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Studies on the Direct Compression of Pharmaceuticals, XXIII[+)]

Pancreatin, 1) Effect of Lubricants on Enzyme Activity after Storage

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The effect of the lubricants Fluon, magnesium stearate, talcum, PEG 6000, PEG 10000, and PEG 20000 on the physical and enzymic stability of pancreatin tablets during storage was investigated. Amylase and lipase activities remaining in the tablets after storage for 30 months at room temperature and further 5 months at 37° C were determined by nephelometry. The lubricants were tested in pancreatin tablets containing Emdex as a direct compression vehicle. Moreover, some of the lubricants were studied employing Avicel instead of Emdex. All tablets containing Emdex exhibited brown discoloration after storage at 37° C, which may be explained by *Maillard*'s Reaction. On the other hand, Avicel containing tablets did not show such discoloration. In addition, formulations containing Avicel exhibited better enzyme stability, in comparison with tablets containing Emdex. Furthermore, it was found that PEG 20000, magnesium stearate, and talcum are more suitable than the other lubricants, as they resulted in the minimum loss of enzyme activity on aging of the tablets at room temperature or 37° C.

Studien zur Direkttablettierung von Arzneistoffen, 23. Mitt.[+)]: Pankreatin, 1) Der Einfluß von Tablettenschmiermitteln auf die Lagerstabilität der Enzyme

Der Einfluß der Schmiermittel Fluon®, Magnesiumstearat, Talk und der Polyethylenglykole (Macrogole) 6000, 10000 und 20000 auf die physikalischen Eigenschaften und die Enzymstabilität von Pankreatintabletten beim Lagern wurde studiert. Nach 30 Monaten Lagern bei Raumtemperatur und abermals nach 5 Monaten bei 37° C wurden die verbliebenen Aktivitäten der Lipasen und Amylasen nephelometrisch gemessen. Die Tabletten enthielten teils Emdex®, teils Avicel ® als Direkttablettier-Hilfsmittel. Erstere erlitten beim Lagern bei 37° Braunfärbung (*Maillard*-Reaktion), letztere nicht. Auch hinsichtlich der Enzymstabilität waren die Avicel®-gebundenen Tabletten besser. Polyethylenglykol 20000, Magnesiumstearat und Talk als Schmiermittel ergaben die Tabletten mit dem geringsten Aktivitätsverlust bei Raumtemperatur wie bei 37°.

The presence of additives, even in solid dosage forms, may result in many physical (e. g.[1-3]), and/or chemical (e.g.[4-6]) stability problems, especially with sensitive drugs like pancreatin[7,8]. Therefore,

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proper preformulation and stability studies highlight the future stability of the respective pharmaceuticals.

The influence of some additives, commonly employed in tablet manufacture, on amylase and lipase activities was previously investigated, for example, direct compressible vehicles[9], lubricant[10], disintegrants[8] and film formers[11]. In addition, the effect of some lubricants on the release of pancreatic enzymes was also studied[12].

The aim of the present work is to investigate the effect of different lubricants on amylase and lipase activities after storage of the tablets at room temperature for 30 months followed by subsequent storage at 37° C for further 5 months.

Experimental Part

1. *Materials:* Pancreatin[1], Avicel PH 102[2], Emdex[3], Talc[4], Magnesium stearate[4], Fluon[5] and Polyethylene glycols[6] (6000, 10000 and 20000).

2. *Preparation of the Tablets*

Tablets were made employing two concentration levels from each lubricant (2 + 10 %), using Emdex as excipient with pancreatin in a ratio of 1 : 1. Furthermore, other tablets were formulated with some of the above lubricants (talc, PEG 10000 and PEG 20000) applying Avicel instead of Emdex as the direct compressible vehicle, keeping all other factors the same as with Emdex tablets. The applied compression force was held constant at 4 kN by using an instrumented tablet press[7].

3. *Analysis of the Enzyme Activity*

Five tablets were taken randomly from each formulation and finely powdered in a mortar prior to analysis. Subsequently, the amylase and lipase activities were determined by nephelometry as previously described[9].

4. *Storage Conditions*

Samples representing all formulations were kept in well closed glass containers at room temp. away from light for 30 months. The same samples were subjected to further storage in a thermostatically controlled oven at 37° C for further 5 months.

Results

1. *Physical Stability*

The appearance of the tablets after storage at room temp. and at 37° was visually examined. Tablets containing either Avicel or Emdex as direct compressible vehicles remained unchanged after storage at room temp. Emdex-tablets developed brown discoloration upon storage at 37° C. The observed discoloration ranged from yellow, brown to dark brown. It is worthy of mention that minimum discoloration was observed in those tablets containing either 2 % from each of talc, PEG 6000 and PEG 20000 or in tablets with 10 % magnesium stearate. Meanwhile, maximum discoloration was detectable with either 2 % Fluon or PEG 10000 and with 10 % PEG 6000. The other tablets exhibited intermediate degrees of discoloration.

2. *Enzyme Stability*

2.1. *Effect of Storage at Room Temperature*

The enzyme activities were determined after aging of the tablets at room temp. for 30 months and the loss % subsequently calculated with reference to the initial activities (Figs. 1 + 2). The loss in enzymic activities amounted to about 45 and 70 % for amylase and lipase, respectively.

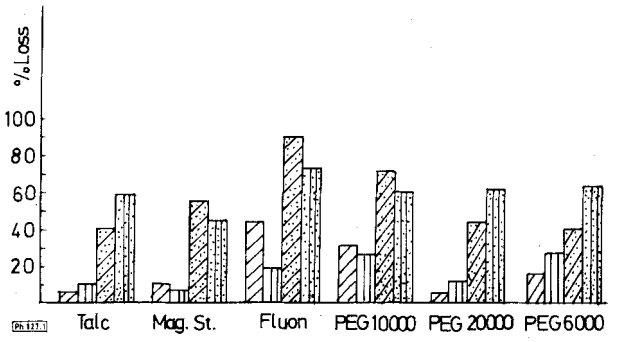

Fig. 1: Percentage Loss in Amylase Activity upon Storage of Emdex Tablets at Room Temperature in the Presence of 2 % ( ) or 10 % ( ) Lubricant; and Subsequently Stored at 37° C Using either 2 % ( ) or 10 % ( ) Lubricant

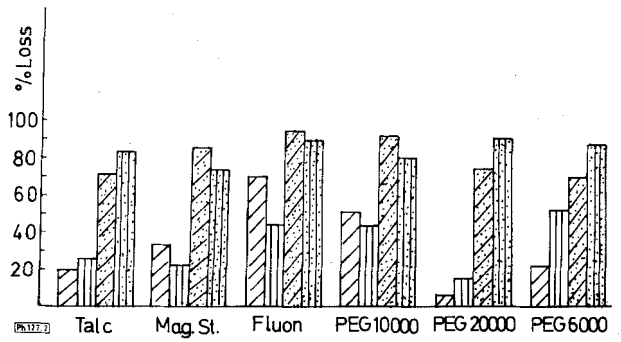

Fig. 2: Percentage Loss in Lipase Activity upon Storage of Emdex Tablets under the Same Conditions Described in Fig. 1

2.2 *Effect of Storage at 37° C*

The percent loss in enzymic activity was calculated after storage of the tablets for further 5 months at 37° C. The results are also presented in Figs. 1 + 2, where maximum loss in each enzyme reached about 90 %.

Discussion

1. *Effect of Lubricants on Enzyme Activity*

The type and concentration of the employed lubricants influenced differently the enzyme activities.

1.1 *Amylase Activity*

Regarding the effect of storage at room temp., it is obvious that tablets containing either 2 or 10 % from talc, magnesium stearate or PEG 20000 exhibited minimum loss in activity, less than 10 % (Fig. 1). Meanwhile, 2 % Fluon or PEG 6000 resulted in about 45 and 15 % loss in activity, respectively, while 10 % from either of them induced 20 and 25 % loss. Moreover, PEG 10000 formulations showed almost the same degree of enzyme inactivation, which is about 30 %. The results of storage at 37° C presented in Fig. 1 point out that tablets containing either 2 or 10 % talc, magnesium stearate, PEG 6000 or PEG 20000 lost 40–60 % of their original activities after storage. Higher degrees of inactivation were observed by incorporating 2 % Fluon or PEG 10000, 90 and 70 %, respectively. However, increasing the concentration of either the last two lubricants to 10 % resulted in about 70 and 60 % loss of amylase activity, respectively. From the above results it could be concluded that increasing the concentration of some lubricants resulted in higher extent of enzyme inactivation, namely, talc, PEG 6000 and PEG 20000. In contrast, addition of 2 % Fluon caused enzyme inactivation which is lower then that observed with 10 %; similar results were observed, but to lesser extent, with magnesium stearate and PEG 10000. The observed decrease in enzyme inactivation by using higher concentration of certain lubricants may be explained, for the hydrophobic lubricants Fluon and magnesium stearate, by their ability to form protective films around pancreatin particles. Such a mechanism is, of course, more easily realisable at higher concentration levels. On the other hand, the diminished amylase activity observed by increasing the concentration of PEG 6000, PEG 20000 and talc from 2 to 10 % may be explained by degradative interaction, which is more obvious at higher concentration levels. Such interaction could be explained for talc by its alkaline nature. Regarding PEG 6000 and PEG 20000, being polyhydroxylic polymers, they could be engaged in esterification or transesterification reactions with the enzyme molecules. Similar observations were reported for PEG's with aspirin[13] and pancreatin[10].

2. *Lipase Activity*

The magnitude of loss in lipase activity during storage was greater than the corresponding values of amylase activity. The losses found at room temp. (Fig. 2) as a result of the different lubricants indicate that talc, magnesium stearate and PEG 20000 led to the minimum lipase inactivation, using either 2 or 10 % from each of them. The extent of loss ranged between 10 and 25 %. The influence of lubricant concentration was more profound with Fluon and PEG 6000, since 2 % induced 70 and 20 % loss, respectively, while 10 % caused 45 and 50 % loss in activity, respectively. However, using 2 or 10 % PEG 10000 resulted in about the same degree of lipase inactivation, being 45 and 50 %, respectively. These results indicate that the pattern of loss in lipase activity, in relation to the different lubricants, is similar to that observed with amylase activity (Fig. 1). However, the relative stabilities of both enzymes appeared to be in favour of amylase rather than lipase, which was also reported earlier[7–11].

On the other hand, storage of the tablets at 37° C resulted in many fold increases in loss of activity, in comparison with the same formula aged at room temp. (Fig. 2). The effect of temp. was, however, more obvious with such lubricants having slight deleterious effects on lipase activity at room temp., e.g. PEG 20000. The observed loss in activity following storage at 37° C was found to be 70–90 %. Using 2 % lubricant, about 70 % loss in activity resulted each of talc, magnesium stearate, PEG 20000, and PEG 6000, while Fluon and PEG 10000 caused about 90 % loss in lipase activity.

Moreover, addition of 10 % lubricant resulted in 80–90 % loss in activity; except with magnesium stearate where the observed loss was about 70 %. From Fig. 2, it could be concluded that Fluon, magnesium stearate, and PEG 10000 induced lower extent of enzyme inactivation at higher concentration level (10 %); while talc, PEG 20000, and PEG 6000 caused a higher degree of loss at the high concentration; in comparison with 2 % lubricant. This behaviour was also observed and discussed under amylase activity.

Generally, it could be concluded that PEG 20000, talc, and magnesium stearate are considered, according to this study, to be the most appropriate lubricants for preparation of pancreatin tablets. Moreover, the same lubricants appeared also in a previous study[10] to be efficient lubricants during the process of tablet compression, since they resulted in minimum loss of activity by increasing the force of compression.

3. *Influence of Direct Compressible Vehicles*

The percent of loss in enzymic activity after storage of pancreatin tablets, containing Avicel instead of Emdex, by employing talc, PEG 10000, and PEG 20 000 as lubricants, is calculated and the results are shown in Fig. 3.

3.1. *Effect of Storage at Room Temperature*

The observed losses in amylase activities as a result of the different lubricants (Fig. 3), are slightly affected by aging the tablets at room temperature, since the maximum loss in activity is found to be not more than 10 %. These results are quite comparable whith the corresponding formulations containing Emdex (Fig. 1). Concerning lipase activity of the Avicel tablets, the observed losses in activity as a result of using 2 % from each of PEG 20000, PEG 10000, and talc were 10, 15 and 35 %, respectively. By comparing these results with those values of the corresponding formulations employing Emdex (Fig. 2), it could be seen that both direct compressible vehicles minimally affected enzyme activity in the presence of PEG 20000. However, Avicel offered better enzyme stability in the presence of PEG 10000, while it resulted in lower lipase stability if talc was used as the lubricant.

3.2 *Effect of Storage at 37° C*

Tablets containing Avicel as the direct compressible vehicle exhibited better amylase and lipase stabilities (Fig. 3) than the corresponding tablets manufactured with Emdex (Figs. 1 + 2). The mean

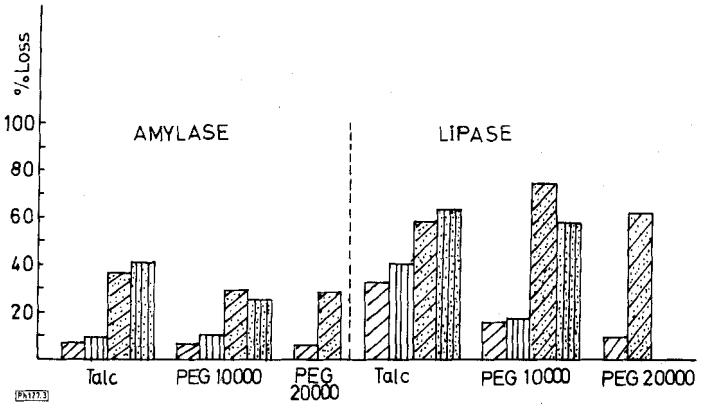

Fig. 3: Percentage Loss in Lipase Activity upon Storage of Avicel-Tablets under the Same Conditions Described in Fig. 1

loss in amylase activity observed with Avicel-containing tablets was found to be about 35 %; and the corresponding value for lipase activity was 65 %. However, the mean values of loss in activity for Emdex-containing tablets appeared to be higher than the above values, being 70 and 80 % in amylase and lipase, respectively.

The overall conclusion for the effect of the studied lubricants on enzyme activity, in the presence of the two direct compressible vehicles, points out that Avicel offered a better enzyme stabilizing effect than Emdex. The observed deleterious effect of Emdex on enzyme activity is probably due to degradative interactions, since brown discoloration was observed in only pancreatin tablets containing Emdex, after storage at 37° C. This interaction of Emdex, being composed of 95 % glucose (*Maillard*'s Reaction), was also previously reported in the literature for many combinations, for example, pancreatin-Emdex[7], Isoniazid-lactose[5], procaine-glucose[14,15] and amphetamine-lactose[16].

Conclusions

a) Magnesium stearate and PEG 20000 appeared to be the most appropriate lubricants for formulation of pancreatin tablets according to their efficiencies during compression and upon storage of the tablets.

b) Comparative study of Avicel and Emdex, in the presence of the same lubricants, reveals that Avicel is better than Emdex, regarding the stability of enzymes upon storage.

c) Aging of the tablets at 37° C for only 5 months resulted in loss of enzyme activity amounting to about five times the corresponding value due to storage of the tablets at room temperature for 30 months.

d) Lipase is more sensitive to aging conditions than amylase.

e) Pharmaceutical preparations containing pancreatin should be kept in a cool place and bear expiratory dates.

(1) Nordmark-Werke GmbH, Hamburg
(2) Lehmann & Voss & Co., Hamburg
(3) E. Mendell & Co., New York (USA)
(4) Ph. Eur. III
(5) ICI Ltd., Welwyn Garden City, Herts (Great Britain)
(6) Hoechst AG, Frankfurt/M.
(7) Korsch AG, W. Berlin, Type EK 0

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N-Acyl-Harnstoffe und ihr Verhalten gegen Amine

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Einige N-Acyl-Harnstoffe ergeben in einer Spaltungsreaktion mit Aminen nicht nur die gleichen Produkte wie freie Isocyanate, sondern zeigen in Abhängigkeit von der Basizität der Nucleophile und den elektronischen Einflüssen der Substituenten eine Reihe nicht erwarteter Reaktionen.

N-Acylureas and Their Behaviour Against Amines

Some *N*-acylureas, in fragmentation reactions with amines, yield the same products as free isocyanats. Depending on the basicity of the nucleophil used and the electronic influences of the substituent they also give some unexpected reactions.

Viele Heterokumulene, die mit biologisch wichtigen Molekülen stabile Addukte zu bilden vermögen, besitzen pharmakologische Wirkungen, die jedoch wegen der hohen Reaktivität und der Pantoxizität der meisten Heterokumulene nicht genutzt werden können. Für Isocyanate ist dies lange bekannt[1]. Obwohl man ferner weiß, daß eine größere Anzahl verschiedenster Verbindungen mehr oder weniger leicht zur Bildung von Isocyanaten befähigt ist[2], ist bisher nicht untersucht worden, ob „verkappte Isocyanate" mit nucleophilen Partnern HY die gleichen Addukte wie freie Isocyanate ergeben.

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