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RESEARCH PAPER

A Stability Study of Ticlopidine Products from 18 Countries

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ABSTRACT

The results of the stability study of ticlopidine formulations (250 mg and 100 mg) show that products available in many countries worldwide exhibit different stability characteristics. Stability testing under the International Conference on Harmonisation (ICH) accelerated test conditions (40°C/75% relative humidity [RH], 3 and 6 months) was performed on a total of 43 products obtained from 18 countries. The samples were visually examined for physical change and analyzed for their content of degradation products, remaining ticlopidine, and in vitro dissolution characteristics (in the case of tablets). Only 6 (16%) of all the samples submitted to this study had a good stability profile. Their appearance remained unchanged during the study; assay results were between 95% and 100%; their impurity content did not exceed 0.25%; and in the dissolution test, at least 75% of ticlopidine was dissolved after 30 min. Three samples had excellent dissolution properties and showed a very high purity level (viz. 21, 40, and 43) over the course of the study.

Key Words: *Liquid chromatography; Products; Stability; Survey; Ticlopidine.*

INTRODUCTION

Ticlopidine is a thieno-[3,2-c]-pyridine derivative synthesized in 1972 by Sanofi Recherche (1). According to pharmacological studies, ticlopidine is an effective inhibitor of platelet aggregation. The drug is used for the prevention of major ischemic events (stroke, myocardial infarctions, vascular death) in patients with cerebral infarction and for transient ischemic attack or peripheral arterial disease. Recently, it has also been used for the prevention of occlusion of coronary stents and bypass grafts (2–6). In the literature, only two papers could be

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found; these were related to assay and purity control for two process-related impurities and employed thin-layer chromatography or capillary electrophoresis (7,8). No thorough study of the stability of drug products has been reported. Therefore, the aim of our work was to provide a comparative study of the stability of ticlopidine in products marketed in different countries. To provide a reliable basis for comparison of the stability within a reasonable timescale, accelerated testing conditions in accordance with those put forth by the International Conference on Harmonisation (ICH) were adopted, i.e. 40°C ± 2°C/75% ± 5% relative humidity (RH) for a maximum period of 6 months.

EXPERIMENTAL

Solvents and Reagents

The following solvents and reagents were used: methanol (Rathburn high-performance liquid chromatography [HPLC] grade, Walkerbutn, Scotland) and analytical reagent grade sodium 1–pentanesulfonic acid (Merck, Darmstadt. Germany), sodium chloride (BDH), phosphoric acid (Riedel-de Haen, Sulze, Germany), and hydrochloric acid (Fisher Scientific, Loughborough, UK). Ticlopidine hydrochloride and its related compounds were supplied by Sanofi Chimie, Gentilly, France (see Fig. 1).

Samples

A total of 43 products (37 tablet and 6 capsule formulations) in their original packages were purchased from 18 different countries. The tested products are listed in Table 1, which includes country of origin, manufacturer, and (when known) the batch number and expiry date.

Appearance

The visual examination of the tablets and capsules was assessed by viewing them against a white background in normal daylight. Any change was noted.

Assay and Content of Impurities

The assay of ticlopidine and the analysis of the content of impurities were carried out by gradient high-performance liquid chromatography (LC). The LC system consisted of a Merck-Hitachi L-6200 Intelligent pump, a Marathon autosampler (Spark Holland) equipped with a 10 µl loop; a 150 × 4.6 mm i.d. Waters Symmetry® C_{18} 5-µm particle size reversed-phase column, a L-4000 UV-Vis (ultraviolet-visible) Merck-Hitachi detector set at 220 nm, and a Hewlett-Packard integrator model HP 3396A series II. The column temperature was maintained at 40°C by a water bath heated by a Julabo EM thermostat.

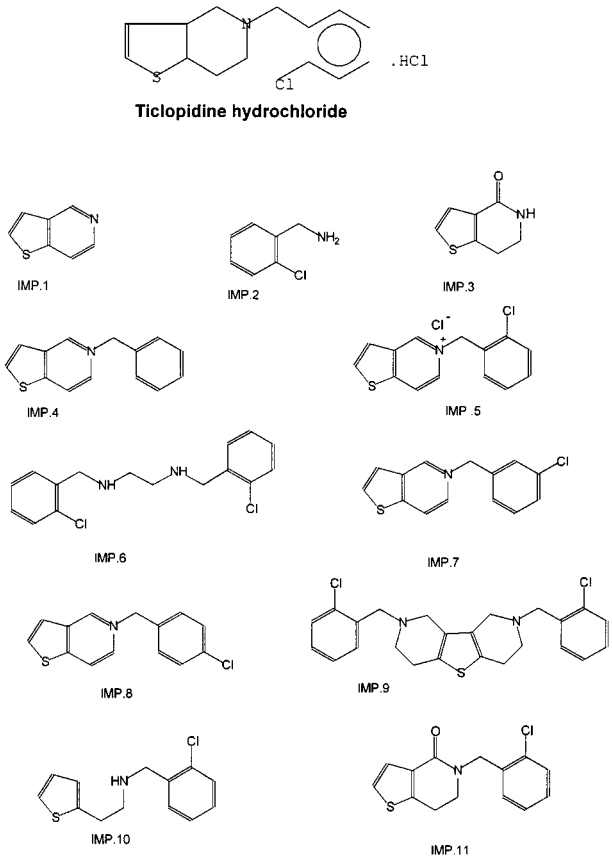


Figure 1. Chemical structure of ticlopidine (TP) and its related substances.

Mobile phase A was an aqueous mixture of 5 mM sodium 1-pentanesulfonic acid solution adjusted to pH 2.12 with 50% (v/v) phosphoric acid and methanol (75:25 v/v). Mobile phase B was a mixture of the same components with a ratio 42:58 v/v. The mixture was degassed by ultrasonication (for 20 min). The flow rate was 1.3 ml/min. A linear gradient from mobile phase A to B over 40 min was used. Under these conditions, ticlopidine could be separated from all known potential impurities (see Fig. 2).

Standard solutions of ticlopidine (I) and its 11 known impurities (II) were prepared by dissolving these compounds in a mixture of water and methanol (50:50 v/v) to obtain a solution containing 2.5 mg/ml of I or 0.25 mg/ml of II, respectively. Prior to injection, solution I

Table 1

Products Examined

Sample	Product[a]	Manufacturer	Country	Batch No.	Expiry Date
1	Ticlocard	Kocak, Ilac Fabrikasi A.S.	Turkey	563	10/97
2	Ticlopin	Laboratorios Leti S.A.V.	Venezuela	607-087	7/99
3	Plaquetil	Laboratorios Rider S.A.	Chile	104536	10/99
4	Ateroclar	Laboratorios Recalcine S.A.	Chile	96149	3/99
5	Plaquetic	Laboratorios Haymann S.A.	Paraguay	116-11/01	Unknown
6	Antiplak	Ethical Pharmaceutical	Dominican Republic	14109	2002
7	Trombenal	Laboratorios Bago S.A.	Argentina	053	2/99
8	Dosier	Laboratorios Casasco S.A.I.C.	Argentina	4227	2/00
9	T.[b] Quesada	Biochimica Aplicada Dr Quesada s.r.l.	Argentina	15001	7/98
10	Gotik	Medical Farmaceutica	Paraguay	01015	1/00
11	Declot	Weidar Chem. and Pharm. Co. Ltd.	China	606002	2/98
12	Licodin	Taiwan Tung Yang Chemical Ind. Co. Ltd., Shanghai Xu Dong Hai Pu Pharmaceutical Co. Ltd.	China	96301-406	Unknown
13	Tabellae	Tianxin	China	960301	Unknown
14	Agulan	P.T. Kenrose-Indonesia	Indonesia	264701	Unknown
15	Tacron	Korea United Pharm. Inc.	Singapur	08C	3/00
16	Antigreg	Vecchi and C. Piam-Genova-Italy	Singapur	920601	9/99
17	Ticlodin		Thailand		Unknown
18	Licodin	Taiwan Tung Yang Chemical Ind. Co. Ltd.	Taiwan	TT502	Unknown
19	Licodin		Taiwan		Unknown
20	Nichistate		Taiwan	NA	Unknown
21	Hishimidon	Hishiyama Pharm. Co. Ltd.	Japan	YH05	4/99
22	Propacall		Japan	7002AB	12/99
23	Ticpilone	Medisa Pharmaceutical Co. Ltd.	Japan	96905	9/99
24	Nichistate	Nichiiko Pharmaceutical Co. Ltd.	Japan	CBD 14A	Unknown
25	Neo-Fulvigal	Anfarm Hellas S.A.	Greece	9701	2/00
26	Anchostan	Biostam E.E.	Greece	691	7/98
27	Neo-Omnipen	Norma-Hellas S.A.	Greece	9295	12/98
28	Ruxicolan	Rafarm S.A.	Greece	46097	4/99
29	Labortina	Kleva	Greece	1694	6/97
30	Etfariol	Vilko S.A.	Greece	10961	9/99
31	Iriflexin	Pharmathen, Pharmaceutical Industry	Greece	17	3/00
32	Opteron	Therabel Pharma S.p.A.	Italy	1604	9/99
33	Antigreg	Vecchi and C. Piam	Italy	19D	10/01
34	T.[b] Dorom	Poli Industria Chimica S.p.A.	Italy	9635B	2/00
35	Fluilast	Laboratorio B and G Prodotti Farmaceutici	Italy	009	10/99
36	Clox	Farmaceutici CABER S.p.A.	Italy	02	10/99
37	Aplaket	Rottapharm s.r.l.	Italy	28	10/99
38	Ticlop	Cadila Healthcare Limited	India	7001	12/98
39	Ticlovas	USV Limited	India	GO7010-USV	4/99
40	Aclotin	Polfa S.A.	Poland	10397	2003
41	Movin	Farmoz LDA	Portugal	Unknown	Unknown
42	Tombopat	Pentafarma S.A.	Portugal	Unknown	Unknown
43	Ticlid	Sanofi Winthrop Industry	France	SWIA 485	12/99

[a] Most of the samples are 250 mg tablets except 3, 25, 26, 28, 29, and 31, which are 250 mg capsules; 11, 18, 20, 21, 22, 23, and 24 are 100 mg tablets.

[b] T. = Ticlopidina.

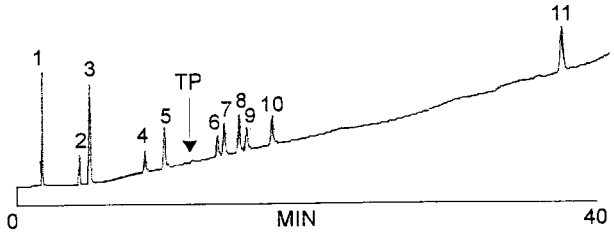


Figure 2. Chromatogram of the 11 known impurities of ticlopidine.

was diluted 10 times with mobile phase A, and solution II was diluted 100 times. The sample solution containing approximately 2.5 mg/ml was prepared by extracting ultrasonically (for 20 min) an accurately weighed quantity of powder from 5 tablets or 5 capsules with a mixture of methanol-water (50:50 v/v). After ultrasonication, solutions were adjusted to volume and filtered through nylon filters (2 μm pore size, Euroscientific), and 10 μl of clear filtrate was injected for the analysis of impurities. The analysis of ticlopidine required 1:10 dilution of the filtrate with mobile phase A prior to injection.

The quantity of ticlopidine and known impurities in each dosage form was calculated using the average weight of the dosage unit, and the concentrations of the solution examined and of the appropriate standard, and the corresponding peak areas. For all unknown impurities and potential degradation products, results were expressed in comparison with a 1% (m/m) dilution of ticlopidine standard solution.

Dissolution of Ticlopidine

The release of ticlopidine from the tablets was measured in vitro using dissolution apparatus (paddle) operated at 50 rpm and 37°C as described in the European Pharmacopoeia (Ph. Eur.) (9). The dissolution medium was prepared by dissolving 2 g of sodium chloride in 0.01 M hydrochloric acid and diluting up to 1000 ml with the hydrochloric acid solution. After 30 min from the start of the dissolution, the concentration of ticlopidine in the dissolution medium, and hence the percentage of ticlopidine released from each of the 6 tablets, was determined by UV spectrophotometry at 232 nm.

Stability Testing Protocol

All samples were examined for appearance and tested for impurities, assay, and dissolution (tablets only), within 2 weeks of receipt. They were immediately stored at 40°C and 75% RH. At 3 months and 6 months, all samples were examined visually for appearance and were tested for impurities, assay, and dissolution (tablets only). All tests were carried out before the expiry date, when known, of the samples.

RESULTS

The LC procedure was applied for the purity control, assay, and stability testing of ticlopidine in tablets and capsules obtained from markets in Europe, Asia, and Central and South America. A typical chromatogram of a commercial sample is presented in Fig. 3.

Appearance

The colors of the tablets and of the capsules at different time points (0, 3, and 6 months) are shown in Table 2. Most of the tablets were either white or off-white. Some of them were beige (no. 16), yellow (nos. 9, 30, and 35), pale blue (no. 39), pale rose (no. 14), and pale red (nos. 7, 8, and 11). The capsules were all green-white when examined initially. Several samples showed a color change during the 6-month period.

Assay of Ticlopidine

In Table 3, the assay results are listed for each sample at each time point and are expressed as a percentage of label claim.

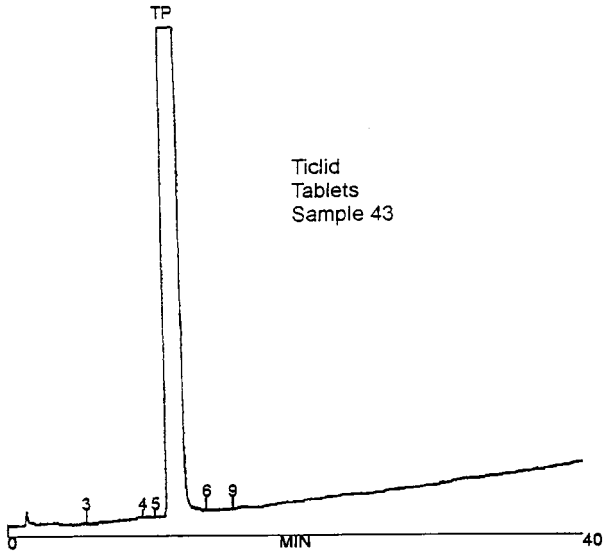


Figure 3. Typical chromatogram of commercial product at 0 months.

Table 2

Visual Examination of the Samples

Sample	Product	0 Time	Month 3	Month 6
1	Ticlocard, tablets	Off-white	NT[a]	NT
2	Ticlopin, coated tablets	White	White	White
3	Plaquetil, capsules	Green-white	Green-beige	Green-beige
4	Ateroclar, tablets	White	Mottled pale brown	Mottled pale brown
5	Plaquetic, double-scored tablets	White	White	White
6	Antiplak, tablets	Off-white	Off-white	Off-white
7	Trombenal, tablets	Pale red	Pale red	Pale red
8	Dosier, tablets	Pale red	Pale red	Pale red
9	Ticlopidina Quesada, tablets	Yellow	Yellow	Yellow
10	Gotik, double-scored tablets	White	White	White
11	Declot, double-scored tablets	Pale red	Pale red	Pale red
12	Licodin, tablets	White	White	White
13	Tabellae, tablets	White	Off white, crackly	Mottled pale brown
14	Agulan, scored tablets	Pale rose	Beige	Beige
15	Tacron, coated tablets	White	White	White, some mottled pale brown
16	Antigreg, tablets	Beige	Beige	Beige
17	Ticlodin, tablets	Off-white	Off-white	Off-white
18	Licodin, tablets	NT	NT	White
19	Licodin, tablets	White	White	Off-white
20	Nichistate, tablets	White	Mottled pale brown	Beige, some sticky
21	Hishimidon, tablets	White	Slightly beige	Off-white
22	Propacall, tablets	White	White	White
23	Ticpilone, tablets	White	White	White
24	Nichistate, tablets	White	Beige	Beige
25	Neo-Fulvigal, capsules	Green-white	Green-beige, crackly	Green-white
26	Anchostan, capsules	Green-white	Green-white	Green-white
27	Neo-Omnipen, coated tablets	Off-white	NT	Beige
28	Ruxicolan, capsules	Green-white	Green-white	Green-white
29	Labortina, capsules	Green-white	Green-white	Green-white, some green-beige
30	Etfariol, tablets	Yellow	Yellow, slightly sticky	Yellow, sticky
31	Iriflexin, capsules	Green-white	Green-white	Green-white
32	Opteron, tablets	White	White, crackly	Off-white, morphology changed, some soft, and some crackly
33	Antigreg, tablets	White	NT	Off white
34	Ticlopidina Dorom, tablets	Off-white	Slightly beige, sticky	Mottled yellow
35	Fluilast, tablets	Mottled yellow	Pale brown	Very mottled yellow
36	Clox, tablets	White	White	White
37	Aplaket, coated tablets	White	White	Off-white
38	Ticlop, tablets	Off-white	Off-white	Off-white
39	Ticlovas, tablets	Pale blue	Pale blue	Pale blue
40	Aclotin, tablets	White	White	White
41	Movin, tablets	White	NT	White
42	Trombopat, tablets	White	NT	White
43	Ticlid, tablets	White	White	White

[a] NT = not tested.

Table 3

Assay Results[a]

Sample	Product	Month 0	Month 3	Month 6
1	Ticlocard	91.40	NT	NT
2	Ticlopin	101.86	95.74	103.77
3	Plaquetil	114.98	105.26	105.74
4	Ateroclar	97.80	96.72	98.29
5	Plaquetic	99.14	98.29	91.44
6	Antiplak	97.91	101.31	99.67
7	Trombenal	96.90	95.85	99.57
8	Dosier	95.39	96.52	94.52
9	Ticlopidina Quesada	97.50	99.51	102.82
10	Gotik	97.83	99.34	98.59
11	Declot	97.58	93.62	92.41
12	Licodin	96.55	96.42	97.16
13	Tabellae	98.55	96.41	96.28
14	Agulan	98.45	99.34	99.23
15	Tacron	96.10	76.31	70.03
16	Antigreg	102.52	95.87	98.23
17	Ticlodin	95.77	95.64	99.23
18	Licodin	NT	NT	98.99
19	Licodin	97.07	95.68	99.70
20	Nichistate	96.60	97.64	96.36
21	Hishimidon	102.87	99.04	98.47
22	Propacall	101.90	97.28	101.24
23	Ticpilone	101.79	99.34	99.66
24	Nichistate	98.80	98.69	100.03
25	Neo-Fulvigal	101.46	97.27	99.85
26	Anchostan	95.36	95.65	97.77
27	Neo-Omnipen	98.50	NT	96.38
28	Ruxicolan	98.36	95.12	95.27
29	Labortina	97.62	95.69	95.76
30	Etfariol	96.74	96.59	100.78
31	Iriflexin	100.21	96.03	98.40
32	Opteron	113.30	79.77	82.03
33	Antigreg	98.09	NT	100.78
34	Ticlopidina Dorom	97.50	98.81	99.62
35	Fluilast	95.86	93.13	93.79
36	Clox	102.30	95.40	96.79
37	Aplaket	95.88	96.67	97.01
38	Ticlop	100.50	99.62	97.53
39	Ticlovas	99.50	97.81	98.85
40	Aclotin	99.20	97.77	100.35
41	Movin	98.80	NT	96.89
42	Trombopat	98.10	NT	99.82
43	Ticlid	97.66	100.03	99.62

NT = not tested.

[a] Assay results are presented as percentage of label claim.

Initially, of the 43 samples tested, two samples (nos. 3 and 32) gave assay results for ticlopidine greater than 105% of the label claim, that is, above the upper content limit generally applicable. Some samples gave assay results near the lower content limit (95%) (e.g., nos. 8, 17, 26, 35, and 37). Sample 1 gave an initial assay value of 91.4%.

At the 3-month time point, two samples (nos. 11 and 35) exhibited a decrease in the ticlopidine content below 95%, and two samples (nos. 15 and 32) gave very low assay values, 76.3% and 79.8%, respectively. For sample 3, the ticlopidine content decreased, but still remained above the upper content limit.

Two more samples (nos. 5 and 8) also showed a ticlopidine content of less than 95% at the 6-month time point.

Decomposition Products

The results for the total content of impurities at each time point are shown in Table 4. Initially, 19 samples (45%) showed impurity levels less than 0.25%, while 26 samples (62%) showed levels less than 0.5%, 36 samples (86%) had levels less than 1.0%, but 6 samples (14%) had levels higher than 1.0%. Seven (17%), including the original product Ticlid, exhibited impurity levels less than 0.05%.

After storage for 3 months under the accelerated conditions, different decomposition rates of the samples occurred. Only 7 samples (19%) showed impurity levels less than 0.25%, while 19 samples (51%) showed levels less than 0.5%, 26 samples (70%) had levels lower than 1.0%, but 11 samples (30%) had levels higher than 1.0%.

The figures after storage for 6 months were similar, as 7 samples (16%) had levels less than 0.25%, 20 samples (47%) had levels less than 0.5%, 32 samples (76%) had levels less than 1.0%, but 10 samples (24%) had levels higher than 1.0%.

Percentages were calculated as a function of the number of samples analyzed at a given time point.

For all the samples stored for 6 months and for which the total content of decomposition products exceeded 1.0%, the chromatogram consisted of many peaks, of which several did not match any of the reference substances. Figure 4 shows two of these chromatograms together with a chromatogram of the original drug product, Ticlid.

Dissolution

The dissolution test was only applied for tablets. The percentage of ticlopidine released from the tablets is summarized in Table 5. Each result is the mean of 6 individual tablets.

When the products were tested on receipt, 28 of the 36 tablets (78%) gave a mean value greater than 75% of the nominal content of ticlopidine (250 mg and 100 mg). Four other samples (nos. 4, 6, 22, and 24) gave values between 60% and 70%. Two samples (nos. 20 and 36) gave values less than 40% and 30%, respectively. Sample 37 gave less than 10%. In the case of sample 15, no dissolution occurred.

Sample 23, with a high initial value, showed a significant reduction in the amount released after 3 months and even more after 6 months. Sample 30 gave a low figure after 3 months of storage, but again, a high value after 6 months. All the other samples with high values gave similar values after both 3 and 6 months.

Discussion

The stability study under accelerated conditions of ticlopidine products focused on the quality parameters that may be altered as a result of chemical or physical instability during storage. These parameters were appearance, content and formation of decomposition products, and in vitro release of ticlopidine.

The appearance of the product was shown to be a good predictor of the level of decomposition products in the formulation. Any tablet or capsule showing a color change contained significant levels of decomposition products.

This observation was of value in demonstrating a different decomposition rate of ticlopidine in different tablets or capsules, even within the same blister. For all the tablets giving different dissolution rates, the appearance had changed.

When the 42 samples were tested on receipt, 3 products gave assay results outside the 95–105% limits usually acceptable to registration authorities as end of shelf life limits. Two products (nos. 15 and 32) showed marked loss of ticlopidine content during the 6-month study, accompanied by a corresponding marked increase in the level of decomposition products. However, the increase in impurities was insufficient to explain the loss of ticlopidine.

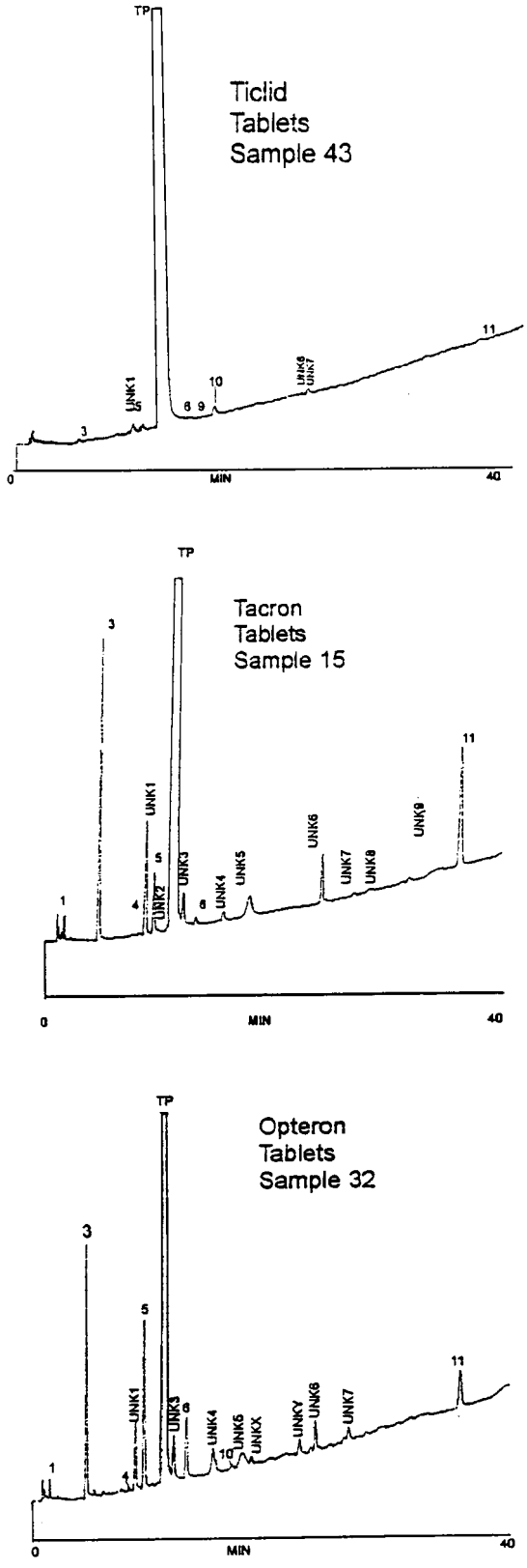
In a draft monograph of ticlopidine drug substance, the content of individual related substances is limited to 0.05% each, while the sum should not exceed 0.1% (10). On the other hand, there are no pharmacopoeial quality standards for ticlopidine preparations against which the levels of decomposition products formed during storage of the products could be assessed. When establishing any

Table 4

Sum of Impurities (%, m/m)

Sample	Product	Month 0	Month 3	Month 6
1	Ticlocard	0.55	NT	NT
2	Ticlopin	<0.05	0.09	0.28
3	Plaquetil	0.82	3.57	1.36
4	Ateroclar	<0.05	0.14	0.43
5	Plaquetic	0.58	0.27	0.40
6	Antiplak	0.13	0.21	0.25
7	Trombenal	0.15	0.49	0.50
8	Dosier	0.72	0.57	0.64
9	Ticlopidina Quesada	0.23	0.39	0.41
10	Gotik	0.54	0.76	0.68
11	Declot	0.40	1.38	0.95
12	Licodin	0.57	0.43	0.44
13	Tabellae	0.77	0.81	0.85
14	Agulan	0.20	0.25	0.32
15	Tacron	0.10	2.16	2.50
16	Antigreg	0.82	0.74	0.82
17	Ticlodin	0.49	0.38	0.53
18	Licodin	NT	NT	0.12
19	Licodin	0.20	0.27	0.40
20	Nichistate	0.21	0.34	0.38
21	Hishimidon	<0.05	0.18	0.09
22	Propacall	0.14	0.44	0.21
23	Ticpilone	<0.05	0.09	<0.05
24	Nichistate	<0.05	0.57	0.48
25	Neo-Fulvigal	0.80	1.44	1.84
26	Anchostan	1.02	1.04	1.01
27	Neo-Omnipen	0.44	NT	0.81
28	Ruxicolan	1.10	1.62	2.00
29	Labortina	1.32	1.60	1.75
30	Etfariol	1.24	1.03	1.01
31	Iriflexin	1.45	2.20	2.21
32	Opteron	0.40	3.05	1.62
33	Antigreg	0.15	NT	0.56
34	Ticlopidina Dorom	0.35	0.61	0.61
35	Fluilast	1.25	1.37	1.20
36	Clox	0.28	0.47	0.50
37	Aplaket	0.69	0.90	0.94
38	Ticlop	0.06	0.46	0.27
39	Ticlovas	0.25	0.28	0.38
40	Aclotin	<0.05	0.17	0.22
41	Movin	<0.05	NT	0.25
42	Trombopat	0.24	NT	0.20
43	Ticlid	<0.05	0.14	0.14

NT = not tested.



limit for individual and total impurities, the most important issue is that it is justified on safety grounds in relation to the toxicological properties. In this study, 0.25% was considered an acceptable limit for the total impurity content. For some samples (nos. 3, 11, 32), the relative content of impurities decreased after an initial increase. This may be due to apparent lack of homogeneity of the tablets, giving different rates of decomposition. Unstable degradation intermediates may have changed into products with lower response factors at 220 nm. Also, the formation of volatile decomposition compounds cannot be excluded. In the literature, the structure of only two related compounds (impurities 2 and 10) that can be formed during synthesis is reported (7,8). Some of the impurities are formed by decomposition (nos. 1, 3, 5, and 11).

After a storage period of 3 months, 10 products (27%) showed no significant increase or even a decrease of the content of impurities, 14 products (38%) showed an increase of up to 0.25%, 4 products (11%) showed an increase between 0.25% and 0.5%, 6 products (16%) had an increase between 0.5% and 1.0%, and finally 3 products (8%) had an increase of over 1.0%.

After a storage period of 6 months, 24 products tested (65%) showed similar amounts of impurities compared to the values obtained at 3 months. On the other hand, 9 products (24%) had an increase of less than 0.5%, while for 4 products (11%), a decrease in impurities was observed.

The Ph. Eur. dissolution test was used to investigate the stability of the dissolution properties. To assess the results, the Ph. Eur. criterion for oral dosage forms was followed; it requires at least 75% of ticlopidine to dissolve after 30 min. Adequate dissolution reduces the risk of unsatisfactory bioavailability. The dissolution test was only applied for the tablets (37 products).

The dissolution behavior for samples with low initial figures was unpredictable. For samples 4 and 6, the release decreased after 3 months, and it remained low after 6 months. In contrast, the values for samples 20, 22, 24, and 37 increased at the 3-month time point far beyond 75%, and values were almost 100% at 6 months. For sample 36, the dissolution properties remained nearly unchanged during the study. Sample 30 gave satisfactory dissolution results initially and after 6 months of storage,

Figure 4. Chromatogram of 3 products after 6 months of storage.

Table 5

Dissolution Results

Sample	Product	Dissolved (Mean in %)		
		Month 0	Month 3	Month 6
1	Ticlocard	95.00	NT	NT
2	Ticlopin	96.70	91.80	94.34
3	Plaquetil	NT	NT	NT
4	Ateroclar	70.20	39.00	45.92
5	Plaquetic	98.30	96.30	101.58
6	Antiplak	60.70	30.60	35.17
7	Trombenal	96.30	95.00	102.91
8	Dosier	95.00	91.80	98.59
9	Ticlopidina Quesada	98.70	96.70	100.30
10	Gotik	98.00	94.70	97.00
11	Declot	103.50	102.60	108.86
12	Licodin	101.48	NT	100.84
13	Tabellae	100.00	86.80	99.37
14	Agulan	98.70	95.40	95.24
15	Tacron	0.00	0.00	7.31
16	Antigreg	87.80	80.80	90.62
17	Ticlodin	91.60	87.40	86.40
18	Licodin	NT	NT	93.34
19	Licodin	98.00	91.90	105.60
20	Nichistate	38.20	99.80	99.97
21	Hishimidon	93.60	94.00	100.34
22	Propacall	67.30	84.40	97.78
23	Ticpilone	91.30	55.10	26.28
24	Nichistate	68.30	99.30	99.08
25	Neofulvigal	NT	NT	NT
26	Anchostan	NT	NT	NT
27	Neo-Omnipen	92.60	NT	65.23
28	Ruxicolan	NT	NT	NT
29	Labortina	NT	NT	NT
30	Etfariol	90.40	61.70	93.03
31	Iriflexin	NT	NT	NT
32	Opteron	92.30	97.70	103.32
33	Antigreg	96.00	NT	104.10
34	Ticlopidina Dorom	97.30	96.40	102.80
35	Fluilast	95.70	93.20	93.83
36	Clox	23.10	26.80	31.06
37	Aplaket	9.70	95.90	101.29
38	Ticlop	98.00	94.10	100.56
39	Ticlovas	93.30	91.30	98.94
40	Aclotin	94.30	90.00	86.76
41	Movin	96.70	NT	103.20
42	Trombopat	99.00	NT	104.64
43	Ticlid	90.60	100.30	102.24

NT = not tested.

but unexpectedly, the dissolution rate decreased after 3 months.

Two products (nos. 23 and 27), which initially gave results of more than 90%, showed significant reduction in the amount released after 6 months of storage. Sample 15 showed no dissolution after 3 months, while after 6 months, only 7.3% of ticlopidine was released. Thus, 11 products (30%) failed to comply with the dissolution test.

CONCLUSION

Stability investigation under accelerated test conditions is normally used to obtain assurance of a product's stability under the recommended storage conditions. Based on the shelf-life estimation method, it can be assumed that the stability profile obtained after 6 months at 40°C is equivalent to 30 months at 25°C (11). For many products in this study, the observed instability in accelerated conditions should draw serious doubt on the stability of the products under the recommended conditions for long term storage and transport.

The results of this study show that 6 products (nos. 18, 21, 40, 41, 42, and 43) exhibited good assay and purity results and dissolution characteristics over the 6-month period. All these products contained not more than 0.25% impurities, while samples 21 and 43 contained only 0.09% and 0.14%, respectively. Samples 4, 6, 27, and 36, with reasonable chemical stability, failed the dissolution test. For samples (nos. 20, 22, 24, and 37) with initially low dissolution results, the dissolution rate increased after a 6-month storage period far beyond the 75% limit. Sample 23 showed excellent chemical stability, but failed the dissolution test after storage. The capsules (nos. 3, 25, 26, 28, 29, and 31) already contained high amounts of degradation products on receipt. This amount increased on storage, except for sample 26. Samples 15 and 32 did not exhibit satisfactory chemical stability; moreover, for sample 15, no dissolution occurred. From these results, it can be deduced that only 6 tablet formulations (16%) complied with the three generally accepted shelf-life quality standards.

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