US005811388A

United States Patent [19]

Friend et al.

[11] **Patent Number: 5,811,388**

[45] **Date of Patent: Sep. 22, 1998**

[54] **DELIVERY OF DRUGS TO THE LOWER GI TRACT**

[75] Inventors: **David R. Friend**, Menlo Park; **David Wong**, San Francisco, both of Calif.

[73] Assignee: **Cibus Pharmaceutical, Inc.**, Burlingame, Calif.

[21] Appl. No.: **602,611**

[22] Filed: **Feb. 16, 1996**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 486,974, Jun. 7, 1995, Pat. No. 5,656,294.

[51] **Int. Cl.**[6] **A61K 9/24**; A61K 9/34; A61K 9/36; A61K 38/00

[52] **U.S. Cl.** **514/2**; 424/85.1; 424/465; 424/474; 424/475; 424/479; 424/481; 424/485; 424/488; 514/3; 514/12; 514/21; 514/177; 514/178; 514/179; 514/180; 514/181; 514/182; 514/777; 514/780; 514/782; 514/960; 514/961

[58] **Field of Search** 514/2, 3, 12, 21, 514/177, 178, 179, 180, 181, 182, 960, 961, 777, 780, 782; 424/85.1, 452, 461, 465, 474, 475, 479, 481, 485, 488, 493, 496, 500

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,629,393	12/1971	Nakamoto et al.	424/470
4,389,393	6/1983	Schor et al.	424/480
4,894,233	1/1990	Sharma et al.	424/440
4,994,276	2/1991	Baichwal et al.	424/440
4,999,200	3/1991	Casillan	424/480
5,108,758	4/1992	Allwood et al.	424/468
5,128,143	7/1992	Baichwal et al.	424/464
5,422,121	6/1995	Lehmann et al.	424/464
5,445,826	8/1995	Kuhrts	424/451
5,525,634	6/1996	Sintov et al.	514/777
5,656,294	8/1997	Friend et al.	424/465

FOREIGN PATENT DOCUMENTS

2053569	4/1992	Canada .
0 343 993 A1	11/1989	European Pat. Off. .
0 371 493 A1	6/1990	European Pat. Off. .
0 481 240 A2	4/1992	European Pat. Off. .
0 485 840 A2	5/1992	European Pat. Off. .
2 667 242	4/1992	France .
2 238 243	5/1991	United Kingdom .
WO 86/06627	11/1986	WIPO .
WO 87/06241	10/1987	WIPO .
WO 89/04673	6/1989	WIPO .
WO 91/16881	11/1991	WIPO .
WO 92/00732	1/1992	WIPO .

OTHER PUBLICATIONS

Adkin et al., "Colonic Transit of Different Sized Tablets in Healthy Subjects" *Journal of Controlled Release* (1993) 23:147–156.

Brondsted and Kopeck, "Hydrogels for Site–Specific Oral Drug Delivery: Synthesis and Characterization", *Biomaterials* (1991):584–592.

Cummings, "Short Chain Fatty Acids in the Human Colon", *Gut* (1981), 22:763–779.

Damgé et al., "New Approach for Oral Administration of Insulin With Polyalkylcyanoacrylate Nanocapsules as Drug Carrier" *Diabetes* (1968) 37:246–251.

Davis et al., "Transit of Pharmaceutical Dosage Forms Through the Small Intestine" *Gut* (1986) 27:886–892.

Feely et al., "Investigating the Gastrointestinal Transit of Controlled Release Mini–Matrices Using Gamma Scintiography", *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.* (1985) 12:94–95.

Hardy et al., (1987) "Evaluation of an Enteric–Coated Delayed–Release 5–Aminosalicyclic Acid Tablet in Patients With Inflammatory Bowel Disease" *Aliment. Pharmacol. Therap.* (1987), 1:273–280.

Holt, et al., "Effect of Gel Fibre on Gastric Emptying and Absorption of Glucose and Paracetamol", *Lancet* (1979) 1:636–639.

Jain et al., "Controlled–Release Tablet Formulation of Isoniazid", *Pharmazie* (1992) 47:277–278.

Khosla et al., (1989) "Gastrointestinal Transit of Non–Disintegrating Tablets in Fed Subjects" *International Journal of Pharmaceutics* (1989) 53:107–117.

Kopecek, "Polymers for Colon–Specific Drug Delivery", *Journal of Controlled Release* (1992) 19:121–130.

Latymer et al., "Measurement of Transmit Time of Digesta Through Sections of Gastrointestinal Tract of Pigs Fed with Diets Containing Various Sources of Dietary Fibre (Non–Starch Polysaccharides)" *Arch. Anim. Nutr. Berlin* (1990) 40:667–680.

Marvola et al., "Gastrointestinal Transit and Concomitant Absorption of Verapamil from a Single–Unit Sustained–Release Tablet", *Drug Development and Industrial Pharmacy* (1987) 13(9–11) :1593–1609.

Miranda et al., "High–Fiber Diets in the Treatment of Diabetes Mellitus" *Annals of Internal Medicine* (1978) 88:482–486.

Moore et al., "Absorption Enhancement of Growth Hormone from the Gastrointestinal Tract of Rats", *International Journal of Pharmaceutics* (1986) 34:35–43.

(List continued on next page.)

Primary Examiner—Jeffrey E. Russel
Attorney, Agent, or Firm—Cooley Godward LLP

[57] **ABSTRACT**

Pharmaceutical compositions for orally delivering a therapeutically effective amount of a drug to the colon without significant release of the drug in the upper GI tract after oral administration of the composition are described. The composition is a unit dosage in the form of a tablet that comprises about 0.01% by weight to about 10% by weight of the drug that is useful in treating a colonic disorder or that is absorbed from the colon; about 40% by weight to about 98% by weight of a hydrocolloid gum obtainable from higher plants; and about 2% by weight to about 50% by weight of a pharmaceutically acceptable binder. The compositions are useful for treating lower GI disorders in human subjects by administering a suitable amount to a subject in need thereof. A particularly preferred aspect is the process for preparing such composition in the form of a tablet.

30 Claims, No Drawings

OTHER PUBLICATIONS

McIntire et al., "Different Fibers Have Different Regional Effects on Luminal Contents of Rat Colon", *Gastroenterology* (1991) 101:1274–1281.

Price et al., "Characterization of Colonic Transit of Nondisintegrating Tablets in Healthy Subjects", *Digestive Diseases and Sciences,* (1993) 38(6) :1015–1021.

Price et al., "The Effect of Meal Composition on the Gastrocolonic Response: Implications for Drug Delivery to the Colon" *Pharmaceutical Research* (1993) 10(5):722–726.

Rubinstein and Gliko–Kabir, "Synthesis and Swelling Dependent Enzymatic Degradation of Borax Modified Guar Gum for Colonic Delivery Purposes" *S.T.P. Pharma Sciences* (1995) 5:41–46.

Sakr and Elsabbagh, "Effect of Particle Size Distribution on the Disintegrating Efficiency of Guar Gum" *Pharm. Ind.* (1976) 38(8) :732–734.

Salyers and Leedle, "Carbohydrate Metabolism in the Human Colon" *Human Intestinal Microflora in Health and Disease,* Chapter 6, pp. 129–146 (1983).

Spiller et al., "Emptying of the Terminal Ileum in Intact Humans: Influence of Meal Residue and Ileal Motility" *Gastroentrology* (1987) 92:724–729.

Trenev, "We Need Friendly Bacteria" *Total Health* (1988) 10:29–29.

Venter and Vorster, "Possible Metabolic Consequences of Fermentation in the Colon for Humans" *Medical Hypotheses* (1989) 29:161–166.

Waaler et al., "Biopharmaceutical Studies of Naftidrofuryl in Hydrocolloids Matrix Tablets" *International Journal of Pharmaceutics* (1992) 87:229–237.

Watanabe et al., "Factors Affecting Prednisolone Release from Hydrogels Prepared with Water–Soluble Dietary Fibers, Xanthan and Locust Bean Gums" *Chem. Pharm. Bull.* (1992) 40(2) :459–462.

Woodley, "Peptidase Activity in the G.I. Tract: Distribution Between Luminal Contents and Mucosal Tissue", *Proceed. Intern. Symp. Control. Rel. Bioct. Mater* (1991) 18:337–338.

Yoshikawa et al., "Comparison of Disapearance from Blood and Lymphatic Delivery of Human Fibroblast Interferon in Rat by Different Administration Route", *J. Pharmacobio–Dyn.* (1985) 8:206–210.

DELIVERY OF DRUGS TO THE LOWER GI TRACT

CROSS-REFERENCE TO RELATED CASES

This is a continuation-in-part application of U.S. patent application Ser. No. 08/486,974, filed Jun. 7, 1995 now U.S. Pat. No. 5,656,294.

INTRODUCTION

1. Technical Field

This invention relates to pharmaceutical compositions for oral administration to preferentially deliver drugs to the lower gastrointestinal (GI) tract, particularly to the colon.

2. Background

At the present time, there are no good orally-deliverable drug compositions that target treatment of various colon diseases such as chronic inflammatory diseases of the colon or diseases that require treatment by drugs that are better-absorbed through the colon than the stomach or upper GI tract. Also, there are no orally-deliverable drug compositions for peptides that release the peptides in a colonic environment where the peptides are not degraded to the same extent as peptides are degraded in the acid environment of the upper GI tract, particularly the stomach.

It is also known that peptides and proteins are large, molecules that are acid labile and polar to cause them to be poorly absorbed in the upper gastrointestinal tract. These molecules are degraded by luminal and brush border peptidases and generally have very short half-lives. As a result they have exceedingly low and variable bioavailability. Certain researchers have concluded that these molecules may be regionally absorbed in the colon. See, e.g., Moore, et al., *Int. J. Pharm* 34:35 (1986) discussing HGH and Yoshikawa, et al., J. Pharmacobiodyn. 8:291 (1985) discussing interferon. There is also evidence that there is much lower peptidase activity in the colon relative to the upper intestinal tract (Woodley, Proc. Int. Syn. Control. Rel. Bioact. Mat. 18:337 (1991).

Colon diseases include such conditions such as Crohn's disease, colitis (particularly ulcerative colitis), irritable bowel syndrome and the like. These diseases include a spectrum of inflammatory bowel disorders with overlapping clinical, epidemiologic and pathologic findings but without a definite etiology. Both Crohn's disease (CD) and ulcerative colitis (UC) are characterized by chronic inflammation at various sites of the GI tract, generally the colon (i.e., that part of the intestine from the cecum to the rectum). In treating these disease states, it is difficult to direct drugs that are specifically anti-inflammatory in nature and act topically to the desired site. For example, CD seems to affect the terminal ileum and the cecum primarily while UC seems to go past the second turn in the colon and affect the splenic flexure.

It One of the families of compounds that are used in the treatment of this family of diseases are glucocorticoids. These are thought to be useful in that the glucocorticoids have the capacity to prevent or suppress the development of the manifestations of this inflammation. The thought is that if the drugs can be administered to the inflamed area, the inflammation will recede and the body will ultimately be able to recover. Unfortunately, there are certain side effects the glucocorticoids exhibit if administered systemically and these side effects can be quite significant in treating any disease state. Another problem stemming from these side effects is that there is no way to deliver the drugs directly to the afflicted portion of the colon. Most of the oral formulations that are presently available disintegrate as they pass through the upper GI tract and thus, the steroids are absorbed into the body systemically and the subject being treated will experience some of the undesirable side effects.

The general approaches to delivering drugs to the lower GI tract (e.g. colon) include: 1) enteric coating designed to release drug in the more alkaline environment of the gastrointestinal tract, 2) bioerodible coatings and matrices, 3) prodrugs, 4) timed-release systems and, 5) enteric polymeric material-based release systems that release drug after they transit through the small and reach the large intestines. A general discussion of these approaches and others may be found in PCT Patent application No. PCT/US91/03014 by Sintov and Rubinstein.

It is known that certain hydrocolloids have a chemical structure that is subject to attack by the enzymes that are present in the colon and will cause the structure of the hydrocolloids to degrade and breakdown. Thus, it has been thought that if a composition could be prepared that would be made of a drug useful for treating the colonic condition that would pass through the upper GI tract without releasing the drug but would preferentially release it in the colon, the problem could be solved. Several attempts have been made to use a galactomannan-based composition (such as guar gum) to prepare compositions that are orally-administratable but which do not deliver a drug in the upper GI tract but instead make it through the tract to the colon. None of these have been entirely successful and some are more complex than desired. A paper by Rubinstein and Gilko-Kabir describes a borax-modified guar gum for colonic delivery purposes. However, that procedure requires that guar gum be chemically modified using borax (which is toxic at certain concentrations) in various concentrations to achieve the desired results. Other attempts have been made using glassy amylose to prepare compositions. These, too, were minimally successful. Still another approach requires that a galactomannan (locust bean gun) be mixed with an acrylate resin and coated around a drug-containing core (See U.S. Pat. No. 5,422,121).

It is also known that hydrocolloids that are obtainable from higher plants, such as guar gum, are used to increase the gastric residence time and provide sustained release of a drug which has the same bioavailability as the formulation of the drug. The concept is spelled out in co-pending application U.S. Ser. No. 08/348,515 filed Dec. 1, 1994 now abandoned. A broad range of hydrocolloid gum obtained from higher plants could be used to achieve those ends. The type of drug that could be used in the composition of that invention generally included nonpeptidic drug categories that exhibit a preferential window of absorption in the upper GI tract and/or that are generally susceptible to sustained release. Generally these drugs are present in high concentrations in the compositions.

It has now been discovered that drugs with high therapeutic activity (i.e., drugs that require less than about 10% weight in an orally-deliverable composition) can be delivered to the lower GI, particularly the colon. By carefully controlling the amount of a hydrocolloid that is obtainable from higher plants, such as guar gum, a composition is prepared for such drugs that is particularly useful for treating conditions of the lower intestinal tract, particularly chronic inflammatory diseases of the colon (and other colon disorders such as irritable bowel syndrome, constipation, diarrhea, etc.) and for delivering compounds (e.g. peptides) to the colon for better absorption. The families of compounds for which this is particularly valuable includes the

glucocorticoids, local anesthetics, anticholenergics, 5-ASA, stimulant laxatives, peptides, certain antibodies and certain vaccines. While the amount of the hydrocolloid is one factor to consider in preparing the compositions of this invention, other important factors include the particle size of the hydrocolloid, the amount and type of other ingredients, the design of the tablet and other factors discussed herein.

OBJECTS OF THE INVENTION

An object of this invention is to provide a unit dosage composition comprising a drug useful for treating lower gastrointestinal disorders, particularly colonic disorders, that is orally-administered and delivers the major amount of the drug preferentially to, e.g. the colon of a human subject in need thereof.

Another object of this invention is to provide an orally-administered unit dosage composition comprising (a) a drug useful for treating lower gastrointestinal disorders, particularly colonic disorders, or (b) a drug that degrades in the upper GI tract, which composition goes through the upper GI tract without releasing significant quantities of the drug to a human subject being treated and releases the majority of the drug to the lower GI, e.g. colon.

Another object of this invention is to provide a unit dosage composition comprising a drug useful for treating lower gastrointestinal disorders, particularly colon disorders, that is orally-administered and minimizes adverse systemic effects to a human subject being treated.

Another object of this invention is to provide an orally-administered, unit dosage composition that delivers the major amount of the drug useful for topically treating colon disorders to the colon so the drug is released for topical treatment while minimizing systemic effects of such drug.

Another object of this invention is to provide an orally-administered, unit dosage composition that systemically delivers drugs, such as peptides, by absorption throughout the lower GI or colon.

Another object of this invention is to provide a method for treating a human subject through oral administration of a unit dosage composition that achieves the foregoing objects of this invention.

Still another object of this invention is to provide a process for preparing a unit dosage tablet composition suitable for oral administration that attains the foregoing objects of this invention.

Other objects of this invention will be apparent to one of ordinary skill by reading the following specification and claims.

SUMMARY OF THE INVENTION

One aspect of this invention is a powdered mixture useful for preparing a tablet for orally delivering a therapeutically effective amount of a drug to the lower GI tract, particularly the colon, without significant release of the drug in the upper GI tract after oral administration of the tablet, which composition comprises

- about 0.01% weight to about 10.0% by weight of such drug;
- about 40% weight to about 98% by weight of a hydrocolloid gum obtainable from higher plants; and
- about 2.0% by weight to about 50% by weight of a pharmaceutically acceptable excipient, wherein said mixture is free of any enteric polymeric material or gas-forming excipients.

Another aspect of this invention is a pharmaceutical tablet having an inner composition optionally coated by a pharmaceutically-acceptable coating (preferably an enteric coating), said tablet designed for orally delivering a therapeutically effective amount of a drug to the lower GI tract, particularly the colon, without significant release of the drug in the upper GI tract after oral administration of the tablet, which inner composition of the tablet comprises

- about 0.01% weight to about 10.0% by weight of a drug useful for treating a lower GI tract disorder;
- about 40% to about 98% by weight of a hydrocolloid gum obtainable from higher plants;
- about 2% to about 50% by weight of a pharmaceutically acceptable excipient; and
- no enteric polymeric material or gas-forming excipients.

Another aspect of this invention is a method for treating a disorder of the lower GI tract, particularly the colon, in a human subject, which method comprises orally-administering to a human subject in need thereof a tablet described above.

Another aspect of this invention is a method for preferentially delivering a drug to the lower GI tract, particularly the colon, wherein such drug is susceptible to enzymatic degradation in the upper GI tract, which method comprises orally-administering to a human subject in need thereof a tablet described above.

Still another aspect of this invention is a process for preparing a composition in the form of a tablet suitable for oral administration to a human subject, wherein the tablet composition preferentially delivers a therapeutically effective amount of such drug to the lower GI tract, particularly the colon, without significant release of the drug in the upper GI tract, which process comprises

(a) mixing about 0.5% weight to about 10.0% by weight of such drug with
  - about 40% weight to about 98% by weight of a hydrocolloid gum obtainable from higher plant; and
  - about 2% by weight to about 50% by weight of a pharmaceutically acceptable excipient to form a uniform mixture

(b) forming a tablet; and

(c) optionally coating the tablet.

Other aspects of the invention will be apparent to one of ordinary skill of the art upon reading the following specifications and claims.

DESCRIPTION OF SPECIFIC EMBODIMENTS

The compositions of this invention are based on the observation that by carefully controlling the percentage of a hydrocolloid obtainable from a higher plant at a very high level in an orally-administered dosage form and combining it with a suitable excipient and a particular family of drugs at low concentrations (i.e., less than about 10% by weight), a composition can be obtained which traverses the upper GI tract without releasing any significant amount of drug, but when it reaches the lower GI tract, e.g. the colon, the drug is preferentially released due at least in part to the action of the enzymatic environment in the lower GI tract that attacks the hydrocolloid to release the drug. The compositions and methods of this invention are of a delayed release nature (as compared to sustained or extended release) particularly useful for colonic delivery of glucocorticoids, as well as other drugs (e.g. peptides) that might be inactivated (e.g., enzymatically degraded) if released in the upper gastrointestinal tract. Thus, for purposes of this application a delayed release composition allows for the release of most of the

active ingredient in the lower GI, particularly the colon without releasing any significant amount of the drug in the upper GI tract as the composition travels through the entire GI tract. This is different than a sustained release composition that releases the active on a regular (i.e. constant) basis throughout the GI. Generally, a relatively high percentage of the hydrocolloid gum obtainable from higher plants is present, namely at least 50% to about 98% (depending in part on the purity of the commercially-available gum), with a lesser amount of a pharmaceutically acceptable excipient that provides lubricating, binding and/or disintegrating capability for the composition as well as providing a minimal hardness for the tablet so that it can be prepared pharmaceutically. This amount is less than about 50% but more than about 2% by weight of the composition. The remainder is a drug present at a level that is therapeutically effective and depends on the relative activity of the drug and its interaction with the composition. The drug may be useful for treating conditions of the lower GI, particularly the colon (e.g., inflammatory diseases) or other conditions requiring drugs that are better absorbed from the colon.

The Compositions

One aspect of this invention is an orally-deliverable tablet having an inner composition optionally surrounded by a pharmaceutically-acceptable coating. The tablet preferentially delivers a therapeutically effective amount of a suitable drug to the lower GI, e.g. the colon, without significant release of the drug in the upper GI tract upon oral administration of the composition to a subject in need thereof. The inner composition of the tablet comprises about 0.01% weight to about 10.0% by weight of a suitable drug (e.g., for treating inflammatory colonic disorders); about 50% by weight to about 98% by weight of a hydrocolloid gum obtainable from higher plants; and about 2% by weight to about 50% by weight of a pharmaceutically acceptable excipient such as a binder. Other optional materials may be present that will assist in establishing the desired characteristics of the pharmaceutical composition. These include materials that may enhance absorption of the drug in the lower GI, may protect the drug against degradation, may prevent dissolution, and the like. Optionally surrounding the inner composition of the tablet is a coating that is preferably of enteric polymeric material.

The solid tablet of this invention is designed to take advantage of (1) the protective characteristics of the hydrocolloid obtainable from higher plants in the upper GI and (2) the disintegrative characteristics of the hydrocolloid in the lower GI. Thus, the inner composition of the tablet may be one of several designs: (a) it may be a matrix of a therapeutically effective amount of the active ingredient uniformly dispersed throughout in combination with a high percentage of the hydrocolloid and a generally lesser amount of other excipients; (b) it may have a core, in which the active ingredient is concentrated, surrounded by a layer of material that is free of the active ingredient and that has a high percentage of the hydrocolloid and a generally lesser amount of other excipients; (c) it may have a concentration gradient of the active ingredient such that there is a greater amount in the core of the tablet with lesser amounts in multiple layers surrounding the core and very little or no active ingredient in the outer layer. Whether the design of the tablet is that of (a), (b) or (c) above, the specificity for regional delivery to the lower GI, especially the colon, is enhanced by enterically coating the tablet with an appropriate enteric coating material.

The hydrocolloid that is used in the subject invention is a hydrocolloid that is obtainable from higher plants. By "higher plant" is meant an organism of the vegetable kingdom that lacks the power of locomotion, has cellulose cell walls, grows by synthesis of inorganic substances and includes the vascular plants (or tracheophytes) of the division Spermatophyta, particularly those of the class Angiospermae. The gums may be extracted from the roots, legumes, pods, berries, bark, etc. Thus, higher plants do not include algae, flagellates, bacteria, slime molds, fungi, mosses, ferns, horsetails and the like. Representative hydrocolloid gums obtainable from higher plants include guar gum, gum tragacanth, karaya gum (also referred to as kadaya gum) and locust bean gum (also referred to as carob). Others may be readily apparent to one of skill in the art. See, for example, "The Chemistry of Plant Gums and Mucilages" by Smith and Montgomery from ACS Monograph Series, No. 141, 1959, Reinhold Publishing Company and the 18th edition of the Merck Index. A particularly convenient and useful hydrocolloid is guar gum which is a neutral polysaccharide and consists of long galactomannan molecules with some side chain attachments. The hydrocolloids used in the subject invention generally have high viscosity exhibited upon hydration, are normally linear (at least about 50% by weight of the compound is the backbone chain), and will normally have high molecular weight, usually about 3×10^5 daltons, more usually greater than about 1×10^6 daltons. Generally, the hydrocolloid comes as a powdered hydrocolloid gum and exhibits a viscosity at a 1% concentration in a neutral aqueous solution of at least about 75 centipoise per second (cps) at 25° C. after 24 hours, using a Brookfield viscometer (model LDF) with a number 3 spindle at 90 rpms, preferably at least 1×10^3 cps and most preferably at least about 2×10^3 cps. Generally, the viscosity increases with increasing molecular weight. See Meer Corporation, "An Introduction to Polyhydrocolloids." Hydrocolloid gums most useful are those where the hydrocolloid is a polysaccharide hydrocolloid which is chemically designated as galactomannan. Galactomannans are polysaccharides consisting of long chains of (1→4) - β-D-mannopyranosyl units to which single unit side chains of α-D-galactopyranosyl are joined by (1→6) linkages. Galactomannans are found in a variety of plants but differ in molecular size and the number of D-galactosyl side chains. The galactomannans useful in this invention are commonly found in the endosperms of the leguminosae. Examples of the family of legumes are set forth in Table 1 which shows the family and the percent endosperm content of leguminous seeds.

TABLE 1

Estimated Endosperm Content of Leguminous Seeds

Family	Endosperm %	Family	Endosperm %
Acacia	1–15	Glottidium	2
Astragalos	2–3	Glymnocladus	15
Baryxylum	30	Indigofera	20
Caesalpinia	8–40	Lespedeza	1–4
Cassia	10–60	Leucaena	15
Cercidium	20	Lotus	2–4
Ceratonia (carob)	50	Lysiloma	4
Chamaecrista	8–15	Melilotus	8–12
Colvillea	30	Mimosa	3–30
Crotalaria	8–25	Onomis	25
Cyamopsis (guar)	50	Parkinsonia	25
Cytisus	15	Parryella	20
Dalea	20	Prosopis	15
Daubentonia	10–15	Schrankia	12
Delonix	25	Sesbania	20
Desmanthus	15	Sophora	20–25

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.