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DISINTEGRATION AND DISSOLUTION PARAMETERS OF COMPRESSED TABLETS PREPARED BY DIRECT COMPRESSION-WET GRANULATION PROCESS AND COMPRESSION OF WET GRANULATION OF BOTH SECTIONS

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ABSTRACT

Hardness, disintegration and dissolution of compressed tablets were assessed by compressing tablets from granulations prepared by dry and wet granulation process of two sections and by composite wet granulation process. Modified USP XVIII apparatus for disintegration, rotating basket apparatus USP XVIII and constant circulation apparatus were employed for measuring dissolution. The constant circulation apparatus was used in the studies as only it proved to be sensitive to reflect the differences in the dissolution rates and was a close analog of physiological situation. Four types of tablets contain-

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ing acetylsalicylic acid, codeine phosphate and propoxyphene hydrochloride were prepared. Tablets prepared by partial dry and wet granulation process did not show significant differences in the rates of dissolution as compared to those prepared by complete wet granulation process.

INTRODUCTION

Dissolution testing has become important in product research and development in recent years. The choice of a sensitive dissolution system for the reflection of the dissolution characteristics due to various formulation factors is also very important. Various dissolution apparati have been reviewed by Baun and Walker(1) and a constant circulation dissolution apparatus was shown to be sensitive to demonstrate the effect upon dissolution rate of various factors. This apparatus was slightly modified and used for studying the dissolution pattern of the compressed tablets.

The modified USP XVIII disintegration apparatus was planned to be used for measuring the dissolution of the drugs from the tablets. The dissolution was incomplete at the end of 20 minutes. Therefore, a stirrer was used on one side under the basket-rack assembly. The system requires a high degree

of agitation to keep the granules circulating in the fluid after having passed through # 10 mesh screen. Rotating basket apparatus USP XVIII was tried for dissolution study with the basket rotating at 50, 100, 150 and 200 rpm. Even this apparatus was not deemed to be satisfactory as it also employs a high degree of agitation. The constant circulation apparatus is being used for the rest of the investigation. The system used combines the characteristics of (a) employing small amount of agitation in the form of eluting effect, (b) using relatively homogenous low volume dissolution medium,(c) using one tablet at a time and (d) preventing excessive accumulation of the drug in the vicinity of dissolution.

This study concerns itself to the formulation of tablets compressed from granulation prepared by partial direct and wet granulation of two sections of one type of tablet and by wet granulation process of both sections of other three types of tablets. The second part of the investigation was to employ a suitable device for studying the dissolution of various ingredients from the compressed tablets. This apparatus would have characteristics approaching to those found in GI tract.

EXPERIMENTAL

Materials- Acetylsalicylic acid BP, codeine phosphate USP and propoxyphene hydrochloride USP were used. Excipients used in preparing the tablets were corn starch USP, ethocel NF, avicel (F.M.C.) BPC, guar gum NF and magnesium stearate USP. Ethanol and methylchloroform were both USP grade.

Preparation of Granules and Tablets - The lubricant section used in all the formulations was prepared by granulating avicel in a planetary mixer (Erweka[1], Type LK5) with methylchloroform and drying at 45°-50° for four hours. The dried mass was then mixed with sifted guar gum and magnesium stearate for 5 minutes and passed through a screen No.20. The ingredients and their amounts used in various formulations are given in Table I. Tablets A were prepared by direct compression of acetylsalicylic acid (ASA) crystals and guar gum with codeine section granulated separately with (II). For formulation A, codeine and starch were mixed for 5 minutes and passed through No.20 screen in a granulator. The powder mix was granulated in the Erweka mixer with (II) to produce satisfactory granulation in about 15 minutes. The mass was passed through an oscillating granulator (Erweka[1], Type FGS) equipped with a No.10 screen and dried over-

TABLE I

Formulations Prepared in this Study

Ingredients	Tablet Formulations, mg/Tablet			
	A	B	C	D
Acetylsalicylic Acid, BP	375	375	375	225
Codeine Phosphate, USP	8	15	30	
Propoxyphene Hydrochloride,USP				65
Corn Starch, USP	18	18	18	18
Guar Gum Sifted, NF	8	8	8	8
Ethocel in 15% Solution[a],(I)	0.8	0.8	0.8	0.8
Ethocel in 15% Solvent[b],(II)	1.5	1.5	1.5	1.5
Lubricant Section				
Avicel,BPC[c]	18	18	18	18
Magnesium Stearate, USP	12	12	12	12
Guar Gum Sifted, NF	38	38	38	38
Methylchloroform, USP[d]				
Total, mg/tablet	479.3	486.3	501.3	368.3

[a]Fifteen percent ethocel in 90% alcohol-water mixture using 17 mg of mixture/tablet.

[b]Fifteen percent ethocel in methylchloroform using 15 mg of solvent/tablet.

[c]Microcrystalline cellulose, (F.M.C.).

[d]Six mg/tablet.

night at 40°-45°. The granulation was sifted through a No.16 screen and mixed with lubricant section before compression. Tablets B and C were manufactured by compression of granulation of (ASA)-guar gum and codeine-starch sections prepared separately with (I)

and (II) respectively. Tablets D were made by compression of granulation of (ASA)-guar gum and propoxyphene-starch sections prepared separately with (I) and (II) respectively. The same equipment and durations as employed in the processing of Tablets A were used for Tablets B, C and D. The granules of the drug sections were finally blended wi with lubricant section for 7 minutes and compressed according to the specifications given below.

Tablets of 0.270 in. thickness were compressed with an Erweka[1] tablet press model EKO using 0.620 in. diameter oval punches and die set. The hardness of tablets as determined by Stokes[2] hardness tester varied between 6.8 to 7.1 Kg and the compression weight of tablets was maintained between the limits of variation for compressed tablets.

Disintegration - The USP method for uncoated tablets was used (2). Mean disintegration time for six tablets of each formulation run in distilled water was found to be between 4 and 7 minutes.

Dissolution - A constant circulation apparatus as described by Baun and Walker(1) was used during this study. The apparatus consists of a stoppered cylindrical tube with screens about 7 cm. apart and a side-arm outlet for the return of the fluid to

reservoir. The tablet is placed on a lower screen of 200 mesh and the size of the upper screen was 60 mesh. A pump circulates the fluid through the column and back to the reservoir at a flow rate of 50 ml per minute. Samples were withdrawn at 2, 5, 10, 20, 40 and 60 minutes intervals from the reservoir and replaced with similar volume of distilled water at 37°.

Analysis - For (ASA) determination, a 2 ml sample was transferred to a 100-ml flask containing approximately 50 ml of 85% methanol (15% water). One ml of 50% W/V solution of sodium hydroxide was added to the flask and mixed thoroughly. After 15 minutes, 3 ml of concentrated hydrochloric acid was added and volume brought to the mark with 85% methanol (3). The solution was read on a spectrophotometer[3] for salicylic acid at 304 nm against 85% methanol solution treated in the same manner as the sample. The amount of the drug dissolved at any time interval was calculated from the standard reference curve.

Determination of codeine phosphate and propoxyphene hydrochloride from the same samples taken at aforesaid intervals was carried out by ion-pair procedure (4).

RESULTS AND DISCUSSION

The average dissolution rates of six tablets of various formulations are plotted

in Figures 1-4. These plots also indicate T 80% values for a group of tablets in each formulation. Even though T 80% value is not a quantitative parameter indicating the differential rate of dissolution of a drug along the integral curve. Nonetheless it is a simple indicator for comparing the over-all dissolution of two formulations.

During dissolution, the tablet disintegrated into granules very fast. The granules were further reduced to fine particles which were eventually dissolved by the circulating fluid. Dissolution occured from all portions-intact tablets, granules and from fine particles of the drug. The dissolution process was in the form of elution in the constant circulation system used.

It can be observed from Figures 1-4 that T 80% for (ASA) in all the formulations ranged from 14 to 18.5 minutes. Comparing the dissolution pattern of the drug in Formulation A with that of other three formulations, no significant difference was observed among T 80% values. The granulation of (ASA) powder with ethocel in formulations B, C and D did not retard the rate of dissolution of (ASA) from the tablets. Essentially 100% drug was dissolved in 60 minutes

The dissolution of codeine from all the formulations was quite rapid. The

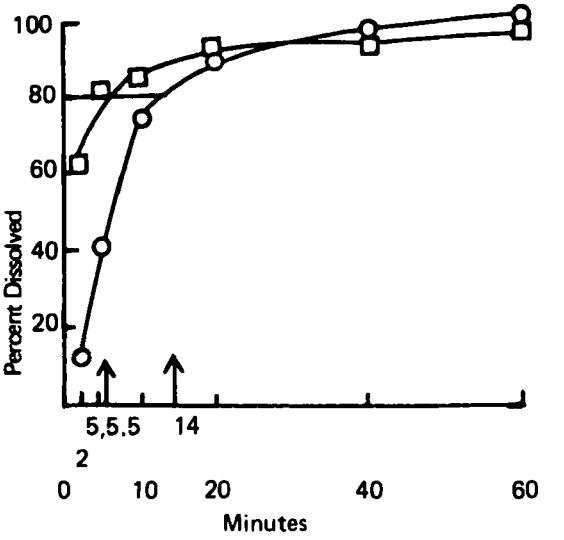

FIGURE 1

Percent dissolved from Tablet Formulation A. Key: O , acetylsalicylic acid; □ , codeine phosphate.

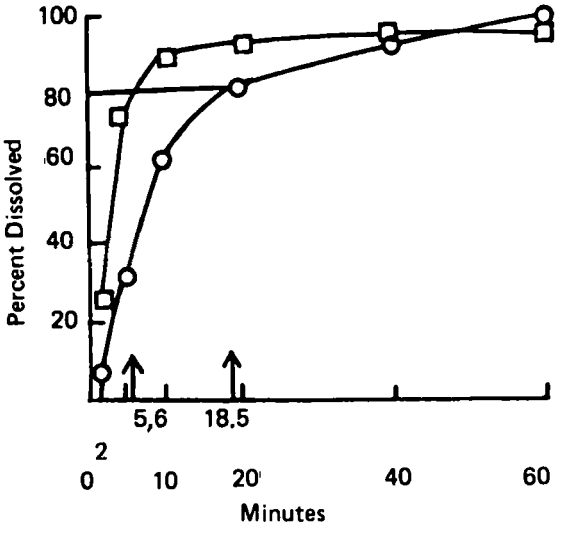

FIGURE 2

Percent dissolved from Tablet Formulation B. Key: O , acetylsalicylic acid; □ , codeine phosphate.

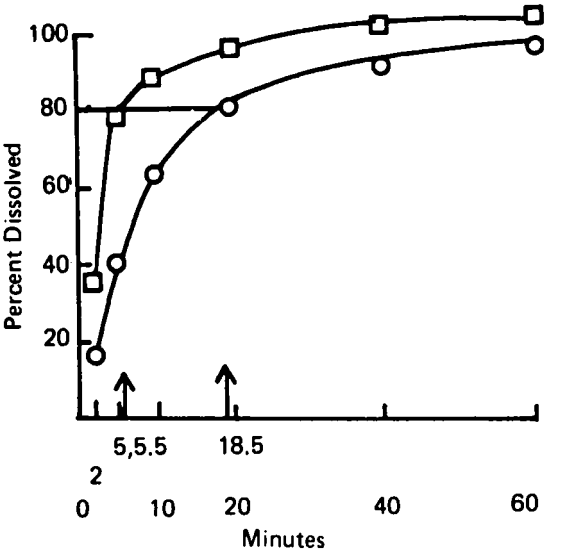

FIGURE 3

Percent dissolved from Tablet Formulation C. Key: O , acetylsalicylic acid; □ , codeine phosphate.

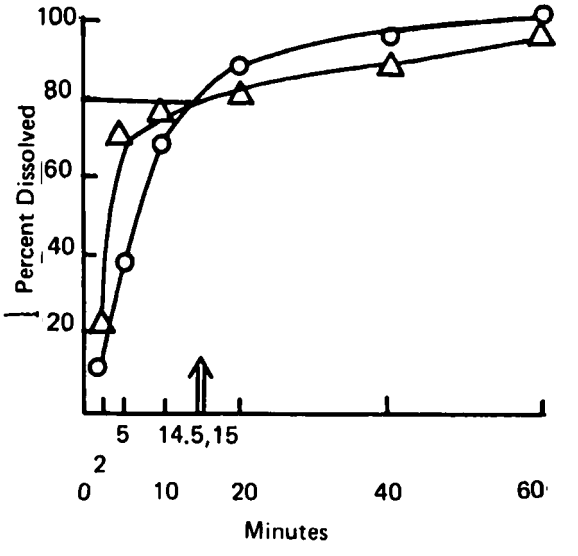

FIGURE 4

Percent dissolved from Tablet Formulation D. Key: O , acetylsalicylic acid; △ , propoxyphene hydrochloride.

average T 80% values for Formulations A, B and C were 5.5, 6 and 5.5 minutes and the drug was completely dissolved in about 60 minutes. As observed from Figures 1-3, the dissolution of the drug was faster in first 10 minutes and the remainder of the dissolution (20%) is distributed over the last 40 minutes. The dissolution of the drug was comparatively faster than that of (ASA). This may be due to the higher solubility of codeine phosphate than that of ASA (5). From Formulation D, complete dissolution of propoxyphene occured in 60 minutes and the average T 80% value was found to be 15 minutes. It can be visualized from the curve in Figure 4 that the drug dissolved off quickly in first 10 minutes and the remainder 25% drug dissolved during the last 50 minutes.

The results of dissolution obtained with individual tablets were not significantly different from one tablet to another tablet in the same formulation. As a corollary, the dissolution and analytical methods employed in this study were able to yield reproducible results.

ACKNOWLEDGEMENT

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FOOT NOTES

[1]Erweka Apparatebau G.m.b.H, Heusenstamm, West Germany

[2]F.J. Stokes Machine Co., Philadelphia, PA.

[3]Spectrophotometer UV, Model 150-02, Shimadzu Seisakusho Ltd., Kyoto, Japan

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