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IN VITRO EVALUATION OF COMMERCIAL ASPIRIN TABLETS MARKETED IN YUGOSLAVIA

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ABSTRACT

Selected 34 batches of 13 brands of 3 types of aspirin tablets were compared with respect to contents of aspirin and salicylic acid, in vitro dissolution characteristics, weight variation, disintegration time, crushing strength and friability. The results indicated that there was significant difference between brands, but between batches of the same brand as well. The greatest disagreement with the official requirement was obtained when dissolution characteristics were evaluated (only 41.93% of batches complied with the USP XXI specifications).

INTRODUCTION

In order to ascertain the quality and equivalency of products, aspirin-conatining preprations were evaluated and compared worldwide with respect to their in vitro dissolution characteristics, as well as with respect to contents of aspirin (acetylsalicylic acid-ASA) and salicylic acid (SA) and their physical properties. Juhl and Kirchhoefer conducted a national survey of aspirin tablets in USA (1) and Keseru et al. studied in vitro equivalence of several ASA tablets in Hungary (2). Blume and Siewert performed a comparative serial investigation of the pharmaceutical quality of 14 batches

of 11 types of commercial ASA-mono-preparations in Germany (3), while Bardakov, Tentsova and Kiseleva did the assesment of aspirin tablets in USSR (4). In all those papers differences between brands and even between batches(4) were reported.

In this paper a survey of aspirin tablets marketed in Yugoslavia was conducted in order to see is there any significant difference between different types of tablets, between brands of the same type of tablets and between batches as well.

EXPERIMENTAL

Materials

In this study the following tablets were used:

- 19 batches of 7 commercialy available products of 500 mg plain aspirin tablets, identified as A_{1-5}; B_{1-5}; C; $D_{1,2}$; $E_{1,2}$;$F_{1,2}$; $G_{1,2}$[☆]
- 3 batches of 2 brands of 500 mg aspirin tablets containing ethylcellulose walled microcapsules, identified as $H_{1,2}$ and I[☆]
- 6 batches of 2 brands of 100 mg plain tablets, namely J_{1-4} and $K_{1,2}$[☆]
- 5 batches of 2 products of 300 mg buffered tablets, identified as L_{1-5} and M[☆].

Products A,B,J and L are the most commonly used, and that's why in those instances 4 or 5 batches were evaluated.

Methods

a) ***Weight variation***: Weight variation was determined according to the Ph. Jug. IV (5).

b) ***Assay***: A high pressure liquid chromatographic method was used to quantitate ASA and SA in tablets. The method applies β naphtol' as internal standard. Mixture

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☆
A_1-batch no. 0490587, A_2-0940687, A_3-3180987, A_4-2610887, A_5-4781287
B_1-44650887,B_2-47740987, B_3-22040484, B_4-58381087
B_5-12010188
C -421024
D_1-406127, D_2-425038
E_1-005-0687, E_2-007-0787
F_1-12260387, F_2-11740287
G_1-35510784 42, G_2-00260287 107
H_1-02640487, H_2-0480587
I -NZ 552L
J_1-505066, J_2-981037, J_3-686126, J_4-5100188
K_1-601-0587, K_2-11197-01
L_1-149126, L_2-97029,L_3-329097, L_4-127117, L_5-258057
M -03190287

of formic acid[2] and methanol[3] was used for extraction. The chromatographic unit consisted of: pump[4], LC controller[5], injector equipped with 10 µl loop[6], reverse phase 10 µm microparticulate column[7], attached to diode array rapid spectral detector with 5 mm flow cell[8]. Peak areas were measured at 290 nm with a reporting integrator[9]. The mobile phase was methanol:water: 1 M phosphoric acid[3] = 60:35:5 (pH=2.6).

c) ***Disintegration time***: The disintegration time was measured at 37±0.5 ℃ in distilled water, using disintegration test apparatus[10].

d) ***Crushing strength***: The crushing strength was determined after 5, 10, 20 and 30 min of rotating in the friabilator[12] at 20 rpm.

f) ***Dissolution rate study***: The dissolution test was performed by the rotating basket method[13], according to the USP XXI (6).The guidelines for dissolution testing were followed throughout the dissolution study (7). A 3 ml samples were withdrawn after 30 min of dissolution, filtered[14] and analyzed UV spectrophotometrically[15] at 268 nm.

In case when microencapsulated tablets were evaluated, drug release over 90 min was followed. To compensate the samples withdrawn volumes of 3 ml of acetate buffer at 37±0.5 ℃ were added to the medium.

RESULTS AND DISCUSSION

The average weight of tablets and the average amount of ASA and SA per tablet are summerised in Table 1, while the results for disintegration time, crushing strength and dissolution are presented in Fig. 1 and 2.

Weight variation

All our results complied with the specified limitations of the number of test tablets that may lie outside certain limits (5), indicating the homogenity of batches.

Content of aspirin and salicylic acid

The aspirin contents of 23 batches (expressed as % of declared content) ranged from 82.57% (G_2) to 114.70% (E^1), while SA contents (expressed as % of declared ASA content) ranged from 0.08% (B_2,J_4) to 2.11% (K_1).

Only 56.52% of batches had the ASA content within specified limits (±8% for 100 mg plain tablets; ±5% for others)(5), and only one batch (E_1) had the amount of aspirin greater than the upper limit.

For 14 of 21 batches (66.67%) of plain tablets with valid shelf life not more than 0.3% of SA was found and they complied with the official specification (6). The highest values for SA content had batches E_1 (1.23%) and K_1 (2.11%), produced by the same company.

TABLE 1. Weight variation, ASA and SA Contents of Commercial Aspirin Tablets

Product	*Tablet weight (g)*		*ASA content (% ASA declared)*	*SA content (% ASA declared)*
	Mean	*S.D.*		
A_1	0.5878	0.0046	98.01	0.13
A_2	0.5886	0.0032	92.46	0.11
A_3	0.5953	0.0041	97.86	0.11
A_4	0.5911	0.0044	98.98	0.18
A_5	0.5949	0.0043	94.59	0.06
B_1	0.5555	0.0161	96.77	0.11
B_2	0.5692	0.0259	96.31	0.08
B_3	0.5644	0.0196	80.02[+]	0.12[+]
B_4	0.5642	0.0155	92.38	0.07
B_5	0.5512	0.0155	94.17	0.09
C	0.5860	0.0111	63.59[+]	0.22[+]
D_1	0.5770	0.0053	92.81	0.58
D_2	0.5728	0.0136	92.38	0.56
E_1	0.6710	0.0081	114.70	1.23
E_2	0.6617	0.0109	95.94	0.67
F_1	0.5581	0.0112	94.97	0.13
F_2	0.5609	0.0091	92.85	0.22
G_1	0.7231	0.0074	82.46[+]	0.30[+]
G_2	0.7214	0.0100	82.57	0.33
H_1	0.5909	0.0797	100.02	0.95
H_2	0.5943	0.0061	103.02	0.83
I	0.6016	0.0045	84.87[+]	1.13[+]
J_1	0.2820	0.0017	93.24	0.44
J_2	0.2840	0.0016	98.51	0.14
J_3	0.2802	0.0018	107.47	0.11
J_4	0.2830	0.0017	99.75	0.08
K_1	0.1948	0.0017	95.04	2.11
K_2	0.1992	0.0029	79.16[+]	4.44[+]
L_1	0.4183	0.0106	76.30[+]	3.46[+]
L_2	0.4215	0.0040	76.48[+]	2.26[+]
L_3	0.4173	0.0059	81.95[+]	3.14[+]
L_4	0.4157	0.0079	89.64[+]	4.60[+]
L_5	0.4164	0.0089	83.57[+]	3.44[+]
M	0.4440	0.0125	81.06[+]	6.47[+]

[+] ASA and SA contents were determined after the stated expiration date

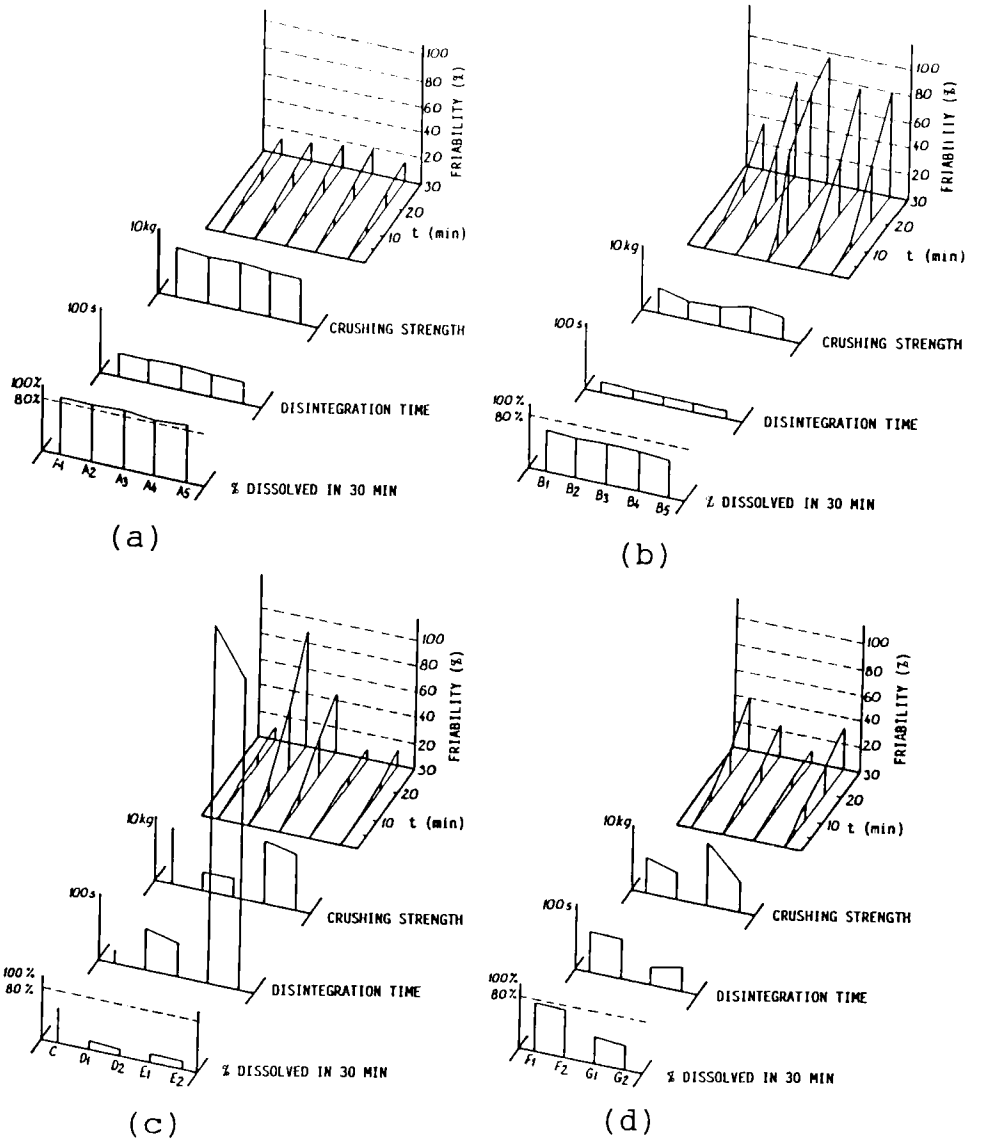

FIGURE 1

Dissolution and physical properties of 500 mg plain tablets: a)product A, b)product B, c)products C,D and E d)products F and G

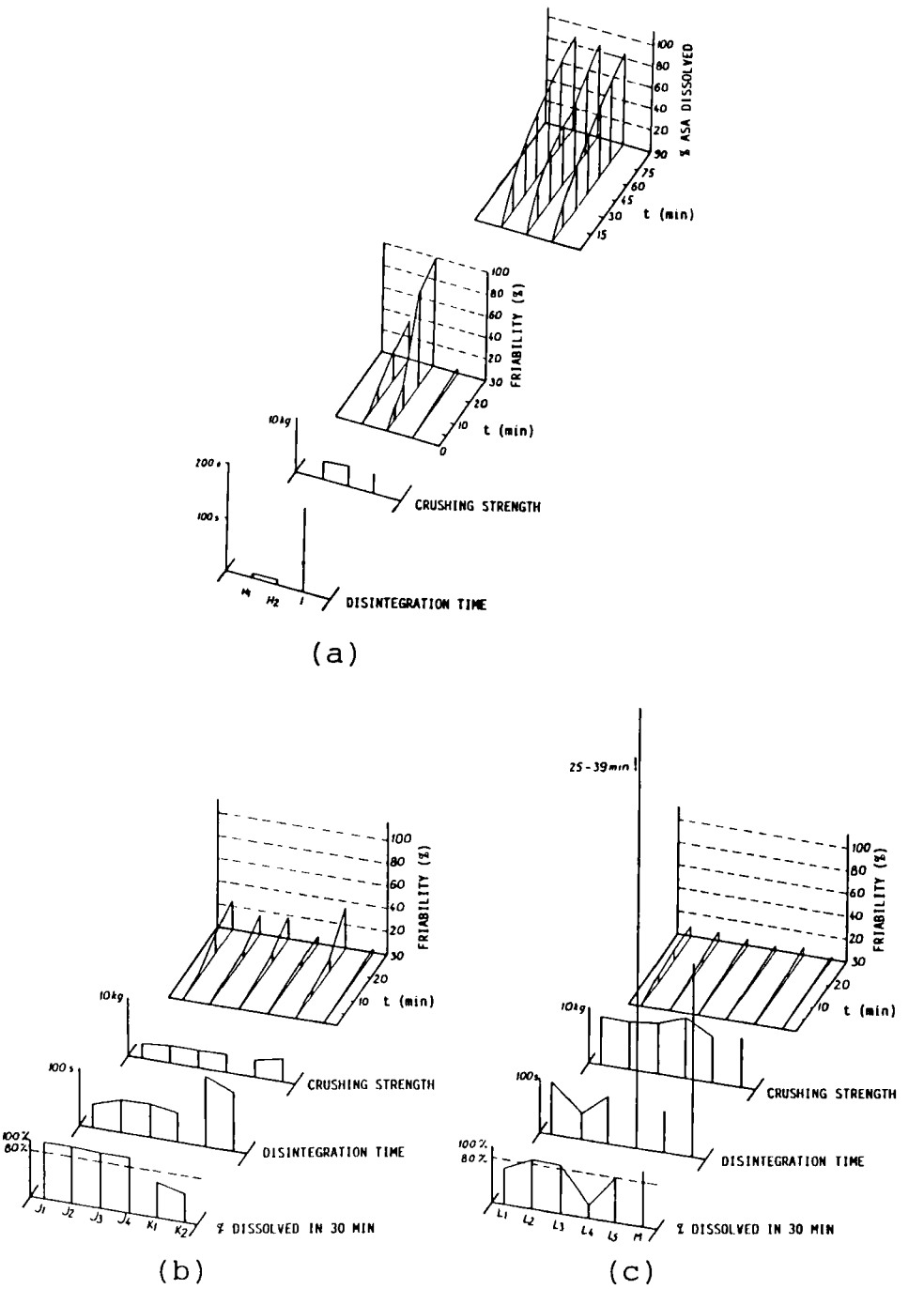

FIGURE 2

Dissolution and physical properties of: a)500 mg micro-encapsulated tablets (products H and I); b)100 mg plain tablets (products J and K); c) 300 mg buffered tablets (products L and M)

Considering microencapsulated tablets to be coated tablets, for which 3% of SA is allowed, all three batches of microencapsulated tablets applied with the USP requirement (6).

The products which were assayed after the expiration date had less content of ASA and gretaer content of SA, indicating the degradation of ASA during storage.

Comparison of the results obtained for product L showed that the gretaest content of ASA, but of SA as well, had batch L_4, the "youngest" among them. It was possible that the released SA left the sample area through sublimation and could not be measured in case of "older" tablets (8).

Disintegration time

For all batches but one (L_4) the obtained disintegration times complied with the official specification.

Dissolution

Even 58.07% of plain and buffered tablets failed the proposed USP requirement. It was observed during the dissolution test of products D and E that tablets did not disintegrate at all, although they passed the disintegration test. These results illustrate that the agitation intensity produced by the rotating basket method is very poor at rather low stirring speed (50 rpm), which is in agreement with results of other autors (9). Out of all tablets studied, only in case of batch L_4 disintegration had been shown to be rate determining step in dissolution, as disintegration times of longer than 25 min were measured (Fig. 2c).

Microencapsulated tablets gave more-less similar dissolution profiles (Fig. 2a).

Hardness

Mean crushing strength values ranged from 2.83 kg (batch J_1, Fig. 2b) to 10.82 kg (batch L_4, Fig. 2c).

Friability

Only 9 batches (B_4, E_1, I, J_4, K_2, L_3, L_4, L_5 and M) complied for friability with the accepted standards (10).

Comparison between brands and batches

Results obtained for 500 mg plain tablets showed significant differences between brands in every investigated parameter (Fig. 1). The highest batch to batch consistency was observed for product A (Fig. 1a), although those batches differed in ASA content (Table 1). It isastounding that, out of 19 selected batches of 500 mg plain tablets, only batches of product A gave more than 80% dissolved after 30 min.

Percentage dissolved after 30 min (P_{30}) for products D and E was in the range of 9 to 13 (Fig. 1c) implying that the potential bioavailability of these products is questionable.

Both batches of product F showed similar behavior, while differences between batches of brand G were more pronounced (Fig. 1d).

Slight differences between batches with respect to tablet hardness and great differences with respect to tablet friability implied that very often correlated hardness and friability of tablets could not be compared in case of microencapsulated tablets (Fig. 2a).

Comparison of 100 mg plain tablets also pointed to inequivalency of different products (Fig. 2b). The differences were most pronaunced for disintegration time and P_{30}. There was no correlation between hardness and friability values.

Differences between batches were observed for buffered tablets as well (Fig. 2c). The most considerable differences between batches of brand L were exibited with respect to disintegration time and P_{30}.

Heterogenous results obtained for any investigated parameter clearly established the differences between different products, brands and even batches, indicating that tablet properties are markedly affected by the tablet formulation and the tablet process conditions.

FOOTNOTES

[1] Carlo Erba, Milano, Italy
[2] Sigma Chemie GmbH, Deisenhafen, Germany
[3] A. Merck, Darmstadt, Germany
[4] *2152 HPLC Pump*, LKB, Bromma, Sweeden
[5] *2152 LC Controller*, LKB, Bromma, Sweeden
[6] Rheodyn, California, USA
[7] *Ultrapack Rp-18 Column (4x200 mm)*, LKB, Bromma, Sweeden
[8] *Dyode Array Rapid Spectral Detector*, LKB, Bromma, Sweeden
[9] *PC Data Print Personal Monitor*, Phillips, England
[10] *Disintegration Test Apparatus, Type ZT3*, Hausenstamm, Germany
[11] *Hardness Tester, Type TB 24*, Erweka, Hausenstamm, Germany
[12] *Friability Tester, Type TA3*, Erweka, Hausenstamm, Germany
[13] *Dissolution Test Apparatus, Type DT6*,Erweka, Hausenstamm,
[14] *Filter Type SM 11107*, Sartorius, Göttingen, Germany
[15] *UV Spectrophotometer, Specord M 40*, Carl Zeiss Jena, Germany

REFERENCES

1. W.E Juhl and R.D. Kirchhoefer, *J. Pharm. Sci.*,69,968(1980)
2. P. Keseru, T.L. Paàl, E. Varsànyi, E. Kiss Csikkos, *Acta Pharm. Hung.*,55, 180, (1985)
3. H.Blume und M. Siewert, *Pharm. Ztg.*, 131, 2953 (1986)
4. A.I. Bardakov, A.I. Tentsova, G.S. Kiseleva,*Farmacyia (Moskow)*,36, 37, (1987)
5. *Pharmacopoea jugoslavica, editio quarta (Ph. Jug. IV)*, Savezni zavod za zdravstvenu zastitu, Beograd, 1984

6. *The United States Pharmacopeia, 21st rev*,United States Pharmacopeial Convection, Inc., Rockville, 1985
7. D.C. Cox, C.L. Douglas, W.B. Furman, R.D. Kirchhoefer, *Pharm. Technol.*, 2, 41, (1978)
8. C.A. Kelly, *J. Pharm. Sci.*, 59, 1053 (1970)
9. M.R. Baichwal, S.G. Deshpande, U.C. Shetty, *Drug Dev. Ind. Pharm.*, 11, 1639, (1985)
10. K.Marchall and E.M.Rudnic, "Tablet Dosage Forms" in *"Modern Pharmaceutics"*, G.S.Banker and C.T.Rhodes, eds., Marcel Dekker Inc., New York, 1990, p. 355