DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(10), 1389-1427 (1988)

DEVELOPMENT AND IN-VITRO CHARACTERIZATION OF SUSTAINED-RELEASE ACETAMINOPHEN TABLETS

M. Kopcha and N.G. Lordi

Department of Pharmacy, Rutgers University

Piscataway, NJ 08855-0789

ABSTRACT

The objective of this study was to evaluate powdered lipids as both granulating agents and retardants in formulated sustained-release acetaminophen tablets. Castor Wax or Durkee 07 powders were premixed with acetaminophen and granulated with boiling water. After cooling, the mass was screened to obtain a 10/20 mesh fraction which was used for tablet production and evaluation. Friability, hardness, dissolution and compression profiles were monitored. As lipid content increased from 5-15% w/w, friability and hardness also increased. Dissolution showed an inverse relationship between level of lipid and release rate. Compression profiles demonstrated good

transmission when Castor Wax was employed. This study demonstrated that a high milligram potency tablet could be fabricated with low levels of lipid, to retard drug release, without significantly increasing tablet weight and size.

INTRODUCTION

A number of methods and techniques have been used in the manufacture of oral tablet dosage forms intended to impart prolonged, sustained or long acting therapeutic effect. Worth noting are those which make use of an inert wax/lipid matrix. The rate of drug availability from such tablet dosage forms may be controlled by the erosion of the matrix, leaching of drug from the matrix, and permeation of the matrix by the surrounding fluid followed by dissolution and diffusion through channels in the matrix. To this end, the porosity of the tablet matrix, level of hydrophobic material, and the wettability of the tablet have been shown to play important roles in the drug release rate profile.

The general methods of preparing wax/lipid drug matrices are: (1) melt-congealing and (2) aqueous dispersions (1-6). In the congealing method, drug is mixed with the wax/lipid material at an elevated temperature to soften and/or melt the retardants and

either congealed and screened or spray congealed. The aqueous dispersion approach involves spraying or placing the molten wax and drug mixture in water and collecting the resulting particles which are later compressed.

Bagaria (7) recently developed a novel process for applying aqueous dispersions of waxes and lipids as protective, enteric and sustained-release coatings. He formulated coating systems consisting of oil-in-water emulsions which could be spray-dried for later dispersion in an aqueous medium. This dispersion was then utilized as a coating system for granules.

It was felt that these aqueous wax/lipid dispersions could be employed as granulating agents to retard the release of a high milligram potency drug from an oral tablet. The drug chosen for the study was acetaminophen based on its high gastrointestinal absorption, short half-life, wide therapeutic index and continued therapeutic use as an acute/chronic analgesic. It was also chosen because interest is now being directed towards techniques to utilize minimal amounts of retardants in high milligram potency tabletted dosage forms to sustain their release. The objective being to incorporate these retardants in

amounts small enough to slow release while maintaining existent tablet size within narrow, specified limits.

Aqueous dispersions of a high melting and a low melting range lipid were fabricated to determine the minimum quantity of each necessary to retard the release of acetaminophen from the tabletted dosage form. The lipids chosen were Castor Wax and Durkee 07. The objective being to optimize the lipid/acetaminophen blend, with appropriate excipients, in terms of utilizing minimum quantities of such excipients. It was also the intent to evaluate the minimum amounts of the spray-dried lipid materials needed to retard the release of drug from compressed tablets.

METHODOLOGY

Materials

The chemicals used in this study were not subjected to any purification procedures or stored in any special way. All chemicals used were of reagent grade or better. The following is a list of the materials employed:

Acetaminophen	Ruger, Irvington, NJ
Acetaminophen-Granular	Mallinckrodt, St. Louis, Missouri
Durkee 07	Durkee Foods, Cleveland, Ohio
Castor Wax	Frank B. Ross Co., Inc., Jersey City, New Jersey

Polysorbate 65 (Tween 65)	ICI Americas Inc., Wilmington, DE
Veegum Regular	Amend Drug and Chemical Co., Irvington, NJ
Magnesium Stearate	Mallinckrodt, St. Louis, Missouri
Cab-O-Sil	Cabot Corp., Boston Mass.
Sodium Chloride	J.T. Baker Chemical Co., Phillipsburg, NJ
Hydrochloric Acid (Baker Analyzed Reagent)	J.T. Baker Chemical Co., Phillipsburg, NJ
Pancreatin USP	Amend Drug and Chemical Co., Irvington, NJ
Sodium Bicarbonate	Fisher Scientific Company Fairlawn, NJ
Methanol (Spectroscopic Grade)	Fisher Scientific Company Fairlawn, NJ

Methods

Emulsion Preparation

The following optimized o/w emulsion formulation of Castor Wax and Durkee 07, as developed by Bagaria (7), was used without alterations.

	Weight (grams)
Durkee 07 or Castor Wax	250
Polysorbate 65	15
Regular Veegum	10
Purified Water	qs 1000

250 g of the lipid was heated in an insulated, jacketed container by circulating steam through the

inlet and outlet ports of the jacket. The temperature achieved was high enough to allow the lipids to melt (ca. 95-98°C). Once the lipid reached this temperature, a homomixer (Gifford-Wood Inc.) was introduced into the molten material. This was done to allow for temperature equilibration of the mixer so as to avoid localized congealing of the lipid. Once the temperature again reached equilibrium, a 10% w/w solution of Tween 65, heated to 90°C, was then slowly added to the molten lipid with constant mixing at moderate to high speed settings. A 4% w/w dispersion of Veegum was made and heated to 90°C. This was then added to the molten mass while adequate mixing was maintained. This was allowed to mix for an additional five minutes at which time the weight was brought up to 1000 grams by adding a sufficient quantity of hot, purified water. The steam was discontinued and cold tap water was circulated within the jacketed container. At this time a smooth emulsion was obtained. Measurement of particle-size range of these emulsions, as recorded by Bagaria (7), was 1-5 microns. The emulsion was passed through gauze to rid the system of any particulate aggregates which may have developed.

Spray-Drying Operation

The emulsion was first diluted with an equal quantity of purified water to decrease its viscosity to

allow for ease of pumping through a peristaltic pump (Cole-Parmer). The inlet temperature was maintained at about 120-140°C while the outlet temperature was kept consistently below the melting range of the lipid used. The Castor Wax spray-dried emulsion had a melting range of 86-88°C while that for the Durkee 07 had a melting range of 56-58°C. An ice bath was placed at the bottom of the outlet piping of the spray drier (Nichols Engineering and Research Corp.) to prevent fusion of the spray dried material to the tube walls as well as to ensure an outlet temperature below that of the lipid melting range. The solution was then sprayed into the spray-drier via an air atomizing nozzle at a pressure of 1.4-1.6 kg/cm². A free flowing powder was obtained.

Granulation of Acetaminophen

The acetaminophen and required amount of spray-dried emulsion, containing the lipid, was mixed in an appropriate V-blender for five minutes. This preblend was placed in a dough mixer (Osrow Products Corp.) followed by 75 ml of boiling purified water. Mixing was continued for five minutes in both the forward and reverse direction. This procedure was verified in preliminary experiments by adding a dye to the mixture and viewing it for homogeneous incorporation of the dye. The mass was discharged and sized by hand through

a 16 mesh screen. The resulting mass was dried in a tray oven (Hotpak) for 1.5 hours at a temperature above that of the melting range of the lipid: Durkee 07-75°C, Castor Wax-100°C. The granulation was cooled to room temperature and then stored in a cool, dry place. No caking of the dried granulation was observed. The granulations were screened to obtain the 10/20 mesh fraction which was used in compression studies. Granulations were prepared to contain 5%, 10%, and 15% of the Castor Wax or Durkee 07.

Tablet Formulation Optimization

Since the formulation contained both acetaminophen and a lipid, steps were taken to decrease the problems of sticking and possibly binding or fusion of the lipid to the punches and die during compression. An anti-adherent, such as Cab-O-Sil, was used to minimize sticking. Magnesium stearate was selected as the lubricant, based on a study published by Kikuta and Kitamari (8).

An instrumented single punch Manesty E2 Press (Manesty Machine LTD.) with a 1/2 inch diameter flat die and punch set was employed to evaluate anti-adherent and lubricant effects on the acetaminophen granulations. Piezo-electronic transducers (Model 108M11, 204MOZ, 200M22, 202MO8, 108M56 Force

Transducers, Piezotronic, Buffalo, New York) were located in both the die wall and lower punch holder to record the forces generated. Calibration of the transducers were done on an Instron and close agreement was found with the calibration curves supplied by the manufacturer. Both the die and punch surfaces were cleaned using methanol after each compression to unbias the results due to accumulation of material on the compression surfaces. 475 mg of the 10% Castor Wax-containing granulation with different levels of the processing aids was compressed and lower punch as well as die-wall forces recorded. The amounts of magnesium stearate and the anti-adherent used were 0.25%, 0.50%, 0.75% and 1.00% w/w. The eccentric dial on the upper punch was used to generate different applied pressures. Since none of the punches were removed during the course of the study, the settings were reproducible. All experiments were done in triplicate.

Tablet Compression

Tablets were compressed on a Stokes B2 Press in which only 4 of the 16 available stations were utilized with 7/16 inch standard concave tooling. The pressure was held constant by running the press slightly below overload, 4.4 tons, giving relatively uniform tablets.

About 300 grams of the granulation was run, and the weight of the tablets produced was determined so that the resulting tablets contained 325 mg of acetaminophen. Granulations less than 10/20 mesh in size were not used since they were too bulky making it difficult to get a sufficient weight of acetaminophen. The formulated tablets were stored in a cool, dry place until further testing was done.

Friability

Tablet friability was determined using a Roche Friabilator. Twenty tablets were dusted and weighed, then placed into the circular pan. The friabilator was run at five minute intervals and stopped once the weight loss was not less than 5 percent of the initial weight. The test was run on granulations with 10% and 15% lipid. Preliminary studies demonstrated high friability at the 5% lipid level, precluding their use in further studies. Commercially available acetaminophen tablets (Tylenol Tablets 325mg, McNeilab, Inc.) tablets were included for comparison.

Tablet Hardness

A Schleuniger Hardness Tester was used to determine the average hardness of 20 tablets from the granulations produced with 10% and 15% lipid. In preliminary studies, it was found that the 5%

granulation produced tablets with minimal hardnesses. Commercially available acetaminophen tablets were included for comparison. The two platens on the hardness tester were mounted with a thin-ply cardboard, so that the tensile stress would be held uniform over a reasonable proportion of the loaded diameter (9). Thus, a consistency of tensile failure would be noted. This would allow for direct comparison of different tablets since only tensile failure, uncomplicated by other modes of failure, was measured.

Dissolution Testing

The U.S.P. rotating paddle at 50 r.p.m., Apparatus 2, was utilized. One tablet was placed in 900 ml of artificial gastric (less pepsin) or artificial intestinal fluid which was previously degassed and warmed to 37°C. The water bath was maintained at 37 ± 0.3°C for the course of the study. When gastric fluid was used, the study measurements were made over a 1.5 hour period, a 6 hour period was used for the artificial intestinal fluid.

For the studies with artificial gastric fluid 3 ml samples were withdrawn every 15 minutes. They were filtered through an 0.45 um nylon filter to remove any particulates. They were then diluted 1/10 with artificial gastric fluid and read

spectrophotometrically (Beckman DU-50 Series Spectrophotometer) at 244 nm. in a 1.000 cm. quartz cell.

During the study with artificial intestinal fluid, 3 ml samples were withdrawn and filtered through a porous disk. The solution was diluted 1/10 or 1/25 with methanol, and finally filtered through a 0.45 um nylon filter. This method was outlined by Dakkuri et al. (10) in their study of tripelennamine release from tablet cores in artificial intestinal fluid. The absorbance was measured at 248 nm.

From these absorbances, and a Beer's Law plot, the amount released was determined which was normalized for the total acetaminophen content in the tablet used. All assays were done in five replicates to determine the reproducibility of the methods. Also, comparisons were made to that of a commercially available acetaminophen tablet.

Compression Profiles

The compression profiles of selected granulations were determined using a fully instrumented Stokes F Press (F.J. Stokes Machine Co.) with a 1/2 inch flat punch and die set. The data was recorded on an oscillographic recorder (Linearecorder Mark VII-WR3101) as well as to a computer (MTU Computer). The punch and

die were not cleaned so that some idea of continuous operation could be ascertained. However, after each batch was run, the punch and die were cleaned with methanol so that individual batches could be effectively analyzed.

Before the compression cycle was executed, a one volt internal calibration was run to set the recorder. Five hundred data points were collected at a sample interval of 1 millisecond. The die wall, upper punch, and lower punch forces as well as an amplified lower punch force, to delineate the details of the ejection forces, were recorded. One thousand data points were collected for each tablet at a sampling interval of 750 microseconds. Therefore, each tablet compression cycle was monitored for a total of 0.75 seconds. The compression profiles were determined for one single upper punch setting. Five replicates were run for each compression profile.

RESULTS AND DISCUSSION

Formulation Optimization

The observed die wall force and the lower punch force during compression were looked upon as a function of percent Cab-O-Sil and magnesium stearate added to 10% Castor Wax/acetaminophen formulations. The results of this study are summarized in Table 1 and Table 2.

TABLE 1

Effect of Cab-O-Sil Addition to 10% Castor Wax/Acetaminophen Granulations.

Percent Excipient	Setting*	Lower Punch (lbs.)	Die Wall (psi)
0	23	952.4	156.9
	24	2292.1	930.5
	25	4022.2	616.7
0.25	23	857.1	787.9
	24	2444.4	837.8
	25	4666.6	894.9
0.50	23	857.1	591.8
	24	1761.9	688.1
	25	4476.1	1140.8
0.75	23	895.2	85.5
	24	2460.3	231.7
	25	4793.6	399.3
1.00	23	1000.0	7.13
	24	2619.0	228.1
	25	4888.8	331.6

*Eccentric dial setting on upper punch holder

It is apparent that 0.75% Cab-O-Sil significantly reduces the residual die wall force during the ejection phase. The 1.00% level of anti-adherent produced similar results. Since the intent of this study was to use minimal amounts of lipid and excipients, the 0.75% level was chosen. Later compression of the 15% lipid granulations showed no significant differences in comparison to the 10% lipid with respect to this study.

TABLE 2

Effect of Magnesium Stearate Addition to 10% Castor Wax/Acetaminophen Granulations.

Percent Excipient	Setting*	Lower Punch (lbs.)	Die Wall (psi)
0	23	952.4	156.9
	24	2292.1	930.5
	25	4022.2	616.7
0.25	23	939.7	1215.4
	24	2092.9	1299.5
	25	3996.8	1422.4
0.50	23	813.8	1237.1
	24	2098.4	1133.7
	25	3914.3	1062.4
0.75	23	920.6	1151.5
	24	2469.9	1333.3
	25	4784.2	1130.1
1.00	23	900.2	862.8
	24	2457.1	1115.9
	25	4784.1	1258.5

*Eccentric dial setting on upper punch holder

It was also noted that increasing levels of magnesium stearate did not significantly decrease the die-wall force noted during ejection as compared to that of Cab-O-Sil. Additional experiments were run in which 0.75% Cab-O-Sil and varying amounts of magnesium stearate were added to the granulation. The data is summarized in Table 3.

TABLE 3

Effect of Magnesium Stearate Addition to 10% Castor Wax/0.75% Cab-O-Sil/Acetaminophen Granulations.

Percent Excipient	Setting*	Lower Punch (lbs.)	Die Wall (psi)
0	23	587.3	67.7
	24	2451.7	266.7
	25	4811.1	511.1
0.25	23	911.1	101.6
	24	2476.2	231.7
	25	4857.1	488.9
0.50	23	857.1	101.6
	24	2476.2	365.1
	25	4746.0	504.8
0.75	23	860.3	101.6
	24	2349.2	308.6
	25	4888.9	527.0
1.00	23	825.4	95.2
	24	2492.1	298.4
	25	5079.4	511.1

*Eccentric dial setting on upper punch holder

It is obvious that addition of magnesium stearate did little to change the residual die wall force. Although these results suggest that addition of magnesium stearate was not necessary, 0.25% was added to ensure the added lubricating effect of the magnesium stearate. Also, it was noted (11) that given amounts of a lubricant, magnesium stearate in particular, will allow for a more even distribution of forces within the

compact. For these reasons magnesium stearate, in the amount specified, was used.

Tablet Production

During this operation, it was noted that the material crept up the punches and showed some signs of sticking to the die wall. This happened irregardless of the percentage of lipid used. The tablets made with both lipids had a shinny white appearance. Mottling of the surface was minimal with the Durkee 07 formulations and some capping was noted. The capping phenomena occurred more notably with the 5% Durkee 07 content than with the rest. This suggested that not enough lipid was present to bind the tablet effectively. With the Castor Wax, a highly mottled tablet was produced with capping again occurring at the lower content. A possible explanation for this mottling effect may have been due to the differences between the lipids employed. During the tableting process, heat was generated within the compact which may have caused the lipid to melt. With the lower melting range lipid, the heat generated may have been sufficient enough to cause partial fusion, spreading over a finite range and effectively enhancing binding of the tablet. However, with the Castor Wax, where the melting range was significantly higher, this may not have occurred. This

TABLE 4

Average Percent Weight Loss (± Standard Deviation) in Friabilator

Time (Min.)	10% Castor Wax	15% Castor Wax	Tylenol
5	2.95 (0.75)	1.12 (0.12)	0.702 (0.002)
10	9.33 (1.01)	3.02 (1.90)	1.60 (0.136)
15	-	5.95 (1.44)	2.69 (0.120)
	10% Durkee 07	15% Durkee 07	
5	1.59 (0.21)	0.733 (0.063)	
10	4.63 (0.47)	3.17 (1.42)	
15	7.35 (0.19)	5.57 (0.40)	

TABLE 5

Average Hardness Values (± Standard Deviation) in KP

Formulation	Hardness
10% Castor Wax	3.74 (0.46)
10% Durkee 07	5.17 (0.83)
15% Castor Wax	6.38 (0.91)
15% Durkee 07	5.96 (0.61)
Tylenol	8.18 (1.05)

would then have lead to weaker as well as mottled tablets, because the Castor Wax did not have a chance to flow leading to splotching of the tablet surface.

Friability/Hardness

The results of this study are outlined in Tables 4 and 5. The data in this study may be misleading. The reason being that when a friability study is undertaken, one usually expects to see powder produced

by the tumbling tablets. However, this was not the case in this study except for the acetaminophen tablets used as the reference. Instead the tablets capped, laminated, or cracked into rather significant pieces which were not friable. The tablets deformed and didn't wear by attrition as was noted with the reference acetaminophen tablets.

The data shows that as the percentage of lipid increased, the percent loss due to attrition decreased. This was a reflection of the improved binding characteristics of these formulations. As expected, hardness increased as the percentage of lipid increased. Hardness of both 15% lipid formulations were relatively close while those for the 10% values were not. Results were consistent with observed friabilities. It was not possible to produce tablets with hardness values approaching those observed for acetaminophen tablets on the Stokes Press.

Dissolution Testing

The results of dissolution testing in artificial gastric fluid demonstrated that as the percentage of lipid increased, the amount released with time decreased. This was expected, since the more lipid present, the harder for the dissolution medium to permeate into the matrix. From performance of a paired

t-test, it became apparent that the two sets of data were not the same ($p<0.02$). It was concluded that the release rate was greater from the Castor Wax-matrix as compared to the Durkee 07-matrix ($p<0.01$). This was true at the 5%, 10%, and 15% levels. In all cases, initial lag times ranged between 10-15 minutes.

The next comparison made was in artificial intestinal fluid. A paired t-test suggested that release from tablets containing 10% and 15% lipid were different ($p<0.01$) with the Castor Wax formulation showing a higher release rate than the Durkee 07 ($p<0.005$). However, at the 5% level no significant difference was observed ($0.05 < p < 0.10$).

The differences observed between the Castor Wax- and Durkee 07-containing tablets in both artificial intestinal and gastric fluid is consistent with friability and hardness. The granulating process worked better with the lower melting range lipid than with the higher melting range lipid, producing a more homogeneous matrix and, therefore, better control of acetaminophen release.

In order to determine the application of the Higuchi square root of time relationship, and establish the relative role of diffusion and erosion in controlling drug release, the average percent of drug

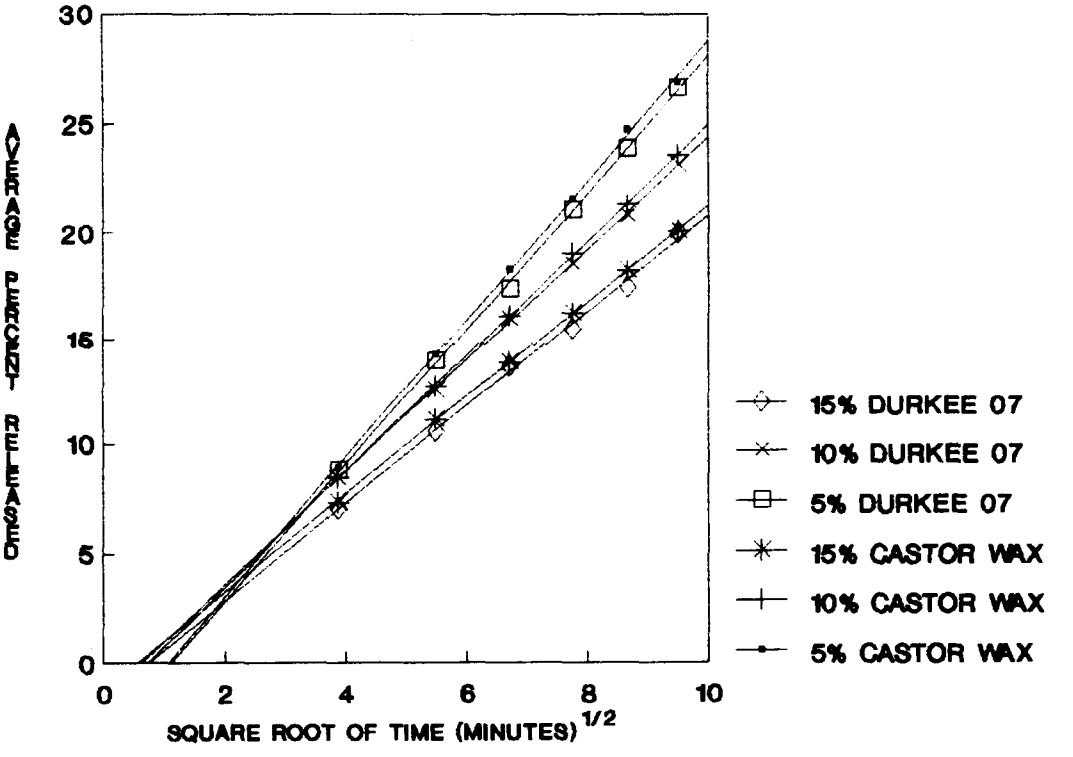

FIGURE 1

Average Percent Released of Acetaminophen from Castor Wax or Durkee 07 Acetaminophen Granulations in Artificial Gastric Fluid at 37°C Versus the Square Root of Time.

release was plotted against the square root of time. The release in artificial gastric fluid appeared to follow the square-root of time relationship which is shown in Figure 1 at all lipid concentration levels investigated. On the other hand, similar plots for release in artificial intestinal fluid (Figure 2) showed non-linearity. It was noted that a biphasic

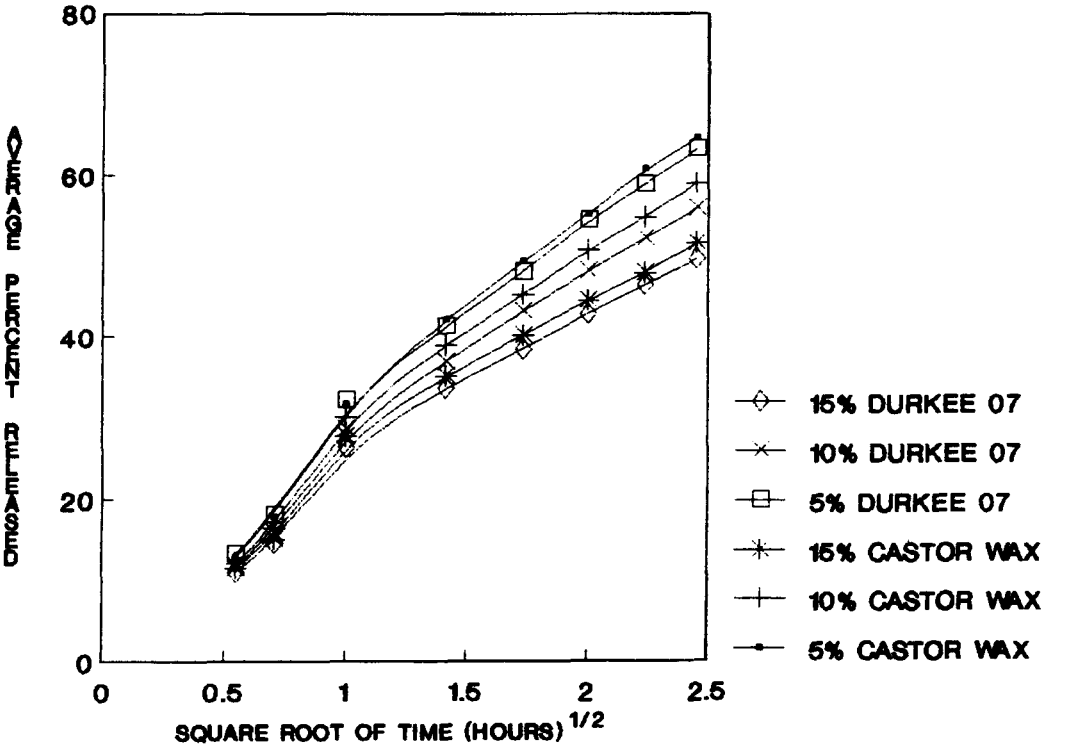

FIGURE 2

Average Percent Released of Acetaminophen from Castor Wax or Durkee 07 Acetaminophen Granulations in Artificial Intestinal Fluid at 37°C Versus the Square Root of Time.

release pattern existed. The first portion appeared to exist for about 90 minutes, followed by a significantly slower rate of release for the duration of the study.

It was observed that tablet integrity existed in both artificial gastric and intestinal fluid for approximately 90 minutes. After that time, erosion and swelling of the tablet surface was noted. This

suggested that the system was erodible, where the surface sloughs off exposing a new surface from which drug would be eventually removed. In this part of the study, a new tablet was used for each experiment irregardless of the dissolution medium employed. To further delineate the biphasic effect, it was decided to perform a single study in which a 10% lipid formulated tablet was allowed to remain in artificial gastric fluid for one hour, removed, and then placed into the artificial intestinal fluid for an additional 6 hours. The results are shown in Figure 3.

It was noted that a linear square root of time relationship existed for release of acetaminophen in artificial intestinal fluid after being pretreated in artificial gastric fluid for one hour. It was concluded that the initial portion of the biphasic curve was due to the surface release of drug. As this was depleted, the surrounding medium penetrated the lipid matrix where it dissolved and leached out the drug, leaving behind a layer of lipid which would later slough off. Upon completion of the dissolution study, the core of the tablet was found to be dry. This signified that penetration of the dissolution medium had not reached the interior, consistent with the observed 58.89% release at the end of the 6 hour

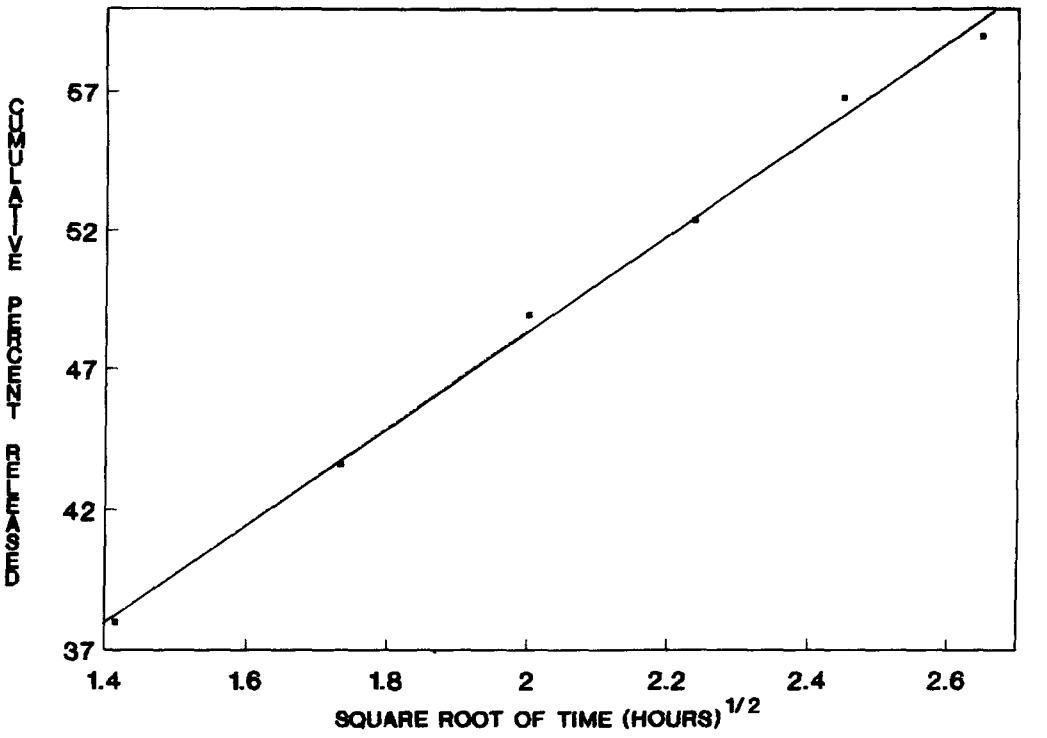

FIGURE 3

Cumulative Percent Released of Acetaminophen from 10% Durkee 07/Acetaminophen Granulation in Artificial Intestinal Fluid at 37°C after Pretreatment in Artificial Gastric Fluid for 1 Hour at 37°C Versus the Square Root of Time.

period. This was in contrast to 55.91% release of acetaminophen observed after 6 hours in artificial intestinal fluid with the same lipid matrix content. This demonstrated that pretreatment in artificial gastric fluid did not significantly affect the overall drug release. Consequently, drug release from the

specific lipid matrices utilized in this study were pH independent.

The data was compared to release obtained from commercially available acetaminophen tablets. After 15 minutes in artificial gastric and intestinal fluids, the percent released from the commercial tablet was 98.46% and 95.65% respectively. This represented more that a 10 fold increase in release in artificial gastric fluid and more than a seven fold increase in artificial intestinal fluid compared to the lipid containing tablets tested.

Compression Profiles

Tables 6, 7, and 8 show the characteristics monitored during the compression cycle for each granulation as well as the observed numerical values.

It was apparent that the applied upper pressure varied, even though the eccentric dial setting was held constant during the tableting process probably the result of nonuniform die filling due to variation in the size distribution in a 10/20 mesh granulation. This inconsistency in die fill caused a different pressure to be exerted each time a tablet was compressed. It was not possible to prepare tablets with sufficient acetaminophen content using a finer granulation.

TABLE 6

Forces Extracted From Compression Cycles of Durkee 07 on a Manesty F Press (± Standard Deviation)

Percent Durkee 07	Upper Punch (lbs.)	Lower Punch (lbs.)	Residual Die Wall (psi)	Ejection (lbs.)
5	1076 (107)	978 (116)	228 (24)	34 (1)
	3225 (150)	3112 (142)	403 (14)	51 (1)
	5043 (502)	4968 (503)	458 (24)	61 (5)
10	1368 (106)	1240 (109)	254 (16)	35 (2)
	1931 (46)	1795 (42)	287 (1)	39 (0.5)
	3534 (477)	3372 (491)	336 (24)	53 (6)
15	4020 (292)	3968 (311)	296 (12)	52 (3)
	2551 (158)	2439 (160)	259 (9)	38 (2)
	688 (60)	610 (56)	156 (11)	23 (1)

As the upper punch setting was varied, an increase in all parameters monitored was noted. This result was expected since larger forces were being applied to the granules. Differences were noted when comparing the 15% Castor Wax formulation with that of the 15% Durkee

TABLE 7

Forces Extracted From Compression Cycles of Castor Wax on a Manesty F Press (± Standard Deviation)

Percent Castor Wax	Upper Punch (lbs.)	Lower Punch (lbs.)	Residual Die Wall (psi)	Ejection (lbs.)
5	822 (76)	538 (60)	226 (30)	132 (6)
	1439 (63)	970 (61)	360 (15)	176 (11)
	2299 (112)	1739 (116)	469 (25)	407 (7)
10	644 (45)	455 (32)	141 (10)	181 (17)
	1662 (197)	1290 (172)	238 (24)	198 (14)
	2391 (214)	2004 (196)	236 (5)	141 (12)
15	385 (44)	324 (37)	99 (18)	26 (3)
	382 (57)	309 (50)	202 (24)	77 (6)
	1597 (209)	1369 (206)	294 (30)	97 (7)

07 formulation. The Durkee 07-containing formulation showed comparable residual die wall forces to that of the Castor Wax-containing formulation at about one-half the upper punch pressure. Also, at the same upper punch pressure, a significantly lower ejection force

TABLE 8

Force Extracted from Compression Cycles of Granular Acetaminophen on a Manesty F Press
(± Standard Deviation)

Upper Punch (lbs.)	Lower Punch (lbs.)	Residual Die Wall (psi)	Ejection (lbs.)
2420 (502)	1975 (444)	519 (156)	187 (62)
1484 (12)	1053 (0)	271 (0)	152 (0)
1220 (52)	900 (38)	275 (25)	142 (44)

for the Durkee 07 matrix tablet was observed. This may have been due, in part, to the inherently better lubricating effect of the lipid. Another possible explanation is that the Durkee 07 coated the granules more homogeneously, imparting a more uniform lubricating effect as compared to that of the Castor Wax. It was also observed that more of the upper punch force was transmitted axial for the Durkee 07- than for the Castor Wax-containing granulations. This implied that these tablets were more plastic in nature than those produced with the Castor Wax.

In the case of the 10% Castor Wax-granulations, the upper and lower punches exhibited a small amount of

material build-up. A considerable build-up of powdered acetaminophen was also noted. This demonstrated how ineffective the proposed granulating method was for producing adequately coated granules with a high melting range lipid. Also observed were capped tablets and tablets which had significant stress cracks on their surfaces. Also, as the Castor Wax content decreased from 15% to 10%, ejection forces increased. This was due to the decreased lubricating efficiency imparted by less material, causing the tablets to be expelled with greater effort. Capping at all pressures studied was observed with the 5% Castor Wax-granulations. Ejection forces also increased drastically, owing to minimal, if any, lubricating effect by the Castor Wax. A great deal of powdered material was observed to coat the tooling, even at moderate to low upper punch pressures.

These effects noted for the Castor Wax-granulations, were not seen with the Durkee 07-granulations. Ejection forces were significantly lower, even at 5% concentration.

Compression profiles (axial versus die wall pressure) were plotted for the 15% lipid/acetaminophen granulations produced. Figure 4 and 5 show the

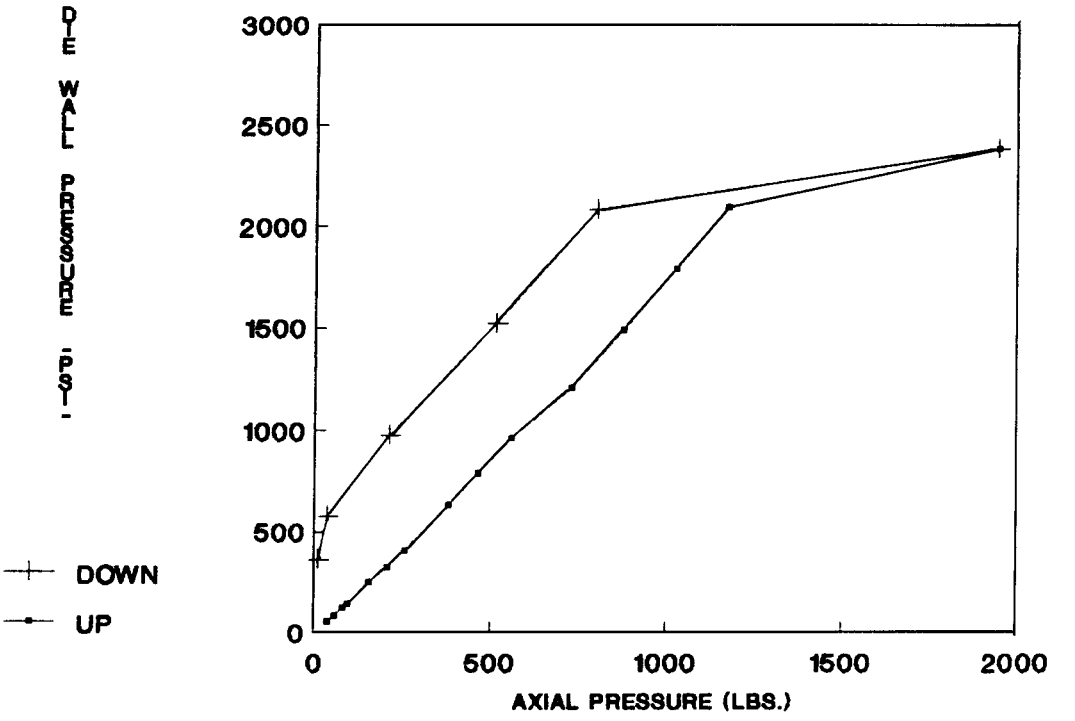

FIGURE 4

Compression Cycle Observed During Tableting on a Manesty F Press for 15% Durkee 07/Acetaminophen Granulation.

characteristic shape of the radial versus axial pressures for these granulations.

A qualitative interpretation of the compression cycle generated for granular, crystalline acetaminophen (Figure 6) will be discussed first so that all subsequent cycles, produced for different granulations, can be compared to this reference. When the axial pressure was increased, the die wall or radial pressure

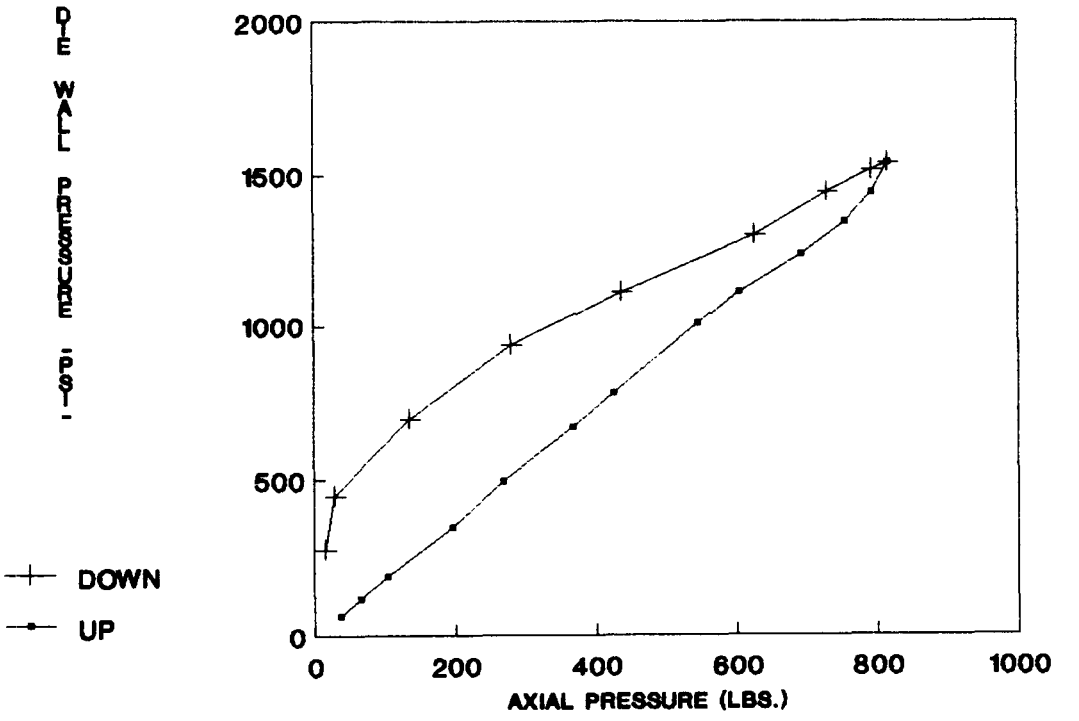

FIGURE 5

Compression Cycle Observed During Tableting on a Manesty F Press for 15% Castor Wax/Acetaminophen Granulation.

also increased. This appeared to be a relatively linear relationship. However, at a given point of axial pressure (ie. about 1170 lbs.) a sharp decrease in slope was noted. This signified that as axial pressure was increased, the die wall pressure increased by a minimal amount. It would appear then that a maximum radial force was achieved at a given level of upper punch pressure. As the applied pressure was

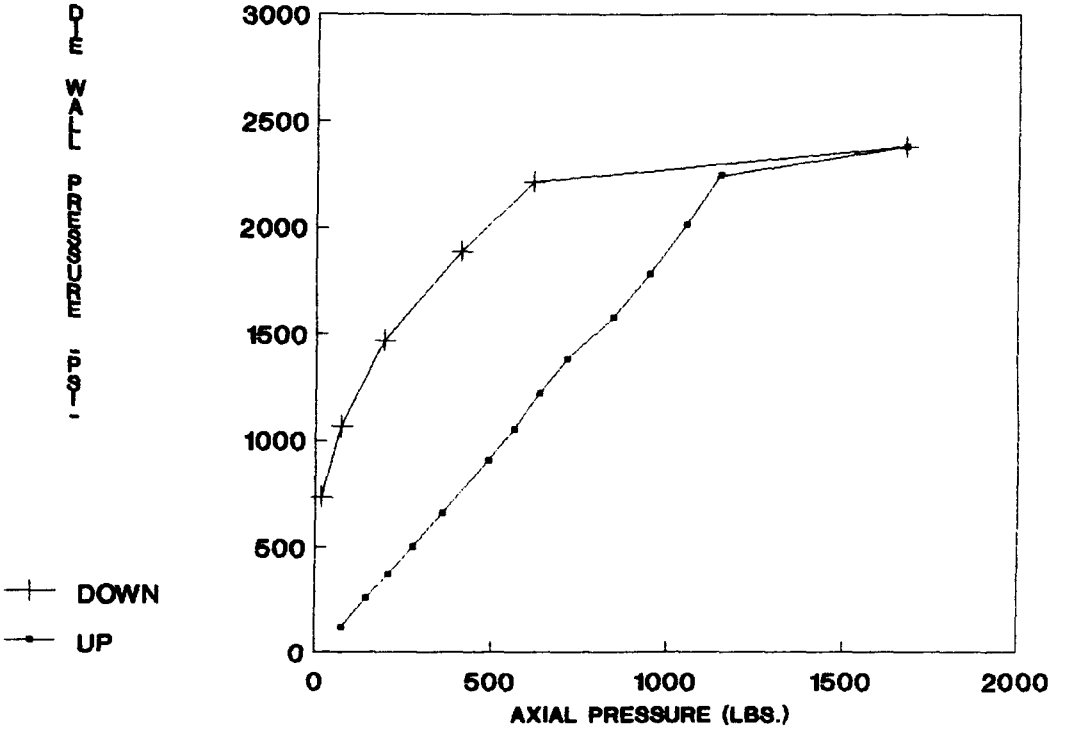

FIGURE 6

Compression Cycle Observed During Tableting on a Manesty F Press for Granular, Crystalline Acetaminophen.

removed, the radial pressure decreased slowly exemplified by the small slope of the receding portion of the compression cycle. As the upper punch was continually removed, the radial pressure was still decreasing however, at a faster rate than previously. It was observed that an adequate conversion of axial pressure to radial pressure was achieved. According to

Obiorah (12), this conversion of axial to radial pressure would produce satisfactory tablets, which was achieved in this study. However, on occasion, capped tablets were noted, while other tablets did show some signs of stress cracks on the outer surface. It was this key parameter of conversion between axial and radial forces that was sought and related to the characteristics of the produced tablets.

Reviewing the cycle plots for the 5%, 10%, and 15% Durkee 07- granulations used, it was apparent that they had the general characteristics noted for the granular acetaminophen compression profile, that is an initial linear relationship between axial and radial pressure with a decreasing slope toward the end of the applied upper punch pressure. This signified, in all cases, an adequate transmission of the applied force radially, giving a satisfactory tablet.

In the case of the Castor Wax-containing formulations, it was apparent that significant differences exist when compared to the granular acetaminophen. The 5% formulation showed the initial linear conversion of axial to radial pressure. However, the decreased slope at the end of the axial pressure application was not observed. Consequently,

it was concluded that the conversion was not as complete as seen previously with the Durkee 07 formulations. The lack of adequate transmission of applied force may be partly related to the unsatisfactory tablets produced, characterized by the sharp linear decrease in die wall pressure as the upper punch was removed. This indicated that radial force did not persist once the upper punch was removed. This signified that the compact expanded in the axial direction while contracting radially. This in turn could have induced considerable strain within the compact, because during recovery, the tablet was subjected to a residual pressure acting from the die wall. Under these conditions, separation or capping can occur along the stress loci.

Both the 10% and 15% Castor Wax-containing formulations showed similar cycles to that of the 5% formulation, implying the production of unsatisfactory tablets. Some capping and stress cracks were noted with these formulations showing that indeed poor quality tablets existed. However, not all tablets exhibited this phenomena, suggesting that the higher levels of Castor Wax were adequate to overcome the opposing die wall stress and, thereby, minimize capping.

SUMMARY AND CONCLUSIONS

Bagaria (7) recently developed a novel process for applying aqueous dispersions of waxes and lipids as protective, enteric and sustained-release coatings. He formulated coating systems consisting of oil-in-water emulsions which could be spray-dried for later dispersion in an aqueous medium. This dispersion was possible due to the use of Polysorbate 65, a water soluble surfactant, in the formulation of the oil-in-water emulsion. This spray-dried material was used in the present study to evaluate its ability in retarding the release of drug from a tabletted dosage form.

The objective of this study was to optimize the lipid and acetaminophen blend, with appropriate excipients, in terms of utilizing minimum quantities of these excipients. It was also the intent to evaluate minimal amounts of the spray-dried lipid materials needed to retard drug release from compressed tablets and to monitor the effect of these levels on tablet friability, hardness, and compressional profiles.

The excipients used in this study were Cab-O-Sil and magnesium stearate. The minimum quantities of these materials were determined with an instrumented Manesty E2 Press and found to be 0.75% and 0.25% for Cab-O-Sil and magnesium stearate respectively. Tablet

friability decreased as the amount of lipid content increased. The tablets in this study did not actually fray but capped and laminated. This accounted for the high weight loss when compared to that of commercially available acetaminophen tablets. Hardness of these tablets also showed a similar trend. Tablets containing the lower melting lipid proved to be superior than those with the higher melting lipid demonstrating that the fusion-based granulating process was more efficient for low melting range lipids than for higher ones.

Acetaminophen was found to be released more slowly as the lipid content increased. This was expected since the matrix enveloped more drug. The release of drug from the Durkee 07 matrix was inhibited more than by an equal amount of the Castor Wax. This again was in line with observations made on tablet friability and hardness. From dissolution studies, it was also noted that surface drug was released initially for about 90 minutes after which time erosion and swelling of the tablet surface was observed. This suggested that the system was erodible, where the surface sloughs off exposing a new surface from which drug would be eventually removed. Compression cycle studies demonstrated that the Durkee 07 containing tablets were

more plastic in nature than those produced with Castor Wax allowing for more of the applied pressure to be transmitted axially. These tablets also demonstrated superior transmission of the applied force radially than those with the Castor Wax. This was related to satisfactory tablets being produced for the low melting lipid as compared to those produced with the high melting lipid.

This study demonstrated that a high milligram potency tablet could be fabricated with low levels of lipid, used to retard drug release, without significantly increasing tablet weight and size. It is realized that extrapolation of the data to an in-vivo situation is not applicable, nor is it applicable to say that a sustained-release oral dosage form had been developed. In this study, the determination of minimal levels of lipid needed to retard drug release was not exactly realized. The study demonstrated that at the 5% level of lipid, drug release was retarded when compared to that of the commercially available tablets. To determine what minimal level of retardant is needed to allow for therapeutic blood levels of drug to be obtained in an in-vivo system, while sustaining drug release over an extended period of time is open to further investigations. Studies with other high

milligram potency drugs such as potassium chloride, procainamide HCl, etc., would have to be done to realize how effective and applicable the lipid matrix system is in terms of retarding drug release. Also, other waxes and lipids would have to be investigated to demonstrate their usefulness as retardants. If the proposed granulating process is to be used, modifications must be made such that high melting range wax/lipids can be fused as easily as the low melting range wax/lipids. By undertaking such extensive testing, it is felt that a low level of retardant can be used to sustain drug release of a high milligram potency active without notably increasing tablet weight or size while at the same time maintaining therapeutic blood levels. This would then open a new approach to formulating orally sustained-release drug products.

ACKNOWLEDGMENTS

A special thanks to Russell Soma of Ciba-Geigy for use of his knowledge and expertise in the area of instrumented tablet presses.

REFERENCES

(1) E.B. Draper and C.H. Becker, J. Pharm. Sci., 55, 376 (1966).

(2) I.C. Robinson and C. H. Becker, J. Pharm. Sci., 57, 49 (1968).

(3) P.M. John and C.H. Becker, J. Pharm. Sci., 57, 584 (1968).

(4) A.G. Cusimano and C.H. Becker, J. Pharm. Sci., 57, 1104 (1968).

(5) Y. Raghunathan and C.H. Becker, J. Pharm. Sci., 57, 1748 (1968).

(6) I.S. Hanid and C.H. Becker, J. Pharm. Sci., 59, 511 (1970).

(7) S. Bagaria. "Aqueous Dispersions of Waxes and Lipids for Pharmaceutical Coating," PhD diss., Rutgers University, 1986.

(8) J. Kikuta and N. Kiramori, Drug Development and Industrial Pharmacy, 11(4), 845 (1985).

(9) A. Rudnick, A.R. Hunter and F.C. Holden, Materials Research and Standards, 283 (1963).

(10) A. Dakkuri, H.G. Schroeder and P.P. DeLuca, J. Pharm. Sci., 67, 354 (1978).

(11) E. Nelson, J. Am. Pharm. Assoc., Sci. Ed., 44, 494 (1955).

(12) B.A. Obiorah, Int. J. Pharm., 241 (1970).