

Drug Delivery & Biomaterials Group, School of Pharmacy, Queen's University of Belfast, 97 Lisburn Road, Belfast. BT9 7BL, UK g.andrews@qub.ac.uk

Poloxamers (Pluronic) are triblock copolymers consisting of poly(ethylene-oxide)-poly(propylene-oxide)-poly(ethylene-oxide) (PEO-PPO-PEO) that have been used as tablet lubricants, wetting agents and also as tablet coatings. They are considered to be non-toxic, non-irritant and are stable in both acid and alkali conditions. Consequently, these polymers have been extensively used in the preparation of solid dosage forms and have recently received considerable attention as a method of improving the aqueous solubility of poorly water-soluble drugs. In addition, poloxamers have been used in numerous applications as thermo-gelling agents and possess a temperature-dependent viscoelastic profile at concentrations greater than 20% w/w in aqueous solution. Hydroxypropylmethylcellulose (HPMC) is a non-ionic cellulose derivative that has been used extensively in the manufacture of solid dosage forms that has been used to prepare solid dispersions of poorly water-soluble drugs possessing improving dissolution profiles. The aim of this investigation was to examine the properties of solid dosage forms manufactured from Poloxamer F127 and hydroxypropylmethylcellulose (HPMC) to determine the interaction between the two polymers through physical mixing and the effect such interactions may have upon the release and solubility of two model drugs. In addition the effect of the thermo-gelling properties of Poloxamer F127 in the gel layer surrounding the solid dosage forms was determined. Conventional flat-edged tablets were manufactured by initially pre-mixing all formulation components (Poloxamer, HPMC, API) in a Copley Scientific Y-cone blender for a period of 5min, after which, samples were selected for statistical analysis of drug content homogeneity. Blended physical mixtures (500 mg) were subsequently compressed for a defined period (3 min) using an O-ring hydraulic press under a defined pressure of 10 tons. Two model drugs were used throughout the study comprising of the highly water-soluble ibuprofen sodium and the poorly water-soluble quinine sulphate, both of which comprised 10% of the final tablet weight. The remainder of the dosage form was composed of various mixtures of Pluronic F127 and HPMC (Mn ~120,000). The drug release, hardness and friability characteristics of the tablets were assessed using standard BP tests, whereas the interaction between formulation components was determined using DSC analysis (TA, Q100 mDSC). Drug release, hardness and friability of the matrix tablets were significantly affected by the concentration of Pluronic, HPMC and drug type. Increased concentrations of Pluronic significantly increased drug release rate, which was attributed to the formation of low viscosity gel channels throughout the tablet matrix allowing extensive water ingress and hence increased drug release. Formulations of quinine sulphate containing 100% poloxamer released their entire drug loading within 150 min, whereas those containing 100% HPMC had only released 82.5% drug after 24 h. Drug release from the ibuprofen sodium tablets showed an expected increased release profile when compared with those of the quinine sulphate, 100% HPMC tablets containing ibuprofen released 100% drug after 24 h, whereas quinine sulphate released only 82.5%. Increasing the ratio of poloxamer within a formulation increased friability and decreased tablet hardness.

214
Preparation of IgG coated microcrystals using a novel three-line continuous flow coprecipitation system

J. Partridge, J. Vos, C. Lyle and B. D. Moore[1]

Xstalbio, University Avenue, Glasgow and [1]University of Strathclyde, Cathedral Street, Glasgow, UK b.d.moore@strath.ac.uk

The production of protein coated microcrystals (PCMC) can be achieved in the laboratory via a simple batch precipitation process. We explored the use of continuous flow coprecipitation method with the aim of obtaining a manufacturing process that was better suited to scale-up. Bovine IgG (Lampire Biological Lab, Pipersville, USA) and valine were coprecipitated into propan-2-ol using both two-line and three-line strategies, to produce IgG-valine PCMC. In the two-line system, IgG and valine were pre-blended in a single vessel prior to coprecipitation. In the three-line system, the IgG and valine were introduced independently from separate vessels in which the pH of each solution could be controlled independently. Subsequently, IgG and valine were coprecipitated by rapid mixing into excess propan-2-ol. After coprecipitation the product was harvested by filtration and air-

dried. The various PCMCs samples were reconstituted into buffer, and the relative amounts of soluble bovine IgG bound to the crystals determined. Measuring the binding of the reconstituted protein to a Protein A column and comparing with unprocessed material was used to determine the percentage of IgG retaining a native conformation. A clear advantage of using the three-line system is that the protein solution can be held under different storage conditions from the excipient. This includes temperature, pH, buffer constituents and stabilizers. For the experiment with IgG a theoretical protein loading of 7.5% w/w was expected. After reconstitution it was demonstrated that the two-line system produces PCMCs with 6.6% w/w of soluble IgG (88% IgG recovery), while the three-line system produced PCMCs that retained 7.7% w/w of soluble IgG (103% IgG recovery). These results show that for bovine IgG a three-line coprecipitation strategy can provide significant improvements over the two-line strategy. In this case it produces PCMCs that contain ~12% more soluble IgG. The reason for the improvement is thought to arise from the better control the three-line system offers over the protonation state of IgG during the coprecipitation process. Bovine IgG PCMCs were produced using two-line and three-line continuous flow coprecipitation strategies. It was demonstrated that for this protein the three-line system produces a superior PCMC formulation.