FISH & RICHARDSON P.C.

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One Marina Park Drive
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Frederick P. Fish
1855-1930

W.K. Richardson
1859-1951

January 29, 2014

Attorney Docket No.: 31215-0011003

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Presented for filing is a new continuation patent application for prioritized examination of:

ATLANTA
AUSTIN
BOSTON
DALLAS
DELAWARE
HOUSTON
MUNICH
NEW YORK
SILICON VALLEY
SOUTHERN CALIFORNIA
TWIN CITIES
WASHINGTON, DC

Inventor(s): AARON DODD, FELIX MEISER, MARCK NORRET, ADRIAN RUSSELL AND H. WILLIAM BOSCH

Title: A NOVEL FORMULATION OF DICLOFENAC

Enclosed are the following papers, including those required to receive a filing date under 37 C.F.R. § 1.53(b):

	Pages
Specification	84
Claims	22
Abstract	1
Declaration	6
Drawing(s)	20

Enclosures:

— Application Data Sheet, 8 pages.
— Preliminary amendment, 7 pages.
— New disclosure information, including:
Information disclosure statement, 1 page.
PTO-1449, 2 pages.
— Power of Attorney, 1 page.
— Statement under rule 3.73, 2 pages.
— Certification and Request for Prioritized Examination (Track I), 1 page

Applicant claims small entity status. See 37 CFR 1.27.

Basic Filing Fee			$70
Search Fee			$300
Examination Fee			$360
Publication fee			$0
Track I processing fee			$70
Track I prioritized examination fee			$2000
Total Claims 23	over 20	**3 x $40**	$120
Independent Claims 2	over 3	**0 x $210**	$0
Fee for Multiple Dependent claims			$0
Application size fee for each 50 pages over 100 Total Sheets: 127x .75 - 100/50 = 0x			$0
Total Filing fee			$2920

The filing fee in the amount of $2920 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply all charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 31215-0011003.

If this application is found to be incomplete, or if a telephone conference would otherwise be helpful, please call the undersigned at (617) 542-5070.

Please direct all correspondence to the following:

26161
PTO Customer Number

Respectfully submitted,

/Anita L. Meiklejohn/

Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283
Enclosures
ALM/mkf
23145505.doc

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	31215-0011003
	Application Number	
Title of Invention	A NOVEL FORMULATION OF DICLOFENAC	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Aaron		DODD	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Centennial Park, new South Wales	Country of Residence i	AU

Mailing Address of Inventor:

Address 1	368/58 Cook Road		
Address 2			
City	Centennial Park, new South Wales	State/Province	
Postal Code	2021	Country i	AU

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Felix		MEISER	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Mount Claremont, Western Australia	Country of Residence i	AU

Mailing Address of Inventor:

Address 1	7 Beecham Road		
Address 2			
City	Mount Claremont, Western Australia	State/Province	
Postal Code	6010	Country i	AU

Inventor 3 Remove

Legal Name

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	31215-0011003
	Application Number	
Title of Invention	A NOVEL FORMULATION OF DICLOFENAC	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Marck		NORRET	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Darlington, western Australia	Country of Residence i	AU

Mailing Address of Inventor:

Address 1	26 Stone Crescent		
Address 2			
City	Darlington, western Australia	State/Province	
Postal Code	6070	Country i	AU

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Adrian		RUSSELL	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Rivervale, western Australia	Country of Residence i	AU

Mailing Address of Inventor:

Address 1	139 Gladstone Road		
Address 2			
City	Rivervale, western Australia	State/Province	
Postal Code	6103	Country i	AU

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	H William		BOSCH	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Bryn Mawr	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	237 Rodney Circle		
Address 2			
City	Bryn Mawr	State/Province	PA
Postal Code	19010	Country i	US

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	31215-0011003
	Application Number	
Title of Invention	A NOVEL FORMULATION OF DICLOFENAC	

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	26161		
Email Address		Add Email	Remove Email

Application Information:

Title of the Invention	A NOVEL FORMULATION OF DICLOFENAC		
Attorney Docket Number	31215-0011003	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	20	**Suggested Figure for Publication (if any)**	

Filing By Reference :

Only compete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	31215-0011003
	Application Number	
Title of Invention	A NOVEL FORMULATION OF DICLOFENAC	

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	26161		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13/266122	2012-02-16
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/266122	a 371 of international	PCT/AU2010/000471	2010-04-23
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/AU2010/000471	Claims benefit of provisional	61172291	2009-04-24

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code [j] (if applicable)
2009901748	AU	2009-04-24	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	31215-0011003
	Application Number	
Title of Invention	A NOVEL FORMULATION OF DICLOFENAC	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	31215-0011003
	Application Number	
Title of Invention	A NOVEL FORMULATION OF DICLOFENAC	

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

(•) Assignee	( ) Legal Representative under 35 U.S.C. 117	( ) Joint Inventor
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. [X]

Organization Name	iCeutica Pty Ltd.		
Mailing Address Information:			
Address 1	Unit 2, 32 Mumford Place		
Address 2			
City	Balcatta	**State/Province**	WA
Country [i]	AU	Postal Code	6021
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. [ ]

PTO/AIA/14 (12-13)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	31215-0011003
	Application Number	
Title of Invention	A NOVEL FORMULATION OF DICLOFENAC	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Anita L. Meiklejohn/			Date (YYYY-MM-DD)	2014-01-29
First Name	Anita L.	Last Name	Meiklejohn	Registration Number	35283

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	A NOVEL FORMULATION OF DICLOFENAC

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Aaron Dodd Date (Optional): 29/1/2013

Signature: Aaron Dodd

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	A NOVEL FORMULATION OF DICLOFENAC

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This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Felix Meiser Date (Optional) : _____

Signature: Felix Meiser

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	A NOVEL FORMULATION OF DICLOFENAC

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Marck Norret Date (Optional): 25/1/2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Doc code: Oath
Document Description: Oath or declaration filed

PTO/AIA/02 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

SUBSTITUTE STATEMENT IN LIEU OF AN OATH OR DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (35 U.S.C. 115(d) AND 37 CFR 1.64)

Title of Invention	A novel formulation of diclofenac

This statement is directed to:

☒ The attached application,

OR

☐ United States application or PCT international application number _____ filed on _____

LEGAL NAME of inventor to whom this substitute statement applies:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Adrian Russell

Residence (except for a deceased or legally incapacitated inventor):

City	State	Country
Rivervale		AU

Mailing Address (except for a deceased or legally incapacitated inventor):

139 Gladstone Road

City	State	Zip	Country
Rivervale		6103	AU

I believe the above-named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application.

The above-identified application was made or authorized to be made by me.

I hereby acknowledge that any willful false statement made in this statement is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Relationship to the inventor to whom this substitute statement applies:

- ☐ Legal Representative (for deceased or legally incapacitated inventor only).
- ☒ Assignee.
- ☐ Person to whom the inventor is under an obligation to assign.
- ☐ Person who otherwise shows a sufficient proprietary interest in the matter (petition under 37 CFR 1.46 is required), or
- ☐ Joint Inventor.

PTO/SB/AIA02 (09-12)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

SUBSTITUTE STATEMENT

Circumstances permitting execution of this substitute statement:

- ☐ Inventor is deceased.
- ☐ Inventor is under legal incapacity.
- ■ Inventor cannot be found or reached after diligent effort, or
- ☐ Inventor has refused to execute the oath or declaration under 37 CFR 1.63.

If there are joint inventors, please check the appropriate box below:

- ☒ An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) naming the entire inventive entity has been or is currently submitted.

OR

- ☐ An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

Name: Matthew Callahan	Date (Optional): 25 JAN 13
Signature:	

Residence (unless provided in an application data sheet, PTO/AIA/14 or equivalent):

City: King of Prussia	State: PA	Country: US

Mailing Address (unless provided in an application data sheet, PTO/AIA/14 or equivalent)

3604 Horizon Drive, Suite 150

City: King of Prussia	State: PA	Zip: 19406	Country: US

Note: Use an additional PTO/AIA/02 form for each inventor who is deceased, legally incapacitated, cannot be found or reached after diligent effort, or has refused to execute the oath or declaration under 37 CFR 1.63.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	A NOVEL FORMULATION OF DICLOFENAC

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: H. William Bosch Date (Optional): 25 Jan 2013

Signature: H. William Bosch

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: iCeutica Pty Ltd.

Application No./Patent No.: _____ Filed/Issue Date: _____

Titled: A NOVEL FORMULATION OF DICLOFENAC

ICEUTICA PTY LTD., a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of the option 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title and interest (check applicable box):

☐ The extent (by percentage) of its ownership interest is _____. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of the options A or B below):

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 030912, Frame 0407, 0145, 0290, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

PTO/AIA/96 (08-129)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy *(i.e.,* a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Anita L. Meiklejohn/	29 January 2014
Signature	Date
Anita L. Meiklejohn, Ph.D.	35,283
Printed or Typed Name	Title or Registration Number

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☒ Practitioners associated with the Customer Number: 26161

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name Registration	Number		Name Registration	Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☒ The address associated with Customer Number: 26161

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

iCeutica Pty Ltd.
Unit 2, 32 Mumford Place
Balcatta WA 6021
AUSTRALIA

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date A	8/26/13
Name	Matthew Callahan	Telephone	610-383-5611
Title	CEO		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: iCeutica Pty Ltd.	Art Unit	: Unknown
Serial No.	: Unknown	Examiner	: Unknown
Filed	: Herewith		
Title	: A NOVEL FORMULATION OF DICLOFENAC		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-1449 Form. Cited U.S. patents and patent application publications will be provided on request.

Under 35 USC §120, this application relies on the earlier filing date of application serial number 13/266,122, filed on February 16, 2012 and 13/750,869, filed on January 25, 2013. The references were submitted to and/or cited by the Office in the prior application and, therefore, are not provided in this application.

This statement is being filed with the application. Please apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: 29 January 2014

/Anita L. Meiklejohn/
Anita L. Meiklejohn, Ph.D.
Reg. No. 35,283

Customer Number 26161
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60901079.doc

Substitute Disclosure Form	U.S. Department of Commerce Patent and Trademark Office	Attorney Docket No. 31215-0011003	Application No. Unknown
Information Disclosure Statement by Applicant (Use several sheets if necessary)		Applicant iCeutica Pty Ltd.	
(37 CFR §1.98(b))		Filing Date Herewith	Group Art Unit Unknown

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	1	5,478,705	11/26/1995	Czekai et al.			
	2	6,634,576	10/21/2003	Verhoff et al.			
	3	7,101,576	09/05/2006	Hovey et al.			
	4	2004/0022846	02/05/2004	Depui et al.			
	5	2009/0028948	01/29/2009	Payne et al.			
	6	2010/0092563	04/15/2010	Cammarano et al.			
	7	2012/0135047	05/31/2012	Dodd et al.			
	8	2013/0209569	08/15/2013	Dodd et al.			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	9	WO 2006/069419	07/06/2006	WIPO				
	10	WO 2006/133954	12/21/2006	WIPO				
	11	WO 2007/070851	06/21/2007	WIPO				
	12	WO 2007/070852	06/21/2007	WIPO				
	13	WO 2008/000042	01/03/2008	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	14	Sharon Hertz, MD; NDA Approval letter, NDA No. 204592; reference ID 3392875; Deputy Director, Division of Anesthesia, Analgesia and Adduction Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research; October 18, 2013; 6 pages

Examiner Signature	Date Considered
EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

Substitute Disclosure Form

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: iCeutica Pty Ltd.	Art Unit	: Unknown
Serial No.	: Not Yet Assigned	Examiner	: Unknown
Filed	: Herewith		
Title	: A NOVEL FORMULATION OF DICLOFENAC		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as indicated on the following pages.

Amendments to the Specification:

Please add the following new paragraph after the Title at page 1, line 3:

Related Applications

This application is a continuation and claims priority to U.S. Application Serial No. 13/266,122, filed February 16, 2012, which is a U.S. national stage under 35 USC §371 of International Application Number PCT/AU2010/000471, filed on 23 April 2010, which claims priority to AU Application No. 2009901748, filed on 24 April 2009 and US Application No. 61/172,291, filed on 24 April 2009, the entire contents of which applications is hereby incorporated by reference.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. -41. (Cancelled)

42. (New) A method for treating pain comprising administering a unit dose of a pharmaceutical composition containing 18 mg of diclofenac acid wherein the particles of diclofenac acid have a median particle size, on a volume average, of less than 1000 nm and greater than 25 nm, wherein the unit dose, when tested in vitro by USP Apparatus I (Basket) method of U.S. Pharmacopoeia at 100 rpm, at 37 °C in 900 ml of 0.05% sodium lauryl sulfate in citric acid solution buffered to pH 5.75, has a dissolution rate of diclofenac acid such that at least 91%, by weight, is released by 45 minutes.

43. (New) The method of claim 42, wherein the particles of diclofenac acid have a median particle size, on a volume average, of less than 800 nm and greater than 25 nm.

44. (New) The method of claim 42, wherein the particles of diclofenac acid have a median particle size, on a volume average, of less than 600 nm and greater than 25 nm.

45. (New) The method of claim 42, wherein the pain is acute pain.

46. (New) The method of claim 42, wherein the pain is chronic pain.

47. (New) The method of claim 42, wherein the unit dose has a dissolution rate of diclofenac acid such that at least 91%, by weight, is released by 30 minutes.

48. (New) The method of claim 43, wherein the unit dose has a dissolution rate of diclofenac acid such that at least 91%, by weight, is released by 30 minutes.

49. (New) The method of claim 44, wherein the unit dose has a dissolution rate of diclofenac acid such that at least 94%, by weight, is released by 45 minutes.

50. (New) The method of claim 42 wherein the unit dose comprises a hard gelatin capsule.

51. (New) The method of claim 43 wherein the unit dose comprises a hard gelatin capsule.

52. (New) The method of claim 44 wherein the unit dose comprises a hard gelatin capsule.

53. (New) A method for treating pain comprising administering a unit dose of a pharmaceutical composition containing 35 mg of diclofenac acid wherein the particles of diclofenac acid have a median particle size, on a volume average, of less than 1000 nm and greater than 25 nm, wherein the unit dose, when tested in vitro by USP Apparatus I (Basket) method of U.S. Pharmacopoeia at 100 rpm at 37 °C in 900 ml of 0.05% sodium lauryl sulfate in citric acid solution buffered to pH 5.75, has a dissolution rate of diclofenac acid such that at least 82%, by weight, is released by 45 minutes.

54. (New) The method of claim 53, wherein the particles of diclofenac acid have a median particle size, on a volume average, of less than 800 nm and greater than 25 nm.

55. (New) The method of claim 53, wherein the particles of diclofenac acid have a median particle size, on a volume average, of less than 600 nm and greater than 25 nm.

56. (New) The method of claim 53, wherein the pain is acute pain.

57. (New) The method of claim 53, wherein the pain is chronic pain.

58. (New) The method of claim 53, wherein the unit dose has a dissolution rate of diclofenac acid such that at least 82%, by weight, is released by 30 minutes.

59. (New) The method of claim 53, wherein the unit dose has a dissolution rate of diclofenac acid such that at least 95%, by weight, is released by 45 minutes.

60. (New) The method of claim 53, wherein the unit dose has a dissolution rate of diclofenac acid such that at least 95%, by weight, is released by 30 minutes.

61. (New) The method of claim 53 wherein the unit dose comprises a hard gelatin capsule.

62. (New) The method of claim 54 wherein the unit dose comprises a hard gelatin capsule.

63. (New) The method of claim 55 wherein the unit dose comprises a hard gelatin capsule.

64. (New) The method of claim 42, wherein the unit dose further comprises lactose and sodium lauryl sulfate.

65. (New) The method of claim 43, wherein the unit dose further comprises lactose and sodium lauryl sulfate.

66. (New) The method of claim 44, wherein the unit dose further comprises lactose and sodium lauryl sulfate.

67. (New) The method of claim 53, wherein the unit dose further comprises lactose and sodium lauryl sulfate.

68. (New) The method of claim 54, wherein the unit dose further comprises lactose and sodium lauryl sulfate.

69. (New) The method of claim 42, wherein the unit dose further comprises lactose and sodium lauryl sulfate.

70. (New) The method of claim 43, wherein the D(90) of the diclofenac particles, on a particle volume basis, is less than 3000 nm.

71. (New) The method of claim 54, wherein the D(90) of the diclofenac particles, on a particle volume basis, is less than 3000 nm.

REMARKS

Upon entry of this amendment, claims 42-71 will be pending in the application. Claims 1-41 have been cancelled, and claims 42-71 have been newly added. No new matter is being added.

Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 31215-0011003.

Respectfully submitted,

Date: 29 January 2014

/Anita L. Meiklejohn/

Anita L. Meiklejohn, Ph.D.
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A Novel Formulation of Diclofenac

Field of the Invention

The present invention relates to methods for producing particles of diclofenac using dry milling processes as well as compositions comprising diclofenac, medicaments produced using diclofenac in particulate form and/or compositions, and to methods of treatment of an animal, including man, using a therapeutically effective amount of diclofenac administered by way of said medicaments.

Background

Poor bioavailability is a significant problem encountered in the development of compositions in the therapeutic, cosmetic, agricultural and food industries, particularly those materials containing a biologically active material that is poorly soluble in water at physiological pH. An active material's bioavailability is the degree to which the active material becomes available to the target tissue in the body or other medium after systemic administration through, for example, oral or intravenous means. Many factors affect bioavailability, including the form of dosage and the solubility and dissolution rate of the active material.

In therapeutic applications, poorly and slowly water-soluble materials tend to be eliminated from the gastrointestinal tract before being absorbed into the circulation. In addition, poorly soluble active agents tend to be disfavored or even unsafe for intravenous administration due to the risk of particles of agent blocking blood flow through capillaries.

It is known that the rate of dissolution of a particulate drug will increase with increasing surface area. One way of increasing surface area is decreasing particle size. Consequently, methods of making finely divided or sized drugs have been studied with a view to controlling the size and size range of drug particles for pharmaceutical compositions.

For example, dry milling techniques have been used to reduce particle size and hence influence drug absorption. However, in conventional dry milling the limit of fineness is reached generally in the region of about 100 microns (100,000 nm), at which point material cakes on the milling chamber and prevents any further diminution of particle size. Alternatively, wet grinding may be employed to reduce particle size, but flocculation restricts the lower particle size limit to approximately 10 microns (10,000 nm). The wet milling process, however, is prone to contamination, thereby leading to a bias in the pharmaceutical art against wet milling. Another alternative milling technique, commercial airjet milling, has provided particles ranging in average size from as low as about 1 to about 50 microns (1,000-50,000 nm).

There are several approaches currently used to formulate poorly soluble active agents. One approach is to prepare the active agent as a soluble salt. Where this approach cannot be employed, alternate (usually physical) approaches are employed to improve the solubility of the active agent. Alternate approaches generally subject the active agent to physical conditions

that change the agent's physical and or chemical properties to improve its solubility. These include process technologies such as micronization, modification of crystal or polymorphic structure, development of oil based solutions, use of co-solvents, surface stabilizers or complexing agents, micro-emulsions, supercritical fluid and production of solid dispersions or solutions. More than one of these processes may be used in combination to improve formulation of a particular therapeutic material. Many of these approaches commonly convert a drug into an amorphous state, which generally leads to a higher dissolution rate. However, formulation approaches that result in the production of amorphous material are not common in commercial formulations due to concerns relating to stability and the potential for material to re-crystallize.

These techniques for preparing such pharmaceutical compositions tend to be complex. By way of example, a principal technical difficulty encountered with emulsion polymerization is the removal of contaminants, such as unreacted monomers or initiators (which may have undesirable levels of toxicity), at the end of the manufacturing process.

Another method of providing reduced particle size is the formation of pharmaceutical drug microcapsules, which techniques include micronizing, polymerisation and co-dispersion. However, these techniques suffer from a number of disadvantages including at least the inability to produce sufficiently small particles such as those obtained by milling, and the presence of co-solvents and/or contaminants such as toxic monomers which are difficult to remove, leading to expensive manufacturing processes.

Over the last decade, intense scientific investigation has been carried out to improve the solubility of active agents by converting the agents to ultra fine powders by methods such as milling and grinding. These techniques may be used to increase the dissolution rate of a particulate solid by increasing the overall surface area and decreasing the mean particle size.

US Patent 6,634,576 discloses examples of wet-milling a solid substrate, such as a pharmaceutically active compound, to produce a "synergetic co-mixture".

International Patent Application PCT/AU2005/001977 (Nanoparticle Composition(s) and Method for Synthesis Thereof) describes, *inter alia*, a method comprising the step of contacting a precursor compound with a co-reactant under mechanochemical synthesis conditions wherein a solid-state chemical reaction between the precursor compound and the co-reactant produces therapeutically active nanoparticles dispersed in a carrier matrix. Mechanochemical synthesis, as discussed in International Patent Application PCT/AU2005/001977, refers to the use of mechanical energy to activate, initiate or promote a chemical reaction, a crystal structure transformation or a phase change in a material or a mixture of materials, for example by agitating a reaction mixture in the presence of a milling media to transfer mechanical energy to the reaction mixture, and includes without limitation "mechanochemical activation", "mechanochemical processing", "reactive milling", and related processes.

International Patent Application PCT/AU2007/000910 (Methods for the preparation of biologically active compounds in nanoparticulate form) describes, *inter alia*, a method for dry milling raloxifene with lactose and NaCl which produced nanoparticulate raloxifene without significant aggregation problems.

One limitation of many of the prior art processes is that they are not suitable for commercial scale milling. The present invention provides methods for overcoming the problems identified by the prior art by providing a milling process which provides particles with increased surface area, yet can also be scaled up to a commercial scale.

One example of a therapeutic area where this technology could be applied in is the area of acute pain management. Many pain medications such as diclofenac are commonly prescribed as pain relief for chronic pain. As a result they are commonly taken on a daily basis to maintain an effective therapeutic level. Diclofenac is a poorly water soluble drug so dissolution and absorbtion to the body is slow. So a method such as the present invention which provides for improved dissolution, will likely provide much faster absorption resulting in a more rapid onset of the therapeutic effect. By using a method such as the present invention, which provides faster absorption, a drug such as diclofenac, could be used more readily to treat acute pain as well as chronic pain.

Although the background to the present invention is discussed in the context of improving the bioavailability of materials that are poorly or slowly water soluble, the applications of the methods of the present invention are not limited to such, as is evident from the following description of the invention.

Further, although the background to the present invention is largely discussed in the context of improving the bioavailability of therapeutic or pharmaceutical compounds, the applications of the methods of the present invention are clearly not limited to such. For example, as is evident from the following description, applications of the methods of the present invention include but are not limited to: nutraceutical and nutritional compounds, complementary medicinal compounds, veterinary therapeutic applications and agricultural chemical applications, such as pesticide, fungicide or herbicide.

Furthermore an application of the current invention would be to materials which contain a biologically active compound such as, but not limited to a therapeutic or pharmaceutical compound, a nutraceutical or nutrient, a complementary medicinal product such as active components in plant or other naturally occurring material, a veterinary therapeutic compound or an agricultural compound such as a pesticide, fungicide or herbicide. Specific examples would be the spice turmeric that contains the active compound curcumin, or flax seed that contains the nutrient ALA an omega 3 fatty acid. As these specific examples indicate this invention could be applied to, but not limited to, a range of natural products such as seeds, cocoa and cocoa solids, coffee, herbs, spices, other plant materials or food materials that contain a biologically active compound. The application of this invention to these types of materials would enable

greater availability of the active compound in the materials when used in the relevant application. For example where material subject to this invention is orally ingested the active would be more bioavailable.

Summary of the Invention

In one aspect the present invention is directed to the unexpected finding that particles of a biologically active material can be produced by dry milling processes at commercial scale. In one surprising aspect the particle size produced by the process is equal to or less than 2000nm. In another surprising aspect the particle size produced by the process is equal to or less than 1000nm. In another surprising aspect the crystallinity of the active material is unchanged or not substantially changed. In a preferred embodiment the present invention is directed to the unexpected finding that particles of diclofenac can be produced by dry milling processes at commercial scale.

Thus in a first aspect the invention comprises a method producing a composition, comprising the steps of dry milling a solid biologically active material and a millable grinding matrix in a mill comprising a plurality of milling bodies, for a time period sufficient to produce particles of the biologically active material dispersed in an at least partially milled grinding material.

In one preferred embodiment, the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the average particle size is equal to or greater than 25nm.

In another preferred embodiment, the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the median particle size is equal to or greater than 25nm. Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 50%, 60%, 70%, 80%, 90%, 95% and 100 % less than 2000nm (% < 2000 nm). Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 50%, 60%, 70%, 80%, 90%, 95% and 100 % less than 1000nm (% < 1000 nm). Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than 500nm (% < 500 nm). Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than 300nm (% < 300 nm). Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than 200nm (% < 200 nm). Preferably, the Dx of the particle size distribution, as

measured on a particle volume basis, is selected from the group consisting of less than or equal to 10,000nm, 5000nm, 3000nm, 2000nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm, and 100 nm; wherein x is greater than or equal to 90.

In another preferred embodiment, the crystallinity profile of the biologically active material is selected from the group consisting of: at least 50% of the biologically active material is crystalline, at least 60% of the biologically active material is crystalline, at least 70% of the biologically active material is crystalline, at least 75% of the biologically active material is crystalline, at least 85% of the biologically active material is crystalline, at least 90% of the biologically active material is crystalline, at least 95% of the biologically active material is crystalline and at least 98% of the biologically active material is crystalline. More preferably, the crystallinity profile of the biologically active material is substantially equal to the crystallinity profile of the biologically active material before the material was subjected to the method as described herein.

In another preferred embodiment, the amorphous content of the biologically active material is selected from the group consisting of: less than 50% of the biologically active material is amorphous, less than 40% of the biologically active material is amorphous, less than 30% of the biologically active material is amorphous, less than 25% of the biologically active material is amorphous, less than 15% of the biologically active material is amorphous, less than 10% of the biologically active material is amorphous, less than 5% of the biologically active material is amorphous and less than 2% of the biologically active material is amorphous. Preferably, the biologically active material has no significant increase in amorphous content after subjecting the material to the method as described herein.

In another preferred embodiment, the milling time period is a range selected from the group consisting of: between 10 minutes and 2 hours, between 10 minutes and 90 minutes, between 10 minutes and 1 hour, between 10 minutes and 45 minutes, between 10 minutes and 30 minutes, between 5 minutes and 30 minutes, between 5 minutes and 20 minutes, between 2 minutes and 10 minutes, between 2 minutes and 5 minutes, between 1 minutes and 20 minutes, between 1 minute and 10 minutes, and between 1 minute and 5 minutes.

In another preferred embodiment, the milling medium is selected from the group consisting of: ceramics, glasses, polymers, ferromagnetics and metals. Preferably, the milling medium is steel balls having a diameter selected from the group consisting of: between 1 and 20 mm, between 2 and 15 mm and between 3 and 10 mm. In another preferred embodiment, the milling medium is zirconium oxide balls having a diameter selected from the group consisting of: between 1 and 20 mm, between 2 and 15 mm and between 3 and 10 mm. Preferably, the dry milling apparatus is a mill selected from the group consisting of: attritor mills (horizontal or vertical), nutating mills, tower mills, pearl mills, planetary mills, vibratory mills, eccentric vibratory mills, gravity-dependent-type ball mills, rod mills, roller mills and crusher mills.

Preferably, the milling medium within the milling apparatus is mechanically agitated by 1, 2 or 3 rotating shafts. Preferably, the method is configured to produce the biologically active material in a continuous fashion.

Preferably, the total combined amount of biologically active material and grinding matrix in the mill at any given time is equal to or greater than a mass selected from the group consisting of: 200 grams, 500 grams, 1 kg, 2kg, 5kg, 10kg, 20kg, 30kg, 50kg, 75kg, 100kg, 150kg, 200kg. Preferably, the total combined amount of biologically active material and grinding matrix is less than 2000kg.

Preferably, the biologically active material is selected from the group consisting of: diclofenac or a derivative or salt thereof.

In another preferred embodiment, the grinding matrix is a single material or is a mixture of two or more materials in any proportion. Preferably, the single material or a mixture of two or more materials is selected from the group consisting of: mannitol, sorbitol, Isomalt, xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, glucose, fructose, mannose, galactose, anhydrous lactose, lactose monohydrate, sucrose, maltose, trehalose, maltodextrins, dextrin, Inulin, dextrates, polydextrose, starch, wheat flour, corn flour, rice flour, rice starch, tapioca flour, tapioca starch, potato flour, potato starch, other flours and starches, milk powder, skim milk powders, other milk solids and dreviatives, soy flour, soy meal or other soy products, cellulose, microcystalline cellulose, microcystalline cellulose based co-blended materials, pregelatinized (or partially) starch, HPMC, CMC, HPC, citric acid, tartaric acid, malic acid, maleic acid fumaric acid, ascorbic acid, succinic acid, sodium citrate, sodium tartrate, sodium malate, sodium ascorbate, potassium citrate, potassium tartrate, potassium malate, sodium acetate, potassium ascorbate, sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, sodium sulfate, sodium chloride, sodium metabisulphite, sodium thiosulfate, ammonium chloride, glauber's salt, ammonium carbonate, sodium bisulfate, magnesium sulfate, potash alum, potassium chloride, sodium hydrogen sulfate, sodium hydroxide, crystalline hydroxides, hydrogen carbonates, ammonium chloride, methylamine hydrochloride, ammonium bromide, silica, thermal silica, alumina, titanium dioxide, talc, chalk, mica, kaolin, bentonite, hectorite, magnesium trisilicate, clay based materials or aluminium silicates, sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188,poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35

castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, sucrose palmitate, sucrose stearate, sucrose distearate, sucrose laurate, glycocholic acid, sodium glycholate, cholic acid, soidum cholate, sodium deoxycholate, deoxycholic acid, sodium taurocholate, taurocholic acid, sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend, calcium dodecylbenzene sulfonate, sodium dodecylbenzene sulfonate, diisopropyl naphthaenesulphonate, erythritol distearate, naphthalene sulfonate formaldehyde condensate, nonylphenol ethoxylate (poe-30), tristyrylphenol ethoxylate, polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, sodium methyl naphthalene formaldehyde sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), triethanolamine isodecanol phosphate ester, triethanolamine tristyrylphosphate ester, tristyrylphenol ethoxylate sulfate, bis(2-hydroxyethyl)tallowalkylamines. Preferably, the concentration of the single (or first) material is selected from the group consisting of: 5 - 99 % w/w, 10 - 95 % w/w, 15 - 85 % w/w, of 20 – 80% w/w, 25 - 75 % w/w, 30 - 60% w/w, 40 -50% w/w. Preferably, the concentration of the second or subsequent material is selected from the group consisting of: 5 - 50 % w/w, 5 - 40 % w/w, 5 - 30 % w/w, of 5 – 20% w/w, 10 - 40 % w/w, 10 -30% w/w, 10 -20% w/w, 20 - 40% w/w, or 20 - 30% w/w or if the second or subsequent material is a surfactant or water soluble polymer the concentration is selected from 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

Preferably, the grinding matrix is selected from the group consisting of:

(a) lactose monohydrate or lactose monohydrate combined with at least one material selected from the group consisting of: xylitol; lactose anhydrous; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium

lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(b) lactose anhydrous or lactose anhydrous combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(c) mannitol or mannitol combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(d) Sucrose or sucrose combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend;

Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(e) Glucose or glucose combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(f) Sodium chloride or sodium chloride combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol;

microcrystalline cellulose; sucrose; glucose; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(g) xylitol or xylitol combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched);

Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(h) Tartaric acid or tartaric acid combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(i) microcrystalline cellulose or microcrystalline cellulose combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; sucrose; glucose; sodium chloride; talc; kaolin; calcium

carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(j) Kaolin combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene

sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

(k) Talc combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

Preferably, the grinding matrix is selected from the group consisting of: a material considered to be 'Generally Regarded as Safe' (GRAS) for pharmaceutical products; a material considered acceptable for use in an agricultural formulation; and a material considered acceptable for use in a veterinary formulation.

In another preferred embodiment, a milling aid or combination of milling aids is used. Preferably, the milling aid is selected from the group consisting of: colloidal silica, a surfactant, a polymer, a stearic acid and derivatives thereof. Preferably, the surfactant is selected from the group consisting of: polyoxyethylene alkyl ethers, polyoxyethylene stearates, polyethylene glycols (PEG), poloxamers, poloxamines, sarcosine based surfactants, polysorbates, aliphatic alcohols, alkyl and aryl sulfates, alkyl and aryl polyether sulfonates and other sulfate surfactants, trimethyl ammonium based surfactants, lecithin and other phospholipids, bile salts, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, Sorbitan fatty acid esters, Sucrose fatty acid esters, alkyl glucopyranosides, alkyl maltopyranosides, glycerol fatty acid esters, Alkyl Benzene Sulphonic Acids, Alkyl Ether Carboxylic Acids, Alkyl and aryl Phosphate esters, Alkyl and aryl Sulphate esters, Alkyl and aryl Sulphonic acids, Alkyl Phenol Phosphates esters, Alkyl Phenol Sulphates esters, Alkyl and Aryl Phosphates, Alkyl Polysaccharides, Alkylamine Ethoxylates, Alkyl-Naphthalene Sulphonates formaldehyde condensates, Sulfosuccinates, lignosulfonates, Ceto-Oleyl Alcohol Ethoxylates, Condensed Naphthalene Sulphonates, Dialkyl and Alkyl Naphthalene Sulphonates, Di-alkyl Sulphosuccinates, Ethoxylated nonylphenols, Ethylene Glycol Esters, Fatty Alcohol Alkoxylates, Hydrogenated tallowalkylamines, Mono-alkyl Sulphosuccinamates, Nonyl Phenol Ethoxylates, Sodium Oleyl N-methyl Taurate, Tallowalkylamines, linear and branched dodecylbenzene sulfonic acids

Preferably, the surfactant is selected from the group consisting of: sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, , poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, Sucrose Palmitate, Sucrose Stearate, Sucrose Distearate, Sucrose laurate, Glycocholic acid, sodium Glycholate, Cholic Acid, Soidum Cholate, Sodium Deoxycholate, Deoxycholic acid, Sodium taurocholate, taurocholic acid, Sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend,Calcium Dodecylbenzene Sulfonate, Sodium

Dodecylbenzene Sulfonate,Diisopropyl naphthaenesulphonate, erythritol distearate, Naphthalene Sulfonate Formaldehyde Condensate, nonylphenol ethoxylate (poe-30), Tristyrylphenol Ethoxylate, Polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, Sodium Methyl Naphthalene Formaldehyde Sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), Triethanolamine isodecanol phosphate ester, Triethanolamine tristyrylphosphate ester, Tristyrylphenol Ethoxylate Sulfate, Bis(2-hydroxyethyl)tallowalkylamines.

Preferably the polymer is selected from the list of: polyvinylpyrrolidones (PVP), polyvinylalcohol, acrylic acid based polymers and copolymers of acrylic acid

Preferably, the milling aid has a concentration selected from the group consisting of: 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

In another preferred embodiment of the invention, a facilitating agent is used or combination of facilitating agents is used. Preferably, the facilitating agent is selected from the group consisting of: surfactants, polymers, binding agents, filling agents, lubricating agents, sweeteners, flavouring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, agents that may form part of a medicament, including a solid dosage form or a dry powder inhalation formulation and other material required for specific drug delivery. Preferably, the facilitating agent is added during dry milling. Preferably, the facilitating agent is added to the dry milling at a time selected from the group consisting of: with 1-5 % of the total milling time remaining, with 1-10 % of the total milling time remaining, with 1-20 % of the total milling time remaining, with 1-30 % of the total milling time remaining, with 2-5% of the total milling time remaining, with 2-10% of the total milling time remaining, with 5-20% of the total milling time remaining and with 5-20% of the total milling time remaining. Preferably, the disintegrant is selected from the group consisting of: crosslinked PVP, cross linked carmellose and sodium starch glycolate. Preferably, the facilitating agent is added to the milled biologically active material and grinding matrix and further processed in a mechanofusion process. Mechanofusion milling causes mechanical energy to be applied to powders or mixtures of particles in the micrometre and nanometre range.

The reasons for including facilitating agents include, but are not limited to providing better dispersibility, control of agglomeration, the release or retention of the active particles from the delivery matrix. Examples of facilitating agents include, but are not limited to crosslinked PVP (crospovidone), cross linked carmellose (croscarmellose), sodium starch glycolate, Povidone (PVP), Povidone K12, Povidone K17, Povidone K25, Povidone K29/32 and Povidone K30, stearic acid, magnesium stearate, calcium stearate, sodium stearyl fumarate, sodium stearyl lactylate, zinc stearate, sodium stearate or lithium stearate, other solid state fatty acids such as oleic acid, lauric acid, palmitic acid, erucic acid, behenic acid, or derivatives (such as esters

and salts), Amino acids such as leucine, isoleucine, lysine, valine, methionine, phenylalanine, aspartame or acesulfame K. In a preferred aspect of manufacturing this formulation the facilitating agent is added to the milled mixture of biologically active material and co-grinding matrix and further processed in another milling device such as Mechnofusion, Cyclomixing, or impact milling such as ball milling, jet milling, or milling using a high pressure homogeniser, or combinations thereof. In a highly preferred aspect the facilitating agent is added to the milling of the mixture of biologically active material and co-grinding matrix as some time before the end of the milling process.

In another preferred embodiment, diclofenac is milled with lactose monohydrate and alkyl sulfates. Preferably diclofenac is milled with lactose monohydrate and sodium lauryl sulfate. Preferably diclofenac is milled with lactose monohydrate and sodium octadecyl sulfate. In another preferred embodiment, Diclofenac is milled with lactose monohydrate, alkyl sulfates and another surfactant or polymers. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyether sulfates. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyethylene glycol 40 stearate. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyethylene glycol 100 stearate. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and a poloxamer. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and poloxamer 407. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and poloxamer 338. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and poloxamer 188. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and a solid polyethylene glycol. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyethylene glycol 6000. Preferably diclofenac is milled with lactose monohydrate, sodium lauryl sulfate and polyethylene glycol 3000. In another preferred embodiment, Diclofenac is milled with lactose monohydrate and polyether sulfates. Preferably diclofenac is milled with lactose monohydrate and polyethylene glycol 40 stearate. Preferably diclofenac is milled with lactose monohydrate and polyethylene glycol 100 stearate In another preferred embodiment diclofenac is milled with lactose monohydrate and polyvinyl-pyrrolidine. Preferably diclofenac is milled with lactose monohydrate and polyvinyl-pyrrolidone with an approximate molecular weight of 30,000-40,000. In another preferred embodiment, diclofenac is milled with lactose monohydrate and alkyl sulfonates. Preferably diclofenac is milled with lactose monohydrate and docusate sodium. In another preferred embodiment, diclofenac is milled with lactose monohydrate and a surfactant. Preferably diclofenac is milled with lactose monohydrate and lecithin. Preferably diclofenac is milled with lactose monohydrate and sodium n-lauroyl sarcosine. Preferably diclofenac is milled with lactose monohydrate and polyoxyethylene alkyl ether surfactants. Preferably diclofenac is milled with lactose monohydrate and PEG 6000. In another preferred formulation diclofenac is milled with lactose monohydrate and silica. Preferably diclofenac is milled with lactose monohydrate and Aerosil

R972 fumed silica. In another preferred embodiment, diclofenac is milled with with lactose monohydrate, tartaric acid and sodium lauryl sulfate. In another preferred embodiment, diclofenac is milled with with lactose monohydrate, sodium bicarbonate and sodium lauryl sulfate. In another preferred embodiment, diclofenac is milled with lactose monohydrate, potassium bicarbonate and sodium lauryl sulfate.In another preferred embodiment, diclofenac is milled with mannitol and alkyl sulfates. Preferably diclofenac is milled with mannitol and sodium lauryl sulfate. Preferably diclofenac is milled with mannitol and sodium octadecyl sulfate. In another preferred embodiment, Diclofenac is milled with mannitol, alkyl sulfates and another surfactant or polymers. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyether sulfates. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyethylene glycol 40 stearate. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyethylene glycol 100 stearate. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and a poloxamer. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and poloxamer 407. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and poloxamer 338. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and poloxamer 188. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and a solid polyethylene glycol. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyethylene glycol 6000. Preferably diclofenac is milled with mannitol, sodium lauryl sulfate and polyethylene glycol 3000. In another preferred embodiment, Diclofenac is milled with mannitol and polyether sulfates. Preferably diclofenac is milled with mannitol and polyethylene glycol 40 stearate. Preferably diclofenac is milled with mannitol and polyethylene glycol 100 stearate In another preferred embodiment diclofenac is milled with mannitol and polyvinyl-pyrrolidine. Preferably diclofenac is milled with mannitol and polyvinyl-pyrrolidone with an approximate molecular weight of 30,000-40,000. In another preferred embodiment, diclofenac is milled with mannitol and alkyl sulfonates. Preferably diclofenac is milled with mannitol and docusate sodium. In another preferred embodiment, diclofenac is milled with mannitol and a surfactant. Preferably diclofenac is milled with mannitol and lecithin. Preferably diclofenac is milled with mannitol and sodium n-lauroyl sarcosine. Preferably diclofenac is milled with mannitol and polyoxyethylene alkyl ether surfactants. Preferably diclofenac is milled with mannitol and PEG 6000. In another preferred formulation diclofenac is milled with mannitol and silica. Preferably diclofenac is milled with mannitol and Aerosil R972 fumed silica. In another preferred embodiment, diclofenac is milled with with mannitol, tartaric acid and sodium lauryl sulfate. In another preferred embodiment, diclofenac is milled with with mannitol, sodium bicarbonate and sodium lauryl sulfate. In another preferred embodiment, diclofenac is milled with mannitol, potassium bicarbonate and sodium lauryl sulfate.

In a second aspect the invention comprises a biologically active material produced by the method described herein and composition comprising the biologically active material as described herein. Preferably, the average particle size, determined on a particle number basis,

is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the average particle size is equal to or greater than 25nm. Preferably, the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the median particle size is equal to or greater than 25nm. Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 50%, 60%, 70%, 80%, 90%, 95% and 100 % less than 2000nm (% < 2000 nm). Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 50%, 60%, 70%, 80%, 90%, 95% and 100 % less than 1000nm (% < 1000 nm). Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than 500nm (% < 500 nm). Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than 300nm (% < 300 nm). Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than 200nm (% < 200 nm). Preferably, the Dx of the particle size distribution, as measured on a particle volume basis, is selected from the group consisting of less than or equal to 10,000nm, 5000nm, 3000nm, 2000nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm, and 100 nm; wherein x is greater than or equal to 90. Preferably, the crystallinity profile of the biologically active material is selected from the group consisting of: at least 50% of the biologically active material is crystalline, at least 60% of the biologically active material is crystalline, at least 70% of the biologically active material is crystalline, at least 75% of the biologically active material is crystalline, at least 85% of the biologically active material is crystalline, at least 90% of the biologically active material is crystalline, at least 95% of the biologically active material is crystalline and at least 98% of the biologically active material is crystalline. Preferably, the crystallinity profile of the biologically active material is substantially equal to the crystallinity profile of the biologically active material before the material was subject to the method described herein. Preferably, the amorphous content of the biologically active material is selected from the group consisting of: less than 50% of the biologically active material is amorphous, less than 40% of the biologically active material is amorphous, less than 30% of the biologically active material is amorphous, less than 25% of the biologically active material is amorphous, less than 15% of the biologically active material is amorphous, less than 10% of the biologically active material is amorphous, less than 5% of the biologically active material is amorphous and less than 2% of the biologically active

material is amorphous. Preferably, the biologically active material has had no significant increase in amorphous content following subjecting the material to the method as described herein.

In one preferred embodiment, the invention comprises compositions comprising the biologically active ingredient together with a grinding matrix, a mixture of grinding matrix materials, milling aids, mixtures of milling aids, facilitating agents and/or mixtures of facilitating agents as described herein, in concentrations and ratios as described herein under the methods of the invention.

In a third aspect the invention comprises a pharmaceutical composition comprising a biologically active material produced by the method described herein and compositions described herein. Preferably, the invention comprises pharmaceutical compositions comprising the biologically active ingredient together with a grinding matrix, a mixture of grinding matrix materials, milling aids, mixtures of milling aids, facilitating agents and/or mixtures of facilitating agents as described herein, in concentrations and ratios as described herein under the methods of the invention. Preferably, the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the average particle size is equal to or greater than 25nm. Preferably, the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm. Preferably, the median particle size is equal to or greater than 25nm. Preferably, the percentage of particles, on a particle volume basis, is selected from the group consisting of: less than 2000nm (% < 2000 nm) is selected from the group consisting of: 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 1000nm (% < 1000 nm) is selected from the group consisting of: 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 500nm (% < 500 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; less than 300nm (% < 300 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %; and less than 200nm (% < 200 nm) is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 %. Preferably, the composition has a T_{max} less than that of the equivalent conventional composition administered at the same dosage, wherein the composition comprises diclofenac. Preferably, the composition has a C_{max} greater than that of the equivalent conventional composition administered at the same dosage, wherein the composition comprises diclofenac. Preferably, the composition has an AUC greater than that of the equivalent conventional composition administered at the same dosage, wherein the composition comprises diclofenac.

In a fourth aspect the invention comprises a method of treating a human in need of such treatment comprising the step of administering to the human an effective amount of a pharmaceutical composition as described herein.

In a fifth aspect, the invention comprises the use of a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of a human in need of such treatment.

In a sixth aspect the invention comprises a method for manufacturing a pharmaceutical composition as described herein comprising the step of combining a therapeutically effective amount of a biologically active material prepared by a method described herein or a composition as described herein, together with a pharmaceutically acceptable carrier to produce a pharmaceutically acceptable dosage form.

In a seventh aspect the invention comprises a method for manufacturing a veterinary product comprising the step of combining a therapeutically effective amount of the biologically active material prepared by a method as described herein or a composition as described herein, together with an acceptable excipient to produce a dosage form acceptable for veterinary use.

In an eighth aspect the invention comprises a method for manufacturing of a pharmaceutical formulation comprising the step of combining an effective amount of the biologically active material prepared by a method described herein together with acceptable excipients to produce a formulation that can deliver a therapeutically effective amount of active to the pulmonary or nasal area. Such a formulation could be, but is not limited to a dry powder formulation for oral inhalation to the lungs or a formulation for nasal inhalation. Preferably the method for manufacturing such a formulation uses lactose, mannitol, sucrose, sorbitol, xylitol or other sugars or polyols as the co-grinding matrix together with surfactant such as, but not limited to lecithin, DPPC (dipalmitoyl phosphatidylcholine), PG (phosphatidylglycerol), dipalmitoyl phosphatidyl ethanolamine (DPPE), dipalmitoyl phosphatidylinositol (DPPI) or other phospholipid. The particle size of the material produced by the invention disclosed herein results in the materials being readily aerosolized and suitable for methods of delivery to a subject in need thereof, including pulmonary and nasal delivery methods.

While the method of the present invention has particular application in the preparation of poorly water-soluble biologically active materials, the scope of the invention is not limited thereto. For example, the method of the present invention enables production of highly water-soluble biologically active materials. Such materials may exhibit advantages over conventional materials by way of, for example, more rapid therapeutic action or lower dose. In contrast, wet grinding techniques utilizing water (or other comparably polar solvents) are incapable of being applied to such materials, as the particles dissolve appreciably in the solvent.

Other aspects and advantages of the invention will become apparent to those skilled in the art from a review of the ensuing description.

Brief Description of the Drawings

Figure 1A. Powder charge composition and particle size distribution of material milled in SPEX mill, examples A to S.

Figure 1B. Powder charge composition and particle size distribution of material milled in SPEX mill, examples T to AL.

Figure 1C. Powder charge composition and particle size distribution of material milled in SPEX mill, examples AM to BE.

Figure 1D. Powder charge composition and particle size distribution of material milled in SPEX mill, examples BF to BX.

Figure 1E. Powder charge composition and particle size distribution of material milled in SPEX mill, examples BY to CQ.

Figure 1F. Powder charge composition and particle size distribution of material milled in SPEX mill, examples CR to DJ.

Figure 1G. Powder charge composition and particle size distribution of material milled in SPEX mill, examples DK to EC.

Figure 1H. The figure shows the X-Ray diffraction patterns: (A) after milling of Naproxen sodium in tartaric acid; (B) unmilled Naproxen sodium and (C) unmilled Naproxen acid.

Figure 2A. Powder charge composition and particle size distribution of material milled in 110 mL HD01 Attritor mill, examples A to F.

Figure 3A. Powder charge composition and particle size distribution of material containing a mixture of 2 matrices, milled in SPEX mill, examples A to E.

Figure 4A. Powder charge composition and particle size distribution of material milled in 1L HD01 Attritor mill, examples A to G.

Figure 5A. Powder charge composition and particle size distribution of material milled in 750mL 1S Attritor mill, examples A to F.

Figure 6A. Powder charge composition and particle size distribution of material milled in ½ Gallon 1S Attritor mill, examples A to R.

Figure 6B. Powder charge composition and particle size distribution of material milled in ½ Gallon 1S Attritor mill, examples S to AK.

Figure 6C. Powder charge composition and particle size distribution of material milled in ½ Gallon 1S Attritor mill, examples AL to AU.

Figure 7A. Powder charge composition and particle size distribution of Metaxalone milled in a variety of mills, examples A to O.

Figure 8A. Powder charge composition and particle size distribution of material milled in HICOM mill, examples A to P.

Figure 9A. Powder charge composition and particle size distribution of material milled in 1½ Gallon 1S Attritor mill, examples A to S.

Figure 9B. Powder charge composition and particle size distribution of material milled in 1½ Gallon 1S Attritor mill, examples T to AL.

Figure 10A. Powder charge composition and particle size distribution of material milled in a variety of large scale mills, examples A to F.

Figure 11A. Powder charge composition and particle size distribution of Naproxen Acid milled in Mannitol in a ½ Gallon 1S Attritor mill, examples A to M.

Figure 12A. Powder charge composition and particle size distribution of Naproxen Acid milled in SPEX mill and particle size distribution after filtration, examples A to L.

Detailed Description of the Invention

General

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and materials referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

The present invention is not to be limited in scope by the specific embodiments described herein, which are intended for the purpose of exemplification only. Functionally equivalent products, compositions and methods are clearly within the scope of the invention as described herein.

The invention described herein may include one or more ranges of values (e.g. size, concentration etc). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range that lead to the same or substantially the same outcome as the values immediately adjacent to that value which defines the boundary to the range.

The entire disclosures of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference. Inclusion does not constitute an admission is made that any of the references constitute prior art or are part of the common general knowledge of those working in the field to which this invention relates.

Throughout this specification, unless the context requires otherwise, the word "comprise" or variations, such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer, or group of integers, but not the exclusion of any other integers or group of integers. It is also noted that in this disclosure, and particularly in the claims and/or paragraphs, terms such as "comprises", "comprised", "comprising" and the like can have the meaning attributed to it in US Patent law; e.g., they can mean "includes", "included", "including", and the like.

"Therapeutically effective amount" as used herein with respect to methods of treatment and in particular drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

The term "inhibit" is defined to include its generally accepted meaning which includes prohibiting, preventing, restraining, and lowering, stopping, or reversing progression or severity, and such action on a resultant symptom. As such the present invention includes both medical therapeutic and prophylactic administration, as appropriate.

The term "biologically active material" is defined to mean a biologically active compound or a substance which comprises a biologically active compound. In this definition, a compound is generally taken to mean a distinct chemical entity where a chemical formula or formulas can be used to describe the substance. Such compounds would generally, but not necessarily be identified in the literature by a unique classification system such as a CAS number. Some compounds may be more complex and have a mixed chemical structure. For such compounds they may only have an empirical formula or be qualitatively identified. A compound would generally be a pure material, although it would be expected that up to 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% of the substance could be other impurities and the like. Examples of biologically active compounds are, but not limited to, pharmaceutical actives, and analogs, homologs and first order derivatives thereof. A substance that contains a biologically active compound is any substance which has as one of its components a biologically active compound. Examples of substances containing biologically active compounds are, but not limited to, pharmaceutical formulations and products.

Any of the terms, "biological(ly) active", "active", "active material" shall have the same meaning as biologically active material.

The term "grinding matrix" is defined as any inert substance that a biologically active material can or is combined with and milled. The terms "co-grinding matrix" and "matrix" are interchangeable with "grinding matrix".

Particle Size

There are a wide range of techniques that can be utilized to characterize the particle size of a material. Those skilled in the art also understand that almost all these techniques do not physically measure the actually particle size, as one might measure something with a ruler, but measure a physical phenomena which is interpreted to indicate a particle size. As part of the interpretation process some assumptions need to be made to enable mathematical calculations

to be made. These assumptions deliver results such as an equivalent spherical particle size, or a hydrodynamic radius.

Amongst these various methods, two types of measurements are most commonly used. Photon correlation spectroscopy (PCS), also known as 'dynamic light scattering' (DLS) is commonly used to measure particles with a size less than 10 micron. Typically this measurement yields an equivalent hydrodynamic radius often expressed as the average size of a number distribution. The other common particle size measurement is laser diffraction which is commonly used to measure particle size from 100 nm to 2000 micron. This technique calculates a volume distribution of equivalent spherical particles that can be expressed using descriptors such as the median particle size or the % of particles under a given size.

Those skilled in the art recognize that different characterization techniques such as photon correlation spectroscopy and laser diffraction measure different properties of a particle ensemble. As a result multiple techniques will give multiple answers to the question, "what is the particle size." In theory one could convert and compare the various parameters each technique measures, however, for real world particle systems this is not practical. As a result the particle size used to describe this invention will be given as two different sets of values that each relate to these two common measurement techniques, such that measurements could be made with either technique and then evaluated against the description of this invention.

For measurements made using a photo correlation spectroscopy instrument, or an equivalent method known in the art, the term "number average particle size" is defined as the average particle diameter as determined on a number basis.

For measurements made using a laser diffraction instrument, or an equivalent method known in the art, the term "median particle size" is defined as the median particle diameter as determined on an equivalent spherical particle volume basis. Where the term median is used, it is understood to describe the particle size that divides the population in half such that 50 % of the population is greater than or less than this size. The median particle size is often written as D50, D(0.50) or D[0.5] or similar. As used herein D50, D(0.50) or D[0.5] or similar shall be taken to mean 'median particle size'.

The term "Dx of the particle size distribution" refers to the xth percentile of the distribution; thus, D90 refers to the 90^{th} percentile, D95 refers to the 95^{th} percentile, and so forth. Taking D90 as an example this can often be written as, D(0.90) or D[0.9] or simialr. With respect to the median particle size and Dx an upper case D or lowercase d are interchangeable and have the same meaning.Another commonly used way of describing a particle size distribution measured by laser diffraction, or an equivalent method known in the art, is to describe what % of a distribution is under or over a nominated size. The term "percentage less than" also written as "%<" is defined as the percentage, by volume, of a particle size distribution under a nominated size -for example the % < 1000 nm. The term "percentage greater than" also written as "%>" is

defined as the percentage, by volume, of a particle size distribution over a nominated size -for example the % > 1000 nm.

The particle size used to describe this invention should be taken to mean the particle size as measured at or shortly before the time of use. For example, the particle size is measured 2 months after the material is subject to the milling method of this invention. In a preferred form, the particle size is measured at a time selected from the group consisting of: 1 day after milling, 2 days after milling, 5 days after milling, 1 month after milling, 2 months after milling, 3 months after milling, 4 months after milling, 5 months after milling, 6 months after milling, 1 year after milling, 2 years after milling, 5 years after milling.

For many of the materials subject to the methods of this invention the particle size can be easily measured. Where the active material has poor water solubility and the matrix it is milled in has good water solubility the powder can simply be dispersed in an aqueous solvent. In this scenario the matrix dissolves leaving the active material dispersed in the solvent. This suspension can then be measured by techniques such as PCS or laser diffraction.

Suitable methods to measure an accurate particle size where the active material has substantive aqueous solubility or the matrix has low solubility in a water based dispersant are outlined below.

1. In the circumstance where insoluble matrix such as microcrystalline cellulose prevents the measurement of the active material separation techniques such as filtration or centrifugation could be used to separate the insoluble matrix from the active material particles. Other ancillary techniques would also be required to determine if any active material was removed by the separation technique so that this could be taken into account.
2. In the case where the active material is too soluble in water other solvents could be evaluated for the measurement of particle size. Where a solvent could be found that active material is poorly soluble in but is a good solvent for the matrix a measurement would be relatively straight forward. If such a solvent is difficult to find another approach would be to measure the ensemble of matrix and active material in a solvent (such as iso-octane) which both are insoluble in. Then the powder would be measured in another solvent where the active material is soluble but the matrix is not. Thus with a measurement of the matrix particle size and a measurement of the size of the matrix and active material together an understanding of the active material particle size can be obtained.
3. In some circumstances image analysis could be used to obtain information about the particle size distribution of the active material. Suitable image measurement techniques might include transmission electron microscopy (TEM), scanning electron microscopy (SEM), optical microscopy and confocal microscopy. In addition to these standard techniques some additional technique would be required to be used in parallel to

differentiate the active material and matrix particles. Depending on the chemical makeup of the materials involved possible techniques could be elemental analysis, raman spectroscopy, FTIR spectroscopy or fluorescence spectroscopy.

Other Definitions

Throughout this specification, unless the context requires otherwise, the phrase "dry mill" or variations, such as "dry milling", should be understood to refer to milling in at least the substantial absence of liquids. If liquids are present, they are present in such amounts that the contents of the mill retain the characteristics of a dry powder.

"Flowable" means a powder having physical characteristics rendering it suitable for further processing using typical equipment used for the manufacture of pharmaceutical compositions and formulations.

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

The term "millable" means that the grinding matrix is capable of being physically degraded under the dry milling conditions of the method of the invention. In one embodiment of the invention, the milled grinding matrix is of a comparable particle size to the biologically active material. In another embodiment of the invention the particle size of the matrix is substantially reduced but not as small as the biologically active material

Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

Specific

In one embodiment, the present invention is directed to a method for producing a composition, comprising the steps of: dry milling a solid biologically active material and a millable grinding matrix in a mill comprising a plurality of milling bodies, for a time period sufficient to produce particles of the biologically active material dispersed in an at least partially milled grinding material.

The mixture of active material and matrix may then be separated from the milling bodies and removed from the mill.

In one aspect the mixture of active material and matrix is then further processed. In another aspect, the grinding matrix is separated from the particles of biologically active material. In a further aspect, at least a portion of the milled grinding matrix is separated from the particulate biologically active material.

The milling bodies are essentially resistant to fracture and erosion in the dry milling process. The quantity of the grinding matrix relative to the quantity of biologically active material in particulate form, and the extent of milling of the grinding matrix, is sufficient to inhibit re-agglomeration of the particles of the active material.

The present invention also relates to biologically active materials produced by said methods, to medicaments produced using said biologically active materials and to methods of treatment of an animal, including man, using a therapeutically effective amount of said biologically active materials administered by way of said medicaments.

Commercial Scale

The present invention is directed to the unexpected finding that particles of a biologically active material can be produced by dry milling processes as described herein at commercial scale. In one surprising aspect the particle size produced by the process is equal to or less than 2000nm. In another surprising aspect the particle size produced by the process is equal to or less than 1000nm. This can result in a more efficient and cost effective process.

One of the key goals of reducing manufacturing costs is the encapsulation of the nanoparticles into materials that do not have to be removed. This enables a simple manufacturing process where conventional formulation technologies can be used to progress the matrix encapsulated nanoparticles directly to a final product. In order to do this the materials used within the matrix must be acceptable to industry regulators. In some cases materials may be acceptable for use but only in limited quantities. Another aspect of matrix choice is functionality. Some matrices that produce good encapsulated nanoparticles may be acceptable from a safety perspective but these materials may make manufacture of a dosage form such as tablet limited.

Improving the dissolution profile

The process results in the biologically active material having an improved dissolution profile. An improved dissolution profile has significant advantages including the improvement of bioavailability of the biologically active material *in vivo*. Preferably, the improved dissolution profile is observed *in vitro*. Alternatively, the improved dissolution profile is observed *in vivo* by the observation of an improved bioavailability profile. Standard methods for determining the dissolution profile of a material *in vitro* are available in the art. A suitable method to determine an improved dissolution profile *in vitro* may include determining the concentration of the sample material in a solution over a period of time and comparing the results from the sample material to a control sample. An observation that peak solution concentration for the sample material was achieved in less time than the control sample would indicate (assuming it is statistically significant), that the sample material has an improved dissolution profile. The measurement sample is herein defined as the mixture of biologically active material with grinding matrix and/or other additives that has been subject to the processes of the invention described here.

Herein a control sample is defined as a physical mixture (not subject to the processes described in this invention) of the components in the measurement sample with the same relative proportions of active, matrix and/or additive as the measurement sample. For the purposes of the dissolution testing a prototype formulation of the measurement sample could also be used. In this case the control sample would be formulated in the same way. Standard methods for determining the improved dissolution profile of a material *in vivo* are available in the art. A suitable method to determine an improved dissolution profile in a human may be after delivering the dose to measure the rate of active material absorption by measuring the plasma concentration of the sample compound over a period of time and comparing the results from the sample compound to a control. An observation that peak plasma concentration for the sample compound was achieved in less time than the control would indicate (assuming it is statistically significant) that the sample compound has improved bioavailability and an improved dissolution profile. Preferably, the improved dissolution profile is observed at a relevant gastrointestinal pH, when it is observed *in vitro*. Preferably, the improved dissolution profile is observed at a pH which is favourable at indicating improvements in dissolution when comparing the measurement sample to the control compound. Suitable methods for quantifying the concentration of a compound in an *in vitro* sample or an *in vivo* sample are widely available in the art. Suitable methods could include the use of spectroscopy or radioisotope labeling. In one preferred embodiment the method of quantification of dissolution is determined in a solution with a pH selected from the group consisting of: pH 1, pH 2, pH 3, pH 4, pH 5, pH 6, pH 7, pH 7.3, pH 7.4, pH 8, pH 9, pH 10, pH 11, pH 12, pH 13, pH 14 or a pH with 0.5 of a pH unit of any of this group.

Crystallization Profile

Methods for determining the crystallinity profile of the biologically active material are widely available in the art. Suitable methods may include X-ray diffraction, differential scanning calorimetry, raman or IR spectrocopy.

Amorphicity Profile

Methods for determining the amorphous content of the biologically active material are widely available in the art. Suitable methods may include X-ray diffraction, differential scanning calorimetry, raman or IR spectroscopy.

Grinding Matrix

As will be described subsequently, selection of an appropriate grinding matrix affords particular advantageous applications of the method of the present invention.

A highly advantageous application of the method of the invention is the use of a water-soluble grinding matrix in conjunction with a poorly water-soluble biologically active material. This

affords at least two advantages. The first being when the powder containing the biologically active material is placed into water – such as the ingestion of the powder as part of an oral medication - the matrix dissolves, releasing the particulate active material such that there is maximum surface area exposed to solution, thereby allowing a rapid dissolution of the active compound. The second key advantage is the ability, if required, to remove or partially remove the matrix prior to further processing or formulation.

Another advantageous application of the method of the invention is the use of a water-insoluble grinding matrix, particularly in the area of agricultural use, when a biologically active material such as a fungicide is commonly delivered as part of a dry powder or a suspension. The presence of a water insoluble matrix will afford benefits such as increased rain fastness.

Without wishing to be bound by theory, it is believed that the physical degradation (including but not limited to particle size reduction) of the millable grinding matrix affords the advantage of the invention, by acting as a more effective diluent than grinding matrix of a larger particle size.

Again, as will be described subsequently, a highly advantageous aspect of the present invention is that certain grinding matrixes appropriate for use in the method of the invention are also appropriate for use in a medicament. The present invention encompasses methods for the production of a medicament incorporating both the biologically active material and the grinding matrix or in some cases the biologically active material and a portion of the grinding matrix, medicaments so produced, and methods of treatment of an animal, including man, using a therapeutically effective amount of said biologically active materials by way of said medicaments.

Analogously, as will be described subsequently, a highly advantageous aspect of the present invention is that certain grinding matrixes appropriate for use in the method of the invention are also appropriate for use in a carrier for an agricultural chemical, such as a pesticide, fungicide, or herbicide. The present invention encompasses methods for the production of an agricultural chemical composition incorporating both the biologically active material in particulate form and the grinding matrix, or in some cases the biologically active material, and a portion of the grinding matrix, and agricultural chemical compositions so produced. The medicament may include only the biologically active material together with the milled grinding matrix or, more preferably, the biologically active material and milled grinding matrix may be combined with one or more pharmaceutically acceptable carriers, as well as any desired excipients or other like agents commonly used in the preparation of medicaments.

Analogously, the agricultural chemical composition may include only the biologically active material together with the milled grinding matrix or, more preferably, the biologically active materials and milled grinding matrix may be combined with one or more carriers, as well as any desired excipients or other like agents commonly used in the preparation of agricultural chemical compositions.

In one particular form of the invention, the grinding matrix is both appropriate for use in a medicament and readily separable from the biologically active material by methods not dependent on particle size. Such grinding matrixes are described in the following detailed description of the invention. Such grinding matrixes are highly advantageous in that they afford significant flexibility in the extent to which the grinding matrix may be incorporated with the biologically active material into a medicament.

In a highly preferred form, the grinding matrix is harder than the biologically active material, and is thus capable of reducing the particle size of the active material under the dry milling conditions of the invention. Again without wishing to be bound by theory, under these circumstances it is believed that the millable grinding matrix affords the advantage of the present invention through a second route, with the smaller particles of grinding matrix produced under the dry milling conditions enabling greater interaction with the biologically active material.

The quantity of the grinding matrix relative to the quantity of biologically active material, and the extent of physical degradation of the grinding matrix, is sufficient to inhibit re-agglomeration of the particles of the active material Preferably, the quantity of the grinding matrix relative to the quantity of biologically active material, and the extent of physical degradation of the grinding matrix, is sufficient to inhibit re-agglomeration of the particles of the active material in nanoparticulate form.The grinding matrix is not generally selected to be chemically reactive with the biologically active material under the milling conditions of the invention, excepting for example, where the matrix is deliberately chosen to undergo a mechanico-chemical reaction. Such a reaction might be the conversion of a free base or acid to a salt or vice versa.

As stated above, the method of the present invention requires the grinding matrix to be milled with the biologically active material; that is, the grinding matrix will physically degrade under the dry milling conditions of the invention to facilitate the formation and retention of particulates of the biologically active material with reduced particle size. The precise extent of degradation required will depend on certain properties of the grinding matrix and the biologically active material, the ratio of biologically active material to grinding matrix, and the particle size distribution of the particles comprising the biologically active material.

The physical properties of the grinding matrix necessary to achieve the requisite degradation are dependent on the precise milling conditions. For example, a harder grinding matrix may degrade to a sufficient extent provided it is subjected to more vigorous dry milling conditions.

Physical properties of the grinding matrix relevant to the extent that the agent will degrade under dry milling conditions include hardness, friability, as measured by indicia such as hardness, fracture toughness and brittleness index.

A low hardness (typically a Mohs Hardness less than 7) of the biologically active material is desirable to ensure fracture of the particles during processing, so that composite microstructures develop during milling. Preferably, the hardness is less than 3 as determined using the Mohs Hardness scale.

Preferably, the grinding matrix is of low abrasivity. Low abrasivity is desirable to minimise contamination of the mixture of the biologically active material in the grinding matrix by the milling bodies and/or the milling chamber of the media mill. An indirect indication of the abrasivity can be obtained by measuring the level of milling-based contaminants.

Preferably, the grinding matrix has a low tendency to agglomerate during dry milling. While it is difficult to objectively quantify the tendency to agglomerate during milling, it is possible to obtain a subjective measure by observing the level of "caking" of the grinding matrix on the milling bodies and the milling chamber of the media mill as dry milling progresses.

The grinding matrix may be an inorganic or organic substance.

In one embodiment, the grinding matrix is selected from the following, either as a single substance or a combination of two or more substances: Polyols (sugar alcohols) for example (but not limited to) mannitol, sorbitol, isomalt, xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, monosaccharides for example (but not limited to) glucose, fructose, mannose, galactose, disaccharides and trisaccharides for example (but not limited to) anhydrous lactose, lactose monohydrate, sucrose, maltose, trehalose, polysaccharides for example (but not limited to) maltodextrins, dextrin, Inulin, dextrates, polydextrose, other carbohyrates for example (but not limited to) starch, wheat flour, corn flour, rice flour, rice starch, tapioca flour, tapioca starch, potato flour, potato starch, other flours and starches, , soy flour, soy meal or other soy products, cellulose, microcrystalline cellulose, microcrystalline cellulose based co blended excipients, chemically modified excipients such as pregelatinized (or partially) starch, modified celluloses such as HPMC, CMC, HPC, enteric polymer coatings such as hypromellose phthalate, cellulose acetate phthalate (Aquacoat®), polyvinyl acetate phthalate (Sureteric®), hypromellose acetate succinate (AQOAT®), and polmethacrylates (Eudragit® and Acryl-EZE®), Milk products for example (but not limited to) milk powder, skim milk powders, other milk solids and dreviatives, other functional Excipients, organic acids for example (but not limited to) citric acid, tartaric acid, malic acid, maleic acid fumaric acid , ascorbic acid, succinic acid, the conjugate salt of organic acids for example (but not limited to) sodium citrate, sodium tartrate, sodium malate, sodium ascorbate, potassium citrate, potassium tartrate, potassium malate, potassium ascorbate, inorganics such as sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate and calcium carbonate. dibasic calcium phosphate, tribasic calcium phosphate, sodium sulfate, sodium chloride, sodium metabisulphite, sodium thiosulfate, ammonium chloride, Glauber's salt, ammonium carbonate, sodium bisulfate, magnesium sulfate, potash alum, potassium chloride, sodium hydrogen sulfate, sodium hydroxide, crystalline hydroxides, hydrogen carbonates, hydrogen carbonates of pharmaceutical acceptable alkali metals, such as but not limited by, sodium, potassium, lithium, calcium, and barium, ammonium salts (or salts of volatile amines), for example (but not limited to) ammonium chloride, methylamine hydrochloride, ammonium bromide, other inorganics for example (but not limited to), thermal silica, chalk, mica, silica,

alumina, titanium dioxide, talc, kaolin, bentonite, hectorite, magnesium trisilicate, other clay or clay derivatives or aluminium silicates, a surfactant for example (but not limited to) sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, poloxamer 407, poloxamer 338, polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, Sucrose Palmitate, Sucrose Stearate, Sucrose Distearate, Sucrose laurate, Glycocholic acid, sodium Glycholate, Cholic Acid, Soidum Cholate, Sodium Deoxycholate, Deoxycholic acid, Sodium taurocholate, taurocholic acid, Sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend,Calcium Dodecylbenzene Sulfonate, Sodium Dodecylbenzene Sulfonate,Diisopropyl naphthaenesulphonate, erythritol distearate, Naphthalene Sulfonate Formaldehyde Condensate, nonylphenol ethoxylate (poe-30), Tristyrylphenol Ethoxylate, Polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, Sodium Methyl Naphthalene Formaldehyde Sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), Triethanolamine isodecanol phosphate ester, Triethanolamine tristyrylphosphate ester, Tristyrylphenol Ethoxylate Sulfate, Bis(2-hydroxyethyl)tallowalkylamines.

In a preferred embodiment, the grinding matrix is a matrix that is considered GRAS (generally regarded as safe) by persons skilled in the pharmaceutical arts.

In another preferred aspect a combination of two or more suitable matrices, such as those listed above, can be used as the grinding matrix to provide improved properties such as the reduction of caking, and greater improvement of the dissolution profile. Combination matrices may also be advantageous when the matrices have different solubility's allowing the removal or partial removal of one matrix, while leaving the other or part of the other to provide encapsulation or partial encapsulation of the biologically active material.

Another highly preferred aspect of the method is the inclusion of a suitable milling aid in the matrix to improve milling performance. Improvements to milling performance would be things such as, but not limited to, a reduction in caking or higher recovery of powder from the mill. Examples of suitable milling aids include surfactants, polymers and inorganics such as silica (including colloidal silica), aluminium silicates and clays.

There are a wide range of surfactants that will make suitable milling aids. The highly preferred form is where the surfactant is a solid, or can be manufactured into a solid. Preferably, the surfactant is selected from the group consisting of: polyoxyethylene alkyl ethers, polyoxyethylene stearates, polyethylene glycols (PEG), poloxamers, poloxamines, sarcosine based surfactants, polysorbates, aliphatic alcohols, alkyl and aryl sulfates, alkyl and aryl polyether sulfonates and other sulfate surfactants, trimethyl ammonium based surfactants, lecithin and other phospholipids, bile salts, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, Sorbitan fatty acid esters, Sucrose fatty acid esters, alkyl glucopyranosides, alkyl maltopyranosides, glycerol fatty acid esters, Alkyl Benzene Sulphonic Acids, Alkyl Ether Carboxylic Acids, Alkyl and aryl Phosphate esters, Alkyl and aryl Sulphate esters, Alkyl and aryl Sulphonic acids, Alkyl Phenol Phosphates esters, Alkyl Phenol Sulphates esters, Alkyl and Aryl Phosphates, Alkyl Polysaccharides, Alkylamine Ethoxylates, Alkyl-Naphthalene Sulphonates formaldehyde condensates, Sulfosuccinates, lignosulfonates, Ceto-Oleyl Alcohol Ethoxylates, Condensed Naphthalene Sulphonates, Dialkyl and Alkyl Naphthalene Sulphonates,Di-alkyl Sulphosuccinates, Ethoxylated nonylphenols, Ethylene Glycol Esters,Fatty Alcohol Alkoxylates, Hydrogenated tallowalkylamines, Mono-alkyl Sulphosuccinamates, Nonyl Phenol Ethoxylates, Sodium Oleyl N-methyl Taurate, Tallowalkylamines, linear and branched dodecylbenzene sulfonic acids

Preferably, the surfactant is selected from the group consisting of: sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, , poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, Sucrose Palmitate, Sucrose Stearate, Sucrose Distearate, Sucrose laurate, Glycocholic acid, sodium Glycholate, Cholic Acid, Soidum Cholate, Sodium Deoxycholate, Deoxycholic acid, Sodium taurocholate,

taurocholic acid, Sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend,Calcium Dodecylbenzene Sulfonate, Sodium Dodecylbenzene Sulfonate,Diisopropyl naphthaenesulphonate, erythritol distearate, Naphthalene Sulfonate Formaldehyde Condensate, nonylphenol ethoxylate (poe-30), Tristyrylphenol Ethoxylate, Polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, Sodium Methyl Naphthalene Formaldehyde Sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), Triethanolamine isodecanol phosphate ester, Triethanolamine tristyrylphosphate ester, Tristyrylphenol Ethoxylate Sulfate, Bis(2-hydroxyethyl)tallowalkylamines.

Preferably the polymer is selected from the list of: polyvinylpyrrolidones (PVP), polyvinylalcohol, Acrylic acid based polymers and copolymers of acrylic acid

Preferably, the milling aid has a concentration selected from the group consisting of: 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 - 2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

Milling bodies

In the method of the present invention, the milling bodies are preferably chemically inert and rigid. The term "chemically-inert", as used herein, means that the milling bodies do not react chemically with the biologically active material or the grinding matrix.

As described above, the milling bodies are essentially resistant to fracture and erosion in the milling process.

The milling bodies are desirably provided in the form of bodies which may have any of a variety of smooth, regular shapes, flat or curved surfaces, and lacking sharp or raised edges. For example, suitable milling bodies can be in the form of bodies having ellipsoidal, ovoid, spherical or right cylindrical shapes. Preferably, the milling bodies are provided in the form of one or more of beads, balls, spheres, rods, right cylinders, drums or radius-end right cylinders (i.e., right cylinders having hemispherical bases with the same radius as the cylinder).

Depending on the nature of the biologically active material and the grinding matrix, the milling media bodies desirably have an effective mean particle diameter (i.e. "particle size") between about 0.1 and 30 mm, more preferably between about 1 and about 15 mm, still more preferably between about 3 and 10 mm.

The milling bodies may comprise various substances such as ceramic, glass, metal or polymeric compositions, in a particulate form. Suitable metal milling bodies are typically spherical and generally have good hardness (i.e. RHC 60-70), roundness, high wear

resistance, and narrow size distribution and can include, for example, balls fabricated from type 52100 chrome steel, type 316 or 440C stainless steel or type 1065 high carbon steel.

Preferred ceramics, for example, can be selected from a wide array of ceramics desirably having sufficient hardness and resistance to fracture to enable them to avoid being chipped or crushed during milling and also having sufficiently high density. Suitable densities for milling media can range from about 1 to 15 g/cm^{3}, preferably from about 1 to 8 g/cm^{3}. Preferred ceramics can be selected from steatite, aluminum oxide, zirconium oxide, zirconia-silica, yttria-stabilized zirconium oxide, magnesia-stabilized zirconium oxide, silicon nitride, silicon carbide, cobalt-stabilized tungsten carbide, and the like, as well as mixtures thereof.

Preferred glass milling media are spherical (e.g. beads), have a narrow size distribution, are durable, and include, for example, lead-free soda lime glass and borosilicate glass. Polymeric milling media are preferably substantially spherical and can be selected from a wide array of polymeric resins having sufficient hardness and friability to enable them to avoid being chipped or crushed during milling, abrasion-resistance to minimize attrition resulting in contamination of the product, and freedom from impurities such as metals, solvents, and residual monomers.

Preferred polymeric resins, for example, can be selected from crosslinked polystyrenes, such as polystyrene crosslinked with divinylbenzene, styrene copolymers, polyacrylates such as polymethylmethacrylate, polycarbonates, polyacetals, vinyl chloride polymers and copolymers, polyurethanes, polyamides, high density polyethylenes, polypropylenes, and the like. The use of polymeric milling media to grind materials down to a very small particle size (as opposed to mechanochemical synthesis) is disclosed, for example, in U.S. patents 5,478,705 and 5,500,331. Polymeric resins typically can have densities ranging from about 0.8 to 3.0 g/cm^{3}. Higher density polymeric resins are preferred. Alternatively, the milling media can be composite particles comprising dense core particles having a polymeric resin adhered thereon. Core particles can be selected from substances known to be useful as milling media, for example, glass, alumina, zirconia silica, zirconium oxide, stainless steel, and the like. Preferred core substances have densities greater than about 2.5 g/cm^{3}.

In one embodiment of the invention, the milling media are formed from a ferromagnetic substance, thereby facilitating removal of contaminants arising from wear of the milling media by the use of magnetic separation techniques.

Each type of milling body has its own advantages. For example, metals have the highest specific gravities, which increase grinding efficiency due to increased impact energy. Metal costs range from low to high, but metal contamination of final product can be an issue. Glasses are advantageous from the standpoint of low cost and the availability of small bead sizes as low as 0.004 mm. However, the specific gravity of glasses is lower than other media and significantly more milling time is required. Finally, ceramics are advantageous from the standpoint of low wear and contamination, ease of cleaning, and high hardness.

Dry Milling

In the dry milling process of the present invention, the biologically active material and grinding matrix, in the form of crystals, powders, or the like, are combined in suitable proportions with the plurality of milling bodies in a milling chamber that is mechanically agitated (i.e. with or without stirring) for a predetermined period of time at a predetermined intensity of agitation. Typically, a milling apparatus is used to impart motion to the milling bodies by the external application of agitation, whereby various translational, rotational or inversion motions or combinations thereof are applied to the milling chamber and its contents, or by the internal application of agitation through a rotating shaft terminating in a blade, propeller, impeller or paddle or by a combination of both actions.

During milling, motion imparted to the milling bodies can result in application of shearing forces as well as multiple impacts or collisions having significant intensity between milling bodies and particles of the biologically active material and grinding matrix. The nature and intensity of the forces applied by the milling bodies to the biologically active material and the grinding matrix is influenced by a wide variety of processing parameters including: the type of milling apparatus; the intensity of the forces generated, the kinematic aspects of the process; the size, density, shape, and composition of the milling bodies; the weight ratio of the biologically active material and grinding matrix mixture to the milling bodies; the duration of milling; the physical properties of both the biologically active material and the grinding matrix; the atmosphere present during activation; and others.

Advantageously, the media mill is capable of repeatedly or continuously applying mechanical compressive forces and shear stress to the biologically active material and the grinding matrix. Suitable media mills include but are not limited to the following: high-energy ball, sand, bead or pearl mills, basket mill, planetary mill, vibratory action ball mill, multi-axial shaker/mixer, stirred ball mill, horizontal small media mill, multi-ring pulverizing mill, and the like, including small milling media. The milling apparatus also can contain one or more rotating shafts.

In a preferred form of the invention, the dry milling is performed in a ball mill. Throughout the remainder of the specification reference will be made to dry milling being carried out by way of a ball mill. Examples of this type of mill are attritor mills, nutating mills, tower mills, planetary mills, vibratory mills and gravity-dependent-type ball mills. It will be appreciated that dry milling in accordance with the method of the invention may also be achieved by any suitable means other than ball milling. For example, dry milling may also be achieved using jet mills, rod mills, roller mills or crusher mills.

Biologically active material

The biologically active material includes active compounds, including compounds for veterinary and human use such as but not limited to, pharmaceutical actives and the like.

The biologically active material is ordinarily a material for which one of skill in the art desires improved dissolution properties. The biologically active material may be a conventional active agent or drug, although the process of the invention may be employed on formulations or agents that already have reduced particle size compared to their conventional form.

Biologically active materials suitable for use in the invention include diclofenac.

As discussed in the context of the background to the invention, biologically active materials that are poorly water soluble at gastrointestinal pH will particularly benefit from being prepared, and the method of the present invention is particularly advantageously applied to materials that are poorly water soluble at gastrointestinal pH.

Conveniently, the biologically active material is capable of withstanding temperatures that are typical in uncooled dry milling, which may exceed 80 °C. Therefore, materials with a melting point about 80 °C or greater are highly suitable. For biologically active materials with lower melting points, the media mill may be cooled, thereby allowing materials with significantly lower melting temperatures to be processed according to the method of the invention. For instance, a simple water-cooled mill will keep temperatures below 50 °C, or chilled water could be used to further lower the milling temperature. Those skilled in the art will understand that a high energy ball mill could be designed to run at any temperature between say -30 to 200 °C. For some biologically active materials it may be advantageous to control the milling temperature to temperatures significantly below the melting points of the biologically active materials.

The biologically active material is obtained in a conventional form commercially and/or prepared by techniques known in the art.

It is preferred, but not essential, that the particle size of the biologically active material be less than about 1000 µm, as determined by sieve analysis. If the coarse particle size of the biologically active material is greater than about 1000 µm, then it is preferred that the particles of the biologically active material substrate be reduced in size to less than 1000 µm using another standard milling method.

Processed biologically active material

Preferably, the biologically active materials, which have been subject to the methods of the invention, comprises particles of biologically active material of an average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

Preferably, the biologically active materials, which have been subject to the methods of the invention, comprises particles of biologically active material of a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

Preferably, the biologically active materials, which have been subject to the methods of the invention, comprises particles of biologically active material and wherein the Dx of the particle size distribution, as measured on a particle volume basis, is selected from the group consisting of less than or equal to 10,000nm, 5000nm, 3000nm, 2000nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm, and 100 nm; wherein x is greater than or equal to 90, These sizes refer to particles either fully dispersed or partially agglomerated.

Agglomerates of biologically active material after processing

Agglomerates comprising particles of biologically active material, said particles having a particle size within the ranges specified above, should be understood to fall within the scope of the present invention, regardless of whether the agglomerates exceed the ranges specified above.

Agglomerates comprising particles of biologically active material, said agglomerates having a total agglomerate size within the ranges specified above, should be understood to fall within the scope of the present invention.

Agglomerates comprising particles of biologically active material should be understood to fall within the scope of the present invention if at the time of use, or further processing, the particle size of the agglomerate is within the ranges specified above.

Agglomerates comprising particles of biologically active material, said particles having a particle size within the ranges specified above, at the time of use, or further processing, should be understood to fall within the scope of the present invention, regardless of whether the agglomerates exceed the ranges specified above.

Processing Time

Preferably, the biologically active material and the grinding matrix are dry milled for the shortest time necessary to form the mixture of the biologically active material in the grinding matrix such that the active material has improved dissolution to minimise any possible contamination from

the media mill and/or the plurality of milling bodies. This time varies greatly, depending on the biologically active material and the grinding matrix, and may range from as short as 1 minute to several hours. Dry milling times in excess of 2 hours may lead to degradation of the biologically active material and an increased level of undesirable contaminants.

Suitable rates of agitation and total milling times are adjusted for the type and size of milling apparatus as well as the milling media, the weight ratio of the biologically active material and grinding matrix mixture to the plurality of milling bodies, the chemical and physical properties of the biologically active material and grinding matrix, and other parameters that may be optimized empirically.

Inclusion of the grinding matrix with the biologically active material and separation of the grinding matrix from the biologically active material

In a preferred aspect, the grinding matrix is not separated from the biologically active material but is maintained with the biologically active material in the final product. Preferably the grinding matrix is considered to be Generally Regarded as Safe (GRAS) for pharmaceutical products.

In an alternative aspect, the grinding matrix is separated from the biologically active material. In one aspect, where the grinding matrix is not fully milled, the unmilled grinding matrix is separated from the biologically active material. In a further aspect, at least a portion of the milled grinding matrix is separated from the biologically active material.

Any portion of the grinding matrix may be removed, including but not limited to 10%, 25%, 50%, 75%, or substantially all of the grinding matrix.

In some embodiments of the invention, a significant portion of the milled grinding matrix may comprise particles of a size similar to and/or smaller than the particles comprising the biologically active material. Where the portion of the milled grinding matrix to be separated from the particles comprising the biologically active material comprises particles of a size similar to and/or smaller than the particles comprising the biologically active material, separation techniques based on size distribution are inapplicable.

In these circumstances, the method of the present invention may involve separation of at least a portion of the milled grinding matrix from the biologically active material by techniques including but not limited to electrostatic separation, magnetic separation, centrifugation (density separation), hydrodynamic separation, froth flotation.

Advantageously, the step of removing at least a portion of the milled grinding matrix from the biologically active material may be performed through means such as selective dissolution, washing, or sublimation.

An advantageous aspect of the invention would be the use of grinding matrix that has two or more components where at least one component is water soluble and at least one component has low solubility in water. In this case washing can be used to remove the matrix component soluble in water leaving the biologically active material encapsulated in the remaining matrix

components. In a highly advantageous aspect of the invention the matrix with low solubility is a functional excipient.

A highly advantageous aspect of the present invention is that certain grinding matrixes appropriate for use in the method of the invention (in that they physically degrade to the desired extent under dry milling conditions) are also pharmaceutically acceptable and thus appropriate for use in a medicament. Where the method of the present invention does not involve complete separation of the grinding matrix from the biologically active material, the present invention encompasses methods for the production of a medicament incorporating both the biologically active material and at least a portion of the milled grinding matrix, medicaments so produced and methods of treatment of an animal, including man, using a therapeutically effective amount of said biologically active materials by way of said medicaments.

The medicament may include only the biologically active material and the grinding matrix or, more preferably, the biologically active materials and grinding matrix may be combined with one or more pharmaceutically acceptable carriers, as well as any desired excipients or other like agents commonly used in the preparation of medicaments.

Analogously, a highly advantageous aspect of the present invention is that certain grinding matrixes appropriate for use in the method of the invention (in that they physically degrade to a desirable extent under dry milling conditions) are also appropriate for use in an agricultural chemical composition. Where the method of the present invention does not involve complete separation of the grinding matrix from the biologically active material, the present invention encompasses methods for the production of a agricultural chemical composition incorporating both the biologically active material and at least a portion of the milled grinding matrix, agricultural chemical composition so produced and methods of use of such compositions.

The agricultural chemical composition may include only the biologically active material and the grinding matrix or, more preferably, the biologically active materials and grinding matrix may be combined with one or more acceptable carriers, as well as any desired excipients or other like agents commonly used in the preparation of agricultural chemical compositions.

In one particular form of the invention, the grinding matrix is both appropriate for use in a medicament and readily separable from the biologically active material by methods not dependent on particle size. Such grinding matrixes are described in the following detailed description of the invention. Such grinding matrixes are highly advantageous in that they afford significant flexibility in the extent to which the grinding matrix may be incorporated with the biologically active material into a medicament.

The mixture of biologically active material and grinding matrix may then be separated from the milling bodies and removed from the mill.

In one embodiment, the grinding matrix is separated from the mixture of biologically active material and grinding matrix. Where the grinding matrix is not fully milled, the unmilled grinding

matrix is separated from the biologically active material. In a further aspect, at least a portion of the milled grinding matrix is separated from the biologically active material.

The milling bodies are essentially resistant to fracture and erosion in the dry milling process.

The quantity of the grinding matrix relative to the quantity of biologically active material, and the extent of milling of the grinding matrix, is sufficient to provide reduced particle size of the biologically active material.

The grinding matrix is neither chemically nor mechanically reactive with the pharmaceutical material under the dry milling conditions of the method of the invention except, for example, where the matrix is deliberately chosen to undergo a mechanico-chemical reaction. Such a reaction might be the conversion of a free base or acid to a salt or vice versa.

Preferably, the medicament is a solid dosage form, however, other dosage forms may be prepared by those of ordinary skill in the art.

In one form, after the step of separating said mixture of biologically active material and grinding matrix from the plurality of milling bodies, and before the step of using said mixture of biologically active material and grinding matrix in the manufacture of a medicament, the method may comprise the step of:

removing a portion of the grinding matrix from said mixture of biologically active material and grinding matrix to provide a mixture enriched in the biologically active material;

and the step of using said mixture of biologically active material and grinding matrix in the manufacture of a medicament, more particularly comprises the step of using the mixture of biologically active material and grinding matrix enriched in the biologically active material form in the manufacture of a medicament.

The present invention includes medicaments manufactured by said methods, and methods for the treatment of an animal, including man, by the administration of a therapeutically effective amount of the biologically active materials by way of said medicaments.

In another embodiment of the invention, a facilitating agent or a combination of facilitating agents is also comprised in the mixture to be milled. Such facilitating agents appropriate for use in the invention include diluents, surfactants, polymers, binding agents, filling agents, lubricating agents, sweeteners, flavouring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents and agents that may form part of a medicament, including a solid dosage form, or other excipients required for other specific drug delivery, such as the agents and media listed below under the heading *Medicinal and Pharmaceutical Compositions*, or any combination thereof.

Biologically active materials and compositions

The present invention encompasses pharmaceutically acceptable materials produced according to the methods of the present invention, compositions including such materials, including compositions comprising such materials together with the grinding matrix with or

without milling aids, facilitating agents, with at least a portion of the grinding matrix or separated from the grinding matrix.

The pharmaceutically acceptable materials within the compositions of the invention are present at a concentration of between about 0.1% and about 99.0% by weight. Preferably, the concentration of pharmaceutically acceptable materials within the compositions will be about 5% to about 80% by weight, while concentrations of 10% to about 50% by weight are highly preferred. Desirably, the concentration will be in the range of about 10 to 15% by weight, 15 to 20% by weight, 20 to 25% by weight, 25 to 30% by weight, 30 to 35% by weight, 35 to 40% by weight, 40 to 45% by weight, 45 to 50% by weight, 50 to 55% by weight, 55 to 60% by weight, 60 to 65% by weight, 65 to 70% by weight, 70 to 75% by weight or 75 to 80% by weight for the composition prior to any later removal (if desired) of any portion of the grinding matrix. Where part or all of the grinding matrix has been removed, the relative concentration of pharmaceutically acceptable materials in the composition may be considerably higher depending on the amount of the grinding matrix that is removed. For example, if all of the grinding matrix is removed the concentration of particles in the preparation may approach 100% by weight (subject to the presence of facilitating agents).

Compositions produced according to the present invention are not limited to the inclusion of a single species of pharmaceutically acceptable materials. More than one species of pharmaceutically acceptable materials may therefore be present in the composition. Where more than one species of pharmaceutically acceptable materials is present, the composition so formed may either be prepared in a dry milling step, or the pharmaceutically acceptable materials may be prepared separately and then combined to form a single composition.

Medicaments

The medicaments of the present invention may include the pharmaceutically acceptable material, optionally together with the grinding matrix or at least a portion of the grinding matrix, with or without milling aids, facilitating agents, combined with one or more pharmaceutically acceptable carriers, as well as other agents commonly used in the preparation of pharmaceutically acceptable compositions.

As used herein "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Preferably, the carrier is suitable for parenteral administration, intravenous, intraperitoneal, intramuscular, sublingual, pulmonary, transdermal or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for the manufacture of medicaments is well known in the art. Except insofar as any conventional media or agent is

incompatible with the pharmaceutically acceptable material, use thereof in the manufacture of a pharmaceutical composition according to the invention is contemplated.

Pharmaceutical acceptable carriers according to the invention may include one or more of the following examples:

(1) surfactants and polymers including, but not limited to polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyvinylalcohol, crospovidone, polyvinylpyrrolidone-polyvinylacrylate copolymer, cellulose derivatives, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, carboxymethylethyl cellulose, hydroxypropyllmethyl cellulose phthalate, polyacrylates and polymethacrylates, urea, sugars, polyols, and their polymers, emulsifiers, sugar gum, starch, organic acids and their salts, vinyl pyrrolidone and vinyl acetate

(2) binding agents such as various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose; and or

(3) filling agents such as lactose monohydrate, lactose anhydrous, microcrystalline cellulose and various starches; and or

(4) lubricating agents such as agents that act on the flowability of the powder to be compressed, including colloidal silicon dioxide, talc, stearic acid, magnesium stearate, calcium stearate, silica gel; and or

(5) sweeteners such as any natural or artificial sweetener including sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and accsulfame K; and or

(6) flavouring agents; and or

(7) preservatives such as potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic chemicals such as phenol, or quarternary compounds such as benzalkonium chloride; and or

(8) buffers; and or

(9) Diluents such as pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing; and or

(10) wetting agents such as corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, crosspovidone, sodium starch glycolate, and mixtures thereof; and or

(11) disintegrants; and or

(12) effervescent agents such as effervescent couples such as an organic acid (e.g., citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts), or a carbonate (e.g. sodium carbonate, potassium carbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate) or bicarbonate (e.g. sodium bicarbonate or potassium bicarbonate); and or

(13) other pharmaceutically acceptable excipients.

Medicaments of the invention suitable for use in animals and in particular in man typically must be stable under the conditions of manufacture and storage. The medicaments of the invention comprising the biologically active material can be formulated as a solid, a solution, a microemulsion, a liposome, or other ordered structures suitable to high drug concentration. Actual dosage levels of the biologically active material in the medicament of the invention may be varied in accordance with the nature of the biologically active material, as well as the potential increased efficacy due to the advantages of providing and administering the biologically active material (e.g., increased solubility, more rapid dissolution, increased surface area of the biologically active material, etc.). Thus as used herein "therapeutically effective amount" will refer to an amount of biologically active material required to effect a therapeutic response in an animal. Amounts effective for such a use will depend on: the desired therapeutic effect; the route of administration; the potency of the biologically active material; the desired duration of treatment; the stage and severity of the disease being treated; the weight and general state of health of the patient; and the judgment of the prescribing physician.

In another embodiment, the biologically active material, optionally together with the grinding matrix or at least a portion of the grinding matrix, of the invention may be combined into a medicament with another biologically active material, or even the same biologically active material. In the latter embodiment, a medicament may be achieved which provides for different release characteristics – early release from the biologically active material, and later release from a larger average size biologically active material.

Pharmacokinetic Properties of Diclofenac Compositions

Suitable animal models to determine pharmacokinetic parameters are described in the prior art, such as the beagle dog model described in United States Patent No. 7,101,576.

Fast Onset of Activity

The diclofenac compositions of the invention exhibit faster therapeutic effects.

In one example, following administration the diclofenac compositions of the invention comprising diclofenac have a T_{max} of less than about 5 hours, less than about 4.5 hours, less than about 4 hours, less than about 3.5 hours, less than about 3 hours, less than about 2.75 hours, less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, less than about 10 minutes, less than about 5 minutes, or less than about 1 minute.

Increased Bioavailability

The diclofenac compositions of the invention preferably exhibit increased bioavailability (AUC) and require smaller doses as compared to prior conventional compositions administered at the same dose. Any drug composition can have adverse side effects. Thus, lower doses of drugs which can achieve the same or better therapeutic effects as those observed with larger doses of conventional compositions are desired. Such lower doses can be realized with the compositions of the invention because the greater bioavailability observed with the compositions as compared to conventional drug formulations means that smaller doses of drug are required to obtain the desired therapeutic effect.

The Pharmacokinetic Profiles of the Compositions of the Invention are not Substantially Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

The invention encompasses diclofenac compositions wherein the pharmacokinetic profile of the composition is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of composition or the rate of composition absorption when the compositions are administered in the fed versus the fasted state. Thus, the compositions of the invention substantially eliminate the effect of food on the pharmacokinetics of the composition.

The difference in absorption of the diclofenac composition of the invention, when administered in the fed versus the fasted state, is less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, or less than about 3%. This is an especially important feature in treating patients with difficulty in maintaining a fed state.

In addition, preferably the difference in the rate of absorption (i.e., T_{max}) of the diclofenac compositions of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, or essentially no difference. Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

Preferably, the T_{max} of an administered dose of a diclofenac composition of the invention is less than that of a conventional drug active composition, administered at the same dosage.

A preferred diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a T_{max} which is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less

than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10% of the T_{max} exhibited by the standard conventional drug active composition.

In addition, preferably the C_{max} of a diclofenac composition of the invention is greater than the C_{max} of a conventional drug active composition, administered at the same dosage. A preferred diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a C_{max} which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% than the C_{max} exhibited by the standard conventional drug active composition.

In addition, preferably the diclofenac composition has an AUC greater than that of the equivalent conventional composition administered at the same dosage. A preferred diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a AUC which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% than the AUC exhibited by the standard conventional drug active composition.

Any standard pharmacokinetic protocol can be used to determine blood plasma concentration profile in humans following administration of a composition, and thereby establish whether that composition meets the pharmacokinetic criteria set out herein. For example, a randomized single-dose crossover study can be performed using a group of healthy adult human subjects. The number of subjects should be sufficient to provide adequate control of variation in a statistical analysis, and is typically about 10 or greater, although for certain purposes a smaller group can suffice. Each subject receives by oral administration at time zero a single dose (e.g., 300 mg) of a test formulation of composition, normally at around 8 am following an overnight fast. The subjects continue to fast and remain in an upright position for about 4 hours after administration of the composition. Blood samples are collected from each subject prior to administration (e.g., 15 minutes) and at several intervals after administration. For the present purpose it is preferred to take several samples within the first hour, and to sample less frequently thereafter. Illustratively, blood samples could be collected at 15, 30, 45, 60, and 90 minutes after administration, then every hour from 2 to 10 hours after administration. Additional blood samples may also be taken later, for example at 12 and 24 hours after administration. If the same subjects are to be used for study of a second test formulation, a period of at least 7

days should elapse before administration of the second formulation. Plasma is separated from the blood samples by centrifugation and the separated plasma is analyzed for composition by a validated high performance liquid chromatography (HPLC) or liquid chromatography mass spectrometry (LCMS) procedure. Plasma concentrations of composition referenced herein are intended to mean total concentrations including both free and bound composition.

Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions and solid dose forms of composition. If the liquid dispersion medium is one in which the composition has very low solubility, the particles are present as suspended particles. The smaller the particles the higher the probability that the formulation will exhibit the desired pharmacokinetic profile.

Thus, an diclofenac composition of the invention, upon administration to a subject, provides improved pharmacokinetic and/or pharmacodynamic properties compared with a standard reference diclofenac composition as measured by at least one of speed of absorption, dosage potency, efficacy, and safety.

Modes of administration of medicaments comprising biologically active materials

Medicaments of the invention can be administered to animals, including man, in any pharmaceutically acceptable manner, such as orally, rectally, pulmonary, intravaginally, locally (powders, ointments or drops), transdermal, parenteral administration, intravenous, intraperitoneal, intramuscular, sublingual or as a buccal or nasal spray

Solid dosage forms for oral administration include capsules, tablets, pills, powders, pellets, and granules. Further, incorporating any of the normally employed excipients, such as those previously listed, and generally 5-95% of the biologically active agent, and more preferably at a concentration of 10%-75% will form a pharmaceutically acceptable non-toxic oral composition.

Medicaments of the invention may be parenterally administered as a solution of the biologically active agent suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, e.g. water, buffered water, 0.4% saline, 0.3% glycine, hyaluronic acid and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration.

For aerosol administration, medicaments of the invention are preferably supplied along with a surfactant or polymer and propellant. The surfactant or polymer must, of course, be non-toxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed.

The surfactant or polymer may constitute 0.1%-20% by weight of the composition, preferably 0.25-5%. The balance of the composition is ordinarily propellant. A carrier can also be included, as desired, as with, e.g., lecithin for intranasal delivery.

Medicaments of the invention may also be administered via liposomes, which serve to target the active agent to a particular tissue, such as lymphoid tissue, or targeted selectively to cells. Liposomes include emulsions, foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions, lamellar layers and the like. In these preparations the composite microstructure composition is incorporated as part of a liposome, alone or in conjunction with a molecule that binds to or with other therapeutic or immunogenic compositions.

As described above, the biologically active material can be formulated into a solid dosage form (e.g., for oral or suppository administration), together with the grinding matrix or at least a portion of it. In this case there may be little or no need to add stabilizing agents since the grinding matrix may effectively act as a solid-state stabilizer.

However, if the biologically active material is to be utilized in a liquid suspension, the particles comprising the biologically active material may require further stabilization once the solid carrier has been substantially removed to ensure the elimination, or at least minimisation of particle agglomeration.

Therapeutic uses

Therapeutic uses of the medicaments of the invention include pain relief, anti-inflammatory, migraine, asthma, and other disorders that require the active agent to be administered with a high bioavailability.

One of the main areas when rapid bioavailability of a biologically active material is required is in the relief of pain. The minor analgesics, such as cyclooxgenase inhibitors (aspirin related drugs) may be prepared as medicaments according to the present invention.

Medicaments of the invention may also be used for treatment of eye disorders. That is, the biologically active material may be formulated for administration on the eye as an aqueous suspension in physiological saline, or a gel. In addition, the biologically active material may be prepared in a powder form for administration via the nose for rapid central nervous system penetration.

Treatment of cardiovascular disease may also benefit from biologically active materials according to the invention, such as treatment of angina pectoris and, in particular, molsidomine may benefit from better bioavailability.

Other therapeutic uses of the medicaments of the present invention include treatment of hair loss, sexual dysfunction, or dermal treatment of psoriasis.

The present invention will now be described with reference to the following non-limiting Examples. The description of the Examples is in no way limiting on the preceding paragraphs

of this specification, but is provided for exemplification of the methods and compositions of the invention.

Examples

It will be apparent to persons skilled in the milling and pharmaceutical arts that numerous enhancements and modifications can be made to the above described processes without departing from the basic inventive concepts. For example, in some applications the biologically active material may be pretreated and supplied to the process in the pretreated form. All such modifications and enhancements are considered to be within the scope of the present invention, the nature of which is to be determined from the foregoing description and the appended claims. Furthermore, the following Examples are provided for illustrative purposes only, and are not intended to limit the scope of the processes or compositions of the invention.

The following materials were used in the examples

Active pharmaceutical ingredients were sourced from commercial suppliers, excipients from either commercial suppliers such as Sigma-Aldrich or retailers, while food ingredients were sourced from retailers.

The following mills were used for the grinding experiments

Spex-type Mill:

Small scale milling experiments were conducted using a vibratory Spex 8000D mixer/mill. Twelve 3/8" stainless steel balls were used as the grinding media. The powder charge and grinding media were loaded into a hardened steel vial with an internal volume of approximately 75 mL. Following milling, the milled material was discharged from the vial and sieved to remove grinding media.

Attritor-type Mill:

Small scale attritor milling experiments were performed using a 1HD Union Process attritor mill with a 110 mL grinding chamber. The grinding media consisted of 330g 5/16" stainless steel balls. The mill was loaded through the loading port, with dry materials added initially, followed by the grinding media. The milling process was conducted with the jacket cooled at 10-20°C and the shaft rotating at 500 rpm. Upon completion of milling, the milled material was discharged from the mill and sieved to remove the grinding media.

Medium scale attritor milling experiments were performed using a 1HD Union Process attritor mill with a 1 L grinding chamber or a 1S Union Process attritor mill with a 750 mL grinding chamber. The grinding media consisted of 3 kg of 5/16" stainless steel balls or 1.5 kg of 3/8" stainless steel balls for the 1S attritor. The 1HD mill was loaded through the loading port, with dry materials added initially, followed by the grinding media, while the grinding media was

added initially, followed by the dry materials in the 1S attritor mill. The milling process was conducted with the jacket cooled at 10-20°C with the shaft rotating at 350 rpm in the 1HD attritor or 550 rpm in the 1S attritor. Upon completion of milling, the milled material was discharged from the mill and sieved to remove the grinding media.

Medium to large scale attritor milling experiments were performed using a 1S Union Process attritor mill with a ½ gallon grinding chamber. The grinding media consisted of 7 kg of 3/8" stainless steel balls. The mill was loaded through the loading port, with the grinding media added initially, followed by the dry powders. The milling process was conducted with the jacket cooled at 18°C and the shaft rotating at 550-555 rpm. Upon completion of milling, the milled powder was discharged from the mill through the bottom discharge port at 77rpm for 5min.

Large scale attritor milling experiments were performed using a 1S Union Process attritor mill with a 1½ gallon grinding chamber. The grinding media consisted of 20 kg of 3/8" stainless steel balls. The mill was loaded through the loading port, with the grinding media added initially, then followed by the dry powders. The milling process was conducted with the jacket cooled to ambient temperature and the shaft rotating at 300 rpm. Upon completion of milling, the milled powder was discharged from the mill through the bottom discharge port at 77rpm for 5 min.

The largest scale attritor millings were done in a 30S Union Process mill with a 25 gallon grinding chamber (Union Process, Akron OH, USA). The grinding media consisted of 454kg of 3/8" stainless steel balls. The mill was loaded through its split top lid, with the grinding media added initially, then followed by the dry powders (25kg). The milling process was conducted with the jacket cooled to 10°C and the shaft rotating at 130 rpm. Upon completion of milling, the milled powder was discharged from the mill through the bottom discharge port at 77rpm for 5 min.

Siebtechnik Mill

Medium scale milling experiments were also performed in a Siebtechnik GSM06 (Siebtechnik ,GmbH, Germany) with two 1 L milling chambers. Each chamber was filled with 2.7 kg stainless steel media with a diameter of 3/8". The media and powder were loaded with the lid off. The mill was operated at ambient temperature. The vibration speed was the standard mill settings. Upon completion of the milling the media was separated from the powder by sieving.

Simoloyer Mill

Medium scale milling experiments were performed in a Simoloyer CM01 (ZOZ GmbH, Germany) with a 2 L milling chamber. The grinding media consisted of 2.5 kg stainless steel media with a diameter of 5 mm. the media was loaded though the loading port followed by the dry materials. The milling vessel was cooled using water at a temperature of about 18°C. The mill speed was operated in cycle mode: at 1300 rpm for two minutes and at 500 rpm for 0.5 min

and so forth. Upon completion of the milling the media was discharged from the mill using a grated valve to retain the grinding media.

Large scale milling experiments were performed in a Simoloyer CM100 (ZOZ GmbH, Germany) with a 100 L milling chamber. The grinding media consisted of 100 kg stainless steel media with a diameter of 3/16". The powder charge (11kg) was added to the milling chamber, which already contained the grinding media, through a loading port. The milling chamber was cooled to 18°C and the powder was milled for a total of 20 minutes using a cycling mode equivalent to a tip speed at 1300/500 rpm for 2/0.5 min in the CM-01 type mill. Upon completion of the milling the mill was discharged by sucking the powder into a cyclone.

Hicom Mill

Millings performed in a nutating Hicom mill utilized 14kg of stainless steel 0.25" grinding media together with a powder charge of 480g. The mill was loaded by pre-mixing media and powder, then adding the mixture to the grinding chamber through the loading port at the top of the mill. The milling was done at 1000rpm and the mill discharged by inverting the mill and emptying through the loading port. The recovered material was sieved to separate the grinding media from the powder.

Variations to the milling conditions set out above are indicated in the variations column in the data tables. The key to these variations is shown in Table A.

Particle size measurement:

The particle size distribution (PSD) was determined using a Malvern Mastersizer 2000 fitted with a Malvern Hydro 2000S pump unit. Measurement settings used: Measurement Time: 12 seconds, Measurement cycles: 3. Final result generated by averaging the 3 measurements. Samples were prepared by adding 200mg of milled material to 5.0mL of 1% PVP in 10mM hydrochloric acid (HCl), vortexing for 1 min and then sonicating. From this suspension enough was added into the dispersant (10mM HCl) to attain a desired obscuration level. If necessary an extra 1-2 minutes of sonication was applied using the internal sonication probe in the measurement cell. The refractive index of the active ingredient to be measured was in the range of 1.49-1.73. Any variations to this general method are summarized in Table B.

XRD Analysis:

Powder X-Ray diffraction (XRD) patterns were measured with a Diffractometer D 5000, Kristalloflex (Siemens). The measurement range was from 5-18 degrees 2-Theta. The slit width was set to 2 mm and the cathode ray tube was operated at 40 kV and 35 mA. Measurements were recorded at room temperature. The recorded traces were subsequently processed using Bruker EVA software to obtain the diffraction pattern.

Variation #	Mill type	Milling Speed (rpm)	Media size (inch)	Media Mass (kg)	Offload spped (rpm)
A	1HD 1L		0.25		
B	1S 0.5gal			5	
C	1S 0.5gal			4	
D	1S 0.5gal	500			
E	1S 0.5gal	550-555			
F	1S 1.5gal	316-318		21	
G	1S 1.5gal	500		21	
H	1S 1.5gal	355		21	
I	1S 1.5gal	355		18	
J	1S 1.5gal			21	
K	1S 1.5gal			18.4	
L	1S 1.5gal	400			
M	1S 1.5gal			21	57
N	1S 1.5gal				57
O	1S 0.5gal	400			400
P	1S 0.5gal	500			350
Q	HICOM		1/8		
R	HICOM			11.7	

Table A. Variations to milling conditions. Only conditions reported in the table have changed as compared to conditions reported above.

Variation #	Sample Dispersant	Measurement Dispersant	Addition Method
1		0.1%PVP in DI water	Powder addition
2	0.2% Pluronic L81 in DI water	DI water	
3		Saturated glyphosate in DI water	Powder addition
4		Saturated glyphosate in DI water	Powder addition
5	1%PVP in DI water	DI water	
6		DI water	Powder addition
7	1%PVP in DI water	Saturated creatine in DI water	
8	1%PVP in DI water	10mM HCl	
9	0.2% Pluronic L81 in DI water	Acidified with 1M HCl	

10	1%PVP in DI water	0.1%PVP in DI water	
11	1%PVP in DI water	1%PVP in DI water	
12			Filtered before PSD measurement

Table B. Variations to particle size measurement conditions.

Abbreviations:

HCl: Hydrochloric acid

Nap: Naproxen acid

PSD: Particles size distribution

PVP: Polyvinyl pyrrolidone

RI: Refractive index

Rpm: Revolutions per minute

SLS: Sodium lauryl sulphate

SSB: Stainless Steel Balls

XRD: X-Ray Diffraction

Other abbreviations used in the data tables are listed below in Table C (for actives), Table D (for matrices) and Table E (for surfactants). In the data tables single letter with example number abbreviations have been used to identify specific sample numbers within the table. The data tables shown in the figures the use of surfactant , matrix are interchangeable and do not necessarily define the nature of that material.

API Name	**Abbreviation**
2,4-Dichlorophenoxyacetic acid	2,4D
Anthraquinone	ANT
Celecoxib	CEL
Cilostazol	CIL
Ciprofloxacin	CIP
Creatine Monohydrate	CRM
Cyclosporin A	CYA
Diclofenac Acid	DIC
Glyphosate	GLY
Halusulfuron	HAL
Diclofenac	IND

Mancozeb	MAN
Meloxicam	MEL
Metaxalone	MTX
Metsulfuron	MET
Naproxen Acid	NAA
Naproxen Sodium	NAS
Progesterone	PRO
Salbutamol	SAL
Sulfur	SUL
Tribenuran	TRI

Table C. Abbreviations used for active pharmaceutical ingredients.

Matrix Name	**Abbreviation**
Calcium Carbonate	CAC
Glucose	GLU
Lactose Anhydrous	LAA
Lactose Monohydrate	LAC
Lactose Monohydrate Food Grade	LFG
Malic Acid	MAA
Maltitol	MAL
Mannitol	MAN
Sodium Bicarbonate	SB
Sodium Chloride	SC
Sorbitol	SOR
Sucrose	SUC
Tartaric Acid	TA
TriSodium Citrate Dihydrate	TCD
Whey Powder	WP
Xylitol	XYL

5 Table D. Abbreviations used for excipients.

Surfactant Name	**Abbreviation**
Aerosil R972 Silica	AS
Benzalkonium Chloride	BC

Brij700	B700
Brij76	B76
Cremophor EL	CEL
Cremophor RH-40	C40
Dehscofix 920	D920
Docusate Sodium	DS
Kollidon 25	K25
Kraftsperse 1251	K1251
Lecithin	LEC
Poloxamer 188	P188
Microcrystalline Cellulose	MCC
Poloxamer 407	P407
Polyethylene Glycol 3000	P3000
Polyethylene Glycol 8000	P8000
Polyoxyethylene 40 Stearate	P40S
Polyvinyl Pyrrolidone (Kollidon 30)	PVP
Primellose	PML
Primojel	PRI
Sodium Deoxycholate	SDC
Sodium Dodecyl Sulphate	SDS
Sodium Dodecylbenzenesulphonic Acid	SDA
Sodium N-Lauroyl Sarcosine	SNS
Sodium Octadecyl Sulphate	SOS
Sodium Pentane Sulphonate	SPS
Soluplus HS15	SOL
Teric 305	T305
Tersperse 2700	T2700
Terwet 1221	T1221
Terwet 3785	T3785
Tween 80	T80

Table E. Abbreviations used for surfactants

Example 1: Spex Milling

A range of actives, matrices and surfactants in a variety of combinations were milled using the Spex mill. The details of these millings are shown in Figures 1A-1G together with the particle size distributions of actives that were milled.

These millings demonstrate that the addition of a small amount of surfactant to the milling matrix delivers a smaller particle size compared to millings of just an active and a single matrix. Some examples of this are samples Z and AA compared to sample Y; Sample AB compared to sample AC; sample AE compared to sample AD; sample AG compared to sample AF; sample AP compared to sample AO; sample AR compared to sample AQ, sample AT compared to sample AS; Samples AX, AY and AZ compared to sample AW; sample BC compared to sample BD; sample BI compared to BH; samples BL-BR compared to sample BK; samples CS-DB compared to sample DC. This last example is particularly noteworthy as these millings were undertaken at 45 % v/v. This demonstrates the broad applicability of this invention. Some other examples of surfactant addition being beneficial for size reduction are samples DD-DG and DI-DK compared to sample DH; sample DM compared to sample DL. Other samples such as samples DY-EC compared to sample DX; sample AV compared to sample AU; samples B-H compared to sample A and samples K-M compared to sample J show this ti be also true when particle size statistics such the % < 1 micron as used.

Note that this applies to mechanochemcial matrix milling as well. This is demonstrated by sample BI where naproxen sodium is milled with tartaric acid and converted to naproxen acid. Figure 1H shows XRD data that demonstrates the transformation.

Other samples such as CB-CR show examples were surfactants suitable for use with IV formulations can be used to manufacture very small particles.

It is also noteworthy that samples DS and DT could be sized using a saturated solution of the active (salbutamol) demonstrating that actives with high water solubility can be measured as long as care is taken when measuring the size.

Two sets of data, samples N-Q and samples R-U, also demonstrate that the invention described herein is unique. In these samples the active milled with a matrix and surfactant produces small particles. When milled with matrix alone the particles sizes are larger, in the case of sample Q they are not even nanoparticles. When the active is milled with just 1% surfactant the resultant particle size is very large. Even when 80 % surfactant is used the size is large.

Example 2: 110mL Attritor

A range of actives, matrices and surfactants in a variety of combinations were milled using the 110 ml stirred attritor mill. The details of these millings are shown in Figure 2A together with the particle size distributions of actives that were milled.

These millings also demonstrate that the addition of a small amount of surfactant to the milling matrix delivers a smaller particle size compared to millings of just an active and a single matrix in a small scale stirred mill as well as the vibratory Spex mill. Sample F also demonstrates that small particles can be achieved at high % actives when a surfactant is present. Sample D and E also show that the addition of the surfactant also increased the yield of powder from the mill.

Example 3: Second Matrix

In this example naproxen was milled with a mixture of two matrices using the Spex mill. The details of these millings are shown in Figure 3A together with the particle size distributions of actives that were milled. Samples A and B were milled in a primary matrix of lactose monohydrate and 20 % of second matrix. The particle size of these millings is smaller than the same milling with just lactose monohydrate (See example 1 sample No AH, Figure 1B). The particle size is also smaller than naproxen milled in the secondary matrices (See example 1 sample No AI and AJ, Figure 1B). This shows the mixed matrices have synergy together.

Samples C-E were milled in anhydrous lactose with 20 % of a second matrix. All these samples had a particle size much smaller than naproxen milled in anhydrous lactose alone (See example 1 sample No AK, Figure 1B).

These millings demonstrate that the addition of a second matrix to the primary milling matrix delivers a smaller particle size compared to millings with just a single matrix.

Example 4: 1L Attritor

Two actives with various combinations of lactose monohydrate and SDS were milled using the 1 L stirred attritor mill. The details of these millings are shown in Figure 4A together with the particle size distributions of actives that were milled.

Sample A and B are millings of meloxicam at 20 %. While sample B has a slightly smaller particle size than sample A there is a dramatic difference in the amount of material recovered from the milling. Sample A, milled with 3 % SDS has a high yield of 90% whereas sample B with no surfactant has practically no yield with all the powder caked in the mill.

In samples C-F the milling of 13 % diclofenac shows that the use of a second matrix (tartaric acid) in combination with 1% SDS delivers the best outcome of a good particle size and high yield. Sample D which has just the mixed matrix has very good particle size but poor yield.

These results show that the addition of a small amount of surfactant improves milling performance.

Example 5: 750mL Attritor

Two actives with various combinations surfactants were milled using the 750 ml stirred attritor mill. The details of these millings are shown in Figure 5A together with the particle size distributions of actives that were milled.

In samples A-C three millings of naproxen are shown. Sample A has just 1% SDS as a surfactant. Samples B and C have a second surfactant present and these samples have a smaller particle size as measured by the %< 500 nm, % < 1000nm and % < 2000 nm.

In samples D-F three millings of diclofenac are shown. Sample D has just 1% SDS as a surfactant. Samples E and F have a second surfactant present and these samples have a smaller particle size compared to sample D.

These examples demonstrate that the use of combination of surfactants can be useful to achieve better reduction in particle size.

Example 6: 1/2Gallon 1S

A range of actives, matrices and surfactants in a variety of combinations were milled using the ½ gallon 1S mill. The details of these millings are shown in Figures 6A-C together with the particle size distributions of actives that were milled.

The following examples demonstrate the increased yield obtained when milling an active in a 1/2gallon 1S attritor mill with a surfactant as compared to no surfactant, with all other factors being identical. Sample C and D (Figure 6A) shows Naproxen acid milled in Mannitol with yields of 92% and 23%, with and without surfactant. Sample S and AL (Figure 6B and C) show the same for glyphosate with yields of 95% and 26%, respectively. Sample AI and AJ (Figure 6B) show Ciprofloxacin yields of 94% and 37% with and without surfactant while sample AM an AN (Figure 6C) show Celecoxib yields of 86% and 57% with and without surfactants. Finally, samples AP and AQ (Figure 6C) shows milling Mancozeb with or without surfactants results in yields of 90% and 56%, respectively.

The following examples illustrates that milling an active in a 1/2gallon 1S attritor mill with a surfactant as compared to without surfactant and all other factors identical, leads to smaller particle size after milling. Sample C and D (Figure 6A) shows a D(0.5) of 0.181 and 0.319 with or without surfactant, while sample AM and AN (Figure 6C) shows D(0.5) of 0.205 and 4.775 with and without surfactants.

The series of samples Q-S are timepoints taken from a single glyphosate milling. The data demonstrates that the size of the actives decreases with milling time.

Other samples such as V-AA show examples were surfactants suitable for use with IV formulations can be used to manufacture very small particles.

Some of the particle size data in Figures 6A-C was converted to a number average particle size and is shown in the tables. This number was calculated in the following way. The Volume distribution was transformed to the number distribution using the Malvern Mastersizer software. For each size bin the size of the bin was multiplied by the % of particles in the bin. This numbers were added together and divided by 100 to give the number average particle size.

Example 7: Metaxalone

Metaxalone was milled with various combinations of matrices and surfactants using a variety of mills. The details of these millings are shown in Figure 7A together with the particle size distributions of actives that were milled. Samples A, B, E, G, H and I were milled in a Spex mill. Samples C, D and F were milled in the 750 ml atrittor. The remaining samples were milled in the ½ gallon 1S mill.

Samples A compared to sample B and sample H compared to sample G demonstrate that the addition of one or more surfactants enables the production of smaller active particles. Other millings such as samples C-F show that metaxalone can be milled small at very high active loadings. Sample I shows that disintegrant can be added during milling and not effect the production of small active particles. Note that the particle size in sample I is after filtration through a 10 micron filter. Sample N shows an alternative way to manufacture a formulation with small particles and disintegrants. In this example the powder from sample M was left in the mill and a wetting agent (PVP) and disintegrant were added. The powder was milled for a further 2 minutes and then unloaded with a very high yield of 97%.

The series of samples J-M are timepoints taken from a single milling. The data demonstrates that the size of the actives decreases with milling time.

Example 8: Hicom

A range of actives, matrices and surfactants in a variety of combinations were milled using the Hicom mill. The details of these millings are shown in Figure 8A together with the particle size distributions of actives that were milled.

The data shows that the invention described herein can be used with the Hicom mill with its nutating action. The data in Figure 8A shows that a variety of actives can be milled small in very short times and give very good yields at 500 gram scale.

Sample N and O show that cocoa powder can be reduced to very fine sizes in short times using the invention describes here in in combination with the Hicom nutating mill. Likewise Sample P shows that this is also the case for cocoa nibs.

Example 9: 1.5Gallon 1S

A range of actives, matrices and surfactants in a variety of combinations were milled using the 1.5 Gallon 1S mill. The details of these millings are shown in Figures 9A-B together with the particle size distributions of actives that were milled.

The following examples demonstrate the increased yield obtained when milling an active in a 1.5gallon 1S attritor mill with a surfactant as compared to no surfactant, with all other factors being identical. Sample J and N (Figure 9A) shows yields of 51% and 80%, without and with surfactant. Sample K and P (Figure 9A) show yields of 27% and 80%, without and with surfactant, while sample L (Figure 9A) show a yield of 94% with surfactant and the control without surfactant (sample M, Figure 9A) resulted in no yield due to caking within the mill.

The following examples illustrates that milling an active in a 1.5gallon 1S attritor mill with a surfactant as compared to without surfactant and all other factors identical, leads to smaller particle size after milling. Sample F and G (Figure 9A) shows a D(0.5) of 0.137 and 4.94 with or without surfactant, while sample K and P (Figure 9A) shows D(0.5) of 0.242 and 0.152 without and with surfactants.

The series of samples AI-AL are timepoints taken from a single meloxicam milling. The data demonstrates that the size of the actives decreases with milling time.

Other samples such as A-E show examples were surfactants suitable for use with IV formulations can be used to manufacture very small particles.

Sample M was a milling of meloxicam in lactose monohydrate without surfactant. 3 minutes into the milling the mill refused to turn. The milling was stopped and started again but only ran for another 3 minutes before stopping again. At this point the mill was taken apart and no evidence of caking was found. However the powder had a gritty feeling to it and was locking the medium and shaft such that it was not possible to turn. The media was weighed and it as found that 150 grams of powder was on the media indicating that it was sticking to the media and making it hard to move. At this point the mill was re-assembled and the powder and media put back in. 30.4 grams of SDS was included in the milling making it similar to milling L. After the addition of the surfactant the mill was run for another 14 minutes (giving a total of 20 mins) without incident. After offloading the powder the media was weighed and the weigh of powder on the media was only 40.5 grams. This indicates the addition of surfactant has improved the milling performance and ability to mill the powder.

Some of the particle size data in Figures 9A-B was converted to a number average particle size and is shown in the tables. This number was calculated in the following way. The Volume distribution was transformed to the number distribution using the Malvern Mastersizer software. For each size bin the size of the bin was multiplied by the % of particles in the bin. This numbers were added together and divided by 100 to give the number average particle size.

Example 10: Large scale 25/11kg

Sample A (Figure 10A) was milled in the Siebtechnik mill for 15 minutes. After this time the powder was completely caked onto the walls of the mill and the media. No powder could be removed to measure the particle size. At this point 0.25 g (1 w/w%) SLS was added to mill chamber and milling was then undertaken for a further 15 minutes. After the second period of milling in the presence of SLS powder was no longer caked onto the media and some free powder was also present. The observations made before and after the addition of the SLS demonstrate that the addition of the surfactant lessens the problem of caking. With the addition of surfactant the caked material could be recovered to become free powder again with small particle size.

Sample B-E was milled in horizontal Simoloyer mills. The details of these millings are shown in Figure 10A together with the particle size distributions of actives that were milled.

The data shows that the invention described herein can be used with Simoloyer mills with their horizontal attritor action. Of particular note is example E which was milled at 11kg scale. This demonstrates the invention described herein is suitable for commercial scale milling.

Sample F was milled in a vertical attritor mill (Union Process S-30). The details of this milling is shown in Figure 10A together with the particle size distribution of the active milled.

The data shows that the invention described herein can be used with a S-30 mills with its vertical attritor action. Of particular note is that this milling was at 25kg scale. This demonstrates the invention described herein is suitable for commercial scale milling.

Example 11: Naproxen

Naproxen was milled in mannitol with a range of surfactants using the 1/2 Gallon 1S mill. The details of these millings are shown in Figures 11A together with the particle size distributions of actives that were milled.

Naproxen acid milled in Mannitol with a surfactant (Sample A, D-J in Figure 11A) leads to higher yields, as compared to Naproxen acid milled in Mannitol without surfactant (Sample K, Figure 11A). Naproxen acid milled in Mannitol and either microcrystalline cellulose or the disintegrant primellose (sample L or M, Figure 11A) leads to small particle size with D(0.5) around 0.25 in both cases.

Example 12: Filtration

Some matrices, milling aids or facilitating agents that are used by this invention are not water soluble. Examples of these are microcrystalline cellulose and disintegrants such as croscarmellose and sodium starch glycolate. In order to more easily characterise the particle size of the active after milling with these materials filtration methods can be used to remove them allowing a characterisation of the active. In the following examples naproxen was milled with lactose monohydrate and microcrystalline cellulose (MCC). The particle size was

characterised before and after filtration and the ability of the filters to let through the naproxen was demonstrated using HPLC assays. The milling details and the particle size are shown in Figure 12a. Note in this table the particle size with milling details is un-filtered. The particle size in the rows with no milling details is after filtration. The sample that was filtered is indicated in the Active material section. The HPLC assays were performed by taking samples before and after filtration through 10 micron poroplast filters. The samples taken were diluted to give a nominal concentration of 100 µg/ml. The HPLC assay data is shown in Table 12

Sample A was milled with 5% MCC. Before filtration the D50 was 2.5 µm, after filtration (sample B) the D50 was 183 nm. When sample B was assayed the concentration was 94 µg/ml indicating that filtration process retained little naproxen. A second milling (sample C) was undertaken without MCC. The D50 was 160nm as would be expected. After filtration (sample D) the particle size was unchanged indicating that if the filtration process did remove any naproxen then it was removed in an even way. Some of sample C was then milled with MCC for 1 minute. This is long enough to incorporate the MCC into the powder but not long enough to affect the particle size distribution. Two millings were undertaken. Sample E incorporated 5 % w/w MCC into the powder and Sample F 9 % w/w. After incorporation of the MCC the particle size increased dramatically. These samples where then filtered (Sample E and F) and the size remeasured. After filtration the particle size is the same as Sample C which was the starting material. The assay of samples E-H indicates that filtration did not remove any naproxen of any significance. The combination of particle size and assay data clearly shows that material such as MCC can easily and successfully be removed allowing the true particle size of the active to be measured.

Samples I and J were millings conducted with 10 and 20 % w/w MCC. The particle size post filtration is show as sample K and L. Again the filtration has delivered a reduction in particle size due to the removal of the MCC component. And again the HPLC assay of sample I-L shows little naproxen was lost during filtration.

This data also demonstrates that MCC can successfully be used as co matrix in the invention disclosed herein.

Sample No.	HPLC Assay (µg/ml)
B	94
D	93
E	99
F	96
G	98
H	97
I	94
J	89
K	91
L	84

Table 12: The HPLC assay of naproxen before and after filtration of samples.

Example 13 : Manufacture of Diclofenac Nanoformulation Capsules

Example 13(a): 18 mg

Diclofenac milled powder (666.2 g, from Example 9, Sample W) was charged into the bowl of a KG-5 high shear granulator. Separately, a 30% w/w solution of povidone K30 was prepared by dissolving 60.0 g of povidone K30 in 140.0 g of purified water. The granulator was operated at a chopper speed of 250 rpm and impeller speed of 2500 rpm. A portion of the povidone solution (88.6 g) was introduced into the granulation over a period of approximately 9 minutes with a peristaltic pump. An additional 30 g of water was then added to the granulation.

The wet granules were spread on to paper-lined trays and dried in an oven at 70°C for 2 hours. They were then manually screened through a 10 mesh hand screen. After approximately 2.25 hours of drying time, the loss on drying was determined to be 0.559%.

The dried granules were processed in a Quadro CoMill fitted with a 200 mesh screen and 0.225 inch spacer, run at 1265 rpm. The process yielded 539.0 g of milled, dried granules.

The granules were filled into size 4 white opaque hard gelatin capsules using an IN-CAP® automated capsule filling machine (Dott. Bonapace & C., Milano, Italy). The machine was set up with size 4 change parts and a 10 mm dosing disc. The target fill weight was 124.8 mg, and the average weight of an empty capsule shell was 38 mg. The machine was run at speed setting #2. Tamping pin #4 was set to 21 mm; all other tamping pin settings were N/A.

The filled capsules were polished in a capsule polishing machine, and the net yield of filled capsules was 480.2 g (approximately 2,910 capsules).

Example 13(b): 35 mg

Two separate granulation sublots were used for the manufacture of Diclofenac Nanoformulation Capsules 35 mg. Granulation sublot A: 642.7 g of milled diclofenac powder (Example 9, Sample X) was charged into the bowl of a KG-5 high shear granulator. Separately, a 30% w/w solution of povidone K30 was prepared by dissolving 60.0 g of povidone K30 in 140.0 g of purified water. The granulator was operated at an impeller speed of 250 rpm and a chopper speed of 2500 rpm. A portion of the binder solution (85.5 g) was introduced into the granulation over a period of approximately 8.5 minutes via a peristaltic pump. An additional 30 g of purified water was then added to the granulation at the same rate. The wet granules were spread on to paper-lined trays to a thickness of approximately ½".

Granulation sublot B: 519.6 g of milled diclofenac powder (Example 9, Sample Y) was charged into the bowl of a KG-5 high shear granulator. Separately, a 30% povidone solution was prepared by dissolving 60.0 g of povidone K30 in 140.0 g of purified water. The granulator was operated at an impeller speed of 250 rpm and a chopper speed of 2500 rpm. A portion of the povidone solution (69.1 g) was added to the granulation over a period of approximately 6.5

minutes. An additional 30 g of water was then added at the same rate. The wet granules were spread on to paper-lined trays to a thickness of approximately ½".

The wet granules from sublots A and B were dried in an oven at 70°C for approximately 2 hours. They were then manually screened through a 10 mesh hand screen and tested for loss on drying. The LOD result was 0.316%.

The dried granules were milled in a Quadro CoMill fitted with a 200 mesh screen and 0.225 inch spacer, operated at 2500 rpm. The milled granules were charged into an 8 qt V-blender and mixed for 5 minutes, yielding 1020.2 g of granules.

The granules were filled into size 3 white opaque hard gelatin capsules using a MiniCap Capsule Filling Machine equipped with size 3 change parts. The target fill weight was 242.7 mg and the average weight of an empty capsule shell was 47 mg. The granules were filled into the capsule shells manually using a scraper. Vibration and tamping were adjusted to achieve the target fill weight. The filled capsules were polished on a capsule polishing machine, yielding 1149.2 g of filled capsules (approximately 3,922 capsules).

Example 14: Dissolution rate of milled diclofenac

In this example, dissolution rate is compared between 18mg and 35mg nanoformulations of the invention (Example 13(a) and 13(b)), and commercial reference diclofenac Voltarol Dispersible Tablets 50mg (Novartis, U.K) which contain 46.5 mg of diclofenac free acid, equivalent to 50 mg of diclofenac sodium. The dissolution method used was Apparatus I (baskets) according to USP <711> with a stirring speed of 100 rpm. The dissolution media was 0.05% sodium lauryl sulfate and citric acid solution buffered to pH 5.75. The dissolution volume was 900 mL and dissolution medium temperature was 37°C. Samples were tested at 15, 30, 45, and 60 minutes and at infinity. Infinity was defined as an additional 15 minutes at a higher rotation speed. A sample of 1 ml was taken at each time point, filtered and assayed by HPLC with the detection wavelength set at 290 nm. The data in Table 14a below report the percent dissolved of the amount of active in each test article, for the specified time points.

	Percent Label Claim Dissolved (%)		
Time	Voltarol Dispersible Tablets 50 mg	Diclofenac Nanoformulation Capsules 18 mg	Diclofenac Nanoformulation Capsules 35 mg
0	0	0	0
15	52	91	82
30	59	94.0	95
45	63	94	95
60	65	94	95

75	87	94	95

Table 14a. Dissolution Profiles for Voltarol® Dispersible Tablets 50 mg, Diclofenac Nanoformulation Capsules 18 mg, and Diclofenac Nanoformulation Capsules 35 mg

The results demonstrate that the milled diclofenac capsules dissolve more quickly and more completely than the commercial reference diclofenac. Those of skill in the art will readily appreciate the advantages conferred by more rapid dissolution -- more active agent is available at any given time point. Put another way, an equal quantity of dissolved diclofenac may be obtained with an initially smaller dosage amount of milled diclofenac, as opposed to the larger initial dose required for the reference diclofenac to reach to the same quantity of dissolved diclofenac. Additionally, as the results make clear, the reference diclofenac does not achieve complete dissolution even by the final time point, while the milled diclofenac achieves about 90% dissolution within 15 minutes. Again, a smaller dose of milled diclofenac yields a quantity of dissolved diclofenac for which a larger dose of reference diclofenac would be required to equal.

Example 15: Bioavailability of milled diclofenac.

This example describes a Single-Dose, Five-Way Crossover, Relative Bioavailability Study of Diclofenac Nanoformulation 18 mg and 35 mg capsules and Cataflam® 50 mg Tablets in Healthy Subjects under Fed and Fasting Conditions.

The pharmacokinetic study described in this example used Diclofenac Nanoformulation Capsules 18 mg and 35 mg manufactured as described in Example 13(a) and 13(b).

Objectives:

1) To determine the relative bioavailability of diclofenac from the 35 mg Test capsule versus the 50 mg Reference tablet when administered to healthy subjects under fasting conditions.

2) To determine the effect of food on the rate and extent of absorption of a single dose of the 35 mg Test capsule formulation of diclofenac nanoformulation administered to healthy subjects under fed and fasting conditions.

3) To determine the effect of food on the rate and extent of absorption of a single dose of the 50 mg Reference tablet formulation of diclofenac potassium administered to healthy subjects under fed and fasting conditions.

4) To evaluate the dose proportionality between 18 mg and 35 mg Test capsule formulations of diclofenac nanoformulation administered to healthy subjects under fasting conditions.

Methodology:

This was a single-center, single-dose, randomized, open-label, 5-period, 5-treatment, 10-sequence crossover study that investigated the relative bioavailability and dose-proportionality of the Test product (i.e., 18 mg and 35 mg nanoformulation capsules of diclofenac acid) vs. the Reference product (50 mg immediate-release tablet of diclofenac potassium [Cataflam]) administered under fed and fasting conditions. Forty (40) healthy adult male and female subjects who met all study eligibility criteria were randomized equally on a 1:1:1:1:1 basis to one of 10 sequences of treatment administration. Each subject received 5 treatments in order of their assigned sequence according to the randomization code. Subjects entered the clinic on Day -1 of Treatment Period 1 and fasted overnight. On the morning of Day 1, subjects were administered the Test or Reference products in the fasted state or 30 minutes after the start of a FDA High-Fat Breakfast (depending on the study treatment). Blood samples for the pharmacokinetic (PK) evaluation of diclofenac plasma concentrations were obtained before and over 12 hours following dosing. Subjects were then discharged and returned to the clinic after a 7-day washout interval to continue the treatment sequence for Periods 2, 3, 4, and 5. A blood sample for safety assessments was collected with the last PK sample in Treatment Period 5. Adverse event (AE) information elicited during confinement or reported at outpatient visits was reviewed and documented.

Number of Subjects (Planned and Analyzed):

Number of subjects planned for enrollment: up to 40
Number of subjects enrolled in study: 40
Number of subjects completing study: 38
Number of subjects bioanalytically analyzed: 30
Number of subjects statistically analyzed: 30

Diagnosis and Main Criteria for Inclusion:

Subjects were males and females who provided written informed consent, were at least 18 years of age, and had a body weight of at least 110 pounds and a body mass index (BMI) between 18 and 30 kg/m^2, and were healthy on the basis of medical history, physical examination, electrocardiogram (ECG), and clinical laboratory test results. All females were non-pregnant and non-nursing; females of child-bearing potential agreed to take precautions to prevent pregnancy. Eligibility criteria required that subjects demonstrate negative test results for hepatitis B, hepatitis C, and human immunodeficiency virus, as well as a negative urine screen for drugs of abuse and breathalyzer test for alcohol.

Test Product, Dose, and Mode of Administration:

The Test products were diclofenac acid nanoformulation 18 mg and 35 mg capsules.

The 18 mg Test product was administered as Treatment A. Subjects assigned to Treatment A received a single 18 mg capsule by mouth with 240 mL of water after an overnight fast.

The 35 mg Test product was administered as Treatments B and C. Subjects assigned to Treatment B received a single 35 mg capsule by mouth with 240 mL of water after an overnight fast. Subjects assigned to Treatment C received a single 35 mg capsule by mouth with 240 mL of water 30 minutes after the start of a FDA High-Fat Breakfast.

Duration of Treatment:

The duration of treatment was a single dose in each period.

Reference Therapy, Mode of Administration, and Lot Number:

The Reference product was Cataflam (diclofenac potassium) 50 mg tablets, manufactured by Patheon Inc, Whitby Operations and distributed by Novartis Pharmaceutical Corporation. A single lot of the Reference product was used in this study (Lot number C7C02722). The Reference product was administered as Treatments D and E. Subjects assigned to Treatment D received a single 50 mg tablet by mouth with 240 mL of water after an overnight fast. Subjects assigned to Treatment E received a single 50 mg tablet by mouth with 240 mL of water 30 minutes after the start of a FDA High-Fat Breakfast.

Criteria for Evaluation:

Pharmacokinetic:

Blood samples for measurement of diclofenac concentrations in plasma were collected pre-dose and 0.083, 0.167, 0.25, 0.33, 0.50, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.67, 4, 4.5, 5, 6, 8, 10, and 12 hours post-dose. Primary PK variables included: area under the concentration-time curve from time zero to the time of the last sample with a quantifiable concentration (AUC_{0-t}); area under the concentration time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$); and, measured maximal concentrations (C_{max}). Secondary PK variables included: time to reach maximum concentration (T_{max}); terminal elimination rate constant (K_e); and terminal elimination half-life ($T_{1/2}$).

Safety:

A physical examination, serology test for HIV, Hepatitis B, and Hepatitis C, as well as a urine drug screen were performed at the Screening Visit. Samples for general clinical laboratory tests were collected, 12-lead ECG tracings were obtained, vital signs were measured, and pregnancy tests (for female subjects) were performed at the Screening Visit and at specified time points. During the study, subjects were monitored for clinical and laboratory evidence of adverse events.

Statistical Methods:

Pharmacokinetic:

Statistical analyses were performed using the mixed model procedure of the SAS® statistical program (PC Version 9.1.3) in a Windows XP Professional environment. The pharmacokinetic parameter estimates were evaluated using mixed model analyses (PROC MIXED). The model included fixed effects for sequence, period, and treatment; and random effects for subject nested within sequence. The least-squares means and the mean standard error values from these analyses were used to construct the 90% confidence intervals for the relative bioavailability evaluations according to the FDA's recommended procedures. The dose normalized AUC and C_{max} values for the 18 mg and 35 mg Test products were ln-transformed and compared by Analysis of Variance (ANOVA). As specified in the protocol, dose proportionality was to be concluded if the overall treatment effect was not significant at the 5% level, or if the 90% confidence intervals for the ratios of geometric means contained the value "1.00".

Safety:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and listed by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs were summarized by incidence, relatedness to study drug, and severity.

SUMMARY – RESULTS

DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS:

Forty (40) subjects were randomized into treatment and 38 subjects (95%) completed all 5 study periods. Two subjects voluntarily withdrew consent prior to dosing in Period 2. The 40 subjects who received at least one dose of study drug were included in the full analysis set and ranged in age from 21 to 56 years, with a mean age of 34.6 years. There were 27 male subjects (67.5%) and 13 female subjects (32.5%). With regard to race/ethnicity, 32 subjects (80.0%) were Black, 6 subjects (15.0%) were Caucasian, and 2 subjects (5.0%) were Hispanic. The mean height was 172.9 cm, with a range of 151 to 189 cm. The mean body weight was 77.4 kg, with a range of 52.9 to 104.8 kg. The mean BMI was 25.8 kg/m^2, with a range of 20.0 to 29.7 kg/m^2. Demographic findings were reflective of a healthy adult population.

PHARMACOKINETIC RESULTS:

Consistent with the Statistical Analysis Plan, all available data from the first 30 of the 38 subjects who completed all 5 periods were used in the pharmacokinetic analyses. Statistical test results on pharmacokinetic parameters for diclofenac are summarized in the Tables 15a-d below.

35 mg Test product vs. 50 mg Reference product – Fasted subjects					
Pharmacokinetic Parameter/Unit		**Test Product 35 mg Fasted[a]**	**Reference Product 50 mg Fasted[a]**	**Ratio[b]**	**90% CI[c]**
$AUC_{(0-t)}$	hr*ng/mL	1132	1432	0.791*	0.758, 0.825
$AUC_{(0-\infty)}$	hr*ng/mL	1152	1449	0.795*	0.764, 0.828
C_{max}	ng/mL	1179	1268	0.930*	0.789, 1.096
T_{max}[d]	hr	0.559 (0.500)	0.737 (0.667)	0.758	-
K_e	1/hr	0.3977	0.3763	1.057	-
$T_{1/2}$	hr	1.83	1.92	0.956	-

Table 15a. Treatments B:D (35 mg Test product vs. 50 mg Reference product [fasting conditions])

$AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ values for the Test (35 mg capsule) product were approximately 20% lower than observed for the Reference product (50 mg tablet). C_{max} for the Reference product was only 7% greater than the Test product and was not statistically significant ($\alpha = 0.05$). The 35 mg Test capsules and the 50 mg Reference tablets (Cataflam) were not bioequivalent when given to fasted subjects.

Abbreviations: ANOVA (analysis of variance); $AUC_{(0-t)}$ (area under the concentration-time curve from zero to the last measurable concentration); $AUC_{(0-\infty)}$ (area under the concentration-time curve from zero to infinity); CI(confidence interval); C_{max} (measured maximal plasma concentration); K_e (terminal elimination rate constant); $T_{1/2}$ (terminal elimination half life); T_{max} (time to achieve maximum concentration).

a. Least-squares geometric means for areas and peak concentrations. Least squares arithmetic means for other parameters.

b. Ratio calculated as Test Fasted least-squares mean divided by the Reference Fasted least-squares mean.

c. Confidence interval on the Test-to-Reference ratio.

d. Mean (median) reported for T_{max}.

* Comparisons were detected as statistically significant with $\alpha = 0.05$.

35 mg Test product - Fed versus Fasted Subjects					
Pharmacokinetic Parameter/Unit		**Test Product**		**Ratio[b]**	**90% CI[c]**
		35 mg Fed[a]	**35 mg Fasted[a]**		
$AUC_{(0-t)}$	hr*ng/mL	1034	1132	0.913*	0.876, 0.952
$AUC_{(0-\infty)}$	hr*ng/mL	1073	1152	0.931*	0.893, 0.970
C_{max}	ng/mL	490	1179	0.416*	0.353, 0.489

T_{max}[d]	hr	1.93 (1.67)	0.559 (0.500)	3.445*	-
K_e	1/hr	0.3275	0.3977	0.824*	-
$T_{1/2}$	hr	2.26	1.83	1.234*	-

Table 15b. Treatments C:B (35 mg Test product [fed vs. fasted subjects])

Food reduced $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ values by 9% and 7%, respectively. C_{max} decreased by 58%. All parameters were statistically significant ($\alpha = 0.05$) indicating a food effect for the 35 mg Test product.

Abbreviations: ANOVA (analysis of variance); $AUC_{(0-t)}$ (area under the concentration-time curve from zero to the last measurable concentration); $AUC_{(0-\infty)}$ (area under the concentration-time curve from zero to infinity); CI(confidence interval); C_{max} (measured maximal plasma concentration); K_e (terminal elimination rate constant); $T_{1/2}$ (terminal elimination half life); T_{max} (time to achieve maximum concentration).

a. Least-squares geometric means for areas and peak concentrations. Least squares arithmetic means for other parameters.

b. Ratio calculated as Test Fed least-squares mean divided by the Test Fasted least-squares mean.

c. Confidence interval on the Test Fed-to-Test Fasted ratio.

d. Mean (median) reported for T_{max}.

* Comparisons were detected as statistically significant by ANOVA, with $\alpha = 0.05$.

50 mg Reference Product - Fed versus Fasted Subjects					
Pharmacokinetic Parameter/Unit		**Reference Product**		**Ratio[b]**	**90% CI[c]**
		50 mg Fed[a]	**50 mg Fasted[a]**		
$AUC_{(0-t)}$	hr*ng/mL	1308	1432	0.914*	0.877, 0.952
$AUC_{(0-\infty)}$	hr*ng/mL	1334	1449	0.920*	0.884, 0.958
C_{max}	ng/mL	922	1268	0.728*	0.619, 0.856
T_{max}[d]	hr	1.70 (1.33)	0.737 (0.667)	2.299*	-
K_e	1/hr	0.3424	0.3763	0.910	-
$T_{1/2}$	hr	2.17	1.92	1.134*	-

Table 15c. Treatments E:D (50 mg Reference product [fed vs. fasted Subjects])

Food reduced $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ by 9% and 8%, respectively. C_{max} decreased by 27%. These PK parameters were statistically significant ($\alpha = 0.05$), indicating a food effect for the Reference product.

Abbreviations: ANOVA (analysis of variance); $AUC_{(0-t)}$ (area under the concentration-time curve from zero to the last measurable concentration); $AUC_{(0-\infty)}$ (area under the concentration-time curve from zero to infinity); CI(confidence interval); C_{max} (measured maximal plasma concentration); K_e (terminal elimination rate constant); $T_{1/2}$ (terminal elimination half life); T_{max} (time to achieve maximum concentration).

a. Least-squares geometric means for areas and peak concentrations. Least squares arithmetic means for other parameters.

b. Ratio calculated as Reference Fed least-squares mean divided by the Reference Fasted least-squares mean.

c. Confidence interval on the Reference Fed-to-Reference Fasted ratio.

d. Mean (median) reported for T_{max}.

* Comparisons were detected as statistically significant by ANOVA, with $\alpha = 0.05$.

18 mg Test Product versus 35 mg Test Product - Fasted Subjects					
Pharmacokinetic Parameter/Unit		**Test Product**		**Ratio[b]**	**90% CI[c]**
		18 mg Fasted[a]	**35 mg Fasted[a]**		
$AUC_{(0-t)}$	hr*ng/mL	1061	1132	0.938*	0.899, 0.977
$AUC_{(0-\infty)}$	hr*ng/mL	1090	1152	0.946*	0.909, 0.984
C_{max}	ng/mL	1174	1179	0.996*	0.847, 01.172
T_{max}[d]	hr	0.571 (0.500)	0.559 (0.500)	1.022	-
K_e	1/hr	0.4760	0.3977	1.197*	-
$T_{1/2}$	hr	1.50	1.83	0.821*	-

Table 15d. Dose proportionality for Treatments A:B (18 mg vs. 35 mg Test Product [Fasted Subjects])

Dose-normalized ln-transformed $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ differences were statistically significant ($\alpha < 0.05$), and the 90% confidence intervals for their ratios did not contain the value "1.00", thus these parameters did not pass the per protocol dose-proportionality test. Alternatively, dose-proportionality may still be concluded for the 18 mg and 35 mg Test products since (1) the 90% confidence intervals of the ratios of the dose-normalized ln-transformed C_{max}, AUC, and AUC were totally contained within the 0.800 and 1.250 acceptance range for bioequivalence; and (2) the ratios of dose-normalized geometric means between the 18 mg and 35 mg Test capsules were 0.996, 0.938, and 0.946, respectively for C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$.

Abbreviations: ANOVA (analysis of variance); $AUC_{(0-t)}$ (area under the concentration-time curve from zero to the last measurable concentration); $AUC_{(0-\infty)}$ (area under the concentration-time curve from zero to infinity); CI(confidence interval); C_{max} (measured maximal plasma concentration); K_e (terminal elimination rate constant); $T_{1/2}$ (terminal elimination half life); T_{max} (time to achieve maximum concentration).

a. Least-squares geometric means for areas and peak concentrations. Least squares arithmetic means for other parameters. $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, and C_{max} for the 18 mg were dose-normalized by multiplying the ratio of 35 mg divided by 18 mg (equal to 1.944).

b. Ratio calculated as dose-normalized least-squares mean for the 18 mg Test product divided by the least-squares mean for the 35 mg Test product.

c. Confidence interval on the dose-normalized 18 mg Test-to-35 mg Test ratio.

d. Mean (median) reported for T_{max}.

* Comparisons were detected as statistically significant by ANOVA, with $\alpha = 0.05$.

SAFETY RESULTS:

A total of 40 (100%) subjects were included in the safety population. Thirteen (13) treatment-emergent adverse events (AEs) were experienced by 7 subjects (18.0%). Six (6) treatment-emergent AEs were reported by 5 subjects (12.5%) who received the Test product and 7 treatment-emergent AEs were reported by 2 subjects (5.0%) who received the Reference product. Ten (10) of the 13 treatment-emergent AEs (76.9%) were considered to be mild in severity; 3 (23.0%) were considered to be moderate (i.e., vomiting and headache [Subject 15]) and none were serious or life-threatening. Fatigue was the treatment-emergent AD with the highest incidence overall, i.e., reported by 3 subjects (8.0%) who received the Test product (diclofenac nanoformulation 35 mg capsule). Six (6) out of 40 subjects (15.0%) reported 9 treatment-emergent AEs that were determined to be at least possibly related to study drug administration. No clinically significant changes in laboratory results or vital signs occurred, in the opinion of the Investigator. There were no deaths or other serious adverse events in this study.

CONCLUSIONS:

This was a single-center, single-dose, randomized, open-label, 5-period, 5-treatment 10-sequence crossover study that investigated the relative bioavailability and dose-proportionality of the Test product (i.e., 18 mg and 35 mg nanoformulation capsules of diclofenac acid) vs. the Reference product (50 mg immediate-release tablet of diclofenac potassium [Cataflam]) administered under fed and fasting conditions. Forty (40) healthy male and female adults were enrolled in the study. Eligible subjects received 5 treatments in order of their assigned sequence according to the randomization schedule. There was a 7-day washout interval between each Treatment Period. Thirty-eight (38; 95%) subjects completed all 5 study periods. Two 92; 5%) subjects voluntarily withdrew prior to dosing in Period 2. Pharmacokinetic blood samples were obtained pre-dose and over 12 hours following dosing. During the study, subjects were monitored for clinical and laboratory evidence of adverse events.

A single dose of diclofenac (18 mg, 35 mg, or 50 mg) was safe and well-tolerated. Seven subjects (7; 18.0%) reported a total of 13 treatment-emergent AEs. Six (6; 15%) subjects reported 9 treatment-emergent AEs that were determined to be at least possibly related to study drug administration. All treatment-emergent AEs were considered to be mild in severity, except for vomiting and 2 occurrences of headache experienced by Subject 15. No deaths or serious adverse events occurred.

All available data from the first 30 subjects who completed all 5 periods of the study were used in the pharmacokinetic analyses. Conclusions based on statistical testing of the PK parameters for diclofenac are summarized below.

35 mg Test product vs. 50 mg Reference product (fasted subjects):

These two formulations were not bioequivalent under fasting conditions since the 90% confidence intervals on the geometric mean and peak concentration ratios for diclofenac were outside the interval 0.800 to 1.250.

35 mg Test product (fed vs. fasted subjects):

Food decreased $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ values by 9% and 7% respectively. C_{max} was decreased by 58%. Conversely, T_{max} was 22 minutes slower when the 35 mg Test product was administered under fed conditions.

50 mg Reference product (fed vs. fasted subjects):

Food decreased $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ values by 9% and 8% respectively. C_{max} was decreased by 27%. Conversely, T_{max} was 58 minutes slower when the 50 mg Reference product was administered under fed conditions.

35 mg Test product vs. 50 mg Reference product (fed subjects):

These two formulations were not bioequivalent under fed conditions since the 90% confidence intervals on the geometric mean and peak concentration ratios for diclofenac were outside the interval 0.800 to 1.250.

Dose proportionality evaluation (18 mg vs. 35 mg Test product in fasted subjects):

Although the 18 mg and 35 mg Test products were not identified as dose-proportional based on the per protocol analysis, dose-proportionality may still be concluded since: (1) the 90% confidence intervals for the ratios of dose-normalized ln-transformed C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ were totally contained within the 0.800 and 1.250 acceptance range for bioequivalence; and (2) the ratios of dose-normalized geometric means between the 18 mg and 35 mg Test capsules were 0.996, 0.938, and 0.946 respectively, for C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$.

Example 16: Efficacy and safety of milled diclofenac

This Example describes a Phase 2, Phase 2, Randomized, Double-Blind, Single-Dose, Parallel-Group, Active- and Placebo-Controlled Study of Diclofenac Nanoformulation Capsules for the Treatment of Pain After Surgical Removal of Impacted Third Molars.

The phase II efficacy study described in this example uses Diclofenac Nanoformulation Capsules 18 mg and 35 mg manufactured as described in Example 13(a) and (b).

OBJECTIVES:

The primary objective of this study is to evaluate the analgesic efficacy and safety of Diclofenac Nanoformulation Capsules compared with placebo in subjects with acute dental pain after third molar extraction. The secondary objective of this study is to evaluate the time to onset of analgesia for Diclofenac Nanoformulation Capsules compared with the standard formulation of celecoxib.

NUMBER OF SUBJECTS:

Planned enrollment (and/or completion): Approximately 200 subjects (50 in each treatment group) will be enrolled.

SUBJECT POPULATION:

Inclusion Criteria:

A subject will be eligible for study entry if all of the following inclusion criteria are met:

1. Is male or female ≥ 18 and ≤50 years of age.
2. Requires extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bone-impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral.
3. Experiences moderate to severe pain intensity within 6 hours after surgery, as measured by a Visual Analog Scale (VAS) score of ≥ 50 mm on a 100-mm scale.
4. Has a body weight of ≥ 45 kg and a body mass index (BMI) ≤ 35 kg/m^2.
5. If female and of childbearing potential, is nonlactating and nonpregnant (has negative pregnancy test results at screening [serum] and on the day of surgery prior to surgery [urine]).
6. If female, is either not of childbearing potential (defined as postmenopausal for at least 1 year or surgically sterile [bilateral tubal ligation, bilateral oophorectomy, or hysterectomy]) or practicing 1 of the following medically acceptable methods of birth control:
    a. Hormonal methods such as oral, implantable, injectable, or transdermal contraceptives for a minimum of 1 full cycle (based on the subject's usual menstrual cycle period) before the study drug administration.

b. Total abstinence from sexual intercourse (since the last menses before study drug administration).
c. Intrauterine device (IUD).
d. Double-barrier method (condoms sponge, diaphragm, or vaginal ring with spermicidal jellies or cream).

7. Is in good health, in the opinion of the investigator.
8. Is able to provide written informed consent to participate in the study and able to understand the procedures and study requirements.
9. Must voluntarily sign and date an informed consent form (ICF) that is approved by an Institutional Review Board (IRB) prior to the conduct of any study procedure.
10. Is willing and able to comply with study requirements (including diet and smoking restrictions), complete the pain evaluations, remain at the study site overnight, and return for follow-up 7 ± 2 days after surgery.

Exclusion Criteria:

A subject will not be eligible for study entry if any of the following exclusion criteria are met:

1. Has a known history of allergic reaction or clinically significant intolerance to acetaminophen, aspirin, or any nonsteroidal anti-inflammatory drug (NSAIDs, including diclofenac and celecoxib); history of NSAID-induced bronchospasm (subjects with the triad of asthma, nasal polyps, and chronic rhinitis are at greater risk for bronchospasm and should be considered carefully); or hypersensitivity, allergy, or significant reaction to sulfa (including sulfonamide) medicines, ingredients of the study drug, or any other drugs used in the study including anesthetics and antibiotics that may be required on the day of surgery.
2. Has tested positive either on the urine drug screen or on the alcohol breathalyzer test. Subjects who test positive at screening only and can produce a prescription for the medication from their physician may be considered for study enrollment at the discretion of the investigator.
3. Has known or suspected history of alcoholism or drug abuse or misuse within 2 years of screening or evidence of tolerance or physical dependence before dosing with the study drug.
4. Has received or will require any medication (except hormonal contraceptives, vitamins, or nutritional supplements) within 5 half-lives (or, if half-life is unknown, within 48 hours) before dosing with study drug.
5. Has any clinically significant unstable cardiac, respiratory, neurological, immunological, hematological, or renal disease or any other condition that, in the opinion of the investigator, could compromise the subject's welfare, ability to communicate with the study staff, or otherwise contraindicate study participation.

6. Has a history or current diagnosis of a significant psychiatric disorder that, in the opinion of the investigator, would affect the subject's ability to comply with the study requirements.
7. Is receiving systemic chemotherapy, has an active malignancy of any type, or has been diagnosed with cancer with 5 years of screening (excluding squamous or basal cell carcinoma of the skin).
8. Has a history of clinically significant (investigator opinion) gastrointestinal (GI) event within 6 months before screening or has any history of peptic or gastric ulcers or GI bleeding.
9. Has a surgical or medical condition of the GI or renal system that might significantly alter the absorption, distribution, or excretion of any drug substance.
10. Is considered by the investigator, for any reason (including, but not limited to, the risks described as precautions, warnings, and contraindications in the current version of the Investigator's Brochure [IB] for Diclofenac Nanoformulation Capsules), to be an unsuitable candidate to receive the study drug.
11. Has history of chronic use (defined as daily use for > 2 weeks) of NSAIDs, opiates, or glucocorticoids (except inhaled nasal steroids and topical corticosteroids), for any condition within 6 months before dosing with study drug. Aspirin at a daily dose of ≤ 325 mg is allowed for cardiovascular (CV) prophylaxis if the subject has been on a stable dose regimen for ≥ 30 days before screening and has not experienced any relevant medical problem.
12. Has a significant renal or hepatic disease, as indicated by the clinical laboratory assessment (results ≥ 3 times the upper limit of normal [ULN] for any liver function test, including aspartate aminotransferase [AST], alanine aminotransferase [ALT], and lactate dehydrogenase, or creatinine ≥ 1.5 times the ULN) or has any clinically significant laboratory findings at screening that in the investigator's opinion contraindicate study participation.
13. Has significant difficulties swallowing capsules or is unable to tolerate oral medication.
14. Previously participated in another study of Diclofenac Nanoformulation Capsules, or received any investigational drug or device or investigational therapy within 30 days before screening.

DESIGN:

This is a phase 2, multicenter, randomized, double-blind, single-dose, parallel-group, active- and placebo-controlled study to evaluate the efficacy and safety of Diclofenac Nanoformulation Capsules (18 mg and 35 mg) in subjects with postoperative dental pain. Eligible subjects will complete all screening procedures within 28 days before the surgery.

At screening, subjects will provide written informed consent to participate in the study before any protocol-specified procedures or assessments are completed. On Day 1, subjects who continue to be eligible for study participation after completing screening procedures and assessments are will undergo extraction of 2 or more third molars. At least 1 of the third molars must be a fully or partially bond-impacted mandibular molar. If only 2 molars are removed, then they must be ipsilateral. All subjects will receive local anesthesia (2% lidocaine with 1:100,000 epinephrine). Nitrous oxide will be allowed at the discretion of the investigator. Subjects who experience moderate to severe pain intensity (a score of ≥ 50 mm on a 100-mm VAS) within 6 hours after surgery and who continue to meet all study entry criteria will be randomized in a 1:1:1:1 ratio to receive 1 oral dose of Diclofenac Nanoformulation Capsules (18 mg or 35 mg), celecoxib capsules (400 mg), or placebo. Study drug will be administered by an unblended, third-party doser who will not conduct any efficacy or safety assessments.

Subjects will assess their baseline pain intensity (VAS) before receiving study drug (predose, Time 0) and their pain intensity (VAS) and pain relief (5-point categorical scale) at the following time points: 15, 30, and 45 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after Time 0; and immediately before the first dose of rescue medication. The 2-stopwatch method will be used to record the time to perceptible and time to meaningful pain relief, respectively. Subjects will complete a global evaluation of study drug 12 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first). Vital signs will be recorded after the subject has been in a sitting position for 5 minutes at the following times: before surgery, before Time 0, 12 hours after Time 0, and/or immediately before the first dose of rescue medication. Adverse events (AEs) will be monitored and recorded from the time of signing of the ICF until the Follow-up Visit (or Early Termination Visit). During the 12 hours following Time 0, subjects will complete efficacy and safety assessments. Subjects will remain at the study site overnight and will be discharged the morning of Day 2. Upon discharge from the study site, subjects will be given a diary to record concomitant medications taken and AEs experienced after discharge.

Acetaminophen (1000 mg) will be permitted as the initial rescue medication. Subjects will be encouraged to wait at least 60 minutes after receiving study drug before taking rescue medication. Additional analgesic rescue medication may be administered at the discretion of the investigator if the protocol-specified rescue medication is deemed inadequate. Subjects are not permitted to take medications (except hormonal contraceptives, vitamins, nutritional supplements, and study drug) within 5 half-lives (or, if half-life is unknown, within 48 hours) before dosing with study drug until discharge from the study (Day 2). Other restrictions include the following: alcohol use is prohibited from 24 hours before surgery until discharge on Day 2; nothing by mouth (NPO) from midnight before surgery until 1 hour after surgery; clear liquids only are allowed starting 1 hour after surgery until 1 hour after dosing; 1 hour after dosing diet may be advanced according to standard practice.

Upon discharge from the study site, subjects may be prescribed pain medication for use at home according to the standard practice of the study site. On Day 8 (± 2 days), subjects will return to the study site for an abbreviated confirmatory physical assessment and concomitant medication and AE assessments.

STUDY DRUG:

Diclofenac Nanoformulation Capsules (18 mg and 35 mg) for oral administration

REFERENCE PRODUCTS:

Celecoxib 200-mg capsules administered as a 400-mg dose

Placebo

TREATMENT REGIMENS

Eligible subjects meeting all study entry criteria will be randomized to receive 1 of the following treatments:

One 18-mg Diclofenac Nanoformulation Capsule and 1 placebo capsule

One 35-mg Diclofenac Nanoformulation Capsule and 1 placebo capsule

Two 200-mg celecoxib capsules

Two placebo capsules

STUDY DURATION:

Up to approximately 5 weeks for each subject, including a 4-week screening period and a posttreatment Follow-up Visit approximately 1 week after dosing with study drug.

INVESTIGATIVE SITES OR COUNTRIES:

Two study sites in the United States (US).

STUDY ENDPOINTS:

Efficacy Endpoints:

The primary efficacy endpoint is the sum of total pain relief (TOTPAR) over 0 to 12 hours (TOTPAR-12) after Time 0.

The secondary endpoints are the following:

- TOTPAR over 0 to 4 hours (TOTPAR-4) and over 0 to 8 hours (TOTPAR-8) after Time 0.
- VAS pain intensity difference (VASPID) at each scheduled time point after Time 0.
- Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief).

- VAS pain intensity score at each scheduled time point.
- VAS summed pain intensity difference (VASSPID) over 0 to 4 hours (VASSPID-4), over 0 to 8 hours (VASSPID-8), and over 0 to 12 hours (VASSPID-12) after Time 0.
- Summed pain relief and intensity difference (sum of TOTPAR and VASSPID [SPRID]) over 0 to 4 hours (SPRID-4), over 0 to 8 hours (SPRID-8), and over 0 to 12 hours (SPRID-12) after Time 0.
- Pain relief score at each scheduled time point after Time 0.
- Peak pain relief.
- Time to peak pain relief.
- Time to first perceptible pain relief.
- Time to meaningful pain relief.
- Proportion of subjects using rescue medication.
- Time to first use of rescue medication (duration of analgesia).
- Patient's global evaluation of study drug.

Safety Endpoints:

The safety endpoints are the incidence of treatment-emergent AEs (TEAEs) and changes in vital sign measurements.

STATISTICAL METHODS SUMMARY:

Analysis Populations:

The analysis populations include the following:

- The intent-to-treat (ITT) population will consist of all subjects who are treated with study drug and who have at least 1 pain relief assessment after Time 0. The ITT population is the primary population for the efficacy analysis.
- The per-protocol (PP) population will consist of all ITT subjects who remain in the study for at least 12 hours of treatment and who do not incur a major protocol violation that would challenge the validity of their data. This population will be utilized to evaluate the sensitivity of the primary efficacy analysis.
- The safety population will include all subjects who are treated with study drug. The safety population is the population for all safety assessments.

Subject Characteristics:

Demographic and baseline characteristics (including age, sec, race, weight, height, BMI, medical history, surgery duration, and baseline values of efficacy variables) will be summarized for each treatment group and for the overall population by descriptive statistics. No formal statistical analyses will be performed.

Efficacy Analyses:

The null hypothesis in this study is that TOTPAR-12 for placebo is equal to TOTPAR-12 for 35-mg Diclofenac Nanoformulation Capsules. It will be analyzed using analysis of covariance (ANCOVA) models, which include treatment effect and significant covariates. The effect of potential covariates, such as sex, baseline pain intensity, and surgical trauma rating, will be assessed using appropriate ANCOVA models. The analysis will be based on a 2-sided test as the significance level of 0.05.

Other comparisons between the treatment regimens, including 18-mg Diclofenac Nanoformulation Capsules versus placebo and 400-mg celecoxib capsules versus placebo will be considered secondary. No *P* value adjustment will be made for multiple endpoints or multiple comparisons. Each efficacy endpoint will be summarized descriptively by treatment group.

For continuous secondary endpoints such as pain intensity score, VASPID at each scheduled time point, peak pain intensity, TOTPAR-4, TOTPAR-8, VASSPID-4, VASSPID-8, VASSPID-12, SPRID-4, SPRID-8, and SPRID-12,descriptive statistics (such as mean, standard error, median, minimum, and maximum) will be provided for each treatment regimen. Nominal *P* values from 2-sample tests comparing the placebo group with other treatment groups will be provided, but no formal statistical inferences will be drawn on the basis of these tests.

For ordinal secondary endpoints, such as pain relief at each scheduled time point, peak pain relief, and global evaluation of study drug, descriptive summaries will be provided to include the number and percentage of subjects within each category for each treatment group. Nominal *P* values from Fisher's exact tests (or chi-square tests, as appropriate) comparing the placebo group with other treatment groups will be provided, but no formal statistical inferences will be drawn on the basis of these tests.

For each time-to-event endpoint, the Kaplan-Meier method will be used to evaluate the treatment effect. Time to onset of analgesia (measured as time to perceptible pain relief confirmed by meaningful pain relief) will be based on data collected using the 2-stopwatch method. Time to onset of analgesia will be right-censored at 12 hours for subjects who do not experience both perceptible pain relief and meaningful pain relief during the 12-hour interval after Time 0. The summary table will provide the number of subjects analyzed, the number of subjects censored, estimates for the quartiles, and 95% confidence intervals (CIs) for the estimated median and the restricted mean estimate. *P* values form the Wilcoxon or log-rank tests (as appropriate) will also be used to examine treatment effect. Cox proportional hazard models will be used to explore such potential covariates as sex, baseline pain intensity, and surgical trauma rating, if appropriate.

For the proportion of subjects using rescue medication, a logistic regression model that adjusts for baseline pain intensity, if appropriate, will be used to evaluate the treatment effect.

Subgroup analysis by sex may be performed if it is confirmed to be a statistically significant covariate for TOTPAR-12. Baseline values are defined as the last measurements taken before dosing with a study drug.

For pain intensity, missing observations will be imputed using baseline-observation-carried-forward (BOCF) for subjects who withdraw from the study due to lack of efficacy or an AE/intolerance to study drug. The BOCF imputation will be applied in place of all scheduled assessments after the time of early termination due to lack of efficacy or an AE/intolerance to study drug using the baseline observation taken before Time 0.

For subjects who withdraw from the study due to reasons other than lack of efficacy or an AE/intolerance to study drug, missing observations for pain intensity and pain relief will be imputed using last-observation-carried-forward (LOCF). The LOCF imputation will be applied in place of all scheduled assessments after the time of early termination due to reasons other than lack of efficacy or an AE/intolerance to the drug.

For subjects who take any dose of rescue medication, subsequent measures after the first dose of rescue medication will be disregarded. Instead, all scheduled assessments after the first dose of rescue medication will be imputed using BOCF using the baseline observation taken before Time 0. Single missing data points will be imputed using linear interpolation, if they do not occur at the end of the study. For other conditions before early termination or rescue medication, missing data will be imputed using LOCF.

Safety Analysis:

Data listings will be provided for protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.1 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Adverse event summaries will include only TEAEs, which will be summarized for each treatment group. Fisher's 2-sided exact test will be used to compare the rates of occurrence between the placebo and Diclofenac Nanoformulation Capsule groups for all TEAEs.

For vital sign measurements, descriptive statistics will be provided at each scheduled time point for each treatment group. Changes from Baseline for vital signs will be calculated for each subject, and descriptive statistics will be provided on changes in vital signs from Baseline for each treatment group at each scheduled time point after Baseline. No formal statistical tests will be performed.

Sample Size:

The standard deviation of TOTPAR-12 is assumed to be ≤ 14.0. A sample size of 50 subjects per treatment group will provide ≥ 80% power to detect a minimal difference of 8.0 in TOTPAR-12 using a 2-sample *t*-test with a 0.05 two-sided significance level (nQuery v6.0).

	A	B[a]						J	K
		C	D						
			E	F	G	H	I		
Written Informed Consent	X								
Assign a screening number	X								
Inclusion/exclusion criteria	X	X							
Demographics	X								
Medical History	X	X[b]							
Physical Examination[c]	X								X
Vital signs[d]	X	X	X				X		X
Height, weight, and BMI	X								
Clinical laboratory tests (hematology, chemistry, urinalysis)	X								
Pregnancy test for female subjects of childbearing potential[c]	X	X							
Urine drug screen	X	X							
Alcohol breathalyzer test		X							
Oral radiography[f]	X								
Review study restrictions with subject	X								
Pain intensity (VAS)[g]			X		X	X	X		
Randomization			X						
Dosing with study drug				X					
Stopwatch assessment[h]				X					
Pain relief (5-point categorical scale)[g]					X	X	X		
Global evaluation of study drug[i]							X		
Concomitant medications		X[b]	X	X	X	X	X	X	X
Adverse events[j]		X	X	X	X	X	X	X	X
Dispense rescue medication/pain medications								X	
Collect unused rescue medication/pain medications									X
Dispense/collect subject diary								X	X
Discharge from study site								X	

Table 16a. Schedule of Events

A: Screening (Days -28 to -1); B: Day of Surgery (Day 1); C: Preop; D: Postop; E: Predose; F: 0 h; G: 15, 30, 45 min; H: 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 h; I: 12 h; J: Day 2; K: Follow-up (Day 8 ± 2 days or ET).

Abbreviations: BMI, body mass index; ET, early termination; h, hour; min, minute; preop, preoperative; postop, postoperative; VAS, Visual Analogue Scale.

[a] Times listed are relative to dosing with study drug.

[b] Medical history and concomitant medication use since screening will be updated on Day 1 before surgery.

[c] A complete physical examination (excluding the genitourinary examination) will be performed at screening. An abbreviated confirmatory physical assessment, including an examination of the subject's mouth and neck, will be performed at the Follow-Up visit (or Early Termination visit)

[d] Vital signs will be recorded after the subject has been in a sitting position for 5 minutes at the following times: at screening, before surgery, before Time 0, 12 hours after Time 0, and/or immediately before the first dose of rescue medication, and the Follow-up Visit (or Early Termination visit).

[e] Serum pregnancy test at screening and urine pregnancy test before surgery on Day 1 (female subjects of childbearing potential only). Test results must be negative for the subject to continue in the study.

[f] Oral radiographs taken within 1 year before screening will be acceptable and do not need to be repeated.

[g] Pain assessments will be conducted at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after Time 0 and immediately before the first dose of rescue medication. Pain intensity will also be assessed predose. At each assessment time point, the pain intensity assessment will be completed first and the pain relief assessment will be completed second. Subjects will not be able to compare their responses with their previous responses.

[h] Two stopwatches will be started immediately after the subject has swallowed the study drug with 8 ounces of water (Time 0). Subjects will record the time to first perceptible and meaningful pain relief, respectively, by stopping the stopwatches.

[i] Subjects will complete a global evaluation of study drug 12 hours after Time 0 or immediately before the first dose of rescue medication (whichever occurs first).

[j] Adverse events will be monitored and recorded from the time of signing of the informed consent form (ICF) until the Follow-up Visit (or Early Termination visit).

CLAIMS:

1. A method for producing a composition, comprising the steps of:

   dry milling a solid biologically active material and a millable grinding matrix in a mill comprising a plurality of milling bodies, for a time period sufficient to produce particles of the biologically active material dispersed in an at least partially milled grinding material,

   wherein the biologically active material is diclofenac.

2. The method of claim 1, wherein the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group consisting of: 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

3. The method of claim 1, wherein the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group consisting of: 20000nm, 15000nm, 10000 nm, 7500nm, 5000nm, 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

4. The method of claim 3, wherein the percentage of particles, on a particle volume basis, is selected from the group consisting of: 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than:

   a. 2000nm (% < 2000 nm); or

   b. 1000nm (% < 1000 nm);

   or is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than:

   c. 500nm (% < 500 nm);

   d. 300nm (% < 300 nm); or

   e. 200nm (% < 200 nm).

5. The method of claim 3, wherein the Dx of the particle size distribution, as measured on a particle volume basis, is selected from the group consisting of less than or equal to 10,000nm, 5000nm, 3000nm, 2000nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm, and 100 nm; wherein x is greater than or equal to 90.

6. The method of any preceding claim, wherein the milling time period is a range selected from the group consisting of: between 10 minutes and 2 hours, between 10 minutes and 90 minutes, between 10 minutes and 1 hour, between 10 minutes and 45 minutes, between 10 minutes and 30 minutes, between 5 minutes and 30 minutes,

between 5 minutes and 20 minutes, between 2 minutes and 10 minutes, between 2 minutes and 5 minutes, between 1 minutes and 20 minutes, between 1 minute and 10 minutes, and between 1 minute and 5 minutes.

7. The method of any preceding claim, wherein the dry milling is undertaken in a mechanically agitated attritor mill (horizontal or vertical), vibratory mill or nutating mill, wherein the milling medium is steel balls having a diameter selected from the group consisting of: between 1 and 20 mm, between 2 and 15 mm and between 3 and 10 mm.

8. The method of any preceding claim, wherein the total combined amount of biologically active material and grinding matrix in the mill at any given time is equal to or greater than a mass selected from the group consisting of: 200 grams, 500 grams, 1 kg, 2kg, 5 kg, 10 kg, 20 kg, 30 kg, 50 kg, 75 kg, 100kg, 150 kg, 200 kg.

9. The method of any preceding claim, wherein the grinding matrix is a single material or is a mixture of two or more materials in any proportion wherein the single material or a mixture of two or more materials is selected from the group consisting of: mannitol, sorbitol, Isomalt, xylitol, maltitol, lactitol, erythritol, arabitol, ribitol, glucose, fructose, mannose, galactose, anhydrous lactose, lactose monohydrate, sucrose, maltose, trehalose, maltodextrins, dextrin, Inulin, dextrates, polydextrose, starch, wheat flour, corn flour, rice flour, rice starch, tapioca flour, tapioca starch, potato flour, potato starch, other flours and starches, milk powder, skim milk powders, other milk solids and dreviatives, soy flour, soy meal or other soy products, cellulose, microcystalline cellulose, microcystalline cellulose based co blended materials, pregelatinized (or partially) starch, HPMC, CMC, HPC, citric acid, tartaric acid, malic acid, maleic acid fumaric acid , ascorbic acid, succinic acid, sodium citrate, sodium tartrate, sodium malate, sodium ascorbate, potassium citrate, potassium tartrate, potassium malate, potassium ascorbate, sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate and calcium carbonate. dibasic calcium phosphate, tribasic calcium phosphate, sodium sulfate, sodium chloride, sodium metabisulphite, sodium thiosulfate, ammonium chloride, Glauber's salt, ammonium carbonate, sodium bisulfate, magnesium sulfate, potash alum, potassium chloride, sodium hydrogen sulfate, sodium hydroxide, crystalline hydroxides, hydrogen carbonates, ammonium chloride, methylamine hydrochloride, ammonium bromide, silica, thermal silica, alumina, titanium dioxide, talc, chalk, mica, kaolin, bentonite, hectorite, magnesium trisilicate, clay based materials or aluminium silicates, sodium lauryl sulfate, sodium stearyl sulfate, sodium cetyl sulfate, sodium cetostearyl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, glyceryl monostearate , glycerol distearate glyceryl palmitostearate, glyceryl behenate, glyceryl caprylate, glyceryl oleate, benzalkonium chloride, CTAB, CTAC, Cetrimide,

cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, , poloxamer 338, poloxamer 407 polyoxyl 2 stearyl ether, polyoxyl 100 stearyl ether, polyoxyl 20 stearyl ether, polyoxyl 10 stearyl ether, polyoxyl 20 cetyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polyoxyl 35 castor oil, polyoxyl 40 castor oil, polyoxyl 60 castor oil, polyoxyl 100 castor oil, polyoxyl 200 castor oil, polyoxyl 40 hydrogenated castor oil, polyoxyl 60 hydrogenated castor oil, polyoxyl 100 hydrogenated castor oil, polyoxyl 200 hydrogenated castor oil, cetostearyl alcohol, macrogel 15 hydroxystearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan trioleate, Sucrose Palmitate, Sucrose Stearate, Sucrose Distearate, Sucrose laurate, Glycocholic acid, sodium Glycholate, Cholic Acid, Soidum Cholate, Sodium Deoxycholate, Deoxycholic acid, Sodium taurocholate, taurocholic acid, Sodium taurodeoxycholate, taurodeoxycholic acid, soy lecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, PEG4000, PEG6000, PEG8000, PEG10000, PEG20000, alkyl naphthalene sulfonate condensate/Lignosulfonate blend,Calcium Dodecylbenzene Sulfonate, Sodium Dodecylbenzene Sulfonate,Diisopropyl naphthaenesulphonate, erythritol distearate, Naphthalene Sulfonate Formaldehyde Condensate, nonylphenol ethoxylate (poe-30), Tristyrylphenol Ethoxylate, Polyoxyethylene (15) tallowalkylamines, sodium alkyl naphthalene sulfonate, sodium alkyl naphthalene sulfonate condensate, sodium alkylbenzene sulfonate, sodium isopropyl naphthalene sulfonate, Sodium Methyl Naphthalene Formaldehyde Sulfonate, sodium n-butyl naphthalene sulfonate, tridecyl alcohol ethoxylate (poe-18), Triethanolamine isodecanol phosphate ester, Triethanolamine tristyrylphosphate ester, Tristyrylphenol Ethoxylate Sulfate, Bis(2-hydroxyethyl)tallowalkylamines.

10. The method of claim 9, wherein the concentration of the single material or the major component in a mixture of two or more materials is selected from the group consisting of: 5 - 99 % w/w, 10 - 95 % w/w, 15 - 85 % w/w, of 20 – 80% w/w, 25 - 75 % w/w, 30 - 60% w/w, 40 -50% w/w and the concentration of the second or subsequent material is selected from the group consisting of: 5 - 50 % w/w, 5 - 40 % w/w, 5 - 30 % w/w, of 5 – 20% w/w, 10 - 40 % w/w, 10 -30% w/w, 10 -20% w/w, 20 - 40% w/w, or 20 - 30% w/w or if the second or subsequent material is a surfactant or water soluble polymer the concentration is selected from 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.

11. The method of any preceding claim, wherein the grinding matrix is selected from the group consisting of:

a. lactose monohydrate or lactose monohydrate combined with at least one material selected from the group consisting of: xylitol; lactose anhydrous; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

b. lactose anhydrous or lactose anhydrous combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and

Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

c. mannitol or mannitol combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol

phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

d. Sucrose or sucrose combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

e. Glucose or glucose combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate

and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

f. Sodium chloride or sodium chloride combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester;

Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

g. xylitol or xylitol combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

h. Tartaric acid or tartaric acid combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and

PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

i. microcrystalline cellulose or microcrystalline cellulose combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene;

Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

j. Kaolin combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

k. Talc combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and

polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

12. The method of any preceding claim, wherein a milling aid or combination of milling aids is used where the milling aid is selected from the group consisting of: colloidal silica, a solid or semi solid surfactant, a liquid surfactant, a surfactant that can be manufactured into a solid or semisolid, a polymer, a stearic acid and derivatives thereof.

13. The method of claim 12, wherein the surfactant is selected from the group consisting of: polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamers, sarcosine based surfactants, polysorbates, alkyl sulfates and other sulfate surfactants, ethoxylated castor oil, polyvinylpyrrolidones, deoxycholate based surfactants, trimethyl ammonium based surfactants, lecithin and other phospholipids and bile salts

14. The method of claims 12 or 13, wherein the surfactant is selected from the group consisting of: sodium lauryl sulfate, sodium docusate, sodium deoxycholate, N-lauroylsarcosine sodium salt, benzalkonium chloride, cetylpyridinium chloride, cetylpyridinium bromide, benzethonium chloride, PEG 40 stearate, PEG 100 stearate, poloxamer 188, Brji 72, Brji 700, Brji 78, Brji 76, Cremophor EL, Cremophor RH-40, Dehscofix920, Kollidon 25, Kraftsperse 1251, Lecithin, Poloxamer 407, polyethyleneglycol 3000, polyethyleneglycol, 8000, polyvinylpyrrolidone, sodium dodecylbenzenesulphonic acid, sodium octadecyl sulphate, sodium pentane sulphonate, soluplus HS15, Teric305, Tersperse 2700, Terwet 1221, Terwet 3785, Tween 80 and polysorbate 61..

15. The method of any one of claims 12 to 14, wherein the milling aid has a concentration selected from the group consisting of: 0.1 -10 % w/w, 0.1 -5 % w/w, 0.1 -2.5 % w/w, of 0.1 – 2% w/w, 0.1 -1 %, 0.5 -5% w/w, 0.5 -3% w/w, 0.5 -2% w/w, 0.5 – 1.5%, 0.5 -1 % w/w, of 0.75 – 1.25 % w/w, 0.75 -1% and 1% w/w.
16. The method of any preceding claim, wherein a facilitating agent is used or combination of facilitating agents is used where the facilitating agent is selected from the group consisting of: surfactants, polymers, binding agents, filling agents, lubricating agents, sweeteners, flavouring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, agents that may form part of a medicament, including a solid dosage form.
17. The method of claims 16, wherein the facilitating agent is added during dry milling at a time selected from the group consisting of: with 100% of the total milling time remaining, with 1-5 % of the total milling time remaining, with 1-10 % of the total milling time remaining, with 1-20 % of the total milling time remaining, with 1-30 % of the total milling time remaining, with 2-5% of the total milling time remaining, with 2-10% of the total milling time remaining, with 5-20% of the total milling time remaining and with 5-20% of the total milling time remaining.
18. The method of any one of claims 16 to 17, wherein a facilitating agent is selected from the group consisting of: crosslinked PVP (crospovidone), cross linked carmellose (croscarmellose), sodium starch glycolate, Povidone (PVP), Povidone K12, Povidone K17, Povidone K25, Povidone K29/32 and Povidone K30
19. A composition comprising diclofenac, produced by the method of any one of claims 1-18.
20. The composition of claim 19, wherein the average particle size, determined on a particle number basis, is equal to or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.
21. The composition of claim 19 wherein the particles have a median particle size, determined on a particle volume basis, equal or less than a size selected from the group 2000 nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.
22. The composition of claim 21, wherein the percentage of particles, on a particle volume basis, is selected from the group consisting of: 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than:
    a. 2000nm (% < 2000 nm); or
    b. 1000nm (% < 1000 nm);

or is selected from the group 0%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90%, 95% and 100 % less than:

c. 500nm (% < 500 nm);

d. 300nm (% < 300 nm); or

e. 200nm (% < 200 nm).

23. The composition of claim 21, wherein the Dx of the particle size distribution, as measured on a particle volume basis, is selected from the group consisting of less than or equal to 10,000nm, 5000nm, 3000nm, 2000nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm, and 100 nm; wherein x is greater than or equal to 90.

24. A composition comprising particles of diclofenac dispersed in at least two partially milled grinding materials, wherein the particles have at least one of

a. a median particle size as measured on a particle volume basis is less than or equal to a size selected from the group consisting of 2000nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm; and

b. an average particle size as measured on a particle number basis is less than or equal to a size selected from the group consisting of 2000nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm and 100 nm.

25. The composition of claim 24, wherein the Dx of the particle size distribution, as measured on a particle volume basis, is selected from the group consisting of less than or equal to 3000nm, 2000nm, 1900 nm, 1800nm, 1700nm, 1600nm, 1500nm, 1400nm, 1300nm, 1200 nm, 1100nm, 1000nm, 900nm, 800nm, 700nm, 600nm, 500nm, 400 nm, 300nm, 200nm, and 100 nm; wherein x is greater than or equal to 90.

26. The composition of claim 24, wherein the grinding materials are selected from the group consisting of:

a. lactose monohydrate or lactose monohydrate combined with at least one material selected from the group consisting of: xylitol; lactose anhydrous; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and

polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

b. lactose anhydrous or lactose anhydrous combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate;

sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

c. mannitol or mannitol combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

d. Sucrose or sucrose combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18;

polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

e. Glucose or glucose combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium

alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

f. Sodium chloride or sodium chloride combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

g. xylitol or xylitol combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length

between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

h. Tartaric acid or tartaric acid combined with at least one material selected from the group consisting of: lactose monohydrate; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid;

Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

i. microcrystalline cellulose or microcrystalline cellulose combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

j. Kaolin combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; talc; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl

sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids; Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

k. Talc combined with at least one material selected from the group consisting of: lactose monohydrate; xylitol; lactose anhydrous; mannitol; microcrystalline cellulose; sucrose; glucose; sodium chloride; kaolin; calcium carbonate; malic acid; tartaric acid; trisodium citrate dihydrate; D,L-Malic acid; sodium pentane sulfate; sodium octadecyl sulfate; Brij700; Brij76; sodium n-lauroyl sacrosine; lecithin; docusate sodium; polyoxyl-40-stearate; Aerosil R972 fumed silica; sodium lauryl sulfate or other alkyl sulfate surfactants with a chain length between C5 to C18; polyvinyl pyrrolidone;; sodium lauryl sulfate and polyethylene glycol 40 stearate, sodium lauryl sulfate and polyethylene glycol 100 stearate, sodium lauryl sulfate and PEG 3000, sodium lauryl sulphate and PEG 6000, sodium lauryl sulphate and PEG 8000, sodium lauryl sulphate and PEG 10000, sodium lauryl sulfate and Brij700, sodium lauryl sulfate and Poloxamer 407, sodium lauryl sulfate and Poloxamer 338, sodium lauryl sulfate and Poloxamer 188; Poloxamer 407, Poloxamer 338, Poloxamer 188, alkyl naphthalene sulfonate condensate/Lignosulfonate blend; Calcium Dodecylbenzene Sulfonate (Branched); Diisopropyl naphthalenesulphonate; erythritol distearate; linear and branched dodecylbenzene sulfonic acids;

Naphthalene Sulfonate Formaldehyde Condensate; nonylphenol ethoxylate, POE-30; Phosphate Esters, Tristyrylphenol Ethoxylate, Free Acid; Polyoxyethylene (15) tallowalkylamines; sodium alkyl naphthalene sulfonate; sodium alkyl naphthalene sulfonate condensate; sodium alkylbenzene sulfonate; sodium isopropyl naphthalene sulfonate; Sodium Methyl Naphthalene; Formaldehyde Sulfonate; sodium salt of n-butyl naphthalene sulfonate; tridecyl alcohol ethoxylate, POE-18; Triethanolamine isodecanol phosphate ester; Triethanolamine tristyrylphosphate ester; Tristyrylphenol Ethoxylate Sulfate; Bis(2-hydroxyethyl)tallowalkylamines.

27. The composition of claim 26, wherein the grinding materials are sodium lauryl sulfate and lactose monohydrate.
28. The composition of claim 27, wherein the composition comprises, w/w, diclofenac 8-20%, sodium lauryl sulfate 0.5-2%, and lactose monohydrate 76-90%.
29. The composition of claim 28, wherein the composition comprises, w/w, diclofenac 15%, sodium lauryl sulfate 1%, and lactose monohydrate 84%.
30. The composition of claim 26, wherein the grinding materials are sodium lauryl sulfate and lactose anhydrous..
31. The composition of claim 24 which, upon administration to a subject, provides improved pharmacokinetic and/or pharmacodynamic properties compared with a standard reference diclofenac composition as measured by at least one of speed of absorption, dosage potency, efficacy, and safety.
32. A pharmaceutical composition comprising the composition of any of claims 20-31.
33. A pharmaceutical composition of claim 32, wherein the diclofenac composition has a T_{max} less than that of the equivalent conventional composition administered at the same dosage.
34. A pharmaceutical composition of claims 32 to 33, wherein the diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a T_{max} which is selected from the group consisting of: less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10%, of the T_{max} exhibited by the standard conventional drug active composition.
35. A pharmaceutical composition of claims 32 to 34, wherein the diclofenac composition has a C_{max} greater than that of the equivalent conventional composition administered at the same dosage.
36. A pharmaceutical composition of claims 32 to 35, wherein the diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard

conventional drug active composition, in oral suspension, capsule or tablet form, a C_{max} which is selected from the groupd consisting of: greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% ,than the C_{max} exhibited by the standard conventional drug active composition.

37. A pharmaceutical composition of claims 32 to 36, wherein the diclofenac composition has a AUC greater than that of the equivalent conventional composition administered at the same dosage.

38. A pharmaceutical composition of claims 32 to 37, wherein the diclofenac composition of the invention exhibits in comparative pharmacokinetic testing with a standard conventional drug active composition, in oral suspension, capsule or tablet form, a AUC which is selected from the group consisting of; greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150%, than the AUC exhibited by the standard conventional drug active composition.

39. A method of treating a human in need of such treatment comprising the step of administering to the human an effective amount of a pharmaceutical composition of any one of claims 32 to 38.

40. Use of a pharmaceutical composition of any one of claims 32 to 38 in the manufacture of a medicament for the treatment of a human in need of such treatment.

41. A method for manufacturing a pharmaceutical composition of any one of claims 32 to 38 comprising the step of combining a therapeutically effective amount of a biologically active material prepared by a method according to any one of the claims 1 to 23 together with a pharmaceutically acceptable carrier to produce a pharmaceutically acceptable dosage form.

Figure 1A

Sample No.	Active material			Primary Matrix		Surfactant #1		Surfactant #2		Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	IND	1.20	12	LAC	8.80	88				30	0.223	45	61	71	77	89		
B	IND	1.20	12	LAC	8.70	87	SPS	0.1	1	30	0.215	47	64	84	83	93		
C	IND	1.20	12	LAC	8.70	87	SDS	0.1	1	30	0.189	53	73	88	95	99		
D	IND	1.20	12	LAC	8.70	87	SOS	0.1	1	30	0.203	49	69	84	92	97		
E	IND	1.20	12	LAC	8.70	87	B700	0.1	1	30	0.167	60	80	93	97	99		
F	IND	1.20	12	LAC	8.70	87	B76	0.1	1	30	0.192	52	72	89	96	99		
G	IND	1.20	12	LAC	8.70	87	SDC	0.1	1	30	0.191	52	67	77	83	93		
H	IND	1.20	12	LAC	8.70	87	SNS	0.1	1	30	0.225	44	63	79	88	96		
I	IND	1.20	12	LAC	8.70	87	LEC	0.1	1	30	0.230	44	61	75	85	95		
J	IND	0.5	10	LAC	4.50	90				20	0.237	44	57	65	73	85		
K	IND	0.5	10	LAC	4.45	89	P40S	0.05	1	20	0.169	58	72	80	89	97		
L	IND	0.5	10	LAC	4.45	89	DS	0.05	1	20	0.249	42	56	68	84	98		
M	IND	0.5	10	LAC	4.45	89	AS	0.05	1	20	0.190	52	67	76	84	92		
N	IND	1.0	20	LAC	3.95	79	SDS	0.05	1	30	0.435	24	38	53	67	83		
O	IND	1.0	20				SDS	4.00	80	30	2.612	0	0	0	6	34		
P	IND	4.95	99				SDS	0.05	1	30	1094	0	0	0	0	2		
Q	IND	1.0	20	LAC	4.00	80				30	5.128	0	0	0	0	8		
R	DIC	1.0	20	LAC	3.95	79	SDS	0.05	1	30	0.153	66	84	95	98	99		
S	DIC	1.0	20				SDS	4.00	80	30	3.173	0	0	0	3	24		

Figure 1B

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			Time (mins.)	Particle Size					Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
T	DIC	4.95	99				SDS	0.05	1				30	117	0	0	0	1	4		
U	DIC	1.00	20	LAC	4.00	80							30	0.178	56	74	86	92	97		
V	DIC	2.00	20	MAN	8.00	80							30	0.2	50	69	84	91	97		
W	DIC	2.00	20	MAN	7.90	79	SDS	0.1	1				30	0.201	50	69	83	91	97		
X	DIC	2.00	20	MAN	7.90	79	SOS	0.1	1				30	0.195	51	71	85	92	97		
Y	NAA	1.75	35	LAC	3.2	65							20	2.9	18	23	25	26	38		
Z	NAA	1.75	35	LAC	3.25	64	P40S	0.05	1				20	0.373	33	45	56	70	87		
AA	NAA	1.75	35	LAC	3.25	64	SDS	0.05	1				20	0.293	38	50	60	65	75		
AB	NAA	4.0	40	LAC	5.9	59	P40S	0.1	1				120	0.285	37	52	66	75	82		
AC	NAA	4.0	40	LAC	6.0	60							120	6.1	0	0	0	0	8		
AD	NAA	1.40	35	MAN	2.60	65							20	0.171	58	73	82	86	88		
AE	NAA	1.40	35	MAN	2.52	63	SDS	0.08	2				20	0.131	76	90	95	96	98		
AF	NAA	1.2	30	MAN	2.8	70							20	0.208	48	64	75	79	84		
AG	NAA	1.2	30	MAN	2.76	69.0	SDS	0	1.0				20	0.173	58	75	86	91	96		
AH	NAA	1.2	30.0	LAC	2.8	70.0							20	0.396	33	44	53	58	70		
AI	NAA	1.2	30.0	TCD	2.8	70.0							20	3.1	18	24	27	27	37		
AJ	NAA	1.2	30.0	CAC	2.8	70.0							20	28	3	4	5	6	10		
AK	NAA	1	25.0	LAA	3	75.0							20	1.07	31	41	46	49	67		
AL	NAA	1	25.0	XYL	3	75.0							20	0.18	57	75	87	92	95		

Figure 1C

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	% v/v	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
AM	NAA	1	25.0		MAA	3	75.0							20	0.153	66	85	96	98	99		
AN	NAA	1	25.0		TCD	3	75.0							20	0.331	35	48	57	62	72		
AO	HAL	1	10.0		LAC	9	90.0							40	2.123	0	0	0	0	5		
AP	HAL	1	10.0		LAC	8.9	89.0	LEC	0.1	1.0				40	0.135	74	90	97	98	99		
AQ	MET	1	10.0		LAC	9	90.0							40	4.727	0	0	0	0	4		
AR	MET	1	10.0		LAC	8.9	89.0	SDS	0.1	1.0				40	0.129	80	93	96	97	98		
AS	TRI	1	10.0		LAC	9	90.0							40	2.622	0	0	0	0	25		
AT	TRI	1	10.0		LAC	8.9	89.0	B700	0.1	1.0				40	0.128	82	96	98	98	99		
AU	SUL	1	10.0		LAC	9	90.0							40	0.388	27	42	56	69	86		
AV	SUL	1	10.0		LAC	8.9	89.0	SDS	0.1	1.0				40	0.455	6	26	55	78	96		
AW	MAN	1	10.0		LAC	9	90.0							40	0.198	50	71	88	97	97		
AX	MAN	1	10.0		LAC	8.9	89.0	B700	0.1	1.0				40	0.17	60	82	96	100	100		
AY	MAN	1	10.0		LAC	8.9	89.0	SDS	0.1	1.0				40	0.171	60	82	97	100	100		
AZ	MAN	1	10.0		LAC	8.9	89.0	LEC	0.1	1.0				40	0.181	56	78	95	100	100		
BA	MAN	2	20.0		LAC	7.9	79.0	SDS	0.1	1.0				40	0.212	47	68	86	96	98		
BB	MAN	3	30.0		LAC	6.9	69.0	SDS	0.1	1.0				40	0.258	36	58	81	94	97		
BC	MTX	1.5	30.0		LAC	3.5	69.0	P407	0.1	1.0				60	0.16	63	77	84	89	93		2
BD	MTX	1.5	30.0		LAC	3.5	70.0							60	0.28	40	52	59	59	71		2
BE	MTX	2.5	50.0		LAC	2.35	47.0	SDS	0.8	2.0	P407	0.1	2	60	0.148	67	83	92	98	99		2

Figure 1D

Sample No.	Active material			Primary Matrix		Surfactant #1			Surfactant #2			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	% v/v	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
BF	NAA	1	25	30	MAN	3	75					20	0.181	55	74	87	94	97		
BG	NAA	1	25	30	XYL	3	75					20	0.177	56	74	85	91	95		
BH	NAS	1.25	25	30	TA	3.75	75					20	0.311	37	49	59	64	75		
BI	NAS	1.25	25	30	TA	3.75	74	P40S	0.1	1		30	0.303	36	50	62	77	89		
BJ	DIC	3	30	31	LAC	6.9	69	SDS	0.1	1		90	0.202	49	69	83	88	92		
BK	2,4D	1	20		LAC	4	80					30	1.205	17	23	29	43	72	93	1
BL	2,4D	1	20		LAC	3.95	79	SDA	0.05	1		30	0.473	20	33	52	75	82	91	1
BM	2,4D	1	20		LAC	3.95	79	T3785	0.05	1		30	0.414	24	38	57	78	94	93	1
BN	2,4D	1	20		LAC	3.95	79	D920	0.05	1		30	0.402	26	40	57	78	91	93	1
BO	2,4D	1	20		LAC	3.95	79	SDS	0.05	1		30	0.276	36	54	74	92	96		1
BP	2,4D	1	20		LAC	3.95	79	B700	0.05	1		30	0.269	38	54	69	86	95	92	1
BQ	2,4D	1	20		LAC	3.95	79	K1251	0.05	1		30	0.252	41	56	71	89	96	91	1
BR	2,4D	1	20		LAC	3.95	79	T305	0.05	1		30	0.231	44	59	73	87	96	94	1
BS	GLY	1	20		LAC	3.95	79	T2700	0.05	1		30	0.976	25	35	43	50	64	59	4
BT	GLY	1	20		LAC	3.95	79	B700	0.05	1		30	1.449	21	27	33	42	57	84	4
BU	GLY	1	20		LAC	3.9	78	B700	0.05	1	T2700	30	0.311	37	49	58	66	79	81	4
BV	GLY	1	20		LAC	3.9	78	B700	0.05	1	K1251	30	1.085	26	34	41	49	66	82	4
BW	GLY	1	20		LAC	3.9	78	B700	0.05	1	P188	30	1.48	8	11	16	33	62	86	4
BX	GLY	1	20		LAC	3.9	78	B700	0.05	1	T2700	60	0.176	57	74	86	94	96	79	4

Figure 1E

Sample No.	Active material			Primary Matrix		Surfactant #1		Surfactant #2		Time (mins.)	Particle Size					Yield (%)	Variations
	Name	Mass (g)	% w/w	% v/v	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
BY	GLY	1	20		LAC	3.9	78	B700	0.05	1	K1251	0.05	1	60	0.658	0	0	21	93	100	81	4
BZ	GLY	1	20		LAC	3.9	78	B700	0.05	1	T2700	0.05	1	60	0.159	63	78	88	94	95	79	4
CA	GLY	1	20		LAC	3.9	78	B700	0.05	1	K1251	0.05	1	60	0.297	34	50	70	95	100	81	4
CB	MEL	0.5	10		LAC	4.4	88	CEL	0.1	2				25	1.128	31	39	42	48	68	68	1
CC	MEL	0.5	10		LAC	4.3	87	P188	0.2	3	BC	0	0	25	0.27	38	53	59	62	81	73	1
CD	MEL	0.5	10		LAC	4.3	87	P188	0.2	3	CEL	0	1	25	0.278	40	52	58	62	76	74	1
CE	MEL	0.5	10		LAC	4.3	87	P188	0.2	3	DS	0	1	25	0.12	82	96	100	100	100	88	1
CF	MEL	0.5	10		LAC	4.4	89	P188	0.1	1	K25	0	1	25	0.249	42	55	59	61	74	69	1
CG	MEL	0.25	5		MAN	4.6	92	P188	0.2	3	LEC	0.02	0.5	25	0.123	81	96	100	100	100	58	1
CH	MEL	0.5	10		LAC	4.3	87	P188	0.2	3	LEC	0.02	0.5	25	0.144	71	88	94	94	97	68	1
CI	MEL	0.5	10		LAC	4.3	87	P188	0.2	3	SDC	0.02	0.5	25	0.184	54	70	79	81	87	63	1
CJ	MEL	0.5	10		LAC	4.3	87	P188	0.2	3	T80	0	1	25	0.224	45	61	70	75	87	68	1
CK	MEL	0.25	5		LAC	4.7	94	P188	0.1	1				25	0.158	63	81	90	90	93	48	1
CL	MEL	0.5	10		LAC	4.4	87	P188	0.2	3				25	0.169	59	76	85	87	93	58	1
CM	MEL	0.25	5		LAC	4.6	92	P188	0.2	3				25	0.221	46	60	68	69	75	68	1
CN	MEL	0.5	10		LAC	4.3	85	P188	0.3	5				25	0.309	39	49	55	56	66	74	1
CO	MEL	0.5	9.5		MAN	4.6	88	P188	0.2	3				25	0.251	43	55	61	62	68	55	1
CP	MEL	0.5	10		MAN	4.5	89	P3000	0.1	1				25	1.343	29	36	39	43	63	61	1
CQ	MEL	0.5	10		MAN	4.5	89	SDC	0.1	1				25	1.699	25	31	32	37	56	77	1

Figure 1F

Sample No.	Active material			Primary Matrix		Surfactant #1		Surfactant #2			Time (mins.)	Particle Size					Yield (%)	Variations
	Name	Mass (g)	% w/w	% v/v	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	
CR	MEL	0.5	10		LAC	4.4	88	T80	0.1	2	25	1.279	28	35	38	44	65	68	1
CS	MAN	2.5	50	45	LAC	2.35	47	SDS	0.15	3	15	0.318	31	48	65	80	84		5
CT	MAN	2.5	50	45	LAC	2.45	49	P188	0.05	1	15	0.33	30	46	64	77	82		5
CU	MAN	2.5	50	45	LAC	2.45	49	P40S	0.05	1	15	0.333	30	46	63	75	80		5
CV	MAN	2.5	50	45	LAC	2.45	49	B700	0.05	1	15	0.337	29	46	63	76	81		5
CW	MAN	2.5	50	45	LAC	2.45	49	P407	0.05	1	15	0.342	28	45	63	76	82		5
CX	MAN	2.5	50	45	LAC	2.45	49	T1221	0.05	1	15	0.411	24	40	56	69	75		5
CY	MAN	2.5	50	45	LAC	2.45	49	DS	0.05	1	15	0.462	22	37	52	65	71		5
CZ	MAN	2.5	50	45	LAC	2.45	49	SDS	0.05	1	15	1.369	1	6	20	43	56		5
DA	MAN	2.5	50	45	LAC	2.45	49	SDA	0.05	1	15	1.766	0	2	14	38	52		5
DB	MAN	2.5	50	45	LAC	2.45	49	CEL	0.05	1	15	1.86	0	2	14	37	51		5
DC	MAN	2.5	50	45	LAC	2.5	50				15	2.578	0	1	11	31	45		5
DD	CEL	0.5	10		LAC	4.3	86	SDS	0.1	2	15	0.134	76	88	91	91	93	88	1
								P40S	0.1	2									
DE	CEL	0.5	10		LAC	4.3	86	SDS	0.1	2	15	0.14	75	83	83	83	86	90	1
								P407	0.1	2									
DF	CEL	0.5	10		LAC	4.3	86	SDS	0.1	1	15	0.181	55	70	79	83	89	90	1
								LEC	0.15	3									
DG	CEL	0.5	10		LAC	4.3	86	SDS	0.1	1	15	1.903	28	37	44	46	51	90	1
								B700	0.15	3									
DH	CEL	0.5	10		LAC	4.5	90				15	5.296	8	11	13	13	16	85	1
DI	CEL	0.5	10		LAC	4.3	86	SDS	0.1	1	15	0.397	33	45	53	59	71	88	1
								P3000	0.15	3									
DJ	CEL	0.5	10		LAC	4.4	88	SDS	0.1	1	15	0.234	44	58	69	77	87	87	1
								P8000	0.05	1									

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
DK	CEL	0.5	10	LAC	4.3	86	DS	0.1	2	P40S	0.1	2	15	0.319	35	48	61	69	74	88	1
DL	CEL	0.5	10	SOR	4.5	90							15	16.031	0	0	0	0	0.8	46	1
DM	CEL	0.5	10	SOR	4.45	89	SDS	0.1	1				15	0.173	57	72	79	80	86	52	1
DN	CYA	0.5	10	LAC	4.45	89	SDS	0.1	1				20	0.159	65	84	95	100	100	79	5
DO	CYA	0.5	10	MAN	4.45	89	SDS	0.1	1				20	0.194	52	68	79	84	84	87	5
DP	PRO	0.5	10	LAC	4.45	89	SDS	0.1	1				20	0.229	43	63	83	97	98	87	5
DQ	PRO	0.5	10	MAN	4.45	89	SDS	0.1	1				20	0.553	15	27	45	77	94	89	5
DR	PRO	0.5	10	LAC	4.45	89	C40	0.1	1				20	0.546	10	23	45	76	89	72	5
DS	SAL	0.51	10	LAC	4.5	89.5	LEC	0.05	1				20	0.128	84	98	100	100	100		
DT	SAL	0.51	10	LAC	4.5	89.5	LEC	0.05	1				20	0.42	31	42	53	57	57		
DU	CIP	0.76	15	MAL	4.1	83	T80	0.05	1	DS			20	0.22	40	74	85	85	92	96	6
DV	CIP	0.76	15	LAC	4.2	85							20	25.909	1	2	3.1	4.8	7	89	6
DW	CIP	0.76	15	MAL	4.3	85							20	0.238	43	56	58	58	61	93	6
DX	CIP	0.75	15	LAA	4.3	85							20	0.205	49	62	65	65	71	97	6
DY	CIP	0.75	15	LAA	4.2	84	T80	0.06	1				20	0.14	75	91	94	94	96	96	6
DZ	CIP	0.75	15	LAA	4.2	84	SOL	0.05	1				20	0.237	35	66	78	78	84	97	6
EA	CIP	0.75	15	LAA	4.2	84	CEL	0.06	1				20	0.23	37	69	81	81	87	87	6
EB	CIP	0.75	15	LAA	4.2	84	DS	0.05	1				20	0.216	42	74	83	83	91	96	6
EC	CIP	0.75	15	LAA	4.2	84	P8000	0.05	1				20	0.243	33	64	75	75	82	97	6

Figure 1G

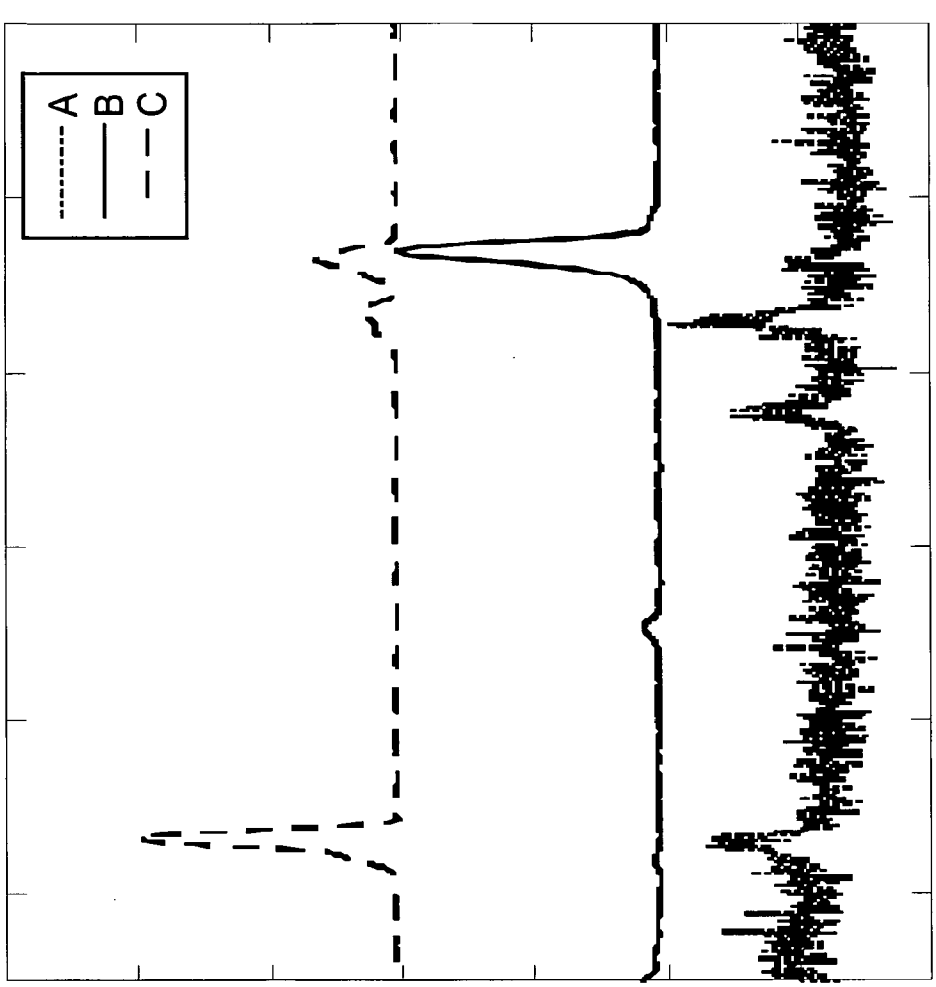
A
B
C
6
8
10
12
14
16
Diffraction Angle [2Θ]
Intensity [arbitrary units]

Figure 1H

Sample No.	Active material			Primary Matrix			Surfactant #1			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	% v/v	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	
A	IND	1.20	12		LAC	8.80	88				30	0.753	25	34	44	55	70		
B	IND	1.20	12		LAC	8.70	87	SDS	0.1	1	30	0.677	14	26	41	65	91		
C	IND	1.20	12		LAC	8.70	87	B700	0.1	1	30	0.621	13	25	43	68	91		
D	MEL	1.2	20.0		MAN	4.62	77	SDS	0.18	3.0	10	0.277	37	53	66	74	86	83	
E	MEL	1.2	20.0		MAN	4.8	80				15	2.493	10	12	12	15	39	33	
F	DIC	3	30	30	MAN	6.7	67	SDS	0.3	3	90	0.157	63	79	86	88	93		

Figure 2A

Sample No.	Active material			Primary Matrix			2nd Matrix			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	NAA	1.2	30.0	LAC	2	50.0	TCD	0.8	20.0	20	0.188	48	64	75	81	92		
B	NAA	1.2	30.0	LAC	2	50.0	CAC	0.8	20.0	20	0.213	47	63	76	84	91		
C	NAA	1	25.0	LAA	2.2	55.0	XYL	0.8	20.0	20	0.2	50	65	75	79	89		
D	NAA	1	25.0	LAA	2.2	55.0	MAA	0.8	20.0	20	0.223	46	60	70	76	87		
E	NAA	1	25.0	LAA	2.2	55.0	TCD	0.8	20.0	20	0.215	47	62	70	73	83		

Figure 3A

Figure 4A

Sample No.	Active material			Primary Matrix			Surfactant #1			2nd Matrix			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	MEL	20	20.0	LAC	77	77.0	SDS	3	3.0				15	0.24	39	64	87	97	100	90	
B	MEL	20	20.0	LAC	80	80.0							15	0.166	59	74	82	87	90	0.7	
C	IND	13	13.0	LAC	87	87.0							30	3.255	0	0	0	4	27	1	
D	IND	13	13.0	LAC	65.5	65.5				TA	22	21.5	30	0.272	34	55	76	87	93	0	
E	IND	13	13.0	LAC	86	86.0	SDS	1	1.0				30	0.836	22	31	39	56	83	76	
F	IND	13	13.0	LAC	64.5	64.5	SDS	1	1.0	TA	22	21.5	30	0.629	15	28	43	67	91	85	
G	MEL	25	25	LAC	72	72	SDS	3	3				15	0.283	33	53	73	84	92		

Figure 5A

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	NAA	17.5	35.0	MAN	32	64.0	SDS	0.5	1.0				80	0.249	42	56	64	67	74		
B	NAA	17.5	35.0	MAN	31.5	63.0	SDS	0.5	1.0	P40S	0.5	1	80	0.261	39	55	67	77	88		
C	NAA	17.5	35.0	MAN	31.5	63.0	SDS	0.5	1.0	P3000	0.5	1	80	0.188	53	70	81	88	95		
D	IND	6	12.0	LAC	43.5	87.0	SDS	0.5	1.0				40	0.231	43	61	78	91	97		
E	IND	6	12.0	LAC	43	86.0	SDS	0.5	1.0	P407	0.5	1	40	0.152	66	85	95	97	98		
F	IND	6	12.0	LAC	43	86.0	SDS	0.5	1.0	P40S	0.5	1	40	0.155	65	85	96	98	98		

Figure 6A

Sample No.	Active material				Primary Matrix			Surfactant #1			Surfactant #2			2nd Matrix			Time (mins.)	Particle Size							Yield (%)	Variations
	Name	Mass (g)	% w/w	% v/v	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	No. Ave. nm		
A	NAA	70	35		LAC	128	64	SDS	2	1							60	0.345	35	47	56	61	73		98	O
B	NAA	70	35		MAN	128	64	SDS	2	1							50	0.73	31	41	48	51	58			C
C	NAA	60	30.0		MAN	138	69.0	SDS	2	1.0							50	0.181	55	73	86	92	96		92	C
D	NAA	60	30.3		MAN	138	69.7										50	0.319	35	48	59	64	75		23	C
E	DIC	52.5	15.0		LAC	294	84.0	SDS	3.5	1.0							40	0.16	64	84	97	99	99		64	E
F	DIC	52.5	13.0		LAC	224	66.0	SDS	3.5	1.0				TA	70	20	40	0.16	63	83	95	98	99		87	E
G	NAA	60	30	35	LAC	138	69	SDS	2	1							40	0.232	44	59	70	78	90		79	E
H	2,4D	40	20		LAC	160	80										30	0.212	47	69	90	100	100		95	
I	2,4D	40	20		LAC	158	79	SDA	2	1							30	0.189	53	72	87	95	97		97	
J	2,4D	40	20		LAC	158	79	K1251	2	1							30	0.2	50	71	89	97	97		97	
K	2,4D	40	20		LAC	158	79	D920	2	1							30	0.204	49	69	86	94	97		94	
L	2,4D	60	20		LAC	234	78	SDA	3	1	PVP	3	1				30	0.281	30	54	82	96	96		93	
M	2,4D	60	20		LAC	234	78	D920	4	1	PVP	3	1				40	0.183	55	75	91	98	98		90	
N	2,4D	60	20		LAC	234	78	K1251	3	1	PVP	3	1				40	0.208	48	68	88	99	100		92	
O	GLY	40	20		LAC	158	79	B700	2	1							90	0.297	38	50	61	74	87		18	
P	GLY	40	20		LAC	156	78	B700	2	1	T2700	2	1				45	0.188	53	71	85	93	96		79	D
Q	GLY	60	20		LAC	234	78	B700	3	1	T2700	3	1				30	4.798	0	0	0	0.2	9.9			D
R	GLY	60	20		LAC	234	78	B700	3	1	T2700	3	1				50	0.204	49	66	79	89	94			D

Figure 6B

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			2nd			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	No. Ave. nm	
S	GLY	60	20	LAC	234	78	B700	3	1	T2700	3	1				70	0.17	58	94	98	95	97		94.7	D
T	MEL	35	10	LAC	311.5	89	LEC	3.5	1							40	0.127	80	94	98	98	99		81	
U	MEL	35	10	MAN	311.5	89	LEC	3.5	1							20	0.199	50	67	76	82	91		59	1
V	MEL	35	10	LAC	309.8	89	P188	3.5	1	DS	1.77	1				20	0.13	77	94	100	100	100		90	1
W	MEL	17.5	5	MAN	323.8	93	P188	7	2	LEC	1.75	0.5				25	0.124	80	96	100	100	100		67	1
X	MEL	17.5	5	LAC	320.3	92	P188	10.5	3	LEC	1.75	0.5				40	0.129	78	94	99	99	99		94	1
Y	MEL	17.5	5	MAN	320.3	92	P188	10.5	3	LEC	1.75	0.5				25	0.14	72	88	93	94	98		97	1
Z	MEL	35	10	LAC	302.8	87	P188	10.5	3	LEC	1.75	0.5				30	0.168	59	75	83	87	94		52	1
AA	MEL	35	10	LAC	311.5	89	P188	3.5	1							40	0.118	87	99	100	100	100		87	1
AB	MEL	35	10	MAN	311.5	89	P188	3.5	1							30	0.164	60	77	87	93	97		32	1
AC	MEL	35	10	LAC	315.0	90										20	0.143	71	89	95	96	98		79	1
AD	MEL	35	10	MAN	315.0	90										25	0.26	39	55	66	73	85		56	1
AE	CRM	60	20	LAC	138	69	LEC	1	2							60	0.152	64	78	84	87	89		79	7
AF	CIL	30	10	LAC	267	89	SDS	3	1							20	0.162	64	86	99	100	100		84	5,D
AG	PRO	30	10	LAC	267	89	SDS	3	1							30	0.62	12	24	42	67	89		74	5,D
AH	PRO	30	10	LAC	270	90										30	0.91	9	18	33	52	61		66	5,D
AI	CIP	30.0	15	LAA	168.0	84	T80	2.00	1							20	0.139	76	91	94	94	95	88	94	E
AJ	CIP	30.1	15	LAA	170.0	85										20	0.171	60	75	79	79	82		36.7	E
AK	CIP	30.0	15	LAA	168.0	84	CEL	2.00	1							20	0.277	41	51	54	54	56		72	E

Sample No.	Active material			Primary Matrix		Surfactant #1			Surfactant #2			2nd			Time (mins.)	Particle Size							Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	No. Ave. nm		
AL	GLY	60.0	20	LAC	240.0	80										70	50.4	0	0	0	0.9	4.4	1282	26	3,P
AM	CEL	20.0	10	LAC	176.1	88	SDS	2.00	1	P40S	2	1				10	0.205	49	66	79	86	92	81	86	1,D
AN	CEL	20.0	10	LAC	180.1	90										10	4.775	0	0	0	0	6.4	2560	57	1,D
AO	CEL	20.0	10	LAC	176.0	88	SDS	2.00	1	P8000	2	1				10	0.353	34	46	56	64	77	80	86	1,D
AP	MAN	150.1	50	LAC	147.1	49	T3785	3.00	3							5	0.22	46	60	72	84	87	89	90	8,D
AQ	MAN	150.1	50	LAC	150.0	50										5	0.292	35	51	67	81	85	109	56	8,D
AR	MAN	150.0	50	LAC	147.0	49	DS	3.02	3							5	0.274	38	53	67	80	84		76	8,D
AS	NAA	105.1	35	MAN	195.0	65										80	0.189	53	70	82	87	91	80	81	
AT	NAA	105.0	35	MAN	180.1	60	MCC	15.00	5							80	0.261	40	54	65	69	75	81	66	D
AU	NAA	105.0	35	MAN	180.0	60	PML	15.10	5							80	0.243	42	58	69	76	85	83	51	D

Figure 6C

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			2nd Matrix			Disintegrant			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	MTX	1.5	30.0	LAC	3.5	69.0	P407	0.1	1.0										60	0.16	63	77	84	89	93		2
B	MTX	1.5	30.0	LAC	3.5	70.0													60	0.28	40	52	59	59	71		2
C	MTX	17.2	43.0	LAC	22	56.0	SDS	0.4	1.0										60	0.142	70	83	88	91	94		2
D	MTX	20	50.0	LAC	10.4	26.0	SDS	0.8	2.0	P407	0.8	2	SB	8	20.0				60	0.137	73	89	95	100	100		9
E	MTX	2.5	50.0	LAC	2.35	47.0	SDS	0.8	2.0	P407	0.1	2							60	0.148	67	83	92	98	99		2
F	MTX	17.2	43.0	MAN	22.4	56.0	SDS	0.4	1.0										60	0.254	42	55	64	67	72		2
G	MTX	1	20	LAC	4	80													60	13.45	0	0	0	0	0	92	2
H	MTX	1	20	LAC	3.9	78	SDS	0.05	1	P407	0.05	1							60	0.13	76	91	96	98	98	97	2
I	MTX	1.25	25	LAC	2.85	68	SDS	0.05	1	P407	0.05	1	PVP	0.05	1	PRI	0.25	5	50	0.201	50	67	80	84	84	85	2
J	MTX	60	30	LAC	137	67	SDS	3	1.5	P407	3	1.5							5	3.943	20	27	30	31	38		2
K	MTX	60	30	LAC	137	67	SDS	3	1.5	P407	3	1.5							10	0.223	46	61	72	77	83		2
L	MTX	60	30	LAC	137	67	SDS	3	1.5	P407	3	1.5							16	0.153	64	79	86	93	96		2
M	MTX	60	30	LAC	137	67	SDS	3	1.5	P407	3	1.5							21	0.142	67	85	92	95	96		2
N	7M	151	94							PVP	1.61	1				PRI	8.04	5	2						97	2
O	MTX	60	30	LAC	137	67	SDS	3	1.5	P407	3	1.5							20	0.8	32	42	48	51	63	70	2,E

Figure 7A

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			2nd Matrix			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	MEL	48	10	LAC	417.6	87	SDS	14.4	3							3	0.15	66	83	90	91	94	97	1
B	MEL	24	5	LAC	439.2	91.5	P188	14.4	3	LEC	2.4	0.5				8	0.159	63	81	91	94	98	97	1
C	MEL	24	5	MAN	439.2	91.5	P188	14.4	3	LEC	2.4	0.5				8	0.144	70	88	94	95	98	92	1
D	IND	62.4	13	LAC	312	65	SDS	4.8	1				TA	100.8	21	4	0.197	51	68	81	88	94	91	
E	IND	62.4	13	LAC	312	66							TA	100.8	21	4	0.19	53	71	85	92	97	74	
F	IND	62.4	13	LAC	312	65	SDS	4.8	1				TA	100.8	21	4	0.194	52	71	86	93	97	84	
G	IND	48	10	SUC	427.2	89	SDS	4.8	1							5	0.213	47	64	76	84	92	93	
H	IND	48	10	SUC	427.2	89	SDS	4.8	1							6	0.192	52	72	87	93	96	94	
I	MTX	144	30	LAC	321.6	67	SDS	7.2	1.5	P407	7.2	1.5				4	0.243	44	58	68	74	84	93	2
J	ANT	50	10	LAC	445	89	SDS	5	1							4	0.288	32	51	73	86	91	90	5
K	DIC	72	15	LAC	403.2	84	SDS	4.8	1							3	0.186	54	74	89	95	98	94	
L	NAA	168	35	MAN	302.4	63	SDS	4.8	1	PVP	4.8	1				6	0.226	44	63	80	88	93	94	
M	NAA	168	35	MAN	297.6	62	SDS	4.8	1	PVP	4.8	1	P3000	4.8	1	7	0.287	31	52	73	85	93	98	
N	COP	48	10	LFG	427.2	89	SDS	4.8	1							7	4.319	0	0	0	3	16	93	10
O	COP	96	20	LFG	374.4	78	LEC	9.6	2							18	2.375	0	0	0	9	39	80	10
P	CON	144	30	LFG	326.4	68	LEC	9.6	2							1.5	4.027	0	0	0	7	23	83	10

Figure 8A

Figure 9A

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			2nd Matrix			Time (mins.)	Particle Size							Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	No.Ave.(nm)		
A	MEL	40	5	MAN	732	91.5	P188	24	3	LEC	4	0.5				40	0.116	84	97	100	100	100		96	1,I
B	MEL	40	5	MAN	732	91.5	P188	24	3	LEC	4	0.5				45	0.122	82	97	100	100	100		95	1,I
C	MEL	40	5	MAN	732	91.5	P188	24	3	LEC	4	0.5				40	0.124	80	96	100	100	100		97	1,I
D	MEL	52.5	5	LAC	960.8	91.5	P188	31.5	3	LEC	5.25	0.5				50	0.156	64	81	89	90	93		88	1,H
E	MEL	40.0	5	MAN	732.0	91.5	P188	24	3	LEC	4	0.5				40	0.142	71	88	93	93	95		96	1,I
F	SAL	100.0	10	LAC	890.0	89	LEC	10.00								15	0.137	72	85	89	90	92	75	92	L
G	SAL	100.0	10	LAC	900.0	90										15	4.954	0	0	2	11	24		95	L
H	IND	130.0	13	LAC	870.0	87										36	0.18	56	74	89	96	98	80	65	
I	IND	130.1	13	LAC	860.1	86	SDS	10.00	1							36	0.192	52	73	90	95	97	83	85	
J	IND	130.1	13	LAA	870.0	87										36	0.186	54	72	86	93	97	80	51	
K	DIC	150.1	15	LAA	850.3	85										36	0.242	41	60	79	92	99	87	27	
L	MEL	105.0	10	LAC	913.5	87	SDS	31.50	3							20	0.137	74	90	95	95	96	79	94	G
M	MEL	105.1	10	LAC	945	90.0										20									1,G
N	IND	130.0	13	LAA	860	86	SDS	10	1							36	0.161	62	79	90	93	95		80	11,N
O	IND	130.0	13	LAA	645	64.5	SDS	10	1				TA	215	21.5	36	0.160	62	79	90	94	96		87	11,N
P	DIC	150	15	LAA	840	84	SDS	10	1							36	0.152	66	84	95	98	99		80	11,N
Q	MEL	75	7.1	LAC	943.5	90.0	SDS	31.5	3							30	0.129	78	94		100			89	1,M
R	MEL	71.6	6.8	LAC	946.9	90.2	SDS	31.5	3							30	0.312	72	89	94	94	96		92	1,F
S	IND	120	12	LAC	435	43.5	SDS	10	1				TA	435	43.5	44	0.168	60	79	92	98	100		80	11,K

Figure 9B

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			2nd Matrix			Time (mins.)	Particle Size							Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm	No.Ave.(nm)		
T	IND	130	13	LAC	645	64.5	SDS	10	1				TA	215	21.5	36	0.160	63	79	93	97	99			11
U	IND	130	13	LAC	645	64.5	SDS	10	1				TA	215	21.5	36	0.179	56	72	89	95	97			11
V	IND	130	13	LAC	645	64.5	SDS	10	1				TA	215	21.5	40	0.182	55	70	83	87	92			11
W	DIC	150	15	LAC	840	84	SDS	10	1							36	0.183	55	72	91	96	97			11
X	DIC	150	15	LAC	840	84	SDS	10	1							36	0.186	54	74	94	98	99			11
Y	DIC	150	15	LAC	840	84	SDS	10	1							36	0.203	49	69	92	97	98			11
Z	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.399	33	44	53	59	69			
AA	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.337	34	47	58	65	71			
AB	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.300	37	50	61	69	76			
AC	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.360	34	46	56	61	69			
AD	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.366	33	45	55	61	69			
AE	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.301	36	50	62	69	75			
AF	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.298	37	50	62	68	74			
AG	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.195	51	65	74	78	83			
AH	NAA	334	35.1	MAN	599	62.9	SDS	9.55	1.0	PVP	9.55	1.0				60	0.294	37	51	62	68	76			
AI	MEL	105	11	LAC	864	86.4	SDS	31.5	3							20	0.189	53	72	84	88	94			F
AJ	MEL	105	11	LAC	864	86.4	SDS	31.5	3							25	0.153	65	84	94	95	98			F
AK	MEL	105	11	LAC	864	86.4	SDS	31.5	3							30	0.138	74	91	96	96	97			F
AL	MEL	105	11	LAC	864	86.4	SDS	31.5	3							35	0.126	79	96	100	100	100		90	F

Sample No.	Active material				Primary Matrix			Surfactant #1			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	% v/v	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	DIC	2.50	10		MAN	22.5	89	SDS	0.25	1	30	0.237	40	63	83	93	97		
B	NAA	70	35		LAC	128	64	SDS	2	1	60	0.224	72	81	92	81	92		
C	NAA	70	35		MAN	128	64	SDS	2	1	60	0.177	57	74	86	90	93		
D	NAA	80	40	40	LAC	118	60				45	2.039	19	26	31	36	49		
E	DIC	1650	15		LAC	9240	84	SDS	110	1	20	0.24	42	58	74	86	94	91	
F	DIC	3750	15		LAC	21000	84	SDS	250	1	25	0.214	49	68	82	93	97	97	

Figure 10A

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			Surfactant #3			Disintegrant			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	% v/v	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	NAA	105	35	39	MAN	189	63	SDS	3	1	P3000	3	1							80	0.19	53	71	84	91	95	90	
B	NAA	105	35	39	MAN	189	63	SDS	3	1	P407	3.1	1							40	0.89	26	36	45	51	57		
C	NAA	105	35	39	MAN	189	63	SDS	3	1	P407	3.1	1							60	0.31	36	49	61	69	76		
D	NAA	105	35	39	MAN	189	63	SDS	3	1	P407	3.1	1							80	0.19	52	70	84	90	93	82	
E	NAA	105.1	35	39	MAN	192	64	SDS	3	1										80	0.24	43	59	72	78	81	84.6	
F	NAA	105	35	39	MAN	171	57	SDS	3	1	P3000	3	1	PVP	3	1	PML	15	5	80	0.27	39	54	67	74	78	89.2	12
G	NAA	105	35	39	MAN	171	57	SDS	3	1	P407	3	1	PVP	3.02	1	PML	15.1	5	80							88.2	
H	NAA	105.2	35	39	MAN	174	58	SDS	3	1	PVP	3	1				PML	15.0	5	80							87.1	
I	NAA	105	35	39	MAN	189	63	SDS	3	1	P3000	3	1							80	0.25	27	67	91	100	100	88	
J	NAA	105.7	35	39	MAN	186	64	SDS	3	1	P3000	3	1	PVP	3.01	1				80	0.24	29	68	90	99	100	89.7	
K	NAA	105.1	35.0	39	MAN	195	65.0													80	0.19	53	70	82	87	91	81	
L	NAA	105	35.0		MAN	180	60.0										MCC	15	5	80	0.26	40	54	65	69	75	66	12,D
M	NAA	105	35.0		MAN	180	60.0										PML	15	5	80	0.24	42	58	69	76	85	51	12,D

Figure 11A

Sample No.	Active material			Primary Matrix			Surfactant #1			Surfactant #2			Time (mins.)	Particle Size						Yield (%)	Variations
	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w	Name	Mass (g)	% w/w		D(0.5) µm	% <0.20 µm	% <0.30 µm	% < 0.5 µm	% < 1.0 µm	% < 2.0 µm		
A	NAA	1.5	30	LAC	3.2	64	SDS	0.05	1	MCC	0.25	5	40	2.6	29	41	47	61	77	86	
B	14A													0.2	68	79	84	94	99		12
C	NAA	1.5	30	LAC	3.45	69	SDS	0.05	1				40	0.2	79	95	98	100	100	95	
D	14C													0.2	80	94	97	100	100		12
E	14C	2.5	95	MCC	0.13	5							1	1.3	34	49	52	56	60	88	
F	14C	2.5	91	MCC	0.25	9							1	0.8	36	52	56	62	72	83	
G	14E													0.2	79	92	96	99	100		12
H	14F													0.2	79	93	97	99	100		12
I	NAA	1.5	30	LAC	2.95	59	SDS	0.05	1	MCC	0.5	10	40	6.4	12	19	25	43	64	96	
J	NAA	1.5	30	LAC	2.45	49	SDS	0.05	1	MCC	1	20	40	8.6	0	0	7	31	56	95	
K	14I													1.7	32	44	53	77	94		12
L	14J													4.1	0	0	12	61	92		12

Figure 12A

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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A61K 9/51 (2006.01)

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23 April 2010 (23.04.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

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(71) Applicant *(for all designated States except US)*: **ICEUTICA PTY LTD** [AU/AU]; 52 Fairfield Street, Mount Hawthorn, W.A. 6016 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DODD, Aaron** [AU/AU]; 368/58 Cook Road, Centennial Park, NSW 2021 (AU). **MEISER, Felix** [DE/AU]; 7 Beecham Road, Mount Claremont, W.A. 6010 (AU). **NORRET, Marck** [DK/AU]; 26 Stone Crescent, Darlington, W.A. 6070 (AU). **RUSSELL, Adrian** [AU/AU]; 139 Gladstone Road, Rivervale, W.A. 6103 (AU). **BOSCH, H., William** [US/US]; 237 Rodney Circle, Bryn Mawr, Pennsylvania 19010 (US).

(74) Agent: **WRAYS**; Ground Floor, 56 Ord Street, West Perth, W.A. 6005 (AU).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: A NOVEL FORMULATION OF DICLOFENAC

(57) Abstract: The present invention relates to methods for producing particles of diclofenac using dry milling processes as well as compositions comprising diclofenac, medicaments produced using diclofenac in particulate form and/or compositions, and to methods of treatment of an animal, including man, using a therapeutically effective amount of diclofenac administered by way of said medicaments.

WO 2010/121327 A1

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	A novel formulation of diclofenac
First Named Inventor/Applicant Name:	Aaron Dodd
Filer:	Anita L Meiklejohn/Mary Florczak
Attorney Docket Number:	31215-0011003

Filed as Small Entity

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Claims:				
Claims in excess of 20	2202	3	40	120
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2920**

Electronic Acknowledgement Receipt

EFS ID:	18061164
Application Number:	14167652
International Application Number:	
Confirmation Number:	7195
Title of Invention:	A novel formulation of diclofenac
First Named Inventor/Applicant Name:	Aaron Dodd
Customer Number:	26161
Filer:	Anita L Meiklejohn/Stacey Hill
Filer Authorized By:	Anita L Meiklejohn
Attorney Docket Number:	31215-0011003
Receipt Date:	29-JAN-2014
Filing Date:	
Time Stamp:	17:20:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2920
RAM confirmation Number	3778
Deposit Account	061050
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal of New Application	31215Transmittal.pdf	89448 d4e4231f5d2b3075607ca179c2c053b7a40ac23e	no	3
Warnings:					
Information:					
2	Application Data Sheet	31215ADS.pdf	1561890 f16a14ddb1d6a95d4fedbb8fb440db2a49c8bec6	no	8
Warnings:					
Information:					
3	Oath or Declaration filed	31215DEC.pdf	1256717 cabea56849357c546c88c7d660bacff45d93a6ab	no	6
Warnings:					
Information:					
4	Power of Attorney	31215POA.pdf	361814 719f91be6b0820696c6bbe8051f8abe86a24cbb1	no	3
Warnings:					
Information:					
5	TrackOne Request	31215Track1.pdf	137869 28861ae7bcfa8518bea6ea2896debafe9ea9b2e8	no	1
Warnings:					
Information:					
6	Information Disclosure Statement (IDS) Form (SB08)	31215IDS.pdf	143133 105beee42773f43aad82561235dfa3b0ef51453e	no	2
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
7		31215Prelim.pdf	71352 5280f710837cec54a3e0cce728a513b3f01f319e	yes	7

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	6
Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:					
Information:					
8		31215App.pdf	7097687 f8cf0c7a1ca90e72e79b91cd3b029e6ed762b30b	yes	127

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	84
	Claims	85	106
	Drawings-only black and white line drawings	107	126
	Abstract	127	127

Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	40116 7d590884e4548af389fedf79b309c5d9ae4b9f3d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	10760026		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Aaron Dodd	Nonprovisional Application Number (if known):	
Title of Invention:	A novel formulation of diclofenac		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form,
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Anita L. Meiklejohn/	Date 29 January 2014
Name Anita L. Meiklejohn, Ph.D. (Print/Typed)	Practitioner Registration Number 35,283

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☒ *Total of 1 forms are submitted.

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Document code: WFEE

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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/167,652	01/29/2014	Aaron DODD	31215-0011003

CONFIRMATION NO. 7195

26161
FISH & RICHARDSON P.C. (BO)
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

FORMALITIES LETTER

OC000000066631693

Date Mailed: 02/18/2014

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings are not in compliance with 37 CFR 1.84 because figures 1A-1F,4A,5A,6A,6B,9A and 9B contain figure or view numbers that have incorrect orientation. Reference characters, sheet numbers, and view numbers must be oriented in the same direction as the view. See 37 CFR 1.84(p)(1).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- A surcharge as set forth in 37 CFR 1.16(f) was not received.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required for a small entity within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are:

- $ **70** surcharge.
- $(**.00**) Previous Payment Amount.
- $ **70** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Adrian RUSSELL
- The substitute statement is signed by a person who is not identified as the applicant under 37 CFR 1.46 in an application data sheet (ADS). Only an applicant under 37 CFR 1.43, 1.45 or 1.46 may execute a substitute statement. See 37 CFR 1.64(a). An application data sheet in compliance with 37 CFR 1.76 identifying the person (i.e., assignee, obligated assignee, or person who otherwise shows sufficient proprietary interest) executing the substitute statement as the applicant, or an inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to the inventor for whom the substitute statement was provided, is required.
  Adrian RUSSELL

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/ctuazon/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/167,652

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10	x 40 =	400	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1130		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/167,652	01/29/2014	Aaron DODD	31215-0011003

CONFIRMATION NO. 7195

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FISH & RICHARDSON P.C. (BO)
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

POA ACCEPTANCE LETTER

OC00000066631717

Date Mailed: 02/18/2014

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/29/2014.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/solbrich/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/167,652	01/29/2014	1615	1130	31215-0011003	30	2

CONFIRMATION NO. 7195

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FILING RECEIPT

OC000000066631692

Date Mailed: 02/18/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Aaron DODD, Centennial Park, AUSTRALIA;
Felix MEISER, Mount Claremont, AUSTRALIA;
Marck NORRET, Darlington, AUSTRALIA;
Adrian RUSSELL, Rivervale, AUSTRALIA;
H William BOSCH, Bryn Mawr, PA;

Applicant(s)

iCeutica Pty Ltd., Balcatta, WA

Assignment For Published Patent Application

iCeutica Pty Ltd., Balcatta, WA

Power of Attorney: The patent practitioners associated with Customer Number 26161

Domestic Priority data as claimed by applicant

This application is a CON of 13/266,122 02/16/2012
which is a 371 of PCT/AU2010/000471 04/23/2010
which claims benefit of 61/172,291 04/24/2009

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
AUSTRALIA 2009901748 04/24/2009 No Access Code Provided

If Required, Foreign Filing License Granted: 02/14/2014
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/167,652**
Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

NOVEL FORMULATION OF DICLOFENAC

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Please consider the references listed on the enclosed PTO-1449 Form. Foreign patent documents are enclosed; the cited U.S. patent application publication will be provided on request.

This statement is being filed before the receipt of a first Office Action on the merits. Please apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: March 21, 2014

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U.S. Patent Documents

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	1	2006/287346	12/21/2006	Van Schie			

Foreign Patent Documents or Published Foreign Patent Applications

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	2	WO 1997/02017	1/23/1997	WIPO				
	3	WO 2006/116596	11/2/2006	WIPO				

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(54) Title: CONTROLLED RELEASE FORMULATIONS FOR POORLY SOLUBLE DRUGS

(57) Abstract

A controlled release formulation for oral administration comprises a solid dispersion of a poorly soluble active ingredient in a hydrophilic poloxamer, the solid dispersion being a component of a core and the core as such or following coating of the core with a polymeric coating being effective to achieve therapeutic levels of the active ingredient over extended periods of time (24 hours or longer) following oral administration. The formulation can be in a multi-particulate form such as pellets or mini-tablets or in the form of tablets. Examples of active ingredients whose solubility and therapeutic effectiveness can be improved with the formulation are cisapride, cyclosporin, diclofenac, felodipine, ibuprofen, indomethacin, nicardipine, nifedipine, terfenadine and theophylline.

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Description

Controlled release formulations for poorly soluble drugs

Technical Field

This invention relates to controlled release formulations for poorly soluble drugs for oral administration.

Background Art

Various controlled absorption/release pharmaceutical formulations are available which have a particular dissolution pattern, resulting in a controlled absorption of the active substance and, therefore, more effective medication. The use of many active substances in therapy is complicated by solubility problems. In the case of some insoluble drugs various methods have been used to enhance solubility such as micronisation, formation of amorphous co-precipitates, or preparation of inclusion complexes using materials such as cyclodextrins. Various surfactants have also been utilised to enhance the solubility of various insoluble compounds using different formulation strategies.

Some drugs, such as nifedipine, are non-ionisible and show a low solubility throughout all regions of the gastrointestinal tract. Other drugs are either basic or acidic in character and show pH dependent limited solubility in different regions of the gastrointestinal tract. One such example is cisapride, which is basic in nature and has only relatively low solubility in acid conditions in the upper part of the gastrointestinal tract and very poor solubility as it passes further down the gastrointestinal tract.

Our EP 0 232 155 B1 and EP 0 274 176 describe adsorbates for use in drug delivery systems. EP 0 232 155 B1 describes adsorbates consisting of a mixture of a pharmaceutically useful active ingredient and an inactive substance adsorbed on a cross-linked polymer which is

granulated and then blended with a polymer or mixture of polymers to form a sustained release drug delivery matrix system. EP 0 274 176 describes sustained release capsule and tablet formulations based on an adsorbate of a mixture of a pharmaceutically useful dihydropyridine and a polyvinylpyrrolidone having an average molecular weight greater than 55,000 adsorbed on a cross-linked polyvinylpyrrolidone, the adsorbate being blended with at least one polymer which gels in the presence of water so as to obtain a sustained release effect.

It is an object of the present invention to provide an improved drug delivery system wherein the bioavailability of an otherwise poorly bioavailable active ingredient is enhanced and effectively controlled.

It is a further object of the present invention to provide controlled release dosage forms of poorly soluble active ingredient which provide therapeutic levels for a period of up to 24 hours or longer, dependent on the half-life of the active ingredient.

Disclosure of Invention

The invention provides a controlled release formulation for oral administration, comprising a solid dispersion of a poorly soluble active ingredient in a hydrophilic poloxamer polymer, said solid dispersion being a component of a core and said core as such or following coating of the core with a polymeric coating being effective to achieve therapeutic levels of said active ingredient over extended periods of time following oral administration.

It is found that incorporation of a poorly soluble active ingredient into a solid dispersion in a formulation according to the invention achieves a significant level of solubility/wettability enhancement, as well as achieving therapeutic levels of said active ingredient over extended periods *in vivo*.

Preferably, the solid dispersion is blended with one or more tabletting ingredients to form a tablet core, said tablet core as such or

following coating of the core with a polymeric coating being effective to achieve therapeutic levels of said active ingredient over extended periods of time following oral administration.

To accommodate the varying solubility of different active ingredients of the type referred to above, the solid dispersion may need to include one or more ingredients to further improve the solubility/wettability enhancement of the active ingredient.

Accordingly, the solid dispersion may include a surfactant component. The surfactant may be an anionic, cationic or non-ionic surfactant. Preferred surfactant components are selected from sodium lauryl sulphate, a sodium carboxylate, an alkyl sulphate, a polyethylene glycol ester, a polyethylene ether, a sorbitan ester, an ethoxylated sorbitan ester and an alkyl trimethylammonium halide and a mixture thereof.

Alternatively, the solid dispersion may include an acid component. Preferred acid components are selected from adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid.

Further, alternatively, the solid dispersion may include a base component. Preferred base components are selected from calcium carbonate, calcium hydroxide, magnesium hydroxide, sodium bicarbonate, sodium carbonate, sodium citrate and sodium hydroxide.

Preferably, the surfactant, acid or base component is present in a ratio of 0.01:1.0 to 5.0:1.0 by weight of the active ingredient.

Any such surfactant, acid or base components are hereinafter collectively referred to as auxiliary agents.

Further, preferably, the active ingredient and the poloxamer are present in an amount of 0.1:1.0 to 10.0:1.0 by weight.

By poloxamer herein is meant also a combination of two or more poloxamers.

The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide.

More specifically, the poloxamer polyols are α-hydro-ω-hydroxypoly(oxyethylene)poly(oxypropylene)poly(oxyethylene) block copolymers, more generally known as polyethylene - propylene glycol copolymer or polyoxyethylene - polyoxypropylene copolymer.

Preferred poloxamers are those which contain between 60% and 90%, more especially between 70% and 80%, by weight of the polyoxyethylene portion.

The polyoxyethylene segment is hydrophilic whilst the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene oxide and ethylene oxide added during manufacture. The hydrophilic segment can comprise between 15 and 90% of the molecule. As indicated above, those recommended for use in accordance with the invention have between 60% and 90%, more especially between 70% and 80%, by weight of the hydrophilic polyoxyethylene segment or sequence. Such poloxamer polyols, hereinafter referred to as poloxamers, are known by the trade names Lutrol, Monolan and Pluronic.

Poloxamers are also defined by a number. The first two digits of the number, when multiplied by 100, correspond to the approximate average molecular weight of the polyoxypropylene (POP) portion of the molecule. The third digit, when multiplied by 10, corresponds to the percentage by weight of the polyoxyethylene (POE) portion. When called by their Pluronic name, the first two digits, when multiplied by 1000 indicate the total molecular weight, and the third digit, multiplied by 10, represents the approximate percentage of POE in the molecule. The associated capital letter indicates the physical state: L = liquid, P =

paste, and F = solid. For further information, reference can be made to Pharmaceutical Technology Europe May 1994.

The preferred poloxamers for use in accordance with the invention are the F series. Especially preferred poloxamers of the F series are F68, F108 and F127, especially those sold under the trade marks Lutrol F 68, Pluronic F 108 and Lutrol F 127 by BASF.

Further information on these poloxamers can be obtained from the technical information sheets supplied by BASF (Ireland) Limited.

The poloxamer is melted and then the active ingredient and any auxiliary agents(s) are dispersed in the molten poloxamer.

The poloxamer is suitably melted in a stainless steel container. To the molten mass the active ingredient, and any auxiliary agent(s) and the inert filler, if used, are added slowly over time. The mixture is stirred while it is cooled and milled to a median particle size in the range 30-300 μm.

Alternatively, the active ingredient, any auxiliary agent(s), and the poloxamer are dissolved in an organic solvent or solvents; the solvent is evaporated and the molten poloxamer is cooled and milled to a median particle size in the range 30-300 μm.

It has been found that various poorly soluble active ingredients are readily dispersible in the melt forms of the poloxamers used in accordance with the invention. When cooled the mixture of active ingredient, auxiliary agent(s), if present, and poloxamer forms a dry, hard solid which can be easily ground or milled. It is for this reason that the poloxamers were chosen herein as the polymer base for the solid dispersion.

The solid dispersion according to the invention can include excipient agents, such as an inert filler. The inert filler is suitably a water soluble inert filler. An example of an inert filler is lactose, more

especially lactose monohydrate. The inclusion of an inert filler such as lactose may have the effect of lowering the melting point of the poloxamer.

The incorporation of an inert filler is found to have no detrimental impact on the solubility obtained. However, it does significantly improve overall processability and lead to a fine, powder material which is very suitable for compression into tablets. The inert filler is suitably used in an amount of 3-35% by weight.

The active ingredient can be any poorly soluble drug of the type mentioned above. Examples of such drugs are cisapride, cyclosporin, diclofenac, felodipine, ibuprofen, indomethacin, nicardipine, nifedipine, terfenadine and theophylline.

An aim of the present invention is to provide poorly soluble active ingredients such as cisapride in a readily solublised and absorbable form at distal sites in the gastrointestinal tract so as to achieve continuing and extended absorption. The aqueous solubility of cisapride, which is inherently low and significantly pH dependent, becomes limiting as cisapride is normally presented to more distal sites in the gastrointestinal tract where the water content and the pH adversely impact on the solubility of cisapride. Although not wishing to be bound by any theoretical explanation of the invention, it is postulated that the increased solubility of cisapride obtained through the use of a solid dispersion as hereinabove described results in an optimal micro-environment which promotes the availability of solublised and absorbable cisapride. Furthermore, the presence of a hydroxy acid in the solid dispersion, combined with the controlled release system employed, results in a gradual availability of the hydroxy acid to promote the solubilisation of the cisapride over the bulk of the release rate curve.

Similar results are obtained with other poorly soluble active ingredients as hereinafter described.

The solid oral dosage form according to the invention can be in the form of capsules.

Thus, capsules in accordance with the invention can contain the formulation according to the invention in a multi-particulate form such as pellets or mini-tablets.

Suitably, the capsules will include an amount of pellets or mini-tablets for immediate release of active ingredient comprising a solid dispersion as hereinbefore defined.

Various multi-particulate forms or a small number of discrete units can be presented in capsule form.

The capsules can be hard or soft gelatin capsules.

Alternatively, the solid oral dosage form according to the invention can be in the form of tablets.

The tablets may consist of a tablet core defined by a solid dispersion as hereinbefore described dispersed in a hydrogel matrix. In this form of tablet, the solid dispersion is compressed into a dosage form containing a polymer or mixture of polymers which when wet will swell to form a hydrogel. The rate of release of the active ingredient from this dosage form is controlled both by diffusion from the swollen tablet mass and by erosion of the tablet surface over time. The rate of release of the active ingredient may be controlled both by the amount of polymer *per* tablet and by the inherent viscosities of the polymers used.

The water swellable polymer is suitably a hydroxy-propylmethylcellulose (HPMC) in an amount of 5-75% by weight. By hydroxypropylmethylcellulose herein is meant a combination of hydroxypropylmethylcelluloses.

Suitably the HPMC or other water swellable cellulose polymer will be present in an amount of from 5% to 75% by weight, more especially from 10% to 60% by weight.

An especially preferred type of HPMC for use in accordance with the invention is HPMC sold under the trade mark Methocel.

The amount of HPMC or other water swellable polymer used will be dependent on the viscosity thereof. In general, the higher the viscosity of the polymer, the lesser amount of the polymer required to give the desired release properties.

Suitable Methocels are Methocel K15M, a 2% solution of which has a viscosity of 15,000 centipoise. Other suitable Methocels include Methocel K4M, K100M, K100LV or E, F and J grades, depending on the release characteristics desired.

As indicated above, the use of hydrogel matrices causes the tablet to swell and release drug in a controlled manner by erosion of the tablet surface and diffusion from the tablet mass. Cellulose polymers with different inherent viscosities are preferably used to control the dissolution rate.

Hydrogels are linear macromolecules which swell in water or biological fluids. Drug release in such systems can be basically modified by varying the following parameters:

Type and viscosity grade of polymers; and
Actual concentrations.

The polymer type chosen in accordance with the invention is determined primarily by the solubility characteristics of the solid dispersion to be compressed. The viscosity grade is dictated by the desired rate of release of active ingredient from the tablet mass.

Tablet hardness is also a parameter to be considered in the case of hydrogel tablets. Suitably the mean hardness of the tablets is in the range 60-260 N.

For tabletting purposes, it will also be usual to use a diluent or compacting agent such as microcrystalline cellulose, more especially microcrystalline cellulose sold under the trade mark Avicel, for example, Avicel pH101.

Other excipient agents may include lubricants such as magnesium stearate and a glidant such as colloidal silicon dioxide sold under the trade mark Aerosil.

The solid oral dosage form according to the invention can also be in the form of tablets comprising a core containing a solid dispersion as hereinbefore described surrounded by a multi-porous, rate-controlling membrane. Suitably the solid dispersion is in the form of an instant release tablet core which is adapted for direct compression followed by coating with the rate-controlling membrane. A primary consideration with such formulations is the selection of suitable tablet ingredients to impart the desired effect while compressing easily. In order to achieve an instant release tablet core the solid dispersion is suitably blended with standard tablet excipients such as a standard compressing base, a compressible sugar, a solubilising agent and a lubricating agent. In this type of dosage form, release of the active ingredient is controlled *via* a diffusion mechanism.

Tablet hardness and friability play an important role in the characterisation of the membrane coated tablet. It is essential that the core tablets are sufficiently rugged to withstand the coating process.

In order to obtain the desired release profile suitable for once-daily administration, the rate-controlling membrane will suitably contain a major proportion of a pharmaceutically acceptable film-forming, water insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer.

The term water soluble polymer as used herein includes polymers which are freely permeable to water, whilst the term water insoluble polymer as used herein includes polymers which are slightly permeable to water, as hereinafter indicated.

Preferably the water soluble polymer in the membrane, if present, is selected from polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carrageenan, xanthan or polyethylene glycol or a mixture thereof.

The incorporation of various hydrophilic agents into the polymer coating so as to form channels in said coating can be used and in general leads to a more linear release rate. Such hydrophilic agents include fumaric acid, citric acid, tartaric acid, sodium citrate, sodium bicarbonate, sodium fumarate, sodium carbonate, monosaccharides and disaccharides. An especially suitable monosaccharide is glucose.

Alternatively, the water soluble polymer in the membrane can be replaced by a polymeric material which is freely permeable to the active ingredient and water and comprises a copolymer of acrylic and methacrylic acid esters.

A suitable polymer which is freely permeable to various poorly soluble active ingredients and water is a polymer sold under the Trade Mark EUDRAGIT RL.

Preferably, the water insoluble polymer in membrane is selected from ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate),

poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) or polyurethane or a mixture thereof.

The water insoluble polymer of the membrane may also comprise naturally occurring polymers or resins.

Thus other preferred water insoluble polymers are selected from a naturally occurring polymer selected from shellac, chitosan, gum juniper or a mixture thereof.

Alternatively, the water insoluble polymer in the membrane can be replaced by a polymeric material which is slightly permeable to the active ingredient and water and comprises a copolymer of acrylic and methacrylic acid esters.

A suitable polymer which is slightly permeable to various poorly soluble active ingredients and water is a polymer sold under the Trade Mark EUDRAGIT RS or a polymer whose permeability is pH dependent and sold under the Trade Mark EUDRAGIT L, EUDRAGIT S or EUDRAGIT E. Especially preferred polymers in this category are EUDRAGIT S.

EUDRAGIT polymers are polymeric lacquer substances based on acrylates and/or methacrylates. The polymeric materials sold under the Trade Mark EUDRAGIT RL and EUDRAGIT RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups and are described in the "EUDRAGIT" brochure of Messrs. Rohm Pharma GmbH (1984) wherein detailed physical-chemical data of these products is given. The ammonium groups are present as salts and give rise to the permeability of the lacquer films. EUDRAGIT RL and RS are freely permeable (RL) or slightly permeable (RS), respectively, independent of pH.

EUDRAGIT S is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water. It becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalis. The permeability of EUDRAGIT S is pH dependent. Above pH 6.0 the polymer becomes increasingly permeable. EUDRAGIT S is described in the "EUDRAGIT S" brochure of Messrs. Rohm Pharma GmbH (1986) wherein detailed physical-chemical data of the product is given.

The solid dispersion can be applied to an inert core before application of the rate-controlling polymer membrane in a manner known *per se*.

Thus, the solid dispersion can be applied to an inert core, such as a non-pareil seed of sugar/starch having an average diameter in the range 0.2-1.4 mm, more especially 0.3-0.8 mm, using a polymeric material as a binder.

The polymeric material used to coat the inert core will suitably contain a major proportion of a pharmaceutically acceptable water soluble polymer.

The inert core will be coated with layers of solid dispersion in powder form and the polymeric material superimposed one upon the other and the polymeric material being present in an amount effective to ensure that all of the solid dispersion is incorporated into the core.

The polymer materials used to form the core can be the same as the polymers hereinabove described for use in the rate-controlling membrane.

In the case of coating in a conventional coating pan, alternate layers of a coating solution/suspension of the polymeric material and the solid dispersion are applied to the central inert core to build up a multi-layer arrangement of the core. In the case of an automatic coating system, the coating solution/suspension of the polymeric

material and the solid dispersion are applied, simultaneously, in conventional manner.

The coating solution/suspension of the polymeric material comprises one or more polymer(s) dissolved/suspended in a suitable solvent or mixture of solvents. The concentration of the polymeric material in the coating solution/suspension is determined by the viscosity of the final solution/suspension. Preferably, between 5 and 50 parts of the central inert cores are used relative to the solid dispersion. The addition of a plasticizing agent to the polymeric solution/ suspension may be necessary depending on the formulation to improve the elasticity and also the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage.

Such changes could affect the drug release rate. Suitable plasticizing agents include polyethylene glycol, propylene glycol, glycerol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and varying percentages of acetylated monoglycerides.

Alternatively, the solid dispersion and polymeric material can be built up on a central active core. The active core is suitably formed by blending the solid dispersion and polymeric material to form a homogeneous powder, shaping a portion of said blend to form a central core and applying the remainder of said blend alternately or simultaneously with a polymer binding solution to form a layered structure on said central core.

Thus, the active core can be formed by blending the solid dispersion and polymeric material to form a homogeneous powder. A portion of the blend is shaped to form a central core. A multi-layer arrangement is then built up by a successive layering and binding process wherein the remainder of the blend and a polymer binding solution are applied to the active core in alternate layers in a conventional coating pan. Alternatively, an automatic coating system

may be used wherein the remainder of the blend and polymer binding solution is applied to the active core, simultaneously. Conventional automated coating systems include for example a CF granulator or a Glatt fluidized bed. The cores are formed to ensure a uniform distribution of the active ingredient and any auxiliary agent(s) throughout the cores.

Coating the active core consisting of the solid dispersion with a differentially permeable membrane allows active dissolution and diffusion from the micro-environment of the active core. Especially, suitable polymers are cellulose and poly(methacrylate) based polymers for use as coating agents. Polymer coating is most suitably performed in a C.F. 360 granulator.

Preferred solvents for use in polymer application/coating include acetone, isopropyl alcohol and industrial methylated spirit.

In order to form mini-tablets and pellets for filling into capsules it will be appreciated by the person skilled in the art that the above methods for forming hydrogel matrix tablets and tablets with a rate-controlling membrane, respectively can be adopted.

Based on the information given above other ways of incorporating the solid dispersion hereinabove described to achieve improved solubilisation/wettability and improved controlled absorption/release will be apparent to one skilled in the art.

Brief Description of the Drawings

Fig. 1 is a plot of plasma levels of nifedipine (ng/ml) *versus* time (hours) after administration for the formulations of Examples 1 and 2;

Fig. 2 is a plot of plasma levels of nifedipine (ng/ml) *versus* time (hours) after administration for the formulations of Examples 3 and 4;

Fig. 3 is a plot of plasma levels of nifedipine (ng/ml) *versus* time (hours) after administration for the formulations of Example 5 and the reference product;

Fig. 4 is a plot of plasma levels of cisapride (ng/ml) *versus* time (hours) after administration for the tablet formulations of Examples 6 and 7 in which: curve a) corresponds to the tablet formulation of Example 6; and curve b) corresponds to the tablet formulation of Example 7; and

Fig. 5 is a plot of plasma levels of cisapride (ng/ml) *versus* time (hours) after administration for the formulations of Examples 8 -11 and the reference product.

Modes for Carrying Out the Invention

This invention will be further illustrated by the following Examples.

Example 1 (Comparative Example)

Preparation of tablet

A tablet formulation was prepared by blending the following tablet ingredients in the indicated proportions:

Ingredient	Weight %
Nifedipine	12.82
Methocel K15M	64.10
Avicel PH101	22.22
Magnesium stearate	0.86

The tablet blend was tabletted to a mean hardness of 55N in a Killian RTS tablet press. The *in vitro* dissolution for the tablets was determined in a USP Apparatus II (paddles) at 100 r.p.m. in 1.25%

SLS aqueous solution at pH 6.8 medium, at a volume of 900ml and a temperature of 37°C ± 0.5.

The following results were obtained:

Time(hours)	% Release
1.0	2.5
2.0	8.7
4.0	21.7
6.0	30.3
8.0	43.3
10.0	52.5
24.0	101.0

Example 2

Preparation of solid dispersion

Lutrol F127 (500g) was melted by heating to 80°C. Nifedipine (500g) was gradually added to, and dispersed in, the molten Lutrol. Mixing was continued for 2hr before the solid dispersion was allowed to cool at room temperature, followed by milling.

Preparation of tablet

A tablet formulation was prepared by blending the solid dispersion with the following tablet ingredients in the indicated proportions:

Ingredient	Weight %
Solid dispersion	23.43
Methocel K15M	56.30
Avicel PH101	19.52
Magnesium stearate	0.75

The tablet blend was tabletted to a mean hardness of 52N in a Killian RTS tablet press. The *in vitro* dissolution for the tablets was determined under the conditions as specified in Example 1. The following results were obtained:

Time(hours)	% Release
1.0	5.3
2.0	8.2
4.0	20.3
6.0	31.6
8.0	42.3
10.0	53.6
24.0	110.8

A comparison of the pharmacokinetic data for the formulations prepared in Examples 1 and 2 is shown in Table 1 and accompanying Fig. 1.

Table 1

Parameter	Example 1	Example 2
AUC*(0-24)	85.54 ± 54.12	153.10 ± 75.85
Cmax**	8.58 ± 4.32	16.10 ± 9.21
Tmax***	12.89 ± 9.05	12.78 ± 9.25

* Area under the plasma drug level *versus* time curve

** Maximum plasma concentration of drug attained

*** The time at which C max is attained

The effect of including the solid dispersion (Example 2) with the attendant increase in bioavailability is clear from a comparison of Example 1 (raw material alone) and Example 2.

Example 3

Preparation of solid dispersion

Lutrol F127 (1500g) was melted by heating to 80°C. Nifedipine (500g) was gradually added to, and dispersed in, the molten Lutrol. Mixing was continued for 2hr before the solid dispersion was allowed to cool at room temperature, followed by milling.

Preparation of tablet

A tablet formulation was prepared by blending the solid dispersion with the following tablet ingredients in the indicated proportions:

Ingredient	Weight %
Solid dispersion	35.29
Methocel K15M	30.00
Methocel K100LV	0.1
Avicel PH101	33.35
Magnesium stearate	0.86
Aerosil 200	0.4

The tablet blend was tabletted to a mean hardness of 73N on a Fette E1 tablet press. The *in vitro* dissolution for the tablets was determined under the conditions as specified in Example 1. The following results were obtained:

Time(hours)	% Release
1.0	9.8
2.0	19.3
4.0	41.7
6.0	55.8
8.0	67.5
10.0	77.3
12.0	88.6
24.0	103.9

Example 4

Preparation of solid dispersion

The solid dispersion corresponded to that prepared in Example 3.

Preparation of tablet

A tablet formulation was prepared by blending the solid dispersion with the following tablet ingredients in the indicated proportions:

Ingredient	Weight %
Solid dispersion	35.29
Methocel K15M	0.10
Methocel K100LV	40.00
Avicel PH101	23.35
Magnesium stearate	0.86
Aerosil 200	0.40

The tablet blend was tabletted to a mean hardness of 73N on a Fette E1 tablet press. The *in vitro* dissolution for the tablets was

determined under the conditions as specified in Example 1. The following results were obtained:

Time(hours)	% Release
1.0	22.2
2.0	38.5
4.0	67.9
6.0	92.1
8.0	103.1
10.0	105.6
12.0	105.5
24.0	106.2

A comparison of the pharmacokinetic data for the formulations prepared in Examples 3 and 4 is shown in Table 2 and accompanying Fig. 2.

Table 2

Parameter	Example 3	Example 4
AUCss	305.22 ± 132.25	321.34 ± 109.66
Cmax	23.38 ± 8.75	43.04 ± 15.40
Tmax	3.70 ± 2.63	2.75 ± 0.98

Example 3 which uses a high percentage of a high viscosity Methocel (relative to Example 4) shows a slower dissolution profile and consequently shows a flatter *in vivo* plasma profile, thus demonstrating the changes in profile that can be achieved with different grades of Methocel.

Example 5

Preparation of solid dispersion

Lutrol F127 (4500g) was melted by heating to 80°C. Nifedipine (1500g) was gradually added to, and dispersed in, the molten Lutrol. Mixing was continued for 2 hrs before the solid dispersion was allowed to cool at room temperature, followed by milling.

Preparation of tablet

A tablet formulation was prepared by blending a solid dispersion with the following tablet ingredients in the indicated proportions:

Ingredient	Weight %
Solid dispersion	35.29
Methocel K15M	15.00
Methocel K100LV	0.1
Avicel PH101	47.95
Magnesium stearate	0.86
Aerosil 200	0.8

The tablet blend was tabletted to a mean hardness of 90N on a Fette E1 tablet press. The *in vitro* dissolution for the tablets was determined under the conditions as specified in Example 1. The following results were obtained:

Time(hours)	% Release
1.0	15.7
2.0	40.0
4.0	63.9
6.0	81.7
8.0	103.8
10.0	109.9

A comparison of the pharmacokinetic data for the formulation prepared in Example 5 with a commercially available once-daily nifedipine tablet (hereinafter referred to as reference) is shown in Table 3 and accompanying Fig. 3.

Table 3

Parameter	Example 5	Reference
$AUC_{(0-36)}$	374.93 ± 107.68	376.24 ± 135.45
Cmax	39.25 ± 13.54	40.87 ± 15.09
Tmax	3.60 ± 1.43	3.45 ± 1.17
F % ****	1.04 ± 0.22	-

**** F % = ratio of Example relative to reference.

Example 6

Preparation of solid dispersion

Lutrol F127 (463 g) obtained from BASF (Ireland) Limited was melted by heating to 80°C. Cisapride (237 g) obtained from Janssen Pharmaceutica N.V., tartaric acid (150 g), obtained from R.B. Chemicals, and lactose (150 g) obtained from Forum Chemicals, were gradually added to, and dispersed in, the molten Lutrol. Mixing was continued for 0.5 hours until the last of the lactose had been added. The resulting solid dispersion was allowed to cool at room temperature, followed by milling thereof.

Preparation of tablet

A tablet formulation was prepared by blending the solid dispersion with the following tabletting ingredients in the indicated proportions:

Ingredient	Weight %
Solid dispersion	24.2
Methocel K15M	20.0
Avicel pH101	55.3
Magnesium stearate	0.5

The tablet blend was tabletted to a mean hardness of 129 N in a Killian RTS tablet press.

The *in vitro* dissolution for the tablets so prepared was determined using the standard U.S.P. apparatus II (paddles) operating at 50 r.p.m. using a 0.01 M HCl dissolution medium, volume 900 ml and temperature 37°C ± 0.5°C. At the indicated sampling times a 6.0 ml aliquot was removed and filtered through a 0.45 μm filter. A 4/10 dilution with 0.01 M HCl was performed and the absorbance at 270 nm measured against 0.01 M HCl. The following results were obtained:

Time (hours)	% Release
0.5	13.8
1.0	16.7
2.0	22.2
4.0	33.0
6.0	41.5
8.0	49.9
10.0	57.0
12.0	61.3
16.0	67.3
24.0	81.2

Plasma levels of cisapride achievable with the tablet formulation prepared above was assessed in 10 healthy male volunteer subjects. The results are shown in accompanying Fig. 4, wherein curve a) corresponds to the present Example.

Example 7

Preparation of solid dispersion

Lutrol F127 (463 g) was melted by heating to 80°C. Cisapride (237 g), tartaric acid (150 g), and lactose (150 g), were gradually added to, and dispersed in, the molten Lutrol. Mixing was continued for 0.5 hours until the last of the lactose had been added. The resulting solid dispersion was allowed to cool at room temperature, followed by milling thereof.

Preparation of tablet

A tablet formulation was prepared by blending the solid dispersion with the following tabletting ingredients in the indicated proportions:

Ingredient	Weight %
Solid dispersion	24.2
Methocel K100LV	40.0
Avicel pH101	35.3
Magnesium stearate	0.5

The tablet blend was tabletted to a mean hardness of 139 N in a Killian RTS tablet press.

The *in vitro* dissolution for the tablets so prepared was determined under the conditions specified in Example 6. The following results were obtained:

Time (hours)	% Release
0.5	8.4
1.0	12.0
2.0	21.3
4.0	43.4
6.0	54.1
8.0	70.5
10.0	87.6
12.0	98.7
16.0	108.3
24.0	112.5

Plasma levels of cisapride achievable with the tablet formulation prepared in accordance with the present Example was assessed in 10 healthy male volunteer subjects as before. The results are shown in Fig. 4, wherein curve b) corresponds to the present Example.

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In the *in vivo* studies based on the tablet formulations of Examples 6 and 7 each of 10 subjects received one 40 mg tablet once a day.

It will be clear from accompanying Fig. 4 that the tablet formulations of Examples 6 and 7 have an extended absorption and plasma level profile. Each product appears to show an absorption phase with an initial more rapid absorption rate (over the first 4 hours) and a slower absorption rate over the remaining 12-16 hours.

The main difference between the plasma level profile of the product of Example 6 relative to the product of Example 7 is that the latter product has a more dominant peak concentration (C max) while the former product has the more extended absorption and plasma level profile. The respective products, while sharing a common solid

dispersion formulation, do differ in release rate characteristics and in the viscosity grade of the cellulose-based polymer used to achieve rate control.

A summary of the pharmacokinetic parameters for the *in vivo* data for Examples 6 and 7 is shown in Table 4.

Table 4

Parameter	Example 6 (40 mg)	Example 7 (40 mg)
AUC (0-infinity) ngxh/ml	1148.10 ± 595.10	1125.85 ± 276.37
Cmax ng/ml	44.14 ± 16.01	55.71 ± 9.72
Tmax hours	7.30 ± 4.72	5.70 ± 3.83
Kel***** 1/hour	0.082 ± 0.027	0.079 ± 0.023
T1/2****** hours	9.24 ± 2.78	9.78 ± 4.13

***** The elimination rate constant

****** The half-life of the drug in the plasma.

Example 8

Preparation of solid dispersion

Lutrol F68 (2087.4g) was melted by heating to 80°C. Cisapride (522.4g) and tartaric acid (391.4g) were gradually added to, and