COMPARATIVE STUDY ON THE PHYSICO-CHEMICAL STABILITY OF ACETYLSALICYLIC ACID TABLETS PREPARED BY MICROENCAPSULATION AND OTHER PREPARATIVE TECHNIQUES

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ABSTRACT

Acetylsalicylic acid (ASA) tablets were prepared using microencapsulation, wet-granulation with hydroalcoholic gelatin dispersion and direct compression using emdex and avicel. Commercially available microencapsulated ASA tablets were used for the comparative study. Batches of tablets that showed good physical and mechanical properties and dissolution characteristics were selected for the stability study. Stability testing was carried out at ambient conditions, 52% R.H. at 20°C and finally at 95% R.H. at the same temperatures. The results were recorded at the start of the accelerated stability investigation and after subsequent one month intervals for six months storage time period. The rate of decomposition under these stress conditions was determined. There was a significant increase in tablets weight, thickness, friability percent and disintegration time. However, a marked decrease in tablet hardness and dissolution rate was observed. Maximum stability was obtained for ASA tablets directly compressed with avicel and by wet-granulation. Emdex could be considered as the most suitable vehicle at low humidity for stability of ASA tablets. The hydrolytic decomposition of the prepared tablets followed the first order pathway. Both prepared and commercial microencapsulated ASA tablets were not suitable for storage at high humidity level.
INTRODUCTION

Ethylcellulose was used as wall material for preparation of microcapsules containing ASA\(^1\)\(^-\)\(^4\). Other procedures were made to prepare ASA coated by sugars, amino acids as well as by mixture of both\(^5\). Many of these methods are complicated and present many difficulties in receiving discreetly coated nuclei. Mineral silicates\(^6\) or cationic surfactants\(^7\) were incorporated into the system to minimize the adhesion and coalescence of microcapsules.

A study of the stability of pharmaceutical products and of stability testing techniques is essential for many reasons\(^8\). It is stated that, if the dissolution of the medicinal compounds from a tablet is slowed upon ageing or storage of the tablet, the biological availability may be seriously affected\(^9\). ASA is not only affected by humidity and temperature, but also by numerous chemical agents with which it may be combined\(^10\). Decomposition of ASA in solid dosage form has been noted and is found dependent on vapour pressure and temperature\(^11\)\(^-\)\(^15\).

The present work handles the problem of sticking of ethylcellulose microcapsules during preparation and the use of the prepared microcapsules in producing ASA tablets for the purpose of stability study. The effect of ageing at two relative humidities and at two temperature levels on the physical and chemical stability of ASA tablets prepared by microencapsulation, wet-granulation and direct compression techniques is also considered.
Comparative Study on the Physico-chemical stability of Acetylsalicylic Acid Tablets Prepared by Micro-encapsulation and Other preparative Techniques.

EXPERIMENTAL

Materials:

ASA (El-Nasr Chemical and Pharmaceutical Co., Cairo, Egypt); avicel ph 101 and Corn Starch (Courtesy of El-Nile pharm. Chem. Co., Egypt); disodium hydrogen phosphate, ethylcellulose and ethyl acetate (B.D.H. Chemicals, England); gelatin 'A' (E.Merck, Darmstadt, FRG); emdex (Emco Inter. Corporation, Carmel, N.Y) and phosphoric acid (Analytical grade).

Viscosity of 5% W/W solution in 20 : 80 ethanol : toluene by weight is ca. 15 cP.

Equipments:

2 - Erweka tablet tester (Erweka-Apparatebau, FRG).
3 - USP dissolution apparatus (Erweka DT, Erweka Apparatebau, FRG).
4 - Millipore filter (Millipore GmbH, Neuisenburg, FRG).
5 - Roch Friabilator(FRG).

Methods:

1 - Preparation of microcapsules containing ASA:

ASA (5 gm) was dissolved in 2% solution of ethylcellulose in ethyl acetate. The resultant solution was mixed with 300 ml of an aqueous solution of 35% disodium hydrogen phosphate for three hours at stirring speed of 400 rev.min⁻¹ and at temperature of 30°C. The pH of the whole solution was adjusted at 4.0 using phosphoric acid. Microcapsules were recovered by 600 ml of cold phosphate buffer in three equal successive portions and
finally dried at room temperature. The whole batch was I-ac- tionated by sieving employing a mechanical shaker for 10 min at a maximum vibration, using a standard sieves set ranging from 315 to 2000 um apertures.

2- Determination of ASA and salicylic acid contents:

A sample of 250 mg from each batch was weighed and transferred to a beaker, 50 ml of chloroform (saturated with acetic acid) were added, and the mixture was stirred thoroughly. The solution was filtered through chloroform-wetted Whatman No.1 filter paper into a 100 ml volumetric flask and completed to volume with chloroform. From this solution a sample of 2 ml was diluted to 25 ml and measured spectrophotometrically at 278 nm for ASA and 308 nm for salicylic acid against blank of chloroform saturated with acetic acid. The amounts of both ASA and salicylic acid were calculated from\(^{16}\):

\[
C = \frac{ay_2A_1 - ay_1A_2}{ay_2ax_1 - ay_1ax_2}
\]

where:

\(C\) = m. Mol of ASA; \(A_1\) = Absorbance at 278 nm; \(A_2\) = Absorbance at 308 nm; \(ay_1\) = Absorptivity index of salicylic acid at 278 nm; \(ay_2\) = Absorptivity index of salicylic acid at 308 nm; \(ax_1\) = Absorptivity index of ASA at 278 nm and \(ax_2\) = Absorptivity index of ASA at 308 nm. The values reported are the mean for three determinations.

3- Preparation of tablets:

The tablet matrix for each preparation I, II and III was formulated according to Table 1. Mixing of the ingredients was done in a twin shell dry blender for a period of 10 min. The tablets were compressed on a single punch Erweka tablet press with 3/8 standard concave punches.
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4- Evaluation of the physical properties of the prepared tablets:

The tablets were evaluated for the uniformity of weight (USP), uniformity of thickness (micrometer), hardness (Erweka tablet hardness tester), friability (Roch friabilator) and disintegration time (USP).

5- In-vitro release study:

The USP dissolution apparatus was used (Erweka DT) with 500 ml of 0.1N HCl as dissolution medium and stirring rate of 50 rpm at 37°C. Samples were taken at different time intervals by withdrawal of 1 ml into 5 ml syringes, filtered through a Millipore filter (Swinex 0.45 μm).

Five ml of chloroform (saturated with acetic acid) were used to extract the dissolved drug and diluted with chloroform to a certain volume. The amounts of ASA and salicylic acid were determined using the previous method. An equivalent quantity of dissolution medium was added to the dissolution vessel immediately after each volume was withdrawn.

6- Physical stability study.

Batches of tablets that showed good physical and mechanical properties and dissolution characteristics were selected. Five sets of storage conditions were employed including ambient conditions, 52% and 95% R.H. at 20°C and 45°C. Saturated solution of sodium dichromate and sodium phosphate were prepared to adjust R.H at 52% and 95% respectively.17 Tablets were sampled weekly at the first month and then monthly. The physical properties and dissolution characteristics of these tablets were determined over a period of six months.
7- Chemical stability study$^{16}$.

Ten tablets from each batch of ASA tablets were crushed in a mortar and mixed thoroughly. From the powdered material, a sample of 250 mg was weighed, transferred to a beaker and treated exactly as previously mentioned to determine the amounts of ASA and salicylic acid contents. The logarithms of the values obtained were calculated and plotted versus time.

RESULTS AND DISCUSSION

1- Reproducibility of the modified method:

The modified method for preparing the ASA microcapsules was highly efficient in producing an individual microcapsule without aggregates. No sign for sticking was observed during the isolation and drying steps as a result of the high speed of rotation used and the washing with cold phosphate buffer three times. The mean diameter of the microcapsules produced was found to be in between 475-1425 μm (Table 2) and it was obvious that the amount of agglomerated microcapsules larger than 1600 μm in diameter, as determined by sieve analysis, never exceeds 0.55% of the total weight of the microcapsule batch. The drug content of different sizes of microcapsules was shown in Table 2. The data show a good reproducibility of the encapsulation process with regard to the ASA content and the trace amount of salicylic acid detected in the microcapsules. Drug content was found to be dependent on the size. To minimise the hydrolytic degradation of ASA to salicylic acid, 35% disodium hydrogen phosphate at pH 4.0 was used. It was stated that$^{3,4}$ the inorganic salts include ammonium
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chloride used as saturated or nearly saturated aqueous solution prevent the dissolution of the ASA into water due to a salting-out action and make the water miscible organic solvents immiscible with the aqueous medium.

The size fraction ranging between 475\(\mu\)m to 715\(\mu\)m was chosen for compression into tablets due to its higher content of ASA and the suitability of this size for the process of tabletting.

2. Physical characteristics of the tablets:

All tablets prepared were found to satisfy the USP requirements for weight uniformity. The uniformity of thickness was parallel to those of the weight. In respect of hardness and friability, all prepared tablets exhibit good mechanical properties. The hardness results for commercial tablets confirmed those of friability.

3. Physical stability:

A) Tablets weight and visual examination

At 95% R.H. there was a more pronounced increase in tablet weight than that obtained at 52% R.H. At ambient condition, all tested formulations showed no significant increase in tablet weight and did not provoke any mould or fungal growth during the period of storage. This might be due to the acidic nature of ASA and the fungicidal effect of salicylic acid resulted from ASA hydrolysis. At 95% R.H. tablets made with emdex and those condalining microencapsules were wet
and the majority of them lost their original shape and deformed within one month.

B) **Tablet thickness**

There was a significant increase in tablet thickness specially at 95% R.H. The increase in tablet thickness was more pronounced in case of tablets made with avicel. This increase in thickness resulted from absorption of moisture from the surrounding atmosphere. Lerk et al.\textsuperscript{18} proved that avicel exhibited extremely fast aqueous penetration even at low porosities, caused by breaking of the hydrogen bonds and subsequent increase in the penetrated pore volume which will lead to tablet expansion.

C) **Tablet hardness and friability**

As being shown from Figure 1, there was a noticeable decrease in tablet hardness of all formulations. This decrease in tablet hardness may be due to the weakening of interparticulate bonding between the particles of tablets resulted from moisture uptake. Rees and Shotton\textsuperscript{19} stated that, tablets with higher moisture content possessed low tensile strength compared to those with lower moisture content due to the weakening of interparticulate bonding by trace moisture. Esezobo and Pilpil\textsuperscript{20} showed that the maximum tensile strength of oxytetracycline tablets made with gelatin binder occurred when the tablets contained between 2.5 and 4.5% W/W of moisture. On increasing the moisture content of tablets, the tensile strength decreased due to the reduction of cohesive forces between the particles.

The friability per cent of tablets increased gradually as the time of storage increased. Tablets of ASA
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prepared by microencapsulation were found to be completely friable within two months at 52% R.H. at 20°C. These results were found to correlate well with the decrease in tablet hardness.

D) Disintegration time (D.T.)

From the results obtained in Table 3, it was observed that, the disintegration time of all types of tablets increased as the time of exposure increased. In case of microencapsulation of ASA tablets (commercial brand) the D.T. was not significantly changed. The resulted increase in disintegration time may be due to the loss of disintegrant efficiency resulted from the saturation of the disintegrant with the absorbed moisture. Khan and Rhodes\textsuperscript{21} stated that the D.T. of tablets under humid condition was increased because the disintegrants within these tablets have lost some of their absorption and swelling character. Pilpel et al\textsuperscript{20} stated that the D.T. of chloroquine phosphate starch tablets increased as the moisture content of the granule increased.

E) Dissolution rate

From the results obtained in Table 3, it was observed that, there was a significant decrease in the dissolution rate of all tested tablets over the six months storage period. The slow rate of dissolution of these tablets correlated well with the prologed D.T.; as the D.T. increased the dissolution rate decreased (Table 3). Ageing under humid condition was slowing the dissolution rate of the tablets prepared from avicel and wet granulation,
as the results of increasing D.T. This may be due to the loss of the efficiency of the disintegrants used and consequently higher D.T. followed by a poor dissolution rate was obtained. It was reported that the disintegrants within the tablets prepared have lost some of their absorption tendency and swelling character on storing under humid conditions\textsuperscript{21}. In previous work\textsuperscript{20}, it was proved that the disintegration time of tablets containing starch as disintegrant was increased as the moisture content of the granules increased.

Tablets prepared from microencapsulated ASA show a slight reduction in the dissolution rate compared to the other prepared tablets, at 52% R.H. (20°C and 45°C). However, at 95% R.H. at both temperature levels the tablets were not suitable to carry out the dissolution test as the tablets became very weak and friable. As the moisture content increased, the tablets tensile strength decreased\textsuperscript{20} so a 95% R.H. was not the suitable condition for storing the tablets prepared from microencapsulated ASA using ethylcellulose as wall material. Commercially available microencapsulated ASA tablets show a slight reduction in the dissolution rate compared to all tested tablets. Also, 95% R.H. was found to be inconvenient for storing these commercial tablets. Alam and parrot\textsuperscript{22} stated that hydrochlorothiazide tablets granulated with acacia, showed an increase in tablet hardness, D.T. and dissolution rate during one year of ageing at room temperature. Also, a similar increase in these parameters was observed when the tablets were stored at 50°C and 80°C for 14 days. Some findings were reported by lauser et al\textsuperscript{23} in case of dibasic calcium phosphate.
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4. Chemical Stability:

From the results shown in Figure 2, it was found that ASA tablets made with avicel and those made by wet granulation using gelatin 10% W/W as a binder gave complete measurable data under the selected storage conditions. In case of tablets made with emdex and microencapsulation it was not possible to obtain complete stability data at 95% R.H. because these tablets were either swelled or completely deformed. At 52% R.H. and 45°C tablets made with emdex gave complete stability data for the period of 6 months. At ambient conditions and 52% R.H., 20°C, all tablet formulations gave complete stability data over the period of 6 months. These findings could be relevant to the presence of excess moisture and higher affinity of emdex to water absorption. It was reported that, in absence of moisture, ASA is practically stable even at relatively higher temperature. From the results obtained, it was found that as the relative humidity increased, the rate of decomposition of ASA increased. The maximum stability data were obtained from tablets made with avicel and those made by wet granulation (using gelatin as binder) due to the smallest amount of moisture absorbed by these tablets relative to those made by other methods. Wisniewski and Biasecha stated that, decomposition of ASA increased with increase in humidity or moisture content of preparation. ASA hydrolysis in solid dosage forms could be considered to proceed in the microfilm of moisture at the surface of ASA particles. The higher the available moisture
content, the more rapidly the hydrolysis proceeds. An increase in temperature greatly increases the rate of hydrolysis due to the increased rate constant governing the reaction and the increased amount of ASA in solution\textsuperscript{26}. Tablets containing microencapsulated ASA either prepared or commercially obtained gave maximum stability at 52\% R.H. than those containing noncapsulated ASA. Microencapsulation cannot yet provide a perfect barrier for material, which degrade in the presence of heat, moisture or oxygen. However, it was possible to reduce the drug degradation rate, as in the case of vitamin A palmitate, whose degradation could be reduced to a rate of 0.5\% per day by microencapsulation\textsuperscript{27}.

Unencapsulated vitamin A palmitate degraded at a rate of 3\% per day when exposed to a temperature of 45\degree C at 75\% R.H. The microcapsule wall can also prevent or control the penetration of foreign components, particularly water, into microcapsules.

In the present study, from the semilogarithmic plots in Figures 3 and 4, straight lines were obtained, which indicated that, the hydrolytic decomposition of ASA followed the first order pathway. The results obtained are in agreement with that obtained by Enezian\textsuperscript{28} who pointed out that, ASA tabletted in a microcrystalline cellulose base degraded by a first order reaction. Kassem\textsuperscript{29} studied the stability of ASA tablets made with avicel and sta-Rx, at 52\% R.H. at two temperature levels: 40\degree C and 60\degree C. He found that, ASA decomposition followed the first order pathway.
5- Conclusion:

1- Under the selected stress condition of storage, there was a significant increase in tablet weight, thickness, friability per cent and disintegration time. However, a marked decrease in tablet hardness and dissolution rate was observed.

2- Physical stability of tablets was seriously affected, which in turn will influence the chemical stability of the incorporated drug.

3- ASA hydrolytic decomposition followed the first-order reaction kinetic.

4- Maximum stability was obtained for ASA tablets directly compressed with avicel or microcapsules (commercial brand) at 52% R.H., 20°C and 45°C.

5- Emdex could be considered as the most suitable vehicle at low humidity for the stability of ASA tablets.

6- Finally, it was shown that both physical and chemical stability of the tested tablets formulations were affected under the selected stress conditions of storage which in turn will modify directly or indirectly the biological availability of these tablets.
Table 1. Composition of Experimental Tablet Matrix

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Preparation I</th>
<th>Preparation II</th>
<th>Preparation III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Compression</td>
<td>60 parts</td>
<td>60 parts</td>
<td></td>
</tr>
<tr>
<td>Wet-granulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microencapsulated ASA.</td>
<td></td>
<td></td>
<td>100 parts x</td>
</tr>
<tr>
<td>Avicel</td>
<td>95 parts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emdex</td>
<td>95 parts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>25 parts</td>
<td>95 parts</td>
<td></td>
</tr>
<tr>
<td>Corn Starch</td>
<td>25 parts</td>
<td>25 parts</td>
<td>30 parts</td>
</tr>
<tr>
<td>Talc</td>
<td>8 parts</td>
<td>8 parts</td>
<td>4 parts</td>
</tr>
<tr>
<td>Binder (Hydroalcohol gelatin dispersion)</td>
<td>10% (W/W)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Microcapsules ASA content was found to be 60.01%

Table 2. Microcapsules Characterization

<table>
<thead>
<tr>
<th>Size Range (µm)</th>
<th>Mean Size (µm)</th>
<th>Weight retained (%)</th>
<th>Core Content (%)</th>
</tr>
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<tbody>
<tr>
<td>315 - 630</td>
<td>475</td>
<td>10.5</td>
<td>ASA 57.4, Salicylic Acid 12x10⁻³</td>
</tr>
<tr>
<td>630 - 800</td>
<td>715</td>
<td>21.5</td>
<td>ASA 64.8, Salicylic Acid 17x10⁻³</td>
</tr>
<tr>
<td>800 - 1000</td>
<td>900</td>
<td>29.5</td>
<td>ASA 59.8, Salicylic Acid 9x10⁻⁴</td>
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<tr>
<td>1000 - 1250</td>
<td>1125</td>
<td>27.0</td>
<td>ASA 66.7, Salicylic Acid 5x10⁻⁴</td>
</tr>
<tr>
<td>1250 - 1600</td>
<td>1425</td>
<td>8.5</td>
<td>ASA 66.9, Salicylic Acid 4x10⁻⁴</td>
</tr>
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### Table 3. Disintegration Time and Dissolution of Prepared ASA Tablets

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Disintegration Time (minutes)</th>
<th>Dissolution T&lt;sub&gt;90&lt;/sub&gt;</th>
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<tr>
<td></td>
<td>I</td>
<td>II</td>
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<tr>
<td>0</td>
<td>1.56</td>
<td>1.50</td>
</tr>
<tr>
<td>1</td>
<td>1.75</td>
<td>1.50</td>
</tr>
<tr>
<td>2</td>
<td>2.25</td>
<td>1.75</td>
</tr>
<tr>
<td>3</td>
<td>2.10</td>
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<tr>
<td>6</td>
<td>3.33</td>
<td>2.75</td>
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<tr>
<td>Ambient conditions</td>
<td>0 % R.H., 20°C</td>
<td>1.50</td>
</tr>
<tr>
<td></td>
<td>1 % R.H., 45°C</td>
<td>1.25</td>
</tr>
<tr>
<td></td>
<td>2 % R.H., 45°C</td>
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<tr>
<td></td>
<td>3 % R.H., 45°C</td>
<td>2.25</td>
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<td></td>
<td>4 % R.H., 45°C</td>
<td>2.50</td>
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<tr>
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<td>5 % R.H., 45°C</td>
<td>2.50</td>
</tr>
<tr>
<td></td>
<td>6 % R.H., 45°C</td>
<td>3.50</td>
</tr>
<tr>
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<td>0.50</td>
<td>1.50</td>
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<td>1 % R.H., 45°C</td>
<td>1.25</td>
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<td>2 % R.H., 45°C</td>
<td>1.25</td>
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<td></td>
<td>3 % R.H., 45°C</td>
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<td>4 % R.H., 45°C</td>
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<td></td>
<td>5 % R.H., 45°C</td>
<td>2.50</td>
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<tr>
<td></td>
<td>6 % R.H., 45°C</td>
<td>3.50</td>
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<td>1 % R.H., 20°C</td>
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<td>4 % R.H., 20°C</td>
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<td>5 % R.H., 20°C</td>
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<td>1 % R.H., 20°C</td>
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<td></td>
<td>2 % R.H., 20°C</td>
<td>38.20</td>
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<td>3 % R.H., 20°C</td>
<td>58.50</td>
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<td>4 % R.H., 20°C</td>
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<td></td>
<td>5 % R.H., 20°C</td>
<td>68.50</td>
</tr>
<tr>
<td></td>
<td>6 % R.H., 20°C</td>
<td>68.00</td>
</tr>
</tbody>
</table>

Figure 1. Effect of Ageing on the Hardness of Prepared ASA Tablets and Commercial Brand of Microencapsulated ASA

Key: ☐, Freshly prepared, ☐, After 6 Months.
Comparative Study on the Physico-Chemical Stability of Acetylsalicylic Acid Tablets Prepared by Microencapsulation and Other Preparative Techniques.

Figure 2. Chemical Stability of ASA Tablets made with Emdex (■), Avicel (☐), Gelatin dispersion 10% W/W (△), Prepared Microencapsulated ASA(□) and Commercial brand of microencapsulated ASA tablets (▲).

Key: Storage conditions: Ambient (A), 52% R.H., 20°C (B), 52% R.H., 45°C (C), 95% R.H., 20°C (D), 95% R.H., 45°C (E).
Figure 3. Degradation of ASA Tablets made with; Microencapsulated ASA (A)
Wet-granulation Using Hydroalcoholic Gelatin Dispersion 10% W/W (B),
Avicel (C) and Commercial Brand of Microencapsulated ASA Tablets (D).

Key. Storage conditions: Ambient (○) 52% R.H., 20°C (●), 95% R.H.,
20°C (△) 52% R.H., 45°C (▲) and 95% R.H., 45°C (□).
Comparative Study on the Physico-Chemical Stability of Acetylsalicylic Acid Tablets Prepared by Microencapsulation and Other Preparative Techniques.

Figure 4. Degradation of ASA Tablets made with Emdex.

Key: As in Figure 3.
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دراسة مقارنة للثبات الطبيعي والكيميائي
لإقراض حامض الاستيل ساليسليك المحترقة بطريقة الحويصلات الدقيقة وطرق أخرى

أحمد طلعت نوح – حسن الصباغ – عبد الجواد حلمي – محمد زكي الشابوري
قسم الصيدلانيات – كلية الميدلية – جامعة المنصورة

١ - قد تم تحضير إقراض حامض الاستيل ساليسليك باستخدام ثلاث طرق هي:
الحويصلات الدقيقة، التجبيب الرطب باستخدام محلول مائي / كحولي للجيلتين (١٠٪)، الكبس المباشر باستخدام الأميدكس والأفيس. كما تم تجربة الاقراض المحترقة بطريقة الاستيل ساليسليك المحترقة في سوق المحترقة بطريقة الحويصلات الدقيقة.

٢ - تم دراسة ثباتية الاقراض عند درجتي حرارة وه٣٠٪ و٩٠٪ و٥٠٪، وقد تم دراسة هذه الاقراض المحترقة عند درجة حرارة ٤٠م، ٥٤م، وقد تم اختبار هذه الاقراض المحترقة في درجة حرارة ٤٠م، ٥٤م.

٣ - قد وجد أن معدل ثباتية الاقراض هو الاقراض المحترقة بطريقة الكبس المباشر:
الكبس المباشر باستخدام الأفيس وبطريق التجبيب الرطب.

٤ - وقد وجد في الدراسة أن هناك زيادة في وزن الاقراض وسمك ومواد التفتت وقوة الاحترام للاقرار، وكم انة وجد أن معدل الاشتعال قد ضخم.

٥ - قد وجد أن استخدام الأميدكس في طريقة الكبس المباشر تعطي انسب اقراض من حيث الثباتية عند درجة حرارة ٤٠٪، ودرجتي الحرارة ٤٠م، ٥٤م.

٦ - الاقراض المحترقة من الحويصلات الدقيقة لحمض الاستيل ساليسليك كذالك الاقراض الموجودة بالسوق والمحترقة بنفس الطريقة وجد انها غير جيدة للتخزين عند درجة حرارة عالية (٩٠٪)، ولكنها تعطي شباتية جيدة عند درجة حرارة مختلفة وخاصة الاقراض الجاهزة الصنع.

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