

STABILITY OF MEDICINAL PRODUCTS IN COMPLIANCE DEVICES

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A MEDICATION compliance device can be defined as a container or device which is normally designed to hold solid oral dosage forms for a defined period and serves to remind a patient to take his medication, reduces dose schedule/timing errors and facilitates self-monitoring of medication intake. A compliance device can be filled by the patient, a carer or a pharmacist.

The above definition excludes controlled dosage systems such as the Manrex, Penn, Baxa and Nomad systems, which are not designed to be filled by the individual patient or their carer.

The use of a medication compliance device by a patient involves the transfer of medication from the manufacturer's original pack, or from the container in which it was dispensed by the pharmacist, to the compliance device. Despite the widespread use of medication compliance devices there is little available data regarding the stability of medicinal products when placed and stored in them or even whether a stability problem does or does not exist.

As a first step to determining if any stability problems exist it was decided to elicit the view of pharmaceutical manufacturers on the stability of their products in medication compliance devices.

METHOD

A letter was forwarded to the United Kingdom addresses of 57 pharmaceutical manufacturers of solid oral dosage forms listed in the 1989/90 Data Sheet Compendium.¹ The letter was mailed in August, 1990. Each manufacturer was asked to indicate which of its solid oral dosage forms could not be transferred to a compliance device. It was said in the letter that the compliance device under study was:

- (i) For use by elderly patients in the home care environment,
- (ii) Designed to hold seven days of solid oral dosage medication,
- (iii) Manufactured from combinations of styrene and acrylic polymers,
- (iv) Not airtight,
- (v) Not resistant to light.

RESULTS

Information from 53 pharmaceutical manufacturers was received between September, 1990, and January, 1991. The replies are summarised in the Table. A follow-up letter was not forwarded to the four manufacturers who failed to supply the required data.

DISCUSSION

The information supplied by manufacturers reflected the anxieties the pharmaceuti-

Manufacturers' views on whether their products can be transferred to compliance devices have been surveyed.

The results are tabulated here. There is a scarcity of short-term stability data

cal industry has regarding the transfer of medication from original packs to compliance devices. The replies also reflected the constraints imposed by legislation and ranged from the pragmatic ("Whilst we have no specific stability data in the device under consideration, our extensive stability studies would indicate that no problems should be anticipated") to the conservative ("Stability testing has not been carried out in the device under consideration, supporting data is lacking and therefore transfer of medication to a compliance device is not recommended").

Even when pragmatic responses were elicited, the response of different manufacturers of the same medicinal product were conflicting. The recommendations for the transfer and storage of nifedipine, and isosorbide dinitrate and mononitrate preparations, serve to illustrate this point. One cannot be sure when examining data from the present survey, and when considering the above examples of conflicting information, whether:

- (i) One manufacturer was being more cautious than another,
- (ii) One manufacturer had more detailed and specific information than another, or
- (iii) The manufacturing process employed by different companies conferred different storage properties.

One must be sympathetic to the position in which each manufacturer was placed when responding to the survey letter. According to the terms of each product licence held by a company, transfer to any type of compliance device could not be recommended without an assessment of the stability of the product in the device in question being carried out, and the product licence changed accordingly. Moreover, it was often difficult for manufacturers to comment about their products in the absence of firm data on the moisture and light resistant properties of the compliance device. From the manufacturers' viewpoint the removal of

any drug from the environment in which it has undergone stability testing, to one where it has not, must reduce or invalidate the shelf life indicated on the label and agreed with the Medicines Control Agency.

Despite the limitations of the survey discussed above, general guidelines for the optimal storage of solid oral dosage forms in compliance devices can be compiled from the results. The guidelines would require that compliance devices should be stored at ambient temperature, in a dry environment and away from direct sunlight. Because compliance devices have a limited available space for each medication dose, are not airtight and offer less moisture and light resistance than original packs, certain medicinal products are particularly unsuitable for transfer to them. Such products include effervescent preparations (eg, Klorof effervescent tablets), dispersible tablets (eg, Madopar and Aspav dispersible tablets, Betnesol and Prednesol tablets), moisture sensitive tablets (eg, Buccastem and Temgesic tablets), large solid oral dosage forms (eg, Gaviscon tablets), and unstable preparations (eg, glyceryl trinitrate tablets).

The survey undertaken would suggest that the majority of solid oral dosage forms ingested by elderly patients could be quite safely transferred and stored in a compliance device for a seven day period. However, there are important exceptions to this rule and patients, pharmacists, clinicians, nurses and other health care staff must be aware of these exceptions.

CONCLUSIONS

There are many pharmaceutical reasons why patients should not use compliance devices (or medication should not be transferred to controlled dosage systems such as the Manrex, Penn, Baxa or Nomad systems). Pharmaceutical companies consider that they go to a great deal of trouble to design packs which protect medicines from adverse forces, with particular regard to light and moisture.

Extensive stability work is carried out to ensure that such packs are suitable.

The pharmaceutical industry considers it a retrograde step to subsequently transfer the contents to other containers.² However, when medication passes into patient ownership a wide array of insults may befall it. Compliance devices will not necessarily make matters worse.

The reality of the situation needs to be recognised. Short-term stability data derived under defined conditions, and without the protection of the original packing should be available for all medicinal products. Alternatively, manufacturers should be required to indicate those products for which there is an absolute contraindication to short term stor-

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age in the absence of original packaging. Such information would permit the patient, pharmacist, doctor or health care worker to assess the true significance of stability problems should a medicinal product need to be removed from its original pack several days prior to administration.

This survey has revealed that whilst some data can be obtained from the pharmaceuti-

cal industry, short term stability data is not readily available in a practical format. This study is a first attempt to remedy the defect.

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REFERENCES

1. Data Sheet Compendium. London: Association of the British Pharmaceutical Industry, 1990-91.
2. Massam ADW. Personal communication from the secretary of the Association of the British Pharmaceutical Industry. On file. November, 1990.

Table: Survey of recommendations from pharmaceutical manufacturers on the storage of their solid oral dosage forms in a compliance device for seven days

Company	Product	Recommendations	Rationale	Other comment
Astra	Losec capsules	Transfer not recommended	Very hygroscopic with resulting damage to enteric coating	
Akzo	All other products	Problems not expected		
	Bolvidon tablets	Problems not expected		Known to be stable in dark polystyrene or polyethylene containers
	Oradexon tablets	Problems not expected		
	Obvestin tablets	Problems not expected		
Bayer	Adalat range	Transfer not recommended	Light sensitive	Degradation likely to be minimal under normal light conditions
Boehringer Ingelheim	All products	Problems not expected		
Boehringer Mannheim	Sustamycin capsules	Transfer not recommended	Must store in well closed containers below 30°C	
Britannia	Eldepryl tablets	Problems not expected		
Ciba-Geigy	Apresoline tablets	Transfer not recommended	Must protect from heat and moisture	
	Esidrex tablets	Transfer not recommended	Must protect from moisture and dispense in a moisture proof container	
	Ismelin tablets	Transfer not recommended	Must protect from moisture	
	Metopirone capsules	Transfer not recommended	Must protect from heat and moisture	
	Navidrex tablets	Transfer not recommended	Must protect from moisture	
	Orimeten tablets	Transfer not recommended	Must protect from heat, light and moisture	
	Rimactane capsules	Transfer not recommended	Must protect from heat and moisture	
	Rimactazid tablets	Transfer not recommended	Must protect from heat and moisture	
	Serpasil tablets	Transfer not recommended	Must protect from heat, light and moisture	
	Serpasil-Esidrex tablets	Transfer not recommended	Must protect from heat, light and moisture	
	Slow Fe tablets	Transfer not recommended	Must protect from heat and moisture	
	Slow Fe Folic tablets	Transfer not recommended	Must protect from heat	
	Trasicor tablets	Transfer not recommended	Must protect from moisture	
	Trasidrex tablets	Transfer not recommended	Must protect from heat, light and moisture	
	Anafranil capsules	Transfer not recommended	Must protect from moisture	
	Anafranil SR tablets	Transfer not recommended	Must protect from heat and moisture	
	Anturan tablets	Transfer not recommended	Must protect from heat and moisture	
	Butacote tablets	Transfer not recommended	Must protect from heat and moisture	
	Butazolidin tablets	Transfer not recommended	Must protect from moisture	
	Lamprene capsules	Transfer not recommended	Must protect from heat and moisture	
	Lopresor tablets	Transfer not recommended	Must protect from moisture	
	Lopresoretic tablets	Transfer not recommended	Must protect from moisture	
	Metoros/Metoros LS tablets	Transfer not recommended	Must protect from heat and moisture	
	Pertofran tablets	Transfer not recommended	Must protect from moisture	
	Sinthrome tablets	Transfer not recommended	Sinthrome is light sensitive. Must store and dispense in original or dark container	
	Symmetrel capsules	Transfer not recommended	Must protect from heat and light	
	Tegretol Chewtabs	Transfer not recommended	Must protect from heat and moisture	
	Tegretol Retard tablets	Transfer not recommended	Must store below 25°C and protect from moisture	
	Tofranil tablets	Transfer not recommended	Must protect from heat and moisture	
	Voltarol tablets	Transfer not recommended	Must protect from heat and moisture	
	Voltarol dispersible tablets	Transfer not recommended	Must protect from heat and moisture	
	Voltarol Retard tablets	Transfer not recommended	Must protect from heat and moisture	
Cilag	All products	Problems not expected		The number of capsules required on a given day may exceed the storage space available in a device
Cox	All products	Transfer not recommended		Unwilling to indicate possible stability
CP	All products	Transfer if deemed necessary		
Delandale	All products	Problems not expected		Uncoated tablets placed next to highly coloured products will become soiled
Evans	Glyceryl trinitrate tablets	Transfer not recommended	Absorption of drug into container and into adjacent dose forms with consequent loss of potency	
Farmitalia	All other products	Problems not expected		
	Cedocard tablets	Transfer not recommended	Deteriorate rapidly when in contact with plastic	
	Mono-Cedocard tablets	Transfer not recommended	Deteriorate rapidly when in contact with plastic	
	All other products	Problems not expected		Unsuitable to split Temazepam Planpack

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Company	Product	Recommendations	Rationale	Other comment
Fisons	Frusene tablets Nalcrom capsules	Transfer not recommended Transfer not recommended	Must protect from light Gelatin capsule will absorb moisture. Sodium cromoglycate is hygroscopic	
Geistlich	Anaflex lozenge	Problems not expected		
Gist-Brocades	All products	Problems not expected		Also expect no problems when stored in close proximity to other tablets or capsules
Glaxo (including Allen & Hanburys, Duncan Flockhart)	Zantac tablets Cephalosporin tablets Volmax tablets	Problems possible at high humidity Caution required Transfer not recommended	If ranitidine hydrochloride rises above UK ambient humidity, dramatic deterioration occurs Cross contamination Performance is a function of coating and laser-drilled hole	Special controls to detect pinholing in Zantac foils in operation Damage to product unlikely if retained in original protective packaging
	All other products	Problems not expected		
ICI	Nolvadex tablets Razoxin tablets	Transfer not recommended Transfer not recommended	Photodegradation Cytotoxic	
Janssen	All products	Transfer not recommended	Stability data not available	
LAB	All products	Problems not expected		
Lederle	Minocin tablets Diamox Sustlets All other products	Transfer not recommended Transfer not recommended Problems not expected	Must protect from light Must protect from light	
Leo	One-alpha capsules Selexid tablets	Transfer not recommended Transfer not recommended	Moisture sensitive Should be kept dry and at a temperature of less than 25°C	
	Treosulfan capsules All other products	Transfer not recommended Problems not expected	Alkylating agent, moisture sensitive	
Lipha	All products	Problems not expected		
Lundbeck	All products	Transfer not recommended	No stability data available	
Macarthy's	Glyceryl trinitrate tablets	Transfer not recommended	Absorption of drug into container and into adjacent dose forms with consequent loss of potency	
	All other products	Problems not expected		
Merck	All products	Problems not expected		Gaminil tablets may discolour as tablet coating is sensitive to humidity
Merck Sharp & Dohme	All products	Transfer not recommended	No stability data available	
Merrell Dow	Merothol lozenges All other products	Transfer not recommended Problems not expected	Odour from menthol	
Napp	All products	Problems not expected		Extensive data available on stability in PVC and polypropylene packaging
Nicholas	All products	Transfer not recommended	No stability data available	
Norgine	All products	Problems not expected		Transfer to compliance device not recommended since stability data not available
Pharmacia	All products	Problems not expected		Extremes of damp and light must be avoided
Pharmax	All products	Problems not expected		
Reckitt & Colman	Buccastem Temgesic	Transfer not recommended Transfer not recommended	Designed to dissolve in oral cavity so will be sensitive to moisture Designed to dissolve in oral cavity so will be sensitive to moisture	
	Senokot	Problems not expected		
Rhône-Poulenc	All products	Transfer not recommended	No stability data available	
3M Riker	Hiprex All other products	Transfer not recommended Problems not expected	Hygroscopic even on short term storage	
Roche	Diamorphine tablets	Transfer not recommended	Must protect from light and store in dry place Must protect from moisture and light Must store in dry place Must protect from light	
	Mestion tablets Natulan capsules Roaccutane capsules Tigason capsules All other products	Transfer not recommended Transfer not recommended Transfer not recommended Transfer not recommended Problems not expected		
Roussel	All products	Problems not expected		
Sanofi	Epilim tablets	Transfer not recommended	Sodium valproate is extremely hygroscopic and may soften and liquefy	
	All other products	Problems not expected		
Schering	All products	Transfer not recommended	No stability data available	
Schwarz	Diocetyl tablets All other products	Transfer not recommended Problems not expected	Must protect from moisture	
Servier	All products	Problems not expected		
Smith & Nephew	All products	Problems not expected		
Smithkline Beecham	All products	Transfer not recommended	No stability data available	
Steinhard	All products	Transfer not recommended	No stability data available	
Stuart	All products	Problems not expected		
Syntex	All products	Problems not expected		
Upjohn	All products	Transfer not recommended	No stability data available	
Warner Lambert	All products	Problems not expected		