J. Pharm. Pharmacol. 1998, 50: 375–382
Received September 30, 1997

Drug-delivery Products and the Zydis Fast-dissolving Dosage Form*

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Abstract

Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medication as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy. The difficulty is experienced in particular by paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water. Such problems can be resolved by means of the Zydis dosage form which does not require water to aid swallowing. The Zydis fast-dissolving dosage form is a unique freeze dried medicinal tablet, made from well known and acceptable materials. When Zydis units are put into the mouth, the freeze dried structure disintegrates instantaneously releasing the drug which dissolves or disperses in the saliva. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In these cases, the bioavailabilities of drugs from Zydis formulations are significantly greater than those observed from standard dosage forms.

This paper deals with the formulation and process technology of the Zydis dosage form. The bioavailability characteristics of Zydis products are summarized, and in particular, the design of Zydis products for the enhancement of oral bioavailability and the improvement of clinical activity, through transmucosal delivery and pregastric absorption, is discussed.

Drug-delivery products

In 1995 the value of the market for new drug-delivery systems (DDS) was estimated to be approximately $20 billion (Anon 1996). Most of the products marketed were concerned with sustained-release oral delivery or transdermal patches. The therapeutic indications were mainly in the areas of hypertension, angina, arthritis, smoking cessation and hormone replacement therapy (Table 1).

The drug-delivery market is expected to grow and to reach a value approaching $60 billion (Anon 1996). The delivery mechanisms will be more complex and the products will cover a wider variety of therapeutic applications, see for example those new drug-delivery products launched in 1996 to treat conditions such as transplanted organ rejection, systemic fungal infections, AIDS-related Kaposi's sarcoma and lymphoblastic leukaemia (Table 2; Anon 1996).

* Presented at the British Pharmaceutical Conference, Scarborough, September 15–18, 1997.

The time taken to develop the first product in a new drug delivery system is governed by the complexity of the technology and the size of the clinical trial programme; it is generally between 7 and 12 years. A sustained-release formulation based on an existing dosage form and process technology is likely to be developed relatively quickly. In this circumstance conventional formulation techniques and process equipment are used to develop the product with the required quality characteristics and pharmacokinetic profile. The development of a novel product, i.e. one based on new technology, takes much longer. Novel formulation and process techniques are required and these might involve many stages of complex product and engineering development.

The long development times are required:

to investigate the feasibility of the technology (2 years);

to develop the technology from the laboratory to pilot-plant scale of operation (2–5 years);

Table 1. Major drug-delivery products in 1995 (various sources).

Company/Marketer	Product	Indication	Sales ($m)
Alza/Bayer/Pfizer	Adalat/Procardia	Hypertension/angina	1000
Elan/HMR	Cardizem CD	Hypertension/angina	759
Alza/Ciba	Transderm-Nitro	Angina	382
Mundipharma	MS Contin	Analgesia	200
Alza/Novartis	DynaCirc CR	Hypertension	161
SkyePharma/RPR	Dilacor XR	Hypertension/angina	146
Biovail/RPR	Oruvail	Arthritis	137
Key/Schering Plough	K-Dur	Hypocalcaemia	125
Alza/Ciba	Nicorette patch	Smoking cessation	100
Alza/Ciba	Estraderm	HRT	100
Elan/Lederle	Verelan	Hypertension/angina	100

Table 2. Recently marketed drug-delivery systems.

Company/Marketer	Product	Drug-delivery system	Indication
Scherer/Novartis	Neoral	Oral microemulsion	Transplant-organ rejection
Alza/Searle	Covera-HS	Oral delayed Oros osmotic pump	Hypertension and angina
Elan/Wyeth-Ayerst	Naprelan	IPDAS multiparticle gastro-protective	Arthritis and analgesia
NeXstar/Fujizawa	AmBisome	Parenteral liposome	Life-threatening systemic fungal infections
NeXstar	DaunoXome	Parenteral liposome	AIDS-related Kaposi's sarcoma
KV/Roche	Femstat	Site-release muco-adhesive emulsion	Vaginal fungal infections
Ethical/Solvay	Fempak	Oestrogen transdermal patch	Hormone replacement
Enzon/RPR	Oncaspar	Pegnology protein/drug compound	Lymphoblastic leukemia

to scale-up the technology to the production scale of manufacture;
to conduct Phase I, Phase II and Phase III clinical trials (2–4 years depending on the complexity of the clinical programme); and
to apply for product licences to obtain regulatory approval for international marketing (1 year).

Further products based on the new method of drug delivery are then developed over shorter periods of time because the technology has been proven and commercial production plant is available for product manufacture.

Many companies are involved in the development of new drug-delivery systems. In general, these companies are small with annual sales revenues less than $50 million. The top 45 drug-delivery companies, for example are shown in Table 3 (Anon 1996); many are funded by venture capital or have recently become public organizations and their technologies are often at early stages of development. They tend to develop products by forming partnerships with larger pharmaceutical organizations. In most situations the drug-delivery company develops the technology to the production scale of operation and the larger partner provides the funds and develops the products.

One new drug-delivery technology that has been developed to the production scale of operation in recent years, and which is being used to develop and commercialize an increasing number of products, is that of the Zydis fast-dissolving dosage form (Virley & Yarwood 1990). Eight products are

Table 3. Top drug-delivery companies.

Company	Approximate sales ($m)	Company	Approximate sales ($m)
Scherer	537	Genta	5
Alza	350	Nastech	3
Elan	193	Genetronics	3
Watson	153	Sequus	2
NeXstar	62	Anesta	2
Andrx	53	Hyal	2
Health-Chem	46	Atrix	2
Dura	43	Verex	2
KV	40	Fountain	1
Ethical	29	Cellegy	1
Theratech	24	GelTex	< 1
Biovail	21	Cima	< 1
Cygnus	19	Zynaxis	< 1
Adv Polymer	16	DynGen	< 1
Enzon	16	Novavax	< 1
Liposome	16	Pharmavene	< 1
LecTec	14	Pharmos	< 1
Alkermes	14	InSite	< 1
Cortecs	12	Emisphere	< 1
Noven	12	MacroChem	< 1
Columbia	10	Matrix	0
Fuisz	6	Sano	0
Penederm	5		

already on the market—oxazepam, lorazepam, piroxicam, loperamide, famotidine, loratidine, enalapril, and phenylpropanolamine/brompheniramine, and five further products, including domperidone and ondansetron, are to be launched during the next two years.

This paper deals with the formulation and process technology of the Zydis dosage form. The bioavailability characteristics of Zydis products are summarized and, in particular, the design of Zydis products for the enhancement of oral bioavailability and the improvement of clinical activity, by transmucosal delivery and pre-gastric absorption, is discussed.

Summary of the Zydis Technology

Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medication as prescribed. It is estimated that 50% of the population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy. The difficulty is experienced in particular by paediatric and geriatric patients, but it also applies to people who are ill in bed and to active working patients who are busy or travelling, especially those who have no access to water.

Such problems can be resolved by means of the Zydis dosage form, a unique freeze-dried tablet made from well known and acceptable materials which does not require water to aid swallowing. When Zydis units are put into the mouth the freeze-dried structure disintegrates instantaneously releasing the drug which dissolves or disperses in the saliva. The saliva containing the dissolved or dispersed medicament is then swallowed in the normal way. Some drugs can be absorbed from the mouth, pharynx and oesophagus as the saliva passes down to the stomach. For these the bioavailability of drugs from Zydis formulations can be significantly greater than for those from standard dosage forms. Those drugs not absorbed from the pre-gastric region dissolve in the gastrointestinal fluid on entering the stomach and are absorbed into the bloodstream in the normal way. The bioavailability of drugs in Zydis dosage forms is therefore equivalent to those of the standard dosage forms.

The benefits of Zydis formulations are therefore:

to aid the administration of drugs to patients who experience swallowing difficulties or to those patients who have no access to water;
to improve the overall clinical performance of drugs by reducing the incidence of non-compliance; and
to enhance the clinical effects of some drugs through pre-gastric absorption from the mouth, pharynx and oesophagus; this leads to an increase in bioavailability and a reduction in side effects, if these problems are caused by first-pass liver metabolism.

Formulation characteristics

Zydis formulations consist of the drug physically entrapped or dissolved within the matrix of the fast-dissolving carrier material.

Drug requirements

Drugs suitable for the Zydis dosage form have several characteristics. The dose of water-insoluble drugs must generally be <400 mg. This is necessary to retain the porous nature and the fast-dissolving characteristics of the product (Figure 1). This limitation also avoids the drug material being sensed in the mouth as the product dissolves in the saliva.

The dose of water-soluble drugs is generally limited to an upper value of 60 mg. The dose is governed by the behaviour of the drug during the freezing process and on its drying characteristics. Eutectic mixtures can be formed for example; these either might not adequately freeze or might melt at the high temperatures used in the freeze-drying process. Also, the dissolved drug might form an amorphous glassy solid on freezing and this might collapse on drying because of the sublimation of ice and the loss of the supporting structure.

The collapse of the structure formed by water-soluble drugs can occasionally be prevented by the inclusion of a crystal-forming excipient in the product. These materials induce crystallinity, and hence rigidity, in amorphous products. Another approach is to bind the water-soluble drug on to an ion-exchange resin to form a water-insoluble complex. Another technique is to dose a non-aqueous solution of the active ingredient on to preformed placebo Zydis units. The organic solvent is then evaporated and the recrystallized drug is deposited in the pores of the Zydis matrix.

By use of these approaches, Zydis units containing a large number of water-soluble drugs can be successfully formulated.

To prevent the sedimentation of material during the manufacturing process, the particle size of insoluble drugs should generally be less than 50 μm. A small particle size is also usually desirable for preventing the sensing of a gritty texture in the mouth and pharynx during swallowing. By use of appropriate formulation techniques and process methods, however, it is possible to develop high-quality products using drug particles with mean diameters of approximately 200 μm.

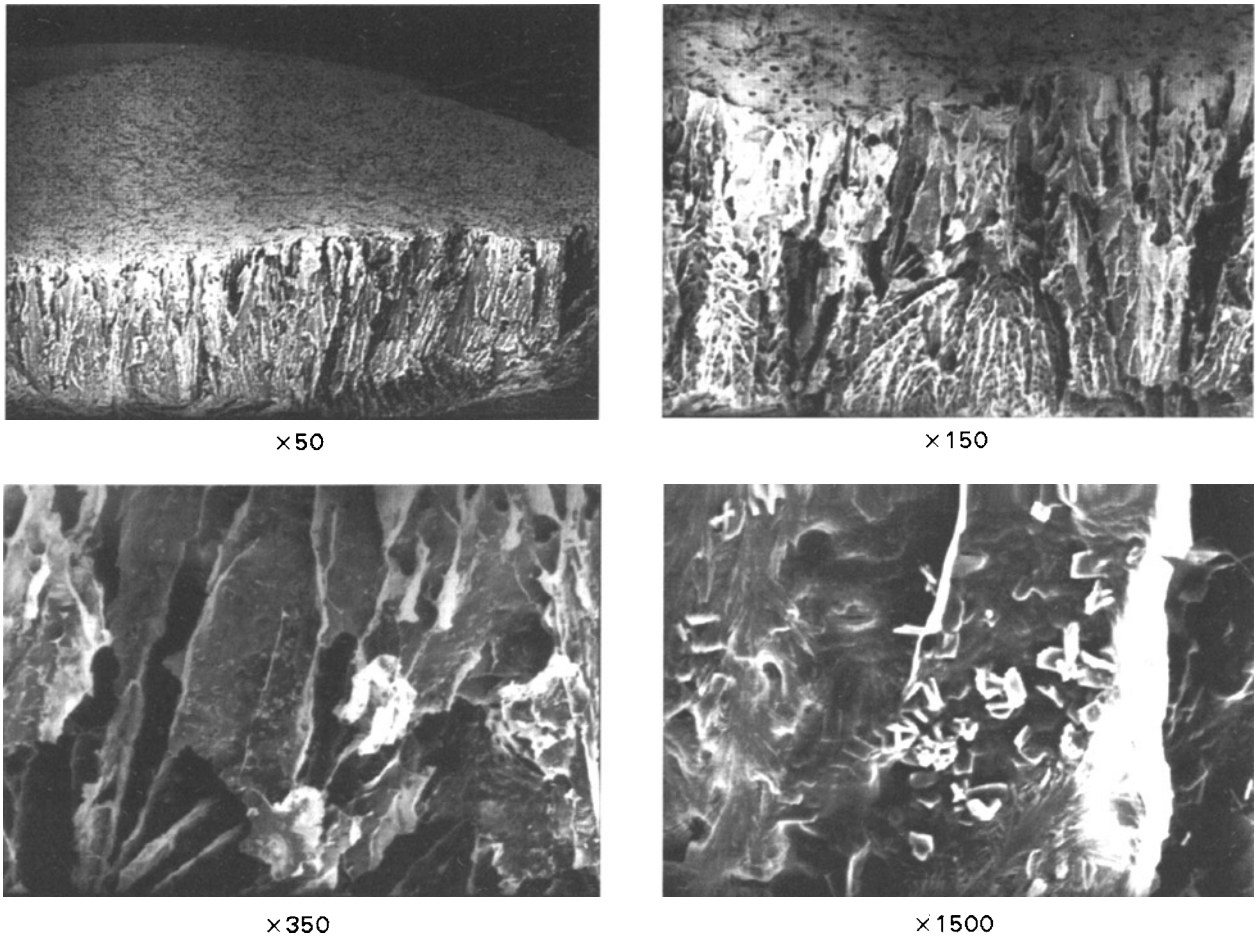

Figure 1. Electron micrographs of a Zydis unit showing particles of drug embedded in a matrix of high porosity.

The chemical stability of the drug substance must be satisfactory over a 24-h period at room temperature. This time is required for storage and dosage of the aqueous solution or suspension of the drug into the pre-formed pockets of a blister tray before the freezing stage of the manufacturing process.

The taste of the drug must be acceptable. Flavours and sweeteners are, therefore, used to mask the taste of the active constituents. For active soluble substances which are extremely bitter, ion-exchange resins might be used to render the drug insoluble. For insoluble compounds, bitter tasting materials can be masked by use of micro-encapsulation techniques. Here, the drug particles are covered by polymers by use of spray-drying, spray-congealing or coacervation process methods.

Matrix characteristics

The Zydis matrix is composed of many materials designed to achieve a number of objectives. Polymers such as gelatin, dextran or alginates are required to form a glassy amorphous structure which imparts strength and resilience during handling. Saccharides such as mannitol or sorbitol give crystallinity, hardness and elegance. Water is used in the manufacturing process to ensure the production of porous units which disintegrate rapidly on the tongue in 2 to 3 s. Preservatives such as the *para*-benzoic acids, at bacteriostatic concentrations, prevent microbiological growth of the aqueous solutions during the manufacturing process. (When the product has been freeze-dried, the preservative has no further function. The water activity within the final formulation is too low to support the growth of micro-organisms.) Suspending or flocculating agents, or both, for example various gums, are used to prevent the sedimentation of dispersed drug particles in the manufacturing process and pH-adjusting excipients such as citric acid and sodium hydroxide are used to optimize the chemical stability of the drug, to minimize the solubility of water-insoluble compounds or to optimize the extent of ionization of drugs which are absorbed into the blood stream through the pre-gastric membranes. Permeation enhancers such as sodium lauryl sulphate to optimize the transmucosal delivery of drugs absorbed through pre-gastric

tissues, and collapse protectants such as glycine prevent the shrinkage of the Zydis units during the freeze-drying process or during long-term storage. Finally, flavours and sweeteners are used to optimize taste, microencapsulation polymers, such as various celluloses, are used to mask the bitter taste of drugs, ion-exchange resins, such as amberlite resins, can be used to mask the bitter taste of drugs and colouring agents can give the product elegance and identity (this objective is also achieved by varying the size and shape of the Zydis units and through the use of embossing marks).

Packaging

Zydis products are packed in blister packs to protect the formulation from moisture in the environment. Poly(vinyl chloride) (PVC) or polyvinyldichloride (PVdC) plastic packs are used for the moderate conditions found in most European markets. Aclar laminates, aluminium foil over-wraps or aluminium blister packs are used for the more challenging environments such as those found in North and South America.

Moisture pick-up properties

Figure 2 shows the effect of relative humidity over a 3-day period at room temperature on the equilibrium water-content of exposed unpackaged Zydis units containing a hygroscopic water-soluble drug. At humidities below 40% there is no significant change in the water content of the units over a 3-day period. When humidity is greater than 40%, however, the units pick up moisture.

In general, Zydis units containing water-insoluble drugs absorb less moisture than products containing water-soluble products. For products containing high-dose insoluble drugs no significant moisture uptake is detectable until the relative humidity is greater than 65%.

Moisture content and collapse on storage

Apart from the potential impact of moisture content on the chemical stability of drugs, increasing amounts of water in Zydis units can affect the physical characteristics of the product, i.e. the product might gradually collapse or shrink on storage resulting in a reduction in the diameter of the units. This phenomenon is shown in Figure 3. The product shown in Figure 2, containing a water-soluble drug, was openly exposed to different relative humidities over a 3-day period. Again, there was no detectable change in diameter when the products were stored at relative humidities <40%. When the relative humidity was higher, however, the Zydis units picked up moisture and the diameters of the units decreased. In general the decrease in the diameter of the Zydis units could be correlated with the extent of moisture uptake; a decrease in diameter of up to 15% can be tolerated without changes in appearance or in fast-dissolving or dispersion characteristics.

The influence of different humidity conditions on the diameter of openly exposed placebo Zydis units after storage for fifteen weeks at 37°C is shown in Figure 4. Even at this elevated temperature the units are seen to be quite stable up to a relative humidity of 55%.

Pack type and product stability

The packaging materials used to form the blister and its lid are especially designed to minimize the rate of moisture uptake to an extent which gives the Zydis units three-year self-life stability. Aluminium foil over-wraps or aluminium blister-packs, for example, can be used to maximize stability.

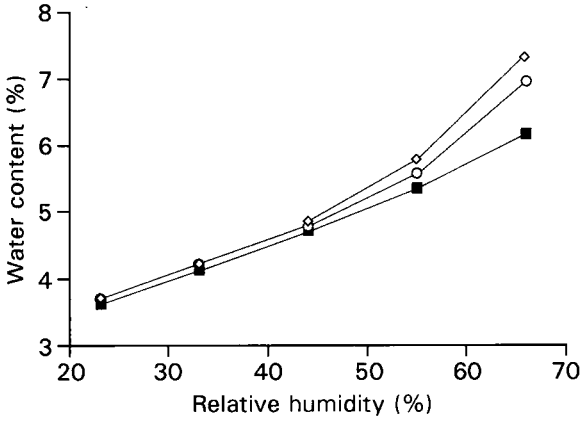

Figure 2. Influence of relative humidity on the water content of exposed, unpacked Zydis units containing a hygroscopic water-soluble drug: ■ day 1; ○ day 2; ◇ day 3.

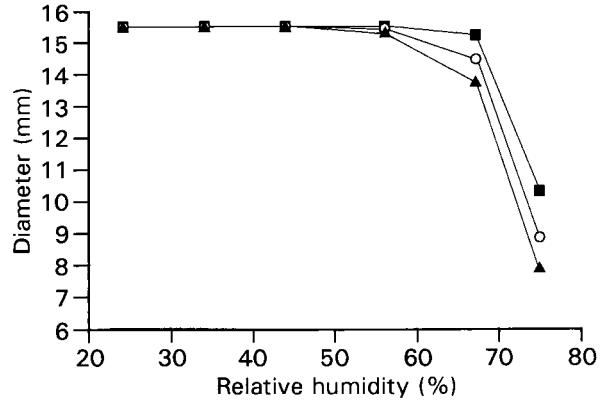

Figure 3. Influence of relative humidity on the diameter of exposed, unpacked Zydis units containing a hygroscopic water-soluble drug: ■ day 1; ○ day 2; ▲ day 3.

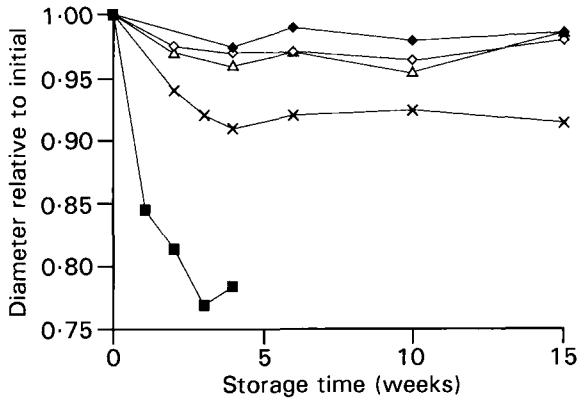

Figure 4. Influence of relative humidity on the diameter of exposed, unpacked Zydis placebo units stored at 37°C: ● ambient; ◇ 50% RH; △ 55% RH; × 62% RH; ■ 75% RH.

The influence of storage conditions on the unit diameter of a typical formulation containing a poorly soluble drug packed in blister packs of several types is shown in Table 4. It is apparent that increasing the moisture protection barrier from $40\,g^{-2}$ PVdC to $90\,g^{-2}$ PVdC improves the physical stability of the Zydis units and with a foil pouch, or aluminium blister, the extent of protection is maximized.

Whichever pack option is chosen, all Zydis products are produced in blister packs with peelable backing foils. Although Zydis units are sufficiently strong to withstand the stresses experienced during transport and handling, the units are not sufficiently resilient that they can be pushed out through the lidding foil before dose administration.

Manufacturing process

During manufacture of Zydis products the drug is dissolved or dispersed in an aqueous solution of carrier material and edible materials such as gelatin and mannitol. This step involves conventional mixing equipment. The mixture is then dosed by weight into the pockets of large preformed blister packs (Figure 5). The dosing process is fully automatic and dose weights accurate to within 2% of the target weight are achieved reproducibly. The dosing system is engineered to ensure that the homogeneity of the suspension is not compromised during the filling of the blister pockets—the fill/form machine was specially designed and built for the Zydis project.

Once dosed, the water in the suspension is frozen within the blister pockets by passing the blister trays through a liquid-nitrogen freezing tunnel. The freezing temperature and duration of transit through the tunnel are carefully controlled to yield frozen units which have the required structural characteristics to ensure the high quality of the finished product with regard to strength, stability and rapid disintegration time. The frozen units are loaded into refrigerated cabinets before the freeze-drying process. This enables dosing and freezing to continue while the freeze dryer is being prepared to process the batch. It also enables amorphous material to be re-crystallized should this change be required for stability.

Figure 5. Form-fill blister-pack machine.

Table 4. Influence of packaging material on diameter of the Zydis unit.

Storage	Packaging material			
	200 μm poly (vinyl chloride)/ $40\,g^{-2}$ PVdC	200 μm poly (vinyl chloride)/ $90\,g^{-2}$ PVdC	200 μm poly (vinyl chloride)/ $40\,g^{-2}$ PVdC in foil pouch	Aluminium blister pack
Initial diameter (mm)	15·0	14·8	15·0	16·3
1 month 37°C; 75% relative humidity	12·2	14·0	14·3	16·3
2 months 37°C; 75% relative humidity	12·5	12·5	14·4	16·3
3 months 37°C; 75% relative humidity	11·1	12·2	14·3	16·4
3 months 37°C; 70% relative humidity	14·3	14·2	14·4	

PVdC, polyvinyldichloride.

Figure 6. Freeze dryer.

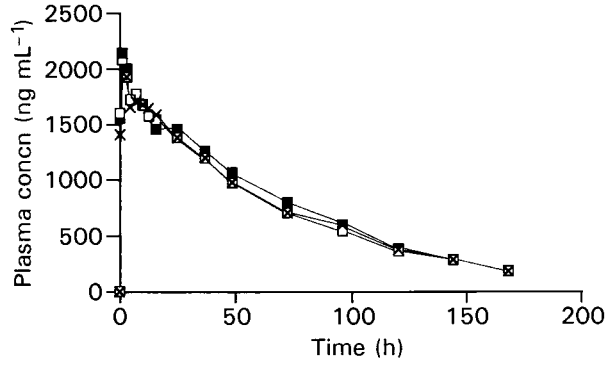

Figure 8. Bioavailability of 20 mg piroxicam from feldene capsules (■) and from the Zydis dosage form with (×) and without (□) water (Data on file).

The frozen units are loaded on to the shelves of a large freeze-dryer (Figure 6) designed to enable rapid processing by rapid removal of large volumes of vapour without melt-back. The dryers used in the production process have shelf areas ranging from 60 to 174 square metres allowing freeze-dried product to be produced economically on the commercial scale. The drying process removes all ice by sublimation and produces Zydis units which are very porous. The pore network is extensive and it is this structure which enables Zydis units to disintegrate instantaneously in the mouth.

Once dried, the Zydis units in the blister packs are sealed by passing the units through a blister-sealing machine loaded with an appropriate covering sheet such as aluminium foil or an aluminium foil-paper laminate. The blister packs are cut into units of the requisite size and the foil is perforated to enable ease of use during dose administration. The blister packs, which might be pouched, are finally packaged, with the appropriate information leaflet, into cartons to produce the labelled product ready for distribution.

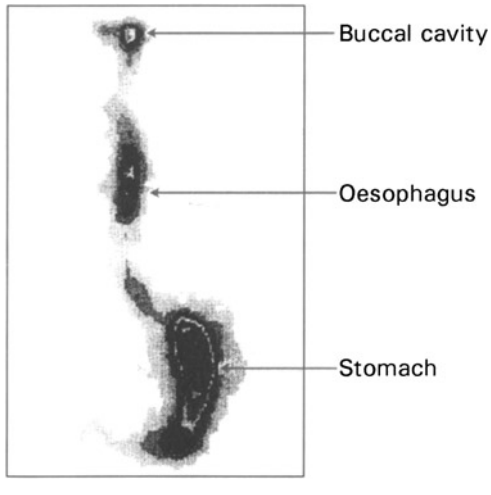

Figure 7. Gamma-scintigraphy photograph showing that particles from Zydis formulations swallowed in saliva coat the buccal, pharyngeal and gastric mucosa.

Bioavailability

When Zydis units are administered orally, the product makes contact with the saliva in the mouth and the structure disintegrates instantaneously. Insoluble drugs disperse in the saliva and are swallowed in the normal way. The time taken for the medication to pass from the mouth to the stomach, as a result of the swallowing process, is between 5 and 10 min (Schroeder 1986; Wilson et al 1987, 1988; Washington et al 1989). On entering the stomach the drug is dispersed over the gastric mucosa (Figure 7) and dissolves in the gastric fluid. The dissolved active material then passes into the small intestine and is absorbed into the bloodstream (Ansseau et al 1984; Barrett et al 1984; Brampton & Plantevin 1985; Smith et al 1985).

The overall dissolution rate of water-insoluble drugs from Zydis dosage forms in the fluids of the gastrointestinal tract is, therefore, similar to that from standard oral dosage forms and the bioavailability of such water-insoluble substances in Zydis units is equivalent to that of high-quality tablets and hard gelatin capsules. A typical blood level curve for a Zydis formulation compared with that of a standard oral dosage form is shown in Figure 8.

Many low doses (<60 mg) of water-soluble drugs of moderate to low molecular weight and with pKa values enabling un-ionized material to exist at buccal pH in reasonable quantities dissolve in the saliva and are absorbed into the bloodstream through the membranes of the mouth, pharynx and oesophagus during the swallowing process. Improved absorption and bioavailability are observed for such drugs; an example is selegiline (Figure 9).

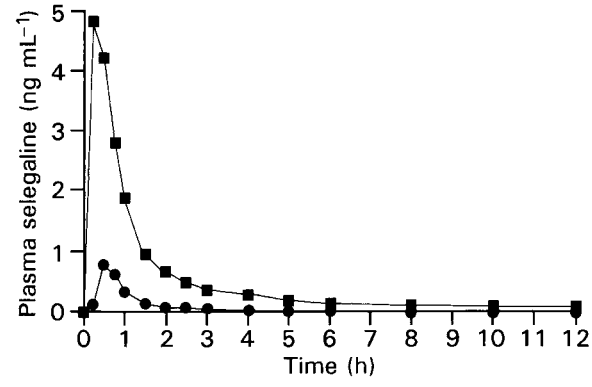

Figure 9. Bioavailability of 10 mg selegiline from Movergan tablets (●) and from the Zydis dosage form (■) (n = 23).

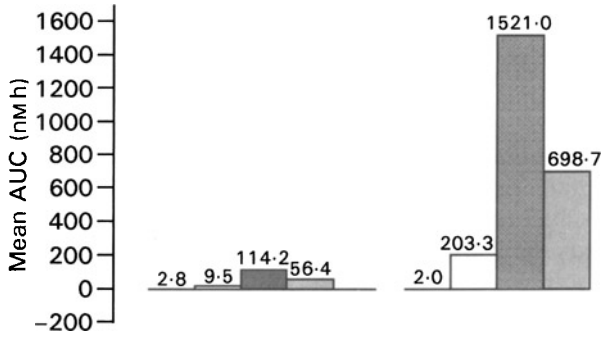

Figure 10. Bioavailability of selegiline and selegiline metabolites (which have undesirable pharmacological activity) from 1.25 mg Zydis selegiline (left) and from 10-mg Movergan tablets (right): ■ selegiline; □ *N*-desmethylselegiline; ■ methamphetamine; ▒ amphetamine.

Lower doses of such drug formulations can therefore be used to furnish blood-level concentrations and therapeutic activities equivalent to those of higher-dose standard products (Figure 10). Also, because pre-gastric absorption avoids the possibility of first-pass hepatic metabolism, the concentrations of the metabolites of such low-dose products are much reduced. This can lead to clinical advantages if the metabolites are responsible for undesirable side-effects.

Conclusions

The Zydis fast-dissolving dosage form is ideal for many groups of patients including geriatrics and paediatrics and for those people who have difficulty swallowing. Many drugs can be formulated in this form and satisfactory stability can be achieved under conditions of high humidity through judicious choice of packaging material.

An important benefit of this dosage form is the ability to provide the advantages of a liquid medication in the form of a solid preparation. This feature enables the patient to take the dose as directed at any time without inconvenience. A second key advantage is that, for some water-soluble drugs, pre-gastric absorption can result in improved bioavailability and, as a result of a reduced dosage, improved clinical performance through a reduction in unwanted side-effects.

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