DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(4), 945-962 (1985)

A CONTRIBUTION TO THE MANUFACTURE OF DIIODOQUIN TABLETS BY DIRECT COMPRESSION

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ABSTRACT

Six direct compression vehicles and their binary blends in ratios of 1:1, 1:3 and 3:1 were investigated to compress diiodoquin directly into tablets. With respect to the mechanical properties of the produced tablets, Avicel, Celutab and STAR-x1500 were the suitable single vehicles for the manufacturing. Five vehicles, except STAR-x1500, produced tablets of fairly long disintegration times (120 min), while the other vehicle could not compress diiodoquin. The results showed that blending of Avicel or Celutab with STAR-x1500 improved the physical standards of the produced tablets. Other than being

0363-9045/85/1104-0945$3.50/0

a powerful disintegrant, STAR-x1500 could recover the disintegrating effect of Avicel. On the other hand, the reduction in disintegration times of the tablets compressed with STAR-/Celutab blends, was due to the incorporation of STAR-x in the formulations.

In such a case of noncompressible drug, a large concentration of a binary blended vehicle was needed to compress tablets of good physical characters. The least concentration needed to compress diiodoquin into tablets was not less than 42.0% w/w.

INTRODUCTION

As it is best tabletting technique, direct compression was used to manufacture diiodoquin tablets. Unlike other techniques, for example wet granulation, direct compression consists of two steps, mixing the drug with the proper quantity of carefully selected vehicles and lubrication with a suitable lubricant. Earlier, many studies were done, to point out the advantages of the technique in terms of its simplicity (1), stability of the products (2) and their biological activity (3). Physicochemical interactions, like mottling of coloured products, drug migration (2) hydrolysis, oxidation or/and reduction, might happen, during the long steps of classical wet granulation method, are prevented with this technique (1) Therefore, great efforts were done to contribute various direct compression vehicles to the tabletting e.g.

Avicel pH 101) (4, 5), anhydrous lactose USP (6), directly compressible starch (7, 8) and dicalcium phosphate dihydrate (9).

In spite of its advantages, direct compression has its limitations. These limitations are greatly related to the physical characters of the tabletted materials. Moreover, the particle size and density variations and the bulk of the active material(s) control to a great extent, the application of the direct technique. In addition to that, Henderson and Bruno (10) found that no single material was suitable for all direct compression formulas.

In this report, six direct compression vehicles and their binary blends in different ratios were used to compress diiodoquin directly into tablets. We suggested the evaluation of the physical standards of the produced tablets prior to testing the in vitro availability and stability of the tabletted drug.

EXPERIMENTAL

Materials: The direct compression vehicles used were: microcrystalline cellulose (Avicel pH 101)[1], directly compressible starch (STAR-x1500)[2], sugartab[3], celutab[3], dicalcium phosphate dihydrate (Emcompress)[3] and anhydrous lactose[4]. Magnesium stearate[5] and stearicacid[5] were used as lubricants. Diiodoquin[5], the active ingredient was used as received from the manufacturer.

METHODS

Physical standards, the mean particle size bulk density and angle of repose of the powdered drug and vehicles were evaluated using the previously reported methods (11) and the results are shown in Table 1.

Five batches containing 0.0, 19.6, 32.6, 42.0 and 49% w/w of a given vehicle were formulated by simple mixing using suitable drum mixer, in each case. The batches were lubricated with 2% w/w of magnesium stearate except, in the case of STAR-x formulations, stearic acid was used, to produce harder tablets (7). On the bases of (HFR) of the tablets compressed with single vehicles (3.12) Avicel, Celutab and STAR-x1500, were selected to be binary blended with the rest and evaluated. The binary blended vehicles in ratios of 1:1, 1:3 and 3:1 were contributed to the formulations using the same levels of concentrations applied for single vehicle formulations.

A Manesty[I] single punch eccentric tabletting machine was used to compress the formulated batches. Flat tablets, each of a diameter of 6.4 ± 0.01 mm and of an average weight of 0.1 g. were produced. At the beginning, the machine was adjusted to compress tablets of least possible loss % (Friability) and of highest possible hardness from the formula containing 49.0% w/w of a given vehicle or blend. The machine settings were kept constant to compress the rest formulations of the same vehicle or blend. Again the machine was readjusted to compress the formulations of the next vehicle or blend. This is to avoid the effect of

Table 1: Physical Properties Of Powdered Diiodoquin and Direct Compression Vehicles.

Material	Average particle size (u)	Packed bulk density g/cc	Angle of repose
Diiodoquin	38.15	0.43	54° 18"
Avicel	82.99	0.355	48° 00"
Anhydrous Lactose	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"

particle size and density variations (13). A minimum of 1000 tablets were compressed from each batch.

The uniformity of weight of the compressed tablets was tested to comply with B.P. 1973. Baty dial micrometer[II] was used to determine the thickness of the produced tablets. Their crushing strength and friability were determined using Erweka Hardness Tester[III] and Roch Friabilator[III] respectively. A disintegration test apparatus[IV] (B.P. 1968) was used to determine the disintegration times. All physical standards were determined according to the previously published procedures (13).

RESULTS AND DISCUSSION

In such a case of formulation, the physical standards of the tablets compressed with single or binary blended

vehicle should be compared with these standards of the control tablets which contain no vehicle. Unfortunately, the control tablets could not be compressed except, in few cases using higher compression forces. This may be attributed to the bad flow properties of drug mixes or/and the poor compressibility of the drug. Therefore, in this report, the physical standards of the tablets compressed with the least concentration of a given vehicle was taken as a guide line to evaluate that tablets compressed with the higher concentrations of the same vehicle.

Uniformity of Weight:

Although, Richman et. al. (4) recommended Avicel as an excellent direct tabletting vehicle, Table 2 shows that the tablets compressed with this vehicle were not uniform in weight. This may be attributed to its bad flow properties. In a comparative study on Avicel grads[14] it was found that this pH 101 grade consists of smaller irregular rode shaped interlocking particles which creat a great resistance to flow. In addition to that, it must be taken in consideration the particle size and density variations and poor compressibility of diiodoquin as effective factors. However, in this table, it is shown that C.V % decreased by increasing the Avicel concentration in the formula, i.e. the increase in Avicel concentration in the formulation decreased the weight variations. On the other hand, anhydrous lactose USP, in higher concen-

Table 2: Physical Characteristics Of Directly Compressed Diiodoquin Tablets With Single Vehicles

Vehicle		Weight(g)		Thickness(mm)		Hardness, Friab.	Disint. Time (min.)	
Name	Conc.% W/W	Mean	C.V.%	Mean	C.V.%	Ratio(HFR)	Mean	C.V.%
	00.00	—	—	—	—	—	—	—
	19.60	0.078	2.07	2.01	1.38	0.39	120	
Avicel	32.60	0.084	1.95	2.10	0.50	0.60	56.74	28.99
	42.00	0.084	1.55	2.12	0.52	0.74	68.72	16.69
	49.00	0.1131	1.04	2.49	0.47	2.65	105.34	15.02
	00.00	—	—	—	—	—	—	—
Anhydrous	19.60	—	—	—	—	—	—	—
Lactose	32.60	0.0897	9.70	2.35	0.56	0.39	106.73	1.39
USP	42.00	0.0990	1.14	2.39	1.86	0.50	83.63	13.78
	49.00	0.1050	1.75	2.44	1.19	0.96	77.03	12.38
	00.00	—	—	—	—	—	—	—
	19.60	—	—	—	—	—	—	—
Celutab	32.60	0.096	3.00	2.42	0.71	0.15	18.59	11.17
	42.00	0.112	1.35	2.46	2.02	1.06	68.46	48.20
	49.00	0.107	3.65	2.51	2.26	1.78	71.56	19.43
	00.00	—	—	—	—	—	—	—
	19.60	—	—	—	—	—	—	—
Sugartab	32.60	0.096	8.86	2.40	2.30	0.133	120	
	42.00	0.110	4.09	2.47	1.78	0.530	120	
	49.00	0.115	6.05	2.44	1.94	0.550	120	
	00.00	0.078	3.68	1.86	1.92	0.130	120	
	19.60	0.091	2.17	1.99	0.63	0.390	14.45	8.5
$STAR_x$	32.60	0.096	2.13	2.20	2.41	0.420	10.29	5.16
	42.00	0.108	1.80	2.31	1.04	1.040	9.14	14.97
	49.00	0.110	1.71	2.34	0.73	1.380	9.03	10.38

tration, produced uniform tablets (2). In fact this vehicle was recommended by Mendell (1) to compress non-compressible materials. He found that this lactose has ability to compress about 30-35% of non-compressible drugs. Moreover, the excellent flow properties of lactose USP (6) is strongly suggested cause for the tablet uniformity. This concept is quite clear in the case of STAR-x, a freely flowing vehicle. All formulations of this vehicle produced uniform tablets. Although, they are freely flowing vehicles, Celutab and sugartab (vehicles of larger particle sizes) did not produce uniform tablets. This may be attributed to the segregation observed during the compression. In contrast to this Emcompress failed to compress diiodoquin into tablets. Logically, the incorporation of a second vehicle in the formulation modifies the properties of the whole mix which of course affect the physical standards of the produced tablets. Through the work it was observed that tablets compressed with Avicel/anhydrous lactose 1:1 binary blend, were of larger weights, and only two batched were uniform. This supports that the incorporation of anhydrous lactose increased the flow properties of the mix. At small concentrations (19.6 and 32.6% w/w) of this blend much more uniform tablets were compressed. More or less, the same results were obtained in the case of Avicel/STAR-x 1:1 binary blend. The other binary blends of Avicel with anhydrous lactose or STAR-x did not produce uniform tablets.

On the other hand, Emcompress when it is blended with Avicel, its ability to compress diiodoquin was recovered. But the problem was still, non-uniform tablets were compressed, from 1:1 binary blend. Only two batches from 1:3 and three batches from 3:1 of Avicel/Emcompress binary blends were produced. In contrast to this, the incorporation of Avicel with sugar vehicles (celutab and sugartab) could improve their tabletting properties. Much more uniform tablets could be compressed from 1:1 binary blends of Avicel/Celutab or Avicel/sugartab. Noticeably, the increase in the ratio of Celutab or sugartab in the blend lead to seggregation which increased the weight variations of the compressed tablets.

Generally STAR-x or celutab blends (1:1) in small conventrations (19.6, 32.6% w/w) produced uniform tablets. The uniformity of thickness which is an additional control to the tablet dimensions (13), was evaluated. Both single and binary blended vehicles produced tablets of the same variations in thickness, more or less parallel to variations in weight. This is clearly shown in Tables 2 and 3.

Crushing Strength:

Figure 1 shows that the crushing strength of the produced tablets was dependent on the concentration of the vehicle used in the formulation. In this order Avicel, STAR-x1500 and celutab, produced the hardest tablets, and this may be attributed to their high pressure hardness profiles (5,7,13).

Table 3: Physical Characteristics of Directly Compressed Diiodoquin Tablets with STAR-$_x$ Binary blends(1:1)

Vehicle Name	Conc.% W/W	Weight(g) Mean	Weight(g) C.V.%	Thickness(mm) Mean	Thickness(mm) C.V.%	Hard. Friab. Ratio(HPR)	Disint. Time (min.) Mean	Disint. Time (min.) C.V.%
STAR$_x$ / Anhydrous lactose	00.00	—	—	—	—	—	—	—
	19.60	0.096	2.52	1.94	0.74	0.55	108.42	20.85
	32.60	0.106	2.55	2.07	1.07	0.69	24.51	5.97
	42.00	0.117	2.58	2.20	1.29	0.05	23.80	11.75
	49.00	0.129	0.86	2.39	1.19	11108	15.55	9.46
STAR$_x$ / Emcompress	00.00	—	—	—	—	—	—	—
	19.60	—	—	—	—	—	—	—
	32.60	—	—	—	—	—	—	—
	42.00	0.119	0.209	2.34	0.8	1.07	4.17	38.40
	49.00	0.124	0.236	2.44	0.76	1.55	4.18	11.93
STAR$_x$ / Celutab	00.00	—	—	—	—	—	—	—
	19.60	—	—	—	—	—	—	—
	32.60	—	—	—	—	—	—	—
	42.00	0.103	3.811	2.41	1.03	0.69	13.311	9.40
	49.00	0.103	2.530	2.32	1.76	1.38	12.99	4.41
STAR$_x$ / Avicel	00.00	0.0781	1.37	2.43	0.50	0.34	>120	
	19.60	0.1040	0.99	2.49	1.69	0.45	4.38	9.87
	32.60	0.106	2.12	2.54	1.86	0.75	2.44	20.16
	42.00	0.119	1.08	2.70	1.29	1.68	1.64	24.26
	49.00	0.1184	1.51	2.64	0.99	2.40	1.42	6.23
STAR$_x$ / Sugartab	00.00	—	—	—	—	—	—	—
	19.60	0.085	2.45	2.19	1.47	0.26	>120	
	32.60	0.1023	2.74	2.30	2.30	1.80	20.21	35.31
	42.00	0.1174	4.73	2.44	1.51	0.51	17.00	10.15
	49.00	0.1180	4.33	2.51	1.39	1.41	13.09	9.69

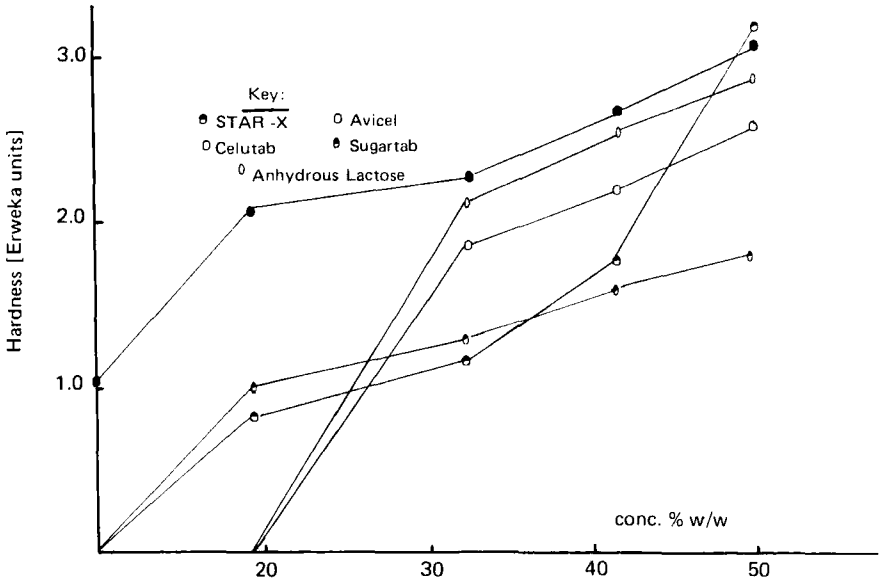

Figure 1. Effect of Various Concentrations of Different Direct Compression Vehicles on the Hardness of Directly Compressed Diiodoquin Tablets

In fact Sixsmith (14) gave an excellent interpretation for the extreme hardness of the compressed tablets with Avicel. He found that Avicel particles (Match stick like bundles) are easily intermished under slight compression, and the numerous sites of hydrogen bonding found in the molecule, enable the finished tablets to exhibit extreme hardness. The high crushing strength of tablets formulated with sugar vehicles, celutab and sugartab, may be attributed to the hardening effect of these vehicles (1). Although STAR-x1500 could compress diiodoquin, the produced tablets were suffering from chipping and in few cases friable tablets were observed.

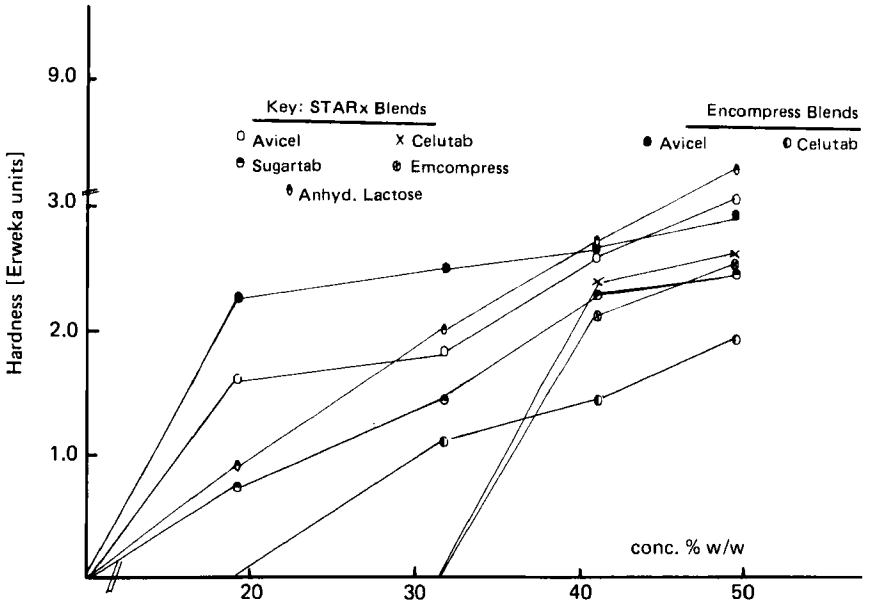

Figure 2. Effect of Various Concentrations of STAR-x and Emcompress (1;1) Binary Blends with other Vehicles on the Hardness of Directly Compressed Diiodoquin Tablets

In Figure 2, it is shown that the incorporation of Avicel or STAR-x1500 as a second vehicle in the formulation, increased the hardness of the produced tablets, and this is due to synergistic effect of these vehicles. The most satisfactory 1:1 blends to produce hard tablets were:

STAR-x/Anhydrouslactos > Avicel/Anhydrous Lactose > Celutab/Anhydrous lactose

Friability

Figures 3 and 4 show that the compressed control tablets were soft and friable. This is due to the

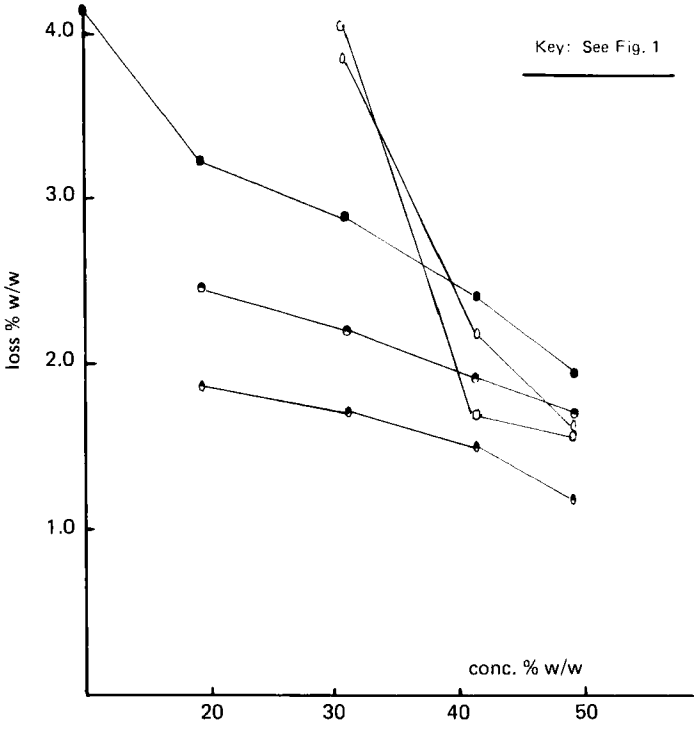

Figure 3. Effect of Various Concentrations of Different Direct Compression Vehicles on Friability of Directly Compressed Diiodoquin Tablets

Emcompressibility of diiodoquin. On the other hand, Emcompress failed singly to compress diiodoquin tablets. Due to their binding properties and high pressure hardness profiles, Avicel and Celutab produced the least friable tablets. In contrast to Batvuios's results (6), ours showed that Anhydrous lactose produced much more friable tablets. Some batches formulated with small concentrations of STAR-x1500 were suffering from capping and this may be due to the high compression force used or/and smaller pressure-hardness profile of this vehicle. On the other

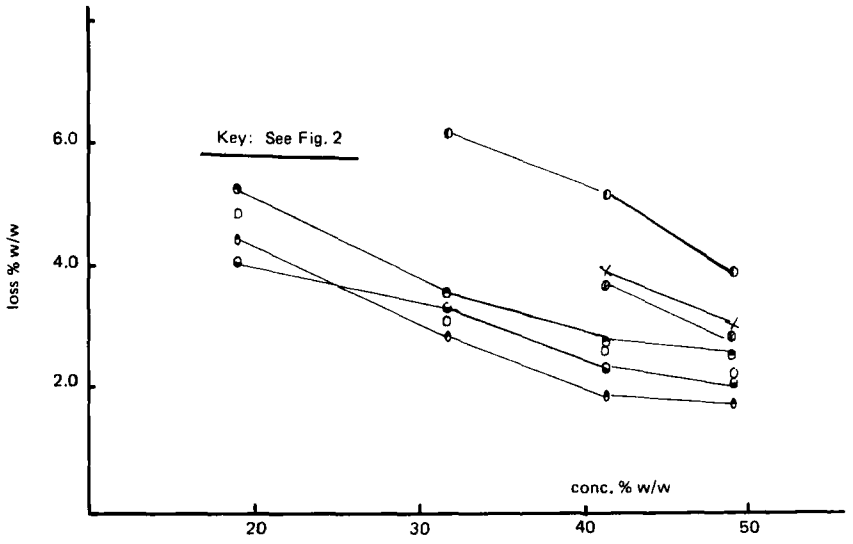

Figure 4. Effect of Various Concentrations of STAR-x and Emcompress (1;1) Binary Blends with other Vehicles on the Friability of Directly Compressed Diiodoquin Tablets

hand, Figure 4 confirms that the incorporation of a second vehicle in formulation, modified the tabletting properties. It is shown in this figure that blending with Avicel, Celutab or STAR-x reduced the friability of the produced tablets due to their synergistic effects.

Disintegration Time:

Table 2 and 3 show that all compressed tablets disintegrated within fairly long disintegration times (120 min.), except those tablets formulated with STAR-x_{1500} or its binary blends with Avicel or Emcompress (in all different ratios) or with celutab (in ratios of 1:1 and 3:1), disintegrated within short

times to comply with pharmacopeal limit (15 min. - B.P. 1973).

Generally, due to the insolubility of diiodoquin (15) and the high compression pressure used, single vehicles, except STAR-x, produced tablets of long disintegration times. Although it was reported that the contribution of Avicel to the tabletting reduced the disintegration times (5) its contribution to diiodoquin tabletting did not show this effect. Solvange and Pinhold (15) strongly suggested the extreme hardness of their tablets prepared with this vehicle, as the most important parameter controlling the disintegration and dissolution. In addition to that, the presence of hydrophobic lubricant (2% w/w magnesium stearate) offered hydrophobic protection which retarded the wetting and water penetration inside the tablet structure (17). As it is a powerful disintegrant (7,8) STAR-x 1500 single or in binary blends reduced the disintegration times of the tablets. Of course, one can expect that the reduction in disintegration times increased by increasing the concentration of this starch in the formula. In the same Table 3 it is shown that the incorporation of STAR-x in the formulation with Avicel, recovered the disintegration effect of this cellulose. In another words, the reduction in disintegration times of the tablets compressed with Avicel/ STAR-x blends was dependant on the Avicel concentration in the formula. In these formulations, starch facilitated

the tting of the tablets (swelling mechanism) which would recover the capillary phenomenon of Avicel particles. In contrast to this, the incorporation of celutab with STAR-x in formulations reduced the disintegration times of the produced tablets, but their disintegration times were longer. Although, celutab is soluble vehicle, the reduction in disintegration times was greatly dependent on STAR-x concentration in the formula i.e. celutab did not show disintegrating effect.

CONCLUSION

From this investigation, it is concluded that direct compression can be used to manufacture diiodoquin tablets. To apply this advanced technique, a large concentration of selected binary blended vehicles should be used. Our results were in agreement with Henderson and Bruna findings (10), who stated that no single material can be used for all formulations. Generally all vehicles except STAR-x produced tablets of fairly long disintegration times. In this report, it was proved that the blending of STAR-x in the formulation with Avicel produced satisfactory tablets. In these formulations, STAR-x recovered the disintegration effect of Avicel. In contrast to this, celutab, when blended with STAR-x, did not reduce the disintegration times of the compressed tablets. The best binary blends needed to manufacture diiodoquin

tablets of good and reasonable physical standards were Avicel/STAR-x in all different ratios.

FOOTNOTES

1. FMC Corporation, Avicel department, Pennsylvania, USA
2. Staley Mfg. Co., Ill, USA
3. E. Mendell Co. Inc., USA
4. Shiffield Union, N.L. 07083, USA
5. Chemical Industries Development, 'Cid' Co., Assiut Branch Assiut, Egypt.

I. Manesty Machines Ltd., Liverpool, England
II. Model 120-1206, Baty Co. Ltd., Sussex, England
III. Erweka-Apparatebau, Frankfurt, West Germany
IV. El. Gomhoria Co. Ltd., Cairo, Egypt.

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17. H. C. Caldwell and W. J. Westlake, ibid, 61, 984 (1972).