Pharmaceutical Research, Vol. 6, No. 7, 1989

Report

In Vitro Dissolution Profile of Water-Insoluble Drug Dosage Forms in the Presence of Surfactants

Vinod P. Shah,[1,5] John J. Konecny,[2] Richard L. Everett,[3] Bruce McCullough,[4] A. Carol Noorizadeh,[1] and Jerome P. Skelly[1]

Received September 7, 1988; accepted February 7, 1989

The determination of the *in vitro* release profile of water-insoluble drug products requires dissolution media different from those used for water-soluble drug products. Since the relevance of drug dissolution in organic solvents is questionable, we investigated the use of surfactants to determine the dissolution profiles of water-insoluble drug products. In most cases, the drug dissolution rate and extent increased as the surfactant concentration in the aqueous dissolution medium increased. Suitable dissolution profiles were obtained in the presence of sodium lauryl sulfate (SLS) for water-insoluble drug products, such as griseofulvin, carbamazepine, clofibrate, medroxyprogesterone, and cortisone acetate. These findings recommend the use of surfactants for determining the aqueous dissolution of water-insoluble drug products rather than adding organic solvents to the dissolution medium.

KEY WORDS: dissolution of water-insoluble drugs; dissolution of griseofulvin, carbamazepine, clofibrate, medroxyprogesterone, cortisone acetate; dissolution with sodium lauryl sulfate; dissolution with surfactants.

INTRODUCTION

Dissolution of drugs from solid oral dosage forms is a necessary criterion for drug bioavailability, i.e., the drug must be solubilized in the aqueous environment of the gastrointestinal (GI) tract in order to be absorbed. Therefore, the dissolution test for solid oral drug products has emerged as the single most important control test for assuring product uniformity and batch-to-batch bioequivalence once its bioavailability has been defined (1). For water-soluble drugs suitable dissolution media are water, dilute buffer solution, simulated gastric fluid, and/or simulated intestinal fluid without enzymes. For drugs that are practically water insoluble (solubility less than 0.01%), an appropriate dissolution medium/or method needs to be developed.

Attempts have been made to conduct dissolution testing for sparingly water-soluble drugs by using a large volume of the dissolution medium or by removing the dissolved drug (2–5). While both these procedures are intended to provide sink conditions, they are cumbersome. Another approach involves increasing the drug solubility with the use of hydroalcoholic dissolution media (6,7). Additionally disintegration tests have been used in lieu of dissolution tests. The use of disintegration or dissolution in alcoholic media as a quality measure is questionable for the following reasons: (i) the use of a hydroalcoholic medium has no relevance to the physiological milieu in which the drug dissolves, and (ii) the disintegration test is not a good quality-control procedure and is not predictive of drug bioavailability (8,9).

Because of the increasing number of water-insoluble solid dosage forms, it is necessary to develop an *in vitro* dissolution test as a quality-control procedure to assure batch-to-batch product bioequivalence once bioavailability has been established. A simple approach is described here to determine the dissolution of the water-insoluble drug products, griseofulvin, carbamazepine, cortisone acetate, clofibrate, and medroxyprogesterone acetate.

MATERIALS AND METHODS

Materials

Attempts were made to obtain all brands and strengths of approved and marketed dosage forms for the drugs studied.

Sodium lauryl sulfate (SLS; Fisher Scientific, King of Prussia, Pa.), sodium cholate, sodium dehydrocholate, sodium deoxycholate, sodium taurocholate (Pfaltz and Bauer, Waterbury, Conn.), bile salts (Sigma Chemical Co., St. Louis, Mo.), sodium oleate, dioctyl sodium sulfosuccinate, Tween 20 [polyoxyethylene (20) sorbitan monolaurate], Brij 35 (polyoxyethylene lauryl ether; Fisher Scientific), and so-

[1] Division of Biopharmaceutics, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland 20857.
[2] Philadelphia District Lab, FDA, Philadelphia, Pennsylvania 19106.
[3] Baltimore District Lab, FDA, Baltimore, Maryland 21201.
[4] Chicago District Lab, FDA, Chicago, Illinois 60616.
[5] To whom correspondence should be addressed.

TABLE I. Effects of Surfactants on Dissolution of Griseofulvin Dosage Forms

Product[a]	Aqueous solution containing	% dissolution 60 min	% dissolution 90 min
I	1% sodium dehydrocholate	10.7	10.9
	1% sodium desoxycholate	15.5	15.4
	2% sodium desoxycholate	24.3	25.3
	4% sodium desoxycholate	42.6	43.2
	2% sodium desoxycholate and 0.54% SLS	36.2	37.9
	1% sodium taurocholate	7.7	8.7
	4% sodium taurocholate	15.7	16.7
	6% sodium desoxycholate (4 parts) and sodium cholate (6 parts)	50.4	52.4
	1% Tween 20	13.3	13.3
	0.6% Brij 35	9.7	9.2
	1% dioctyl Na sulfosuccinate	27.2	27.5
	4% sodium oleate	98.5	100.9
	0.2% sodium bistridecyl sulfosuccinate	9.6	9.6
	0.54% sodium lauryl sulfate	74.9	79.4
	1.0% sodium lauryl sulfate	94.0	98.6
	2.0% sodium lauryl sulfate	99.3	102.0
	4.0% sodium lauryl sulfate	102.0	102.0
II	1% sodium cholate	15.1	15.4
	1% sodium cholate and 0.54% SLS	52.2	57.7
	4% sodium oleate	69.5	72.7
	0.54% sodium lauryl sulfate	54.2	59.3
	1.08% sodium lauryl sulfate	63.5	72.2
	2% sodium lauryl sulfate	74.9	79.8
	4% sodium lauryl sulfate	82.8	87.6

[a] I, 500 mg, manufacturer C; II, 500 mg, manufacturer A.

dium bistridecyl sulfosuccinate (American Cyanamide Co., Wayne, N.J.) were used as received. All reference standards were obtained from the USP (USP Convention, Inc., Rockville, Md.) and used as received.

Dissolution Medium

For griseofulvin several surfactants and bile acids, in various amounts and combinations, were studied. The dissolution profile of the other drug products was determined in an aqueous medium containing gradually increasing concentrations of sodium lauryl sulfate.

Procedure

All dissolution tests were performed using the USP XXI apparatus 2 (paddle method) at 37°C. The dissolution apparatus was calibrated using USP prednisone and salicylic acid calibrators as well as DDA (Division of Drug Analysis, CDER, FDA, St. Louis, Mo.) prednisone performance

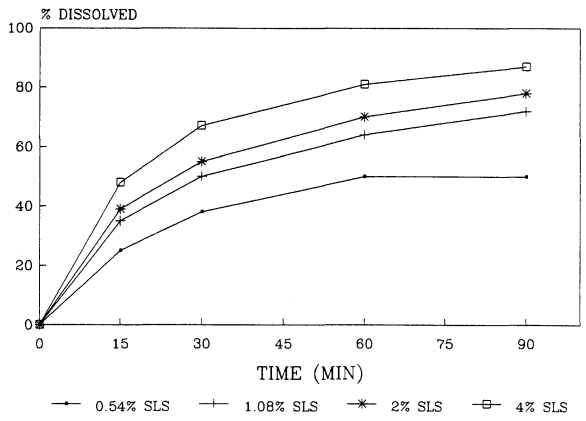

Fig. 1. Dissolution profile of 250-mg griseofulvin tablets (manufacturer A) in sodium lauryl sulfate solution.

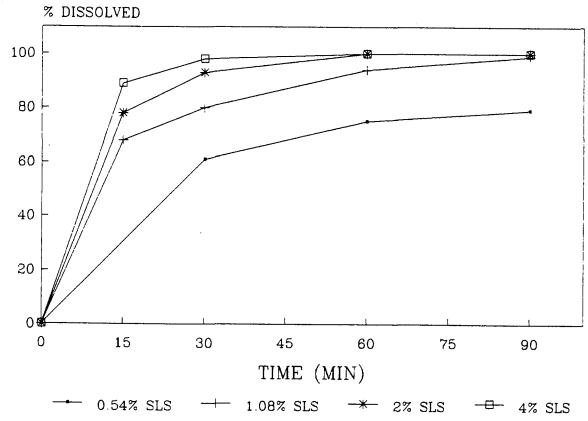

Fig. 2. Dissolution profile of 500-mg griseofulvin tablets (manufacturer C) in sodium lauryl sulfate solution.

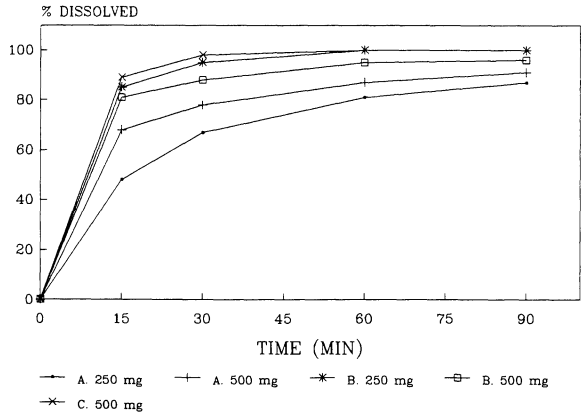

Fig. 3. Dissolution profile of 250- and 500-mg griseofulvin tablets in 4% sodium lauryl sulfate at 100 rpm by the paddle method.

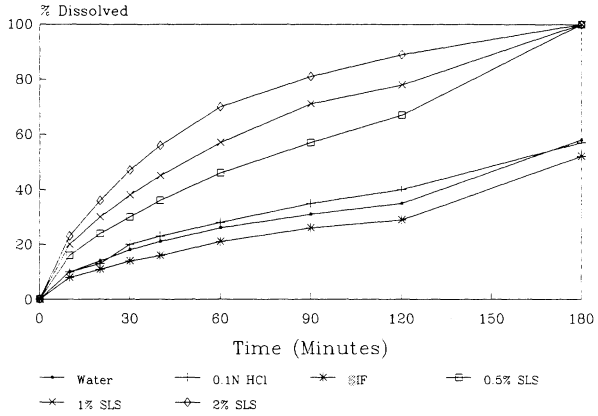

Fig. 5. Dissolution profile of 200-mg carbamazepine tablets in different dissolution media by the paddle method at 50 rpm.

standard, before initiating the studies. The dissolution results were found to be within specified limits with all three calibrators.

The dissolution studies were conducted using a paddle speed of 50, 75, or 100 rpm in 900–1000 ml of the dissolution medium. Several dissolution media were studied for a given drug product. Samples were analyzed at frequent time intervals to obtain the dissolution profile of the products.

Griseofulvin

Dissolution studies were carried out at 75 and 100 rpm in 1000 ml of the medium. A 20-ml aliquot was removed at 15, 30, 60, and 90 min. Each aliquot was replaced with fresh medium. A syringe with a stainless-steel cannula was used to draw up the test solution. The aliquot was forced through an 0.8-μm porosity membrane filter (Type AA, Millipore Corp., Bedford, Mass.). The first 10 ml was discarded to wash the filter free of material that might interfere with the assay and to saturate the filter with drug. A measured portion of each of the filtered aliquots was diluted with a solution of methanol and water (4:1) and compared to a standard in the same medium at the wavelength of maximum absorbance (about 293 nm). A UV blank of dissolution medium was prepared in the same manner. This solution was read at 293 nm and any absorbance value was subtracted from that of the sample absorbance.

The solubility of griseofulvin was determined in water, 2% SLS in water, and 4% SLS in water. An excess amount of griseofulvin USP reference standard was shaken in 100 ml of the medium at room temperature (25°C) for 8 hr, then allowed to stand overnight, and the amount of drug dissolved was determined by UV procedure. This procedure was repeated until the last two UV measurements gave the same results.

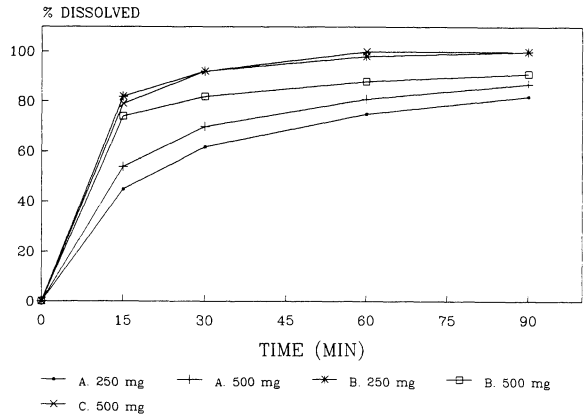

Fig. 4. Dissolution profile of 250- and 500-mg griseofulvin tablets in 4% sodium lauryl sulfate at 75 rpm by the paddle method.

Carbamazepine

Dissolution profiles of 200-mg carbamazepine tablets were studied using the paddle method at 50, 75, and 100 rpm in water, 0.1 *N* HCl, simulated intestinal fluid (SIF) without enzymes, and 0.5–2% SLS. Products A (Ciba-Geigy) and B (Colmed) were also studied using the paddle method at 75 and 100 rpm and a medium containing 10.5% alcohol and 0.1% Tween 20 (10). After establishing the dissolution test parameters using the Ciba-Geigy product, all marketed 200-mg carbamazepine tablets (A, Ciba-Geigy; B, Colmed; C, Inwood; D, Lemmon) were evaluated using the paddle method at 75 rpm in 1% SLS. Dissolution samples were analyzed by the UV method at 285 nm.

Clofibrate

Dissolution of clofibrate capsules from two manufacturers (A, Ayerst; B, Geneva) were determined in 1000 ml of water and in increasing amounts of SLS by the paddle method at 75 rpm. All samples were analyzed by a high-performance liquid chromatographic (HPLC) procedure with detection at 226 nm. The HPLC procedure employed a 10-μm C18 column (30 cm × 4 mm) and an isocratic mobile phase of methanol and water (80:20).

Medroxyprogesterone Acetate

Dissolution profiles of three marketed brands (A, Upjohn; B, Carnick; C, Reid Provident) of medroxyprogester-

Table II. Dissolution of Carbamazepine Tablets Using the Paddle Method and a Hydroalcoholic Medium[a]

	100 rpm		75 rpm	
Manufacturer	1 hr	3 hr	1 hr	3 hr
A. Ciby-Giegy	68.6 ± 2.2[b]	96.5 ± 2.4	63.5 ± 4.0	89.6 ± 4.1
B. Colmed	93.7 ± 1.3	101.6 ± 0.6	88.2 ± 3.1	100.8 ± 1.2

[a] 10.5% 3A alcohol and 0.1% Tween 20.
[b] Mean of six tablets ± %CV.

one acetate tablets were determined by the paddle method at 50 rpm in 900 ml of water and 0.5 and 1% SLS. Samples were removed at 15, 30, 45, 60, 90, and 120 min and analyzed by the UV method at 240 nm.

Cortisone Acetate

Dissolution profiles of nine brands of marketed cortisone acetate tablets were studied. All dissolution samples were analyzed by the UV method at 240 nm. All samples were also tested using the official USP XXI method, which requires a medium containing 30% isopropyl alcohol in water.

RESULTS

Griseofulvin

The role of surfactants in the release of sparingly soluble drugs from the tablet matrix (11) and their ability to solubilize water-insoluble materials are well described (12,13), and considerable work has been done to study the dissolution of griseofulvin products. Bile salts (sodium deoxycholate) and surfactants such as SLS and sodium oleate have been shown to increase significantly the dissolution rates of griseofulvin over that in water alone (12).

For comparison of the solubilization of microsized griseofulvin, solutions of all the bile salts and surfactants were tested on two commercial tablet samples. Dissolution results are given after 60 and 90 min (Table I). The dissolution values observed represent the combined effect of the solubilizing property of the surfactant and nature of the formulation itself. Because of formulation effects, two products may show different dissolution profiles in spite of the same solubilizing effect of the surfactants. Examination of the dissolution data show that SLS and sodium oleate were the most efficient solubilizers. A dissolution medium containing 6% bile salts (60 parts sodium cholate and 40 parts sodium desoxycholate) resulted in about 50% dissolution within 60 min, whereas as little as a 0.54% solution of SLS resulted in 75% dissolution. Solubility of griseofulvin using the USP reference standard was found to be 0.00908g/liter in water, 1.915g/liter in 2% SLS aqueous solution, and 3.535g/liter in 4% SLS aqueous solution. The solubilizing properties of other bile salts such as sodium glycochenodesoxycholate, sodium glycodesoxycholate, sodium taurochenodesoxycholate, and sodium taurodesoxycholate were also considered. Because of the observed low solubilization properties (Table I) and the relatively high cost of these bile salts, it was decided to terminate further testing of bile salts. In these experiments sodium lauryl sulfate and sodium oleate were found to be better solubilizers than the other surfactants. However, solutions of sodium oleate gave high UV absorbance and interference at 293 nm, the maxima at which griseofulvin is spectrophotometrically determined. Therefore, sodium lauryl sulfate was selected for all other additional studies.

The concentration of SLS in the dissolution medium was progressively increased from 0.54 to 4% in order to study the rate and extent of dissolution of griseofulvin tablets. The dissolution of all products was initially studied us-

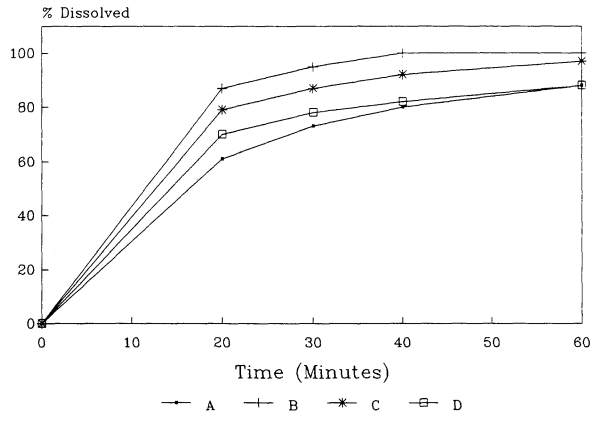

Fig. 6. Dissolution profile of marketed 200-mg carbamazepine tablets in 1% SLS by the paddle method at 75 rpm.

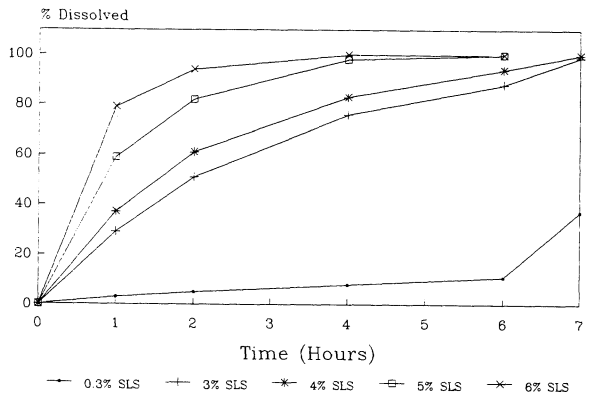

Fig. 7. Dissolution profile of clofibrate soft gelatin capsules in different dissolution media by the paddle method at 75 rpm.

Table III. Dissolution Profile of 500-mg Clofibrate Capsules: Paddle Method; 75 rpm; 5% SLS

	% dissolved[a] in				
Manufacturer	30 min	60 min	120 min	180 min	240 min
A. Ayerst	33 (10)	57 (6)	75 (5)	85 (4)	91 (4)
B. Geneva	29 (19)	53 (11)	73 (8)	83 (6)	89 (5)

[a] Mean of six capsules (%CV).

ing the paddle method at 100 rpm (the USP-recommended agitation). The results of the griseofulvin tablet dissolution are summarized in Figs. 1, 2, and 3. The dissolution coefficient of variation at each time interval was less than 10% in all cases. The more rapid dissolution of griseofulvin tablets from manufacturers B and C than of tablets from manufacturer A may be due to the formulation of the products and the interaction of the surfactant with the formulation. The dissolution studies for these dosage forms were also carried out in 2 and 4% SLS aqueous solutions using the paddle method at 75 rpm. The results indicate that there was no significant increase in rate and extent of dissolution with an increase in agitation from 75 to 100 rpm (Figs. 3 and 4). Tablets from manufacturers A and C disintegrated rapidly (1–3 min) compared to tablets from manufacturer B (10 min). The results in Figs. 3 and 4 indicate that there is no necessity for conducting dissolution studies at a high agitation (100 rpm). The high agitation intensity may reduce the discriminative power of the dissolution test as a quality-control procedure for detecting any manufacturing-process changes. Using the paddle method at 75 rpm and 4% SLS, all griseofulvin microsize tablets achieved not less than (NLT) 75% dissolution in 60 min. On the basis of these studies, the USP has now accepted a dissolution medium with 4% SLS for griseofulvin tablets.

Carbamazepine

Dissolution of 200-mg Tegretol (carbamazepine) tablets was initially studied by the paddle method at 50, 75, and 100 rpm using water, 0.1 *N* HCl, simulated intestinal fluid, and increasing amounts of SLS (0.5, 1, and 2%) as the medium.

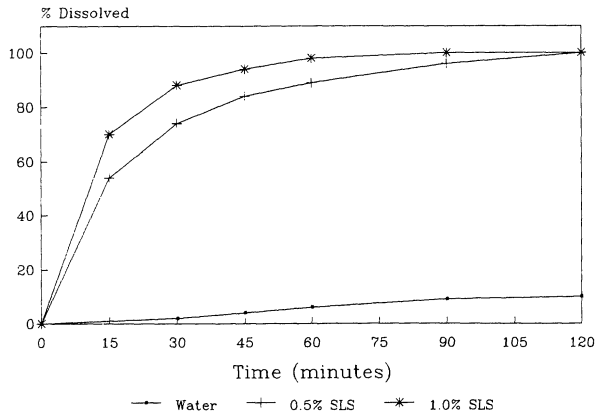

Fig. 8. Dissolution profile of medroxyprogesterone acetate tablets in different media by the paddle method at 50 rpm.

The results are shown in Fig. 5. Again, the rate and extent of dissolution increased with an increase in SLS. Four marketed brands of carbamazepine were studied using the paddle method at 75 rpm in 1% SLS. The *in vitro* dissolution studies were also conducted using 10.5% alcohol and 0.1% Tween 20 in water by the paddle method at 75 and 100 rpm for products A (Ciba-Geigy) and B (Colmed) and by the paddle method at 75 rpm in 1% SLS. From the results, Table II and Fig. 6, respectively, it is clear that SLS can be used as a dissolution medium for carbamazepine tablets. The results of all four brands of carbamazepine tablets are shown in Fig. 6. The Colmed product showed the fastest dissolution, 95% in 30 min. Using the paddle method at 75 rpm and 1% SLS, all four brands of carbamazepine tablets dissolved NLT 75% in 60 min.

Clofibrate

The dissolution profile of two marketed clofibrate capsules was determined in water and in increasing amounts of SLS. Clofibrate is available as a soft gelatin capsule formulation. Following the capsule rupture, dissolution of the drug is required as a condition of drug absorption. For clofibrate also, the dissolution increased with increases in SLS concentration (Fig. 7). It was necessary at 75 rpm (paddle method) to increase the amount of SLS to 5% in order to obtain at least 70% dissolution in a 2-hr time period. The results are shown in Table III. The USP has no dissolution test requirement for this product; however, in a recent Stimuti article (14) the USP has proposed a first-case (Apparatus 2) dissolution requirement for soft gelatin capsules using water as the medium.

Medroxyprogesterone Acetate

Dissolution profiles of medroxyprogesterone acetate tablets in water and in 0.5 and 1% SLS are shown in Fig. 8. Dissolution significantly increased with increasing concentrations of SLS. There was a slight increase in the rate of dissolution in 1% SLS, compared to the profile in 0.5% SLS. The dissolution profiles (0.5% SLS) for all approved marketed medroxyprogesterone acetate tablets are shown in Table IV. The USP has no dissolution test requirements for this product.

Cortisone Acetate

The current USP procedure requires the use of 30% isopropyl alcohol in water as the dissolution medium. Dissolution profiles of cortisone acetate tablets in water and 0.5

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.