CHAPTER 2

MATERIALS, APPARATUS, METHODS AND PRELIMINARY INVESTIGATIONS.

2.1 Introduction.

This chapter describes the preliminary steps and methods necessary to derive a formulation suitable to study the effect of some of the factors involved in tablet production on those tablets. The materials used were taken from the same batches except for the bulk concentrated hydrochloric acid, the technetium solutions used in the liquid uptake studies and the distilled water. Table 2.1 is a summary of the apparatus and manufacturers. Table 2.2 lists the materials and the suppliers.

2.2 Material Preparation

Two size fractions of paracetamol were prepared on an Alpine Multiplex Zigzag classifier model A100MZR. This separates the input material by means of centrifugal force opposed by an airstream. Heavier particles are thrown to the rim of a spinning disc through zig-zag channels whilst lighter particles are carried to a central outlet port by the airstream, (Figure 2.1). The disc speed and airflow were calculated from calibration data provided with the machine based on limestone dust samples and Equations 2.1 and 2.2.

$$V = 55 - N / 1000 \qquad (2.1)$$

where V is the volumetric airflow in m^3hr^{-1}
and N is the rotor speed in rpm.

Table 2.1 Apparatus and Suppliers

Apparatus	Supplier
Tablet Manufacturing	
Single Punch Tablet Machine Model F3	Manesty Machines Ltd.
Amplifier FE-154-ABS	Fylde Electronic Labs.Ltd.
Galvanometer 40000 series with SMI/M galvanometers	Bryans Southern Instruments
Hobart Mixer Model VCM 15-3 (modified)	Hobart Manufacturing Co.
Erweka Mixer Model KVI	Copley Instruments Ltd.
'Y' cone blender	Neco Rite
Dissolution Apparatus	
Erweka Model DT-D6	Copley Instruments Ltd.
Spectrophotometers	
Uvikon 810	Kontron Instruments Ltd.
Cecil CE 292	Cecil Instruments
Chart Recorders	
Model E478	Metrohm
Uvikon 21	Kontron Instruments Ltd.
Pump tubing	
Cat No 116-0532-180	Elkay Lab. Products UK Ltd.
Filter 178.3985.01	Technicon
Pump 501 (S100)	Watson Marlow Ltd.
Data capture	
computer CBM 8032	Commodore Business Machines
disc CBM 8050	
printer CBM 4022P	
interface serial, bidirectional B300	Small Systems Engineering Ltd.

continued

Table 2.1 (continued)

Disintegration	
Erweka Type ZT	Copley Instruments Ltd.
Sieves	
Shaker Model EFL 1 Mk II	Endecotts (test sieves) Ltd.
Test Sieves BS 410	" " "
Air jet sieve A200 LS	Alpine Lavino (London) Ltd.
Test sieves BS 410 1962	Harver & Boecker
Balances	
Sartorious 2354 max 1Kg	Sartorious
Sauter AR70 max 30g	Augustus Sauter KG
Sauter D7470 max 200g	
Particle Size Analysis	
Coulter Counter Model TA	Coulter Electronics Ltd.
Fisher sub-sieve sizer	
MOPS system	Kontron Instruments Ltd.
Stage micrometer 0.01mm	Watson, Barnet
Microscope AFX 104	Nikon
Miscellaneous	
Micrometer 25mm	Moore & Wright Sheffield
Ultrasonic bath FS100	Decon Ultrasonics Ltd.
Pycnometer,	
Air Comparison Model 930	Beckman Instruments Inc.
Zig-Zag Classifier	Alpine Lavino (London) Ltd.
Model A100MZR	

Table 2.2 Materials and Suppliers.

Material	batch	Supplier
Paracetamol BP		Sterling Organics Ltd. Cramlington,Northumberland
Aspirin BP		Monsanto,
Avicel PH101	6042/1925	FMC International, Co.Cork Ireland.
Aerosil 200		Degussa,D-6000, Frankfurt 1
Maize Starch BP	SIN66603	Boots, Nottingham.
Magnesium Stearate	SS14670	Bush Boake Allen Ltd. London.
Hydrochloric Acid SG 1.18		Fisons Scientific
Magnesium Chloride (General Purpose Reagent)		BDH, Poole,Dorset.
Isoton II		Coulter Electronics Ltd.,
Toluene (General Purpose Reagent)		BDH, Poole, Dorset

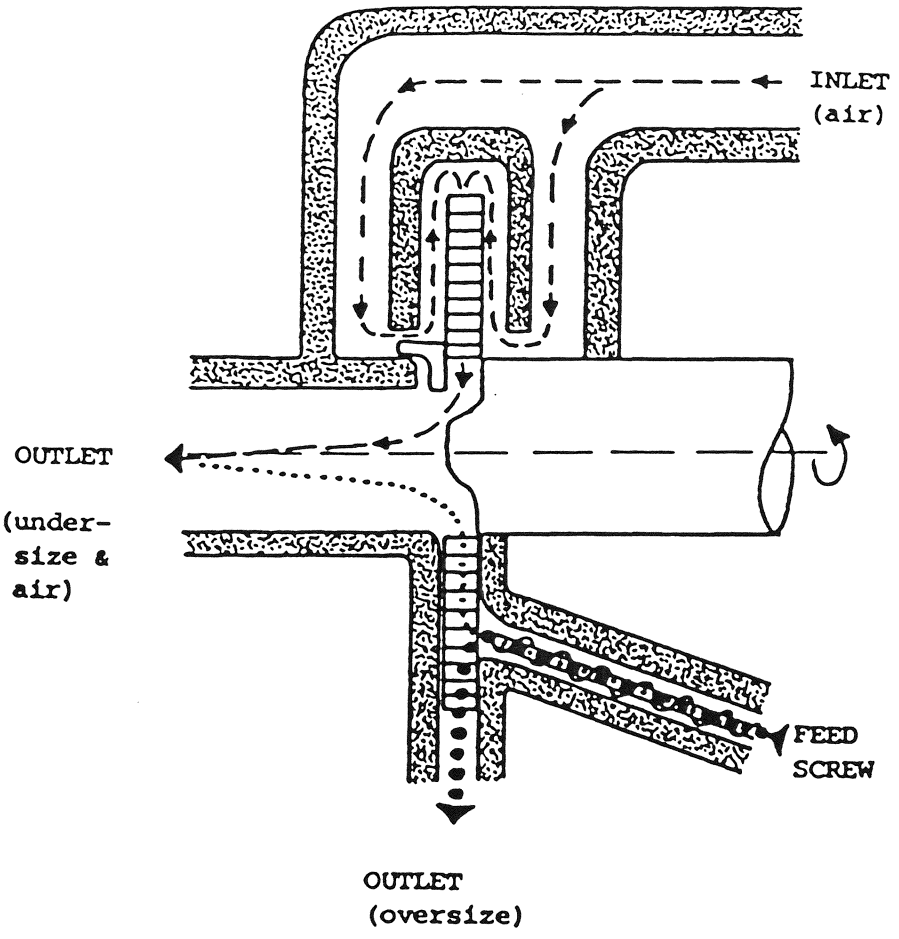

Figure 2.1

The principal components of an
Alpine Zig-Zag Classifier

$$D = D_o \sqrt{\frac{p}{p_o}} \qquad (2.2)$$

where D is the required cut size in micrometers
D_o is the theoretical cut size for limestone
p is the sample density and
p_o is the density of limestone

The machine settings used were 50.7 m^3hr^{-1} air flow and a disc speed of 4300 rpm giving a theoretical cut size of 20μm. Preliminary experimental settings indicated that this would result in approximately equal weights of under and over sized material. The undersize material produced was a fine, poorly flowing, cohesive powder whereas the oversize material was free flowing.

Two size fractions of aspirin were produced on an Endecott sieve shaker fitted with 0.2m diameter nested sieves until the change in weight on the appropriate sieve was less than 0.1% of the initial load per minute. The size fractions collected were those greater than 355μm but less than 450μm and greater than 300μm but less than 355μm.

The apparent particle densities of some of the materials were determined by measuring the volume of a known weight of the powder in a Beckman Air Comparison Pycnometer. These are shown with values determined by other authors in Table 2.3.

Table 2.3.

The Apparent Particle Densities of the powders used determined using a Beckman Air Comparison Pycnometer.

Material	Measured Density (Kgm^{-3})	Literature Value (Kgm^{-3})
Paracetamol	1291	1290 Fairbrother (1974)
Aspirin	1350	1350 Merck Index (1976)
Avicel	1541	1534 Roberts & Rowe (1985)
Aerosil	--	2200 Degussa (1971)
Magnesium stearate	1093	
Maize starch	1469	1475 Roberts & Rowe (1985)
Paracetamol mixes	1469	---- ----
Aspirin mixes	1440	---- ----

2.3 Paracetamol Particle Sizing Methods.

2.3.1 Initial Methods.

Preliminary sizing of the two fractions of paracetamol was attempted using an Alpine Airjet sieve with 0.2m diameter Haver & Boecker test sieves. This method was found to be unsatisfactory due to the drug sticking to both the perspex lid and the mesh of the sieve despite repeated tapping to dislodge it.

A size analysis using a Coulter model TAII using a 200μm orifice tube calibrated according to the Coulter manual half count method and 14.6μm Bilberry pollen was also attempted. The suspension medium was a filtered (0.2μm) saturated solution of paracetamol in Isoton. Three methods of adding the sample were used :-

i) A slurry of medium sample and a drop of non-ionic surfactant (NonIdept P42) were mixed with a small brush prior to stirring into the bulk medium.

ii) As i) except the bulk medium was then placed in an ultrasonic bath for 1 minute.

iii) Powder was sprinkled on the surface of the bulk medium.

The medium and sample were continuously stirred with a small glass stirrer. The sample was read as rapidly as possible using the 2ml manometer setting. The results were inconsistent on repeat samples and repeat testing. A similar result was obtained by Macharia (1972) and may be due to flocculation as a result of the high surface charge of paracetamol powders.

Andreasen sedimentation size analysis using toluene or filtered deaerated water saturated with paracetamol as

the suspension medium was found to have the same problems as the Coulter method. Two percent w/v mixtures of powder sample in suspending medium were stirred for 30 minutes. This mixture was rapidly transfered to an Andreasen cylinder, the top pipette fitted and the whole inverted three times. Aqueous media experiments were performed at room temperature and 4^{o}C. In the latter case all the operations including saturation were performed in a waterbath maintained at 4^{o}C. Timing was commenced after the last inversion and the apparatus was not disturbed during sampling. Samples were taken from the vessel by means of the fitted 10ml pipette at specified time intervals and discharged into either a preweighed petri dish or 100ml volumetric flask. Liquid heights were recorded at the same time from the engraved scale. Gravimetric analysis samples were dried overnight at 105^{o}C in an oven, stored over silica gel in a dessicator then weighed on a Sauter (model AR 70) balance. The saturated filtered suspending medium was also sampled using the same pipette prior to the test. This sample was compared to a sample from the supernatant of the centrifuged mixture and found to be similar. Spectrophotometric analysis was performed in some experiments by diluting the sample to 100ml with distilled water, diluting 100 times and measuring the absorbance at 245nm in a 10mm silica cell in a Cecil Instruments CE292 ultra violet spectrophotometer.

Flocculation took place within 3 minutes using Toluene as the suspending medium and was apparent on calculating the percentage undersize distribution from both the 4^{o}C and room temperature aqueous experiments. The solubility (1.4% at 20^{o}C, Martindale (1982)) of paracetamol giving high background readings of the same order of magnitude as the precipitated sample, combined with the problem of

flocculation rendered this method unsuitable for the size analysis of these samples of paracetamol.

2.3.2 Microscopic Methods.

Microscopic examination of paracetamol powder was attempted according to BS 3406 Part 4 (1963) but the particle length/width ratio was found to be greater than 4. This meant that the standard graticule method was inapplicable (BS 3406 Part 4 1963). The lack of consistency of shape as shown by Figures 2.2 and 2.3 also precluded the use of an acicular graticule. Automatic sizing by scanning microscopy using a Quantimet 720 Image analysing system was found to be impractical due to the lack of contrast in the crystals, however this system allowed the calculation of the Ferets diameter, that is, the perpendicular distance between two tangents on opposite sides of the particle parallel to some fixed direction (Allen 1975). Slides were prepared dry due to the problems previously encountered with paracetamol in liquid systems. This involved placing a small amount of powder on a clean slide and spreading it over the whole surface using a fine brush. Excess loading was removed by wiping half the surface clean without tipping the slide then spreading the the remainder over the clean surface. When a suitable dispersion was obtained the slide was tapped from the side to orientate the particles. The slide was placed on the microscope stage and the projected image examined through a 10X or 40X objective and 10X eyepiece. A superimposed grid enabled the length of particles between two vertical lines to be recorded. The line separation was calibrated by means of a stage micrometer.

Figure 2.2.
Photomicrograph of the undersize cut of paracetamol obtained from a Zig Zag classifier (X125).

Figure 2.3.
Photomicrograph of the oversize cut of paracetamol obtained from a Zig Zag classifier (X125).

An alternative microscopic examination was carried out using a Kontron MOPS system to determine the projected area of particles on slides prepared as above. This system uses a prismatic eyepiece to superimpose the image of a light-spot on the field of view. The light-spot was generated by the moveable cursor of an adjacent digitising tablet with an associated integrator and printer. The cursor was moved by hand such that the light-spot traces the perimeter of the particle under examination with an arbitrary area figure being printed when the perimeter trace is completed. Calibration was by means of an eyepiece square grid and a stage micrometer. The size of several squares being determined by comparison with the stage micrometer and the arbitrary area being determined by tracing squares of various sizes with the light-spot and cursor.

Under both techniques overlapping particles were not counted and all the particles in at least 25 different fields of view were counted giving a total of 600 particles.

2.3.3 Fisher Subsieve Sizing.

The paracetamol fractions were also sized by means of a Fisher subsieve sizer. The BS 4359 Part 2 (1971) method was used with a weight in the sample tube the same as the apparent particle density. Aspirin was not tested by this method as specific sieve fractions were used in the tabletting experiments. Aerosil was found to be outside the testing range of the Fisher sub-sieve sizer. This agrees with the manufacturers specification (Degussa Technical Bulletin 1971).

2.3.4 Laser diffraction.

Samples of both size fractions of paracetamol were sent to Malvern Instruments Ltd. for sizing by a laser diffraction method on their 2600HSD device. This consisted of dispersing the powder in a high velocity airstream perpendicular to a laser beam and measuring the light intensity in a series of concentric rings about the centre of the original beam. The size of a particle passing the beam is related to the angle of diffraction and a particle size distribution of the whole sample is produced from the varying intensity recorded by the concentric rings. The drawback with this method is that the particles may be damaged in transporting them to the laser beam. It does however provide corroborative particle size analyses.

2.4 Preliminary formulation work.

The initial formulations were attempts to produce a direct compression powder mix containing a model drug capable of producing acceptable tablets on compression. Paracetamol was chosen as the model drug for its availability, its structural simplicity and because it is difficult to compress (Leigh et al. 1967). Aspirin was subsequently included as an alternative model drug because of its history of use in tablet formulation experiments. It was not employed in the initial studies. A lubricant was employed to reduce tablet damage due to sticking in the die during ejection. A diluent was included since paracetamol, like most other drugs, will not form an adequate compact on its own. No attempt was made to produce tablets containing the normal dosage of

paracetamol as this would not then have been a representative direct compression formulation. This type of formulation being most suitable for low to medium dose drugs whilst paracetamol is usually classified as a high dose drug. A disintegrant was also included and, in some of the formulations, a dry binder to improve tablet cohesion. The initial batch size was approximately 100g. The ingredients except the lubricant were mixed either by continuous inversion in a 'Y' cone blender (Neco Rite) for 30 minutes or by 15 minutes vigorous shaking in a glass jar of at least twice the initial volume of the powder. In either case the lubricant was then added to the vessel which was mixed for a further two minutes. Tabletting was carried out using the apparatus described in Section 2.5.2 at a compaction pressure of approximately 100 MNm^{-2} with 10mm flat-faced punches.

The criteria used to examine a batch were essentially qualitative, that is, if the mix flowed very poorly or produced tablets with a high proportion of lamination or poor appearance, then the batch was discarded as unsuitable. This arbitrary method satisfied the aim of finding a formulation which tabletted easily and would be likely to accept changes in composition or processing. For this reason no comment is made on the particular criterion for discarding a batch, in fact some adequate batches were discarded because similar batches were not suitable thus indicating that that type of batch would not be flexible enough.

Aerosil 200 was added to later formulations as it was found to considerably improve powder flow. The two diluents tested were spray dried lactose and Avicel PH101 as being representative of the most common direct compression excipients. Magnesium stearate and stearic

acid were tested as lubricants and maize starch as a simple disintegrant with some binding properties.

The most promising formulations consisted of paracetamol, maize starch, Avicel, Aerosil and magnesium stearate. This was used as the starting point for studies aimed at finding a formulation suitable for a designed experiment.

2.5 Tablet Manufacture.

This section describes the methods used in producing and the initial testing of the experimental tablets. Dissolution, friability and liquid uptake tests are considered in Sections 2.6 and 2.7.

2.5.1 Mixing.

Three types of mixer were used in the first formulation studies. The cross-sections of these are shown in Figure 2.4. The first type was a planetary mixer (Erweka KV 1) with a 10 litre bowl and a whisk type stirring blade. The second type was an unmodified Hobart (VCM 15-3) mixer with a bottom centre driven blade running parallel to the base. The bowl was covered and about 15 litres capacity. The mixing blade was felt to be inefficient for dry powder mixing so the blades were modified on the basis of a high shear mixer which is extensively used in tablet manufacturing. The blade system is shown in Figure 2.5. The bottom of the vessel was also flattened by means of a fitted false base such that the bottom of the blade only just cleared the base. Rotation in the

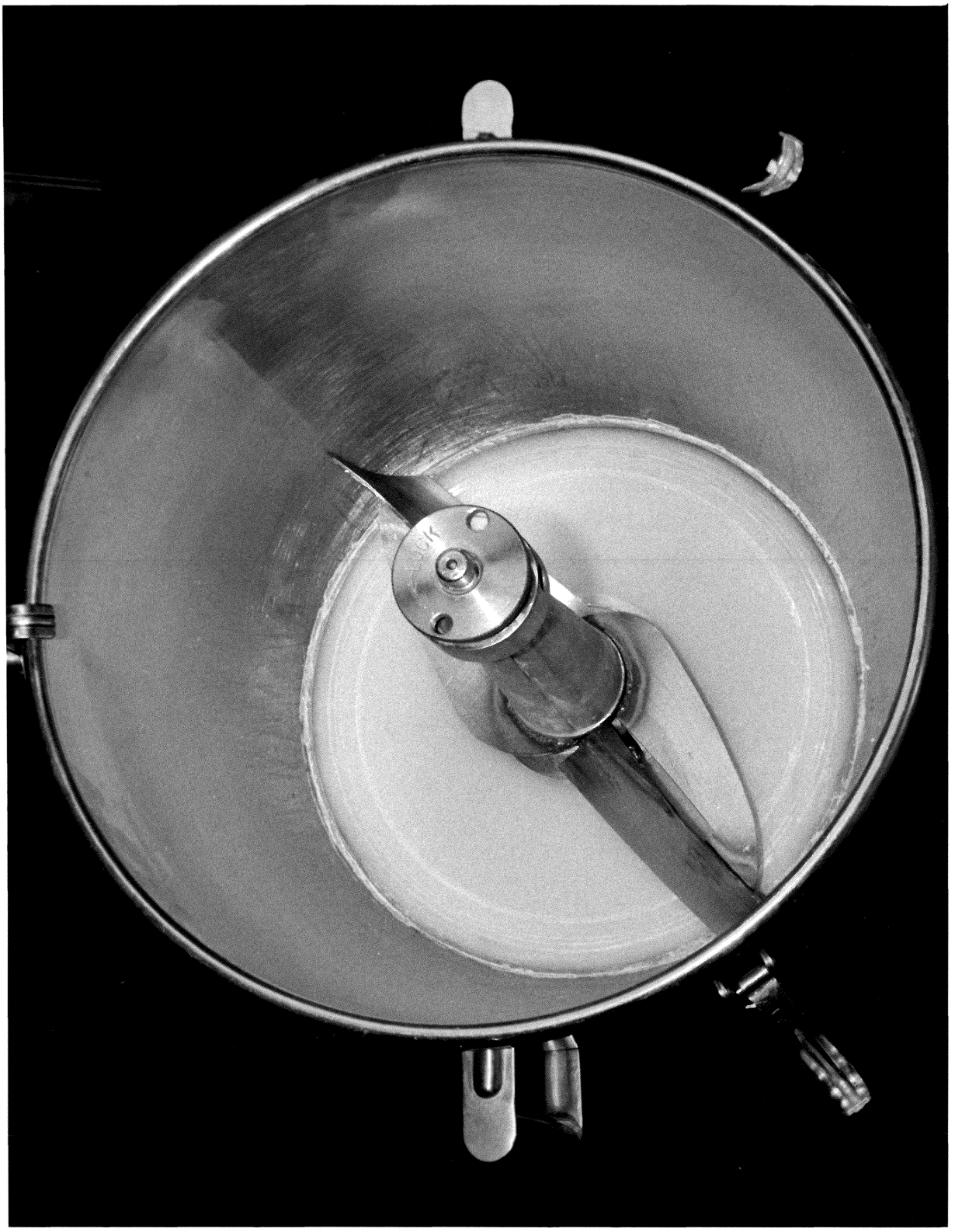

Figure 2.5

Detail of blades on the modified Hobart mixer

unmodified and modified mixers was 1750rpm. Powders to be mixed were weighed into a tared polythene bag on a Sartorius balance (model 2354) to +/-0.01g. The bags were emptied into the mixer bowl in order of decreasing weight to form a heap at the side of the bowl. In the case of the Hobart mixer the lid was clipped into place before the mixer was switched on and timing started. After the desired mixing time the power to the mixer was switched off, the bowl removed and the powder slowly tipped out onto a large sheet of paper. Opposite edges of the paper were raised to form a chute to pour the powder at the lowest angle possible into a polythene bag. Care was taken to minimise subsequent mixing and to make it as consistent as possible during powder transfers. The bags were sealed and stored in the same room as the tabletting equipment.

2.5.2 Tabletting.

Tablets were manufactured on a Manesty F3 reciprocating tablet machine with modified punch holders. The punches were held in steel cups, the cups in turn being held against a load washer by a spring washer. This is illustrated in Figure 2.6. As a force was applied to a punch and thus to the load washer, a proportionate change occurred in the electrical resistance of the four strain gauges incorporated in the load washer. The strain gauges were arranged as a full bridge so as to be temperature compensating. The resistance change was measured by means of a Wheatstone bridge and amplifier circuit (Fylde Electronic Labs. Ltd.). After adjusting the bridge operating voltage and balancing the bridge current, subsequent resistance changes in the strain gauges caused by forces acting on the punch resulted in

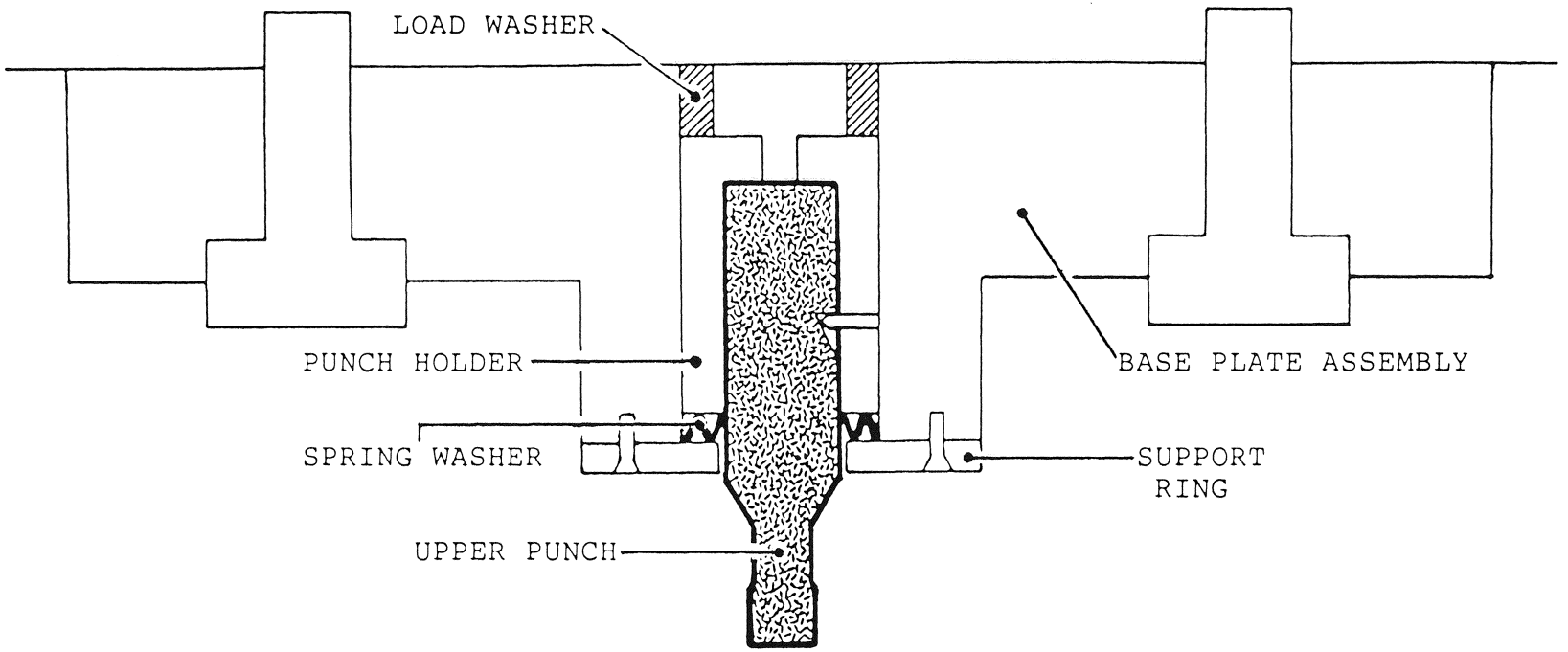

FIGURE 2.6
Detail of the upper punch and load washer assembly.

an ´out-of-balance´ current. This current, after amplification, was recorded by an ultra-violet galvanometer (Bryans Southern Instruments), fitted with SMI/M galvanometers, as a trace of deflection against time on u-v sensitive paper.

The instrumentation was calibrated by compressing the load washer and its mounting in a mechanical testing device (Instron Ltd. model 1195) and measuring the ´out-of-balance´ current produced under given loads. This was recorded with both increasing and decreasing loads via the same circuitry used in tablet manufacturing. No significant differences were noted between loading and unloading over repeated checks. A routine check prior to every tablet machine operation was achieved by switching a resistor, eqivalent to a known load, into the Wheatstone bridge circuit to produce a deflection on the u-v galvanometer.

The tablet machine was fitted with cleaned 12.5mm flat-faced punches and a standard Manesty F machine feed shoe and stainless steel hopper (except where stated otherwise). Prior to use the machine was turned over by hand to ensure safe operation, the amplifier adjusted and the calibration deflections recorded on the u-v chart paper. The bag containing the powder was placed inside and as far down the hopper as possible and slowly inverted to load the feed shoe and hopper. After removing the bag and closing the hopper lid the machine was again turned over by hand. The motor was engaged and 20 tablets manufactured, the last ten being collectively weighed on a Sauter balance (model 414/13). This figure was used as the basis for adjusting the tablet weight by altering the collar on the lower plunger unit. Simultaneous recording of the upper punch pressure was

used as the basis for adjusting the upper punch penetration into the die and hence the compaction pressure. This process was repeated until satisfactory weight and pressure settings were obtained.

The tablets were collected in strict order of production at the rate of 50 tablets per minute on a large flat board fitted to the die table output chute. The rate of production was monitored by means of an internal timer on the u-v galvanometer which superimposed timing marks at one second intervals on the u-v chart record. The tablets were labelled in production order in pencil and stored in air-tight screw-capped glass bottles. Where further tablets were to be produced from the same powder mix with different settings, the complete process was repeated except the hopper and feed shoe loading.

The peak heights on the ultra-violet chart for upper and lower punch pressures were measured by means of a computer digitising device capable of discriminating 0.1mm (System 4 digitiser).

2.5.3 Tablet Tests.

Tablets were stored for 24 hours in glass screw top bottles after production to allow any stress relaxation and equilibration to take place before any tests were performed. The jars were kept in an incubator at 25^{o}C and 33%RH maintained by a saturated solution of magnesium chloride (BDH). The jars were returned to the incubator between tests.

The tablets were weighed on a Sauter balance (Model 414/13, +/-0.0001g). The thickness of each tablet and

the diameter of ten tablets from each batch was measured (+/-0.01mm) using a Moore and Wright micrometer screw gauge.

The diametral breaking load of at least 15 tablets from each batch was determined on a CT40 tablet strength tester made by Engineering Systems (Nottingham) Ltd.. This compressed the tablet between two parallel steel plattens at a rate of $1mmmin^{-1}$ and displayed the peak load recorded by the load cell. Calibration was by means of a high quality resistor switched into the load cell Wheatstone bridge circuit. Further details of this device are given by Kennerley (1980). After checking the calibration figure and adjusting the zero reading, the tablet under test was inserted vertically and centrally between the plattens. The tablet was always orientated in the same direction. The top platten was lowered manually until it was close to the tablet but approximately 1 mm away. The motor was switched on with the peak hold in operation until fracture had visibly occurred. After recording the peak load reading, the upper platten was raised manually, the tablet removed and examined for signs of lamination and checked to ensure that tensile fracture had taken place. A tablet was considered to have failed in tension if it split across the diameter without fragmentation, (Fell and Newton 1970).

The individual tablet weight, thickness, deflections from the u-v chart record, and where applicable the breaking load, were used in conjunction with the mean tablet diameter, the apparent particle density and compression calibration deflections to calculate the tablet porosity, relative density, compaction pressures and tensile fracture stress. The calculations were

perfomed simultaneously using a Fortran program based on the flow diagram given in Figure 2.7 on either an ICL 2900 VME or DEC VAX computer. The program is in three main parts, calculations from the input data, regression analyses on sets of data and plotting of the data sets. Certain facets of the data selection are of interest. The program routinely excluded the first ten tablets of a batch to eliminate discrepancies due to variable tablet machine operation until the motor reached its operating speed. Tablets with weight or upper punch pressures outside the range of 2 standard deviations from the mean of all the tablets except the first ten were also excluded to account for the occasional sticking tablet or powder flow disruption. The results presented are therefore calculated on the basis of the remaining tablets after these exclusions.

Equations 2.3 to 2.5 were used for the calculations carried out by the computer programme. Equation 2.3 shows how the chart deflection distance was converted to a compaction pressure for each tablet.

$$P = \frac{d.F^{o}.4}{d^{o}.D^{2}.\pi} \qquad (2.3)$$

where P is the compaction pressure
d is the chart deflection
d^{o} is the chart calibration deflection
F^{o} is the calibration load
and D is the tablet diameter

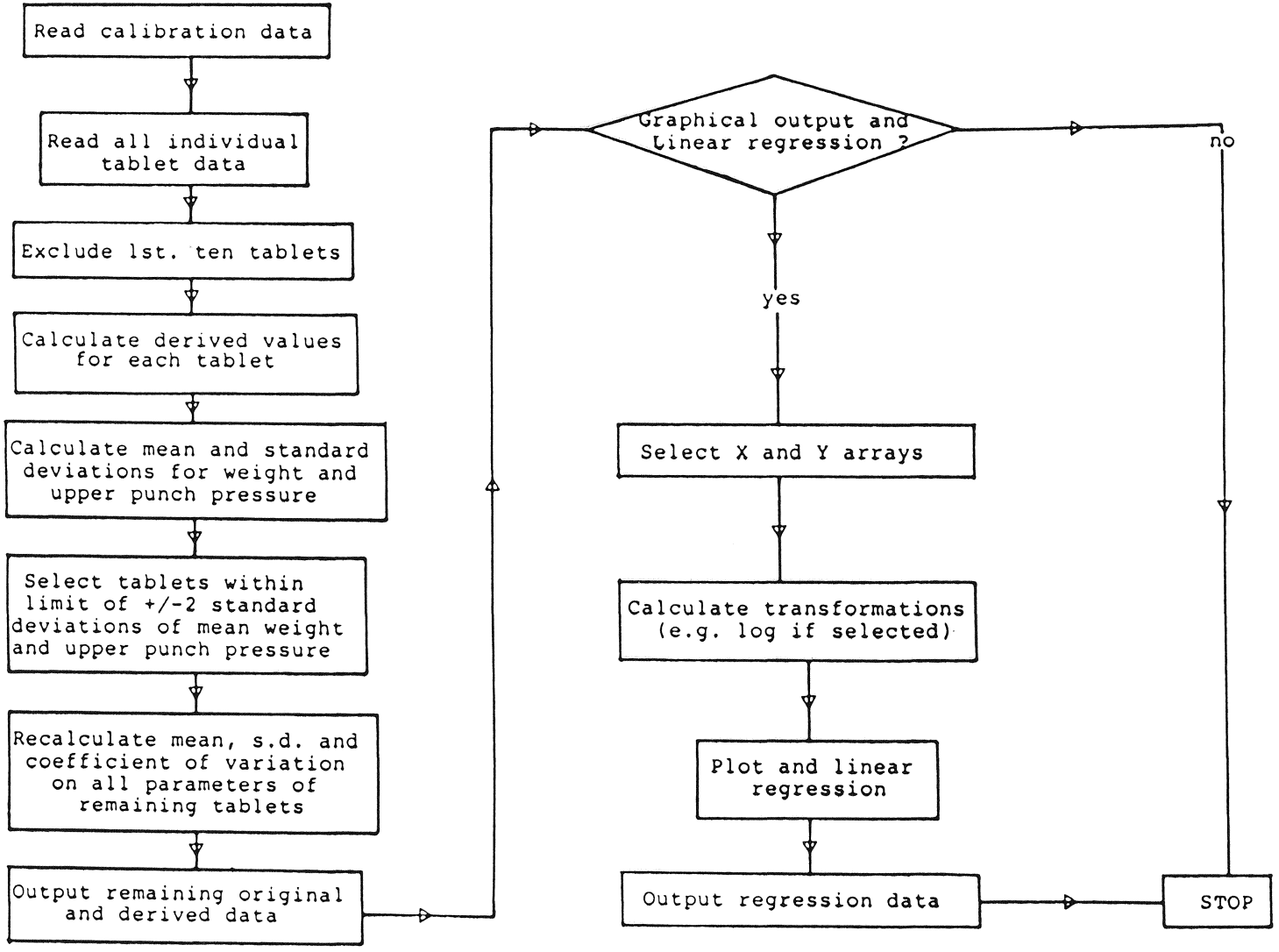

Figure 2.7

Flow diagram of the Fortran program used to process tabletting data.

The tensile fracture stress was calculated from the breaking load of those tablets apparently breaking in tension using the method of Fell and Newton (1970) given in Equation 1.1.

The tablet relative density i.e. the ratio of the compact density to the density of the material, was calculated using Equation 2.4.

$$p_r = \frac{w.4}{t.\pi.MD.D^2} \qquad (2.4)$$

where p_r is the tablet relative density,
MD is the apparent particle density,
w is the tablet weight,
D is the tablet diameter and
t is the tablet thickness.

The tablet porosity was calculated from the relative density as shown in Equation 2.5.

$$POR = 1 - p_r \qquad (2.5)$$

where POR is the tablet porosity and
p_r is the tablet relative density.

2.6 Dissolution Tests.

Two dissolution systems were used in these studies. The Cecil system used in some of the initial studies was found to be imprecise with respect to the cell location on operation of the cell change mechanism. This was therefore replaced by a Kontron system which was found to be a considerable improvement.

2.6.1 Dissolution Apparatus.

The Cecil system consisted of a Cecil Instruments CE292 spectrophotometer fitted with a CE230 4 cell change controller. This was linked to a Metrohm chart recorder (Model E478) which recorded the absorbance / time profile from four 2mm silica stream cells connected via a Watson Marlow 501 (type S100) pump to four USP XX (1980) 1 litre vessels in an Erweka DT-D6 dissolution bath. This was fitted with paddles similar to the USP XX (1980) specification but 4cm shorter. The vessels contained 900ml 0.1M HCl stirred at 100rpm. The absorbance was read at 245nm and the flow rate was 63ml min^{-1} .

The Kontron system consisted of a Kontron Uvikon 810 spectrophotometer incorporating a 6 cell changer and Kontron Uvikon 21 chart recorder. This was linked via a serial interface to a computer, disc drive and printer for simultaneous digital data capture (Table 2.1). This recorded the absorbance from six 10mm silica flow cells at 1 minute intervals. The dissolution was carried out in USP XX (1980) covered glass vessels filled with 900ml 0.1M HCl in an Erweka DT-D6 dissolution apparatus stirred at 100 rpm with paddles complying with the USP XX (1980) specification. The vessel contents were

transfered to the cells through a sintered PTFE filter (Technicon) supported on a 3mm o.d. stainless steel tube and circulated by a Watson Marlow S50 pump with a flow rate between 7 and 10 ml/min. The filter was positioned 15mm below the surface of the liquid at the midpoint between the stirrer shaft and vessel wall. In both systems 2mm i.d. translucent vinyl tubing was used with Elkay 3mm i.d. pump tubing. The system is illustrated in Figure 2.8.

The shorter cell path length in the Cecil system enabled absorbance readings to be taken at 243nm, the λmax for paracetamol. The longer path length in the Kontron system meant that a wavelength (270nm) on the side of a peak was used to keep the absorbance readings within the spectrophotometers operating range.

The results presented in Chapter 3 relate solely to work carried out on the Kontron system, so that the calibration of the Cecil system is not described but was carried out in a similar manner to the Kontron system. Calibration of the apparatus was carried out as closely as possible to the experimental conditions using the same cells, tubing, pump and filters as in the tablet dissolution tests.

2.6.2. Calibration of the Kontron dissolution system.

Five solutions of paracetamol were prepared by weighing the drug on tared weighing boats on an analytical balance (Sauter KG) and washing the contents into five 1 litre volumetric flasks with 0.1M HCl. The flasks were shaken until no solid was visible, made up to volume and placed in an ultrasonic bath for 5 minutes to

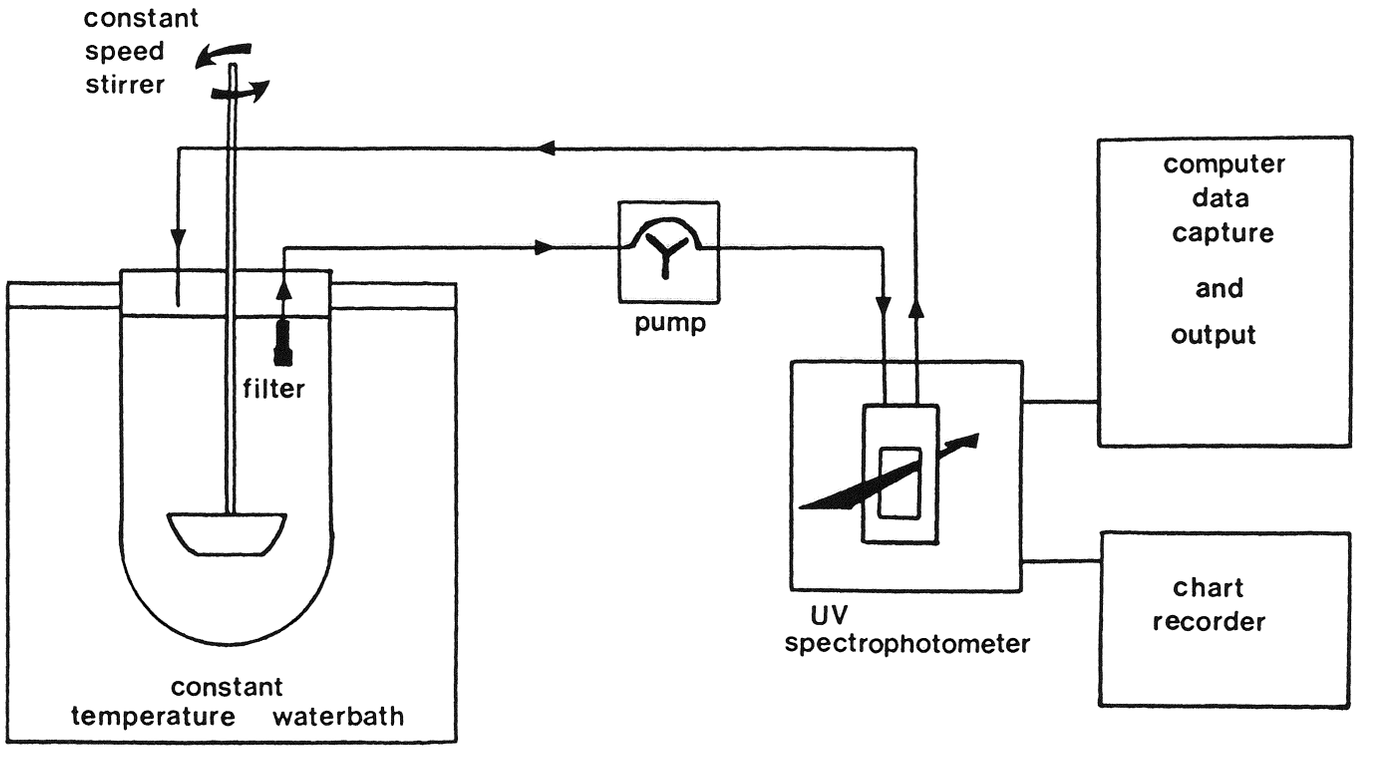

Figure 2.8

Schematic diagram of the Kontron dissolution apparatus.

ensure complete solution. The five solutions and one litre of solvent were placed in the six vessels of the dissolution apparatus and covered. Approximately 20ml of each vessels contents were pumped through the tubing, cell and filter system to waste. The contents were then recirculated for three hours with absorbance readings being taken at 270nm at 15 minute intervals. The vessels were stirred at 100rpm throughout this process. The calibration figures are shown in Table 2.4 and Figure 2.9.

Table 2.4.
Calibration of Kontron Dissolution System with Paracetamol at 270nm using 10mm cells.

Concentration mg/l	Initial absorbance (AU)	Absorbance after 3hrs (AU)	Solvent
22.3	0.383	0.383	0.1M HCl
47.6	0.822	0.822	"
70.6	1.212	1.211	"
98.8	1.708	1.706	"
154.3	2.556	2.555	"
0	0.000	0.001	"

Figure 2.9 shows a good adherence to Beers Law up to 1.7 absorbance units (AU) with a minor deviation above that. The lack of change in absorbance with time indicated that there was no significant adsorption of paracetamol by the tubing or filters.

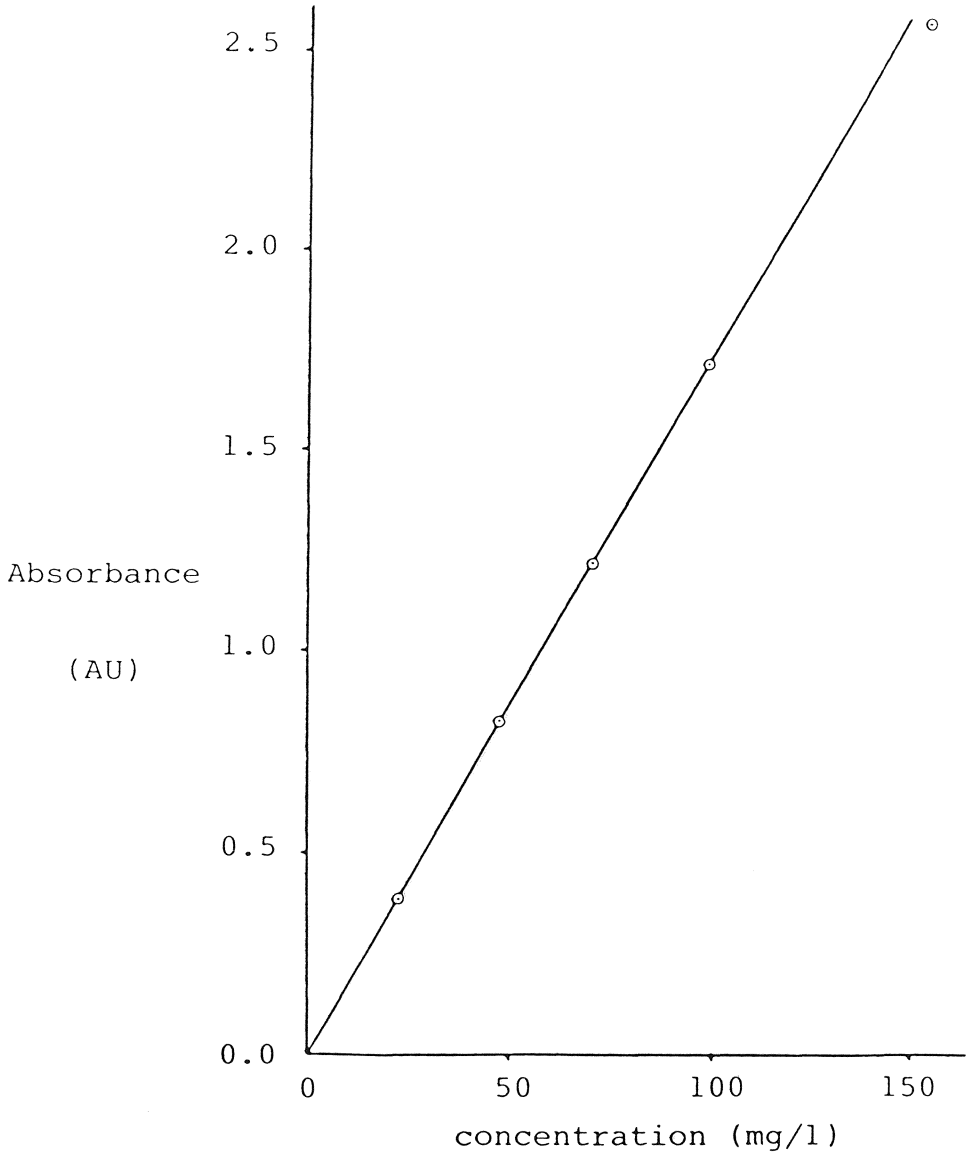

Figure 2.9

Beer calibration plot for paracetamol in 0.1M HCl at 37°C and 270nm.

Aspirin hydrolyses in dilute acids to form salicylic acid. As both of these molecules absorb in the ultra violet region a dissolution study involving aspirin must take into account the degradation process. To examine the changes in absorbance due to hydrolysis a solution of 100mg aspirin in 900ml distilled water at 37^{o}C was prepared and circulated through the dissolution system. After a short stabilisation period the solution was acidified with 9ml concentrated hydrochloric acid. This produced a solution of aspirin in 0.1M HCl. Absorbance readings were taken at 1 nm intervals over the range 274 - 280 nm every 10 minutes for six hours then every 30 minutes for a further 14 hours. This simultaneously checked the wavelength reproducibility and the change due to degradation. The wavelength reproducibility was shown by the lack of scatter of the absorbance readings near the isobestic point, that is the wavelength where no change occurred in the absorbance despite degradation. This point was identified by plotting the change in absorbance against wavelength at different times. The first absorbance reading after acidification being taken as an arbritary zero. Figure 2.10 is a graphical representation of these changes. This method indicated that the isobestic wavelength was slightly greater than 278nm under these conditions. Dissolution studies were therefore carried out at 278nm to compensate for any changes in absorbance due to degradation occurring during dissolution. A Beer calibration plot for aspirin is shown in Figure 2.11. This was produced by a similar method to that for paracetamol except at 278nm.

The time for liquid to pass from the filter in the dissolution vessel to be detected by the spectrophoto--meter was also determined. This was accomplished by

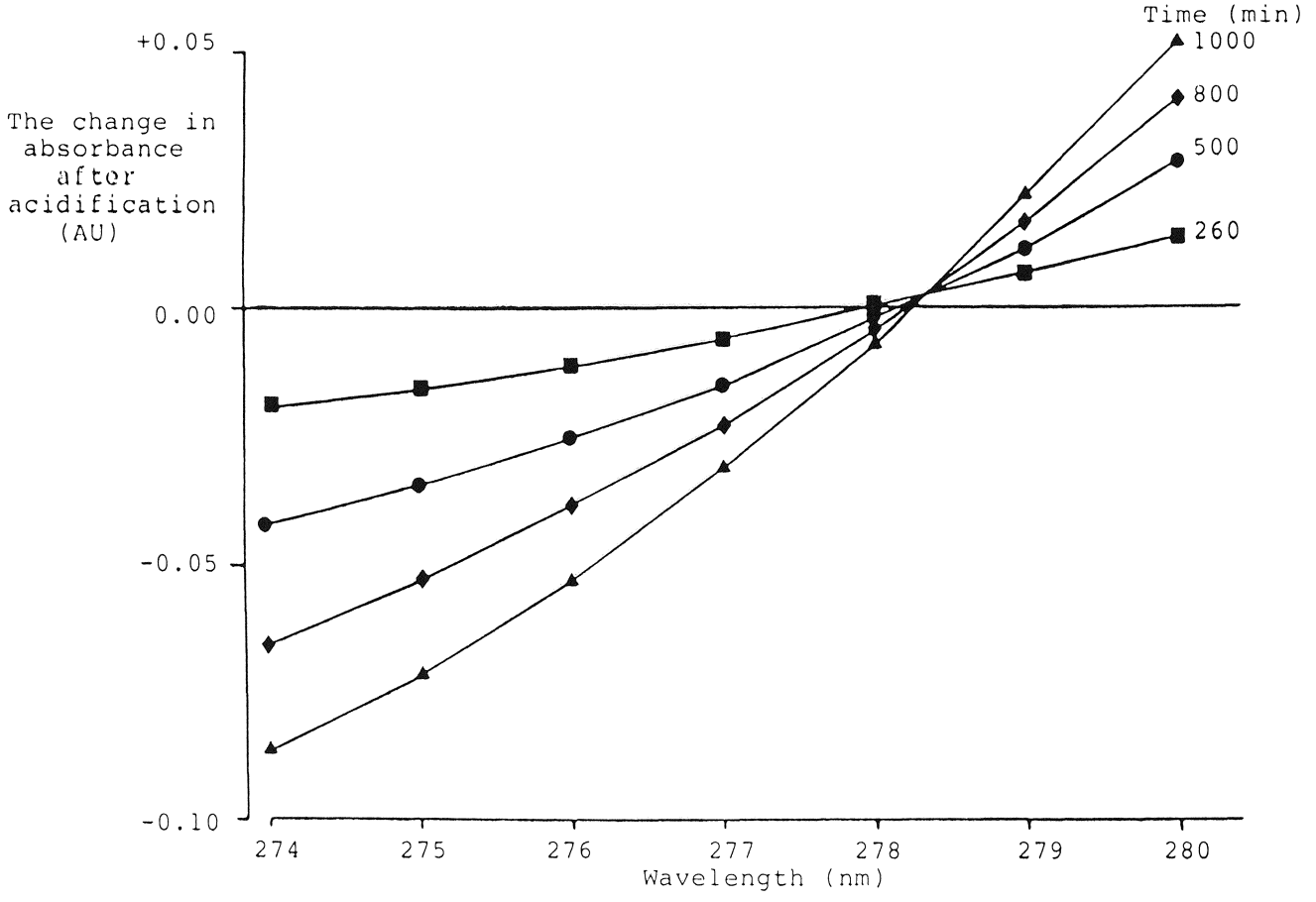

Figure 2.10

The change in absorbance with time at different wavelengths due to acid hydrolysis of aspirin.

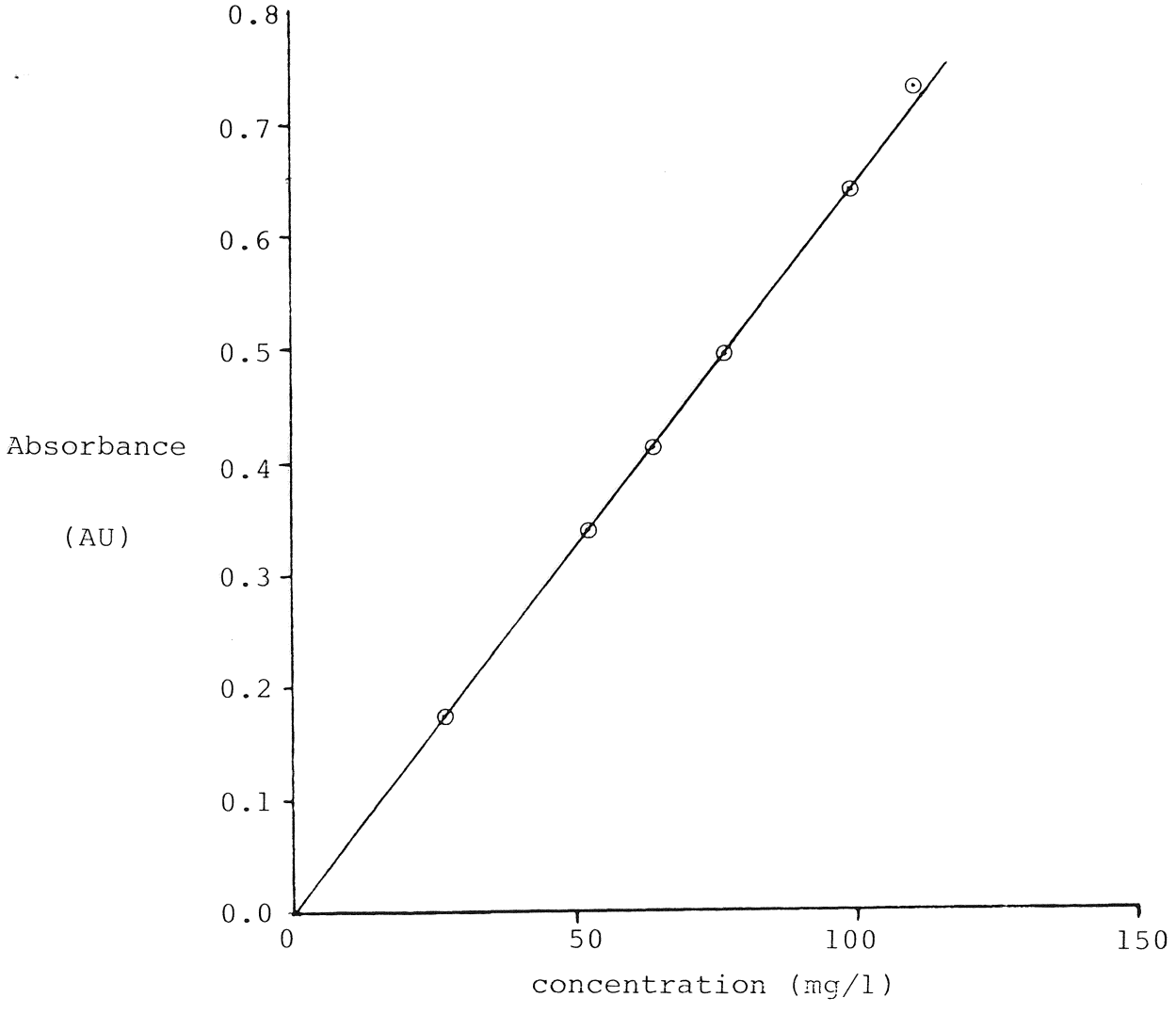

Figure 2.11

Beer calibration plot for aspirin in 0.1M HCl at 37°C and 278nm.

recirculating water through the system from one vessel, switching off the pump, and transfering the tubing and filter assembly to another vessel containing a drug solution at the same temperature (37^{o}C). Timing commenced when the pump was restarted. The lag time was 45s to initial detection and 60s before the absorbance reading became constant. The longer time including the time required to completely flush the absorbance cell.

2.6.3. Dissolution Methods.

The water bath and vessel contents were allowed to equilibrate at 37+/-0.5^{o}C for at least one hour prior to use. Temperature was monitored in the vessels during equilibration but not during testing. The water bath temperature was monitored throughout testing and equilibration. Solvent was pumped continuously and the absorbance recorded in each cell during the warm up period. Vessels contained 900ml 0.1M HCl measured in a 1 litre measuring cylinder at room temperature. The solvent was not deaerated prior to use but it was found that any bubble formation due to dissolved gases could be removed by periodically stirring the vessel rapidly during warmup. No degassing was observed to take place during actual tests. The solvent, 0.1M HCl, was prepared by diluting concentrated hydrochloric acid (Fisons Scientific) with distilled water. This was done in 10 litre batches and stored in a 25 litre collapsible plastic container. The bulk solutions were titrated against a freshly prepared solution of sodium hydroxide (BDH GPR) in distilled water using methyl orange indicator. Using a pipette, 25ml of sodium hydroxide (0.1M) was put into a conical flask with 1 drop of indicator, the bulk acid solution was then titrated from

a burette until the indicator just changed colour (yellow to red). The acid strength was then calculated. Any adjustment necessary was then made by calculating the strength of the concentrated acid and the amount needed to bring the acid up to 0.1M. The titration was repeated after the adjustments.

Tablets were inserted after equilibration by lifting the vessel cover and pushing the tablet into the vessel such that it did not stick to the vessel wall. The first tablet was inserted immediately after starting the cell change mechanism on the spectrophotometer; subsequent tablets were inserted as the cell change was heard to operate. This ensured that the first reading for each cell was at zero time. The tablets were observed to fall through the solvent to below the centre of the paddle and remain there throughout the test. All readings were made against a sealed reference cell containing 0.1M HCl.

The absorbance and time readings were processed by means of a computer program, the flow diagram of which is shown in Figure 2.12. The program, run on an ICL 2900 VME computer, was used to subtract the cell zero offset, that is the absorbance with only solvent flowing through the cell after equilibration. It was also used to calculate the mean absorbance of the six cells at each time point and calculate the time for 50%, 60% and 90% of the drug to dissolve by linear interpolation between the time points above and below those percentages. This program also facilitated the normalised plotting of dissolution profiles and dissolution models.

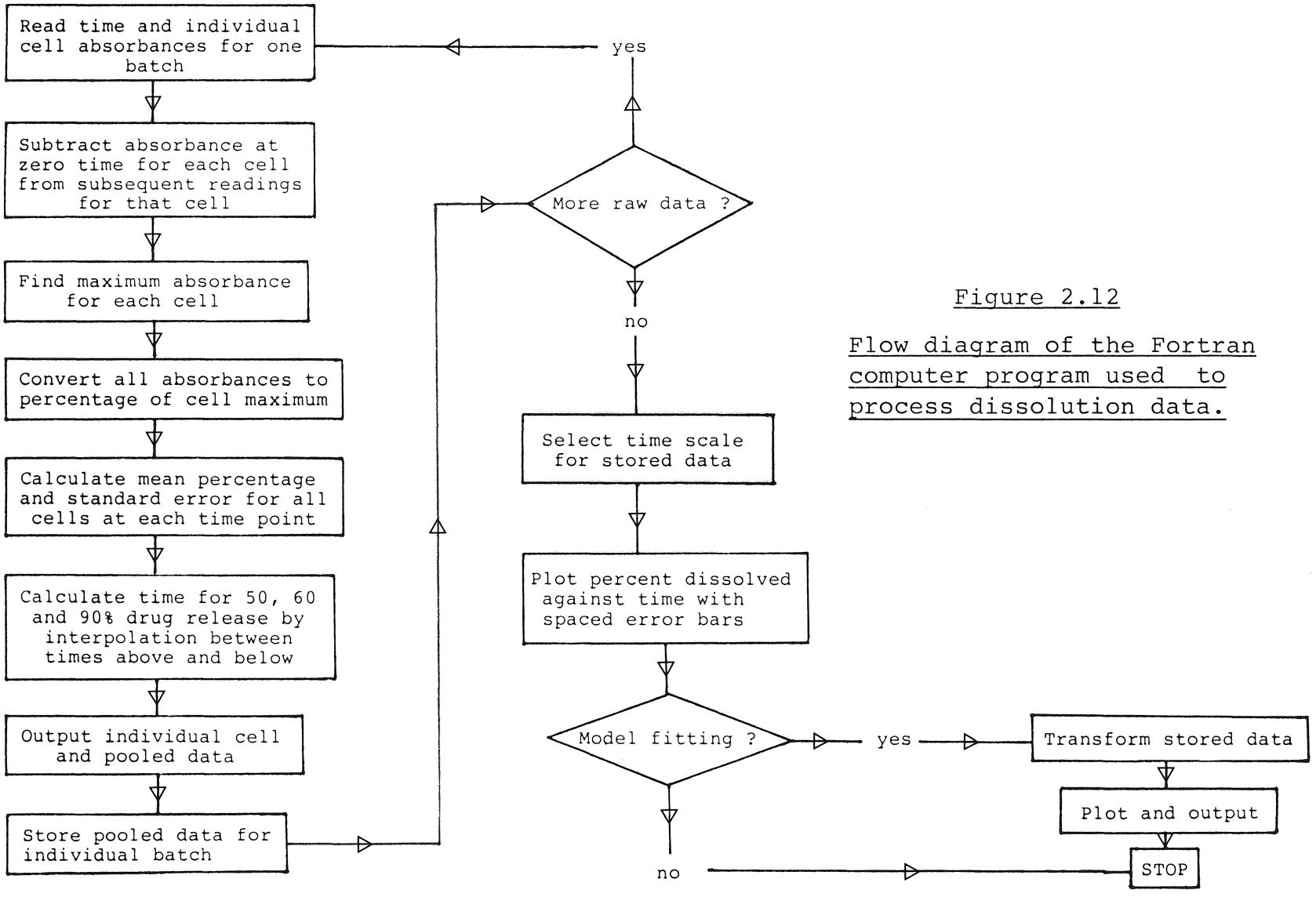

Figure 2.12

Flow diagram of the Fortran computer program used to process dissolution data.

2.7 The Determination of suitable mixing times and disintegrant concentrations.

A series of batches were manufactured to determine suitable levels for mixing time and disintegrant concentrations. Four batches of tablets were manufactured using the formulation shown in Table 2.5, the only difference in preparation being the mixing times of 10, 30, 60 and 300 seconds.

Table 2.5.
The formulation used in mixing Experiments.

Paracetamol	25.0%
Avicel	68.9%
Maize starch	5.0%
Aerosil	0.1%
Magnesium stearate	1.0%

The tablets were made according to the method described in Section 2.5.2 with 10mm flat-faced punches. The tensile fracture stress of all the tablets were calculated from the breaking load data determined by the method of Section 2.5.3 and the computer program (Figure 2.7) with only the first ten tablets excluded. A plot of the logarithm of the mixing time against mean tensile fracture stress (Figure 2.13) was linear up to 60 seconds but 300 seconds mixing time probably represents the minimum tensile fracture stress under these conditions. This agrees with the work of Bolhuis et al. (1975) who found a similar relationship. The 300 second time point was therefore taken as representing a state of maximum mixing whilst 60 seconds was taken as an intermediate state for further studies.

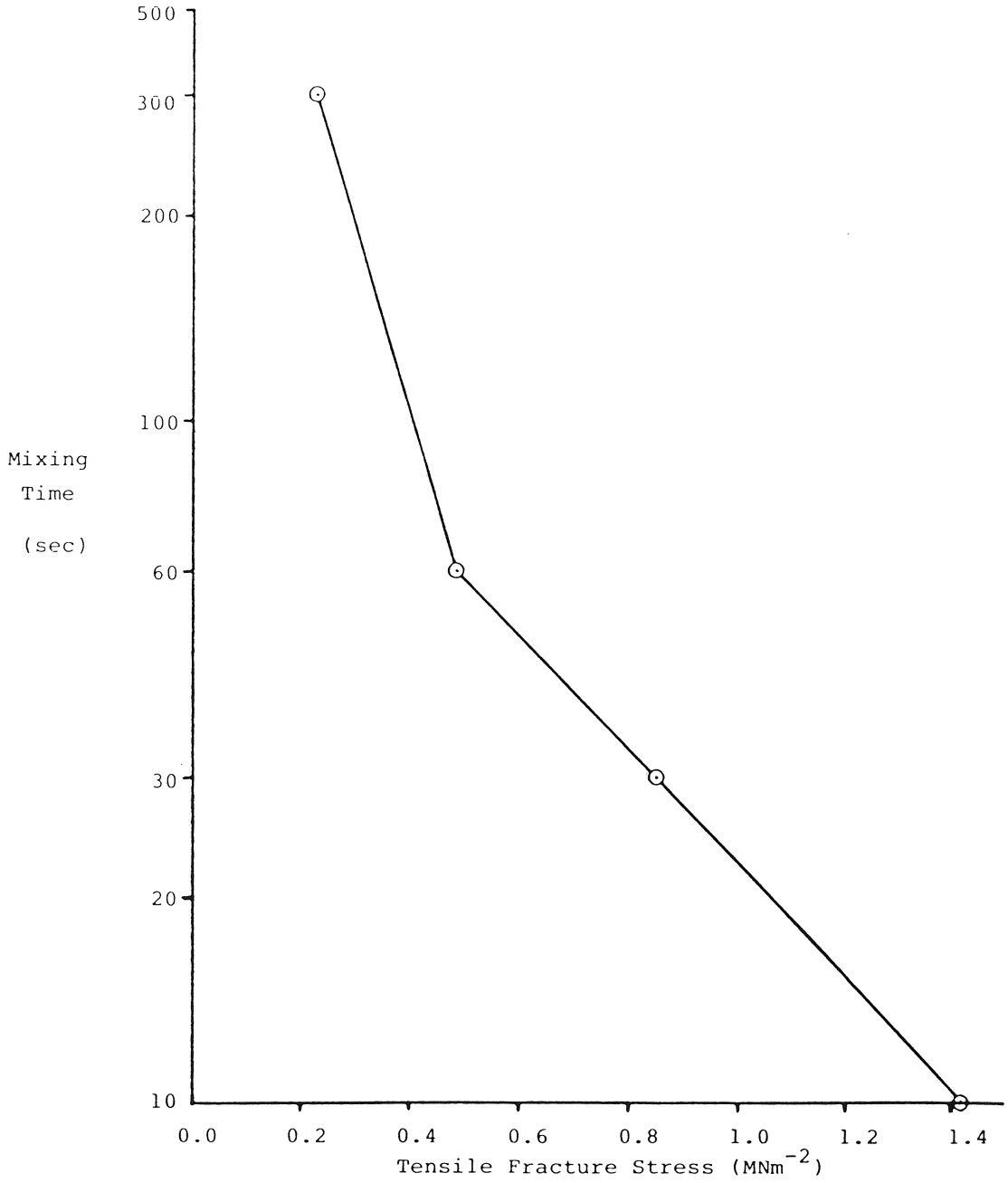

Figure 2.13.

The relationship between the tensile fracture stress and the mixing time in preformulation studies.

Two series of experiments were performed to determine suitable disintegrant concentrations. The two series reflect the differences in the disintegration apparatus used to test the tablet, with or without discs. The formulations used for the disintegration tests are shown in Table 2.6.

Table 2.6.
Formulations used for disintegration tests (%w/w).

FORMULATION	1	2	3	5	7	10
Paracetamol	25.0	25.0	25.0	25.0	25.0	25.0
Maize starch	1.0	2.0	3.0	5.0	7.0	10.0
Avicel	72.9	71.9	70.9	68.9	66.9	63.9
Aerosil	0.1	0.1	0.1	0.1	0.1	0.1
Mag.stearate	1.0	1.0	1.0	1.0	1.0	1.0
Total	100.0	100.0	100.0	100.0	100.0	100.0

The tablets were prepared in the same manner as for the mixing tests but with a mixing time of 300 seconds. The disintegration test was carried out in an Erweka ZT apparatus using a standard method (BP 1980) with distilled water at 37^{o}C. Timing commenced on immersion of the loaded basket-rack assembly and ceased when no residue remained on the mesh. Initial experiments using the apparatus with discs did not adequately discriminate between batches but more satisfactory results were obtained when the discs were removed. The mean disintegration time for the different starch concentrations are shown in Table 2.7.

Table 2.7.

The change in disintegration time with starch concentration (mean of 12 tablets).

starch (%) concentration	with discs (seconds)	without discs (minutes)
1	42	9.1
3	47	7.3
5	44	5.1
7	45	4.2
10	55	2.8

The disintegrant concentrations of 1 and 7% were chosen for further study as being well separated in disintegration time. The disintegration test without discs, although adequate to discriminate between these test formulations, was not considered suitable for further studies because of a lack of consistency in the results. The variability arose during the initial stages of disintegration when the tablets tended to be kept at the liquid surface by the vertical motion of the rack assembly. There was also a difficulty in estimating the end point.

2.8. Friability and Liquid Penetration Tests.

Two additional tests were utilised in the main experiments but not in the preliminary studies:- a friability test and a liquid penetration test. The friability test was carried out in a 20cm diameter perspex drum with a single curved radial arm which raised the tablets and dropped them from the centre once

every revolution (Figure 1.2a). Twenty tablets were brushed and weighed before loading in the drum. After 200 revolutions the tablets were removed, brushed and reweighed. The friability was calculated as a percentage of the original weight using Equation 2.6. Tablets breaking apart during the test were included in the final weight as those parts greater than or equal to half the initial tablet volume by visual inspection. This aspect is discussed in the Section 4.5.

$$\text{friability}(\%) = \frac{(\text{initial weight} - \text{final weight}) \times 100}{\text{initial weight}} \qquad (2.6)$$

A measure of the liquid uptake of the tablets was obtained by mounting a tablet on white soft paraffin in the centre of a petri dish, filling the dish to half way up the side of the tablet with a radiolabelled liquid and monitoring the radioactivity in the tablet. The liquid was technetium-99m (a gamma emitter) in normal saline diluted approximately 1:20 with distilled water. The experiments were carried out at room temperature using an Anger type scintillation camera with a pinhole collimator (GEC Maxicamera, Figure 2.14). Recording the cumulative count within the tablet every 10 seconds up to 1 minute then every 30 seconds enabled a profile of the total count within the tablet against time to be produced. Assuming that there was no selective absorption, then this profile represents the rate of liquid uptake by the tablet. The difficulty of relating count rate to liquid volume means that the figures produced represent the time to attain percentages of the maximum uptake. No correction was made for radioactive

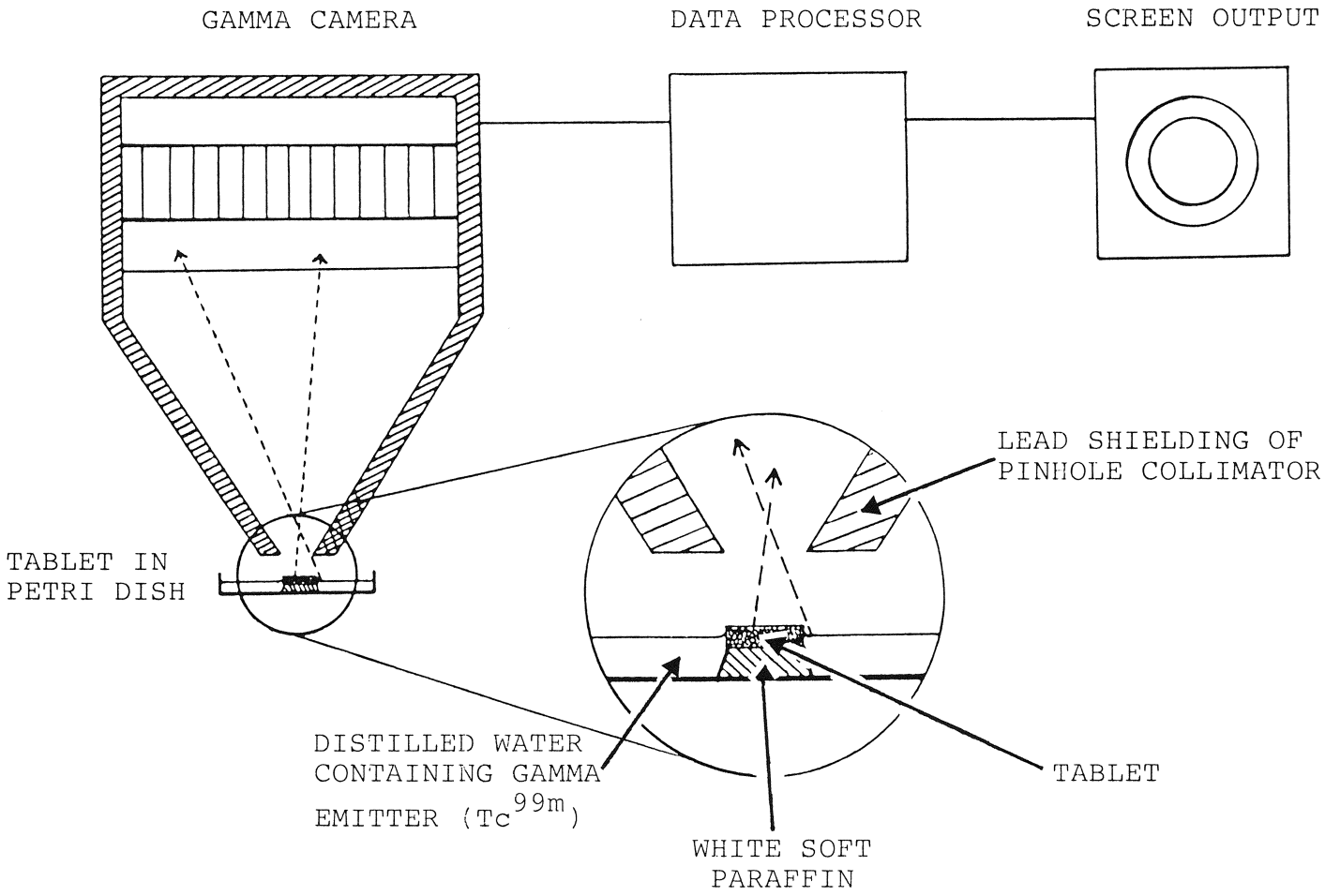

FIGURE 2.14
Schematic diagram of the equipment used in liquid uptake studies.

decay as most of the tablets attained maximum uptake within a few minutes whilst this isotope has a half-life of 6 hours. The white soft paraffin excluded liquid penetration through the lower tablet face and the liquid meniscus meant that the liquid was in contact with all of the sides of the tablet but not the top face. The volume of the petri dish was large compared to the volume of the tablet. This meant that the sides of the tablet did not lose contact with the liquid during the tests, the uptake therefore took place over an area dependent only on the tablet thickness.

2.9 Conclusions from the preliminary formulations.

The preliminary formulation studies suggested that a tablet composed of the model drug in an Avicel base with starch as a disintegrant, Aerosil as a flow aid and magnesium stearate as a lubricant would be suitable for more detailed examination. An arbitrary drug concentration of 25%w/w was chosen to represent an acceptable loading for a direct compression tablet. A full factorial design was considered to be the most efficient way of examining the effects of four critical variables in the tabletting process. The mixing time and the compaction pressure were selected as the most influential processing factors, and the drug particle size and the starch concentration as factors affecting the formulation. To maintain the number of experiments at a manageable level, it was decided to use two levels of the factors under consideration. The preliminary studies were used to determine suitable levels, thus mixing times of 1 or 5 minutes and starch concentrations of 1 or 7% were chosen. The variation in particle size was qualitative in that the size was either small or

large. The compaction pressure offered more scope for change than the other factors without increasing the necessary number of mixes, it was accordingly set at three levels representing the lowest pressure at which normal, if soft, tablets could be produced, the highest pressure before lamination became a problem, and the midpoint of these.

The following chapter contains the details of the experimental design and the results of the tests applied to the tablets produced, according to the methods described in this chapter.