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# FORMATION OF SUSTAINED RELEASE WAX MATRICES WITHIN HARD GELATIN CAPSULES IN A FLUIDIZED BED.

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## ABSTRACT

Sustained release wax matrices were formed within hard gelatin capsules during fluidization in a hot air stream. The capsules were filled with drug (propranolol HCl or theophylline) - wax (Precirol ATO-5 or Gelucire 50/13) powder blends and suspended in a fluidized bed to induce fusion of the wax. Upon cooling, wax matrices with embedded drug were formed in the ends of the capsules. The use of blends of waxes with different HLB values allowed good control over the drug release pattern. The drug release from the matrices was independent of the pH of the dissolution medium. Differential scanning calorimetry was used to study the physical state of the drugs in the matrices. Propranolol HCl was insoluble and completely dispersed in the wax matrix while theophylline was partially dissolved in the wax.



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## INTRODUCTION

The incorporation of drugs into inert matrices is a popular approach to prolong the drug release. Numerous carrier materials have been evaluated in the development of controlled or sustained release matrix systems. Besides the overwhelming use of either water-soluble or water-insoluble polymers, waxes have received considerable attention. Melt (1) and solvent granulations (2, 3) have been used to prepare drug-wax granules to be compressed into tablets. Beads and beads compressed into tablets were prepared from drug-wax-inert excipient powder blends (4, 5). The dosage forms had to be heated to result in prolonged drug release.

Waxes are difficult to compress at higher levels. The energy imparted during compaction causes melting of the waxes resulting in sticking and picking of the formulation. This necessitates dilution of the drug-wax granules with inert fillers. Although the final concentration of the wax in the formulation is generally kept below 30%, the drug : wax ratio is mostly in the range of 1 : 1 to 1 : 3, depending on the drug solubility. Hard gelatin capsules have been liquid-filled with solutions or dispersions of drugs in melted waxes. Upon cooling, drug-wax matrices with sustained release properties were obtained (6, 7).

The objective of this study was to evaluate sustained release wax matrices formed in a novel way within hard gelatin capsules filled with drug-wax powder blends. The waxes melted within the capsules in a heated fluidized bed and formed solid drug-wax matrices upon cooling. This method is simple, rapid, allows the use of drug-wax powder blends, and obviates the need of granulation and compression steps and of additional excipients.

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## MATERIALS AND METHODS

### Materials

The following chemicals were used as received: propranolol HCl, theophylline (Sigma Chemicals, St. Louis, MO); Gelucire 50/13, polyethylene glycol fatty ester; Precirol ATO-5, glyceryl palmitostearate (Gattefosse Corporation), hard gelatin capsules (Eli Lilly & Co., Indianapolis, IN).

### Methods

The drug and wax were blended (400 mg) and filled into hard gelatin capsules (# 0). The capsules were sealed with a warm gelatin solution (10% w/w). The capsules were then loaded into a fluidized bed (Wurster unit with uniform air distribution plate without partition and nozzle; Uni-Glatt laboratory unit, Glatt Air Techniques, Inc., Ramsey, NJ). The fluidization conditions were as follows: inlet temperature = 80 - 85°C, outlet temperature = 60 - 65°C, holding time = 15 min. The following preparative variables were investigated in this study: propranolol HCl loading (10, 20, 30, 40, 50, 60 w/w%), theophylline loading (10, 20, 30, 40, 50 w/w%), Gelucire 50/13 : Precirol ATO-5 ratio (10:0, 5:5, 3:7, 2:8, 1:9, 0:10), and capsule (# 0) loading (200, 300, 400, 500 mg).

The release properties of the wax matrices were studied in 0.1M HCl or 0.1M pH 7.4 phosphate buffer using the USP XXI rotating paddle apparatus (500 ml, 37°C, 50 rpm, n = 3). The samples were assayed spectrophotometrically either directly or after appropriate dilution with the release medium (theophylline: $\lambda = 270$ nm; propranolol HCl: $\lambda = 288$ nm).

Thermograms of the drug-wax matrices before and after dissolution study were obtained on a computer-interfaced Perkin-Elmer differential scanning

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calorimeter, Model DSC 2 (scanning rate = 20°C/min, nitrogen atmosphere). The heat of fusion was calculated by the instrument.

## RESULTS AND DISCUSSION

Gelucires are semi-synthetic glycerides derived from natural hydrogenated food-grade fats and oils. They are characterized by their melting point (range: 33 - 64°C) and HLB value (range = 1-13). In this study, Precirol ATO-5 (melting point = 53°C, HLB = 2) and the more hydrophilic Gelucire 50/13 (melting point = 50°C, HLB = 13) were selected as the drug carriers.

The drugs (propranolol HCl and theophylline) and waxes were mixed in various ratios and filled into the hard gelatin capsules. Initially, the capsules were heated in an oven above the melting temperature of the waxes. Upon cooling, solid drug-wax matrices were formed within the capsules. However, the shape of the wax matrix within the capsules depended on the position of the capsules during the heating and cooling cycle. The drug release varied with different shapes of the solidified matrices. From an industrial and scale-up point of view, it would be impractical to keep all capsules in a vertical position in an oven. A fluidized bed system represented an attractive alternative to prepare the wax matrices. The capsules were suspended in an upward-moving, heated air stream and circulated within the chamber. During fluidization, the capsules rotated and centrifugal forces caused the drug-wax melt to flow into the ends of the capsules. The mixture solidified after ending the heating of the air-stream and two solid wax matrices with dispersed drug were obtained in the ends of the capsules (Figure 1). A thin film was formed between the two wax plugs on the inside of the capsules. This process was highly reproducible and would be possible to scale-up.

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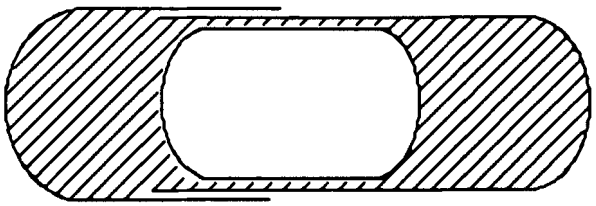

FIGURE 1
Schematic of the distribution of the drug-wax matrix within hard gelatin capsules after fluidization.

The drug release from the capsules was studied as a function of the ratio of high HLB to low HLB carrier (Gelucire 50/13 to Precirol ATO-5), the drug loading, the pH of the dissolution medium, the capsule content within a #0 capsule at a fixed drug : wax ratio.

During the dissolution study, the capsule shell dissolved rapidly in the dissolution fluid. The wax matrix within the capsules broke into two halves at high stirring speeds (>100 rpm). The study was run at 50 rpm and capsules which did not break into two parts were gently hit with a glass rod. The pressure necessary to sepearate the two plugs was minimal. The mechanical stresses exerted on solid dosage forms during the passage through the gastrointestinal tract would guarantee the rupture of the thin film between the two plugs under in vivo conditions (8).

The cumulative amount of theophylline or propranolol HCl released as a function of Gelucire 50/13 : Precirol ATO-5 ratio is shown in Figures 2 and 3. Less than 5 % theophylline and 20% propranolol HCl were released from the Precirol ATO-5 matrices. Hydrophilic substances such as mannitol and hydroxypropyl methylcellulose were added to theophylline - Precirol tablets to increase the drug release (9). Surfactants have also been used to increase the drug release from wax matrices (10). In this study, the drug release could be increased significantly by

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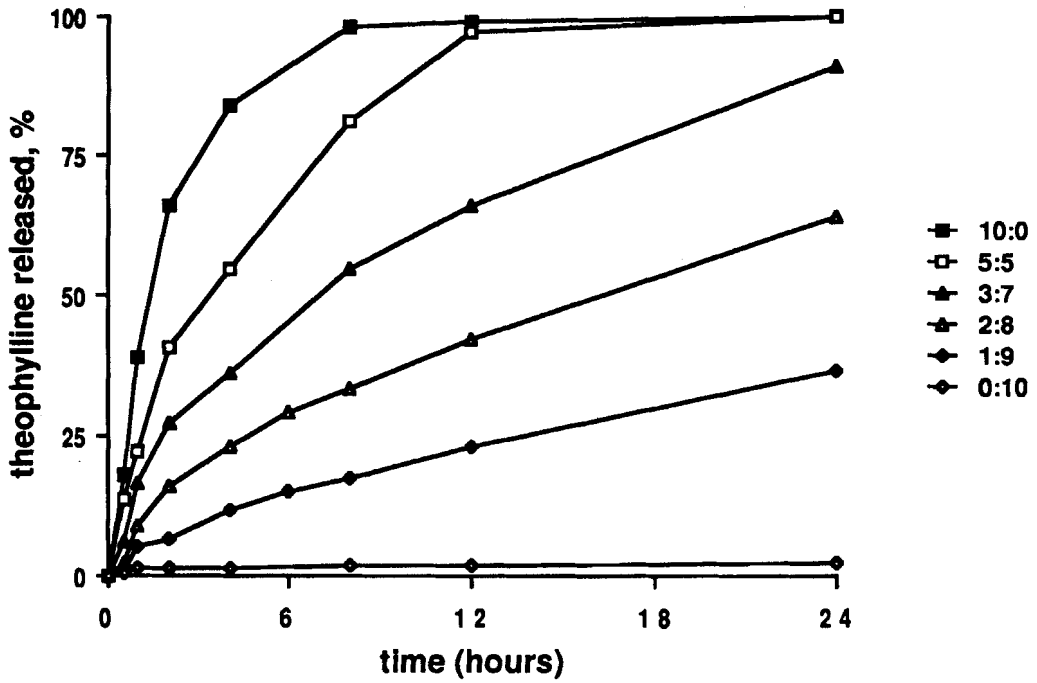


FIGURE 2
Effect of the ratio of Gelucire 50/13 : Precirol ATO-5 on the release of theophylline (33% w/w) from the wax matrices in 0.1M HCl.

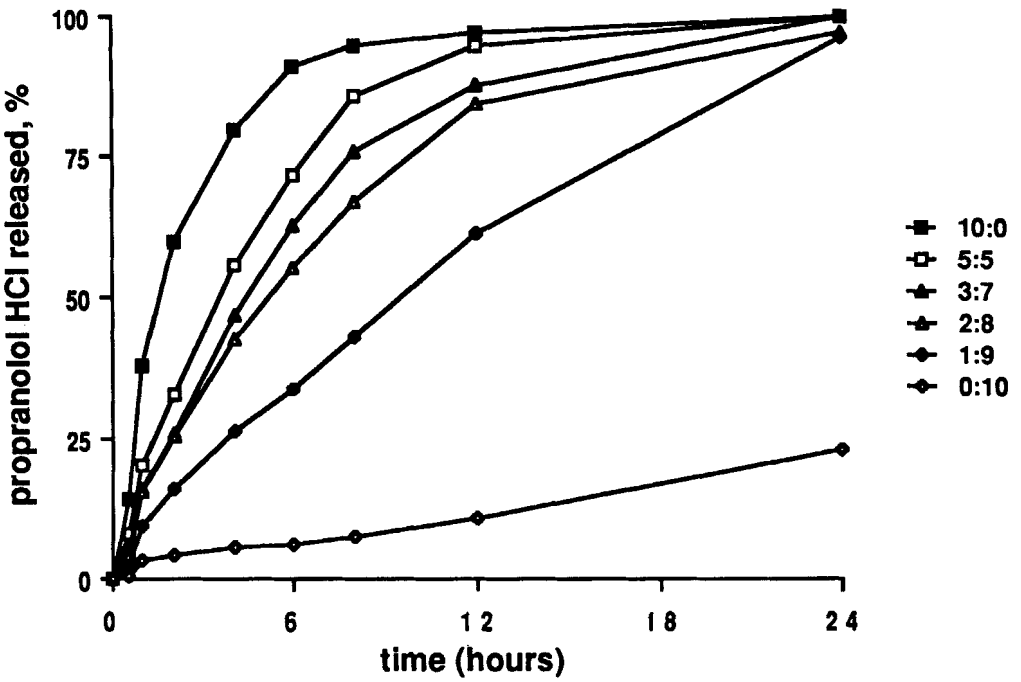


FIGURE 3
Effect of the ratio of Gelucire 50/13 : Precirol ATO-5 on the release of propranolol HCl (33% w/w) from the wax matrices in 0.1M HCl.

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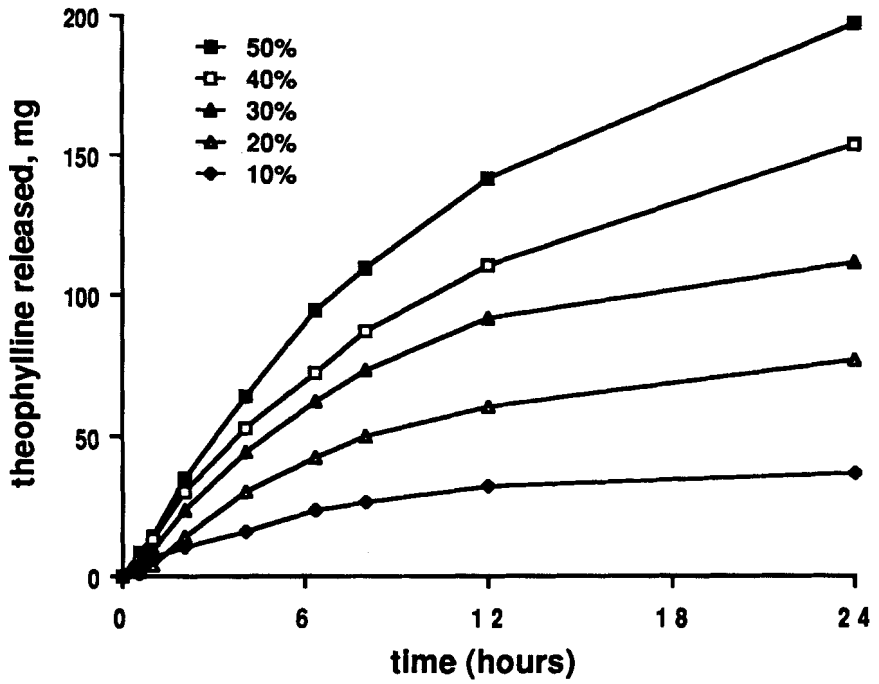


FIGURE 4
Effect of drug loading on the amount of theophylline released from Gelucire 50/13 : Precirol ATO-5 (3:7) matrices in 0.1M HCl.

adding the more hydrophilic wax, Gelucire 50/13. Gelucire 50/13 leached out as indicated by the milky appearance of the dissolution medium. Matrices containing only Gelucire 50/13 as drug carrier hydrated and disintegrated during the dissolution study.

The effect of drug loading on the drug release is shown in Figures 4 and 5. As expected, the amount of drug released increased with increasing loading. Surprisingly, when the percent of drug released was plotted versus time, the release profiles overlapped for both drugs embedded within Gelucire 50/13 : Precirol ATO-5 (3 : 7) matrices as exemplified with propranolol HCl (Figure 6). The dissolution medium apparently penetrated the wax matrix at the same rate, irrespective of the

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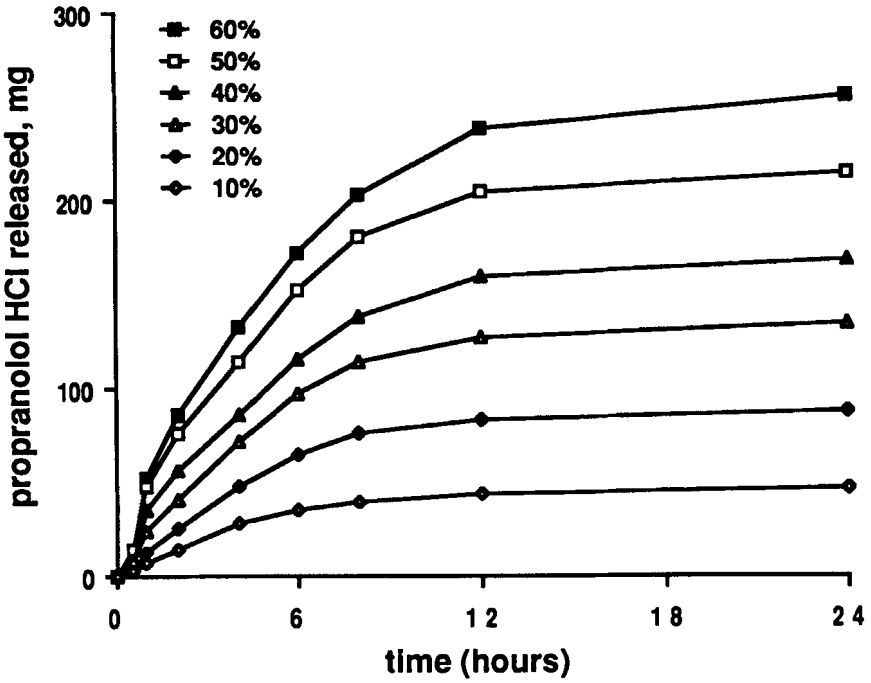


FIGURE 5
Effect of drug loading on the amount of propranolol HCl released from Gelucire 50/13 : Precirol ATO-5 (3:7) matrices in 0.1M HCl.

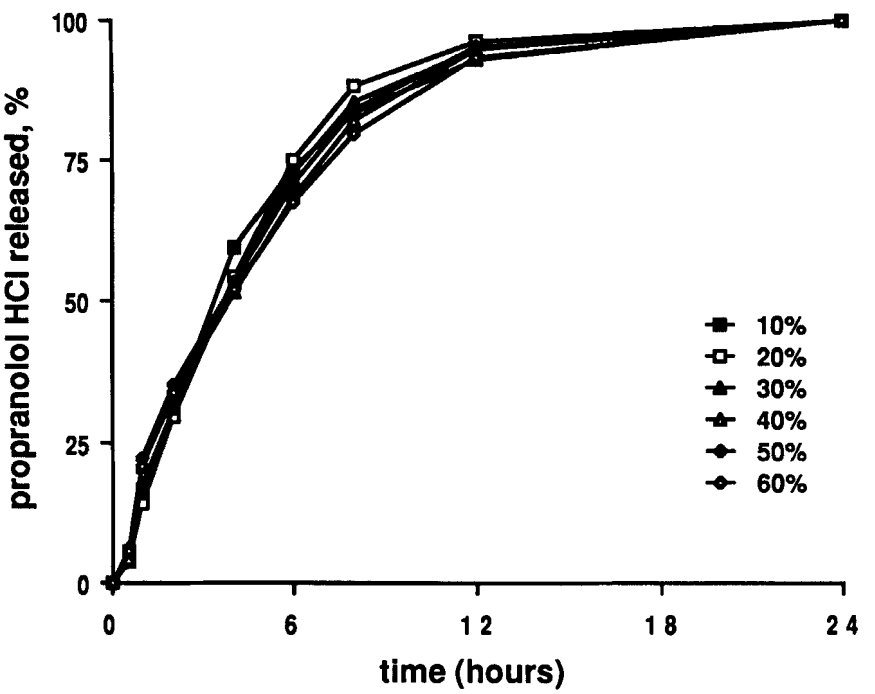


FIGURE 6
Effect of drug loading on the percentage of propranolol HCl released from Gelucire 50/13 : Precirol ATO-5 (3:7) matrices in 0.1M HCl.

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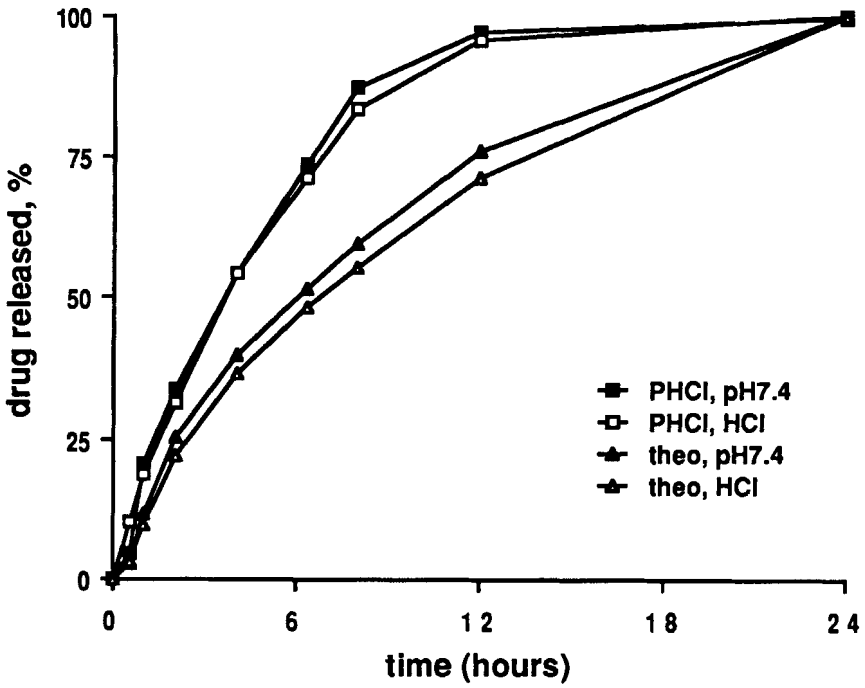


FIGURE 7
Effect of the dissolution medium (0.1M HCl or 0.1M pH 7.4 phosphate buffer) on the release of propranolol HCl (PHCl, 33% w/w) or theophylline (theo, 33% w/w) from Gelucire 50/13 : Precirol ATO-5 (3:7) matrices in 0.1M HCl.

drug loading. The drug release was primarily a function of the composition of the wax matrix. It is expected that the drug release increases with increasing loading on a percentage basis, this observation becoming more pronounced with decreasing levels of the Gelucire 50/13, the wax with the high HLB value.

No significant differences were seen between the release profiles of propranolol HCl or theophylline - Gelucire 50/13 : Precirol ATO 5 (3 : 7) matrices in 0.1M HCl or 0.1M pH 7.4 phosphate buffer (Figure 7). The two drugs were chosen as model compounds because their solubilities were independent of the pH of the dissolution media. This eliminated drug solubility as a variable to be

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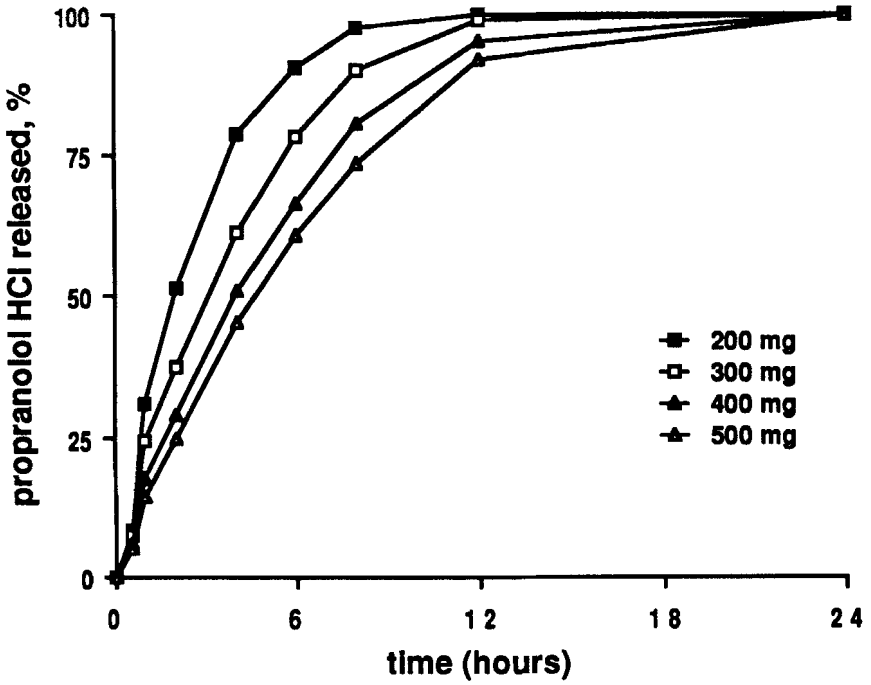


FIGURE 8
Effect of capsule content on the release of propranolol HCl (33% w/w) from Gelucire 50/13 : Precirol ATO-5 (3:7) matrices in 0.1M HCl.

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considered influential on drug release (11). Propranolol HCl has a pKa of 9.45 and was fully ionized in both dissolution media. As with most matrix materials, pH-independent drug release is desired and was proven to be an inherent property of the waxy drug carriers. Although the solubilities of propranolol HCl and theophylline differed by a factor of almost 20, the release rates (obtained from a plot of cumulative amount of drug released versus the square root of time) varied only by a factor of 1.5. This showed that the principal factor governing the drug release was the presence of the waxes in the matrix.

The release of propranolol HCl from the capsules increased with decreasing capsule content at a fixed drug : wax ratio in # 0 capsules (Figure 8). This could be

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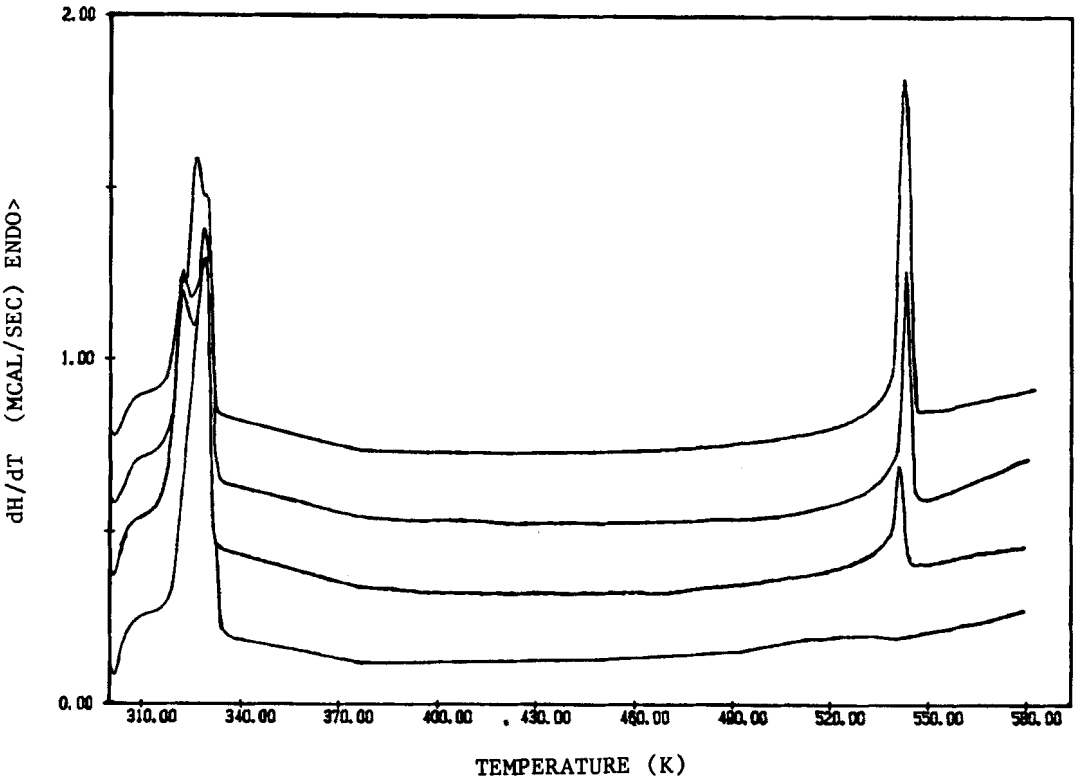


FIGURE 9
DSC thermograms of theophylline - Precirol ATO-5 matrices.

explained with an increasing proportion of the drug-wax mixture located on the capsule walls between the two plugs in the ends of the capsules with decreasing capsule content. At 200 mg loading, 37 % of the capsule content were located in the film between the plugs, compared to 26% and 9% at 300 mg and 500 mg, respectively. The surface area available for drug release was therefore proportionally higher at lower capsule contents.

After cooling the wax melt, the drug could be dispersed, dispersed/dissolved or dissolved in the wax matrix. Differential scanning calorimetry was used to

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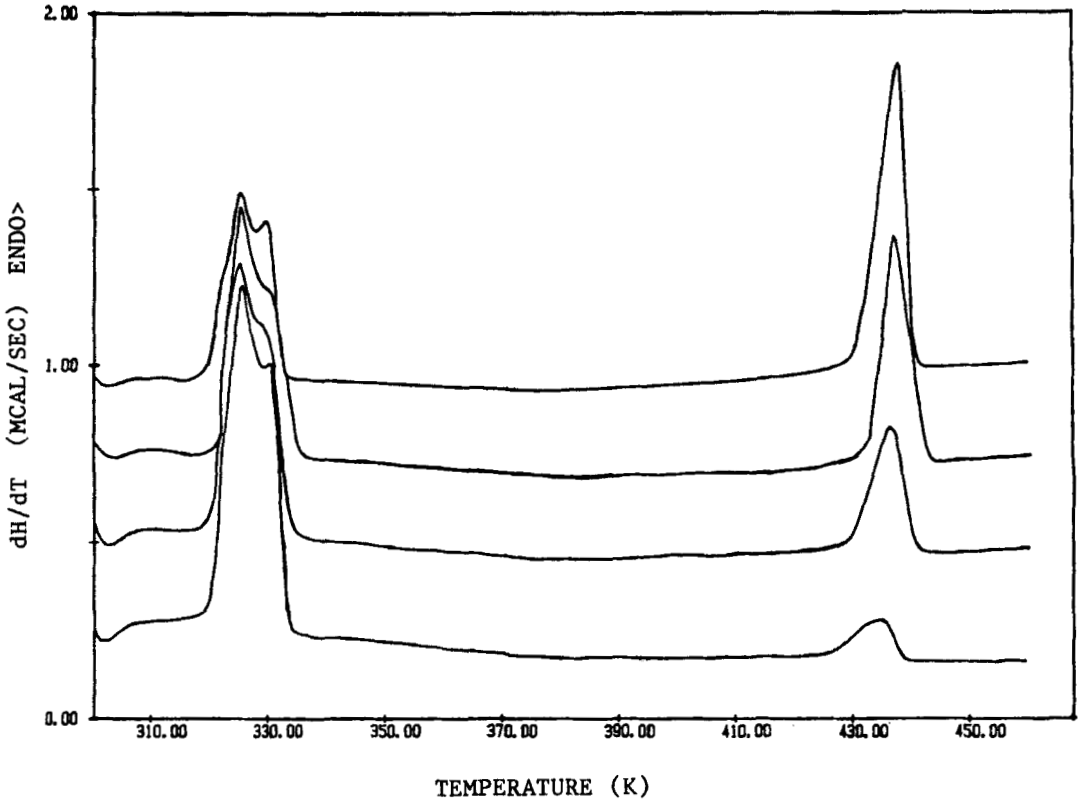


FIGURE 10
DSC thermograms of propranolol HCl - Precirol ATO-5 matrices.

characterize the physical state of propranolol HCl and theophylline after formation of the wax matrix. Thermograms of theophylline and propranolol HCl - Precirol ATO-5 matrices are shown in Figures 9 and 10. The melting transitions of the drugs and waxes were clearly visible. The melting transition of theophylline was absent at a concentration of 10%. A linear relationship existed between the heat of fusion and the amount of drug in the wax matrix (Figure 11). The solubility of the drug in the matrix at its melting point corresponded to the intercept of the line (12).

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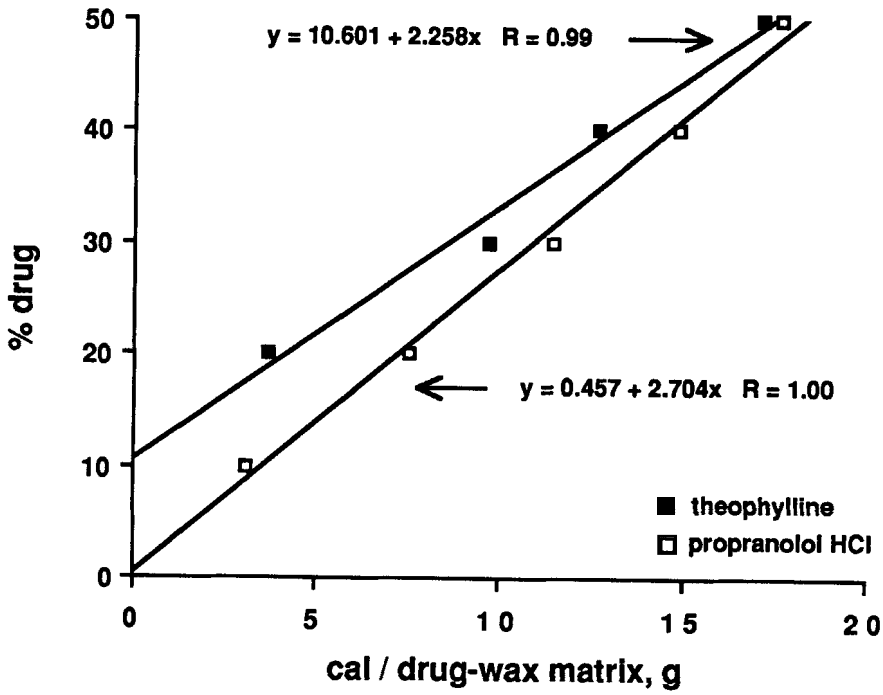


FIGURE 11

Relationship of propranolol HCl and theophylline loading and the heat of fusion.

Propranolol HCl was insoluble and completely dispersed in the wax matrix while a fraction of theophylline (approximately 10%) was dissolved in the wax. The solubility of the drug is an important variable to be considered in this process. If the amount of drug dissolved in the wax during the melting process exceeds the solubility of the drug in the matrix at the storage temperature, the drug may crystallize over time and cause stability problems. In addition, temperature and holding time of the capsules at elevated temperatures will be more critical with

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drugs being partially soluble in the matrix when compared to insoluble drugs. The melting transitions of the drug and Gelucire 50/13 were absent after dissolution studies. The more hydrophilic wax leached out during the dissolution study leaving an exhausted matrix of Precirol ATO-5.

In conclusion, fluidization of hard gelatin capsules containing drug-wax powder blends in a hot air stream was a successful method to prepare sustained release wax matrices. The use of blends of waxes with different amphiphilic properties allowed control over the drug release pattern.

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