Journal of Thermal Analysis, Vol. 38 (1992) 1729-1744

THE USE OF SOLUTION THERMOCHEMISTRY IN QUALITY CONTROL METHODS IN PHARMACEUTICAL ANALYSIS

L. S. Bark and E. J. Greenhow+*

*UNIVERSITY OF SALFORD, SALFORD, M5 4WT
+BIRKBECK COLLEGE, UNIVERSITY OF LONDON, LONDON, ENGLAND

(Received March 8, 1992)

Some of the procedures that have been reported for the determination of the active ingredients in dosage forms of some ethical pharmaceutical products are reviewed. The requirements of methods for quality control and the advantages of using thermochemical methods to achieve them are discussed.

Keywords: dosage form, pharmaceutical products, quality control, solution analysis

Introduction

In the pharmaceutical industry there are several categories of analysis depending on the stage of production of the pharmaceutical product and use of the results provided by the analysis. Analysis for "Quality Control" is concerned with the analysis of starting products, intermediaries and the synthesized active ingredients. Such analysis may use many of the methods used for the determination of the purity of single organic substances.

One of the main areas of analysis for "Quality Control" is concerned with the analysis of the substance used as the active ingredient in the pharmaceutical product after its incorporation into the dosage form. Other areas of analysis are

* Correspondence to whom should be addressed.

John Wiley & Sons, Limited, Chichester
Akadémiai Kiadó, Budapest

associated with clinical analyses when the active ingredient, or its metabolites are assayed after a clinical use of the active ingredient.

The amount of active ingredient in a dosage form depends upon the activity of the active ingredient. Some active substances are dispensed in microgramme amounts per dose, others, less active, are dispensed in milligramme amounts and some are dispensed in even larger amounts.

This review is restricted to the assay of those active substances which are dispensed in milligramme or greater amounts per dose. This covers the bulk of the ethical chemicals sold world-wide.

The use of some thermal methods for the determination of substances of pharmaceutical interest has been reviewed by several workers, for example, classical thermal analysis by Giron [1] and some thermometric by Burgot [2]. Grime [3] has given a fairly comprehensive review of some of the methods used up to 1985. These reviews are, however, restricted to the determination of the pure compounds which could be used as the active ingredients in dosage forms for medicinal purposes and could be considered to be applicable to quality control methods.

This present review is concerned with the application of methods of solution thermochemistry to the determination of dosage forms of ethical pharmaceuticals and the use of the results, for control purposes, at any point in the various stages from formulation to the presentation of the product to the user.

The determination of the active ingredient in ethical pharmaceutical products has formed the raison d'être for the publication of the many pharmacopoeia that are currently being used in analytical laboratories. However, most pharmaceutical products are formulated in "dosage forms" in which the active ingredient may only be a minor constituent (with respect to concentration) and assay of the dosage form and the dosage amount are very important. Dosage forms are usually of one of the following types: Injection solutions, tablets and capsules, lignites and solutions for oral ingestion and salves and ointments (in paste or cream forms) for external application.

Dosage forms of those substances, which may be dispensed as simple, relatively dilute solutions of the active ingredients, may be assayed by the "usual" methods of analysis, but many dosage forms have the active ingredient associated with solid diluents, which are incorporated to allow for ease of dispensing and in many cases to give a dosage form (say a tablet) of such size that accidental overdosage is minimised. Other dosage forms may be diluted with liquids to enable easy dispensation and there is often the introduction of other non-active ingredients to give the commercial product aesthetic appeal such as an acceptable apparent homogeneity and colour or to increase the commercial value by increasing storage and shelf life of the product. It is important that these diluents be inert towards the active ingredient and towards the patient.

The diluents added to allow for ease of dispensing of solid dosage forms often include substances such as starch, sugars (sucrose, glucose, fructose and lactose,

which are often used in the hard coatings used for tablets), hydroxycelluloses, calcium stearate, calcium lactate and the equivalent magnesium compounds. Salves, ointments etc. are often diluted with gums, hydrocarbons of medium molecular weight (oils and low melting point waxes), and with emulsifying agents if aqueous systems are used. Lictus etc. often contain the active ingredient diluted with water and non-toxic alcohols such as ethanol and glycerol.

The aesthetic additives are generally legally accepted food colourants and flavourings. The colourings also serve to identify and distinguish some dosage forms. Additionally during the manufacture of the dosage form it may be necessary to use mould release agents such as salts of long-chain fatty acids applied to the mould to ensure the rapid release of the commercial product. With so many materials additional to the active ingredients, it is found that many of the usual methods proposed in the pharmacopoeia cannot be used on the dosage form without prior separation of the active ingredients. This is done either to enable the active ingredient to be made volatile, as for GLC, or to remove materials with analytical functionalities similar or sufficiently similar to the active ingredient to interfere with the spectrometric assay of the active ingredient. It is also necessary to remove those materials which are insoluble in the solvents used in these techniques and which would interfere either by absorption or scattering of radiation. Mass spectroscopic methods require removal of at least some of the additives in order to give spectra which are sufficiently simple to allow of quantitative determination. Many electrometric methods suffer interference from the diluents which are frequently surface-active agents. Since many of the additives are insoluble in the solvents used in HPLC to chromatograph the active ingredient, separation of these from the active ingredient becomes necessary when using this technique.

Approved pharmacopoeia methods often require the use of relatively large amounts of the dosage form to be sampled and then subdivided to obtain the amount appropriate to the specified technique. Many of these techniques are highly sensitive and hence require very small amounts of total sample. If the active ingredient is in a relatively low concentration in the sample, it may be necessary to separate it from the other substances in order to obtain an analysis sample containing a sufficiently high concentration to give the precision required. Whenever separation of the active ingredient is necessary, labour costs, the time for analysis and the probability of error are increased.

In many cases the amount of active ingredient analysed has little correspondence to the amount required for an actual dose and it may be argued that for quality control purposes it is better to be able to assay random single dosage amounts, in the dosage form, than to have to use several dose amounts with inequalities in individual dose amounts being "smoothed out" by the sampling procedures.

Several of the techniques of solution thermochemistry have been used in quality control situations. Whilst some of the procedures reported involve the use

of aqueous media, the majority of the analyte reactions involved may be classified as "organic reactions" and require the use of non-aqueous media for dissolution of the analyte and the availability of fast reactions. The various techniques and problems associated with the use of solution thermochemistry for organic functional group analyses have been previously reviewed [4].

In contradistinction to many of the procedures recommended in pharmacopoeia which require the media used to be rendered either radiation transparent or electroconducting, one of the main advantages of using solution thermochemical methods is that the use of organic solvents as the media offers many advantages. Since all of the solvents used have a specific heat less than that of water, and energy changes in them are manifested as greater thermal changes than would occur in aqueous media, the sensitivity of the procedure is enhanced. Similarly, since in these commercial formulations, the organic active ingredient is not chemically combined with any of the inorganic fillers, but is simply mixed with them, the organic parts of the dosage form may be dissolved, leaving the inorganic parts as inert suspensions in the stirred reaction medium where they will have no effects on the accuracy or reproducibility of the procedure.

Many of the active ingredients used in pharmacy contain analytically functional groups which are either acidic or basic. Many are relatively weak organic acids or bases. The nature of the particular non-aqueous solvents selected for use can enhance the acid-base properties of the functional group of the analytes. The strength of a substance as an acid or a base in a particular solvent depends upon the type and degree of ionisation of the compound. This is determined by the dielectric constant of the medium and on its autoprolytic constant. In a solvent with a stronger acidity than that of water, the strength of acids weaken or disappear while those of bases increase; the basicity of strong bases is levelled and that of weak bases, especially very weak bases, is differentiated. In a solvent with a stronger basicity than water, the above phenomena are reversed. In a differentiating solvent with a low dielectric constant, e.g. isobutyl methyl ketone, both acids and bases can be titrated within certain limits.

The thermometric titrimetric methods used include those incorporating both simple direct and indirect titrations using the heat changes produced by the reaction of the analyte with the titrant as the indicator system and also catalysed systems using a reaction of the solvent with the titrant as the indicator.

The technique of "Direct Injection Enthalpimetry" (DIE) has also been widely used. The advantages of using this technique in routine analysis have been previously discussed [5]. Since it is essentially a "comparison method" capable of giving results rapidly and generally reproducible within 1%, it is appropriate as a method for quality control purposes.

In most methods of analysis recommended by the pharmacopoeia there are problems posed by the excipients. These are generally obviated in assays employing solution thermochemistry. Excipients are generally designed to be inert towards acidic solutions with *pH* values above 0.5–1.0 since they would other-

wise react with the gut fluids, possibly with deleterious side reactions, and from a commercial standpoint they must not be affected by water or moisture. Any reactions they undergo with solvents having aqueous acidic properties cannot affect the analyte or else stability on storage of the dosage form would be affected adversely unless stringent precautions were taken to exclude all moisture from the packing even after a multiple package (such as a glass container) was opened and the moist ambient air was allowed to enter. Thus, any reactions such as these will not affect the amount of the analyte if the dosage form is dissolved or suspended in aqueous media. Any thermal effects from any such reactions will have no effects on the ease of location of the equivalence points in thermometric titrations and are accounted for in DIE systems when the system is allowed to come to thermal equilibrium before the reagent is injected into the sample solution. It is therefore generally not necessary to separate the analyte from the excipients in the type of assay procedures described in this paper.

Tests must be made to ascertain whether any of the excipients react with the reagents used to determine the analyte. Since quality control is generally done in the laboratories of the manufacturer formulating the dosage form, samples of the pure analyte and of the excipients are readily available. This enables calibration to be made using samples of the dosage form spiked with pure analyte or with any of the excipients. If the plot of amounts of dosage form, (spiked and unspiked) against the heat pulse (in DIE) or against the volume of titrant (in thermometric titrations) pass through the origin then it may be concluded that the excipients do not interfere in the assay.

The choice of the method used to ascertain the effects of excipients is arbitrary. In one of the authors' (LSB) laboratories, various methods have been used depending generally on the availability of the materials in the dosage form. For example:

Using samples "spiked" with the active ingredient

In thermometric titration procedures

Antitubercular formulations have been determined using a thermometric titration procedure [6] in which the possible effects of added excipients was ascertained by using known amounts of the active ingredient to "spike" samples of the dosage form.

Known weights (20–70 mg) of crushed isoniazid tablets nominally containing 0.1 g of isoniazid per 0.3 g tablet were stirred with distilled water and aqueous potassium hydroxide (14 ml of 20%w/w) and titrated with potassium ferricyanide solution (0.6 *M*).

Known weights of recrystallised isoniazid were treated in an identical manner and a factor relating the concentration of the KOH solution to the amount of isoniazid was obtained.

Known amounts of the recrystallised isoniazid were mixed with known weights of the crushed tablets and the mixtures treated as above.

From the three series of results obtained it was possible to calculate the effects of any excipients present in the tablets. No effect was noted.

In DIE procedures

An amoebicide formulation containing Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) was assayed by using the reaction between the analyte and bromine in glacial acetic acid in a DIE procedure. To investigate the effects of excipients, a calibration curve was prepared using the pure analyte.

Known amounts of the dosage form were assayed with and without added analyte. The results indicated that the additional heat changes caused by the additions of extra analyte were in agreement with the previously prepared calibration curve [7].

Effect of mixing active ingredient with excess amounts of excipients

Catalysed thermometric titrimetry

Several barbiturates were assayed thermometrically by use of a catalysed solvent system [8].

Known amounts of the authentic active drug were mixed with excess amounts of the excipients known to be used in the formulation of the dosage forms. The results are given in Table 1.

Table 1

Compound	Excipient	Weight of active ingredient	
		Added / mg	Found / mg
Quinalbarbitone	Talc (1.0 g)	47.66	47.74
	Magnesium stearate (0.15 g)	47.66	47.59
	Lactose (1.3 g)	47.66	47.60
	Starch (1.0 g)	47.66	48.50

Similar results were reported for butobarbitone, pentobarbitone, hexobarbitone and phenobarbitone.

A fairly wide range of pharmaceutical compounds has been assayed during the last few decades. All of the modern instrumental techniques of solution ther-

mochemistry have been used, the choice being generally governed by the chemical nature of the analyte and in some cases by the nature of the excipients. Table 2 lists those materials which have been so assayed. (Earlier works, involving manual titrations are omitted. Reference for these should be made to standard texts on thermometric titrimetry).

Table 2 The application of solution thermochemistry to selected pharmaceutical products

Classification	Analytes	Reagents/ technique	Reference
Analgesics and	Antipyrine (phenazone)	F, G, G, H	14, 28, 35, 36, 37
Anti-inflammatory	Methyl salicylate	N	29
agents	Sodium salicylate.	J, G, G.	28, 35, 36.
	Acetylsalicylic acid	S	41
	Antipyrine	G	38
	Procain	B	9
Antibacterial	Tetracycline hydrochloride	L	24
agents	Phthalylsulphathiazole		
	Sulpha-(Sulfa-) drugs	A, N	20,21
Antidepressants	Amitryptyline hydrochloride.	J	13.
	Clomipramine hydrochloride	J	13.
	Imipramine hydrochloride	J	13.
	Imipramine maleate	J	13.
	Tryptophan	M	34.
Antiepileptics	Phenobarbitone (phenobarbital)	N	17, 28
Antihistamines	Diphenhydramine	K	12.
	Alimemazine tartrate	R, B	39, 2.
	Dimethothiazine mesylate	B	39
	Promethazine hydrochloride	R, B.	39, 2.
	Chlorpheniramine maleate	D, R	40
Antihypertensive	α-Methyl-L-Dopa	F, K&N, J&N	14, 22. 25.
agents	Propanolol	F	14
	1-phenyl-3-methyl-pyrazolone	F	14

Table 2 Continued

Classification	Analytes	Reagents/ technique	Reference
Antimalarial agents	Chloroquine	K, J&K	15, 23
	Chloroquine phosphate	J&K, L	23, 24
	Hydroxychloroquine	K	15
	Quinine/quinine hydrochloride	K	11
	Proguanil hydrochloride	K	15
	Pyrimethamine	K	15
	2,4-diaminopyrimidines	R	46
	Cinchonine	B, G	9, 36
Antimuscarinic agents	Atropine	B, K, K	9, 11, 12
	Atropine methonitrate	K	11
Antimycobacterial agents	Isonicotinoyl hydrazide (INA)	C, P, P, C	6, 26, 30, 43
	INA + ethambutol	K	16
	INA + rifampicin	K	16
Antiprotozal agents	Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline)	E	7
Anxiolytic Sedatives, Hypnotics and Neuroleptics	Barbitone (Barbital)	H, N	17, 28
	Substituted Barbitones	H	17
	Diazepam	J,L,J&K,J&K,D	19, 24, 25, 18
	Oxazepam	D	18
	Nitrazepam	D, J	18, 19
	Librium hydrochloride	L	24
	Chlordiazepoxide hydrochloride	D, L, J	18, 19, 24
	Lorazepam	J	19
	Medazepam	J	19
	Prochlorperazine maleate	J	19
Dermatological agents	Salicylic acid	J, N, N, M, S	27, 29, 31, 33, 41
	Resorcinol	N, N, M, S	29, 31, 32, 41
Disinfectans	Cetyltrimethylammonium bromide	P	30
	Cetylpyridinium bromide	P	30

Table 2 Continued

Classification.	Analytes	Reagents/ technique	Reference
Dopaminergic Anti-Parkinsonian agent	L-Dopa	F, K&N, J&K	14, 22, 25
Nutritional agents and Vitamins	Glycine	N, M	32, 34
	Valine	N, M	32, 34
	Histidine	M	34
	Cysteine	J&K, N	25, 32
	Cysteine hydrochloride	J&K, P	25, 26
	L-Alanine	J&K	25
	L-Leucine	J&K	25
	Vitamin B6	G	35
	Arginine	N	32
	D-α-alanine		
	DL-α-aminobutyric acid		
	DL-Norvaline		
	DL-Valine		
	DL-Leucine		
	L-Aspartic acid		
	L-Arginine hydrochloride		
	L-Serine		
	L-Threonine		
	DL-Methionine		
	L-Cysteine hydrochloride		
	L-Cystine		
	DL-β-phenyl-α-alanine		
	L-Tyrosine		
	L-Hystidine hydrochloride		
	DL-Tryptophan		
	L-proline	S	41
	Ascorbic acid	U, C	44, 45
	Thiamine	B	9
	Nicotinamide	D&R	40
Opoid Analgesics	Codeine and Codeine phosphate	B, K, K	9, 11, 12

Table 2 Continued

Classification	Analytes	Reagents/ technique	Reference
Penicillins	Penicillin G	T	42
	Ampicillin sodium	T	42
	Penicillin VK	T	42
Stimulants and Anorectics	Brucine	B, G, H	9, 38, 10
	Strychnine	B, K	9, 11
Supplementary drugs	Papaverine	H, K	10, 11
	Aminopromazine fumarate	R	2
Sympathometrics	Adrenaline acid tartrate	K&N, L, J&K	22, 24, 25
	Dopamine hydrochloride	K&N, J&K	22, 25
	DL-Noradrenaline acid tartrate	K&N, J&K	22, 25
	Ephedrine hydrochloride and sulphate		3
Tranquilisers	Trifluoroperazine hydrochloride	B	39
	Prochlorerazine bis-maleate acid	B	39
	Thioproperazine bis-methane sulphonate	B, R	39, 2
	Chlorpromazine hydrochloride	B, D&R	39, 40
	Levomepromazine hydrochloride	B	39
Xanthines	Aminophylline	A, R	40
	Caffeine (Theine)	H, K, K, L, J, G, H	9, 10, 11, 24, 27, 36, 37
	Theophylline	K, J	10, 27

The classification used is according to martindales extra pharmocopoeia

Reagents and techniques

	Reagents	Technique
A	Silver ion	T.T.
B	Silicotungstic acid	T.T.
C	Potassium Hexacyanoferrate(III)	D.I.E.
D	HCl in 50% ethanol	T.T.
E	Bromine in HOAc	T.T.

F	N-Bromosuccinimide	T.T.
G	Perchloric acid in HOAc/H_2O/Ac_2O	Cat.
H	Perchlorate in HOAc. Protons generated electrically	C.C.T.
J	Perchloric acid in HOAc; Ac_2O+diacetone alcohol	Cat.
K	Perchloric acid in HOAc; α-methyl styrene	Cat.
L	Perchloric acid in HOAc; acetals or cyclic ethers	Cat.
M	KOH in propan-2-ol; aldehydes or ketones	Cat.
N	KOH in propan-2-ol; acrylonitrile	Cat.
P	Iodine in dimethylformamid; vynil ethyl ether	Cat.
Q	Hypochlorite	T.T.
R	NaOH (aqueous)	T.T.
S	Hypobromite	D.I.E.
T	Enzyme	D.I.E.
U	Iodine monochloride	T.T.

Techniques

T.T.	=	Thermometric titrimetry
D.I.E.	=	Direct injection enthalpimetry
Cat.	=	Catalytic thermometric titrimetry
C.C.T.	=	Coulometric catalytic thermometric titrimetry

Discussion

The primary purpose of quality control is to ensure that the finished formulation in its dosage form is leaving the production line in a commercially acceptable condition and the composition, especially with regard to the active ingredient, is within the previously established commercial specifications.

A secondary purpose is to check if the product is still within these specifications after having been stored under normal conditions and under any accentuated commercial conditions, as may occur when the finished product is being sold where the standards of storage are not as strictly controlled as in manufacturers' storage facilities.

There are several viewpoints regarding the precision required for quality control measurements. For most pharmaceutical formulations the precision of the prescribed dose is not very high. For many of the drugs dispensed, it is still unusual to have amounts of individual doses calculated with relation to the exact body weight of the patient and for many of the salves and creams, which are applied externally, the dosage instructions are often "cover the affected area" or "apply sparingly" or "apply liberally". Thus methods of assay giving an accuracy

of 98% or better are generally industrially acceptable. Such a level of accuracy and precision is readily obtained by the various solution thermochemistry techniques available.

Although assurance of quality is essential in manufacturing processes, it adds to the overall costs of production. The costs incurred in quality control include: – the initial cost of apparatus; the running costs for the assay including costs of consumables and those incurred with maintenance and replacement of apparatus; all labour costs and the costs associated with the time required for the assay which in turn influence the costs of storage required whilst the results of the quality control are being assessed for possible use.

The overall cost of apparatus suitable for solution thermal analysis using either a thermometric titration system or a DIE system are approximately the same and it has been previously reported [5] to be significantly less than that of providing for chromatograph, UV/VIS and/or IR spectroscopy and of the same order as that for electrometric titrations using potentiometry.

Savings can be made using thermal methods in the running costs since the procedures generally use cheaper consumable materials than do other techniques. It is possible to use low cost disposable items for reaction vessels saving both on apparatus and the labour costs incurred in cleaning the apparatus prior to the next assay. The apparatus used is usually very robust, the procedures are mechanically simple and thus many procedures can be readily fully or partly automated.

All routine tests or assays are time-consuming and procedures must be devised to achieve results and useful information rapidly so that the information may be relayed to the various stages of manufacturing to correct any errors that have occurred. With modern industrial methods, any delays in the production line, caused by stopping the line to adjust the feed of one of the components of the dosage form can be very costly.

Any parts of the procedure which are time-consuming and which could be eliminated or shortened must be closely appraised. The various stages in the assay procedures from the receipt of the samples of the dosage form to the use of the information are generally as follows:

(i) Ensuring complete homogeneity of the material of the various tablets, capsules or samples or liquids, followed by sampling the homogeneous material.

(ii) Obtaining a known amount of the homogenised dosage form, either by weighing or by dispensing a known volume.

(iii) Dissolution of the known amount to obtain a solution of known concentration.

(iv) Separation of the active ingredient by reaction with one or more reagents, followed by either filtration or volatilisation of one or more of the components of the dosage form.

(v) Introduction of the sample of the active ingredient, in an analysable form (the analytical sample), to the apparatus of choice and processing it to obtain a

signal (usually electrical) which can be related to a parameter associated with the amount of active ingredient used in the analytical sample.

(vi) Calculation of the amount of active ingredient in the original sample of dosage form used to prepare the analytical sample and translation of the results from (v) to usable information (Stages (iii) and (iv) may be reversed, depending on the particular materials involved).

Additional time is required for cleaning the various pieces of apparatus to be reused in the next assay sample. These are often fragile glassware or precision instruments requiring careful handling to ensure long service.

Since one of the main costs in running an analytical laboratory is that of skilled labour, if any of the above stages (ii) to (vi) can be eliminated or made such that only semi-skilled labour is required, then costs associated with time and labour may be reduced. Additionally, if it is possible to eliminate all or parts of the washing and cleansing protocols by the use of low cost disposable apparatus, then costs will be further reduced.

Tablet making machines used in modern pharmaceutical manufacturing processes produce tablets and capsules of uniform weight. The reproducibility of tablet weights was studied in a series of investigations in one (LSB) of the authors' laboratories in which several batches of different tablets from different manufacturers were weighed.

The procedures involved weighing tablets using an analytical balance to obtain the weight of individual tablets (to the nearest 0.1 mg) from the following experiments:

(i) weighing each individual tablet from a manufacturer's sample batch (up to 1000 in a batch);

(ii) weighing individual tablets from a sample of randomly selected tablets (25 individually selected from a batch of 100 of the same tablet from the same manufacturer);

(iii) obtaining the average weight of a single tablet from weighing a series of 10 tablets (10x10 tablets obtained randomly from a batch of 1000);

and

(iv) obtaining the weights of 10 single tablets weighed individually 100 times.

The results showed that for tablets from any one manufacturer the differences in the weights of individual tablets, the apparent weight of a tablet in repeated weighings and the average obtained from weighing multiple numbers of tablets were within 1% of all means and generally were within experimental error.

Thus for use in quality control assays, with the dosage forms from any particular manufacturer, it is not necessary to weigh the tablets, it is necessary only to use one typical tablet as the analytical sample. Removal of the necessity for weighing the sample saves considerable time during a working day. It also eradi-

cates, to a large extent, minor errors caused by incorrect recording of the weights used since any error in the number of tablets used is immediately obvious, the results being a multiple of that expected. Since individual tablets are used, the total number of tablets used for quality control is significantly decreased and hence further cost savings are made.

When non-tabletted products are to be assayed it is possible to save time and money in analogous ways. For example, with salves and creams that are dispensed from tubes, it is noteworthy that the sizes of the orifices of a particular batch of tubes are constant. Thus, to dispense a constant amount of the product, it is only necessary to dispense a fixed length (volume) from the tube and the analyte samples are constant within experimental error. A simple platform capable of supporting a 1 cm^2 microscope cover slide arranged so that a length of the salve may be extruded from the tube onto the slide and then trimmed at the edges will enable a fixed amount of the salve to be placed (along with the cover slide) into the reaction vessel. The salve is removed by stirring the slide and contents in the reaction medium. The presence of the glass has no practical effect on the stirring and hence of the distribution of any heat changes. The heat capacity of the slides is very small and is constant and thus if calibration is done using the same procedure, any effect of the slide is thereby compensated.

Liquids and liquid emulsions, have been dispensed into the reaction vessel using plastic disposable syringes (2–5 ml capacity), the accuracy of such syringes is acceptable.

Conclusions

In all industrial procedures costs must be kept to a minimum. A rapid turnover of assured product in essential. Modern factory procedures endeavour to obviate packing errors both by "labelling" (often by colour-coding) the finished products and by having the finished products packed as soon as the quality is assured, this reduces the costs incurred in storing all the materials involved in the manufacture of the dosage formulation and the dosage form prior to its being packed ready for commercial distribution. Any errors of quality discovered after packaging and despatching the dosage form are extremely costly to correct.

It is generally recognized that automation can be a significant factor in speeding up the quality control procedures and methods which are simple to automate fully or partially are assuming importance in this field of industrial analysis.

The use of solution thermochemical methods in the quality control procedures for the pharmaceutical industry has not yet been explored and exploited to its full potential. Although Greenhow [47] reviewed the solution thermochemistry of many of the organic reactions that may be of potential use for assaying the purity

of organic substances in the pharmaceutical industry, only a few have been used for the analysis of dosage forms.

Grime [3] has reviewed the use of calorimetric methods of high sensitivity using biochemically selective reactions for the assay of biochemical systems of use in the pharmaceutical industry, but this area has not been explored to any great extent for formulations in dosage forms.

Chemical thermal methods, such as TG, DTA etc. have uses for the determination of the stability of solid pharmaceutical products and after identification of the decomposition products, the assay of these decomposition substances could well be done by procedures involving solution thermochemistry. Some initial studies are being done in this area for antimalarial agents. Although a fairly wide range of products can be assayed by thermal methods, there is no doubt that several aspects of the various fields of thermal analysis have yet to achieve their full potential in the field of quality control.

References

1 D. Giron, J. Pharm. Biomed. Anal., 4 (1986) 755.
2 J. L. Burgot, Talanta, 25 (1978) 339.
3 J. K. Grime, in "Analytical Solution Calorimetry" ed. by J. K. Grime, Wiley-Interscience, New York 1985. p. 215.
4 L. S. Bark, J. Thermal Anal., 21 (1981) 119.
5 L. S. Bark and N. Hadipranoto., J. Thermal Anal., 37 (1991) 183.
6 L. S. Bark and L. Kershaw, J. Thermal Anal., 18 (1980) 371.
7 A. A. Ankawi and L. S. Bark, J. Thermal Anal., 26 (1983) 139.
8 O. Ladipo, Ph.D. Thesis, University of Salford, 1974 (see also ref. 17).
9 L. S. Bark and J. K. Grime, Anal. Chim. Acta, 64 (1973) 276.
10 L. S. Bark and O. Ladipo, Unpublished work.
11 E. J. Greenhow and L. E. Spencer, Analyst, 98 (1973) 98.
12 Wu Qiao, Yang Qinghua and Yui Rugu, Nanjing Yaoxueyuan Xuebo, 15 (1984) 8 (see CA 101, (1984) 78927).
13 E. J. Greenhow and O. Ladipo, Anal. Chim. Acta, 172 (1985) 387.
14 U. M. Abassi, F. Chand, M. I. Bhanger and S. A. Memon, Talanta, 33 (1986) 173.
15 S. I. Ajiboye and L. S. Bark, J. Thermal Anal., 35 (1989) 1739.
16 S. I. Ajiboye and L. S. Bark, J. Thermal Anal., (in press)
17 L. S. Bark and O. Ladipo, Analyst, 101 (1976) 203.
18 P. Marcu and I. Grecu, Pharmazie, 31 (1976) 167.
19 E. J. Greenhow and O. Ladipo, Z. Anal. Chem., 321 (1985) 485.
20 L. S. Bark and J. K. Grime, Analyst, 98 (1973) 452.
21 E. J. Greenhow and L. E. Spencer, Anal. Chem., 47 (1975) 1384.
22 E. J. Greenhow and L. E. Spencer, Analyst, 98 (1973) 485.
23 P. C. Ngaramba, M.Sc. Dissertation, Chelsea College, University of London, 1984.
24 E. J. Greenhow and M. Kashnipour, Analyst, 110 (1984) 1209.
25 E. J. Greenhow and P. Vinas, Talanta, 31 (1984) 611.
26 E. J. Greenhow, Chem. and Ind., (1973) 697.
27 E. J. Greenhow, Analyst, 102 (1977) 584.
28 S. Duan, S. Li, M. Luo and P. Zhang., Yaoxue Tongbao, 21 (1988) 518 (see Analyt Chem., 62 (1990) (12) 4418 Ref 11).
29 E. J. Greenhow and L. E. Spencer, Analyst 98 (1973) 90.

30 E. J. Greenhow and L. E. Spencer, Analyst, 99 (1974) 82.
31 E. J. Greenhow and A. A. Shafi, Analyst, 101 (1976) 421.
32 E. J. Greenhow and A. A. Shafi, Talanta, 23 (1976) 73.
33 E. J. Greenhow, Chem. and Ind., (1974) 456.
34 E. J. Greenhow and L. E. Spencer, Talanta, 24 (1977) 201.
35 V. J. Vajgand, T. Pastor, T. Todorowski, F. F. Gaal and M. Todorovic, Proc. Anal. Chem. Conf., Budapest, 1966, 152.
36 V. J. Vajgand and F. F. Gaal, Talanta, 14 (1967) 345.
37 V. J. Vajgand, F. F. Gaal and S. S. Brusin, Talanta, 17 (1970) 415.
38 V. J. Vajgand, T. A. Kiss, F. F. Gaal and I. J. Zsigrai, Talanta, 15 (1968) 609.
39 J. L. Burgot, Ann. Pharm. France, 37 (1979) 125.
40 A. B. De Leo and M. J. Stern, J. Pharm. Sciences, 53 (1964) 993.
41 N. Malingerova and M. Malinger, J. Thermal Anal., 13 (1978) 149.
42 J. K. Grime and B. Tan., Anal. Chim. Acta., 107 (1979) 319.
43 L. S. Bark and L. Kershaw, Analyt. Proc., 18 (1981) 307.
44 L. S. Bark and J. K. Grime, Analyst. 99 (1974) 38.
45 L. S. Bark and L. Kershaw, Analyst., 100 (1975) 873.
46 E. Bosh, J. Guiteras, A. Izqueirdo and M. D. Prit., Mikro. Chim. Acta., (II) (1985) 339.
47 E. I. Greenhow, Chem. Revs, 77 (1977) 835.

Zusammenfassung Es wird der Überblick über einige beschriebene Verfahren zur Bestimmung der Wirkstoffe in Darreichungsformen einiger rezeptpflichtiger pharmazeutischer Erzeugnisse gegeben. Die Anforderungen an Verfahren zur Gütekontrolle und der Vorteil von thermochemischen Methoden dabei wird diskutiert.