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# COMPARATIVE EVALUATION OF CERTAIN EXCIPIENTS AND THEIR BINARY BLENDS FOR DIRECT COMPRESSION OXYTETRACYCLINE HYDROCHLORIDE TABLETS

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## ABSTRACT

Five direct compression excipients as well as their binary blends in ratios of 1:1, 1:3 and 3:1 were comparatively evaluated to compress oxytetracycline hydrochloride into tablets. With respect to the mechanical properties of the produced tablets, Avicel PH101, Celutab and STAR-x1500 in this order, were the most suitable single excipients for the production. The results showed that the incorporation





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of a second excipient in the formulation changes the physical standards of the produced antibiotic tablets. It was found that not only the type of the incorporated excipient is effective but also, its concentration in the formula. The investigation proved that Avicel/STAR-x1500 blends in all different ratios followed by some blends of **celutab** with Avicel or STAR-x1500 were the best blended excipients to produce satisfactory antibiotic tablets.



## INTRODUCTION

Although the traditional methods of tablet manufacture either by wet or dry granulation procedures are the most effective methods, a great deal of attention is given to direct compression as a new and simple tabletting technique. In this field, great efforts have been done to evaluate different material as direct compression excipients e.g. collidal silica (1), dicalcium phosphate dihydrate (2), anhydrous lactose (3) STAR-x1500 (4,5), microcryslalline cellulose (Avicel PH101) (6,7) Avicel PH102, Elcema G250 and amylose V(8). Infact, Kanig(9) has listed the properties which an ideal excipient must fulfill. In their excellent review article, khan and Rhodes(10) discussed the properties of different direct compression excipients.

In direct compression technique there is no need to modify the physical properties of the active ingre-

dient(s). Only the proper mixing with suitable excipient(s) and lubricant(s) should be carried out. Many reports have been written to point out the advantages of this technique (11,12). Aly and Abu-Taleb(13) emphasized the statement of Henderson and Bruno (14) that no single material has been found to be suitable for all direct compression formulas.

The goal of this work is to evaluate some direct compression excipients and their binary blends in order to compress oxytetracycline hydrochloride directly into tablets. We suggested the evaluation of physical standards of the produced tablets prior to testing the in-vitro, in-vivo availabilities and stability of the tabletted antibiotic.

## EXPERIMENTAL

Material: The excipients used were microcrystaline cellulose (Avicel PH101)[1], directly compressible starch (STAR-x1500)[2], celutab[3], sugartab[3], and anhydrous lactose USP[4]. Oxytetracycline hydrochloride[5], the active ingredient, was used as received. Magnesium stearate[6] and stearic acid[6] were used as lubricants.

## METHODS

Physical standards, mean particle size, bulk density and angle of repose of the powdered drug and excipients were evaluated using the previously reported methods (15) and the results are shown in table 1

Table 1 Physical properties of powdered oxytetracycline hydrochloride and direct compression excipients.

| Materials | Average Particle size (U) | Packed bulk density glcc | Angle of repose |
|---|---|---|---|
| Oxytetracycline Hcl | 75.00 | 0.72 | 26° 63" |
| Avicel PH101 | 82.99 | 0.355 | 48° 00" |
| Anhydrous Lactose USP | 185.07 | 0.559 | 40° 00" |
| Celutab | 342.58 | 0.683 | 31° 58" |
| Sugartab | 661.12 | 0.641 | 36° 42" |
| STAR-x1500 | 113.21 | 0.668 | 28° 30" |

Five batches containing 0.0, 19.6, 32.6, 42.0 and 49.0% w/w of a given excipient were formulated and compressed into tablets using single punch tabletting machine[1]. The same technique published by Aly and Abu-Taleb (13) was used to compress flat tablets each had a diameter of 6.4 0.01mm and an average weight of 0.1gm. The directly compressed tablets were evaluated according to the previously reported procedures (13,16).

## RESULTS AND DISCUSSIONS

On the bases of HFR (13,17) it was found that Avicel, Celutab and STAR-x1500 in this order were the most suitable single excipients to produce satisfactory tablets.

Uniformity of weight: The uniformity of weight of the directly compressed antibiotic tablets was evaluated to comply with B.P. 1973 test. Table 2 shows that the control tablets were not uniform (high C.V%). In one case, the control tablets of anhydrous lactose USP formulations could not be compressed. From the given data in this table, only two batches.formulated with 49.0 and 42.0% w/w of Avicel were uniform. This expected result may be attributed to its bad flow properties of Avicel may be due to its smaller irregular rode shaped interlocking particles which would create great resistance to flow (18). The effect of particles size variation became pronounced with the blends of celutab and sugartab (excipients of larger particle sizes see Table 1) and hence non uniform tablets were produced. As it is shown in Table 2 STAR-x1500 was the only single excipient which produced uniform tablets (19, 20). The small particle size variation or/and the good flow properties of STAR-x1500 may be the acceptable explanation for this.

Logically, the physical properties of a given excipient can be modified by the addition of certain additives or mixing with another excipient. The new properties of the mixture are not clear or simple to state that the modification is simple additive function (4,21). However, Table 3 shows that the incorporation

Table 2 Some physical standards of directly compressed oxytetracycline hydrochloride tablets with single excipients.

| Vehicle Name | Conc. % w/w | Weight (g) Mean | Weight (g) C.V. % | Thickness (mm) Mean | Thickness (mm) C.V. % | Hardness Friab. Ratio (HFR) | Disint. Time (Min.) Mean | Disint. Time (Min.) C.V.% |
|---|---|---|---|---|---|---|---|---|
| | 00.0 | 0.139 | 1.42 | 3.17 | 1.06 | 1.53 | 18.61 | 12.9 |
| | 19.6 | 0.127 | 1.47 | 2.90 | 9.02 | 7.01 | 27.10 | 7.05 |
| **Avicel** | 32.6 | 0.116 | 7.60 | 2.66 | 5.90 | 7.33 | 42.10 | 7.05 |
| | 42.0 | 0.110 | 9.26 | 2.57 | 1.29 | 7.75 | 53.10 | 6.54 |
| | 49.0 | 0.105 | 6.50 | 2.57 | 2.03 | 8.82 | 75.10 | 23.36 |
| | 00.0 | -- | -- | -- | -- | -- | -- | -- |
| Anhydrous | 19.6 | 0.089 | 6.50 | 2.22 | 4.60 | 0.56 | 6.81 | 9.18 |
| Lactose | 32.6 | 0.122 | 1.57 | 2.61 | 11,85 | 0.93 | .95 | 15.06 |
| USP | 42.0 | 0.122 | 1.53 | 2.55 | 9.11 | 1.17 | 8.85 | 14.87 |
| | 49.0 | 0.121 | 7.58 | 2.54 | 5.16 | 1.18 | 9.85 | 17.69 |
| | 00.0 | 0.1153 | 3.21 | 2.7 | 2.12 | 0.78 | 12.15 | 7.91 |
| | 19.6 | 0.1248 | 1.57 | 2.88 | 1.25 | 4.84 | 13.70 | 5.59 |
| Celutab | 32.6 | 0.1335 | 51.37 | 2.99 | 6.60 | 5.09 | 14.14 | 9.99 |
| | 42.0 | 0.1165 | 3.21 | 2.65 | 2.94 | 7.02 | 15.76 | 19.94 |
| | 49.0 | 0.1228 | 1.84 | 2.80 | 1.29 | 7.32 | 16.83 | 8.14 |
| | 00.0 | 0.1112 | 3.22 | 2.39 | 1.60 | 8.24 | 8.85 | 17.6 |
| | 19.6 | 0.1204 | 4.98 | 2.50 | 11.70 | 4.56 | 9.46 | 23.09 |
| Sugartab | 32.6 | 0.1252 | 2.88 | 2.78 | 2.48 | 4.06 | 10.81 | 28.27 |
| | 42.0 | 0.1045 | 1.46 | 2.33 | 1.65 | 3.43 | 13.95 | 13.79 |
| | 49.0 | 0.0916 | 3.13 | 2.16 | 22.24 | 3.42 | 10.02 | 9.23 |
| | 00.0 | 0.1031 | 3.88 | 2.43 | 2.17 | 3.31 | 4.99 | 5.78 |
| | 19.6 | 0.1037 | 3.26 | 2.49 | 1.27 | 5.99 | 7.53 | 9.39 |
| STAR-x | 32.6 | 0.1068 | 3.40 | 2.52 | 1.98 | 5.40 | 6.24 | 10.57 |
| | 42.0 | 0.1068 | 2.11 | 2.54 | 5.78 | 6.60 | 5.93 | 4.29 |
| | 49.0 | 0.1077 | 3.19 | 2.56 | 2.35 | 8.00 | 5.94 | 4.89 |

Table 3 Some physical standards of directly compressed oxytetracycline hydrochloride tablets with binary blended excipients (1:1).

| Vehicle Name | Conc. % w/w | Weight (g) Mean | Weight (g) C.V. % | Thickness Mean | Thickness C.V. % | Hard. Friab. Ratio | Disint. Time (Min.) Mean | Disint. Time (Min.) C.V. % |
|---|---|---|---|---|---|---|---|---|
| | 00.0 | 0.1080 | 2.78 | 2.47 | 2.50 | 1.08 | 10.47 | 2.02 |
| Avicel/ | 19.6 | 0.1052 | 2.83 | 2.55 | 2.48 | 2.20 | 11.58 | 7.65 |
| Anhydrous | 32.6 | 0.1079 | 2.35 | 2.47 | 2.13 | 9.03 | 11.26 | 9.69 |
| Lactose | 42.0 | 0.1074 | 3.93 | 2.45 | 3.02 | 12.21 | 12.42 | 6.77 |
| | 49.0 | 0.1059 | 3.19 | 2.56 | 2.35 | 18.61 | 9.79 | 3.66 |
| | 00.0 | 0.0960 | 3.95 | 2.20 | 4.05 | 3.17 | 5.83 | 7.41 |
| Avicel/ | 19.6 | 0.0989 | 1.71 | 2.26 | 1.75 | 6.13 | 9.73 | 7.74 |
| Celutab | 32.6 | 0.1011 | 2.06 | 2.31 | 2.51 | 11.61 | 13.57 | 6.12 |
| | 42.0 | 0.1002 | 1.31 | 2.39 | 2.38 | 16.12 | 16.19 | 4.49 |
| | 49.0 | 0.1062 | 1.22 | 2.39 | 1.17 | 19.13 | 16.59 | 7.27 |
| | 00.0 | 0.0866 | 1.7 | 2.07 | 1.85 | 2.72 | 5.36 | 2.67 |
| Avicel/ | 19.6 | 0.0970 | 4.43 | 2.2 | 3.99 | 2.16 | 9.76 | 5.61 |
| STAR-x | 32.6 | 0.1082 | 1.88 | 2.41 | 1.87 | 4.23 | 9.39 | 9.36 |
| | 42.0 | 0.1096 | 2.66 | 2.43 | 2.77 | 7.62 | 17.83 | 6.03 |
| | 49.0 | 0.1124 | 2.32 | 2.46 | 2.24 | 8.15 | 20.37 | 3.59 |
| | 00.0 | 0.0866 | 1.7 | 2.07 | 1.85 | 2.72 | 5.73 | 5.16 |
| Celutab/ | 19.6 | 0.0970 | 4.43 | 2.2 | 3.99 | 2.16 | 5.22 | 7.53 |
| Anhydrous | 32.6 | 0.1082 | 1.88 | 2.41 | 1.87 | 4.23 | 5.95 | 8.62 |
| Lactose | 42.0 | 0.1096 | 2.66 | 2.43 | 2.77 | 7.62 | 9.43 | 18.09 |
| | 49.0 | 0.1124 | 2.32 | 2.46 | 2.24 | 8.15 | 6.31 | 8.11 |
| | 00.0 | 0.0866 | 18.52 | 2.13 | 2.6 | 1.43 | 4.09 | 12.91 |
| Celutab/ | 19.6 | 0.0962 | 2.75 | 2.29 | 2.11 | 8.65 | 4.83 | 7.41 |
| STAR-x | 32.6 | 0.1011 | 1.75 | 2.39 | 1.47 | 15.06 | 5.85 | 5.06 |
| | 42.0 | 0.1063 | 1.56 | 2.50 | 1.45 | 17.35 | 6.52 | 2.28 |
| | 49.0 | 0.1103 | 2.24 | 2.58 | 1.67 | 26.80 | 8.32 | 5.6 |
| | 00.0 | 0.107 | 2.96 | 2.41 | 1.91 | 3.14 | 5.52 | 9.27 |
| STAR-x | 19.6 | 0.0922 | 3.26 | 2.40 | 10.41 | 4.85 | 5.03 | 12.57 |
| Anhydrous | 32.6 | 0.0912 | 2.74 | 2.19 | 2.18 | 6.08 | 5.23 | 8.64 |
| Lactose | 42.0 | 0.0987 | 4.48 | 2.31 | 3.77 | 6.11 | 7.46 | 3.71 |
| | 49.0 | 0.1060 | 1.780 | 2.48 | 1.70 | 7.78 | 9.05 | 5.81 |

of a second excipient affected the uniformity of weight of the produced tablets. Not only was this effect dependent on the concentration of the incorporated excipient, but also its type was effective. Compressed tablets with binary blended excipients were more uniform in weight. Table 3 shows that 1:1 Avicel binary blends were most suitable excipients to produce uniform tablets.

The uniformity of thickness, which is an additional control to the tablet dimensions to ensure the reproducibility(5) was evaluated. Both single and binary blended excipients produced tablets of the same variations in thickness, more or less parallel to variations in weight.

Crushing strength:

The incorporation of single excipients in the formulation increased the hardness of the tablets as shown in Fig. 1. In this figure it is shown that the crushing strength of the compressed tablets was dependent on the type, as well as, the concentration of the incorporated excipient. STAR-x, Celutab and Avicel, in this order produced hardest tablets. The good flow or/and the high pressure hardness profile of STAR-x1500 (20,21) may explain why the compressed tablets with this excipient were of higher hardness level. In the case of sugar excipients celutab and sugartab, the higher level of hardness of the produced tablets is due to the hardening

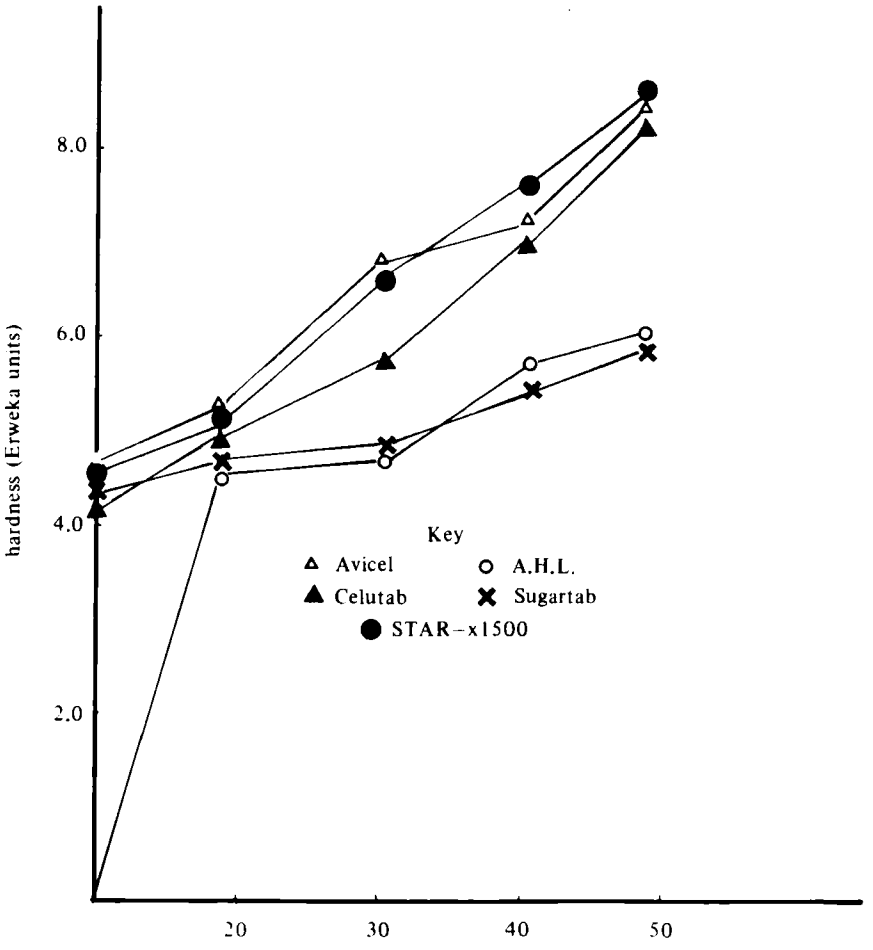


FIGURE 1

Effect of varying concentrations of different direct compression excipients on the hardness of directly compressed oxytetracycline Hcl tablets.

effect of these excipients (11). The case is quite different with Avicel. Its match-stick like particles, are easily intermished under slight compression force, and the numerous sites of hydrogen bonding found in the molecule, enabled the finished tablets to exhibit

extreme hardness (6). However, with respect to hardness of the compressed tablets with 49.0% w/w single excipients can be arranged as follows

STAR-x > Celutab > Avicel > Anhydrous > Lactose > Sugartab.

Figure 2 shows that Avicel/Anhydrous Lactose blends, produced the hardest tablets. This may be attributed to the synergistic effect of Avicel. Due to its higher pressure-hardness profile and good tabletting properties, STAR-x when blended with Avicel produced satisfactory tablets (4,21).

With respect to the hardness of the produced tablets formulated with 49.0% w/w, 1:1 binary blends of Avicel, can be arranged as follows:

Avicel/Anhydrous Lactose > Avicel/STAR-x > Avicel/Celutab > Avicel/Sugartab.

Friability (Loss %)

Figures 3 and 4 show that the control tablets were friable (high loss % w/w). The incorporation of single excipients in the formulation reduced the friability. Among the tried excipients, Avicel, STAR-x and Celutab; in this order, were also the best excipients to compress antibiotic tablets of small loss %. This may be attributed to their high pressure hardness profiles. On the other hand, the lactose produced friable tablets.

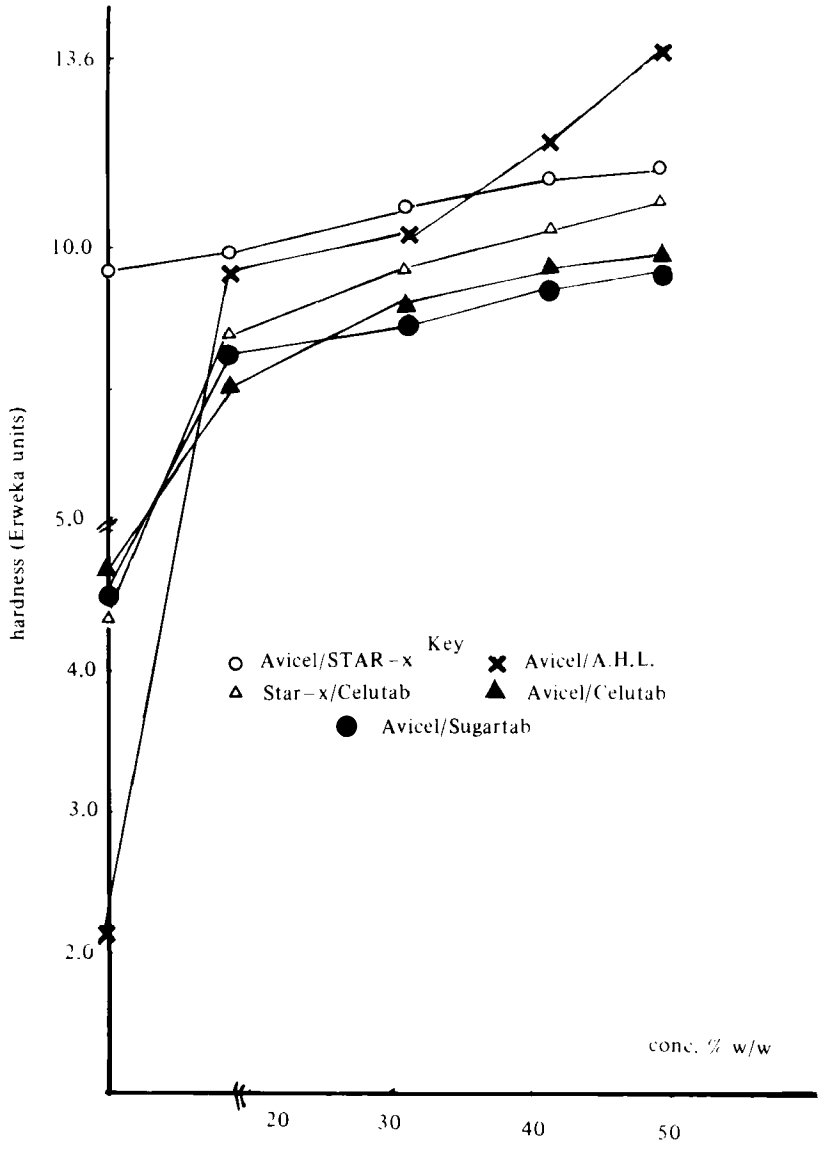


FIGURE 2

Effect of varying concentrations of different binary blended excipients (1 : 1) on the hardness of directly compressed oxytetracycline Hcl tablets.

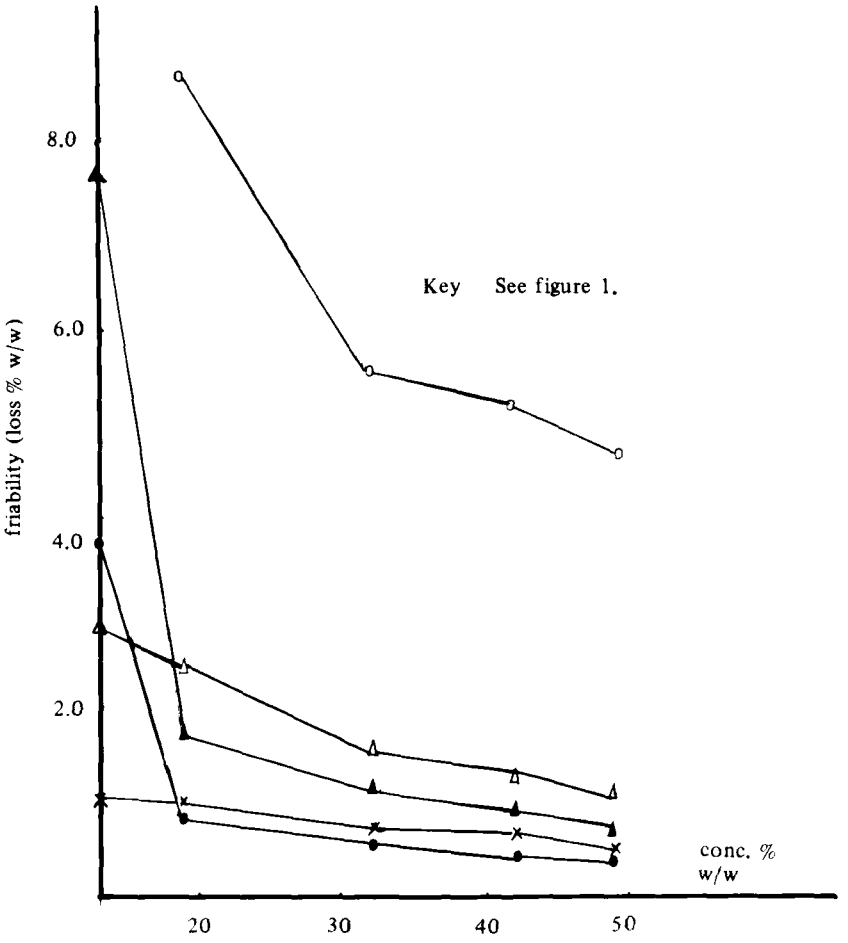


FIGURE 3

**Effect of varying concentrations of different direct compression excipients on the friability of directly compresses oxytetracycline Hcl tablets.**

Although it was reported that it has good tabletting properties (11), this result may be attributed to the small compression force used.

Figure 4 confirms that the incorporation of a second excipient in formulation modified the tabletting

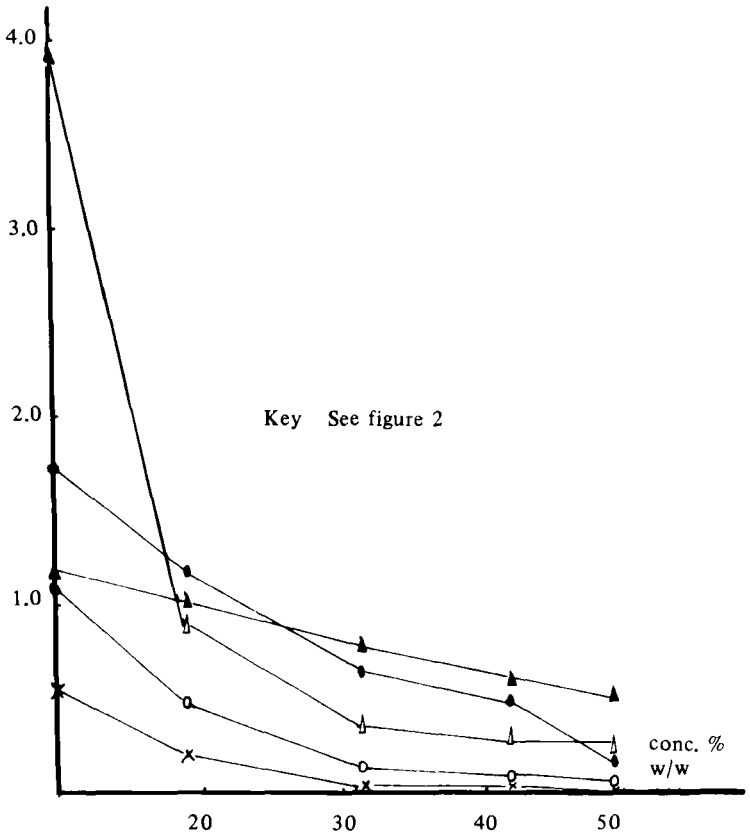


FIGURE 4

Effects of varying concentrations of different binary blended excipients (1:1) on the friability of directly compressed oxytetracycline Hcl tablets.

properties. In this figure it is shown that blending with Avicel, STAR-x or Celutab reduced the friability of the produced tablets. With respect to the friability of the compressed tablets, single excipients can be arranged as follows

Avicel < STAR-x < Celutab < Sugartab < Anhydrous Lactose

Disintegration time

Table 2 shows that all the formulated tablets passed the pharmacopiel limit (30 min. according to B.P 1973), except those formulated with 32.6, 42.0 and 49.0% w/w of Avicel.

Due to the solubility of the active ingredient, the control tablets disintegrated within the limit, and their disintegration times were not uniform (high C.V. %). It was not expected that the contribution of Avicel to the formulation would delay the disintegration times of the compressed tablets. Although it was reported as a disintegrant (6) the disintegration times of the tablets increased by increasing the concentration of Avicel in the formulas. This may be attributed to the high compression force under which the tablets were compressed. The other suggested cause is the failure of disintegration medium (0.1N HCL) to destroy the strong hydrogen bonding. Earlier, it was reported that this excipient failed to be either extra or intera disintegrant (22). On the other hand, Celutab produced fastly disintegrated tablets. This may be due to the solubility of the vehicle and the antibiotic. As it is a starch, STAR-x reduced considerably the disintegration times of the formulated tablets (5).

The effects of the binary blended vehicles on the disintegration times of the produced tablets, are shown

in table. Generally, except in the case of STAR-x and anhydrous lactose blends, binary blended vehicles increased the disintegration times. With respect to their effect on disintegration times of the produced tablets, binary blends of anhydrous lactose with other vehicles can be arranged as follows:

STAR-x/Anhydrous Lactose 1:3 > 3:1 > 1:1

Celutab/Anhydrous Lactose 3:1 > 1:3 > 1:1

## CONCLUSION

From the previous discussion, it is concluded that, the direct compression technique can be applied to manufacture oxytetracycline hydrochloride tablets of reasonable physical standards. Avicel, Celutab and STAR-x1500 were found to be the suitable single excipients for tabletting. Although they produced tablets of good mechanical properties, we recommend the binary blends of any of these excipients with the other or with anhydrous Lactose in the ratio of 1:1 or 3:1.

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## FOOT NOTES

1. F.M.C. Corporation, Pennsylvania, U.S.A.
2. Staley Mg. Co., Ill., U.S.A.
3. E. Mendell Co. Inc., U.S.A.
4. Shiffield Union, N.J. 07083 U.S.A.
5. Pliva Pharmac. and Chem. Works, Zagreb, Yogoslavia.
6. Chemical Industries Development Assiut Branch Assiut Egypt.

I. Manesty Machines Limited, Liverpool, England.

## REFERENCE

1. R.E. King, In "Remington's Pharmaceutical Sciences Mack Publishing Company, Easton, Pennsylvania, U.S.A., Chap. 81 (1970).
2. F. Jaminet, Bull. Tech. Galtefosse SFPA, 63, 63 (1968).
3. N.A. Batuyios, J.Pharm. Sci., 51, 727 (1962).
4. K.S. Manudhone, A.M. Contractor, Y.H. Kim, and R.F. Shangraw, ibid 58, 616 (1969).
5. A.M. Sakr, H.M. El. Sabbagh and K.M. Emara, Arch. Pharm. Chem. Sci., 2, 14 (1974).
6. M.D. Richman, D.C. Fox, and R.F. Shangraw J.Pharm. Sci., 54, 447 (1965).
7. S.T. Horhota, J.Burgio, L. Lonski and C.T. Rhodes, ibid 65 1746 (1976).
8. C.F. Lerk, G.K. Bolhuis Pharm. Weekblad, 108, 469 (1973).

9. J.L. Kaing, In paper presented at "Emcompress Symposium", London (1970).

10. K. Khan and C.T. Rhodes, Canad, J. Pharm. Sci., 8 1 (1973).

11. E. Mendell, J. Manuf. Chem. and Aerasel News, 43 43 (1972).

12. J.W. Warren and J.C. Price, J.Pharm. Sci., 66 1406 - 1409 (1977).

13. S.A.S. Aly and A.E. Abu-Taleb, Drug Develop. and Indust. Pharm. J. in press.

14. N.J. Henderson and A.J. Bruno J.Pharm. Sci., 59 1336 (1940).

15. A.M. Kassem, In Thesis submitted for M.Pharm. to the Faculty of Pharmacy, Cairo University, Cairo, Egypt. (1975).

16. A.E. Sakr, A.A. Kassem, A.A. Aziz and A.H. Shalaby, Canad J.Pharm. Sci., 8 6 (1973).

17. J.E. Broadbent, A.C. Mitchell and W.J.O. Reilly, Aust. J.Pharm. Sci., 47, 592 (1966).

18. D. Sixsmith, J.Pharm. and Pharmacol, 29, 28 (1977).

19. S.A. Sangekar, M. Sarli and P.R. Sheth, J.Pharm. Sci., 61, 939 (1972).

20. J.M. Esnard, J.Clerc, H.Tebbi, D.Ducheme, J.Levy and F.Puisieux, Ann. Pharmac., 31 103 (1973).

21. J.M. Newton and D.J.W. Grant, Powder Tech. 9 295 (1974).

22. E. Shotton and G.S. Leonard, J.Pharm. Sci., 65, 1170 (1976).