PREPARATION AND EVALUATION OF DIRECTLY COMPRESSED MEDAZEPAM HYDROCHLORIDE TABLETS

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ABSTRACT

Medazepam, the well known benzodiazepine derivative used as a tranquilizer and in alcohol withdrawal, was prepared in directly compressed tablets. The directly compressible vehicles which were used singly or in binary blends 1:1, were Avicel, Lactose, STA-Rx 1500, Emcompress and the recently introduced vehicle, Compactrol. It was found that Avicel and Emcompress represent the most suitable efficient single vehicles used for the preparation of Medazepam hydrochloride tablets. In case of binary blends it was found that the best quality batches were prepared using Avicel: Emcompress blend 1:1. Physical characteristics including uniformity of weight, thickness, hardness, friability were investigated for the prepared batches. The effect of directly compressible vehicle variation on the uniformity of drug content and the dissolution rates of Medazepam hydrochloride tablets was also studied.

INTRODUCTION

Medazepam, used in treatment of anxiety, tension, and alcoholism, is manufactured in the form of capsules. The present work aimed to prepare directly compressed Medazepam hydrochloride tablets.

* F. Hoffman-La Roche, Basle, Switzerland.
The direct compression technique offers several advantages over the traditional wet granulation methods. These include reduced costs, improved product stability and increased product reliability\(^1\). It was stated that no single directly compressible vehicle has been found to be suitable for all directly compressed formulae. Thus, comparative studies on the efficiency of various directly compressible excipients with medicaments are very essential in formulation to select the most suitable vehicle or mixed vehicles for each drug.

In this project, directly compressed Medazepam hydrochloride tablets were prepared using single directly compressible vehicles and their binary blends in 1:1 ratio. The produced tablets were evaluated with regard to their physical standards and uniformity of drug content in order to evaluate the direct compression as a technique for preparing Medazepam hydrochloride tablets. The dissolution rate of the prepared tablets was also investigated in order to study the effect of various vehicles on the availability of Medazepam from the prepared tablets\(^2\).

**EXPERIMENTAL**

**Materials:**

Medazepam hydrochloride\(^a\), dibasic calcium phosphate dihydrate (Emcompress)\(^b\), calcium sulphate dihydrate (Compactrol)\(^b\), microcrystalline cellulose (Avicel pH 101)\(^c\), STA-R\(_X\) 1500 Starch\(^d\) and lactose\(^e\) were used as direct compressible vehicles. Magnesium stearate and stearic acid\(^f\) were used as lubricating agents.

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\(^a\) Hoffman-La Roche & Co. Ltd. Basle, Switzerland.

\(^b\) Edward Mendell Co., Carmel, New York U.S.A.

\(^c\) F.M.C. Corporation, New York, Delaware.

\(^d\) Staley MFG Co. Deesantr, Illinois, U.S.A.

\(^e\) U.S.P. Shiffed Chemical Union, NL, 07033 U.S.A.

\(^f\) Chemical Industrial Development, CID. Co., Egypt.
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Equipment:

- A single punch eccentric tablet machine, Erweka hardness tester, Erweka friabilator, dissolution apparatus, U.S.P. dissolution apparatus, micrometer, and SP6 - 400 spectrophotometer were the equipment used.

Procedures:

Medazepam hydrochloride powder was used as received from the manufacturer. The tablets were prepared by mixing the drug with a certain amount of the tested vehicle and lubricant. The last mentioned directly compressible vehicles were used singly or in blends to enable the preparation of the desired tablets. Different batches of directly compressible tablets were prepared, each containing 2.5% w/w medazepam hydrochloride, 2% w/w magnesium stearate and stearic acid, 95.5% w/w of each vehicle. The powder ingredients were blended in a cubic mixer for 15 minutes at 50 r.m.p. The mixed powder then compressed into 8-mm diameter flattened tablets using an eccentric tablet machine adjusted for each excipient to produce 200 mg tablets.

Evaluation of Tablets:

a) Physical standards:

All the manufactured tablets were evaluated for uniformity of weight (B.P. 1960), uniformity of thickness, hardness, friability and disintegration time according to the previously published procedures.
b) **Uniformity of drug content:**

Ten tablets from each batch were individually assayed for its drug content. The absorbance was read at 254 nm using 1-cm cell. The mean drug content, the standard deviation and c.v % are given in Tables 1 and 2.

c) **Dissolution Rate:**

The dissolution rate was determined in 500 ml of 0.1 N hydrochloric acid equilibrated at 37 ± 0.5°C, stirred at 100 r.p.m. Samples were taken every 5 minutes over 15 minutes, then every 15 minutes over total dissolution time of 120 minutes. Fresh dissolution medium was added in each time to substitute the withdrawn samples. Samples were then analyzed according to the procedures of McGinity & Hill. The drug contents were assayed spectrophotometrically at 254 nm using 1 cm cell. Data obtained are shown in Figs. 1-3.

**RESULTS AND DISCUSSION**

**Uniformity of weight and thickness:**

All the manufactured tablets fulfilled the requirements of the B.P. 1980 for weight uniformity regardless of the type of the excipient. The physical characteristics of the batches produced using various single vehicles and their blends are given in Tables 1 and 2. The excipients investigated can be arranged in a descending order regarding their capability of yielding weight and thickness uniform tablets as follows: Avicel> Emcompress> STA-Rx 1500> Lactose> Compactrol. For their blends in 1:1 ratio they can be arranged as follows: Avicel: Emcompress> Lactose: Compactrol > Lactose: STA-Rx 1500>
Encompass= compactrol> STA-R_x 1500 : compactrol> Avicel:
Lactose> Avicel: Compactrol> Lactose: Emcompress. The 
coefficient of variation, shown in Tables 1 and 2 is con-
sidered a measure for the last observed uniformity. The 
weight and thickness variation of the produced tablets 
are a function of the powders flowability.

Mechanical Properties:  

The mechanical properties of the produced tablets 
were tested. The results are shown in Tables 1 and 2. 
From the obtained results, it is clear that Avicel produ-
uced the hardest tablets while STA-R_x 1500 did the reverse 
till the immeasurable extent. The friability results ob-
tained, Table 1, confirmed those of the hardness; Avicel 
produced the lowest friability value for the tablets while 
STA-Rx produced the highest friability value.

In binary blends, Avicel: Emcompress blend produced 
the highest hardness value and the lowest coefficient of 
variation percent value, whereas STA-R_x 1500: compactrol 
blend produced the lowest hardness value and the highest 
coefficient of variation percent value.

The hardness values depend on the type of the excipi-
ent used. Thus, the hardness of the produced tablets can 
be arranged as follows : Avicel> Emcompress> Lactose> comp-
actrol> STA-R_x -500, while for blends: Avicel: Emcompress>
Avicel: Lactose> Avicel: STA-R_x 1500> Lactose: Emcompress>
Lactose: STA-R_x 1500> Avicel: compactrol> STA-R_x 1500: Emcomp-
ress> Emcompress: Compactrol> Lactose: Compactrol> STR-R_x  
1500: Compactrol.
Friability values of the produced tablets also depend upon the type of excipient used. Thus, the friability values could be arranged as follows: Avicel > Emcompress > Compactrol > Lactose > STA-R 1500. For mixed vehicles the order was Avicel: Lactose > Avicel: Emcompress > Lactose: STA-R 1500 > Avicel: Compactrol > STA-R x: Emcompress > Avicel: STA-R 1500 > STA-R 1500:Compactrol > Lactose: Emcompress > Emcompress: Compactrol > Lactose: Compactrol. Comparison of the hardness-friability ratio revealed that Avicel is superior to all other excipients investigated as it improves the mechanical properties of Medazepam hydrochloride tablets as shown in Table 1 and 2.

Disintegration Time:

Medazepam hydrochloride tablets prepared by Avicel, STA-R 1500 and Lactose answer the B.P. 1980 disintegration test, the reverse is true for the tablets prepared by Emcompress and Compactrol, as shown in Table 1. Tablets prepared by blend of vehicles comply with the test for disintegration stated by the B.P. 1980 except for blends of Emcompress: Lactose and Emcompress: Compactrol produced tablets, Table 2. The last findings revealed the role of Avicel and STA-R 1500 in improving the disintegration time for Emcompress and Compactrol in blends to be within 15 minutes. Such results may be explained on the basis of the disintegrating properties of STA-R 1500 and Avicel.

Uniformity of Drug Content:

The drug content of Medazepam hydrochloride tablets prepared by various directly compressible vehicles is shown in Tables 1 and 2. It was found that all the prepared batches were uniform in drug content according to
the B.P. 1980 except those tablets prepared by lactose and Compactrol in blend. This can be attributed to segregation which may occur during mixing and compression due to differences in particle size and bulk density as well as the angle of repose between the particles of Lactose and Compactrol\textsuperscript{17, 18}.

The obtained results indicated the possibility of producing directly compressed Medazepam hydrochloride tablets having reasonable uniformity of drug content. Hence, upon choosing the suitable vehicle and adjusting the conditions of mixing, the difficulty of manufacturing tablets containing small doses of active medicaments by direct compression technique can be overcome\textsuperscript{19}.

\textbf{Dissolution behaviour:}

The obtained dissolution data are treated diagrammatically in Figs 1-3 while the $T_{50\%}$ of the prepared Medazepam hydrochloride tablets are shown in Tables 1 and 2. Dissolution results revealed that the dissolution rate is greatly affected by the type of the excipient incorporated within the tablets. This may be due to the decrease in the disintegration time of the produced tablets, perhaps due to absorption of excessive quantities of the dissolution fluid by the tablets, leading to faster breakdown of the tablet structure\textsuperscript{20}. The tablets prepared by STA\textsubscript{R} 1500 and Avicel showed the highest dissolution rate among the obtained tablets with the smallest $T_{50\%}$. This may be due to the increased capillary which promotes the penetration of the dissolution medium into the tablets.
Tablets prepared by Emcompress and Compactrol exhibited low dissolution rates among the obtained tablets with the highest $T_{50\%}$. This may be due to the difficulty of the dissolution medium to penetrate into tablets.
<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Losartan (mg)</th>
<th>Friability Loss (%)</th>
<th>Hardness (kgf/cm²)</th>
<th>Thickness (mm)</th>
<th>Weight (g)</th>
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<tr>
<td>S.D. × C.V. (%)</td>
<td>H.P. × R.</td>
<td>Vehicle Weight (g)</td>
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<td>-----------------</td>
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<tr>
<td>Drug Concentration (mg)</td>
<td>Density (g/cm³)</td>
<td>Mechanical Properties</td>
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</tr>
<tr>
<td>70%</td>
<td>3.75</td>
<td>Hardness (H)</td>
<td>Thickeness (T)</td>
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<tr>
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<td>5.78</td>
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<td>0.47</td>
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<td>3.75</td>
<td>0.07</td>
<td>2.12</td>
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</tbody>
</table>

TABLE 2: Physical properties of Medazepam hydrochloride tablets prepared by binary blends of directly compressible vehicles.
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Fig. (1): Effect of single directly compressible vehicles on the dissolution of Medazepam hydrochloride tablets.

- O Avicel
- STA-Rx 1500
- □ Emcompress
- ■ Lactose
- Δ Compactrol
Fig. (2): Effect of blends of directly compressible vehicles on the dissolution of Medazepam hydrochloride tablets.

- ○ Avicel: STA-Rx
- □ Avicel: Emcompress
- △ Lactose: Emcompress
- ● Avicel: lactose
- ▲ Avicel: compactrol
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Fig. (3): Effect of blends of directly compressible vehicles on the dissolution of Medazepam hydrochloride tablets.

- Lactose : Compactrol
- Lactose : STA-Rx
- STA-Rx : Emcompress
- STA-Rx: Compactrol
- Emcompress : Compactrol.
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تحضير وتقسيم اقراص هيدروكلوريد الميدازيبام المحضرة بطريقة الكبس المباشـر

السيد احمد عثمان أحمد
قسم الصيدلة الصناعية- كلية الصيدلة- جامعة أسيوط

الميدازيبام المعروف كAADC مشتقات البنزوديبازيبين والمستعمل كمضمن
وفي علاج ادمام الكحولات، حضر كاقراص بطريقة الكبس المباشـر، ولـلـتـأكيد
استخدمت موجات الكبس المباشـر بملفها أو في مخلوط شنائي (1 : 1) وهـي
الفسيل، سكر اللبن اللاعشي، آس، تي، أر، أكس، الإمكيرس، المواد
المستخدمة حديثاً الكمبكترول.

ولقد وجد أن الفسيل والإمكيرس هما أفضل الموجات التي استخدمت
بمفردها في تحضير اقراص هيدروكلوريد الميدازيبام وفي حالة الموجات
التي استخدمت في مخلوط شنائي وجد أن احسن خواص الاقراص هي التي استخدمت
فيها الفسيل، الإمكيرس بنسبة 1 : 1.

ولقد درس تأثير هذه الموجات على الخواص المختلفة للإقراص المحضره
وتشمل تجاسس المحتوى الدوائي ودرجة الطلابة، وتجاسس السمك، ودرجة هدوء
الاقراص، وتجاسس وزن الاقراص، ومعدل الإمالة الدوائية.

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received in 25/9/1985 & accepted in 22/1/1986