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PHYSICAL AND CHEMICAL CHARACTERIZATION OF THERMOSOFTENED BASES FOR MOLTEN FILLED HARD GELATIN CAPSULE FORMULATIONS.

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ABSTRACT

Dynafill, Dynasan-114, Lutrol-F68, PEG-10000 and PEG-20000 have been examined as potential bases for the preparation of fusion formed solid dispersions for molten filling into hard gelatin capsules. Investigations included, an examination of thermal effects on crystal structure by DSC and XRD, a rheological study to evaluate capsule filling characteristics, dissolution studies on drug/base formulations, chemical analysis for free fatty acid impurities in Dynafill and Dynasan-114, and detailed studies on selected drug/base formulations. PEG-20000 and Dynasan-114 were not examined in detail, after preliminary investigations had shown high viscosity and poor filling characteristics for PEG-20000 and poor dissolution characteristics for Dynasan-114. Dynafill provided good release profiles when formulated with a variety of model drugs (Acetohexamide, Ibuprofen, Indomethacin, Quinidine sulphate and Theophylline). Results from hot stage photomicrography supported

by DSC and XRD were used to construct a phase diagram of the Ibuprofen/Lutrol-F68 system. The evidence from the phase diagram indicated the formulation of a simple eutectic system with no solid solubility and a eutectic composition at approximately 35% w/w Ibuprofen.

INTRODUCTION.

As part of the continuing search for improvement in the quality and efficacy of pharmaceutical dosage forms, thermosoftened materials[1,2] have been examined as potential carriers for drugs formulated as solid dispersions[3]. The use of solid dispersions in pharmaceutical systems has been established for some time[4] and in some instances the dispersion has been granulated and filled into capsules or alternatively tabletted; more recently, the molten solid dispersion has been filled in hard gelatin capsules.

There are several advantages of liquid filled capsules over conventional capsule formulations and some of the more common benefits are mentioned here.

The filling of liquids into capsules presents no dust hazard and the possibility of cross contamination via airborne particles is also eliminated. It is possible to obtain much better capsule weight uniformity by liquid filling than with powder filled capsules. The base can provide protection against moisture and oxygen by totally surrounding the drug particles thus improving the formulation of very hygroscopic drugs and extending their shelf life, e.g.. vancomycin[5]. It should be possible to produce fast release preparations of poorly water soluble hydrophobic drugs by dispersing micronised drug particles in a very soluble base, alternatively a very soluble drug may be formulated with a suitable base to give controlled release characteristics.

The selection of the base is clearly important as this may affect the filling process, drug release and stability of the product. Mixed systems have been investigated eg Gelucires (a group of inert excipients derived from hydrogenated fats and oils with controlled hydrophilic properties)[6] and also single component bases eg polyethylene glycol 6000 (PEG-6000)[5,7,8]. Gelucires have the advantage that by altering the relative proportions of the components it is possible to produce a range of bases with different properties eg fast and slow drug release.

One component systems on the other hand have the advantage of simplicity of formulation and easier characterization.

Gelatin remains the most suitable material for capsule manufacture but has limitations when used for liquid fill formulations eg systems which promote excessive migration of moisture will affect the integrity of the gelatin shell. However, several excipients do not affect the gelatin and may be filled using a thermosoftened or thixotropic formulation. Both options have their relative merits but this presentation is restricted to the consideration of thermosoftened formulations.

It is possible to propose the ideal base for liquid filling into hard gelatin capsules using thermosoftening techniques by consideration of the following criteria. The base must be non-toxic, pharmacologically inert and the melting point must be low enough so that thermal damage to the capsule body or degradation of the drug is avoided, yet high enough to prevent melting during transportation and storage. The base should not affect the integrity of the shell and should afford maximum protection to the drug and thus aid stability. The solubility of the base should reflect the drug release requirements of the formulation.

Whilst liquid filling of capsules is now an established technique[9], detailed investigations are needed into the possible changes caused by the melting/cooling and recrystallization cycle, with particular reference to drug release and also storage effects of the melt prior to and after filling.

This work forms part of a detailed investigation with the principal aims of; elucidation of the mechanisms of drug release from molten filled drug/base formulations and, to develop a greater understanding of these systems for use in a manufacturing environment.

Preliminary work was concerned with the selection of bases for detailed examination by consideration of the following factors: toxicity, purity, melting point, stability to heat and hygroscopicity. Several materials satisfied these criteria and five were selected for further study since detailed investigations for their use as thermosoftened bases had not been previously reported in the literature. The materials selected were PEG-10000 (Hoechst), PEG-20000 (Hoechst), Dynasan-114 (a myristic acid triglyceride-Huls UK), Dynafill (a

polyethylene oxide/polypropylene oxide block copolymer with palmitic acid end groups-Huls UK) and Lutrol-F68 (a poloxamer-BASF). Other suitable bases eg. PEG-4000 and PEG-6000, have already been examined in some detail[8,10-12] and were not considered for this investigation.

With the above aims in mind the following studies were undertaken:
a) Thermal effects on crystal structure of base and drug base formulations.
b) Rheology with respect to filling. c) *In-vitro* drug release from model drug/base formulations. d) A study of the chemical composition and purity of the novel bases, Dynasan-114 and Dynafill. e) Characterization of a model drug/base system.

METHODS.

a) Thermal analysis.

Preliminary thermal investigation of the materials was undertaken using an FP5 control unit, with FP52 hot stage (Mettler Instrument Corp.) and M17 polarising light microscope fitted with a camera and JS35 autoexposure unit (Vickers Microscopes Ltd.). In most cases interference filters were used in addition to the polarisers to enhance quality of the photomicrographs. Samples were placed on a microscope slide inside the hot stage and heated to at least 10°C above the melting point of the base in order to ensure complete melting of the whole sample. Cooling rates of 0.2°C/min, 1.0°C/min, 3.0°C/min and 10°C/min were used to investigate the base from a temperature of 10°C above its melting point down to the temperature of complete solidification. Photomicrographs were taken at intervals during each cooling programme.

Differential Scanning calorimetry (DSC) was performed on a Stanton Redcroft DSC 700 Differential Scanning Calorimeter (P.L. Thermal Sciences) with output to a chart recorder. The reference was dried alumina and samples were heated in open aluminium crucibles (P.L. Thermal Sciences). To investigate the effects of cooling rate, samples were initially heated to a temperature at least 10°C above the established melting point of the base, held at this temperature for five minutes and then cooled at either 8.0°C/min or 1.0°C/min to below the temperature at

which the sample completely solidified. The samples were remelted and the DSC traces examined in order to determine the effects of previous cooling rate on the sample.

X-ray diffraction (XRD) was carried out on powder samples of the base using a diffractometer PW1050/5 and PW1710 (Philips). The effect of different cooling rates was investigated for samples prepared using the method described in the hot stage procedure. The 2-theta range was 10 to 40° utilising a copper source.

b) Rheology and capsule filling.

The rheology of the molten bases was investigated using an RV3 Rotaviscometer (Haake inc.) fitted with concentric cylinders and a heating jacket for temperature control. Samples were examined over the temperature range from just above the melting point to 90°C.

Capsule filling studies were carried out using a capsule filling simulator (Hibar Systems Ltd.) and size one clear hard gelatin capsules (Elanco, Basingstoke, UK.). The fill volume was set to 0.5ml for all bases and the filling temperatures were from 60 to 70°C depending on the melting point of the base. The first twelve capsules were always discarded to ensure air bubbles had been cleared from the system.

c) Drug release studies.

Dissolution studies were all carried out using apparatus fitted with the six basket/beaker system as defined by the British Pharmacopoeia 1980. Basket rotation speed was 100 rpm, the dissolution media was generally pH 7.6 buffer, although alternatives were investigated. Solutions for analysis were circulated continuously from the beaker by a peristaltic pump (Watson Marlow) through the 1cm path length flow cells fitted in the programmable carriage changer of a UV spectrophotometer model 594 (Cecil Instruments) fitted with a cell programmer. Absorbance values were measured automatically at five minute intervals for each cell and produced on a chart recorder.

d) Characterization of drug/base mixtures.

A range of mixtures of the base Lutrol-F68 and Ibuprofen were prepared by accurate weighing, and then fusion. All samples after thorough mixing were then allowed to cool to room temperature and recrystallize without any temperature control. The following compositions were prepared: 0, 10, 20, 25, 30, 35, 40, 45, 50, 60, 70, 85 and 100% Ibuprofen. The zero and 100% samples were prepared for reference purposes.

Hot stage photomicrography of these mixtures was carried out using a heating rate of 0.2°C/min and the temperatures for the start and completion of melting were recorded. Photomicrographs were taken as before at selected times during the melting of each sample.

DSC of the Ibuprofen/Lutrol-F68 fractions was undertaken at a heating rate of 3.0°C/min. The equipment was calibrated for enthalpy of fusion determination by the use of a naphthalene standard (melting point 81°C - National Physics Laboratory). All analyses were carried out in duplicate. In addition, XRD studies of the Ibuprofen/Lutrol-F68 formulations were carried out on a Diffrac-500 XRD facility (Siemens at The University of Bradford).

e) Chemical analysis.

Two methods were developed. (i) for the determination of the total fatty acid content of the material, and (ii) determination of free fatty acid content.

(i)Total fatty acid method.

An SGE 25m fused silica capillary column with internal diameter 0.25mm was used in a Shimadzu GC-9A programmable oven (Dyson Instruments) linked to a flame ionization detector and Shimadzu C-R4A integrator (Dyson Instruments). Injections were made on column using an SGE 5μL syringe, steel needle and an SGE-OCI3 on column injection port. The carrier gas was helium and a temperature programme was employed starting at 100°C and increasing to 200°C at a rate of 20°C/minute. The run time was five minutes and the injection volume was 1.0μl.

Calibration was carried out using a mixture of methyl esters (C12-18), whilst samples for analysis were first hydrolysed to release their fatty acids, followed by esterification to the methyl ester. The esters were extracted into heptane prior to injection.

(ii) Free fatty acid method.

The microbore column (Capital HPLC Specialists. - 100mm x 2.1mm) was packed with porous graphitic carbon (PGC) with 99.6% Hexane 0.4% isopropyl alcohol as the mobile phase. The pump LC-6A (flow rate 0.5ml/min), integrator C-R5A and detector SPD-6AV (Dyson instruments), set to 211nm.

A mixture of the four fatty acids (lauric, myristic, palmitic and stearic acid) most likely to be present as impurities in Dynasan-114 or Dynafill was prepared as a test mixture for development of this analysis. Calibration solutions of lauric, myristic and palmitic acid with stearic acid as the internal standard gave a linear response over the range of concentrations 0.02-0.3mg/ml ($r>0.9995$). Samples of Dynasan-114 or Dynafill with internal standard were dissolved in mobile phase and all injections were performed in triplicate.

RESULTS AND DISCUSSION.

a) Thermal Analysis.

Cooling rate often affects the crystallinity of solid dispersions[13] or pure bases[14], and hence this was investigated for the cooling of each selected excipient from its molten state. When the samples of PEG-10000, PEG-20000, Dynafill and Lutrol-F68 were examined by hot stage microscopy after pretreatment by melting and cooling at different rates, there was no evidence of changes in crystal structure. In all cases only one type of structure was evident, typified by the photomicrograph for Dynafill (Plate 1). However, clear differences were observed by this technique for samples of Dynasan-114 which showed one crystal structure when cooled at 0.2°C/minute (Plate 2) but three distinct types at 3.0°C/ minute (Plate 3).

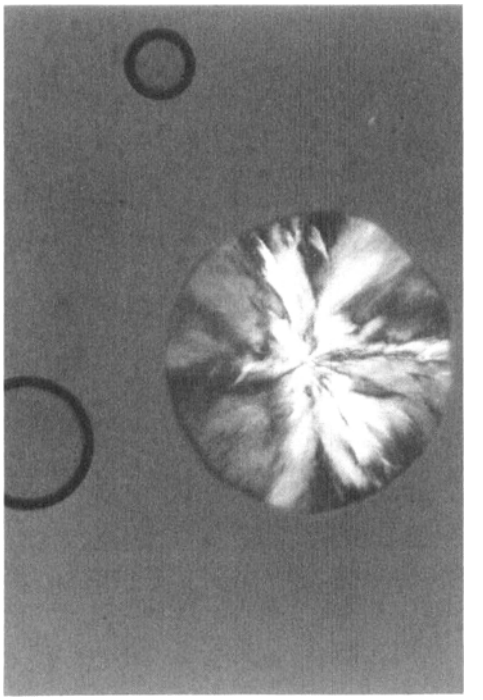


PLATE 1
Dynafill recrystallizing.

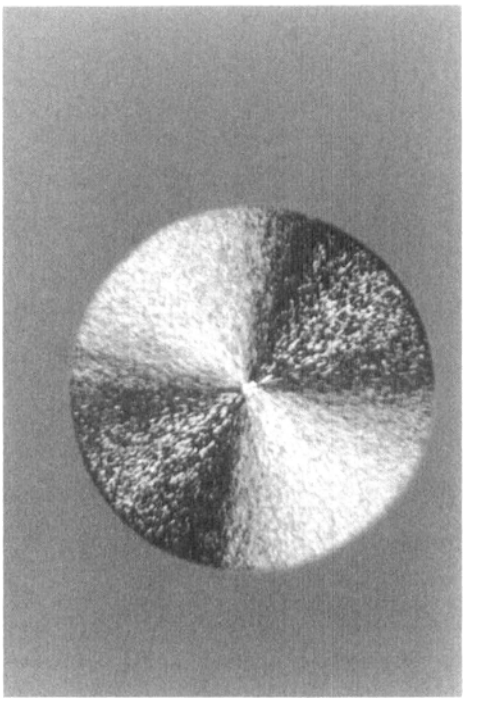


PLATE 2
Dynasan-114 recrystallizing (cooling rate=0.2°C/min).

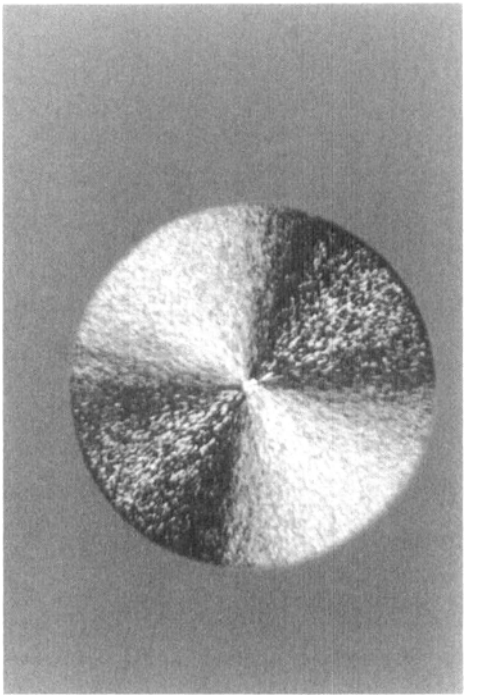
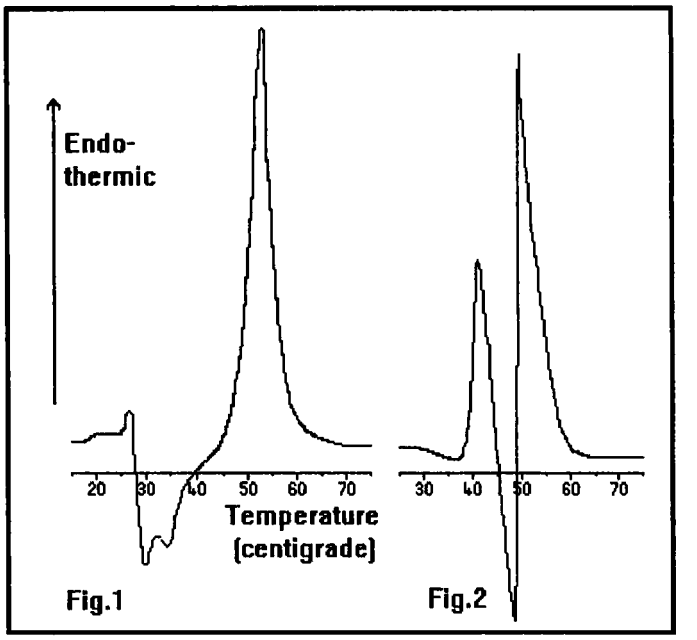


PLATE 3
Dynasan-114 recrystallizing (cooling rate=3.0°C/min).

PLATE 4
Ibuprofen and Lutrol-F68 recrystallizing separately.



FIGURES 1 and 2
DSC of Dynasan-114 (heating rate=10°C/minute).

Further evidence to support these findings was obtained from DSC. All the bases, except Dynasan-114, always gave one endotherm on melting, which was very similar to that for untreated base, regardless of the previous cooling rate from the molten state. However, it was found that a sample of Dynasan-114 that had been recrystallized at 8.0°C/minute gave a characteristic exotherm followed by an endotherm (fig.1) when remelted at a heating rate of 10°C/min.

Comparison with a sample which had been recrystallized at 1.0°C/min gave a different trace when remelted (fig.2); here two endotherms are produced. Both these traces differ from that of an untreated sample of Dynasan-114 (one sharp endotherm) and these results could provide evidence for polymorphic transitions in Dynasan-114 or degradation of the triglyceride. Additional evidence was obtained by storage of samples of recrystallized Dynasan-114 for several weeks, followed by comparison with freshly recrystallized samples. Investigation of all

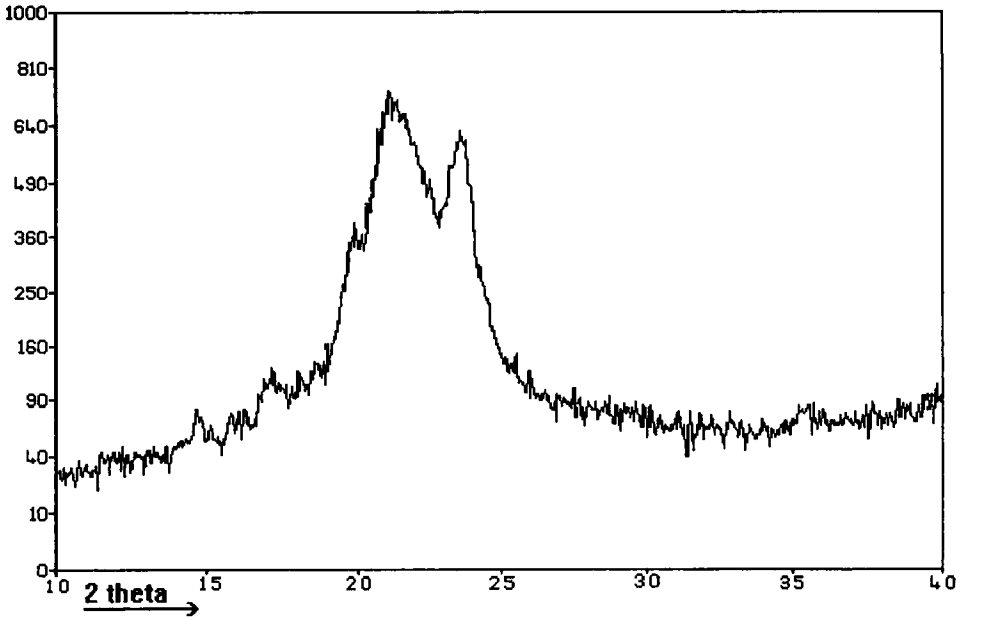


FIGURE 3
XRD of a recently recrystallized sample of Dynasan-114.

samples of Dynasan-114 stored for one month at room temperature produced DSC traces which were indistinguishable from those of untreated samples, regardless of their previous treatment.

Similar investigations were carried out using XRD and it was found that recently recrystallized Dynasan-114 gave a different pattern from that of an untreated sample (figs.3 and 4). When the same recrystallized sample was examined after one month, it was found to have changed and was indistinguishable from the untreated sample. These findings are in close agreement with those from the DSC studies and provide evidence for reversible polymorphic transitions in Dynasan-114 samples.

It appears that melting and recrystallization of Dynasan-114 produces at least one metastable polymorph, depending on the cooling rate, which on storage reverts back to the original form. Further detailed investigations revealed this reversion was temperature dependent and took less than 24 hours at 37°C and one

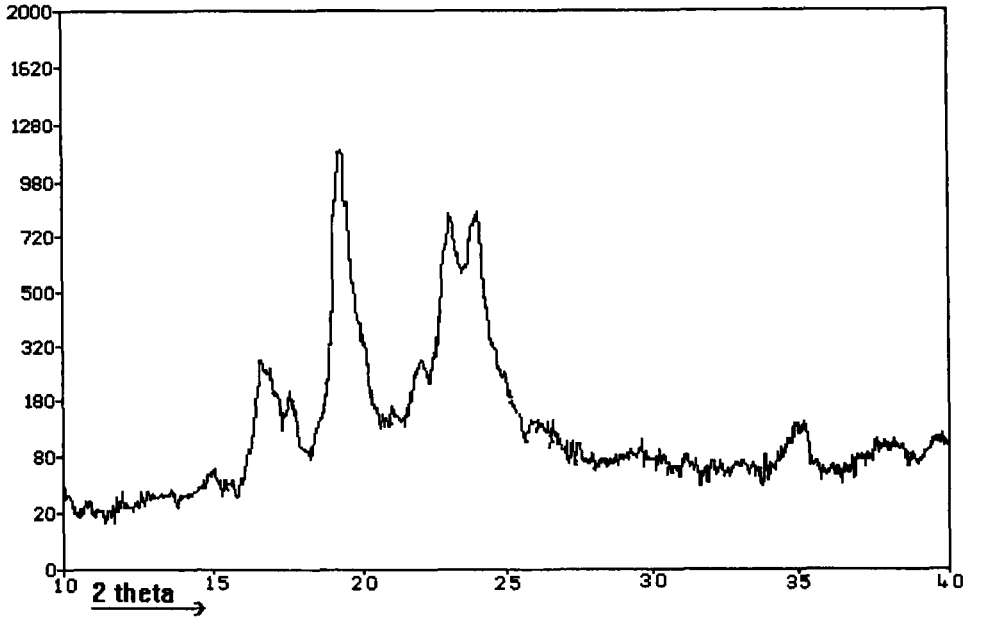


FIGURE 4
XRD of an untreated sample of Dynasan-114.

month at ambient temperatures. None of the other four bases were affected by any of these tests and there is no evidence for polymorphic transitions at temperatures and cooling rates likely to be encountered during large scale manufacturing processes.

b) Rheology and capsule filling.

Filling capsules with molten materials will be limited by the viscosity of the formulation and hence it is necessary to investigate the rheological properties of the bases. The rheograms indicated that all the examples were Newtonian over the temperature range of base melting point to 90°C.

PEG-20000 had a much higher viscosity (24000 mPaS.) than the other materials(<= 5500 mPaS.) (Table 1) and would possibly be more difficult to fill into capsules.

TABLE 1

Viscosity of thermosoftened bases at 70°C.

Material	mPaS.
Dynasan-114	12
Dynafill	1600
Lutrol-F68	1200
PEG-10000	5500
PEG-20000	24000

TABLE 2

Filling statistics of thermosoftened bases.

Material	Hopper temp °C	Fill weight mg	CV%	Sample size
Dynasan-114	60	413	0.42	70
Dynafill	70	499	0.21	70
Lutrol-F68	60	504	0.49	66
PEG-10000	70	521	0.31	70
PEG-20000	70	503	3.06	48

(CV%=coefficient of variation)

A capsule filling exercise was thus carried out in order to investigate the possible filling difficulties with PEG-20000 and to confirm that the other bases would fill satisfactorily. The PEG-20000 could be pumped satisfactorily, however, a tailing of the base between the capsules was the main reason for the higher variation of fill weight (Table 2). Inclusion of a particulate drug in this base would increase the viscosity still further and probably accentuate the tailing effect, therefore PEG-20000 was excluded from further study. The other materials showed excellent filling properties all with CV <0.5% however, the effect of drug dispersion on viscosity needs to be investigated in relation to the filling properties of these bases.

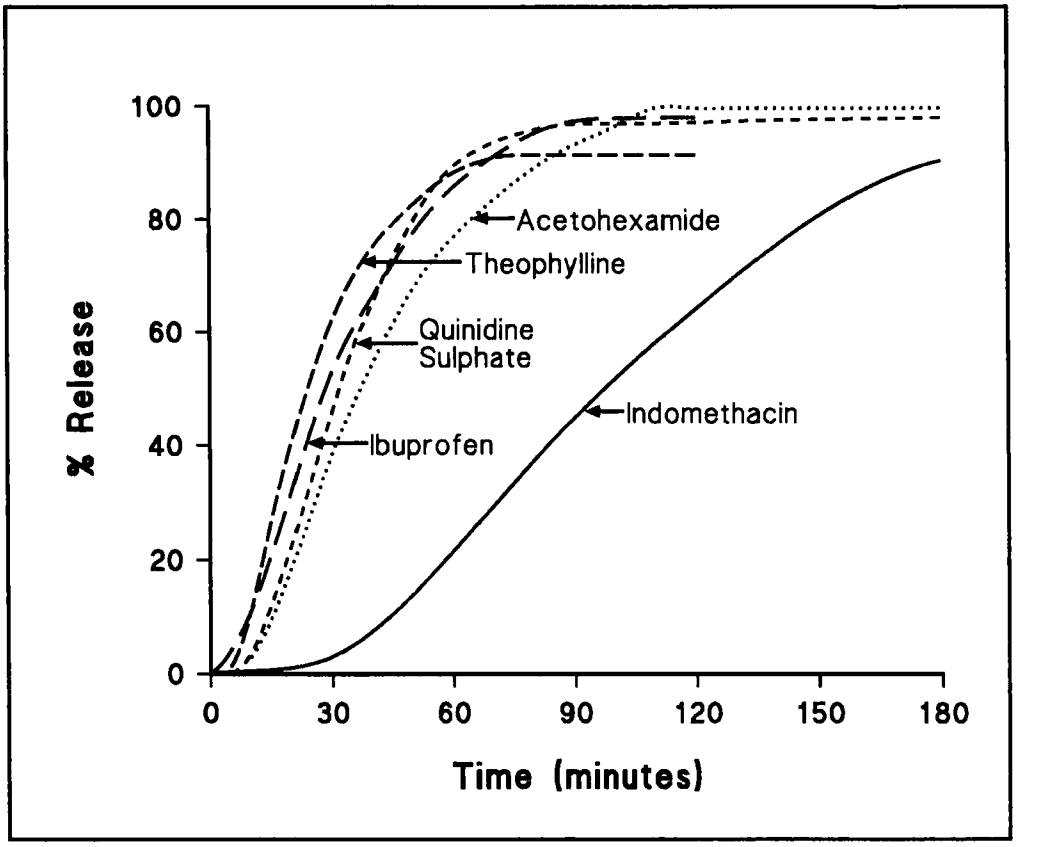


FIGURE 5
Dissolution of Dynafill with a selection of model drugs.

c) Drug release studies.

Dissolution studies from hard gelatin capsules have been undertaken for selected model drugs (Ibuprofen, Theophylline, Quinidine Sulphate, Indomethacin, and Acetohexamide) formulated as solid dispersions (fig.5). Ibuprofen was found to be of particular interest since, with a melting point of 76°C, it formed a homogeneous mixture with all the molten bases. This was not the case for any of the other model drugs. The Ibuprofen/base formulations illustrated the considerable differences in release rate from a 50%w/w drug/base

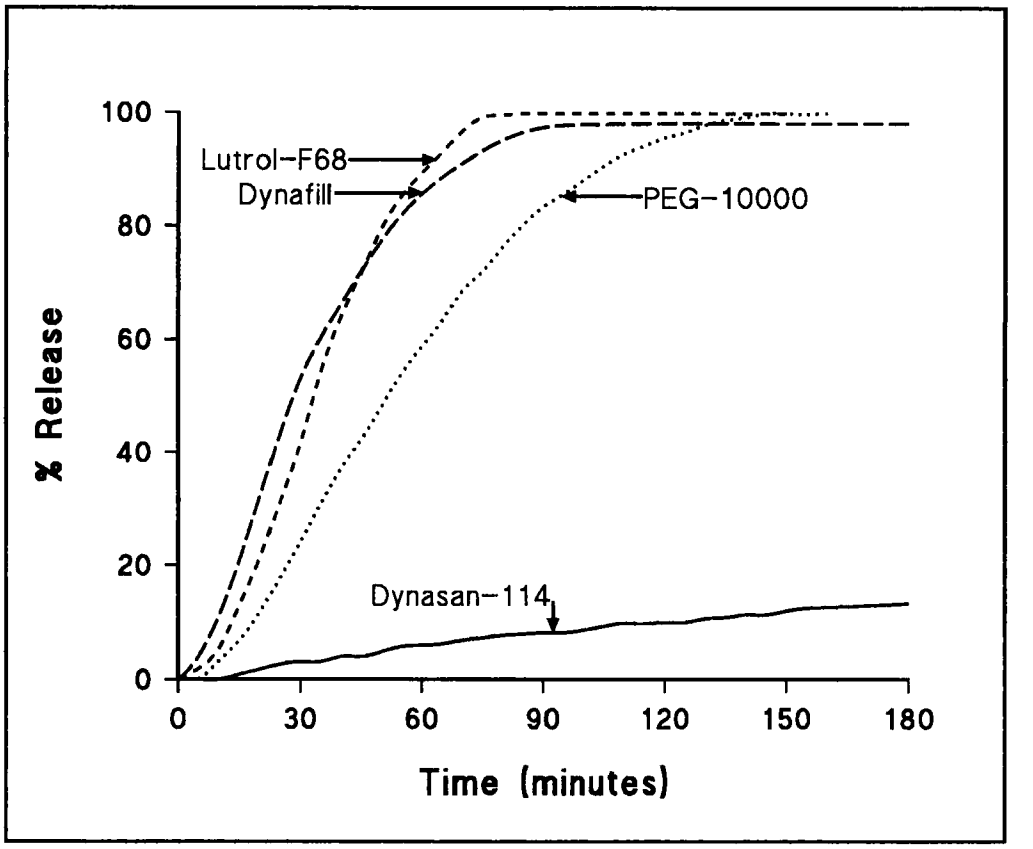


FIGURE 6
Dissolution of four bases with Ibuprofen as the model drug.

filled in hard gelatin capsules (fig.6). It was not possible to obtain a satisfactory release profile with any of the model drugs formulated with Dynasan-114. Release was below 15% even after four hours for Ibuprofen and there was no improvement even when very water soluble drugs eg Theophylline and Quinidine Sulphate were examined.

If drug release is controlled by slow erosion and dissolution of the base then low release rates would be produced however, there are many examples of controlled drug release from insoluble matrix structures by diffusion. This is not

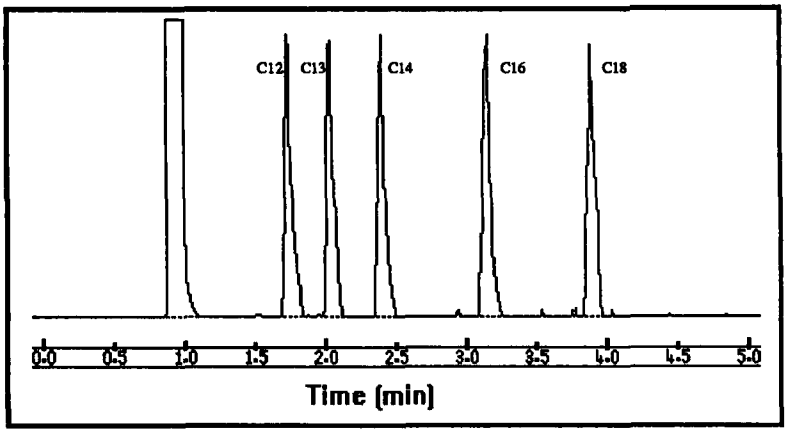


FIGURE 7
Capillary-GC of esterified fatty acid mixture.

the case with the insoluble Dynasan-114 matrix since drug diffusion rates appear to be very low in this system.

The presence of lipase in the dissolution media could provide disintegration/ dissolution of the triglyceride and although results from a preliminary investigation of the Ibuprofen/Dynasan-114 system in such a media do not support this, more detailed investigations are in progress.

The release profiles of Ibuprofen from the other bases were very similar, the T_{50} values for Dynafill and Lutrol-F68 were approximately 30 minutes whereas that for PEG-10000 was 55 minutes. The T_{50} value for Ibuprofen from Lutrol-F68 is in agreement with a previous study on a selection of poloxamers where the T_{50} of methylparahydroxybenzoate was also found to be in the region of 30 minutes[15].

d) Chemical analysis.

The method for total fatty acid analysis gave excellent separation when a test mixture of esterified fatty acids was injected (fig.7). Resolution of the test mixture of fatty acids for the analysis of free fatty acid contamination was

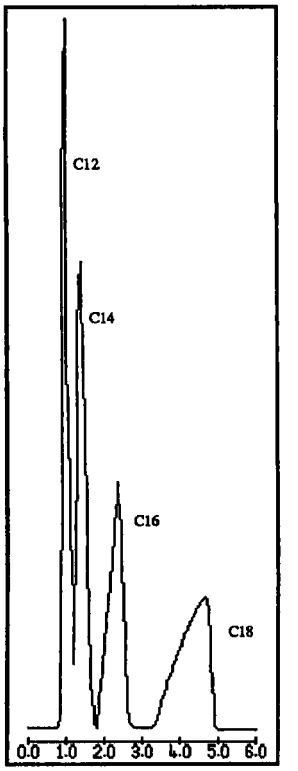


FIGURE 8
HPLC of fatty acid mixture.

incomplete (fig.8), however, an excellent linear response was obtained for both methods when calibration samples were injected (r>.9995).

Results from these analyses showed that both materials were free from fatty acid contamination down to the detection limits of the methods.

e) Examination of drug/base mixtures.

A detailed investigation of the mixtures of Ibuprofen and Lutrol-F68 was undertaken using hot stage photomicrography, DSC and XRD. Normally, a phase diagram can be constructed from results obtained by cooling the system and analysis of the cooling curve for recrystallization of each mixture. However,

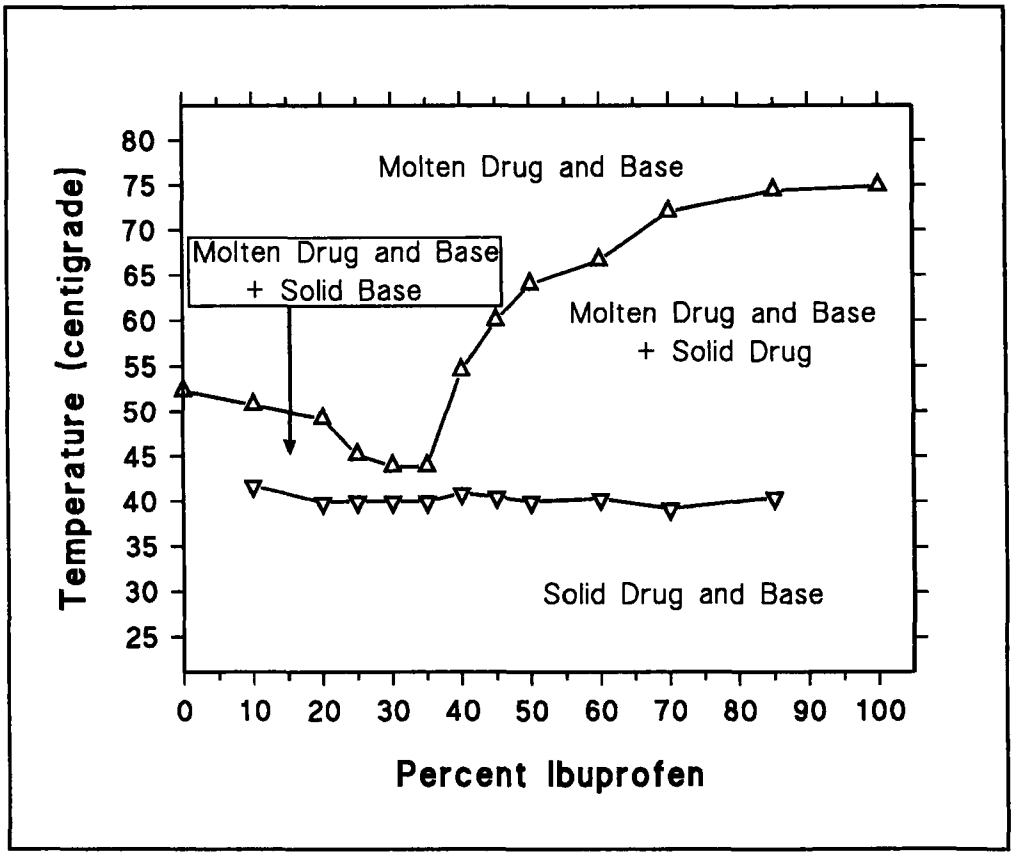


FIGURE 9
Phase diagram of the Lutrol-F68 Ibuprofen system.

preliminary studies showed that some of the mixtures demonstrated severe supercooling and did not recrystallize at room temperature for some time eg. an hour for the 50% Ibuprofen/50% Lutrol-F68 system. The problems associated with crystallization on cooling prohibited the use of the cooling curve method for construction of a phase diagram and as an alternative, the construction of the phase diagram was attempted by using a heating programme to monitor the sample melting by hot stage microscopy. Figure 9 illustrates the phase diagram produced from this technique and as can be seen there is a eutectic point probably between 30 and 35%w/w Ibuprofen.

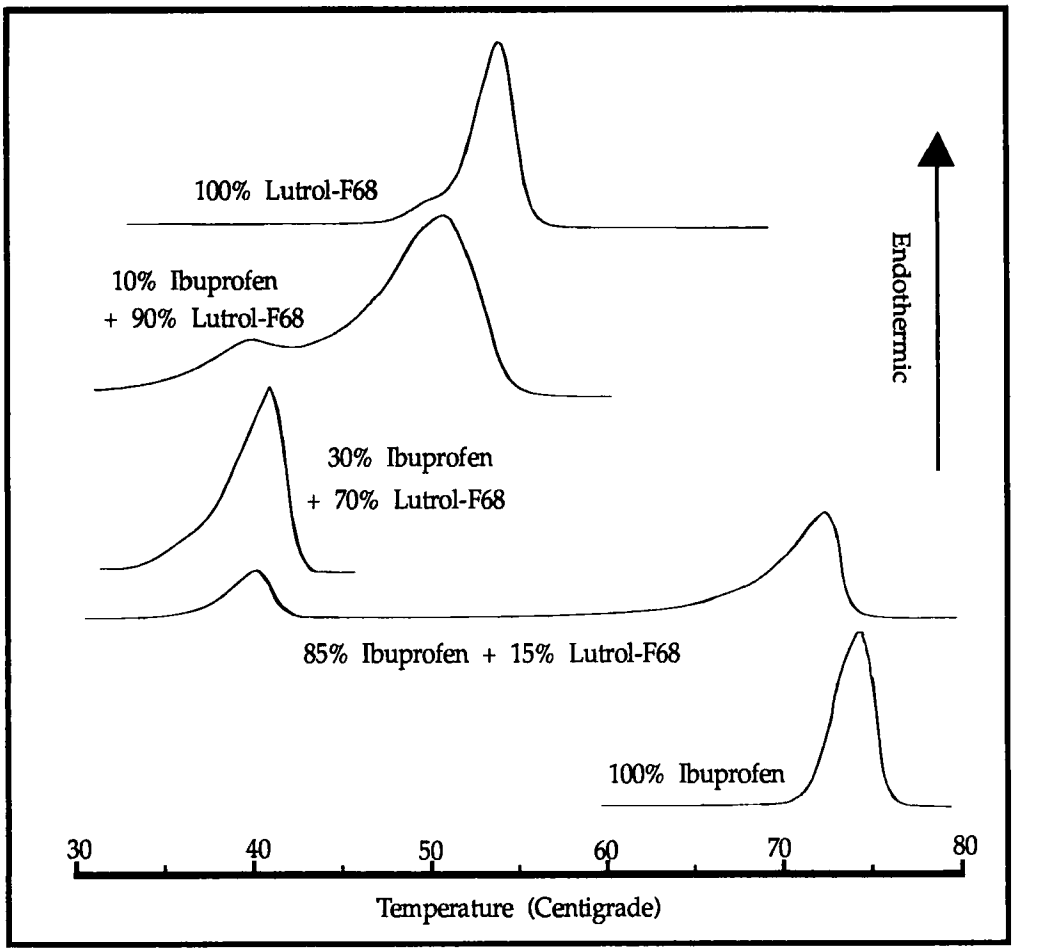


FIGURE 10
DSC of Ibuprofen/Lutrol-F68 mixtures.

DSC of the 10% Ibuprofen sample gave two peaks, one for the mixture of Ibuprofen and Lutrol-F68 and the other for the excess Lutrol-F68. All compositions from 20% to 45% Ibuprofen gave only one peak corresponding to the mixture of Ibuprofen and Lutrol-F68 but from 50-85% Ibuprofen a separate peak was observed which increased in size with Ibuprofen concentration (fig.10).

Diagramatic representation of the height of the peak due to the Ibuprofen/ Lutrol-F68 mixture (fig.11) reached a maximum at 30% Ibuprofen which points

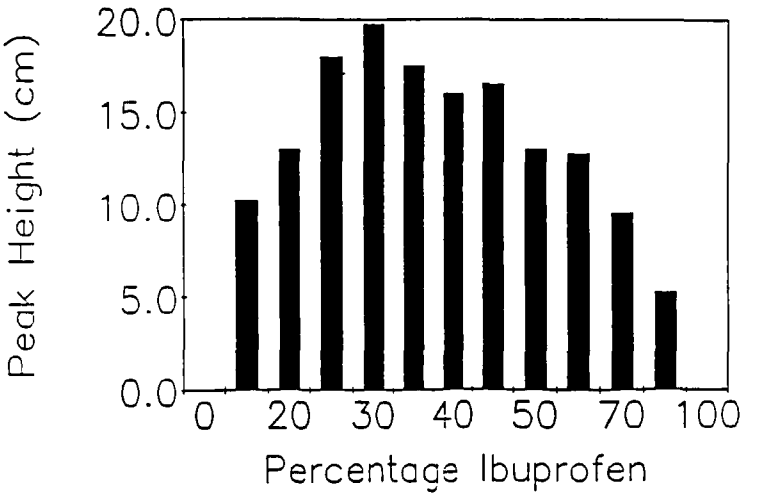


FIGURE 11
Peak heights produced on DSC of Ibuprofen/Lutrol-F68 mixtures.

to a probable eutectic point in this region and is therefore in agreement with the hot stage photomicrography. At many of the mid-range compositions, two types of crystal could be identified ie. the pointed rod-shaped Ibuprofen crystals and the snowflake structures of the Lutrol-F68. When the 40% Ibuprofen sample was allowed to cool it was possible to see both types of crystal growing at the same time (Plate 4).

All the dispersions were analysed by XRD, Diffrac-500 (Siemens) in order to investigate; (i) the cryatallinity of the drug base system, and (ii) for the presence or absence of solid solutions in the Ibuprofen/Lutrol-F68 system. The occurrence of a solid solution either Ibuprofen in Lutrol-F68 or Lutrol-F68 in Ibuprofen would alter the D spacing in the crystal lattice of the host material which should be detected by the instrument.

In all cases peaks for both Ibuprofen and Lutrol-F68 were visible and D spacings of major peaks, due to both components, remained unchanged from those produced by XRD of either pure Ibuprofen or pure Lutrol-F68. Both these factors provide strong evidence against significant solid solubility in the Ibuprofen/Lutrol-F68 system.

CONCLUSION.

From these findings Dynafill, Lutrol-F68 and PEG-10000 appear to be suitable bases for molten filling and further detailed examination with respect to the aims is being undertaken. However, the results for Dynasan-114 and PEG-20000 show certain limitations for the use of these bases in thermosoftened formulations. Future work will examine the physical properties of the drug base system with reference to the differences in chemical structure of Dynafill, Lutrol-F68 and PEG-10000.

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