dried system of partially-hydrated sugars. Three types of sugar (sucrose, lactose and trehalose) were measured by dielectric spectroscopy. Freeze dried powders were prepared from 10% aqueous sugar solutions using a standard procedure. Samples with different moisture content were prepared by re-hydrating from atmospheric moisture under controlled conditions. Dielectric measurements were performed using Solartron 1296 dielectric interface connected to a Solartron 1255 frequency response analyser. The frequency and temperature ranges investigated were 0.1–1 MHz and −120°C to 60°C, respectively. Analysis of the complex dielectric permittivity spectra reveals three relaxation processes, for each type of sugar. All these processes can be associated with the relaxation behaviour of water molecules adsorbed onto the surface of the porous sugar matrix. The first relaxation process (at low temperature) is ascribed to the reorientation of water molecules in ice-like structures comprising either parallel or anti-parallel arrangements of dipoles (depending on temperature). The second process is thought to be due to a single water molecule reorientation in the vicinity of a defect. The third process is observed at low frequency and at higher temperatures (> 0°C) and is due to the self-diffusion of charge carriers through the porous network. These charge carriers are most probably protonic and originate from the water adsorbed on the porous medium. Relaxation parameters for each process were obtained by fitting to the Havriliak-Negami formula (Gutina et al 2003). Comprehensive analysis is presented of the influence of moisture content, temperature and type of sugar on the dielectric parameters extracted from fitting.

We are grateful to Pfizer Global R&D for funding of this study.

Gutina, A. et al (2003) *Microporous Mesoporous Mat*. **58**: 237–254

028
Effect of rheology modifiers on tablet disintegration

D. A. Raval, D. N. Parikh[1] and V. M. Patel[2]

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To provide better prediction of in vivo performance of a dosage form, thorough assessment of test media is necessary. In recent years, interest has been focused on the development and utilization of physiologically relevant medium components, which attempt to simulate the in vivo conditions of the gastrointestinal tract (e.g., in the body certain natural surfactants aid in the dissolution and subsequent adsorption of drugs with limited aqueous solubility). Thus for enhancing solubility, dissolution medium are being incorporated with surfactants (sodium lauryl sulfate) or hydrophilic polymers (Jones et al 2004). But it is also true that alterations in media composition with such agents would influence factors such as surface tension and viscosity, which in turn will affect tablet disintegration time. The purpose of this study was to examine the disintegration of tablet in media under the influence of rheology modifiers. It was also intended to study whether the rheology modification of medium has a controlling effect on the disintegration time of tablets. Commercially available fast disintegrating antacid tablets were employed to assess the disintegration time in media under the influence of rheology modifiers. Poly (vinyl acetate-co-maleic anhydride), VAMA, was used as a rheology modifier for test medium. VAMA with varying monomer ratio was prepared by precipitation polymerization. The copolymer was characterized by acid value, softening point and molecular weight determination (Raval et al 1997). The surface tension and viscosity of a range of aqueous solutions of VAMA was determined by capillary action method and U tube viscometry, respectively (Fell et al 2005). The disintegration time of tablets was determined using disc as per Indian standard. The results are reported in Table 1. Increasing viscosity and simultaneous decrease in surface tension retards the disintegration time of tablets possibly by reducing the penetration rate of liquid into tablets.

Table 1 Influence of VAMA concentration on tablet disintegration time

Polymer system	Monomer ratio (VA:MA)	Polymer concn (%)	Surface tension (dynes/cc)	Relative viscosity	Disintegration time (s)
VAMA1	1:1.5	1	70.57	1.05	52
		3	65.78	2.56	64
		5	61.64	3.95	69
VAMA3	1:1	1	70.60	2.14	53
		3	68.22	4.43	66
		5	65.84	5.43	76
VAMA5	1:0.5	1	76.28	2.80	55
		3	73.20	8.00	71
		5	69.51	9.85	88

Fell, J. T. et al (2005) *Int. J. Pharm*. **290**: 121–127
Jones, D. S. et al (2004) *J. Pharm. Pharmacol*. **56**: 50–51
Raval, D. A. et al (1997) *Indian J. Pharm. Sci*. May–June: 152–157

Poster Session 1 – Pharmaceutical Technology

029
Stomach specific anti-*Helicobacter pylori* therapy: preparation and evaluation of amoxicillin-loaded chitosan mucoadhesive microspheres

J. K. Patel and M. M. Patel

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Amoxicillin is widely used for the treating gastric and duodenal ulcers, which are associated with *Helicobacter pylori* (Vakil & Cutler 1999). However, some reports and clinical trials indicate that the therapies cannot bring about compete eradication of *H. pylori* and suggest that the therapeutic effect needs more investigation (Kawabami et al 2001). One probable reason for the incomplete eradication of *H. pylori* is the short residence time of the dosage form in the stomach so that effective antimicrobial concentration cannot be achieved in the gastric mucous layer or epithelial cell surfaces where *H. pylori* exists. Thus, the purpose of this research was to formulate and systemically evaluate in vitro and in vivo performances of mucoadhesive microspheres of amoxicillin. Amoxicillin mucoadhesive microspheres (Amo-mu-ms) containing chitosan as mucoadhesive polymer were prepared by a simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicate that the volume of cross-linking agent, time for cross-linking, polymer-to-drug ratio, and speed of rotation affected characteristics of microspheres. A 3^2 full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio and stirring speed on dependent variables % mucoadhesion, t_{80}, drug entrapment efficiency, particle size and swelling index (Table 1). The best batch exhibited a high drug entrapment efficiency of 70% and a swelling index of 1.39%; mucoadhesion after 1 h was 79%. The drug release was also sustained for more than 12 h. The morphological characteristics of the Amo-mu-ms were studied under SEM. In vitro release test showed that amoxicillin released faster in pH 1.0 hydrochloric acid than in pH 7.8 phosphate buffer. In vitro and in vivo mucoadhesive tests showed that Amo-mu-ms adhered more strongly to the gastric mucous layer and could be retained in the gastrointestinal tract for an extended period of time. In vivo *H. pylori* clearance tests were also carried out by administering Amo-mu-ms and powder, to *H. pylori* infectious Wistar rats under fed conditions at single dose by the oral route. The results showed that Amo-mu-ms had a better clearance effect than amoxicillin powder. In conclusion, the prolonged gastrointestinal residence time and enhanced amoxicillin stability resulting from the Amo-mu-ms might make a contribution to *H. pylori* clearance.

Table 1 3^2 full factorial design layout

Batch no.	Polymer-to-drug ratio	Stirring speed (rpm)	Mucoadhesion after 1 h (%)	t_{80} (min)	Drug entrapment efficiency (%)
S1	1:1	500	53	225	45
S2	1:1	1000	46	223	42
S3	1:1	1500	43	211	38
S4	1:3	500	75	196	65
S5	1:3	1000	67	228	62
S6	1:3	1500	60	241	58
S7	1:6	500	79	465	70
S8	1:6	1000	72	447	68
S9	1:6	1500	64	371	64

Vakil, N., Cutler, A. (1999) *Am. J. Gastroenterol*. **94**: 1197–1199
Kawabami, E. et al (2001) *Arq. Gastroenterol*. **38**: 203–206

dried system of partially-hydrated sugars. Three types of sugar (sucrose, lactose and trehalose) were measured by dielectric spectroscopy. Freeze dried powders were prepared from 10% aqueous sugar solutions using a standard procedure. Samples with different moisture content were prepared by re-hydrating from atmospheric moisture under controlled conditions. Dielectric measurements were performed using Solartron 1296 dielectric interface connected to a Solartron 1255 frequency response analyser. The frequency and temperature ranges investigated were 0.1–1 MHz and −120°C to 60°C, respectively. Analysis of the complex dielectric permittivity spectra reveals three relaxation processes, for each type of sugar. All these processes can be associated with the relaxation behaviour of water molecules adsorbed onto the surface of the porous sugar matrix. The first relaxation process (at low temperature) is ascribed to the reorientation of water molecules in ice-like structures comprising either parallel or anti-parallel arrangements of dipoles (depending on temperature). The second process is thought to be due to a single water molecule reorientation in the vicinity of a defect. The third process is observed at low frequency and at higher temperatures (> 0°C) and is due to the self-diffusion of charge carriers through the porous network. These charge carriers are most probably protonic and originate from the water adsorbed on the porous medium. Relaxation parameters for each process were obtained by fitting to the Havriliak-Negami formula (Gutina et al 2003). Comprehensive analysis is presented of the influence of moisture content, temperature and type of sugar on the dielectric parameters extracted from fitting.

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028
Effect of rheology modifiers on tablet disintegration

D. A. Raval, D. N. Parikh[1] and V. M. Patel[2]

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To provide better prediction of in vivo performance of a dosage form, thorough assessment of test media is necessary. In recent years, interest has been focused on the development and utilization of physiologically relevant medium components, which attempt to simulate the in vivo conditions of the gastrointestinal tract (e.g., in the body certain natural surfactants aid in the dissolution and subsequent adsorption of drugs with limited aqueous solubility). Thus for enhancing solubility, dissolution medium are being incorporated with surfactants (sodium lauryl sulfate) or hydrophilic polymers (Jones et al 2004). But it is also true that alterations in media composition with such agents would influence factors such as surface tension and viscosity, which in turn will affect tablet disintegration time. The purpose of this study was to examine the disintegration of tablet in media under the influence of rheology modifiers. It was also intended to study whether the rheology modification of medium has a controlling effect on the disintegration time of tablets. Commercially available fast disintegrating antacid tablets were employed to assess the disintegration time in media under the influence of rheology modifiers. Poly (vinyl acetate-co-maleic anhydride), VAMA, was used as a rheology modifier for test medium. VAMA with varying monomer ratio was prepared by precipitation polymerization. The copolymer was characterized by acid value, softening point and molecular weight determination (Raval et al 1997). The surface tension and viscosity of a range of aqueous solutions of VAMA was determined by capillary action method and U tube viscometry, respectively (Fell et al 2005). The disintegration time of tablets was determined using disc as per Indian standard. The results are reported in Table 1. Increasing viscosity and simultaneous decrease in surface tension retards the disintegration time of tablets possibly by reducing the penetration rate of liquid into tablets.

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Raval, D. A. et al (1997) *Indian J. Pharm. Sci*. May–June: 152–157

Poster Session 1 – Pharmaceutical Technology

029
Stomach specific anti-*Helicobacter pylori* therapy: preparation and evaluation of amoxicillin-loaded chitosan mucoadhesive microspheres

J. K. Patel and M. M. Patel

Shree S. K. Patel College of Pharmaceutical Education and Research, Ganpat Vidyanagar, India. E-mail: jayvadan04@yahoo.com

Amoxicillin is widely used for the treating gastric and duodenal ulcers, which are associated with *Helicobacter pylori* (Vakil & Cutler 1999). However, some reports and clinical trials indicate that the therapies cannot bring about compete eradication of *H. pylori* and suggest that the therapeutic effect needs more investigation (Kawabami et al 2001). One probable reason for the incomplete eradication of *H. pylori* is the short residence time of the dosage form in the stomach so that effective antimicrobial concentration cannot be achieved in the gastric mucous layer or epithelial cell surfaces where *H. pylori* exists. Thus, the purpose of this research was to formulate and systemically evaluate in vitro and in vivo performances of mucoadhesive microspheres of amoxicillin. Amoxicillin mucoadhesive microspheres (Amo-mu-ms) containing chitosan as mucoadhesive polymer were prepared by a simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicate that the volume of cross-linking agent, time for cross-linking, polymer-to-drug ratio, and speed of rotation affected characteristics of microspheres. A 3^2 full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio and stirring speed on dependent variables % mucoadhesion, t_{80}, drug entrapment efficiency, particle size and swelling index (Table 1). The best batch exhibited a high drug entrapment efficiency of 70% and a swelling index of 1.39%; mucoadhesion after 1 h was 79%. The drug release was also sustained for more than 12 h. The morphological characteristics of the Amo-mu-ms were studied under SEM. In vitro release test showed that amoxicillin released faster in pH 1.0 hydrochloric acid than in pH 7.8 phosphate buffer. In vitro and in vivo mucoadhesive tests showed that Amo-mu-ms adhered more strongly to the gastric mucous layer and could be retained in the gastrointestinal tract for an extended period of time. In vivo *H. pylori* clearance tests were also carried out by administering Amo-mu-ms and powder, to *H. pylori* infectious Wistar rats under fed conditions at single dose by the oral route. The results showed that Amo-mu-ms had a better clearance effect than amoxicillin powder. In conclusion, the prolonged gastrointestinal residence time and enhanced amoxicillin stability resulting from the Amo-mu-ms might make a contribution to *H. pylori* clearance.

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Kawabami, E. et al (2001) *Arq. Gastroenterol*. **38**: 203–206

030
A novel approach in the formulation development of a blend of solid dispersion and mucoadhesive microspheres for glipizide in the management of non-insulin dependent diabetes mellitus

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Glipizide (GZ) is a second-generation sulfonylurea that can acutely lower the blood glucose level in man by stimulating the release of insulin from the pancreas and typically prescribed to treat type II diabetes (Brogden et al 1979). Its has low aqueous solubility but the absolute bioavailability is close to 1. Its short biological half-life (3.4 ± 0.7 h) necessitates the need to be administered in two or three doses of 2.5–10 mg per day. It has been observed from the report that the marketed extended release preparation takes a longer time to reach peak plasma concentration, although it is capable of delivering the drug for a longer period and at the same time the conventional dosage forms of GZ, although reaching plasma concentration within a very short time, fail to maintain the plasma concentration for long time (Berelowitz et al 1994). The development of controlled release dosage forms thus would clearly be advantageous. Dosage forms that release a loading dose immediately and are retained in the stomach, releasing a maintenance dose, would increase the absorption, improve drug efficiency and decrease dose requirements. Thus, the purpose of this research was to formulate and systematically evaluate in vitro and in vivo performances of capsules containing solid dispersion of glipizide (S-D-GZ) and mucoadhesive microspheres of glipizide (M-M-GZ). S-D-GZ and M-M-GZ were prepared using by solvent evaporation and emulsification solvent evaporation technique, respectively. A 3^2 full factorial design was adopted for the formulation. Prepared S-D-GZ and M-M-GZ were subjected to various physicochemical evaluations and in vitro drug release study. The microspheres exhibited a good mucoadhesive property in the in vitro wash off test, showed high % drug entrapment efficiency and the drug release was also sustained for more than 14 h. Finally, statistical optimization was directed towards preparation of optimized formulation by blending both S-D-GZ and M-M-GZ in a capsule shell, which would deliver GZ at the target release rate of not less than 35% of the total dose (10 mg) of GZ at 60 min (t_{60}) and not less than 95% of the total dose of GZ at 720 min (t_{720}). Release of GZ in the first 60 min is mainly contributed from release from S-D-GZ and, along with some amount of the drug, is also released from the M-M-GZ as well. In the subsequent phase (60–720 min) it is expected that remaining portion of the drug from the S-D-GZ will be released and release of GZ is mainly contributed from the M-M-GZ. An optimized blend for encapsulation was prepared by taking S-D-GZ equivalent to 3 mg of GZ and M-M-GZ equivalent to 7 mg of GZ. Predicated release profiles and dissolution profile of the optimized blend formulation were compared with theoretical dissolution profile of GZ using a model-independent pair-wise approach, of similarity factor f_2 and was found to be 67.5 and 79.4 respectively, which indicate a close similarity between three dissolution profiles. In vivo testing of the optimized formulation to Wistar rats demonstrated the significant hypoglycaemic effect of GZ.

Berelowitz, M. et al (1994) *Diabetes Care* **17**: 1460–1464
Brogden, R. N. et al (1979) *Drugs* **18**: 329–353

031
Automation of drug solubility determination under refrigerated conditions

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The rapid profiling of the physicochemical properties of drug candidates, in particular solubility determination, has become increasingly important in the pharmaceutical industry as part of the ongoing initiative to reduce compound attrition at each stage of the drug development process. Assessment of candidate solubility is an essential element of the development of liquid dosage forms where the behaviour of the drug molecule under proposed storage and in-use conditions is inherently linked to its solubility. Manual techniques for pH-solubility profiling are labour intensive and time/material consuming. Previous studies (Igo et al 2001; Dehring et al 2004) with high throughput technology have demonstrated that automation of the solubility screen at room temperature can reduce material requirements and save time, liberating the investigator to perform other tasks. Using a model compound, the aim of this study was to further develop and optimise automated methodology to determine drug solubility under refrigerated conditions, representing the most stressful environment for many liquid dosage forms. The automated methodology employed Powdernium Autodose and TECAN robots integrated with LC-MS analysis. The Autodose robot was programmed to weigh a defined quantity of compound into 12 wells in a 96-well plate. The TECAN robot was programmed to dispense a fixed volume of one of twelve media, covering the pH spectrum, on to the drug samples. This process was performed in triplicate. Standard solutions were prepared in situ in the plate to generate a calibration plot for sample analysis. The plate was sealed and agitated for 24 h at 4°C. Due to a temperature-induced modification of sample consistency, incubation of the plate under refrigerated conditions significantly restricted the ability of the TECAN robot to manipulate the contents of each well. Successful resolution of this challenge required re-programming of robotic methods, an increase in media–drug ratio in each well and adaptation of centrifuge tooling. Post-agitation, saturated solution was separated from solid drug substance by centrifuge-enabled filtration and pH of the solutions was measured. Test and standard samples were then diluted appropriately to facilitate analysis of drug content by LC-MS. To maintain controlled temperature during processing of samples between agitation and analysis, the TECAN plate holder cooling system was utilised. A comparison of selected data generated with manual and automated techniques is presented in Table 1. By optimising room temperature methodology, this investigation has shown that it is possible to automate the process of pH-solubility profiling of drug under refrigerated conditions. Future work will focus on further development of the methodology to determine drug solubility in probe formulations comprising standardly used excipients (e.g. tonicity adjustors, antimicrobial preservative agents and sweeteners) to expedite development of liquid dosage forms.

Table 1 Mean drug solubility determined at 4°C

Buffer media	Manual method		Automated method	
	pH	Concn (mg mL^{-1})	pH	Concn (mg mL^{-1})
Lactic acid	3.85	2.23	3.84	2.36
Acetic acid	4.67	3.19	4.85	2.78
Citric acid	5.75	0.12	6.06	0.00

Dehring, K. A. et al (2004) *J. Pharm. Biomedical Anal.* **36**: 447–456
Igo, D. H. et al (2001) *J. Pharm. Biomedical Anal.* **26**: 495–500

032
Investigating some factors affecting the swelling of hydrophilic matrix tablets using live image analysis

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Matrix swelling leading to the formation of a gel layer is the most important feature associated with hydrophilic matrix dosage forms due to the crucial role of the gel layer, as a physical barrier, in modifying drug release. Several methods have been reported in the literature for studying matrix swelling, the properties of the forming gel layer, and the influence of various formulation and production variables on them. A large number of the reported methods depend on monitoring and comparing the dimensional changes occurring within the different dosage forms during their hydration, using techniques ranging from simple visual observations (Talukdar & Kinget 1995) to more advanced imaging techniques (Rajabi-Siahboomi et al 1994; Moussa & Cartilier 1998). In this work we investigated the effect of tablet face curvature and porosity and the type of drug used on the in vitro swelling of xanthan gum matrix tablets, using a live image analysis technique that allows intensive in situ monitoring of the dimensional changes occurring within freely hydrating matrix tablets. Blank and drug containing hydrophilic matrix tablets were prepared by direct compression using xanthan gum, spray dried lactose, dibasic calcium phosphate dihydrate, magnesium stearate and the drugs; orphenadrine hydrochloride and orphenadrine citrate. Flat round tablets and biconvex round tablets with radial face curvature ratios of 1 and 1.43 were prepared at three porosities of 12.5%, 15% and 17.5%. Swelling studies were conducted using an apparatus comprising of a glass vessel coated with matt black adhesive paper, and containing distilled degassed water maintained at 37°C. Tablets were placed within the hydration medium on a set of pins to allow complete surface hydration. Tablet swelling and radial expansion were recorded in situ at consecutive time intervals for 8 h by means of a black and white video camera placed on top of the hydration vessel, and connected to an image analysis software which allowed accurate measurements of the changing

tablet dimensions depending on the colour contrast in the recorded image. The swelling indices of the various tablets were calculated based on the increase in tablet diameter. Analysis of variance of the results at several time points revealed a significant effect of the three studied factors, tablet face curvature, tablet porosity and the type of drug used, on the swelling index of hydrophilic matrix tablets, in addition to a significant effect caused by the interaction between all three factors. Moreover, the effect of tablet properties, in terms of face curvature and porosity, on tablet swelling seems to be governed mainly by the type of drug used. The results of this work demonstrate the potential use of live in situ image analysis as a method for studying and comparing the in vitro behaviour of various hydrophilic matrix tablets.

Moussa, I. S., Cartilier, L. H. (1996) *J. Control. Release* **42**: 47–55
Rajabi-Siahboomi A. R. et al (1994) *J. Control. Release* **31**: 121–128
Talukdar, M. M., Kinget, R. (1995) *Int. J. Pharm.* **120**: 63–72

033
Formulation of sustained release tablets using suitable grade of hydroxypropylmethyl cellulose (HPMC)

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Hydrophilic matrix systems have been widely used for preparing sustained release formulations, as these can be prepared conveniently and economically, with little fear of dose dumping. The objectives of this study were to sustain the release of drug from tablets, using different grades of hydrophilic polymers, and to select the best polymers for sustained release tablets, based on the results of an in vitro dissolution study. Propranolol HCl IP was used as a model drug. For sustaining the drug release, two different grades of hydroxypropylmethyl cellulose (HPMC K15M and HPMC K4M) were used as hydrophilic polymer in various concentrations (5, 10, 15, 20, 25 and 30%). The drug was mixed with the polymers in a modified rotary flask shaker, inclined at an angle of 30°, using lactose as a diluent. By wet granulation technique, tablets of 200 mg were prepared by compression on an R&D tablet machine using 8 mm diameter punches. The tablets were evaluated for uniformity of content, hardness (Monsanto hardness tester), friability and in vitro dissolution. The dissolution study was carried out in the USP – Apparatus 1 using 900 mL 0.1 N HCl solution as the dissolution media at 100 rev min^{-1} and the drug was analysed using UV-visible spectrophotometer at 290 nm against a suitable blank. The average weight (200 mg) of prepared tablet was observed to be within the Pharmacopoeial limit (±5%). The crushing strength and friability of the prepared tablets was observed to be 6.0 ± 0.25 kg cm^{-2} and 2.0 ± 0.10%, respectively. From the in vitro dissolution study, it was observed that with HPMC K15M (20%), the rate of release was 23.0 ± 0.67% after 1 h and 66.0 ± 0.23% after 8 h. This indicates that more than 30% of drug still remained in the tablet after 8 h. By changing the polymer (HPMC K4M 20%), the rate of release was 26.0 ± 1.02% and 94.0 ± 1.42% after 1 h and 8 h, respectively, showing that more than 90% of drug was released within 8 h. From this study, it was concluded that HPMC K4M (20%) was the most suitable for the preparation of sustained release tablets. Tablet prepared with this polymer released the maximum amount (94%) of drug after 8 h, with less initial drug release (26%) during the first hour ($T_{50\%}$ and $T_{90\%}$ were 2.5 h and 7 h, respectively).

034
Design and characterization mucoadhesive buccal devices of propranolol hydrochloride

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The aim of this study was to prepare and evaluate a novel buccal adhesive system containing propranolol hydrochloride. Absorption of therapeutic agents from the oral cavity provides a direct entry of such agents into the systemic circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal degradation. Successful buccal delivery provides drug release in a unidirectional way toward the mucosa with controlled release of drug with efficient bioadhesion. Bilayered buccal tablets consisted of drug with bioadhesive polymers carbopol-934, Sodium-CMC and PVP-K30, mannitol in different ratios and were prepared by direct compression with a backing layer of ethyl cellulose. The multilayered tablets were prepared by direct compression of the adhesive core layer in a die of 9 mm. The core was then removed and placed in the centre of an 11-mm die and recompressed with coat material containing the Na-CMC and carbopol-934 and backing layer. A swelling index study was performed with the core facing the gel surface on 2% agar gel plates (Garnpimol et al 1999). Ex vivo buccoadhesion was studied by modified physical balance on sheep buccal mucosa (Gupta et al 1994). In vitro drug release was studied using a USP XXIII dissolution rate test apparatus-II (50 rev min^{-1}, 37°C, phosphate buffer pH 6.8) and analysed spectrophotometrically at 290 nm. In vitro drug permeation through a sheep buccal mucosa was studied using a Keshary-Chien diffusion cell at 37 ± 1°C, using 12.5 mL of phosphate buffer pH 7.4. A bilayered tablet was also evaluated for thickness, surface pH (Bottenberg et al 1991), drug content uniformity and friability. Propranolol hydrochloride with Na-CMC:carbopol-934 in different ratios was prepared for bilayered tablets. The tablets were found to be satisfactory when evaluated for weight variation, friability, drug content uniformity and surface pH. D-mannitol has been used to accelerate the release of drug from polymer matrices. The optimum release of the drug was obtained on addition of 4% D-mannitol. Addition of 6% PVP K30 was found to increase the release of drug in bilayered tablets. The progressive decrease in the amount of drug release and the rate from formulation F4 to F9 may be attributed to increase in carbopol content, and a consistent decrease in sodium-CMC content. The swelling index study indicated that the rate of swelling was proportional to the sodium-CMC and inversely proportional to the carbopol content of tablets. A higher proportion of carbopol-934 was found to absorb less amount water. The results also indicated that the tablets did not show any appreciable change in the shape and form during the 8 h. After increasing contact time (5 min), mucoadhesion increased linearly with an increase in the concentration of carbopol. The multilayered devices release the drug in a unidirectional and sustained manner. Buccal devices of propranolol hydrochloride were developed to a satisfactory level with respect to drug release and bioadhesion. D-mannitol, and PVP-k30 were found to increase the release of drug from the polymer matrix. The multilayered structure design was expected to provide drug delivery in a unidirectional fashion to the mucosa and avoid loss of drug due to wash out with saliva.

Bottenberg, P. et al (1991) *J. Pharm. Pharmacol.* **43**: 457–464
Garnpimol, C. R. et al (1999) *Int. J. Pharm.* **178**: 11–22
Gupta, A. et al (1994) *Drug Dev. Ind. Pharm.* **20**: 315–325

035
Characterization of CR matrix formulations based on sucrose-fatty-acid-esters processed by hot-melt extrusion

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Modern drug development has yielded many potent compounds. For these to be useful as drug products, scientists need to find effective routes to the drug targets and additionally fulfill requirements for convenient dosing. Controlled release (CR) dosage forms have become a widely used approach to help meet these requirements, while extrusion has proved to be a very flexible process for developing and manufacturing pharmaceuticals including CR dosage forms (Breitenbach 2002). This study examined the possibility of preparing CR matrix formulations of theophylline using sucrose-fatty-acid-ester (Ryoto S 1670; Mitsubishi Kagaku Food Corp., Japan) as the matrix-forming agent, with processing by hot-melt extrusion. Granulates with a theophylline loading of 25, 50 and 75% w/w were manufactured using a twin-screw-extruder (Haake Rheomex PTW16/25) and granulated with a Frewitt GLA sieve machine. Magnesium stearate (1% w/w) was added to granulates prior to final blending (for 2 min) and tablets (containing 100 mg theophylline) were manufactured using a Korsch EK0 single-station tablet press (Seiler et al 2003). Bulk and tap densities were measured with an Erweka SVM apparatus; sieve analysis with a Fritsch Analysette 3 Pro; hardness with a Holland C50; and friability with an Erweka TA20 apparatus. Dissolution was tested with a VanKel VK7000 USP II device using phosphate buffer pH 6.8 (900 mL, 50 rev min^{-1}, 8 h). Samples were analysed at 272 nm with a Shimadzu 2501PC UV/VIS-spectrophotometer. Results were expressed as mean % w/w dissolved for each sampling time ($n \geq 3$). Hot-melt extrusion was feasible for all formulations, though process parameter adjustment was necessary to complete the range of drug loadings. Extrusion/granulation decreased the compressibility indices (Aulton 2002) of all formulations (Table 1) and produced good flowability. Mean particle size increased significantly, while the proportions of fines present were 15–18% w/w. Generally, processing of formulations by extrusion/ granulation improved critical parameters (flowability and particle size) for compaction processes. Therefore, hot-melt extrusion proved to be a suitable technique to manufacture granulates from Ryoto S 1670. Manufactured tablets (from

50 and 75% w/w theophylline-loaded granulates) generally corresponded to pharmacopeial standards. Up to 75% w/w of drug, in addition to excipients, were successfully formulated into matrix tablets using hot-melt extrusion. Although hardness tended to be poor (mean 15–17 N for 9.0 mm tablet diameter), friability corresponded to pharmacopeial requirements (mean 0.2–0.3% w/w). Tablets, compressed from 25% w/w theophylline-loaded granulates also showed low hardness (mean 18 N for 10.0 mm tablet diameter), but friability did not correspond to pharmacopeial requirements (mean 1.2% w/w) in this case. Although sucrose-fatty-acid-esters proved generally suitable as an excipient for tablet manufacture, due to the pilot nature of these formulations, it is anticipated that the addition of fillers, such as mannitol or microcrystalline cellulose, with better tabletting properties would improve the end product. All formulations showed a controlled drug release (30–37% release at 8 h). Drug release was accelerated with increased drug load. On the basis of manufacturability and performance, sucrose-fatty-acid-esters were deemed to be a generally suitable excipient for controlling release from theophylline dosage forms prepared by hot melt extrusion.

Table 1 Compressibility indices (± s.d.) of formulations

Drug load (% w/w)	Powdered blend (%)	Granulates (%)
25	26 (± 2.6)	13 (± 0.8)
50	20 (± 2.4)	12 (± 1.7)
75	20 (± 1.8)	12 (± 2.6)

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Compression and re-compression properties of hypromellose/lactose mixtures

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The compaction properties of some pharmaceutical excipient mixtures have previously been studied (e.g. Kochhar et al 1995) but remain of interest. A dry granulation (DG) process comprising compression ('slugging'), milling (slugs to granules) and re-compression (granules to tablets) is intended to improve the tabletting properties of formulations. Previously, Beten et al (1994) reported the negative effect of slugging on the compressibility of microcrystalline cellulose. However, re-working of mixtures via such processes merits attention. The aim was to investigate the properties of hypromellose/lactose tablets prepared via direct compression (DC), DG via double compression or compression following milling of the initial formulations (MC). Formulations comprised lactose–hypromellose 99:0 (formulation i), 69.5:29.5 (ii), 49.5:49.5 (iii), 29.5:69.5 (iv), or 0:99% w/w (v) (lactose – Tablettose 80, Meggle, Germany; hypromellose – Methocel 2208, K4M, Dow Chemicals Co., USA). Each contained 0.5 % w/w colloidal silica (Aerosil 200, Degussa, Germany) and 0.5% w/w magnesium stearate (BDH, UK). DC was performed at 10, 20 or 30 kN using an instrumented Manesty (Knowsley, UK) F3 single-punch press fitted with 12.5 mm flat-faced punches. DG was performed by initially compressing each formulation at a compaction force of 10 kN and subsequently milling the 'slugs' using a sample mill (Cyclotec 1093). The resultant granules were re-compressed at 10, 20 or 30 kN. To assess the DG milling stage in isolation, a third batch of formulations were milled as described previously and compressed at 10, 20 or 30 kN as described for DC. Tablet crushing strength (Dr Schleuniger 6D Hardness Tester), thickness and diameter were used to calculate tensile strength as described by Fell & Newton (1970). Tensile strength of DC tablets increased significantly ($P < 0.05$) with both compaction force and % of hypromellose, suggesting stronger cohesive bonding between hypromellose particles compared with adhesive hypromellose–lactose bonding and cohesive bonding between lactose particles (Table 1). DC tablets were stronger than DG tablets at each compaction force, indicating that double compression resulted in work hardening of the materials (particularly hypromellose), which has been reported to reduce the plastic deformation of particles (Kochhar et al 1995). However, milling of formulations before compression also resulted in lower tablet strength and may have contributed to the reduced compressibility of the materials.

Table 1 Tensile strength (MPa) of hypromellose: lactose tablets prepared by DC, DG or MC

Formul[n]	i	ii	iii	iv	v
Direct compression					
10 kN	1.8 ± 0.1	1.7 ± 0.1	2.7 ± 0.1	3.2 ± 0.1	4.0 ± 0.1
20 kN	2.8 ± 0.2	2.6 ± 0.1	3.4 ± 0.1	4.5 ± 0.1	4.7 ± 0.1
30 kN	3.5 ± 0.2	3.2 ± 0.1	4.2 ± 0.1	5.2 ± 0.2	5.0 ± 0.2
Dry granulation					
10 kN	1.2 ± 0.2	1.6 ± 0.1	2.3 ± 0.1	2.8 ± 0.1	1.4 ± 0.2
20 kN	1.8 ± 0.1	2.2 ± 0.1	3.0 ± 0.1	3.3 ± 0.1	1.6 ± 0.1
30 kN	2.9 ± 0.2	2.7 ± 0.3	3.8 ± 0.1	3.8 ± 0.1	1.7 ± 0.1
Milled before compression					
10 kN	1.0 ± 0.1	1.5 ± 0.1	1.8 ± 0.1	1.9 ± 0.1	1.8 ± 0.1
20 kN	1.7 ± 0.1	2.3 ± 0.1	2.4 ± 0.1	2.5 ± 0.1	2.1 ± 0.1
30 kN	2.7 ± 0.1	3.3 ± 0.1	3.1 ± 0.1	3.0 ± 0.1	2.5 ± 0.1

Mean ± s.d., n = 10 for each data set.

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Investigation into transfer techniques used in pharmacy aseptic preparation

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During transfer of items between areas of aseptic clean rooms there is a risk of contamination and disinfectant sprays are used to minimise this risk. The disinfectant should effectively remove contamination and leave no residue on the surface of the item. Currently ethanol sprays and wipes are used for disinfection and the action of wiping is important in the removal of bacterial spores, as ethanol is not sporicidal (Cockcroft et al 2001). The process of wiping can be time consuming (Hiom et al 2004) and is difficult for some items. Hydrogen peroxide (H_2O_2) is a sporicidal agent (Russell et al 1992) and if it can be used as a spray alone this would be ideal. Its use, however, would be undesirable if a large amount of residue remains after its use. The aim of this investigation was to determine the amount of H_2O_2 residue remaining on a surface after the use of various disinfection methods. Before the determination of residue, the extraction of H_2O_2 from a swab was investigated as well as its rate of degradation, which was determined to be first order. Titration was used for the determination of H_2O_2 residue based on the British Pharmacopoeia 2004 assay. The main findings were that the use of a spray alone leaves more residue than when it is used in combination with a wipe. The use of either wipe reduces the amount of residue as they remove the excess. 6% H_2O_2 wipes alone leave less residue than the 6% H_2O_2 spray. There is no difference between the amount of residue remaining following the use of a dry or a 6% H_2O_2 wipe, after the use of 6% H_2O_2 spray alone or with ethanol. 6% H_2O_2 wipes removed more residue than dry wipes when used after 0.125% H_2O_2 spray. 0.125% H_2O_2 spray left less residue than 6% H_2O_2 spray but it is unknown whether this is due to the difference in concentrations of the solutions or due to the difference in droplet size. The use of 70% ethanol after 6% H_2O_2 spray had no effect on the amount of residue present and this is also seen when 70% ethanol is used in combination with 6% H_2O_2 wipes. I would recommend the use of a 6% H_2O_2 wipe in practice, as the concentration of H_2O_2 should be effective at killing spores and leave little or no residue. Wiping, however, can be time consuming (Hiom et al 2004) and difficult for some items and in this case a spray would be required. The use of 6% H_2O_2 spray alone would be ideal, although its use may be restricted to within the isolator to control its exposure limits and standing time increased to allow the residue to evaporate. Alternatively, therefore, the use of 0.125% H_2O_2 in 70% ethanol spray used in combination with 6% H_2O_2 wipes is recommended. This combination should minimise, or eliminate, any sources of contamination, including spores, leave the least residue and not exceed the exposure limit of 1 ppm.

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