AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/25/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	SANDOZ INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,791,270	7/29/2014	CEPHALON, INC.
2			
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In the above entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/25/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	AGILA SPECIALTIES INC. f/k/a STRIDES, INC., and ONCO THERAPIES LIMITED

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,791,270	7/29/2014	CEPHALON, INC.
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In the above entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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DECISION/JUDGEMENT

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In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/25/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	INNOPHARMA, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,791,270	7/29/2014	CEPHALON, INC.
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In the above entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13-2046-GMS	12/19/2013	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	HETERO LABS LTD. and HETERO USA, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY			
11/6/2014	☑ Amendment	☐ Answer	☐ Cross Bill	☐ Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 8,791,270 B2	7/29/2014	Cephalon, Inc.
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
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AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/21/2014	District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	WOCKHARDT BIO LTD., WOCKHARDT LTD., and WOCKHARDT USA, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,445,524 B2	5/21/2013	Cephalon, Inc.
2	US 8,436,190 B2	5/7/2013	Cephalon, Inc.
3	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
4	US 8,791,270 B2	7/29/2014	Cephalon, Inc.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313-1450**	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/2/2014	District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	NANG KUANG PHARMACEUTICAL CO., LTD. and CANDA NK-1, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,445,524 B2	5/21/2013	Cephalon, Inc.
2	US 8,436,190 B2	5/7/2013	Cephalon, Inc.
3	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
4	US 8,791,270 B2	7/29/2014	Cephalon, Inc.
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Dismissed Voluntarily — See Attached

CLERK	(BY) DEPUTY CLERK	DATE
~~John A Cerino, Clerk~~ United States District Court 844 N. King Street, Unit 18 ~~Wilmington, DE 19801~~		10/3/14

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13-2095-GMS	9/18/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	ACCORD HEALTHCARE, INC. and INTAS PHARMACEUTICALS LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,445,524	5/21/2013	CEPHALON, INC.
2	8,436,190	5/7/2013	CEPHALON, INC.
3	8,609,863	12/17/2013	CEPHALON, INC.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 8,791,270	7/29/2014	CEPHALON, INC.
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DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/2/2014	District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	SAGENT PHARMACEUTICALS, INC. and SAGENT AGILA LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,445,524 B2	5/21/2013	Cephalon, Inc.
2	US 8,436,190 B2	5/7/2013	Cephalon, Inc.
3	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
4	US 8,791,270 B2	7/29/2014	Cephalon, Inc.
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	9/2/2014	District of Delaware

PLAINTIFF	DEFENDANT
CEPHALON, INC.	NANG KUANG PHARMACEUTICAL CO., LTD. and CANDA NK-1, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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2	US 8,436,190 B2	5/7/2013	Cephalon, Inc.
3	US 8,609,863 B2	12/17/2013	Cephalon, Inc.
4	US 8,791,270 B2	7/29/2014	Cephalon, Inc.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

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Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/969,724	07/29/2014	8791270	102085.004604	6392

46347 7590 07/09/2014

Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Cephalon, Inc., Frazer, PA, Assignee (with 37 CFR 1.172 Interest);
Jason Edward Brittain, El Cajon, CA;
Joe Craig Franklin, Tulsa, OK, Deceased;

Substitute for Form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
				Examiner Name	Soroush, Ali
Sheet	2	of	8	**Attorney Docket Number**	CEPH-4604/CP391D US

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/A.S./	**25**	5,130,305 A	07-14-1992	Palepu et al.
	26	5,183,746 A	02-02-1993	Shaked et al.
	27	5,192,743 A	03-09-1993	Hsu et al.
	28	5,204,335 A	04-20-1993	Sauerbier et al.
	29	5,227,373 A	07-13-1993	Alexander et al.
	30	5,227,374 A	07-13-1993	Alexander et al.
	31	5,268,368 A	12-07-1993	Palepu
	32	5,413,995 A	05-09-1995	Alexander et al.
	33	5,418,223 A	05-23-1995	Palepu et al.
	34	5,750,131 A	05-12-1998	Wichert et al.
	35	5,770,230 A	06-23-1998	Teagarden et al.
	36	5,776,456 A	07-07-1998	Anderson et al.
	37	5,955,504 A	09-21-1999	Wechter et al.
	38	5,972,912 A	10-26-1999	Marek et al.
	39	6,034,256 A	03-07-2000	~~Maeferrer~~ Carter et al.
	40	6,077,850 A	06-20-2000	~~Maeferrer~~ Carter et al.
	41	6,090,365 A	07-18-2000	Kaminski et al.
	42	6,271,253 B1	08-07-2001	~~Maeferrer~~ Carter et al.
	43	6,380,210 B1	04-30-2002	Desimone et al.
	44	6,492,390 B2	12-12-2002	~~Maeferrer~~ Carter et al.
	45	6,545,034 B1	04-08-2003	Carson et al.
	46	6,569,402 B1	05-27-2003	Cheesman et al.
	47	6,573,292 B1	06-03-2003	Nardella
	48	6,613,927 B1	09-02-2003	Kwok

Change(s) applied to document.
/G.R.P./
6/25/2014

Examiner Signature	/Ali Soroush/	**Date Considered**	06/01/2014

Substitute for Form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
				Examiner Name	Soroush, Ali
Sheet	1	of	8	**Attorney Docket Number**	CEPH-4604/CP391D US

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/A.S./	**1**	2002/0102215 A1	08-01-2002	Klaveness et al.
	2	2003/0232874 A1	12-18-2003	Nardella
	3	2004/0053972 A1	03-18-2004	Nara
	4	2004/0058956 A1	03-25-2004	Akiyama et al.
	5	2004/0072889 A1	04-15-2004	Masferrer
	6	2004/0096436 A1	05-20-2004	Carson et al.
	7	2004/0152672 A1	08-05-2004	Carson et al.
	8	2004/0247600 A1	12-09-2004	Leoni
	9	2005/0020615 A1	01-27-2005	Rubino
	10	2005/0060028 A1	03-17-2005	Horres et al.
	11	2005/0176678 A1	08-11-2005	Horres et al.
	12	2006/0051412 A1	03-09-2006	Petereit et al.
	13	2006/0128777 A1	06-15-2006	Bendall et al.
	14	2009/0264488 A1	10-22-2009	Cooper et al.
	15	2011/0190363 A1	08-04-2011	Drager et al.
	16	2012/0071532 A1	03-22-2012	Cooper et al.
Change(s) applied to document, /G.R.P./ 6/25/2014	**17**	2013/0041003 A1	02-14-2013	~~Cephalon, Inc.~~ Brittain et al.
	18	2013/0123316 A1	05-16-2013	Brittain
	19	3,590,028 A	06-29-1971	Report et al.
	20	4,012,448 A	03-15-1977	Smith et al.
	21	4,537,883 A	08-27-1985	Alexander et al.
	22	4,659,699 A	04-21-1987	Francis
	23	4,670,262 A	06-02-1987	Battelli et al.
	24	5,066,647 A	11-19-1991	Palepu et al.

Examiner Signature	/Ali Soroush/	**Date Considered**	06/01/2014

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

46347 7590 06/09/2014
Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/969,724	08/19/2013	Jason Edward Brittain	102085.004604	6392

TITLE OF INVENTION: BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/09/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, ALI	1617	548-304700

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Baker & Hostetler LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: CEPHALON, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): FRAZER, PENNSYLVANIA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 23-3050 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Stephanie A. Lodise/ Date June 12, 2014

Typed or printed name Stephanie A. Lodise Registration No. 51430

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	13969724
Filing Date:	19-Aug-2013
Title of Invention:	BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Jason Edward Brittain
Filer:	Stephanie A. Lodise/Lillian Schultz
Attorney Docket Number:	102085.004604

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	19289602
Application Number:	13969724
International Application Number:	
Confirmation Number:	6392
Title of Invention:	BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Lodise/Lillian Schultz
Filer Authorized By:	Stephanie A. Lodise
Attorney Docket Number:	102085.004604
Receipt Date:	12-JUN-2014
Filing Date:	19-AUG-2013
Time Stamp:	16:05:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$960
RAM confirmation Number	3433
Deposit Account	233050
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Issue_fee_transmittal.PDF	95714 e3cd2bbabd345f6617eca8ff1e7acf801cd14eaa	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30432 10811b2782fd11d647631802e5713e1f867ff6a9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	126146		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

46347 7590 06/09/2014

Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

EXAMINER
SOROUSH, ALI

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/09/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/969,724	08/19/2013	Jason Edward Brittain	102085.004604	6392

TITLE OF INVENTION: BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/09/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

46347 7590 06/09/2014
Baker & Hostetler LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/969,724	08/19/2013	Jason Edward Brittain	102085.004604	6392

TITLE OF INVENTION: BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/09/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
SOROUSH, ALI	1617	548-304700

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/969,724	08/19/2013	Jason Edward Brittain	102085.004604	6392

46347 7590 06/09/2014

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CIRA CENTRE, 12TH FLOOR
2929 ARCH STRET
PHILADELPHIA, PA 19104-2891

EXAMINER	
SOROUSH, ALI	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 06/09/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 12 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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.

Notice of Allowability	Application No. 13/969,724	Applicant(s) BRITTAIN ET AL.	
	Examiner ALI SOROUSH	Art Unit 1617	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the response filed 01/29/2014*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-6 and 11-27*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 12182013, 02172014, 04072014, 05082014
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions.

Acknowledgement of Receipt

Applicant's response filed on 01/29/2014 to the Office Action mailed on 12/30/2013 is acknowledged.

Claim Status

Claims 1-6 and 11-27 are pending.

Claims 7-10 are cancelled.

Claims 18-27 are newly added.

Claims 1-6 and 11-27 have been examined.

Claims 1-6 and 11-27 are allowed.

Election/Restrictions

Applicant's election without traverse of Group III (claims 1-6 and 11-27) in the reply filed on 01/29/2014 is acknowledged.

Priority

Priority to CON 13/719409 filed 12/19/2012, which claims priority to CON 13/654898 filed on 10/18/2012 and CON 11/330868 filed on 01/12/2006, which claims priority to application 60/644354 filed on 01/14/2005 is acknowledged.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 12/18/2013, 02/17/2014, 04/07/2014, and 05/08/2014 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: the prior art teaches a formulation of bendamustine and mannitol to be lyophilized. The prior art also teach a combination of mannitol, tertiary-butyl alcohol, water, and an anti-neoplastic agent can be lyophilized. The prior art suggests using a combination of mannitol and tertiary-butyl alcohol with bendamustine to produce a formulation to be lyophilized. However, Applicant has unexpectedly found that the addition of a solvent stabilizes the formulation such that bendamustine degradation is negligible (no more than 0.5% formation of bendamustine ethyl ester). Therefore, claims 1-6 and 11-27 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 1-6 and 11-27 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALI SOROUSH whose telephone number is (571)272-9925. The examiner can normally be reached on M, W-F (9am-7:30pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571)272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ALI SOROUSH/
Primary Examiner, Art Unit 1617

June 1, 2014

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13969724	BRITTAIN ET AL.
	Examiner	Art Unit
	ALI SOROUSH	1617

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
34	284	06/01/2014	AS
EAST	304.7	06/01/2014	AS

SEARCH NOTES		
Search Notes	Date	Examiner
see search history printouts	06/01/2014	AS
Inventor/Assigness search EAST/PALM (Jason Edward Brittain, Joe Craig Franklin, Cephalon Inc.)	06/01/2014	AS

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
34	284	06/01/2014	AS
548	304.7	06/01/2014	AS

/ALI SOROUSH/ Primary Examiner.Art Unit 1617	

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13969724	BRITTAIN ET AL.
	Examiner	**Art Unit**
	ALI SOROUSH	1617

CPC						
Symbol					**Type**	**Version**
A61K		47	/	10	I	2013-01-01
A61K		31	/	4184	I	2013-01-01
A61K		9	/	19	F	2013-01-01
A61K		9	/	0019	I	2013-01-01
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NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 23	
/ALI SOROUSH/ Primary Examiner.Art Unit 1617 (Primary Examiner)	06/01/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13969724	BRITTAIN ET AL.
	Examiner	**Art Unit**
	ALI SOROUSH	1617

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
548	304.7	C	0	7	D	235 / 04 (2006.01.01)						

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
34	284				

NONE	Total Claims Allowed:	
(Assistant Examiner) (Date)	23	
/ALI SOROUSH/ Primary Examiner.Art Unit 1617 06/01/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner) (Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13969724	BRITTAIN ET AL.
	Examiner	**Art Unit**
	ALI SOROUSH	1617

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	17	21												
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NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 23	
/ALI SOROUSH/ Primary Examiner.Art Unit 1617 (Primary Examiner)	06/01/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Substitute for Form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Brittain et al.
				Art Unit	1617
				Examiner Name	Ali Soroush
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Examiner Signature	/Ali Soroush/	**Date Considered**	06/01/2014

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3	"8461350".pn. "8436190".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/06/01 17:41
L2	1	13/719409.app.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/06/01 17:42
L3	808	548/304.7.ccls. 34/285.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2014/06/01 17:56

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				Examiner Name	Soroush, Ali
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				Art Unit	1617
				Examiner Name	Soroush, Ali
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				Art Unit	1617
				Examiner Name	Soroush, Ali
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Substitute for Form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/969,724
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(use as many sheets as necessary)				**Examiner Name**	Soroush, Ali
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				Examiner Name	Soroush, Ali
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				Examiner Name	Soroush, Ali
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Examiner Signature	/Ali Soroush/	**Date Considered**	06/01/2014

Substitute for Form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
				Examiner Name	Soroush, Ali
Sheet	7	of	8	**Attorney Docket Number**	CEPH-4604/CP391D US

NON PATENT LITERATURE DOCUMENTS			
/A.S./	**107**	Weide et al., "Bendamustine/Mitoxantrone/Rituximab (BMR): A Very Effective, Well Tolerated Outpatient Chemoimmunotherapy for Relapsed and Refractory CD20-positive Indolent Malignancies. Final Results of a Pilot Study", Leukemia & Lymphoma, December 2004, 45(12), 2445-2449	
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Examiner Signature	/Ali Soroush/	**Date Considered**	06/01/2014

Substitute for Form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
				Examiner Name	Soroush, Ali
Sheet	8	of	8	**Attorney Docket Number**	CEPH-4604/CP391D US

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/A.S./	**121**	Teagarden et al., "Practical Aspects Of Lyophilization Using Non-Aqueous Co-Solvent Systems," European Journal of Pharmaceutical Sciences, March 2002, 15(2), 115-133	
/A.S./	**122**	Wittaya-Areekul et al., "Freeze-Drying Of Tert-Butyl Alcohol/Water Cosolvent Systems: Effects Of Formulation And Process Variables On Residual Solvents," Journal of Pharmaceutical Sciences, April 1998, 87(4), 491-495	

Examiner Signature	/Ali Soroush/	**Date Considered**	06/01/2014

Substitute for Form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Brittain et al.
				Art Unit	1617
(use as many sheets as necessary)				**Examiner Name**	Ali Soroush
Sheet	1	of	1	**Attorney Docket Number**	102085.004604

U. S. PUBLICATION AND PATENT DOCUMENTS				
Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	1	2002/0031527 A1	03-14-2002	Wu et al.

Examiner Signature		**Date Considered**	

Electronic Acknowledgement Receipt

EFS ID:	18975078
Application Number:	13969724
International Application Number:	
Confirmation Number:	6392
Title of Invention:	BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Lodise/Danielle Langdon
Filer Authorized By:	Stephanie A. Lodise
Attorney Docket Number:	102085.004604
Receipt Date:	08-MAY-2014
Filing Date:	19-AUG-2013
Time Stamp:	10:40:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	102085_004604_SIDS_TRANS.PDF	103400 37d23ae4f270b1d57219b363ee2ab9c4ba4f481a	no	4

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Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	102085_004604_SIDS_1449.PDF	116064 f25100acb953923be715f0268176f75ef81838d2	no	1

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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.

DOCKET NO.: 102085.004604 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Brittain et al. **Confirmation No.: 6392**

Application No.: 13/969,724 **Group Art Unit: 1617**

Filing Date: August 19, 2013 **Examiner: Ali Soroush**

For: BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

Filed Via EFS

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR § 1.56 and in accordance with 37 CFR §§ 1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 CFR § 1.56(b).

☒ **IDS Filed Under 37 CFR 1.97(b)**

In accordance with § 1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in § 1.491, before the mailing date of a first Office Action on the merits of the above-identified application, or before the mailing date of a first Office Action after the filing of request for continued examination under § 1.114, no additional fee is required.

☐ **IDS filed Under 37 CFR 1.97(c)**

In accordance with § 1.97(c), this Information Disclosure Statement is being filed after the period set forth in § 1.97(b) above but before the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311, or before an action that otherwise closes prosecution in the application, therefore:

☐ Certification in Accordance with § 1.97(e) is attached; or

☐ The fee of ☐ **$180.00** (Undiscounted)

☐ **$90.00** (Small entity)

☐ **$45.00** (Micro entity) as set forth in § 1.17(p) is attached.

☐ **IDS filed Under 37 CFR 1.97(d)**

In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission of ☐ **$180.00** (Undiscounted) ☐ **$90.00** (Small entity) ☐ **$45.00** (Micro entity) as set forth in § 1.17(p).

CONTENT OF IDS PURSUANT TO 37 CFR 1.98

☒ A copy of reference number 1 listed on the attached Form 1449/PTO or Substitute for Form 1449/PTO is not required to be submitted pursuant to 37 CFR § 1.98(a)(2)(iii).

☐ Copies of reference numbers listed on the attached Form 1449/PTO or Substitute for Form 1449/PTO are enclosed herewith.

☐ Copies of reference numbers are not being submitted because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application number , filed for which a claim for priority under 35 U.S.C. § 120 has been made in the instant application.

☐ The month of publication for reference numbers is not available. However, the year of publication for these references is sufficiently earlier than the effective US filing date and any foreign priority date so that the particular month of publication is not in issue pursuant to 37 CFR § 1.98(b).

REFERENCES IN A LANGUAGE OTHER THAN ENGLISH

☐ The following documents are not in the English language. Accordingly, a concise explanation of the relevance of the document was incorporated in the specification passages identified below, the document was identified in a foreign communication as identified below or an English language counterpart application has been provided as indicated below.

Foreign Language Document	Cite No.	Pages of Reference in Specification or Relevance of Document

Foreign Language Document	Cite No.	English Language Counterpart	Cite No.

☐ **CERTIFICATION IN ACCORDANCE WITH § 1.97(e)**

I hereby certify that:

☐ Each item of information contained in this information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

☐ No item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in this information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this information disclosure statement.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: May 8, 2014

/Stephanie A. Lodise/
Stephanie A. Lodise
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Substitute for Form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Brittain et al.
				Art Unit	1617
(use as many sheets as necessary)				**Examiner Name**	Ali Soroush
Sheet	1	of	1	**Attorney Docket Number**	102085.004604

U. S. PUBLICATION AND PATENT DOCUMENTS				
Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	1	8,420,130 B1	04-16-2013	Nuijen et al.

Examiner Signature		**Date Considered**	

Electronic Acknowledgement Receipt

EFS ID:	18689011
Application Number:	13969724
International Application Number:	
Confirmation Number:	6392
Title of Invention:	BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Lodise/Danielle Langdon
Filer Authorized By:	Stephanie A. Lodise
Attorney Docket Number:	102085.004604
Receipt Date:	07-APR-2014
Filing Date:	19-AUG-2013
Time Stamp:	13:43:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	102085_004604_SIDS_Trans.PDF	104133 9f1ebf21b3f912882c5bd42c0c85e0557c21af00	no	4

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	102085_004604_SIDS_1449.PDF	115827 16b87286554249681ec01dcf7ef4d3870c0e09cf	no	1

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New Applications Under 35 U.S.C. 111
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New International Application Filed with the USPTO as a Receiving Office
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DOCKET NO.: 102085.004604 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Jason Edward Brittain **Confirmation No.: 6392**

Application No.: 13/969,724 **Group Art Unit: 1617**

Filing Date: August 19, 2013 **Examiner: Soroush, Ali**

For: BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS

Filed Via EFS

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 CFR § 1.56 and in accordance with 37 CFR §§ 1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 CFR § 1.56(b).

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☐ **IDS filed Under 37 CFR 1.97(c)**

In accordance with § 1.97(c), this Information Disclosure Statement is being filed after the period set forth in § 1.97(b) above but before the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311, or before an action that otherwise closes prosecution in the application, therefore:

☐ Certification in Accordance with § 1.97(e) is attached; or

☐ The fee of ☐ **$180.00** (Undiscounted)

☐ **$90.00** (Small entity)

☐ **$45.00** (Micro entity) as set forth in § 1.17(p) is attached.

☐ **IDS filed Under 37 CFR 1.97(d)**

In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission of ☐ **$180.00** (Undiscounted) ☐ **$90.00** (Small entity) ☐ **$45.00** (Micro entity) as set forth in § 1.17(p).

CONTENT OF IDS PURSUANT TO 37 CFR 1.98

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REFERENCES IN A LANGUAGE OTHER THAN ENGLISH

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Foreign Language Document	Cite No.	English Language Counterpart	Cite No.

☐ **CERTIFICATION IN ACCORDANCE WITH § 1.97(e)**

I hereby certify that:

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☐ No item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in this information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this information disclosure statement.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: April 7, 2014

/Stephanie A. Lodise/
Stephanie A. Lodise
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Substitute for Form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
(use as many sheets as necessary)				**Examiner Name**	Soroush, Ali
Sheet	1	of	3	**Attorney Docket Number**	102085.004604

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	123	4,959,215 A	09-25-1990	Sauerbier et al
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Examiner Initials	Cite No.	Foreign Patent Document Country Code- Number -Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T
	126	DE 3907079	09-28-1989	ASTA PHARMA AG	X
	127	EP 334083 A1	09-27-1989	ASTA PHARMA AG	
	128	WO 2003/077882 A2	09-27-2003	LABOPHARM INC	
	129	WO 2004/041118 A2	05-21-2004	UMD, INC	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.	Include name of the author, title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), Volume-issue Number(s), publisher, city and/or country where published.	T
	130	Avis et al., "Pharmaceutical Dosage Forms: Parenteral Medications Volume 1" Marcel Dekker Inc, 1992, pp 217-227	
	131	Excerpt from Rote Liste 2003, Arzneimittelverzeichnis fur Deutschland, 2 pages	
	132	Flamberg, et al., "Low Temperature Vacuum Drying of Sterile Parenterals from Ethanol" Bulletin of the Parenteral Drug Association, September-October 1970, 24(5), 209-217	
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	134	Gandhi et al., "Bendamustine in B Cell Malignancies: The New, 46-year old kid on the Block" Clinical Cancer Research, December 2009, 15(24), 7456-7461	
	135	Jennings,Thomas A., “Extracts from "Lyophilization. Introduction and Basic Principles". 2002, by CRC Press LLC, Boca Raton, Florida, 33431	

Examiner Signature		**Date Considered**	

Substitute for Form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	13/969,724
				Filing Date	August 19, 2013
				First Named Inventor	Jason Edward Brittain
				Art Unit	1617
(use as many sheets as necessary)				**Examiner Name**	Soroush, Ali
Sheet	2	of	3	**Attorney Docket Number**	102085.004604

NON PATENT LITERATURE DOCUMENTS			
	136	Jonkmann-de Vries et al., "Pharmaceutical Development of (Investigational) Anticancer Agents for Parenteral Use-A Review Drug Development and Industrial Pharmacy", 1996, 22(6), 475-494	
	137	Kasraian et al., "The Effect Of Tertiary Butyl Alcohol On The Resistance Of The Dry Product Layer During Primary Drying", 1995, Pharm. Res, 12(4), 491-495, hier: Zusammenfassung	
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Substitute for Form 1449/PTO				*Complete if Known*	
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Espacenet

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Ifosfamide/mesna lyophilisate and process for its production

No documents available for this priority number.

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Abstract of DE3907079 (A1)

Ifosfamide/mesna lyophilisate essentially consisting of ifosfamide, 0.1-1.0 parts by weight of mesna and 0.1 to 17 parts by weight of hexitol.

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(54) Ifosfamid-Mesna-Lyophilisat und Verfahren zu dessen Herstellung

Ifosfamid-Mesna-Lyophilisat, bestehend im wesentlichen aus Ifosfamid, 0,1-1,0 Gewichtsteilen Mesna und 0,1 bis 17 Gewichtsteilen Hexit.

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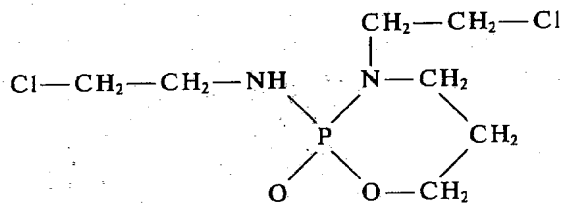
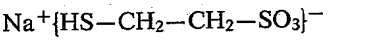
Beschreibung

Der chemische Name für den Wirkstoff Ifosfamid ist 3-(2-Chlorethyl)-2-(chlorethylamino)-tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxid



Ifosfamid gehört wie Cyclophosphamid zur chemischen Gruppe der Oxazaphosphorine und wird therapeutisch zur Behandlung von Tumor-Erkrankungen eingesetzt.

Der chemische Name für den Uroprotektor Mesna ist Natrium-2-mercaptoethansulfonat



Mesna schützt beispielsweise die harnableitenden Organe bei der Therapie von Tumor-Erkrankungen mit Ifosfamid, wobei diese uroprotektive Wirkung von Mesna insbesondere bei gleichzeitiger und synchroner Verabreichung zusammen mit dem Ifosfamid gegeben ist.

Ifosfamid ist ein weißes, kristallines Pulver mit einem Schmelzpunkt von 48° C bis 51° C und stark hygroskopischen Eigenschaften. Bereits unterhalb des Schmelzpunktes beginnt Ifosfamid zu sintern; es muß deshalb bei möglichst niedrigen Temperaturen (Raumtemperatur und darunter) gelagert werden. Außerdem ist ein Kontakt mit Luftfeuchtigkeit möglichst zu vermeiden.

Ifosfamid löst sich zu etwa 10 Gewichtsprozent in Wasser, ist aber in wäßriger Lösung nur begrenzt haltbar (maximal 3 bis 4 Stunden bei 20° C bis 22° C beziehungsweise 36 Stunden bei 4 bis 6° C).

Ifosfamid wird ausschließlich parenteral appliziert. Die Injektionsflaschen enthalten 200 bis 5000 mg Ifosfamid in Form eines Sterilkristallisats, das vor der Applikation in Wasser für Injektionszwecke gelöst wird, so daß eine 4%ige Konzentration nicht überschritten wird. Diese Lösung ist zur intravenösen Injektion geeignet. Zur intravenösen Kurzinfusion wird die Ifosfamid-Lösung in 500 ml Ringer-Lösung oder ähnlichen Infusionsflüssigkeiten aufgelöst. Die Infusionsdauer beträgt ca. 30 Minuten, eventuell 1 bis 2 Stunden. Bei der 24-Stunden-Infusion wird die Ifosfamid-Lösung beispielsweise in insgesamt 3 Liter 5% Dextrose-Kochsalzlösung aufgelöst.

Ifosfamid verursacht bei der Herstellung und Verarbeitung mannigfaltige Probleme. Bei der Herstellung des steril kristallisierten Ifosfamids resultiert ein Produkt von wechselnder physikalischer Beschaffenheit. Durch die unterschiedliche Rieselfähigkeit wird insbesondere die Dosierungsgenauigkeit bei der Abfüllung in hohem Maße beeinträchtigt.

Die Verarbeitung des Ifosfamids wird weiterhin erschwert durch seine Hygroskopizität und den niedrigen Schmelzpunkt. Bei längerer Lagerung sintert das Sterilkristallisat und die Lösungsgeschwindigkeit vermindert sich. Mit beginnender Sinterung des Ifosfamids nehmen auch die Klarlöslichkeit und der pH-Wert der Lösung bei gleichzeitiger Gelbfärbung ab; eine therapeutische Verwendung ist dann im allgemeinen nicht mehr möglich.

Mesna ist ebenfalls eine Substanz, die nur unter besonderen Bedingungen stabil und haltbar ist.

Eine Kombinationsmöglichkeit aus Ifosfamid und Mesna, welches einen großen Vorteil hinsichtlich Lagerung und praktischer Handhabung darstellen würde, existiert bis jetzt nicht.

Aufgabe der Erfindung ist es daher, Ifosfamid und Mesna in einer Form mit verbesserten Eigenschaften, wie verbesserte pharmazeutische Qualität, Dosierbarkeit und Löslichkeit, bereitzustellen, die leichter anzuwenden ist, und insbesondere zur Herstellung von injizierbaren Lösungen geeignet ist.

Es wurde nun überraschend gefunden, daß die bisherigen Nachteile und Schwierigkeiten bei der Handhabung und Lagerung von Ifosfamid und Mesna durch Verwendung eines bestimmten Ifosfamid-Mesna-Lyophilisats behoben werden können. Insbesondere ist es überraschend, daß das erfindungsgemäße Lyophilisat eine größere Thermostabilität des Ifosfamids besitzt als die bislang verwendete Ifosfamid-Trockenabfüllung.

Trockenabfüllungen mit Ifosfamid sind bei 40° C bereits nach einer Lagerzeit von 1 Monat nachgedunkelt; nach 2 Monaten ist der Flascheninhalt gesintert und gelb verfärbt. Bei einer Lagerungstemperatur von 55° C ist das trocken abgefüllte Ifosfamid bereits innerhalb von 4 Tagen geschmolzen.

Demgegenüber ist bei erfindungsgemäß hergestellten Lyophilisat unter den vorgenannten Lagerbedingungen weder eine Verfärbung noch eine Veränderung der Konsistenz des Ifosfamids erkennbar. Ebenfalls zeigen sich keine Veränderungen bei dem Mesna.

Die Lösungsgeschwindigkeit des Ifosfamid-Mesna-Lyophilisats ist gegenüber der Ifosfamid-Trockenabfüllung deutlich erhöht. Während sich das Lyophilisat unabhängig von der Lagerdauer bei der Zugabe des Lösungsmittels sofort löst, müssen die Injektionsflaschen mit der Trockenabfüllung nach Einspritzen des Lösungsmittels $^1/_2$ bis 3 Minuten kräftig geschüttelt werden. Wenn hierbei die Auflösung nicht sofort restlos erfolgt, und dies ist bei länger gelagerten Injektionsflaschen der Fall, ist es sogar erforderlich, die Lösung einige Minuten stehen zu lassen. Die Anwendung des Präparates in der Klinik wird dadurch erschwert.

Ifosfamid-Mesna-Lyophilisat zeigt im Gegensatz zu Sterilkristallisat auch nach der Lagerung von mehreren Jahren noch optimale Lösungseigenschaften. Außerdem ist die Ifosfamid-Trockenabfüllung (das heißt das reine Ifosfamid-Kristallisat) viel empfindlicher gegen Luftfeuchtigkeit als das Lyophilisat. So verflüssigt sich die

Ifosfamid-Trockenabfüllung bereits bei einer relativen Luftfeuchtigkeit von unter 75%, während das Lyophilisat selbst bei 100% relativer Luftfeuchtigkeit zwar feucht wird, aber seine äußere Form behält.

Bei der Abfüllung des Sterilkristallisats ist ferner die Gefahr einer partikulären oder mikrobiellen Kontamination in wesentlich stärkerem Maße als beim Lyophilisat gegeben.

Bei der Herstellung des Ifosfamid-Mesna-Lyophilisats erfolgt die Sterilfiltration der Lösung hingegen erst unmittelbar vor der Abfüllung in die Injektionsflaschen. Dadurch ist gegenüber der Abfüllung von Sterilkristallisat eine größere mikrobiologische Sicherheit gegeben. Auch partikuläre Verunreinigungen, die bei der Trockenabfüllung gelegentlich Anlaß zu Beanstandungen geben, lassen sich durch die Filtration der Lösung mit größerer Sicherheit vermeiden.

Die Lyophilisation des Ifosfamids in Kombination mit Mesna führt jedoch nicht nur zu einer Produktverbesserung, sondern ist in der Herstellung und praktischen Anwendung auch wirtschaftlicher als die getrennte Herstellung von Sterilkristallisat und Mesna-Injektionslösung.

Darüber hinaus besitzt die erfindungsgemäße Kombination auch bei der Anwendung eine überraschende bessere Wirkung als die bisherige getrennte Applikation von Ifosfamid und Mesna:
So erfolgt beispielsweise bei der erfindungsgemäßen Kombination bei intravenöser, kontinuierlicher Infusion (zum Beispiel in der Zusammensetzung 5,0 g Ifosfamid + 2,0 g Mesna) eine kontinuierliche Uroprotektion, und zwar durch die gleichzeitige kontinuierliche renale Elimination von urotoxischen Metaboliten und Mesna. Dadurch wird der uroprotektionsmindernde Effekt einer Blasenentleerung minimiert. Die fixe Dosisrelation von Ifosfamid und Mesna im Lyophilisat vermeidet bei dem Einsatz als kontinuierliche intravenöse Infusion (zum Beispiel 5 g Ifosfamid + 2 g Mesna über 6 Stunden oder 10 g Ifosfamid + 4 g Mesna über 24 Stunden kontinuierlich infundiert) eine unzureichende Uroprotektion, wie sie durch wiederholte Bolusinjektionen von Mesna oder auch eine zu niedrige Infusionsdosis auftreten kann. Der Einsatz des Kombinationslyophilisats als Kurzzeitinfusion über 30 Minuten bis zu 2 Stunden in den Mengen von beispielsweise 500 mg bis 5 g Ifosfamid zusammen mit 20% der Ifosfamid-Menge als Mesna garantiert eine ausreichende Uroprotektion in den ersten 4 Stunden. Bevorzugte Dosierungen für die Anwendung am Menschen sind zum Beispiel:

0,5 g Ifosfamid + 0,1 g Mesna
1 g Ifosfamid + 0,2 g Mesna
2 g Ifosfamid + 0,4 g Mesna
5 g Ifosfamid + 1,0 g Mesna
5 g Ifosfamid + 2,0 g Mesna

Es hat sich gezeigt, daß nur das erfindungsgemäße Verfahren unter Verwendung eines Hexits, wie zum Beispiel Mannit, ein verbessertes Ifosfamid-Mesna-Lyophilisat ergibt. Beispielsweise konnte durch Beimischung von Kochsalz, wie sie bei Trockenabfüllungen von anderen Oxazaphosphorinen üblich ist, kein Lyophilisat erhalten werden.

Erfindungsgemäß wird beispielsweise eine wäßrige Lösung, die 1—13 Gewichtsprozent an Ifosfamid und 0,05—13 Gewichtsteile Mesna enthält, sowie als Gerüstbildner 0,1—17 Gewichtsteile Hexit, bezogen auf einen Gewichtsteil Ifosfamid, gefriergetrocknet. Vorzugsweise enthält diese wäßrige Lösung 5—12 Gewichtsprozent Ifosfamid und 0,5—12 Gewichtsprozent Mesna, insbesondere 8—10 Gewichtsprozent Ifosfamid und 0,8—10 Gewichtsprozent Mesna.

Es können auch entsprechende Ethanol-Wasser-Lösungen von Ifosfamid und Mesna anstelle einer reinen wäßrigen Lösung verwendet werden (Ethanolanteil einer solchen Lösung bis zu 45% m/m (Definition gemäß Deutsches Arzneibuch 9. Ausgabe: Prozent Masse in Masse), beispielsweise 1—20% Ethanol). In solchen Fällen wird möglichst zuerst das Ethanol vorzeitig im Vacuum entfernt, bevor das restliche Eis sublimiert wird. Die Bedingungen für die zuerst erfolgte Ethanolentfernung sind zum Beispiel: Druck $5-10^{-1}$ mbar, Temperatur von —25° C auf —5° C steigend innerhalb von 10 Stunden, anschließend wird die Temperatur der Stellplatten auf 15° C erhöht. Im einzelnen hängen diese Bedingungen auch von den unterschiedlichen Schichthöhen des zu trocknenden Gutes in den Injektionsflaschen ab und sind entsprechend zu variieren.

Die Menge an Hexit in dieser wäßrigen beziehungsweise wäßrig-ethanolischen Lösung beträgt im allgemeinen 1—17, vorzugsweise 3—12, insbesondere 5—9 Gewichtsprozent. Bezieht man die Hexit-Menge auf einen Gewichtsteil Ifosfamid, dann ist die Hexit-Menge 0,1—17, vorzugsweise 1 bis 2,5 insbesondere 0,6—0,8 Gewichtsteile Hexit pro 1 Gewichtsteil Ifosfamid. Bezogen auf 1 Gewichtsteil Mesna beträgt die Hexit-Menge zum Beispiel 0,1—17, vorzugsweise 1—6, insbesondere 3—4 Gewichtsteile.

Als Hexit kommen in Frage: Mannit, Glucit (Sorbit, wie D-Sorbit), Dulcit, Allit, Altrit (z. B. D- und L-Altrit), Idit (z. B. D- und L-Idit), deren optisch aktive Formen (D- bzw. L-Formen), sowie die entsprechenden Racemate. Insbesondere wird Mannit, wie D-Mannit, L-Mannit, DL-Mannit verwendet und zwar hiervon vorzugsweise D-Mannit. Als Hexit können auch Mischungen der genannten Hexite verwendet werden, z. B. Mischungen von Mannit und Sorbit und/oder Dulcit.

Neben dem Hexit können auch noch andere, übliche pharmazeutische Hilfsstoffe zugefügt werden, wie zum Beispiel Glycin, Lactose, Polyvinylpyrrolidon, Glukose, Fructose, Albumin und äquivalente gerüstbildende Stoffe. Die Gesamtmenge an solchen Stoffen in der Lösung, die für die Gefriertrocknung eingesetzt wird, ist beispielsweise 0—16,8 Gewichtsteile, bezogen auf 1 Gewichtsteil Ifosfamid bzw. Mesna. In dem fertigen Lyophilisat kann die Gesamtmenge an solchen Hilfsstoffen bis zu 16,8 Gewichtsteile, bezogen auf einen Gewichtsteil Hexit, betragen. Im einzelnen richtet sich die Menge an solchen Hilfsstoffen nach der vorhandenen Menge Hexit und zwar derart, daß die Gesamtmenge an Hexit und solchen anderen Hilfsstoffen in dem fertigen Lyophilisat maximal nicht mehr als 17 Gewichtsteile beträgt, bezogen auf 1 Teil Ifosfamid bzw. Mesna. Falls in dem Lyophilisat beispielsweise nur 0,1 Gewichtsteile Hexit vorliegen, können also bis zu 16,9 Gewichtsteile an

anderen Hilfsstoffen vorliegen; falls beispielsweise 8,5 Gewichtsteile Hexit vorliegen, kann z. B. die Menge an anderen Hilfsstoffen bis zu 8,5 Gewichtsteile, bezogen auf 1 Teil Ifosfamid bzw. Mesna, betragen.

Zur Herstellung der für die Gefriertrocknung einzusetzenden Lösung werden etwa 70 bis 80%, vorzugsweise 75% der erforderlichen Wassermenge bzw. ethanolischer Wassermenge vorgelegt und die entsprechenden Mengen Ifosfamid, Mesna und Mannit nacheinander (das heißt erst wird das Ifosfamid, dann das Mesna und anschließend der Hexit (z. B. Mannit) unter ständigem Rühren beziehungsweise unter ständiger Bewegung gelöst). Das zur Herstellung der Lösung verwendete Wasser wird zwecks Verdrängung von Sauerstoff mit einem inerten Gas wie zum Beispiel Stickstoff, Kohlendioxid oder einem Edelgas begast. Auch während der Herstellung der Lösung wird das inerte Gas in die Lösung eingeleitet. Die Verdrängung von Sauerstoff ist wichtig, da Mesna leicht zum Disulfid oxydiert wird. Nach vollständiger Auflösung wird auf das Endvolumen aufgefüllt und der pH-Wert gemessen. Der pH-Wert dieser Lösung soll beispielsweise nach dem Verdünnen zwischen 4 und 7 liegen. Vorzugsweise wird zur pH-Messung eine 4%ige Lösung, bezogen auf Ifosfamid, hergestellt.

Die so erhaltene Ifosfamid-Mesna-Lösung wird dann durch Filtration über hierfür übliche, keimdichte Filter sterilisiert, als Druckgas wird Stickstoff verwendet. Die Aufbewahrungszeit bis zur Abfüllung in die Injektionsbehälter soll einschließlich der Zeit der Lösungsherstellung eine Zeit von 3—4 Stunden nicht überschreiten, sofern es sich um Raumtemperatur (18° C bis 22° C) handelt.

Falls die anschließende Gefriertrocknung noch nicht sofort möglich ist, kann eine solche Lösung, gegebenenfalls auch nach Abfüllung in die Injektionsbehälter, beispielsweise noch bis zu 36 Stunden bei niedrigen Temperaturen, beispielsweise zwischen —5° und +10° C, vorzugsweise +4° bis +6° C, aufbewahrt werden, bevor die Gefriertrocknung beginnt.

Zur Durchführung des erfindungsgemäßen Verfahrens wird dann die so erhaltene Ifosfamid-Mesna-Lösung in Behälter für Injektionspräparate, beispielsweise Ampullen oder andere Glasgefäße eingefüllt. Die Behälter werden vor und nach der Befüllung mit sterilen und partikelfreien inerten Gas (z. B. Stickstoff) begast. Anschließend werden die Gefriertrocknungsstopfen aufgesetzt und lyophilisiert.

Zur Sterilisation werden übliche keimdichte Filter, beispielsweise übliche Bakterienfilter mit einer Porengröße von etwa 0,2 µm verwendet. Die verwendeten Glasgefäße beziehungsweise Ampullen werden vorher in üblicher Weise sterilisiert.

Der verwendete Hexit (vorzugsweise Mannit, insbesondere D-Mannit) soll den Anforderungen der Britischen Pharmakopoeia 1980 entsprechen.

Der eingesetzte Hexit muß pyrogenfrei sein (Pyrogene sind Fieber erzeugende Endotoxine, die von Bakterien gebildet werden). Dasselbe gilt für das verwendete Ifosfamid und Mesna. Die Entfernung bzw. Zerstörung der Pyrogene erfolgt auf übliche Weise (beispielsweise wird die Wirkstofflösung vor der Sterilfiltration mit Aktivkohle behandelt). Ebenfalls muß das verwendete Injektionswasser steril und pyrogenfrei sein und den Anforderungen des Deutschen Arzneibuches, 9. Ausgabe 1986 entsprechen.

Als Injektionsgefäße werden zweckmäßig solche aus Röhrenglas beziehungsweise Hüttenglas der III hydrolytischen Klasse verwendet (beispielsweise 10 R, 30 R und 50 H). (Siehe hierzu Deutsches Arzneibuch, 9. Ausgabe 1986 Seiten 161—164 und DIN-Normen 58 366, Teil 1 und Teil 5). Weiterhin sollen die Injektionsgefäße sowie die weiteren Hilfsstoffe, wie Gummistopfen und Bördelkappen, den Anforderungen der DIN-Normen 58 366, Teil 2 und Teil 3 sowie 58 367, Teil 1 entsprechen.

Die Lösungsmengen der Ifosfamid-Mesna-Lösungen, die für die Lyophilisation vorgesehen sind, in den jeweiligen Behältern (Ampullen) oder sonstigen Behältern für Injektionspräparate liegen pro Behälter zum Beispiel zwischen 1 und 500, vorzugsweise 1 und 250, insbesondere 2 und 50 ml. Die Behälter sind jeweils so zu bemessen, daß das hierin enthaltene Lyophilisat später in einer größeren Menge Flüssigkeit aufgelöst werden kann. Sie sollen daher im allgemeinen ein Volumen besitzen, das ausreicht, um eine gebrauchsfertige Endlösung herzustellen, die etwa das 2 bis 5, vorzugsweise 2 bis 4, insbesondere 2 bis 2,5fache des Volumens der ursprünglich eingefüllten Lyophilisat-Lösung hat.

Wie bereits erwähnt, wird vorzugsweise jede Ampulle beziehungsweise jedes Glasgefäß mit einer Einzeldosis von Ifosfamid und Mesna gefüllt, wobei die Ifosfamid-Menge pro Glasgefäß beispielsweise zwischen 100 mg bis 10 g, vorzugsweise 200 mg bis 5 g, die Mesna-Menge 10 mg bis 10 g, vorzugsweise 20 mg bis 5 g beträgt. Anschließend wird die Lösung in diesem Glasgefäß oder der Ampulle in herkömmlicher Weise gefriergetrocknet. Es ist jedoch auch möglich, größere Mengen Ifosfamid-Mesna, das heißt ein entsprechend größeres Lösungsvolumen der Ifosfamid-Mesna-Lösung in einem entsprechend größeren Gefäß zu lyophilisieren, und anschließend das erhaltene Lyophilisat in entsprechende kleinere Dosierungen zu unterteilen beziehungsweise abzupacken.

Die Lyophilisierung selbst wird so durchgeführt, daß die Ampullen oder Glasgefäße oder sonstige Gefäße, welche die Ifosfamid-Mesna-Lösung enthalten, unmittelbar auf eine Stellplatte oder in Tabletts auf einer Stellplatte in eine Gefriertrocknungskammer eingestellt werden. Nach dem Verschließen der Kammer werden die Ampullen beziehungsweise Gefäße auf Temperaturen unter 0° C abgekühlt, so daß das Wasser vollständig ausfriert. Beispielsweise wird auf Temperaturen zwischen —70° C bis 0° C vorzugsweise zwischen —70° C und —5° C, insbesondere —50° C bis —30° C, oder —45° C bis —35° C abgekühlt. Sobald die Lösungen vollständig gefroren sind, wird die Gefriertrocknungskammer allmählich evakuiert und mit dem Trocknen begonnen. Hierbei wird zuerst das nicht-adsorptiv gebundene Lösungsmittel entfernt und zwar bei Temperaturen zwischen —30° C bis +40° C, vorzugsweise 0° bis +30° C, insbesondere +10° C bis +20° C, wobei ein Druck zwischen 10^{-3} bis 6, vorzugsweise 10^{-2} bis 2, insbesondere 10^{-1} bis 1 mbar eingestellt wird. Bei den zuvor angegebenen Temperaturen beziehungsweise Temperaturbereichen handelt es sich um die Temperatur der Stellplatten. Der Prozeß wird dabei so gesteuert, daß die über die Plattentemperatur zugeführte Wärme vollständig als Sublimationswärme verbraucht wird, und die Temperatur der gefrorenen Ifosfamid-Mesna-haltigen Lösung stets unter-

halb ihrer eutektischen Temperatur bleibt. Die jeweils gewünschte Temperatur der Stellplatte kann zum Beispiel durch Programmscheiben oder Computer programmiert werden. Die Dauer zur Entfernung dieses nichtadsorptiv gebundenen Lösungsmittels ist von der Größe der einzelnen Behälter abhängig und liegt beispielsweise zwischen etwa 8 bis 50 Stunden bei einer Plattentemperatur von +15°C und einem Druck von 0,8 mbar. Beispielsweise wird in diesem Zusammenhang auf die in dem Beispiel angegebenen Zeiten verwiesen.

Die vollständige Entfernung des nicht-adsorptiv gebundenen Wassers zeigt sich wie folgt an: Nicht adsorptiv gebundenes Wasser liegt als Eis vor. Durch die sogenannte Druckanstiegsmessung wird festgestellt, ob derartiges Wasser noch im Lyophilisat vorhanden ist. Dazu wird ein Ventil zwischen Trockenkammer und Kondensatorraum, an dem auch die Vakuumpumpe angeschlossen ist, geschlossen. Vorhandenes Eis würde dann schnell sublimieren und einen Druckanstieg in der Trockenkammer herbeiführen. Bei der Druckanstiegsmessung darf der Druck in der Kammer nach 15 Minuten vom Ausgangswert, zum Beispiel 0,8 mbar, höchstens auf 1 mbar ansteigen. Ein stärkerer Anstieg würde bedeuten, daß die Haupttrocknung noch nicht abgeschlossen ist.

Das noch vorhandene, restliche adsorptiv gebundene Lösungsmittel wird dann durch eine Nachtrocknung entfernt. Diese beträgt beispielsweise 3 bis 12 Stunden bei einem Vakuum von 10^{-1} bis 10^{-4} mbar, insbesondere 3—4 Stunden bei einem Vakuum von 10^{-3} bis 10^{-4} mbar.

Der Lyophilisationsprozeß ist beendet, wenn die Restfeuchte (bestimmt nach K. Fischer) unter 1%, vorzugsweise unter 0,5% liegt. Insbesondere erfolgt die Nachtrocknung zur Entfernung von adsorptiv gebundenem Wasser bei Temperaturen zwischen 0 bis 40, vorzugsweise 10 bis 35, insbesondere 20 bis 30°C und einem Druck zwischen 10^{-4} bis 10^{-1}, vorzugsweise 10^{-3} bis 10^{-2}, insbesondere 10^{-3} bis 5×10^{-3} mbar, wobei diese Nachtrocknung beispielsweise 2 bis 36, vorzugsweise 6 bis 24, insbesondere 3 bis 12 Stunden in Anspruch nimmt.

Nach Beendigung der Gefriertrocknung werden die Gefäße verschlossen. Das erfindungsgemäße Verfahren wird in sämtlichen Stufen unter aseptischen Bedingungen durchgeführt.

Der Verschluß der Injektionsflaschen erfolgt dann zum Beispiel nach Belüftung der Gefriertrocknungskammer auf Normaldruck durch Zufuhr eines trockenen inerten Gases (z. B. Stickstoff) mit besonderen Gefriertrocknungs-Gummistopfen, die zur Vermeidung von Abrieb und zwecks Verbesserung der Gleitfähigkeit silikonisiert sind.

Mit Ausnahme des Einfrierens und der Entfernung des Lösungsmittels im Vakuum erfolgen alle Operationen unter inerter Gasatmosphäre (z. B. Stickstoff, Kohlendioxid, Edelgase).

Beispiel 1

Zur Gefriertrocknung wird folgende Lösung eingesetzt:

Mesna	20 mg
Ifosfamid	100 mg
D-Mannit	70 mg
Injektionswasser, ad	1 ml

Die Dichte dieser Lösung beträgt 1,061 g/ml bei +20°C.

Die anzusetzende Lösungsmenge richtet sich nach der jeweiligen Abfüll- und Gefriertrocknungs-Kapazität.

Sämtliche Verfahrensschritte bei der Herstellung der Lösung und der Abfüllung werden unter Stickstoff beziehungsweise Stickstoffbegasung durchgeführt.

Herstellung der Lösung

Es werden ca. 80% Injektionswassermenge vorgelegt und die entsprechende Menge Mesna, Ifosfamid und Mannit in dem Wasser nacheinander unter ständigem Rühren und Stickstoffbegasung gelöst. Nach vollständiger Auflösung wird auf das Endvolumen aufgefüllt und der pH-Wert gemessen.

Die fertige Lösung wird durch Filtration über hierfür übliche keimdichte Filter sterilisiert (zum Beispiel Sartorius SM 11 107 oder SM 11 307, 0,2 µm Porenweite, Pall Filter NRP (Porenweite 0,2 µm) und unter Vermeidung partikulärer und bakterieller Kontamination bis zur Abfüllung aufbewahrt. Als Druckgas bei der Filtration wird Stickstoff verwendet. Eine Lagerung bei Raumtemperatur (20—22°C) soll einschließlich der Zeit der Lösungsherstellung 3—4 Stunden nicht überschreiten. Bei nicht sofortiger anschließender Gefriertrocknung kann die Lösung noch etwa 36 Stunden bei +4°C bis +6°C aufbewahrt werden.

Zur Sterilfiltration können zusätzlich übliche Vorfilter (zum Beispiel Sartorius SM 13 400 oder Pall LPA) zum Schutz der Sterilfilter eingesetzt werden.

Reinigung der Injektionsflaschen

Die Injektionsflaschen werden mit demineralisiertem Wasser warm und kalt und Luft gespült. Sämtliche Reinigungsmedien werden durch Filtration von Schwebstoffen befreit.

Unter Vermeidung von Rekontamination durch Partikel aus der Luft werden die Flaschen mittels Heißluft getrocknet und sterilisiert (diskontinuierlich bei 180°C/2 Stunden).

Die Reinigung der Gummistopfen, mit denen die Injektionsflaschen verschlossen werden, erfolgt unter Verwendung von demineralisiertem Wasser und beispielsweise einem Reinigungsmittel, bestehend aus nichtionogenen Tensiden und Phosphorsäureestern in wäßriger Lösung.

Die gereinigten Stopfen werden unter Verwendung von demineralisiertem Wasser oder filtriertem demineral-

lisiertem Wasser faser- und flusenfrei gespült. Die so gereinigten Stopfen werden dann mittels Dampf sterilisiert.

Die so gereinigten und sterilisierten Injektionsflaschen werden nun aseptisch mit der Ifosfamid-Mesna-Lösung gefüllt und mit dem Gummistopfen versehen, wobei die Behälter vor und nach der Füllung mit Stickstoff begast werden.

Füllmengen:

Ifosfamid	Mesna	Füllmenge	Anwendungsvolumen*)
200 mg	40 mg	2 ml	5 ml
500 mg	100 mg	5 ml	12,5 ml
1 g	0,2 g	10 ml	25 ml
2 g	0,4 g	20 ml	50 ml
5 g	1,0 g	50 ml	125 ml
5 g	2,0 g	50 ml	125 ml

*) Für die spätere Verdünnung des Lyophilisats.

Die Füllvolumina sollen folgende Grenzen nicht überschreiten:

Füllvolumen	Grenzwerte der Einzelfüllvolumina	Durchschnittsgrenzwerte des Füllvolumens
2 ml	1,9—2,1 ml	1,95—2,05 ml
5 ml	4,8—5,2 ml	4,9—5,1 ml
10 ml	9,7—10,3 ml	9,85—10,15 ml
20 ml	19,4—20,6 ml	19,7—20,3 ml
50 ml	48,5—51,5 ml	49,25—50,75 ml

Die Füllvolumina sind statistisch zu überwachen, wobei mindestens alle 30 Minuten das Füllvolumen je Füllstelle einmal gemessen werden soll.

Die abgefüllten Injektionsflaschen werden so schnell wie möglich auf —40° C eingefroren.

Die Bedingungen für die Gefriertrocknung sind für die einzelnen Größen der Injektionsflaschen unterschiedlich. Es gelten beispielsweise die folgenden Werte:

Dauer der Haupttrocknung bei einer Plattentemperatur von +15° C und 0,6 mbar:

ca. 8—10 Stunden für Gefäße mit 200 mg Ifosfamid + 40 mg Mesna
ca. 12—15 Stunden für Gefäße mit 500 mg Ifosfamid + 100 mg Mesna
ca. 13—16 Stunden für Gefäße mit 1000 mg Ifosfamid + 200 mg Mesna
ca. 25—32 Stunden für Gefäße mit 2000 mg Ifosfamid + 400 mg Mesna
ca. 44—50 Stunden für Gefäße mit 5000 mg Ifosfamid + 1000 mg Mesna

Dauer der Nachtrocknung ca. 3—4 Stunden unter Vakuum von 5×10^{-4} mbar, bei einer Plattentemperatur von +25° C.

Die Restfeuchte (nach K. Fischer bestimmt) soll unter 0,5% liegen.

Nach Beendigung der Gefriertrocknung werden die Injektionsflaschen verschlossen.

Zur Sicherung der Gummistopfen werden Bördelklappen aufgesetzt und anrolliert. Die fertigen Injektionsflaschen werden auf mechanische Defekte (Sprünge, fehlerhafter Verschluß etc.) kontrolliert.

Beispiel 2

Zur Gefriertrocknung wird folgende Lösung eingesetzt:

Mesna	100 mg
Ifosfamid	100 mg
D-Mannit	70 mg
Inj.-Wasser, ad	1 ml

Die Dichte dieser Lösung beträgt 1,101 g/ml bei +20° C. Die anzusetzende Lösungsmenge richtet sich nach der jeweiligen Abfüll- und Gefriertrocknungs-Kapazität.

Sämtliche Verfahrensschritte bei der Herstellung der Lösung und der Abfüllung werden unter Stickstoff beziehungsweise Stickstoffbegasung durchgeführt.

Herstellung der Lösung

Es werden ca. 80% Injektionswassermenge vorgelegt und die entsprechende Menge Mesna, Ifosfamid und Mannit in dem Wasser nacheinander unter ständigem Rühren und Stickstoffbegasung gelöst. Nach vollständiger Auflösung wird auf das Endvolumen aufgefüllt und der pH-Wert gemessen.

Die fertige Lösung wird durch Filtration über hierfür übliche keimdichte Filter sterilisiert (zum Beispiel 0,2 µm Porenweite) und unter Vermeidung partikulärer und bakterieller Kontamination bis zur Abfüllung aufbewahrt. Als Druckgas bei der Filtration wird Stickstoff verwendet. Eine Lagerung bei Raumtemperatur (20—22° C) soll einschließlich der Zeit der Lösungsherstellung 3—4 Stunden nicht überschreiten. Bei nicht sofortiger anschließender Gefriertrocknung kann die Lösung noch etwa 36 Stunden bei +4° C bis +6° C aufbewahrt werden.

Zur Sterilfiltration können zusätzlich übliche Vorfilter (zum Beispiel Sartorius SM 13 400 oder Pall LPA) zum Schutz der Sterilfilter eingesetzt werden.

Reinigung der Injektionsflaschen

Die Injektionsflaschen werden mit demineralisiertem Wasser warm und kalt und Luft gespült. Sämtliche Reinigungsmedien werden durch Filtration von Schwebstoffen befreit.

Unter Vermeidung von Rekontamination durch Partikel aus der Luft werden die Flaschen mittels Heißluft getrocknet und sterilisiert (diskontinuierlich bei 180° C/2 Stunden).

Die Reinigung der Gummistopfen, mit denen die Injektionsflaschen verschlossen werden, erfolgt unter Verwendung von demineralisiertem Wasser und beispielsweise einem Reinigungsmittel, bestehend aus nichtionogenen Tensiden und Phosphorsäureestern in wäßriger Lösung.

Die gereinigten Stopfen werden unter Verwendung von demineralisiertem Wasser oder filtriertem demineralisiertem Wasser faser- und flusenfrei gespült. Die so gereinigten Stopfen werden dann mittels Dampf sterilisiert.

Die so gereinigten und sterilisierten Injektionsflaschen werden nun aseptisch mit der Ifosfamid-Mesna-Lösung gefüllt und mit dem Gummistopfen versehen, wobei die Behälter vor und nach der Füllung mit Stickstoff begast werden.

Füllmengen:

Ifosfamid	Mesna	Füllmenge	Anwendungsvolumen*)
200 mg	200 mg	2 ml	5 ml
500 mg	500 mg	5 ml	12,5 ml
1 g	1 g	10 ml	25 ml
2 g	2 g	20 ml	50 ml
5 g	5 g	50 ml	125 ml

*) Für die spätere Verdünnung des Lyophilisates.

Die Füllvolumina sollen folgende Grenzen nicht überschreiten:

Füllvolumen	Grenzwerte der Einzelfüllvolumina	Durchschnittswerte des Füllvolumen
2 ml	1,9—2,1 ml	1,95—2,05 ml
5 ml	4,8—5,2 ml	4,9—5,1 ml
10 ml	9,7—10,3 ml	9,85—10,15 ml
20 ml	19,4—20,6 ml	19,7—20,3 ml
50 ml	48,5—51,5 ml	49,25—50,75 ml

Die Füllvolumina sind statistisch zu überwachen, wobei mindestens alle 30 Minuten das Füllvolumen je Füllstelle einmal gemessen werden soll.

Die abgefüllten Injektionsflaschen werden so schnell wie möglich auf —40° C eingefroren.

Die Bedingungen für die Gefriertrocknung sind für die einzelnen Größen der Injektionsflaschen unterschiedlich. Es gelten beispielsweise die folgenden Werte:

Dauer der Haupttrocknung bei einer Plattentemperatur von +15° C und 0,6 mbar:

ca. 8—10 Stunden für Gefäße mit 200 mg Ifosfamid + 200 mg Mesna
ca. 12—15 Stunden für Gefäße mit 500 mg Ifosfamid + 500 mg Mesna
ca. 13—16 Stunden für Gefäße mit 1 g Ifosfamid + 1 g Mesna
ca. 25—32 Stunden für Gefäße mit 2 g Ifosfamid + 2 g Mesna
ca. 44—50 Stunden für Gefäße mit 5 g Ifosfamid + 5 g Mesna

Dauer der Nachtrocknung ca. 3—4 Stunden unter Vakuum von 5×10^{-4} mbar, bei einer Plattentemperatur von +25°C. Die Restfeuchte (nach K. Fischer) soll unter 0,5% liegen. Nach Beendigung der Gefriertrocknung werden die Injektionsflaschen verschlossen. Zur Sicherung der Gummistopfen werden Bördelkappen aufgesetzt und anrolliert. Die fertigen Injektionsflaschen werden auf mechanische Defekte (Sprünge, fehlerhafter Verschluß etc.) kontrolliert.

Patentansprüche

1. Lyophilisiertes Präparat, bestehend aus Ifosfamid, 0,05—1,0 Gewichtsteilen Mesna und 0,1 bis 17 Gewichtsteilen Hexit, Mesna und Hexit jeweils bezogen auf einen Gewichtsteil Ifosfamid sowie gegebenenfalls anderen üblichen pharmazeutischen Hilfsstoffen.
2. Lyophilisiertes Präparat nach Anspruch 1, dadurch gekennzeichnet, daß es als Hexit Mannit enthält.
3. Verfahren zur Herstellung eines Ifosfamid-Mesna-Lyophilisates, dadurch gekennzeichnet, daß man unter einem inerten Gas eine wäßrige oder wäßrig-ethanolische Lösung, die 1 bis 13 Gewichtsprozent Ifosfamid enthält sowie 0,05—13 Gewichtsteile Mesna, 0,1 bis 17 Gewichtsteile Hexit (Mesna und Hexit jeweils bezogen auf einen Gewichtsteil Ifosfamid) und gegebenenfalls 0 bis 16,9 Gewichtsteile (bezogen auf 1 Gewichtsteil Ifosfamid) weitere pharmazeutische Hilfsstoffe, zwischen −70°C und 0°C einfriert, und dem so erhaltenen Produkt im gefrorenen Zustand das Wasser entzieht.
4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß zuerst das nicht adsorptiv gebundene Wasser bei einer Temperatur zwischen −30°C und +40°C und einem Druck zwischen 10^{-3} bis 10 mbar und anschließend adsorptiv gebundenes Wasser bei einer Temperatur zwischen 0°C und 40°C und einem Druck zwischen 10^{-4} bis 10^{-1} mbar entfernt wird.
5. Verfahren nach einem oder mehreren der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß als Hexit Mannit verwendet wird.
6. Ifosfamid-Mesna-Lyophilisat, erhalten nach einem oder mehreren der vorangegangenen Ansprüche.

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(54) Ifosfamid-Mesna-Lyophilisat und Verfahren zu dessen Herstellung.

(57) Ifosfamid-Mesna-Lyophilisat, bestehend im wesentlichen aus Ifosfamid, 0,1 - 1,0 Gewichtsteilen Mesna und 0,1 bis 17 Gewichtsteilen Hexit.

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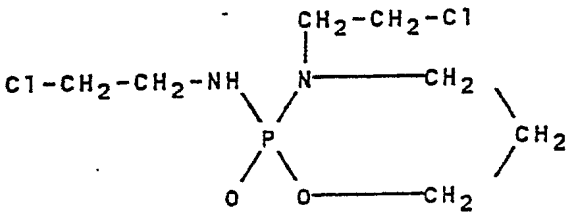
Ifosfamid-Mesna-Lyophilisat und Verfahren zu dessen Herstellung

Der chemische Name für den Wirkstoff Ifosfamid ist 3-(2-Chlorethyl)-2-(chlorethylamino)-tetrahydro-2H-1, 3,2-oxazaphosphorin-2-oxid



Ifosfamid gehört wie Cyclophosphamid zur chemischen Gruppe der Oxazaphosphorine und wird therapeutisch zur Behandlung von Tumor-Erkrankungen eingesetzt.

Der chemische Name für den Uroprotektor Mesna ist Natrium-2-mercaptoethansulfonat
$Na^{+}\{HS\text{-}CH_2\text{-}CH_2\text{-}SO_3\}^{-}$
Mesna schützt beispielsweise die harnableitenden Organe bei der Therapie von Tumor-Erkrankungen mit Ifosfamid, wobei diese uroprotektive Wirkung von Mesna insbesondere bei gleichzeitiger und synchroner Verabreichung zusammen mit dem Ifosfamid gegeben ist.

Ifosfamid ist ein weißes, kristallines Pulver mit einem Schmelzpunkt von 48° C bis 51° C und stark hygroskopischen Eigenschaften. Bereits unterhalb des Schmelzpunktes beginnt Ifosfamid zu sintern; es muß deshalb bei möglichst niedrigen Temperaturen (Raumtemperatur und darunter) gelagert werden. Außerdem ist ein Kontakt mit Luftfeuchigkeit möglichst zu vermeiden.

Ifosfamid löst sich zu etwa 10 Gewichtsprozent in Wasser, ist aber in wässriger Lösung nur begrenzt haltbar (maximal 3 bis 4 Stunden bei 20° C bis 22° C beziehungsweise 36 Stunden bei 4 bis 6° C).

Ifosfamid wird ausschließlich parenteral appliziert. Die Injektionsflaschen enthalten 200 bis 5000 mg Ifosfamid in Form eines Sterilkristallisats, das vor der Applikation in Wasser für Injektionszwecke gelöst wird, so daß eine 4%ige Konzentration nicht überschritten wird. Diese Lösung ist zur intravenösen Injektion geeignet. Zur intravenösen Kurzinfusion wird die Ifosfamid-Lösung in 500 ml Ringer-Lösung oder ähnlichen Infusionsflüssigkeiten aufgelöst. Die Infusionsdauer beträgt ca. 30 Minuten, eventuell 1 bis 2 Stunden. Bei der 24-Stunden-Infusion wird die Ifosfamid-Lösung beispielsweise in insgesamt 3 Liter 5 % Dextrose-Kochsalzlösung aufgelöst.

Ifosfamid verursacht bei der Herstellung und Verarbeitung mannigfaltige Probleme. Bei der Herstellung des steril kristallisierten Ifosfamids resultiert ein Produkt von wechselnder physikalischer Beschaffenheit. Durch die unterschiedliche Rieselfähigkeit wird insbesondere die Dosierungsgenauigkeit bei der Abfullung in hohem Maße beeinträchtigt.

Die Verarbeitung des Ifosfamids wird weiterhin erschwert durch seine Hygroskopizität und den niedrigen Schmelzpunkt. Bei längerer Lagerung sintert das Sterilkristallisat und die Lösungsgeschwindigkeit vermindert sich. Mit beginnender Sinterung des Ifosfamids nehmen auch die Klarlöslichkeit und der pH-Wert der Lösung bei gleichzeitiger Gelbfärbung ab; eine therapeutische Verwendung ist dann im allgemeinen nicht mehr möglich.

Mesna ist ebenfalls eine Substanz, die nur unter besonderen Bedingungen stabil und haltbar ist.

Eine Kombinationsmöglichkeit aus Ifosfamid und Mesna, welches einen großen Vorteil hinsichtlich Lagerung und praktischer Handhabung darstellen würde, existiert bis jetzt nicht.

Aufgabe der Erfindung ist es daher, Ifosfamid und Mesna in einer Form mit verbesserten Eigenschaften, wie verbesserte pharmazeutische Qualität, Dosierbarkeit und Löslichkeit, bereitzustellen, die leichter anzuwenden ist, und insbesondere zur Herstellung von injizierbaren Lösungen geeignet ist.

Es wurde nun Überraschend gefunden, daß die bisherigen Nachteile und Schwierigkeiten bei der Handhabung und Lagerung von Ifosfamid und Mesna durch Verwendung eines bestimmten Ifosfamid-Mesna-Lyophilisats behoben werden können. Insbesondere ist es überraschend, daß das erfindungsgemäße Lyophilisat eine größere Thermostabilität des Ifosfamids besitzt als die bislang verwendete Ifosfamid-Trockenabfüllung.

Trockenabfüllungen mit Ifosfamid sind bei 40° C bereits nach einer Lagerzeit von 1 Monat nachgedunkelt; nach 2 Monaten ist der Flascheninhalt gesintert und gelb verfärbt. Bei einer Lagerungstemperatur von

55° C ist das trocken abgefüllte Ifosfamid bereits innerhalb von 4 Tagen geschmolzen.

Demgegenüber ist bei erfindungsgemäß hergestellten Lyophilisat unter den vorgenannten Lagerbedingungen weder eine Verfärbung noch eine Veränderung der Konsistenz des Ifosfamids erkennbar. Ebenfalls zeigen sich keine Veränderungen bei dem Mesna.

Die Lösungsgeschwindigkeit des Ifosfamid-Mesna-Lyophilisats ist gegenüber der Ifosfamid-Trockenabfüllung deutlich erhöht. Während sich das Lyophilisat unabhängig von der Lagerdauer bei der Zugabe des Lösungsmittels sofort löst, müssen die Injektionsflaschen mit der Trockenabfüllung nach Einspritzen des Lösungsmittels 1/2 bis 3 Minuten kräftig geschüttelt werden. Wenn hierbei die Auflösung nicht sofort restlos erfolgt, und dies ist bei länger gelagerten Injektionsflaschen der Fall, ist es sogar erforderlich, die Lösung einige Minuten stehen zu lassen. Die Anwendung des Präparates in der Klinik wird dadurch erschwert.

Ifosfamid-Mesna-Lyophilisat zeigt im Gegensatz zu Sterilkristallisat auch nach der Lagerung von mehreren Jahren noch optimale Lösungseigenschaften.

Außerdem ist die Ifosfamid-Trockenabfüllung (das heißt das reine Ifosfamid-Kristallisat) viel empfindlicher gegen Luftfeuchtigkeit als das Lyophilisat. So verflüssigt sich die Ifosfamid-Trockenabfüllung bereits bei einer relativen Luftfeuchtigkeit von unter 75 %, während das Lyophilisat selbst bei 100 % relativer Luftfeuchigkeit zwar feucht wird, aber seine äußere Form behält.

Bei der Abfüllung des Sterilkristallisats ist ferner die Gefahr einer partikulären oder mikrobiellen Kontamination in wesentlich stärkerem Maße als beim Lyophilisat gegeben.

Bei der Herstellung des Ifosfamid-Mesna-Lyophilisats erfolgt die Sterilfiltration der Lösung hingegen erst unmittelbar vor der Abfüllung in die Injektionsflaschen. Dadurch ist gegenüber der Abfüllung von Sterilkristallisat eine größere mikrobiologische Sicherheit gegeben. Auch partikuläre Verunreinigungen, die bei der Trockenabfüllung gelegentlich Anlaß zu Beanstandungen geben, lassen sich durch die Filtration der Lösung mit größerer Sicherheit vermeiden.

Die Lyophilisation des Ifosfamids in Kombination mit Mesna führt jedoch nicht nur zu einer Produktverbesserung, sondern ist in der Herstellung und praktischen Anwendung auch wirtschaftlicher als die getrennte Herstellung von Sterilkristallisat und Mesna-Injektionslösung.

Darüberhinaus besitzt die erfindungsgemäße Kombination auch bei der Anwendung eine überraschende bessere Wirkung als die bisherige getrennte Applikation von Ifosfamid und Mesna:

So erfolgt beispielsweise bei der erfindungsgemäßen Kombination bei intravenöser, kontinuierlicher Infusion (zum Beispiel in der Zusammensetzung 5,0 g Ifosfamid + 2,0 g Mesna) eine kontinuierliche Uroprotektion, und zwar durch die gleichzeitige kontinuierliche renale Elimination von urotoxischen Metaboliten und Mesna. Dadurch wird der uroprotektionsmindernde Effekt einer Blasenentleerung minimiert. Die fixe Dosisrelation von Ifosfamid und Mesna im Lyophilisat vermeidet bei dem Einsatz als kontinuierliche intravenöse Infusion (zum Beispiel 5 g Ifosfamid + 2 g Mesna über 6 Stunden oder 10 g Ifosfamid + 4 g Mesna über 24 Stunden kontinuierlich infundiert) eine unzureichende Uroprotektion, wie sie durch wiederholte Bolusinjektionen von Mesna oder auch eine zu niedrige Infusionsdosis auftreten kann. Der Einsatz des Kombinationslyophilisats als Kurzzeitinfusion über 30 Minuten bis zu 2 Stunden in den Mengen von beispielsweise 500 mg bis 5 g Ifosfamid zusammen mit 20 % der Ifosfamid-Menge als Mesna garantiert eine ausreichende Uroprotektion in den ersten 4 Stunden. Bevorzugte Dosierungen für die Anwendung am Menschen sind zum Beispiel:

0,5 g	Ifosfamid + 0,1 g Mesna
1 g	Ifosfamid + 0,2 g Mesna
2 g	Ifosfamid + 0,4 g Mesna
5 g	Ifosfamid + 1,0 g Mesna
5 g	Ifosfamid + 2,0 g Mesna

Es hat sich gezeigt, daß nur das erfindungsgemäße Verfahren unter Verwendung eines Hexits, wie zum Beispiel Mannit, ein verbessertes Ifosfamid-Mesna-Lyophilisat ergibt. Beispielsweise konnte durch Beimischung von Kochsalz, wie sie bei Trockenabfüllungen von anderen Oxazaphosphorinen üblich ist, kein Lyophilisat erhalten werden.

Erfindungsgemäß wird beispielsweise eine wässrige Lösung, die 1 - 13 Gewichtsprozent an Ifosfamid und 0,05 - 13 Gewichtsteile Mesna enthält, sowie als Gerüstbildner 0,1 - 17 Gewichtsteile Hexit, bezogen auf einen Gewichtsteil Ifosfamid, gefriergetrocknet. Vorzugsweise enthält diese wässrige Lösung 5 - 12 Gewichtsprozent Ifosfamid und 0,5 - 12 Gewichtsprozent Mesna, insbesondere 8 - 10 Gewichtsprozent Ifosfamid und 0,8 - 10 Gewichtsprozent Mesna.

Es können auch entsprechende Ethanol-Wasser-Lösungen von Ifosfamid und Mesna anstelle einer reinen wässrigen Lösung verwendet werden (Ethanolanteil einer solchen Lösung bis zu 45 m/m*), beispielsweise 1 -20 % Ethanol). In solchen Fällen wird möglichst zuerst das Ethanol vorzeitig im Vacuum entfernt, bevor das restliche Eis sublimiert wird. Die Bedingungen für die zuerst erfolgte Ethanolentfernung sind zum Beispiel: Druck 5 - 10^{-1} mbar, Temperatur von -25° C auf -5° C steigend innerhalb von 10 Stunden, anschließend wird die Temperatur der Stellplatten auf 15° C erhöht. Im einzelnen hängen diese Bedingungen auch von den unterschiedlichen Schichthöhen des zu trocknenden Gutes in den Injektionsflaschen ab und sind entsprechend zu variieren.

Die Menge an Hexit in dieser wässrigen beziehungsweise wässrig-ethanolischen Lösung beträgt im allgemeinen 1 - 17, vorzugsweise 3 - 12, insbesondere 5 - 9 Gewichtsprozent. Bezieht man die Hexit-Menge auf einen Gewichtsteil Ifosfamid, dann ist die Hexit-Menge 0, 1 -17, vorzugsweise 1 bis 2,5 insbesondere 0,6 - 0,8 Gewichtsteile Hexit pro 1 Gewichtsteil Ifosfamid. Bezogen auf 1 Gewichtsteil Mesna beträgt die Hexit-Menge zum Beispiel 0,1 - 17, vorzugsweise 1 - 6, insbesondere 3 - 4 Gewichtsteile.

*) Definition gemäß Deutsches Arzneibuch 9. Ausgabe: Prozent Masse in Masse)

Als Hexit kommen in Frage: Mannit, Glucit (Sorbit, wie D-Sorbit), Dulcit, Allit, Altrit (z.B. D- und L-Altrit), Idit (z.B. D- und L-Idit), deren optisch aktive Formen (D- bzw. L-Formen), sowie die entsprechenden Racemate. Insbesondere wird Mannit, wie D-Mannit, L-Mannit, DL-Mannit verwendet und zwar hiervon vorzugsweise D-Mannit. Als Hexit können auch Mischungen der genannten Hexite verwendet werden, z.B. Mischungen von Mannit und Sorbit und/oder Dulcit.

Neben dem Hexit können auch noch andere, Übliche pharmazeutische Hilfsstoffe zugefügt werden, wie zum Beispiel Glycin, Lactose, Polyvinylpyrrolidon, Glukose, Fructose, Albumin und äquivalente gerüstbildende Stoffe. Die Gesamtmenge an solchen Stoffen in der Lösung, die für die Gefriertrocknung eingesetzt wird, ist beispielsweise 0 - 16,8 Gewichtsteile, bezogen auf 1 Gewichtsteil Ifosfamid bzw. Mesna. In dem fertigen Lyophilisat kann die Gesamtmenge an solchen Hilfsstoffen bis zu 16,8 Gewichtsteile, bezogen auf einen Gewichtsteil Hexit, betragen. Im einzelnen richtet sich die Menge an solchen Hilfsstoffen nach der vorhandenen Menge Hexit und zwar derart, daß die Gesamtmenge an Hexit und solchen anderen Hilfsstoffen in dem fertigen Lyophilisat maximal nicht mehr als 17 Gewichtsteile beträgt, bezogen auf 1 Teil Ifosfamid bzw. Mesna. Falls in dem Lyophilisat beispielsweise nur 0,1 Gewichtsteile Hexit vorliegen, können also bis zu 16,9 Gewichtsteile an anderen Hilfsstoffen vorliegen; falls beispielsweise 8,5 Gewichtsteile Hexit vor liegen, kann z.B. die Menge an anderen Hilfsstoffen bis zu 8,5 Gewichtsteile, bezogen auf 1 Teil Ifosfamid bzw. Mesna, betragen.

Zur Herstellung der für die Gefriertrocknung einzusetzenden Lösung werden etwa 70 bis 80 %,vorzugsweise 75 % der erforderlichen Wassermenge bzw. ethanolischer Wassermenge vorgelegt und die entsprechenden Mengen Ifosfamid, Mesna und Mannit nacheinander (das heißt erst wird das Ifosfamid, dann das Mesna und anschließend der Hexit (z.B. Mannit) unter ständigem Rühren beziehungsweise unter ständiger Bewegung gelöst. Das zur Herstellung der Lösung verwendete Wasser wird zwecks Verdrängung von Sauerstoff mit einem inerten Gas wie zum Beispiel Stickstoff, Kohlendioxid oder einem Edelgas begast. Auch während der Herstellung der Lösung wird das inerte Gas in die Lösung eingeleitet. Die Verdrängung von Sauerstoff ist wichtig, da Mesna leicht zum Disulfid oxydiert wird. Nach vollständiger Auflösung wird auf das Endvolumen aufgefüllt und der pH-Wert gemessen. Der pH-Wert dieser Lösung soll beispielsweise nach dem Verdünnen zwischen 4 und 7 liegen. Vorzugsweise wird zur pH-Messung eine 4 %ige Lösung, bezogen auf Ifosfamid, hergestellt.

Die so erhaltene Ifosfamid-Mesna-Lösung wird dann durch Filtration über hierfür übliche, keimdichte Filter sterilisiert, als Druckgas wird Stickstoff verwendet. Die Aufbewahrungszeit bis zur Abfüllung in die Injektionsbehälter soll einschließlich der Zeit der Lösungsherstellung eine Zeit von 3 - 4 Stunden nicht überschreiten, sofern es sich um Raumtemperatur (18° C bis 22° C) handelt.

Falls die anschließende Gefriertrocknung noch nicht sofort möglich ist, kann eine solche Lösung, gegebenenfalls auch nach Abfüllung in die Injektionsbehälter, beispielsweise noch bis zu 36 Stunden bei niedrigen Temperaturen, beispielsweise zwischen -5° und +10° C, vorzugsweise +4° bis +6° C, aufbewahrt werden, bevor die Gefriertrocknung beginnt.

Zur Durchführung des erfindungsgemäßen Verfahrens wird dann die so erhaltene Ifosfamid-Mesna-Lösung in Behälter für Injektionspräparate, beispielsweise Ampullen oder andere Glasgefäße eingefüllt. Die Behälter werden vor und nach der Befüllung mit sterilen und partikelfreien inerten Gas (z.B. Stickstoff) begast. Anschließend werden die Gefriertrocknungsstopfen aufgesetzt und lyophilisiert.

Zur Sterilisation werden übliche keimdichte Filter, beispielsweise übliche Bakterienfilter mit einer Porengröße von etwa 0,2 µm verwendet. Die verwendeten Glasgefäße beziehungsweise Ampullen werden vorher in üblicher Weise sterilisiert.

Der verwendete Hexit (vorzugsweise Mannit, insbesondere D-Mannit) soll den Anforderungen der

Britischen Pharmakopoeia 1980 entsprechen.

Der eingesetzte Hexit muß pyrogenfrei sein (Pyrogene sind Fieber erzeugende Endotoxine, die von Bakterien gebildet werden). Dasselbe gilt für das verwendete Ifosfamid und Mesna. Die Entfernung bzw. Zerstörung der Pyrogene erfolgt auf übliche Weise (beispielsweise wird die Wirkstofflösung vor der Sterilfiltration mit Aktivkohle behandelt). Ebenfalls muß das verwendete Injektionswasser steril und pyrogenfrei sein und den Anforderungen des Deutschen Arzneibuches, 9. Ausgabe 1986 entsprechen.

Als Injektionsgefäße werden zweckmäßig solche aus Röhrenglas beziehungsweise Hüttenglas der III hydrolytischen Klasse verwendet (beispielsweise 10 R, 30 R und 50 H). (Siehe hierzu Deutsches Arzneibuch, 9. Ausgabe 1986 Seiten 161 - 164 und DIN-Normen 58366, Teil 1 und Teil 5). Weiterhin sollen die Injektionsgefäße sowie die weiteren Hilfsstoffe, wie Gummistopfen und Bördelkappen, den Anforderungen der DIN-Normen 58366, Teil 2 und Teil 3 sowie 58367, Teil 1 entsprechen.

Die Lösungsmengen der Ifosfamid-Mesna-Lösungen, die für die Lyophilisation vorgesehen sind, in den jeweiligen Behältern (Ampullen) oder sonstigen Behältern für Injektionspräparate liegen pro Behälter zum Beispiel zwischen 1 und 500, vorzugsweise 1 und 250, insbesondere 2 und 50 ml. Die Behälter sind jeweils so zu bemessen, daß das hierin enthaltene Lyophilisat später in einer größeren Menge Flüssigkeit aufgelöst werden kann. Sie sollen daher im allgemeinen ein Volumen besitzen, das ausreicht, um eine gebrauchsfertige Endlösung herzustellen, die etwa das 2 bis 5, vorzugsweise 2 bis 4, insbesondere 2 bis 2,5fache des Volumens der ursprünglich eingefüllten Lyophilisat-Lösung hat.

Wie bereits erwähnt, wird vorzugsweise jede Ampulle beziehungsweise jedes Glasgefäß mit einer Einzeldosis von Ifosfamid und Mesna gefüllt, wobei die Ifosfamid-Menge pro Glasgefäß beispielsweise zwischen 100 mg bis 10 g, vorzugsweise 200 mg bis 5 g, die Mesna-Menge 10 mg bis 10 g, vorzugsweise 20 mg bis 5 g beträgt. Anschließend wird die Lösung in diesem Glasgefäß oder der Ampulle in herkömmlicher Weise gefriergetrocknet. Es ist jedoch auch möglich, größere Mengen Ifosfamid-Mesna, das heißt ein entsprechend größeres Lösungs volumen der Ifosfamid-Mesna-Lösung in eimem entsprechend größeren Gefäß zu lyophilisieren, und anschließend das erhaltene Lyophilisat in entsprechende kleinere Dosierungen zu unterteilen beziehungsweise abzupacken.

Die Lyophilisierung selbst wird so durchgeführt, daß die Ampullen oder Glasgefäße oder sonstige Gefäße, welche die Ifosfamid-Mesna-Lösung enthalten, unmittelbar auf eine Stellplatte oder in Tabletts auf einer Stellplatte in eine Gefriertrocknungskammer eingestellt werden. Nach dem Verschließen der Kammer werden die Ampullen beziehungsweise Gefäße auf Temperaturen unter 0 ° C abgekühlt, sodaß das Wasser vollständig ausfriert. Beispielsweise wird auf Temperaturen zwischen -70 ° C bis 0 ° C vorzugsweise zwischen -70 ° C und -5 ° C, insbesondere -50 ° C bis -30 ° C, oder -45 ° C bis -35 ° C abgekühlt. Sobald die Lösungen vollständig gefroren sind, wird die Gefriertrocknungs-kammer allmählich evakuiert und mit dem Trocknen begonnen. Hierbei wird zuerst das nicht-adsorptiv gebundene Lösungsmittel entfernt und zwar bei Temperaturen zwischen -30 ° C bis +40 ° C, vorzugsweise 0 ° C bis +30 ° C, insbesondere +10 ° C bis +20 ° C, wobei ein Druck zwischen 10^{-3} bis 6, vorzugsweise 10^{-2} bis 2, insbesondere 10^{-1} bis 1 mbar eingestellt wird. Bei den zuvor angegebenen Temperaturen beziehungsweise Tempe-raturbereichen handelt es sich um die Temperatur der Stellplatten. Der Prozeß wir dabei so gesteuert, daß die über die Plattentemperatur zugeführte Wärme vollständig als Sublimationswärme verbraucht wird, und die Temperatur der gefrorenen Ifosfamid-Mesna-haltigen Lösung stets unterhalb ihrer eutektischen Temperatur bleibt. Die jeweils gewünschte Temperatur der Stellplatte kann zum Beispiel durch Programmscheiben oder Computer programmiert werden. Die Dauer zur Entfernung dieses nichtadsorptiv gebundenen Lösungsmittels ist von der Größe der einzelnen Behälter abhängig und liegt beispielsweise zwischen etwa 8 bis 50 Stunden bei einer Plattentemperatur von +15 ° C und einem Druck von 0,8 mbar. Beispielsweise wird in diesem Zusammenhang auf die in dem Beispiel angegebenen Zeiten verwiesen.

Die vollständige Entfernung des nicht-adsorptiv gebundenen Wassers zeigt sich wie folgt an: Nicht adsorptiv gebundenes Wasser liegt als Eis vor. Durch die sogenannte Druckanstiegsmessung wird festgestellt, ob derartiges Wasser noch im Lyophilisat vorhanden ist. Dazu wird ein Ventil zwischen Trockenkammer und Kondensatorraum, an dem auch die Vakuumpumpe angeschlossen ist, geschlossen. Vorhandenes Eis würde dann schnell sublimieren und einen Druckanstieg in der Trockenkammer herbeiführen. Bei der Druckanstiegmessung darf der Druck in der Kammer nach 15 Minuten vom Ausgangswert, zum Beispiel 0,8 mbar, höchstens auf 1 mbar ansteigen. Ein stärkerer Anstieg würde bedeuten, daß die Haupttrocknung noch nicht abgeschlossen ist.

Das noch vorhandene, restliche adsorptiv gebundene Lösungsmittel wird dann durch eine Nachtrocknung entfernt. Diese beträgt beispielsweise 3 bis 12 Stunden bei einem Vakuum von 10^{-1} bis 10^{-4} mbar, insbesondere 3 - 4 Stunden bei einem Vakuum von 10^{-3} bis 10^{-4} mbar.

Der Lyophilisationsprozeß ist beendet, wenn die Restfeuchte (bestimmt nach K. Fischer) unter 1 %, vorzugsweise unter 0,5 liegt. Insbesondere erfolgt die Nachtrocknung zur Entfernung von adsorptiv gebun-

denem Wasser bei Temperaturen zwischen 0 bis 40, vorzugsweise 10 bi 35, insbesondere 20 bis 30 ° C und einem Druck zwischen 10^{-4} bis 10^{-1}, vorzugsweise 10^{-3} bis 10^{-2}, insbesondere 10^{-3} bis 5 x 10^{-3} mbar, wobei diese Nachtrocknung beispielsweise 2 bis 36, vorzugsweise 6 bis 24, insbesondere 3 bis 12 Stunden in Anspruch nimmt.

Nach Beendigung der Gefriertocknung werden die Gefäße verschlossen. Das erfindungsgemäße Verfahren wird in sämtlichen Stufen unter aseptischen Bedingungen durchgeführt.

Der Verschluß der Injektionflaschen erfolgt dann zum Beispiel nach Belüftung der Gefriertrocknungskammer auf Normaldruck durch Zufuhr eines trockenen inerten Gases (z.B. Stickstoff) mit besonderen Gefrietrocknungs-Gummistopfen, die zur Vermeidung von Abrieb und Zwecks Verbesserung der Gleitfähigkeit silikonisiert sind.

Mit Ausnahme des Einfrierens und der Entfernung des Lösungsmittels im Vakuum erfolgen alle Operationen unter inerter Gasatmosphäre (z.B. Stickstoff, Kohlendioxid, Edelgase).

Beispiel 1

Zur Gefriertrocknung wird folgende Lösung eingesetzt:

Mesna	20 mg
Ifosfamid	100 mg
D-Mannit	70 mg
Injektionswasser ad	1 ml

Die Dichte dieser Lösung beträgt 1,061 g/ml bei + 20 ° C.

Die anzusetzende Lösungsmenge richtet sich nach der jeweiligen Abfüll- und Gefriertrocknungs-Kapazität.

Sämtliche Verfahrensschritte bei der Herstellung der Lösung und der Abfüllung werden unter Stickstoff beziehungsweise Stickstoffbegasung durchgeführt.

Herstellung der Lösung:

Es werden ca. 80 % Injektionswassermenge vorgelegt und die entsprechenden Menge Mesna, Ifosfamid und Mannit in dem Wasser nacheinander unter ständigem Rühren und Stickstoffbegasung gelöst. Nach vollständiger Auflösung wird auf das Endvolumen aufgefüllt und der pH-Wert gemessen.

Die fertige Lösung wird durch Filtration über hierfür übliche keimdichte Filter sterilisiert (zum Beispiel Sartorius SM 11107 oder SM 11307, 0,2 µm Porenweite, Pall Filter NRP (Porenweite 0,2 µm) und unter Vermeidung partikulärer und bakterieller Kontamination bis zur Abfüllung aufbewahrt. Als Druckgas bei der Filtration wird Stickstoff verwendet. Eine Lagerung bei Raumtemperatur (20 - 22 ° C) soll einschließlich der Zeit der Lösungsherstellung 3 - 4 Stunden nicht überschreiten. Bei nicht sofortiger anschließender Gefriertrocknung kann die Lösung noch etwa 36 Stunden bei + 4 ° C bis + 6 ° C aufbewahrt werden.

Zur Sterilfiltration können zusätzlich übliche Vorfilter (zum Beispiel Sartorius SM 13400 oder Pall LPA) zum Schutz der Sterilfilter eingesetzt werden.

Reinigung der Injektionsflaschen:

Die Injektionsflaschen werden mit demineralisiertem Wasser warm und kalt und Luft gespült. Sämtliche Reinigungsmedien werden durch Filtration von Schwebstoffen befreit.

Unter Vermeidung von Rekontamination durch Partikel aus der Luft werden die Flaschen mittels Heißluft getrocknet und sterilisiert (diskontinuierlich bei 180 ° C / 2 Stunden).

Die Reinigung der Gummistopfen, mit denen die Injektionsflaschen verschlossen werden, erfolgt unter Verwendung von demineralisiertem Wasser und beispielsweise einem Reinigungsmittel, bestehend aus nichtionogenen, Tensiden und Phosphorsäureestern in wässriger Lösung.

Die gereinigten Stopfen werden unter Verwendung von demineralisiertem Wasser oder filtriertem demineralisiertem Wasser faser- und flusenfrei gespült. Die so gereinigten Stopfen werden dann mittels Dampf sterilisiert.

Die so gereinigten und sterilisierten Injektionsflaschen werden nun aseptisch mit der Ifosfamid-Mesna-Lösung gefüllt und mit dem Gummistopfen versehen, wobei die Behälter vor und nach der Füllung mit Stickstoff begast werden.

Füllmengen:

Ifosfamid	Mesna	Füllmenge	Anwendungsvolumen*
200 mg	40 mg	2 ml	5 ml
500 mg	100 mg	5 ml	12,5 ml
1 g	0,2 g	10 ml	25 ml
2 g	0,4 g	20 ml	50 ml
5 g	1,0 g	50 ml	125 ml
5 g	2,0 g	50 ml	125 ml

* für die spätere Verdünnung des Lyophilisats

Die Füllvolumina sollen folgende Grenzen nicht überschreiten:

Füllvolumen	Grenzwerte der Einzelfüllvolumina	Durchschnittsgrenzwerte des Füllvolumens
2 ml	1,9 - 2,1 ml	1,95 - 2,05 ml
5 ml	4,8 - 5,2 ml	4,9 - 5,1 ml
10 ml	9,7 - 10,3 ml	9,85 - 10,15 ml
20 ml	19,4 - 20,6 ml	19,7 - 20,3 ml
50 ml	48,5 - 51,5 ml	49,25 - 50,75 ml

Die Füllvolumina sind statistisch zu überwachen, wobei mindestens alle 30 Minuten das Füllvolumen je Füllstelle einmal gemessen werden soll.

Die abgefüllten Injektionsflaschen werden so schnell wie möglich auf -40° C eingefroren.

Die Bedingungen für die Gefriertrocknung sind für die einzelnen Größen der Injektionsflaschen unterschiedlich. Es gelten beispielsweise die folgenden Werte:

Dauer der Haupttrocknung bei einer Plattentemperatur von +15° C und 0,6 mbar:
ca. 8 - 10 Stunden für Gefäße mit
200 mg Ifosfamid + 40 mg Mesna
ca. 12 - 15 Stunden für Gefäße mit
500 mg Ifosfamid + 100 mg Mesna
ca. 13 - 16 Stunden für Gefäße mit
1000 mg Ifosfamid + 200 mg Mesna
ca. 25 - 32 Stunden für Gefäße mit
2000 mg Ifosfamid + 400 mg Mesna
ca. 44 - 50 Stunden für Gefäße mit
5000 mg Ifosfamid + 1000 mg Mesna

Dauer der Nachtrocknung ca. 3 - 4 Stunden unter Vakuum von 5×10^{-4} mbar, bei einer Plattentemperatur von +25° C.

Die Restfeuchte (nach K. Fischer bestimmt) soll unter 0,5 % liegen.

Nach Beendigung der Gefriertrocknung werden die Injektionsflaschen verschlossen.

Zur Sicherung der Gummistopfen werden Bördelkappen aufgesetzt und anrolliert. Die fertigen Injektionsflaschen werden auf mechanische Defekte (Sprünge, fehlerhafter Verschluß etc.) kontrolliert.

Beispiel 2

Zur Gefriertrocknung wird folgende Lösung eingesetzt:

Mesna	100 mg
Ifosfamid	100 mg
D-Mannit	70 mg
Inj.-Wasser ad	1 ml

Die Dichte dieser Lösung beträgt 1,101 g/ml bei +20° C Die anzusetzende Lösungsmenge richtet sich nach der jeweiligen Abfüll- und Gefriertrocknungs-Kapazität

Sämtliche Verfahrensschritte bei der Herstellung der Lösung und der Abfüllung werden unter Stickstoff beziehungsweise Stickstoffbegasung durchgeführt.

Herstellung der Lösung:

Es werden ca. 80% Injektionswassermenge vorgelegt und die entsprechende Menge Mesna, Ifosfamid und Mannit in dem Wasser nacheinander unter ständigem Rühren und Stickstoffbegasung gelöst. Nach vollständiger Auflösung wird auf das Endvolumen aufgefüllt und der pH-Wert gemessen.
Die fertige Lösung wird durch Filtration über hierfür übliche keimdichte Filter sterilisiert (zum Beispiel 0,2 µm Porenweite) und unter Vermeidung partikulärer und bakterieller Kontamination bis zur Abfüllung aufbewahrt. Als Druckgas bei der Filtration wird Stickstoff verwendet. Eine Lagerung bei Raumtemperatur (20 - 22° C) soll einschließlich der Zeit der Lösungsherstellung 3 - 4 Stunden nicht überschreiten. Bei nicht sofortiger anschließender Gefriertrocknung kann die Lösung noch etwa 36 Stunden bei +4° C bis +6° C aufbewahrt werden.

Zur Sterilfiltation können zusätzlich übliche Vorfilter (zum Beispiel Sartorius SM 13400 oder Pall LPA) zum Schutz der Sterilfilter eingesetzt werden.

Reinigung der Injektionsflaschen:

Die Injektionsflaschen werden mit demineralisiertem Wasser warm und kalt und Luft gespült. Sämtliche Reinigungsmedien werden durch Filtration von Schwebstoffen befreit.
Unter Vermeidung von Rekontamination durch Partikel aus der Luft werden die Flaschen mittels Heißluft getrocknet und sterilisiert (diskontinuierlich bei 180° C / 2 Stunden).
Die Reinigung der Gummistopfen, mit denen die Injektionsflaschen verschlossen werden, erfolgt unter Verwendung von demineralisiertem Wasser und beispielsweise einem Reinigungsmittel, bestehend aus nicht ionogenen Tensiden und Phosphorsäureestern in wässriger Lösung.
Die gereinigten Stopfen werden unter Verwendung von demineralisiertem Wasser oder filtriertem demineralisiertem Wasser faser-und flusenfrei gespült. Die so gereinigten Stopfen werden dann mittels Dampf sterilisiert.
Die so gereinigten und sterilisierten Injektionsflaschen werden nun aseptisch mit der Ifosfamid-Mesna-Lösung gefüllt und mit dem Gummmistopfen versehen, wobei die Behälter vor und nach der Füllung mit Stickstoff begast werden.

Füllmengen:

Ifosfamid	Mesna	Füllmenge	Anwendungsvolumen*
200 mg	200 mg	2 ml	5 ml
500 mg	500 mg	5 ml	12,5 ml
1 g	1 g	10 ml	25 ml
2 g	2 g	20 ml	50 ml
5 g	5 g	50 ml	125 ml

* für die spätere Verdünnung des Lyophilisates *

Die Füllvolumina sollen folgende Grenzen nicht überschreiten:

Füllvolumen	Grenzwerte der Einzelfüllvolumina	Durchschnittswerte des Füllvolumen
2 ml	1,9 - 2,1 ml	1,95 - 2,05 ml
5 ml	4,8 - 5,2 ml	4,9 - 5,1 ml
10 ml	9,7 - 10,3 ml	9,85 - 10,15 ml
20 ml	19,4 - 20,6 ml	19,7 - 20,3 ml
50 ml	48,5 - 51,5 ml	49,25 - 50,75 ml

Die Füllvolumina sind statistisch zu überwachen, wobei mindestens alle 30 Minuten das Füllvolumen je Füllstelle einmal gemessen werden soll.
Die abgefüllten Injektionsflaschen werden so schnell wie möglich auf -40 °C eingefroren.
Die Bedingungen für die Gefriertrocknung sind für die einzelnen Größen der Injektionsflaschen unterschiedlich. Es gelten beispielsweise die folgenden Werte:
Dauer der Haupttrocknung bei einer Plattentemperatur von +15 °C und 0,6 mbar:
ca. 8 - 10 Stunden für Gefäße mit
200 mg Ifosfamid + 200 mg Mesna
ca. 12 - 15 Stunden für Gefäße mit
500 mg Ifosfamid + 500 mg Mesna
ca. 13 - 16 Stunden für Gefäße mit
1 g Ifosfamid + 1 g Mesna
ca. 25 - 32 Stunden für Gefäße mit
2 g Ifosfamid + 2 g Mesna
ca. 44 - 50 Stunden für Gefäße mit
5 g Ifosfamid + 5 g Mesna
Dauer der Nachtrocknung ca. 3 - 4 Stunden unter Vakuum von $5x10^{-4}$ mbar, bei einer Plattentemperatur von 25 °C. Die Restfeuchte (nach K. Fischer) soll unter 0,5% liegen. Nach Beendigung der Gefriertrocknung werden die Injektionsflaschen verschlossen. Zur Sicherung der Gummistopfen werden Bördelkappen aufgesetzt und anrolliert. Die fertigen Injektionsflaschen werden auf mechanische Defekte (Sprünge, fehlerhafter Verschluß etc.) kontrolliert.

Ansprüche

1. Lyophilisiertes Präparat, bestehend aus Ifosfamid, 0,05 - 1,0 Gewichtsteilen Mesna und 0,1 bis 17 Gewichtsteilen Hexit, Mesna und Hexit jeweils bezogen auf einen Gewichtsteil Ifosfamid sowie gegebenenfalls anderen üblichen pharmazeutischen Hilfsstoffen.

2. Lyophilisiertes Präparat nach Anspruch 1, dadurch gekennzeichnet, daß es als Hexit Mannit enthält.

3. Verfahren zur Herstellung eines Ifosfamid-Mesna-Lyophilisates, dadurch gekennzeichnet, daß man unter einem inerten Gas eine wässrige oder wässrig-ethanolische Lösung, die 1 bis 13 Gewichtsprozent Ifosfamid enthält sowie 0,05 - 13 Gewichtsteile Mesna, 0,1 bis 17 Gewichtsteile Hexit (Mesna und Hexit jeweils bezogen auf einen Gewichtsteil Ifosfamid) und gegebenenfalls 0 bis 16,9 Gewichtsteile (bezogen auf 1 Gewichtsteil Ifosfamid) weitere pharmazeutische Hilfsstoffe, zwischen -70 °C und 0 °C einfriert, und dem so erhaltenen Produkt im gefrorenen Zustand das Wasser entzieht.

4. Verfahren nach Anspruch 3,
dadurch gekennzeichnet,
daß zuerst das nicht adsorptiv gebundene Wasser bei einer Temperatur zwischen -30° C und +40° C und einem Druck zwischen 10^{-3} bis 10 mbar und anschließend adsorptiv gebundenes Wasser bei einer Temperatur zwischen 0° C und 40° C und einem Druck zwischen 10^{-4} bis 10^{-1} mbar entfernt wird.

5. Verfahren nach einem oder mehreren der vorangegangenen Ansprüche,
dadurch gekennzeichnet,
daß als Hexit Mannit verwendet wird.

6. Ifosfamid-Mesna-Lyophilisat, erhalten nach einem oder mehreren der vorangegangenen Ansprüche.

Europäisches Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 89 10 3844

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Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
Y	EP-A-0 002 495 (ASTA) * Ansprüche 1,4-9; Seite 9: "Herstellungsbeispiel für Zubereitungen" *	1-3,5,6	A 61 K 31/675 A 61 K 47/00
Y	EP-A-0 251 657 (CETUS-BEN VENUE) * Ansprüche 1,4,5,7,9,11,12; Seite 9, Beispiel II *	1-3,5,6	
P,Y	EP-A-0 265 812 (ASTA) * Ansprüche 1-6 *	1-3,5,6	

RECHERCHIERTE SACHGEBIETE (Int. Cl.4)

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KATEGORIE DER GENANNTEN DOKUMENTE

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
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P : Zwischenliteratur

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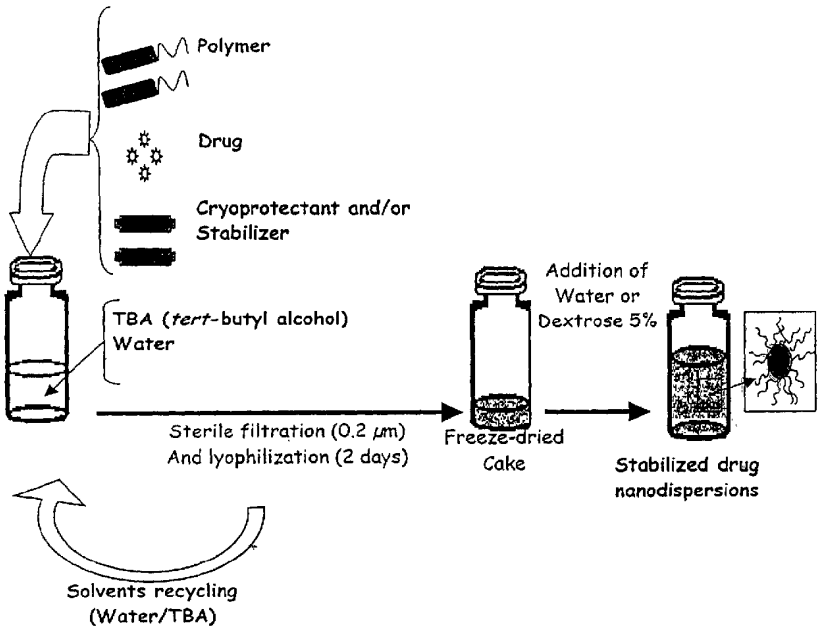
(54) Title: PREPARATION OF STERILE STABILIZED NANODISPERSIONS



(57) Abstract: The instant invention is directed toward a process for the production of a sterile, stabilized nanodispersion or loaded micelle comprising a polymer and a biologically active composition; particularly to nanodispersions produced by rehydration of a freeze-dried cake produced via the direct lyophilization of a stabilized solution comprising a polymer, such as an amphiphilic block copolymer or a small molecular weight surfactant, a biologically active agent, an optional additive, and a suitable solvent.

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PREPARATION OF STERILE STABILIZED NANODISPERSIONS

FIELD OF THE INVENTION

This application relates to sterile, stabilized nanodispersions or micelles comprising a polymer and a biologically active composition; particularly to nanodispersions or micelles produced by rehydration of a freeze-dried cake produced via the direct lyophilization of a solution comprising a dispersing agent such as an amphiphilic block copolymer, or a small molecular weight surfactant, a biologically active composition, a suitable solvent, and optionally, an additive.

BACKGROUND OF THE INVENTION

Many important biologically active agents, such as drugs, are hydrophobic and have limited solubilities in water. In order to attain the expected therapeutic effect of such agents, it is usually required that a solubilized form or nanodispersed form of the agent be administered to a patient.

Thus, a number of methods have been developed which are based on the use of auxiliary solvents; surfactants; soluble forms of the drug, e.g., salts and solvates; chemically modified forms of the drug, e.g., prodrugs; soluble polymer-drug complexes; special drug carriers such as liposomes; and others. Indeed, the use of amphiphilic block copolymer micelles has attracted a great deal of interest as a potentially effective drug carrier which is capable of solubilizing a hydrophobic drug in an aqueous

environment. Each of the above methods is hampered by one or more particular problems, e.g., the method based on the use of surfactant micelles to solubilize hydrophobic drugs has problems in that some of the surfactants are relatively toxic and that precipitation of hydrophobic drugs occurs when subjected to dilution.

A variety of methods and procedures have been described in the prior art for preparing nanodispersions of hydrophobic compounds, particularly pharmaceutical preparations. It is known to incorporate hydrophobic biologically active agents having limited solubility in an aqueous or hydrophilic environment into block copolymers which form micelles capable of acting as carriers for the biologically active agents.

A variety of methods have been utilized, either alone or in combination, in order to incorporate or solubilize one or more biologically active agents, within polymer carriers. Included among these prior art methods are:

(1) Stirring

This method consists in adding the drug to a polymeric micelle solution and permitting the drug to dissolve in the micellar core. Such a procedure yields generally poor entrapment efficiency mainly because of the poor affinity of the drug for the aqueous medium. The water solution can then be freeze dried;

(2) Heating

A drug and a block copolymer are dissolved in an organic solvent and the solvent is evaporated off at an elevated temperature (from about 40°C to about 80 °C under a nitrogen atmosphere or by rotary evaporator under vacuum). The resulting mixture is kept at a temperature of

20°C to about 80 °C, preferably at about 40-70°C, for 2 hours. Then, warm water (about 40°C to about 70°C) is added thereto, and the mixture is stirred until a polymeric micelle containing drug is formed.

(3) Ultrasonic Treatment

A mixture of a drug and an aqueous solution of a block copolymer is subjected to ultrasonic treatment for a period ranging from about 1 second to 1 hour and then stirred at room temperature to obtain micelles containing the drug.

(4) Solvent Evaporation

A drug is dissolved in a water-immiscible organic solvent, for example, dichloromethane, chloroform and the like, and then added to an aqueous solution of a block copolymer. Subsequently, the organic solvent is slowly evaporated off, e.g. at 25-40°C while stirring, optionally under vacuum, and then filtered to remove undissolved drug.

(5) Dialysis

A drug and a block copolymer are dissolved in a water-miscible organic solvent. The solution is dialyzed against a buffer solution and then against water.

In the dialysis method, suitable water-miscible organic solvents for dissolving drugs may include members selected from the group comprising acetonitrile, dimethylformamide (DMF), dimethylsulfoxide (DMSO), dioxane, dimethylacetamide (DMAC) and the like.

The unloaded drug can diffuse with the organic solvent and/or precipitate in the dialysis bag. The precipitated drug can be removed by filtration. The

colloidal dispersion is then generally freeze-dried.

(6) Emulsification-Evaporation/Salting Out Procedure

The drug and polymer are dissolved in a water-immiscible organic solvent which is emulsified in water. The aqueous phase may or may not contain stabilizers. The organic solvent is then removed by evaporation or other methods. If needed, the nanodispersion can be further purified to remove the stabilizers. Then, the colloidal dispersion can be freeze-dried.

(7) Spray-Drying

The drug is dissolved in an organic solvent which is then nebulized so as to obtain drug loaded nanoparticles. Such a process may not be adapted for temperature-sensitive drugs and is not optimal to produce particles of less than 1 μm.

(8) Micronization/Controlled Precipitation/High Pressure Homogenization

These methods are aimed at producing nanoscaled drug dispersions. Such techniques can be applied to almost any kinds of hydrophobic drugs. All require specific specialized equipment and/or are difficult to control.

Each of the above procedures are associated with certain drawbacks. For example, with some of the procedures the stabilizers need to be removed. Others yield poor entrapment efficiencies (e.g. equilibration), relatively large particle sizes (e.g. spray drying) or are time-consuming (e.g. dialysis).

DESCRIPTION OF THE PRIOR ART

Many studies, literature articles and patents have been directed toward the use of amphiphilic block

copolymers having surfactant-like properties, particularly regarding their use as carriers for hydrophobic drugs.

For example, EP No.0397307A2 discloses polymeric micelles of an AB type amphiphilic diblock copolymer which contains poly(ethylene oxide) as the hydrophilic component and poly(amino acid derivatives) as the hydrophobic component, wherein therapeutically active agents are chemically bonded to the hydrophobic component of the polymer.

EP No. 0583955A2, on the other hand, discloses a method for physically incorporating hydrophobic drugs into amphiphilic diblock copolymer micelles described in EP No. 0397307A2. This method, thus, solves the above disadvantage of the chemical bond type polymeric micelle drug

U.S. Pat. No. 4,745,160 discloses a pharmaceutically or veterinary acceptable amphiphilic, non-cross linked linear, branched or graft block copolymer having polyethylene glycol as the hydrophilic component and poly(D-, L- and DL-lactic acids) as the hydrophobic components. In the preparation process, a water-miscible and lyophilizable organic solvent is used. When a mixture of the polymer, drug and organic solvent is mixed with water, precipitates are formed and then the mixture is directly lyophilized to form particles. Thereafter, when this particle is dispersed in water, it forms a colloidal suspension containing fine particles wherein hydrophilic components and hydrophobic components are mixed.

In contrast to that which is disclosed in the prior art, the present invention forms a clear solution that can

be sterilized by filtration (220 nm pore size filter) prior to freeze-drying, and yields a storable powder which is readily reconstituted. What is particularly unique, is that the micelle or nanodispersion is produced directly and spontaneously upon addition of an aqueous medium. This is in direct contrast to prior art processes which must first produce a nanodispersion which is subsequently lyophilized and then reconstituted. Furthermore, the instant process suffers no loss of drug during the loading procedure.

U.S. Patent No. 6,322,805 discloses a biodegradable polymeric drug carrier micelle composition capable of solubilizing a hydrophobic drug in a hydrophilic environment. The patent discloses a biodegradable polymeric drug carrier micelle and a hydrophobic drug wherein the drug is physically trapped within and not covalently bonded to the polymeric drug carrier micelle. The drug carrying micelle is capable of dissolving in water to form a solution thereof, and the drug carrier comprises an amphiphilic block copolymer having a hydrophilic poly(alkylene oxide) component, and a biodegradable hydrophobic polymer component selected from the group consisting of poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), poly(ε-caprolactone), a derivative thereof and a mixture thereof. The disclosed micelle is characterized as a solubilizing agent for a hydrophobic drug. The drug solution thus obtained may be freeze-dried for long-term storage, and the lyophilized biodegradable polymeric micelle-type drug composition may be restored to its original solution by using water or an isotonic solution. This patent also

fails to disclose or suggest a process wherein a sterile nanodispersion is spontaneously created upon reconstitution of a lyophilized cake.

U.S. Pat. No. 5,543,158 discloses nanoparticles or microparticles formed of a block copolymer consisting essentially of poly(alkylene glycol) and a biodegradable polymer, poly(lactic acid). In the nanoparticle or microparticle, the biodegradable moieties of the copolymer are in the core of the nanoparticle or microparticle and the poly(alkylene glycol) moieties are on the surface of the nanoparticle or microparticle in an amount effective to decrease uptake of the nanoparticle or microparticle by the reticuloendothelial system. In this patent, the molecular weight of the block copolymer is too high to be soluble in water, and a nanoparticle can only be prepared by first dissolving the block copolymer and a drug in an organic solvent, forming an o/w emulsion by sonication or stirring, and then collecting the precipitated nanoparticles containing the drug. The patent fails to provide the concept of solubilization of hydrophobic drugs, nor does it teach or suggest the formation of a clear, sterilizable solution containing the polymer/drug blend and subsequent lyophilization thereof, resulting in a readily dispersible nanodispersion, formed upon reconstitution.

EP 0520888 A1 discloses a nanoparticle made of a poly(lactic acid) and poly(alkylene oxide) block copolymer. A high molecular weight poly(lactic acid) is used and a surfactant is employed in preparing a colloidal suspension of the nanoparticles. In this patent, nanoparticles are prepared by dissolving the block

copolymer and a drug in an organic solvent, emulsifying the organic solution in water, and evaporating the organic solvent to precipitate the nanoparticles containing the drug. The resulting nanoparticles are fine particles having both hydrophilic and hydrophobic components and they are not soluble in water.

U.S. Patent 4,370,349 and 4,311,712 disclose a process for preparing a freeze-dried, potential liposome, mixture which comprises either (a) dissolving at least one liposome-forming amphiphilic lipid, at least one biologically-active compound, and optionally one or more adjuvants, in a suitable solvent, and then freeze-drying the solution, or (b) preparing by any known method an aqueous liposome composition containing at least one biologically-active compound, and then freeze-drying the said aqueous liposome composition. The patents are particularly directed toward a process for preparing an aqueous liposome composition which comprises dispersing said freeze-dried, potential liposome, mixture, obtained by procedure (a) or (b), in a suitable aqueous medium. The process of the instant invention is not directed toward liposome production.

The patents fail to disclose the formation of a clear solution that can be sterilized by filtration (e.g. by use of a filter media having a pore size of about 220 nm) prior to freeze-drying, yields a storable powder which is readily reconstituted, and suffers no loss of drug during the loading procedure. Furthermore, the patents fail to teach a method for producing a sterile drug formulation which, upon the addition of water, produces drug-loaded micelles or drug nanodispersions stabilized by an

amphiphilic biodegradable polymer.

SUMMARY OF THE INVENTION

In order to overcome the problems encountered by the prior art, the instantly disclosed invention relies on the lyophilization of an organic solvent or mixture thereof, or a mixture of water and organic solvent in which the biologically active agent, e.g. a drug, the dispersing agent, e.g. a polymer, copolymer, small molecular weight surfactant, or the like, and optionally an additive, non-limiting examples of which include a bulk forming additive, a cryoprotectant, and a lyoprotectant, is dissolved. Such a solution can be sterilized by filtration before lyophilization and subsequently freeze-dried, forming a powder or cake. The resulting freeze-dried material can be stored and then redispersed prior to use by the addition of an aqueous solution. The organic solvent can be collected on the condenser and recycled for future use.

The instant process illustrates a simple and elegant procedure for directly obtaining nanodispersions upon reconstitution, thereby resulting in the formation of drug-loaded micelles or drug nanodispersions which are stabilized by a suitable dispersing agent, e.g. an amphiphilic biodegradable polymer or copolymer, or alternatively a small molecular weight surfactant. There is no loss of the drug during the loading procedure.

Examples of suitable dispersing agents include, but are not limited to amphiphilic polymers such as linear, branched or star-shaped block amphiphilic copolymers where the hydrophilic part may include at least one member

selected from a group consisting of poly(ethylene oxide), poly(N-vinylpyrrolidone), poly(N-2-hydroxypropylmethacrylamide), poly(2-ethyl-2-oxazoline), poly(glycidol), poly(2-hydroxyethylmethacrylate), poly(vinylalcohol), polymethacrylic acid derivatives, poly(vinylpyridinium), poly((ammoniumalkyl)methacrylate), poly((aminoalkyl)methacrylate) and combinations and derivatives thereof; and

wherein the hydrophobic segment may include at least one member which is selected from a group consisting of a poly(ester), poly(ortho ester), poly(amide), poly(ester-amide), poly(anhydride), poly(propylene oxide), poly(tetrahydrofuran) and combinations thereof.

The poly(ester) may be at least one member selected from a group consisting of poly(ε-caprolactone), poly(lactide), poly(glycolide), poly(lactide-co-glycolide), poly(hydroxy alkanoates) (e.g. poly (γ-hydroxybutyrate), poly(δ-hydroxy valerate)), poly (β-malic acid), and derivatives thereof.

Non-limiting illustrative examples of low molecular weight surfactants may include at least one member selected from the group consisting of sodium lauryl sulfate, hexadecyl pyridinium chloride, polysorbates, sorbitans, poly(oxy ethylene) alkyl ethers, poly(oxyethylene) alkyl esters and the like, including various combinations thereof.

Without limiting the scope of the present invention, suitable biologically active agents for incorporation in a nanodispersion produced in accordance with the teachings of the instant invention may include agents such as anti-

cancer drugs, antiphlogistic anodynes, immuno-suppressants, hepatism remedies, hormone compositions, chemotherapeutics, metabolic pharmaceuticals, digestive disease remedies, respiratory disease remedies, anti-allergic pharmaceuticals, central nervous system disease remedies, peripheral disease remedies, and circulatory disease remedies. In their broadest sense, the "biologically active agents" of the present invention will include both human and veterinary medicaments, hormones, marker compounds, and the like.

The instant invention is most suitable for the manufacture of formulations containing biologically active agents which are sensitive or which may be degraded by exposure to adverse pH, temperature, and certain types of solvent environments.

Hydrophobic drugs which are of particular interest for incorporation in the present invention may include, but are not limited to members selected from the group comprising paclitaxel, doxorubicin, melphalan, docetaxel, teniposide, etoposide, daunomycin, vinblastine, indomethacin, ibuprofen, cyclosporine, tacrolimus, ketoconazole, amphotericin B, fenobibrate and biphenyl dimethyl dicarboxylate(DDB).

Suitable solvents or mixtures thereof will have the ability to dissolve appropriate amounts of the drug, without denaturation or degradation thereof. Preferred solvents (or mixtures of solvents) should remain solid during the freeze-drying process and should be relatively inert with regard to rubber seals. The solvent should also be easily removed under reduced pressure. While numerous solvents are capable of functioning in accordance with the

process of the instant invention, non-limiting illustrative examples of such solvents include t-butanol, n-butanol, dioxane, pyridine, pyrimidine, and piperidine, which are useful either alone or in combination, and may be further admixed, e.g. with water, to form a binary mixture. It is known that the latter 4 solvents may pose potential toxicity problems.

Other solvents may be added in small amounts (< 10%) to facilitate the dissolution of the drug.

Accordingly, it is a principle objective of the instant invention to provide a process for the formation of a sterile, loaded micelle or nanodispersion comprising an amphiphilic biodegradable polymer.

It is a further objective of the instant invention to provide a process whereby a clear solution of the biologically active agent, polymer and optionally an additive (e.g. a bulk forming agent, a cryoprotectant, a lyoprotectant) and/or stabilizer is initially formed with a suitable solvent prior to lyophilization.

It is a further objective of the instant invention to provide a process whereby the solvent used in forming the clear solution is recyclable.

It is a still further objective of the invention to produce a stable freeze-dried cake which is readily dispersible to form a stabilized drug nanodispersion.

Other objectives and advantages of this invention will become apparent from the following description taken in conjunction with the accompanying drawings wherein are set forth, by way of illustration and example, certain embodiments of this invention. The drawings constitute a part of this specification and include exemplary

embodiments of the present invention and illustrate various objectives and features thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a schematic representation of the drug loading procedure using tert-butyl alcohol;

Figure 2 shows the stability of formulation 9 over time following the addition of water.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the schematic representation set forth in Figure 1, predetermined amounts of biologically active agent, dispersing agent, e.g. a suitable polymer, copolymer or small molecular weight surfactant and, optionally, an additive, e.g. a cryoprotectant/ a lyoprotectant/ a bulk forming agent or the like (e.g. commercially available poly (vinylpyrrolidone) Kollidon 12 PF® or 17 PF®, BASF) and/or additional stabilizers are dissolved in a suitable solvent, e.g. tert-butyl alcohol (TBA) or a binary mixture of TBA and water. For purposes of this invention cryoprotectant, lyoprotectant and bulk forming agents will be used interchangeably and referred to as an "additive". Other suitable additives include, but are not limited to poly(ethylene glycol), sugars (lactose, trehalose), polyols (mannitol) and amino acids soluble in the solvent or solvent mixture. As broadly recited herein, the term "solvent" is understood to mean a single solvent, a mixture of solvents, or a binary mixture of one or more solvents and water. In one illustrative embodiment, additional dissolution enhancing means may be

employed to aid in the forming of a solution. Illustrative, but non-limiting examples of said dissolution enhancing means may include a process, for example, wherein the mixture may be vortexed and sonicated for 30 sec, if needed. For some polymers, the solution may also need to be heated to speed up dissolution. The clear solution thus obtained is stirred gently on a rotary shaker table at room temperature for 30 minutes. The solution is filtered, e.g. through a 0.2μm filter. Subsequently, the solution is rapidly frozen and lyophilized for two days, whereby a dry cake of drug dispersed polymer is obtained.

Lastly, the freeze-dried cake may be rehydrated with a predetermined amount of water or a solution of saline 0.9% or dextrose 5%, whereby a stable nanodispersion is spontaneously produced. The mean particle size is determined by dynamic light scattering.

Example 1. Incorporation of docetaxel (DCTX) in PVP-b-PDLLA diblock copolymer micelles via a lyophilization method using tert-butyl alcohol (TBA) and water mixture.

The PVP-b-PDLLA diblock copolymer was prepared by ring opening polymerization of D,L-lactide using a PVP-OH initiator (US Patent 6,338,859 (2002)). It was characterized by gel permeation chromatography, elemental analysis and nuclear magnetic resonance spectroscopy. The number average molecular weight (M_n), the polydispersity index and PDLLA content were 4600, 1.3 and 37 mol%, respectively.

The polymer was dissolved in water, resulting in a concentration of 146.15 mg/mL. The drug was dissolved in TBA, resulting in a concentration of 7.14 mg/mL. In order to obtain a final polymer concentration of 27.14 mg/mL (total final volume 0.7 mL), a pre-determined volume of pure water was added to the polymer solution (Table 1). A pre-determined volume of pure TBA was thereafter added to the aqueous polymer solution to obtain different water/TBA ratios, taking into account the volume of drug solution added thereafter.

Finally, the solution of drug in TBA was added, to reach a final **5 %** (w/w) drug loading level. The clear solution obtained was gently stirred for 3½ hours at about 6°C.

Table 1. Docetaxel Incorporation Protocol.

water/TBA	80:20	70:30	60:40	50:50
Volume of polymer solution (mL)	0.130	0.130	0.130	0.130
Weight of polymer (mg)	19	19	19	19
Volume of pure water (mL)	0.430	0.360	0.290	0.220
Volume of pure TBA (mL)	0	0.070	0.140	0.210
Volume of drug solution (mL)	0.140	0.140	0.140	0.140
Weight of drug (mg)	1	1	1	1
Total volume (mL)	0.7	0.7	0.7	0.7

Tert-butanol/water ratio = 80:20 v/v.

The solution was filtered through a 0.2 μm filter, rapidly frozen at -80°C and lyophilized for 48 hours. The freeze-dried cake was rehydrated with 3 mL of 5% dextrose. The mean particle size was determined by dynamic light scattering and monitored for 120h.
The size results are summarized in table 2.

Table 2.

Size of DCTX-loaded PVP-b-PDLLA block copolymer micelles prepared by tert-butyl alcohol lyophilization method.

%TBA	Size (nm)								
	15 min	1h	2h	4h	6h	8h	24h	72h	120h
20	38 (75%) 205 (25%)	38 (71%) 224 (29%)	39 (69%) 246 (31%)	39 (71%) 269 (29%)	44 (82%) 355 (18%)	46 (81%) 344 (19%)	42 (78%) 277 (22%)	41 (87%) 157 (13%)	38 (85%) 121 (15%)
30	37	36	39	37	37	37	36 (89%) 302 (11%)	37 (89%) 123 (11%)	40
40	46	45	46	39	43	49	41 (82%) 224 (18%)	43 (88%) 291 (12%)	41 (75%) 224 (25%)
50	42 (69%) 100 (31%)	47	46	46	45	46	49		

Example 2. Incorporation of paclitaxel (PTX) in PVP-b-PDLLA diblock copolymer micelles via a lyophilization method using tert-butyl alcohol (TBA) and water mixture.

The PVP-b-PDLLA diblock copolymer was prepared and characterized as described in example 1. The number average molecular weight (M_n), the polydispersity index and PDLLA content were 4600, 1.3 and 37 mol%, respectively. The polymer was dissolved in water, resulting in a concentration of 146.15 mg/mL. The drug was dissolved in TBA, resulting in a concentration of 7.14 mg/mL.

In order to obtain a final polymer concentration of 27.14 mg/mL (total final volume 0.7 mL), a pre-determined volume of pure water was added to the polymer solution (Table 3). A pre-determined volume of pure TBA was added to the aqueous polymer solution to obtain different water/TBA ratios, taking into account the volume of drug solution added thereafter.

Finally, the solution of drug in TBA was added, to reach a final **5 %** (w/w) drug loading level.
The clear solution obtained was gently stirred for 3 hours at about 6°C.

Table 3. PTX incorporation protocol.

water/TBA	70:30
Volume of polymer solution (mL)	0.130
Weight of polymer (mg)	19
Volume of pure water (mL)	0.360
Volume of pure TBA (mL)	0.070
Volume of drug solution (mL)	0.140
Weight of drug (mg)	1
Total volume (mL)	0.7

The solution was filtered through a 0.2 μm filter, rapidly frozen at -80°C and lyophilized for 48 hours.
The freeze-dried cake was rehydrated with 3 mL of 5% dextrose. The mean particle size was determined by dynamic light scattering and monitored for 24h.
The size results are summarized in table 4.

Table 4.

Size of PTX-loaded PVP-b-PDLLA block copolymer micelles prepared by tert-butyl alcohol lyophilization method.

% tert-butyl alcohol	Size (nm)	
	2h30	24h
30	50 (35%%) < 3 (33%) 558 (32%)	49 (31%) < 3 (28%) 423 (40%)

Example 3. Incorporation of teniposide in PVP-b-PDLLA diblock copolymer micelles via a lyophilization method using 1,4-dioxane.

The PVP-b-PDLLA diblock copolymer was prepared and characterized as described in example 1. The number average molecular weight (M_n), the polydispersity index and PDLLA content were 4600, 1.3 and 37 mol%, respectively. The polymer was dissolved in water, resulting in a concentration of 50 mg/mL). The drug was dissolved in 1,4-dioxane, resulting in a concentration of 5 mg/mL. In order to obtain a final polymer concentration of 19 mg/mL (total final volume 0.7 mL), a pre-determined volume of pure water was added to the polymer solution (Table 5). A pre-determined volume of pure 1,4-dioxane was added to the aqueous polymer solution to obtain different water/1,4-dioxane ratios, taking into account the volume of drug solution added thereafter.

Finally, the solution of drug in 1,4-dioxane was added, to reach a final **5.3 %** (w/w) drug loading level. The clear solution obtained was gently stirred for 2 hours

at about 6°C.

Table 5. Teniposide incorporation protocol.

water/1,4-dioxane	80:20
Volume of polymer solution (mL)	0.266
Weight of polymer (mg)	13.3
Volume of pure water (mL)	0.294
Volume of pure 1,4-dioxane (mL)	0
Volume of drug solution (mL)	0.140
Weight of drug (mg)	0.7
Total volume (mL)	0.7

The solution was filtered through a 0.2 μm filter, rapidly frozen at -50°C and lyophilized for 48 hours.
The freeze-dried cake was rehydrated with 3 mL of 5% dextrose. The mean particle size was determined by dynamic light scattering and monitored for 24h.
The size results are summarized in table 6.

Table 6.

Size of teniposide-loaded PVP-b-PDLLA block copolymer micelles prepared by 1,4-dioxane lyophilization method.

	Size (nm)	
% 1,4-dioxane	1h	24h
20	235 (97%) < 3 (3%)	184 (65%) < 3 (23%) 51 (12%)

Example 4. Incorporation of etoposide in PVP-b-PDLLA diblock copolymer micelles via a lyophilization method using 1,4-dioxane.

The PVP-b-PDLLA diblock copolymer was prepared and characterized as described in example 1. The number average molecular weight (M_n), the polydispersity index and PDLLA content were 4600, 1.3 and 37 mol%, respectively. The polymer was dissolved in water, resulting in a concentration of 50 mg/mL. The drug was dissolved in 1,4-dioxane, resulting in a concentration of 5 mg/mL.
In order to obtain a final polymer concentration of 19 mg/mL (total final volume 0.7 mL), a pre-determined volume of pure water was added to the polymer solution (Table 7). A pre-determined volume of pure 1,4-dioxane was thereafter added to the aqueous polymer solution to obtain different water/1,4-dioxane ratios, taking into account the volume of drug solution added thereafter.
Finally, the solution of drug in 1,4-dioxane was added, to reach a final **5.3 %** (w/w) drug loading level.
The clear solution obtained was gently stirred for 2 hours at about 6°C.

Table 7. Etoposide incorporation protocol.

water/1,4-dioxane	80:20	70:30	65:35	50:50
Volume of polymer solution (mL)	0.266	0.266	0.266	0.266
Weight of polymer (mg)	13.3	13.3	13.3	13.3
Volume of pure water (mL)	0.294	0.224	0.189	0.084
Volume of pure 1,4-dioxane (mL)	0	0.070	0.105	0.210
Volume of drug solution (mL)	0.140	0.140	0.140	0.140
Weight of drug (mg)	0.7	0.7	0.7	0.7
Total volume (mL)	0.7	0.7	0.7	

The solution was filtered through a 0.2 μm filter, rapidly frozen at -50°C and lyophilized for 48 hours.
The freeze-dried cake was rehydrated with 3 mL of 5%

dextrose. The mean particle size was determined by dynamic light scattering and monitored for 24h.
The size results are summarized in table 8.

Table 8.

Size of etoposide-loaded PVP-b-PDLLA block copolymer micelles prepared by 1,4-dioxane lyophilization method.

% 1,4-dioxane	Size (nm)	
	1h	24h
20	284 (65%) < 3 (26%) 51 (9%)	257 (68%) < 3 (23%) 58 (9%)
30	265 (74%) < 3 (17%) 45 (9%)	273 (77%) < 3 (16%) 56 (7%)
35	272 (76%) < 3 (16%) 51 (8%)	274 (75%) < 3 (17%) 56 (8%)
50	224 (70%) < 3 (20%) 56 (10%)	168 (75%) < 3 (19%) 32 (6%)

Table 9 shows that upon the addition of water, colloidal drug dispersions (< 1 μm) were spontaneously obtained.

TABLE 9

DRUG NANODISPERSIONS OBTAINED BY THE TERT-BUTANOL LYOPHILIZATION METHOD

Ex	Polymer (*w/w*)	M_n*	Additive	Drug	Drug loading (*w/w*%)**	Drug concentration in water (mg/mL)	Mean size of resulting particles (water,25°C) (nm)
1	PVP-*b*-PDLLA (80 :20)	15079	None	Paclitaxel	15	0.75	66% : 210 ± 64 34% < 3
2	PVP-*b*-PDLLA (80 :20)	15079	Kollidon 12PF 50% (*w/w*)	Paclitaxel	15	0.75	75% : 153 ± 66 25% < 3
3	PVP-*b*-PDLLA (80 :20)	15079	None	Indomethacin	10	0.5	80% : 148 ± 41 20% < 3
4	PVP-*b*-PDLLA (80 :20)	15079	Kollidon 12PF 50% (*w/w*)	Indomethacin	10	0.5	80% : 141 ± 42 20% < 3
5	PHPMA-*b*-PCL-*b*-PHPMA (71:29)	9100	None	Paclitaxel	15	0.75	64% : 270 ± 71 36% : 44 ± 15
6	PHPMA-*b*-PCL-*b*-PHPMA (71:29)	9100	Kollidon 12PF 50% (*w/w*)	Paclitaxel	15	0.75	60% : 177 ± 26 40% : 33 ± 6
7	PVP-*b*-PCL-*b*-PVP (79:21)	11400	None	Paclitaxel	15	0.75	87% : 294 ± 57 12% : 60 ± 13 1% : 10 ± 2
8	PHPMA-*b*-PCL-*b*-PHPMA (79:21)	13400	None	Doxorubicin	15	0.75	60% : 350 ± 65 40% < 3
9	PHPMA-*b*-PCL-*b*-PHPMA (71:29)	9100	Kollidon 12PF 50% (*w/w*)	Paclitaxel	5	0.75	65% : 32 ± 10 23% : 255 ± 75

** Based on the amount of (polymer + drug)

Nomenclature of the polymers :

- PVP-*b*-PDLLA : Poly(*N*-vinyl-2-pyrrolidone)-*block*-poly(D,L-lactide)
- PHPMA-*b*-PCL-*b*-PHPMA : poly(N-2-hydroxypropyl methacrylamide)-block-poly(ε-caprolactone)-block-poly(N-2-hydroxypropyl methacrylamide)
- PVP-*b*-PCL-*b*-PVP : poly(N-vinyl pyrrolidone)-block-poly(ε-caprolactone)-block-poly(N-inyl pyrrolidone)

Figure 2 shows the stability of formulation 9 following the addition of water. The obtained solution was optically transparent suggesting the formation of polymeric micelles (or secondary aggregates of polymeric micelles). This formulation was stable for at least 13 hours when kept at room temperature.

It is to be understood that while a certain form of the invention is illustrated, it is not to be limited to the specific form or arrangement herein described and shown. It will be apparent to those skilled in the art that various changes may be made without departing from the scope of the invention and the invention is not to be considered limited to what is shown and described in the specification and drawings/figures. One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objectives and obtain the ends and advantages mentioned, as well as those inherent therein. The embodiments, methods, procedures and techniques described herein are presently representative of the preferred embodiments, are intended to be exemplary and are not intended as limitations on the scope. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention and are defined by the scope of the appended claims. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in

the art are intended to be within the scope of the following claims.

CLAIMS

What is claimed is:

Claim 1. A process for the production of a stabilized nanodispersion or loaded micelle containing a biologically active agent comprising:

forming a solution including at least one dispersing agent, at least one biologically active agent, and at least one solvent;

lyophilizing said solution wherein a solid product is formed; and

rehydrating said solid product;

whereby said stabilized nanodispersion or loaded micelle is produced.

Claim 2. A process for the production of a stabilized nanodispersion or loaded micelle containing a biologically active agent comprising:

forming a solution including at least one dispersing agent, at least one biologically active agent, at least one additive, and at least one solvent;

lyophilizing said solution wherein a solid product is formed; and

rehydrating said solid product;

whereby said stabilized nanodispersion or loaded micelle is produced.

Claim 3. A process for the production of a stabilized nanodispersion or loaded micelle containing a biologically active agent comprising:

forming a solution including at least one dispersing

agent, at least one biologically active agent, and at least one solvent;

filtering said solution to yield a sterile filtrate;

lyophilizing said filtrate wherein a solid product is formed; and

rehydrating said solid product;

whereby said stabilized nanodispersion or loaded micelle is produced.

Claim 4. A process for the production of a stabilized nanodispersion or loaded micelle containing a biologically active agent comprising:

forming a solution including at least one dispersing agent, at least one biologically active agent, at least one additive, and at least one solvent;

filtering said solution to yield a sterile filtrate;

lyophilizing said filtrate wherein a solid product is formed; and

rehydrating said solid product;

whereby said stabilized nanodispersion or loaded micelle is produced.

Claim 5. The product produced in accordance with the process of claim 1.

Claim 6. The product produced in accordance with the process of claim 2.

Claim 7. The product produced in accordance with the process of claim 3.

Claim 8. The product produced in accordance with the process of claim 4.

Claim 9. A process in accordance with any one of claims 1 or 2 or 3 or 4 wherein said step of rehydrating includes combining said solid product with a sufficient amount of water, saline solution or dextrose solution.

Claim 10. A process in accordance with any one of claims 1 or 2 or 3 or 4 wherein said solvent is at least one solvent selected from the group consisting of t-butanol, n-butanol, dioxane, pyridine, pyrimidine, piperidine, combinations thereof, and binary mixtures including any of said solvents or combinations thereof in admixture with water.

Claim 11. A process in accordance with any one of claims 2 or 4 wherein said additive is at least one member selected from the group consisting of poly(vinylpyrrolidone, poly(ethylene glycol), lactose, trehalose, mannitol, amino acids soluble in said solvent, or combinations thereof.

Claim 12. A process in accordance with any one of claims 1 or 2 or 3 or 4 wherein said forming step further includes at least one dissolution enhancing means selected from the group consisting of sonicating, vortexing and heating.

Claim 13. A process in accordance with any one of

claims 1 or 2 or 3 or 4 wherein said dispersing agent is at least one member selected from the group consisting of a polymer, a copolymer, a small molecular weight surfactant, and combinations thereof.

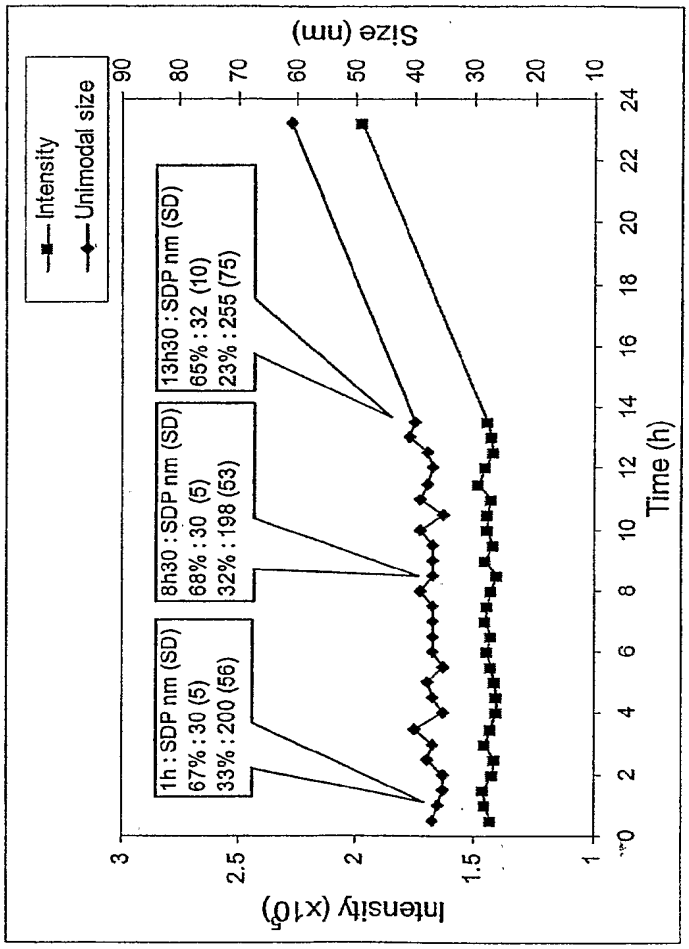
Claim 14. A process in accordance with any one of claims 1 or 2 or 3 or 4 wherein said biologically active agent is at least one member selected from the group consisting of anti-cancer drugs, antiphlogistic anodynes, immuno-suppressants, hepatism remedies, hormone compositions, chemotherapeutics, metabolic pharmaceuticals, digestive disease remedies, respiratory disease remedies, anti-allergic pharmaceuticals, central nervous system disease remedies, peripheral disease remedies, circulatory disease remedies, and combinations thereof.

Claim 15. A process in accordance with any one of claims 1 or 2 or 3 or 4 wherein said biologically active agent is at least one hydrophobic pharmaceutical composition selected from the group consisting of paclitaxel, doxorubicin, melphalan, docetaxel, teniposide, etoposide, daunomycin, vinblastine, indomethacin, ibuprofen, cyclosporine, tacrolimus, biphenyl dimethyl dicarboxylate, ketoconazole, amphotericin B, fenobibrate, and combinations thereof.

Figure 1

Polymer
Drug
Cryoprotectant and/or
Stabilizer
TBA (tert-butyl alcohol)
Water
Addition of
Water or
Dextrose 5%
Sterile filtration (0,2 µm)
And lyophilization (2 days)
Freeze-dried
Cake
Stabilized drug
nanodispersions
Solvents recycling
(Water/TBA)

FIGURE 2


Intensity
Unimodal size
1h : SDP nm (SD)
67% : 30 (5)
33% : 200 (56)
8h30 : SDP nm (SD)
68% : 30 (5)
32% : 198 (53)
13h30 : SDP nm (SD)
65% : 32 (10)
23% : 255 (75)
Intensity (x10⁵)
Size (nm)
Time (h)

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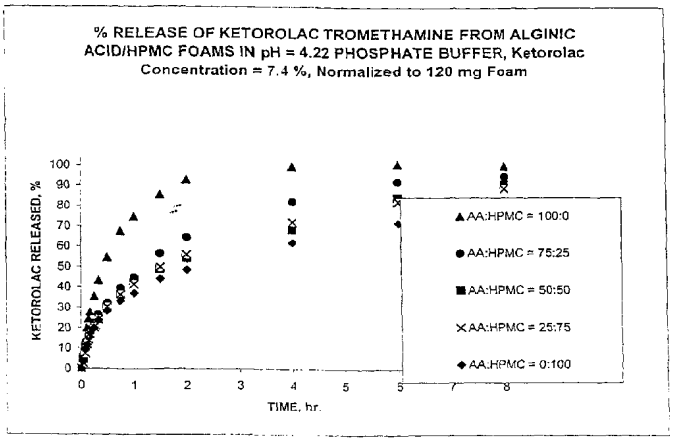

(57) Abstract: Polymer foams and films for delivery of therapeutic agents to and through nasal, oral or vaginal mucosa and cornified or non-cornified epithelium of labia and scrotum. Polymer foams or absorbable or non-absorbable films containing a therapeutic agent incorporated therein wherein said agent is released from said foams or films upon placement of said foam or film on the surface epithelium of nasal, oral, or vaginal labia or scrotum. The foam or the film has a controllable rate of gelling, swelling and degradation and is preformed into a device or is applied as a coating to a surface of a more complex drug delivery system.

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THERAPEUTIC COMPOSITIONS FOR DRUG DELIVERY TO AND THROUGH COVERING EPITHELIA

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention concerns therapeutic compositions suitable for delivery of therapeutic agents to and through covering epithelia of nasal, oral or vaginal cavities as well as through the epithelium of labia and scrotum. In particular, the invention concerns the compositions comprising a therapeutic agent and a polymer, further optionally in combination with mucoadhesive agents, penetrations enhancers, release modifiers and/or other additives and excipients. These compositions may be prepared as biodegradable or non-biodegradable foams or films of solid structure or semi-solid or liquid preparation comprising a therapeutic agent incorporated therein wherein said agent is released from said compositions upon placement thereof on the surface of or in the close proximity of a nasal, buccal, vaginal, labial or scrotal epithelium. Depending on a presence of specific components present in said compositions, the compositions of the invention act either locally on the covering epithelium or are delivered through such epithelium to a systemic circulation. The compositions of the invention have a controllable rate of gelling, swelling and degradation. The compositions are either preformed into a device such as a foam tampon, tampon-like cylinder, strip, pad, pillow, tube, sheet, sphere, tablet, ring or bead or single or double sided film sheet or are applied, as one component, to a surface of a more complex drug delivery system which comprises, as a second component, a device made of a different material, such as a conventional tampon, tampon-like device, pessary, ring, strip, pad,

pillow, sheet, tube, sphere, tablet or a bead covered by said composition. Liquid composition is supplied and stored as a sprayable system which upon spraying onto an epithelial surface rapidly gels into a foam layer. The film is either preformed into sheets of a desirable shape and size or is sprayed onto the mucosal, labial or scrotal epithelial surface wherein it gels and forms the foam, film or gel or is applied to a surface and covers and coats such surface of the vaginal, nasal, buccal, scrotal or labial device.

Background of the Invention and Related Disclosures

The skin, scrotal and labial epithelium and mucous membranes such as those that line the vagina or nasal and oral cavity, serve as a protective barrier against the outside environment so that bacteria and viruses are excluded and prevented from entering the body through this route. Besides excluding harmful bacteria and viruses, the above described barrier is also very effective at excluding chemicals, drugs and pharmacological agents that are applied to the skin, labia, scrotum or mucosa. This barrier is composed of several layers.

In the skin, the stratum corneum represents a cornified layer, epidermis is formed of a layer of stratified squamous epithelial cells, dermis is formed of a thin layer of cells that interdigitates with the epidermis and a basement membrane covers the capillary plexus leading to the systemic circulation.

Like the skin, the covering epithelium of nasal, vaginal or oral cavities, labia and scrotum are lined by multiple layers of stratified, squamous epithelium that forms a protective barrier for exclusion of bacteria and other foreign substances. The epithelium lining the nasal, vaginal or oral cavity represents the surface of a mucus-secreting mucosa. Mucosa is thus a mucus-

secreting membrane lining body cavities and canals. Labia is formed by non-mucosal non-cornified epithelium. Scrotum is formed by non-mucosal lightly cornified epithelium which is not the same as the cornified layer of the skin.

Because of the presence of the barrier preventing the entry of bacteria, viruses and various chemicals, problems were encountered with attempted delivery of pharmacological agents through these tissues. Consequently, the therapeutic effect of nasal, buccal or vaginal medications were, until now, confined primarily to the external or internal topical use. It would thus be advantageous to provide compositions which would conveniently, efficiently and practically permit a drug delivery topically or to the systemic circulation via nasal, buccal, vaginal, labial or scrotal epithelium.

In order to permit passage of pharmacological agents through the skin barrier, attempts were made to discover and/or develop compounds which would enhance their penetration through these barriers. The most well known of these penetration enhancers is dimethyl sulfoxide (DMSO). DMSO has the ability to rapidly alter the cell membrane characteristics to allow substances to pass between the cells, into the cell and through the cell. These unique characteristics have made this compound useful in the laboratory as a permeation enhancer and as a cryoprotectant for cell freezing. Unfortunately DMSO is not safe for human use and has been banned for human use by the Food and Drug Administration.

A second skin permeation enhancer, ethoxydiglycol, known under its trade name TRANSCUTOL®, has been recently developed and introduced for topical use and is primarily used to promote delivery of skin tanning agents into the epidermis and into the dermal layer of the skin.

In vitro evaluation of ethoxydiglycol as permeation

enhancer for transdermal delivery of clonazepam is described in Eur. J. Pharm. Sci., 9:365-372 (2000). This publication evaluates the influence of ethoxydiglycol alone or in combination with propylene glycol, on clonazepam permeation through an artificial membrane and on excised (*ex vivo*) rabbit ear skin from carbopol hydrogels. The article describes an increase of drug permeation through the skin as a function of ethoxydiglycol content in the formulation, and concludes that ethoxydiglycol is a good enhancing carrier for clonazepam and increases the flux of the drug into the skin and across the skin if combined with propylene glycol which has penetration and carrier properties.

Until recently, however, ethoxydiglycol has not been used for or shown to promote the transmucosal delivery of the drug across the nasal, buccal and vaginal mucosa or through the labia or scrotum into the systemic circulation or described to have such properties. Prior use of ethoxydiglycol to promote transvaginal delivery was disclosed by inventors and such use is described in patents 6,086,909, 6,197,327 B1, 6,416,779 B1, 6,572,874 B1 and pending applications Ser. Nos.: 10/226,667 filed on August 21, 2002 and 10/349,029 filed on January 22, 2003, all hereby incorporated by reference.

While these patents and applications describe mucosal and transmucosal drug delivery, they do not describe in great details such delivery using a biodegradable or non-degradable compositions, although these compositions could provide advantage of being efficacious, convenient, practical, simple, functional, soft and pliable and non-intrusive when prepared and easily confirming to a surface of the scrotal, labial, vaginal, oral or nasal epithelium when sprayable or dried into a film when prepared as foams and films and easily confirming to a surface of cornified and non-cornified

epithelia.

Thus, it would be advantageous to have available therapeutic compositions which would promote delivery of pharmacological agents to the cornified or non-cornified epithelium of the labia, scrotum, vaginal, nasal or oral cavity and facilitate access of these pharmacologically active agents locally or through these tissues into the general systemic circulation.

Transvaginal compositions for delivery of drugs to the uterus through vaginal mucosa have been recently discovered and described in patents 6,086,909, 6, 416,779 B1, 6,572,874 B1 and 6,197,327 B1. These compositions are typically prepared as transmucosal formulations or, preferably, as a device incorporated with said transmucosal formulation.

It has now been discovered that specifically formulated compositions, particularly those formulated into solid, semi-solid or liquid foams or films can overcome generally observed problems caused by the above described protective barriers which effectively prevent translabial, transscrotal or transmucosal drug delivery through the nasal, buccal, vaginal, labial or scrotal epithelium into the general circulation.

It is therefore an object of the present invention to provide a therapeutically useful compositions for delivery of therapeutic agents to and through cornified and non-cornified epithelia lining the nasal, oral, or vaginal cavity and the labia and scrotum. Such delivery comprises compositions formed into biodegradable or non-degradable foam and film formulations that are soft, pliable, and non-intrusive when prepared and easily conformable to the surface of the scrotum, labia, nasal, oral, or vaginal cavity.

All patents, patent applications and publications cited herein are hereby incorporated by reference.

SUMMARY OF THE INVENTION

One aspect of the present invention is a therapeutically useful composition comprising at least a substrate polymer compound or a mixture thereof and a therapeutically effective agent formulated into a biodegradable or non-degradable foam or film of different rigidity and viscosity as solid, semi-solid, or liquid formulation.

Another aspect of the current invention is a therapeutic composition comprising a substrate polymer formulated into a biodegradable or non-degradable solid, semi-solid or liquid foam or film, said composition additionally containing a mucoadhesive agent, release modifier, penetration enhancer, sorption promoter and/or another pharmacologically acceptable excipient and additive.

Still another aspect of the current invention is a polymeric foam or film composition particularly suitable for a vaginal, nasal, buccal, labial, scrotal topical or transepithelial delivery of therapeutically effective agents locally topically or to the general circulation.

Yet another aspect of the current invention is a polymeric foam or film composition having incorporated therein a therapeutically effective agent selected from the group consisting of anti-inflammatory agents, local anesthetics, calcium channel antagonists, potassium channel blockers, β-adrenergic agonists, vasodilators, cyclooxygenase inhibitors, antimicrobial, antiviral, antifungal, antipsychotic, anti-osteoporotic, anti-migraine, anti-HIV, anti-epileptic, anti-neoplastic, chemotherapeutic, anti-psychotic, anti-neurogenerative agents, opioid analgesics and biotechnology-derived pharmacological agents, such as proteins and peptides.

Still another aspect of the current invention is a method for using a polymeric bio-degradable or non-

degradable foam or film compositions for delivery of therapeutic agents locally or systemically to the general blood circulation wherein said compositions comprise a therapeutically effective agent selected from the group consisting of anti-inflammatory agents, local anesthetics, calcium channel antagonists, potassium channel blockers, β-adrenergic agonists, vasodilators, cyclooxygenase inhibitors, antimicrobial, antiviral, antifungal, antipsychotic, anti-osteoporotic, anti-epileptic, anti-psychotic and-neurogenerative anti-migraine, anti-HIV, anti-neoplastic and chemotherapeutic agents and biotechnology-derived pharmacological agents, such as proteins and peptides.

Still yet another aspect of the current invention is a biodegradable or non-degradable mucosal, transmucosal, labial, translabial, scrotal and transscrotal foam or film composition for delivery of a therapeutic agent to and/or through nasal, buccal, vaginal, labial or scrotal epithelium, said composition consisting of from about 1 to about 95% of a polymer selected from the group consisting of microcrystalline cellulose, polyacrylic acid, polyethylene glycol, polypropylene glycol, divinyl glycol, polyethylene oxide, polypropylene oxide, carboxymethyl cellulose, hydroxyethyl cellulose, polylactide, polyglycolide, polymethacrylic acid, poly-γ-benzyl-L-glutamate, polypropylene fumarate, poly-ε-caprolactone, polybutylene terephthalate, polyvinyl alcohol, polyvinyl ether, poly-1-vinyl-2-pyrrolidinone, 2,5-dimethyl-1,5-hexadiene, divinyl benzene, polystyrene-divinyl benzene, polyanhydrides such as poly-bis(*p*-carboxy-phenoxypropane)-*co*-sebacic acid, polyhydroxyalkanoates, poly-β-hydroxybutyrate, poly-β-butyrolactone, alkyl-substituted silica gel, tetraethylorthosilicate, dimethyldiethoxysilane, pectin, collagen, or a mixture thereof, wherein said composition is prepared into a foam

preformed into a device such as a tampon, tampon-like cylinder, strip, pad, pillow, tube, film, sheet, sphere, tablet, ring or bead, or prepared as a film, or incorporated into or applied, as one component, to a surface of a more complex drug delivery system which comprises, as a second component, a device made of different material, such as a conventional tampon, tampon-like device, pessary, ring, strip, pad, pillow, sheet, tube, sphere, tablet or a bead partially or totally covered or coated by said foam or film wherein said composition is supplied and stored as solid, semi-solid, or liquid preparation, which upon contact with the epithelial tissue or on the surface of a device maintains or rapidly changes the physical appearance to accommodate the anatomical and therapeutic needs at the site of administration.

Still yet another aspect of the current invention is a foam tablet or a dissolvable foam tablet for administration of a pharmacologically effective agent alone or incorporated into a device for insertion into nasal, oral or vaginal cavity or placed in close contact to the labia or scrotum.

Yet another aspect of the current invention is a biodegradable or non-degradable film comprising a pharmacologically effective agent suitable for placement on a surface of nasal, oral, vaginal, labial or scrotal epithelium.

DEFINITIONS

As used herein:

"Covering epithelia" means tissues in which cells are organized in layers that cover the external surface or line cavities of the body. Histologically, epithelial tissues can be divided into covering epithelia and glandular epithelia. This invention concerns covering mucus-secreting epithelia, such as the nasal, buccal and vaginal but also covering labial and scrotal keratinized epithelia.

"Mucosal" means delivery of the drug locally to the vaginal, nasal or buccal mucus-secreting epithelia.

"Transmucosal" means delivery of the drug systemically through the vaginal, nasal or buccal mucus-secreting epithelia into the systemic circulation.

"Buccal" means delivery of the pharmacological agent to the mucosa lining the oral cavity.

"Labial" means delivery of the pharmacological agent locally to the labia.

"Translabial" means delivery of the pharmacological agent systemically through the non-mucosal non-cornified labial epithelium to the systemic circulation.

"Scrotal" means delivery of the drug locally to the scrotum.

"Transscrotal" means delivery of the drug systemically through the scrotal non-mucosal lightly cornified epithelium into the systemic circulation.

"Cornified" means keratinized tissue.

"Agent", "pharmacologically effective agent", "pharmacologically acceptable agent", "pharmacological agent", "an active pharmacologically acceptable agent" or "drug" means a natural or synthetic chemical compound which induces a biological or therapeutic effect when administered to a mammal, including human subject, through the mucosal or labial or scrotal epithelium.

"Pharmaceutical agent" or "pharmaceutically acceptable agent" means an excipient, typically pharmacologically inactive.

"Release modifier" or "carrier" means a compound able to aid in the release of the drug from the composition.

"Alginic acid" means alginic acid or a salt thereof, such as alginic acid sodium salt.

"Non-ionizable glycol derivative" means a synthetic or non-naturally occurring conjugate of aliphatic glycol or a conjugate of aliphatic glycol with aliphatic or aromatic

alcohol or ether, such as ethoxydiglycol known under its trade name TRANSCUTOL®, or mixtures thereof.

"TRANSCUTOL®" means ethoxydiglycol also known under the name of diethyleneglycol monoethyl ether.

"AVICEL®" means microcrystalline cellulose of nominal size 50 microns, commercially available from FMC Biopolymers.

"NOVEON®" means polycarbophil or polyacrylic acid crosslinked by di-vinyl glycol.

"Poloxamer" means a family of ethylene oxide-propylene oxide block copolymers, also known as a copolymers of polyoxyethylene and polyoxypropylene.

"Carbopol" means polyacrylic acid polymers lightly cross-linked with a polyalkenyl polyether, commercially available from B. F. Goodrich.

BRIEF DESCRIPTION OF FIGURES

Figure 1 illustrates a release of ketorolac tromethamine from the alginic acid hydroxypropyl methylcellulose foams into a pH 4.2 phosphate buffer.

Figure 2 shows a release of ketorolac from alginic acid film into a synthetic vaginal fluid at pH 4.2.

Figure 3 shows a water uptake and dissolution of hydroxypropyl methylcellulose and hydroxypropyl methylcellulose-Avicel foams at different percentile mixtures.

DETAILED DESCRIPTION OF THE INVENTION

The current invention describes therapeutically useful biodegradable or non-degradable foam or film compositions and a method for topical epithelial or transepithelial delivery of therapeutic agents to and across a nasal, buccal, vaginal, labial or scrotal epithelium into the general systemic circulation.

The foam or film compositions of the invention permit efficacious delivery of pharmacologically active agents locally directly to the vaginal, nasal or buccal epithelia

or through a penetration of the vaginal, nasal, buccal, labial or scrotal epithelium into the general systemic circulation. The new compositions, in combination with new delivery routes, avoid problems connected with the oral administration which often leads to drug deactivation, or with the invasive intravenous, intramuscular, intraperitoneal, intracutaneous, cutaneous or subcutaneous routes of delivery requiring injections, visit to the doctor's office and/or assistance of medical personnel.

The newly discovered routes of topical epithelial or transepithelial nasal, buccal, vaginal, labial or scrotal administration are noninvasive, require no assistance by medical personnel or visit to the doctor's office, eliminate the need for excessive doses of the drug needed for oral delivery, and are altogether more convenient, practical and economical. The transepithelial delivery of drugs across the vaginal, nasal, buccal, labial, or scrotal epithelium according to the invention bypasses the gastrointestinal tract absorption, liver metabolism and kidney deactivation and delivers the drug locally or directly to the systemic blood circulation. Moreover, all foam or film compositions are eminently practical, non-intrusive and comfortable as they are soft and pliable and easily conformable to a tissue surface.

The foam compositions may be preformed into a structural foam which is either biodegradable or non-degradable and easily takes on the contouring of the tissue surface. The film compositions may be conveniently used alone as a one or multilayered one-sided or a two sided nasal, buccal, vaginal or labial film inserts or placed or sprayed on the scrotal and other tissue surface or used as a coating on the non-film devices, even as a coating on the foam device.

Moreover, the compositions of the invention, due to the chemical properties of their components combined with their

processing, promote and permit delivery of the drug with variable chemical properties, such as drugs with variable drug stability, solubility and absorption into the tissue, and permit elimination of side effects observed with administration of higher doses of these drugs, because the drug is delivered locally or directly to the blood circulation aided by the composition's mucoadhesive, adhering and penetration properties. These variable chemical properties depend on the presence of a compound acting as a mucoadhesive or release modifying agent, typically a hydrophilic or hydrophobic polymer, alone or in a combination with another polymer, and/or further in combination with appropriate penetration enhancers or sorption promoters and/or release modifiers, depending on the drug.

I. Therapeutic Compositions

Therapeutic compositions according to the invention comprise essentially a hydrophilic or hydrophobic polymer component, preferably the hydrophilic polymer, in combination with a pharmacologically effective agent, said combination processed into a polymer foam or film. This combination has been found to efficaciously deliver the therapeutic agents to and through nasal, oral or vaginal mucosal epithelium as well as through the non-cornified or lightly cornified epithelium of labia and scrotum. A therapeutic agent incorporated into the foam or film is released from said composition upon placement of said composition on the surface of vaginal, nasal or oral mucosal epithelium and the epithelium of the labia and scrotum and acts either locally or penetrates through the tissue, or both. The foam or film of the invention has a controllable rate of gelling, swelling and degradation.

The foam or film composition of the invention comprises at least two components, namely a polymer, preferably a hydrophilic polymer or a mixture thereof, which typically

has mucoadhesive or carrier properties, and a therapeutic agent or a mixture thereof, but may, additionally, contain another mucoadhesive agent, release modifier, penetration enhancer, sorption promoter and/or another pharmaceutically acceptable excipient and additive.

The foam or film compositions of the invention are particularly suitable for a topical and transepithelial vaginal, nasal, buccal, labial and scrotal delivery of therapeutic agents locally or to the general circulation. Representative therapeutic agents are anti-inflammatory agents, local anesthetics, calcium channel antagonists, potassium channel blockers, β-adrenergic agonists, vasodilators, cyclooxygenase inhibitors, antimicrobial, antiviral, antifungal, antipsychotic, anti-osteoporotic, anti-migraine, anti-HIV, anti-neoplastic, anti-epileptic, anti-neurodegenerative and chemotherapeutic agents, and biotechnology-derived pharmacological agents, such as proteins and peptides.

The compositions of the invention are preferably formulated into the solid, semi-solid or liquid foams or films.

A. Foam Formulations

The foam formulations suitable for delivery of pharmacological agents comprise a foam preformed into a specific shape of solid structure or a semi-solid or liquid preparation, which forms a foam layer upon contact with the epithelial tissue or the surface of a device. The pharmacologically effective agent may be incorporated before foam formation or by coating of the inner pores of a prefabricated polymeric foam scaffold or coating or surface of the foam or film.

Drugs and other additives can be added to a prefabricated polymeric foam scaffold by spraying the foam with a dilute solution of the drug or additive in methylene chloride or ethanol. Preferably the quantity of solution,

the temperature, and the ambient air velocity are such that the solvent evaporates immediately after the solution is absorbed within the foam or on its surface. This process is similar to that used when applying coatings to pills.

The volume of solution applied per gram of foam is selected such that a substantial portion of the foam is coated. Having determined the appropriate solution volume, the drug concentration is selected so that the desired drug dose per unit weight or per unit volume is obtained.

Alternatively, drugs and additives can be incorporated by emulsion coating where water-in-oil or oil-in-water emulsions prepared in polymer solution is forced through a prefabricated foam scaffold by applying vacuum. After solvent evaporation, a polymer film containing the drugs and additives is then deposited on the porous scaffold surface. Processing parameters of this emulsion coating are known to the skilled in the art and any type of process, additives and equipment required to optimize stability and release of pharmacological agents from within the scaffold structure are intended to be within the scope of this invention.

1. Fabrication of Foams

The present invention concerns foam compositions suitable for delivery of therapeutic agents to and through the nasal, buccal, vaginal, labial, and scrotal cornified and non-cornified epithelia. Said compositions of biodegradable or non-degradable foams having solid, semi-solid, or liquid structure may be prepared by processes known in the art that introduce porosity in a polymer matrix, namely by lyophilization, aeration, freeze drying, hydrocarbon templating, salt or particulate leaching, gel or solvent casting, gas expansion, sintering, polymerization of high internal phase emulsions, and free form fabrication techniques such as three-dimensional polymer printing. The most preferred process to fabricate foams is lyophilization, which is described in detail below. Examples of the process

applications that may be used to fabricate foams included in the invention have been disclosed previously. See, for example, Proc. Natl. Acad. Sci. USA, 97, 1970-1975 (2000); Polymer, 35, 1068-1077 (1994); J. Biomat. Sci. Polym. Ed., 7, 23-28 (1995); Biomaterials, 17, 1417-1422 (1996); J. Biomed. Mat. Res., 30, 449-461 (1996); J. Controlled Rel., 40, 77-87 (1996); Biomaterials, 24, 3133-3137 (2003) and J. Controlled Rel., 87, 57-68 (2003)).

Lyphilized foams are open cell, high-surface-area, biodegradable or non-degradable constructs that can be manufactured from a variety of polymers, preferably from hydrophilic polymers. The foam materials are characterized by controlled chemical and physical properties that can be tailored according to their intended application.

Tuneable properties include hydrophilicity, rate of fluid absorption, degradation profile and dissolution rate, a measure of which is the time needed to complete disappearance of the foam. The release of the drug, water uptake and dissolution of the foams or films are illustrated in Figures 1-3.

The invention thus can be a foam that hydrates and forms a gel quickly and is capable of dispersing over a relatively large area. The invention can also be a foam that hydrates and forms a gel slowly to provide sustained release of a therapeutic agent over hours or days. These properties are advantageously modifiable by changing polymers, ratios of the polymers to each other or to the drug and/or additives, as seen in Figures 1 and 3.

Typically, the lyophilized foam is prepared by dissolving an appropriate polymer, preferably a hydrophilic polymer, or a mixture thereof serving as a substrate material, as listed below in section C, in an amount needed to prepare solution from 1 to 10% (w/w) in an aqueous or non-aqueous solvent, such as methanol, ethanol, glycerine, methylene, chloride, propylene glycol, propylene carbonate,

glycofurol, cetyl alcohol, difluroethane and isopropyl alcohol, preferably a purified water. Alternatively, polymeric solutions with the drug and additives may be prepared in acetic acid, cyclohexane, acetonitrile, *tert*-butanol, ethanol, and isopropanol or in mixtures of aqueous and non-aqueous solvents.

Compositions are prepared by dissolving an appropriate amount from about 0.01 to about 2000 mg or more, of a selected pharmacological agent or a mixture of two or more of such agents in a suitable solvent, preferably purified water, mixing this solution together with the polymer solution for from about 10 minutes to about several hours, preferably about 15-60 minutes, freezing said mixture at from -60°C to about -100°C, preferably at -80°C, into a desirable shape, for example by pouring said mixture, before freezing, into a vial, pan, plate, tube, etc., of a desirable shape or into a foam sheet and, when frozen, cutting said sheet into a structure of a desirable shape and lyophilizing said frozen mixture by using any type of appropriate lyophilizer or lyophilizing equipment. Lyophilization conditions and apparatuses and equipment are known in the art and any type of lyophilization process or equipment is intended to be within the scope of this invention.

Typically, the polymer or polymer mixture and drug solution, as described above, is first frozen for at least 15 minutes, and typically at least 30 minutes, in a form having the shape and size desired for the finished lyophilized foam. For water solutions, the freezing temperature is from 0°C to -80°C and preferably less than -10°C. After freezing, the frozen samples are ejected or removed from the forms, optionally by brief warming on the outside of the forms. The frozen samples are placed in trays pre-cooled to a temperature below the freezing point of the solvent. While under vacuum, the samples are then

converted to foams by lyophilization (freeze-drying) at 0°C to -80°C and preferably below -20°C for about 48 hours to about 144 hours. Less time or more time may be required depending on the foam or film thickness and composition. After the water has been removed, the foams or films are warmed to room temperature, typically while still under vacuum. The procedure yields therapeutically useful foams or films containing a drug incorporated therein.

In the alternative, a closed-cell form can be prepared by aeration process. In this process, a polymer solution is rapidly mixed in a mixer such as Oakes mixer, by high-shear mixing blades, while air or another gas is injected. The resulting foam can be metered into molds or spread as a thin layer onto a substrate film. The foam can then be dried under ambient conditions or with heat.

Alternatively, the above foam can be frozen and lyophilized according to the procedures described above.

2. Biodegradable and Non-Degradable Foam

In one embodiment, this invention concerns compositions formulated into a foam for delivery of therapeutic agents to or through nasal, buccal, vaginal, labial, and scrotal epithelia. Physical and chemical properties of foams of the invention can be tailored to optimize their intended use, which is achieved by controlling the rate of release of the pharmacologically active agents incorporated into foams with said compositions. Drug release from the delivery device can occur by diffusion or erosion, or by a combination of both, leading to immediate, controlled, or pulsed delivery of the agent to or through the nasal, buccal, vaginal, labial, or scrotal epithelia.

The rate of drug release depends on physicochemical properties of the drug, the composition of the foam, and the surrounding media at the site of administration wherein pH, ionic strength, temperature, buffer capacity, enzyme activity, and cellular activity are only a few examples of

variable that have an influence.

Foam scaffolds, fabricated from compositions that undergo degradation at the site of administration into smaller units or polymers by various mechanisms, are classified as biodegradable systems. Biodegradable polymers are preferably designed to allow drug release by bulk or surface erosion and include natural and synthetic polymers alone or in combination with representative but not limiting examples of polysaccharides such as alginate, dextran, cellulose, collagen, and chemical derivatives thereof, proteins such as albumin and gelatin and copolymers and blends thereof, polyhydroxy acids such as polylactides, polyglycolides and co-polymers thereof, polyethylene terephthalate, polybutiric acid, polyvaleric acid, polylactide-co-caprolactone, polyanhydrides, polyorthoesters, and blends and co-polymers thereof.

Non-degradable foam systems in this invention are the system wherein compositions resist a destruction of the three-dimensional function of the delivery system at the site of administration allowing drug release predominantly by diffusion from the composition. Representative but not limiting examples of non-biodegradable polymers that may be used exclusively or in combination with biodegradable polymers to fabricate foam compositions with desired characteristics as described by this invention include polyamides, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polymethacrylic acid, and derivatives thereof alone or as co-polymeric mixtures thereof.

3. Shape of Foam

Foam compositions can be prepared by lyophilization in a range of sizes and a variety of shapes including foam films, sheets, pillows, tubes, cylinders, spheres, tablets, rings, beads or any other desirable shape using an appropriate processes known in the art that introduce porosity in a polymer matrix, namely lyophilization,

aeration or freeze drying, hydrocarbon templating, salt or particulate leaching, gel or solvent casting, gas expansion, sintering, polymerization of high internal phase emulsions, and free form fabrication techniques such as three-dimensional polymer printing.

The foam is preformed into a device such as a tampon, tampon-like cylinder, strip, pad, pillow, tube, film, sheet, sphere, tablet, ring, bead or any other shape as might be desirable or is applied, as a one component, to a surface of a more complex drug delivery system which comprises, as a second component, a device made of a different material, such as, for example, a conventional vaginal tampon, tampon-like device, pessary, ring, strip, pad, pillow, sheet, tube, sphere, tablet or a bead covered by said foam.

Drug-containing foams can be utilized as stand-alone drug delivery platforms wherein the drug is incorporated into and is a part of the foam, or they can be used as one component of a more complex drug delivery system which may also comprise a suppository, tampon, or tampon-like device. The drug can be incorporated into the composition before foam formation of solid, semi-solid, or liquid structure, or it can be incorporated by partially or totally coating of the inner pores or a surface of a prefabricated polymeric foam scaffold.

A preferred route to deposit the drug would be to spray the foam with a concentrated drug solution, followed by drying of the solvent.

Drugs and other additives can be added to a lyophilized foam by spraying the foam with a dilute solution of the drug or additive in methylene chloride or ethanol. Preferably the quantity of solution, the temperature and the ambient air velocity are such that the solvent evaporates immediately after the solution is absorbed within the foam. This process is similar to that used when applying coatings to pills.

The volume of solution applied per gram of foam should be selected so that a substantial portion of the foam is coated. Having determined the appropriate solution volume, drug concentration is selected so that the desired drug dose per unit weight or per unit volume is obtained.

Alternatively, and less preferably, the drug solution can be metered by a nozzle onto the foam. This method may give less uniform coverage and slower solvent removal that the spraying method described above.

4. Release of the Drug From the Foam

In use, the preformed foam device is placed in a close contact with the epithelium in the nasal, oral, vaginal cavity or covering the labia and scrotum or the foam is formed *in situ* at the desired site of administration using a suitable composition that generates a porous foam structure immediately after administration, for example using sprayable or gellable compositions. The time of contact is determined by the desired therapeutic action of the drug and the release profile of the agents from the foam composition. Most preferred contact with the epithelium is at least two hours following *in vivo* placement. Optimal release of pharmacologically active agents can be attained up to 72 hours by the teachings of this invention. Longer drug release is possible by utilizing mixtures of polymers and/or additives permitting a long-term sustained extended drug release.

The release profiles are controlled by varying the composition of incorporated polymers and other additives, which affect porosity and density as well as by varying size of the device as will be apparent to those skilled in the art. Biodegradable foam systems begin to disintegrate into smaller units upon interaction with components at the site of administration. As the breakdown of the device occurs, drug is released from the foam following immediate, controlled or pulsed release kinetics.

Preferably, the active ingredient is continuously released for at least 8 hours after contact with the epithelium. Pulsed release can be desired for the first few hours, followed by a slower "maintenance" release rate up to 72 hours. Similar delivery profiles of drugs may be achieved using non-biodegradable foam systems whereas the rate of delivery of the pharmacologically active agent to or through the epithelial tissue is predominantly controlled by dissolution.

The device of the invention has good adhesive properties to maintain close contact to the epithelium at the site of administration. Adhesion may require interaction of polymeric compositions in this device with components at the site of administration such as water or ions.

Alternatively, foam compositions in the inventions may contain excipients that promote inherent adhesive properties of the device after administration. Adhesion of the device permits secure positioning of the device when worn and assures desired delivery of the active agent over the time frame beneficial to the therapy of the disease.

The active ingredient can primarily affect the surface of the epithelium where administered, which results in topical or local treatment of a disease or, alternatively, the primary effect occurs at a therapeutic target that is distinctly separated from the site of administration and, therefore, relies on systemic distribution of the active agent following transfer across the epithelial tissue into the systemic circulation. Upon contact with the mucus layer covering the vaginal epithelium, the lyophilizied foam first adsorbs fluid, which initiates the release of the active agent by dissolution and, simultaneously, supports the degradation process of the foam structure into a gel that possesses good structural integrity to deliver sumatriptan for a prolonged period prior to further dissolution into a liquid. This feature facilitates adhesion of the device and

helps to control the rate of delivery of the active ingredient.

The time required for the devices of the invention to attain substantial dissolution to a liquid up to a point when the foam or film device structure is no longer evident is called the dissolution time and can be determined using *in vitro* dissolution techniques. At the time of complete dissolution, the biodegradable foam has completely dispersed as smaller polymer units within the nasal secretion, saliva or vaginal fluid. Therefore, there is no need to remove the device and normal excretion from the nasal, buccal or vaginal cavity will be completed by the continuous flow of physiological vaginal secretion.

A dissolution pattern and water uptake are seen in Figure 3. Drug release from the foams or films of the inventions is controllable and may be changed by design. Specifically, certain polymers permit faster water uptake into the foam or gel resulting in faster release of the drug. Other polymers or mixtures, particularly those containing hydroxypropyl methylcellulose contribute to a slower water uptake and a decreased rate of the drug release. Water uptake rate is one indicator of the ability of a foam to release a drug. To determine the water uptake rate from foams, microcrystalline cellulose (Avicel) and HPMC, alone or in combination, were evaluated. Foams were prepared for this study according to Examples 5-7.

B. Film Compositions

In one embodiment, the invention concerns a polymer formulated into a film for topical or transepithelial vaginal, buccal, nasal, labial or scrotal delivery of therapeutic agents. The polymer films of the invention are high-surface-area sheets that are prepared from a variety of polymer solutions which are processed into a film.

Similarly to the foams, films of the invention are characterized by their controlled chemical and physical

properties that can be tailored according to their intended application. Tuneable properties include hydrophilicity, rate of fluid absorption and degradation profile including a dissolution rate. The films of the invention thus release the active ingredient by dissolution or erosion or a combination of these mechanisms which may depend on interaction of the film composition with components at the site of administration, including but not limiting to fluid and ions. This will attain desired bioadhesive properties of the film and control the release rate of the agent as required by the therapeutic regimen for hours or days.

Typically, the film is prepared by dissolving an appropriate polymer, preferably a hydrophilic polymer, or a mixture thereof serving as a substrate material, as listed below, in an amount needed to prepare a solution of from about 1 to about 10% (w/w), in an aqueous or non-aqueous solvent, such as methanol, ethanol, glycerine, methylene, chloride, propylene glycol, propylene carbonate, glycofurol, cetyl alcohol, difluroethane and isopropyl alcohol, preferably purified water. A selected pharmacological agent or mixture of two or more such agents in an appropriate amount from about 0.01 to about 2000 mg and occasionally more, is then dissolved in an aqueous or non-aqueous solvent, preferably a purified water. Both solutions are mixed together for from about 10 minutes to about several hours, preferably about 15-60 minutes, said mixture is spread over the flat surface or plate, such as a glass plate in a layer from 0.5 to about 2 mm, preferably about 1 mm, using, for example, a TLC coater and let dry at 25°C for as long as it takes for the water to completely evaporate. The film layer typically dries in about 24 to about 148 hours, usually in about 70 hours. Alternatively, the film may be prepared by spraying said mixture and drying.

In alternative embodiments, polymeric solutions with

the drug and additives may be prepared in acetic acid, cyclohexane, acetonitrile, *tert*-butanol, ethanol, and isopropanol or in mixtures of aqueous and non-aqueous solvents.

1. Single Layer Films and Multiple-layer Films

Single-layer films containing drugs would be particularly useful applications where the film is in contact with tissue on both sides. Thus the drug would be able to diffuse out from both sides of the film.

Two-layer or more than two-layer films will be useful when a distinct function is required from the second layer. For example, for buccal applications, a drug-eluting layer is most desirable against the mucous membrane. On the opposite side, however, a second barrier film layer may be useful to prevent loss of the drug into the saliva and the digestive system. Useful barrier film polymers include polyethylene terephthalate, polyethylene, and nylon.

As a functional example of a multi-layer film, a multi-layer film would consist of a barrier film as described above, a middle layer which serves as the primary reservoir for the drug, and a third layer comprising mucoadhesives and/or release modifiers, which contacts the body and controls the adhesion of the film to the tissue and the rate at which the drug is released from the reservoir layer.

2. Film v. Foam Compositions

A polymer film is a uniform layer of material, usually less than 4 mm thickness, composed at least partly of a polymer which provides structural integrity. A film can optionally have a multilayer structure where each layer has a distinct composition. Normally the entrapped air in a film will be much less than 10% by volume. Thicker polymer layers up to 0.5 inches thick are usually referred to as sheets.

For the films of the current invention, the production method is to create a solution of at least one polymer.

This solution can contain additional soluble and non-soluble polymers, drugs, transcutol, excipients, etc. The solution can be uniformly spread or sprayed over a flat surface (glass, paper, or another polymer sheet) and allowed to dry under ambient conditions or optionally with some heat. After the solvent evaporates, a film remains which can be peeled off. Films, due to their thinness, provide good patient comfort for nasal, buccal, vaginal, labial or scrotal applications.

In contrast, a polymeric foam may consist of a polymer composition, as described above, which contains at least 10%, and usually greater than 50%, void volume filled by air or another gas. For lyophilized foams, one starts with a solution of polymers and additives. Normally at least one polymer is water-soluble. After pouring the solution into molds of the desired shape, the solution is frozen solid. The frozen solutions, optionally after removal from the molds, are lyophilized at a low temperature, e.g. -40°C, and at low pressure until the water content has been reduced to a low level. After warming the samples under dry conditions, lyophilized foams in the shape of the mold are obtained. Foams are soft three-dimensional devices which can be particularly convenient for vaginal and labial treatments.

C. Substrate Materials for Producing Foam or Film Compositions

Substrate materials for preparation of foam or film compositions of the invention are polymers, hydrophilic or hydrophobic, preferably hydrophilic polymers. These polymers may be used singly or in combination with each other. They may be used in variable concentrations and ratio to each other when in admixture of two or several polymers.

Non-exclusive list of substrate polymers comprises cellulose and cellulose derivatives, microcrystalline cellulose, polyacrylic acid, polyethylene glycol,

polypropylene glycol, divinyl glycol, polyethylene oxide, polypropylene oxide. Other possible polymers include the cellulose derivatives such as carboxymethyl cellulose, hydroxyethyl cellulose, polylactide, polyglycolide, polymethacrylic acid, poly-γ-benzyl-L-glutamate, polypropylene fumarate, poly-ϵ-caprolactone, poly-butylene terephthalate, polyvinyl alcohol, polyvinyl ether, poly-1-vinyl-2-pyrrolidinone, 2,5-dimethyl-1,5-hexadiene, divinyl benzene, polystyrene-divinyl benzene, polyanhydrides such as polybis*p*-carboxy-phenoxypropane-*co*-sebacic acid, polyhydroxyalkanoates such as poly-β-hydroxybutyrate or poly-β-butyrolactone, and alkyl-substituted silica gel such as tetraethylorthosilicate and dimethyldiethoxysilane.

1. Hydrophilic Polymers

Examples of hydrophilic polymers suitable for a foam or film manufacture include hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, polyethylene glycol (PEG), alginic acid, alginic acid sodium salt, pectin, gelatin, collagen, polyvinyl pyrrolidone, poloxamer, acrylic-acid based polymers, such as carbopol, noveon, polyurethanes, polyvinyl alcohol, chitosan, hydroxypropyl cellulose, polyethylene oxide, fibronectin, hyaluronic acid, polysaccharide gums such as karaya gum, polyacrylamide, polycarbophil, dextran, xanthan gum, polyacrylamide, polyacrylamide, crosslinked polymethyl vinyl ether-co-maleic anhydride, commercially available as Gentrez™, gelatin, corn starch and mixtures thereof.

2. Hydrophobic Polymers

Examples of hydrophobic polymers suitable for formation of the foam and or film are, among others, polypropylene oxide, polyamides, polystyrene, and polymethacrylic acid.

Examples of suitable and preferred substrate materials and mixtures thereof for preparation of foams and films are listed in Table 1.

Table 1

Polymers	Composition (% polymer)	Form
HPMC	1.0 2.5 5.0	Films Films Films
Gelatin	1.0 2.5 5.0 10.0	Films Films, Rods Films, Rods Films, Rods
Gelatin/HPMC (50/50)	1.0 2.5 5.0 10.0	Films Films Films Films
Alginic Acid	1.0 2.5 5.0 10.0	Films Films, Rods Films, Rods Films
Alginic Acid/HPMC (50/50)	1.0 2.5 5.0	Films Films Films
Alginic Acid/PEG 400 (25/75)	5.0	Films, Rods
Alginic Acid/PEG 1400 (25/75)	5.0	Films, Rods
Alginic Acid/PEG 4000 (25/75)	5.0	Films, Rods
Alginic Acid/PEG 400 w/ Ketoconazole (25/75)	5.0	Rods
Carbopol	0.5 1.0 2.5	Films Films Films
Noveon	0.5 1.0 2.5	Films Films Films
Pectin	1.0 2.5 5.0 10.0	Films Films, Rods Films, Rods Rods
Pectin/HPMC (50/50)	1.0 2.5 5.0	Films Films Films
Collagen	0.5 1.0 2.5	Films Films Films

Alginic acid used is alginic acid sodium salt.

3. Additives

Foam and film formulations can comprise solely of two components, namely the polymer described above and the therapeutic agent described below in section D, or they can contain additional components including a variety of excipients and additives, such as release modifiers, mucoadhesive agents, and/or penetration enhancers/sorption promoters, fillers, dyes, etc., or other pharmaceutically acceptable excipients and additives.

a. Mucoadhesive Agents

As described above, the foam or film compositions of the invention contain a polymer, which may or may not have mucoadhesive properties. In many cases, the polymer, particularly a hydrophilic polymer, has a certain degree of mucoadhesive properties. Such properties advantageously support ability of the composition of the invention to adhere to the mucosal, labial or scrotal epithelium, however, it may or may not be sufficient to achieve the complete mucoadhesion for local adherence of the composition to the tissue or provide a sufficient support for a transepithelial, translabial or transscrotal delivery of the pharmacological agents. In such a case, the composition may conveniently contain still another mucoadhesive agent to achieve the prolonged and close contact with the tissue, adhesion of the composition to the tissue and interaction of the drug with the mucosal, labial or scrotal surface.

The mucoadhesive agent used to increase the adhesion of a film or foam device to a mucous membrane is preferably a polymer such as hydroxypropyl methylcellulose, carboxymethylcellulose, polylactide-co-glycolide, chitosan, chitosan ester or trimethylene chloride chitosan, sodium alginate, poloxamer, carbopol, pectin, or another cellulose derivative. Hydroxypropyl methylcellulose (HPMC) is particularly preferred for use in the present invention as

it can be one of the substrates for preparation of the foam or film. Other examples of mucoadhesive agents include polyacrylic acid, hyaluronic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polycarbophil and carbopol.

The mucoadhesive agent is typically present in from about 0.5 to about 10%.

b. Penetration Enhancers/Sorption Promoters

For delivery of drugs into the systemic circulation using transmucosal, translabial or transscrotal compositions, the composition additionally comprises a sorption promoter or penetration enhancer.

Sorption promoters or penetration enhancers are either ionizable or non-ionizable molecules that alter physical and/or biochemical barrier properties of the epithelia resulting in enhanced transfer of pharmacologically active agent to the systemic circulation.

Ionizable permeation enhancers include cationic, anionic, and zwitterionic excipients that are suitable to improve transfer of hydrophilic and lipophilic drug molecules across covering epithelia of the vaginal, nasal, oral cavity and labial or scrotal surfaces.

Preferred anionic permeation enhancers include derivatives of fatty acids, bile acids, phosphoric acid esters, carboxylates, and sulfates/sulfonates. For simplicity, sodium counterion is shown for anionic permeation enhancers, which is not limiting and includes any other biocompatible counterion that is currently known to the skilled in the art or will be discovered in the future.

Specifically, preferred anionic permeation enhancers include sodium caproate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate, sodium palmitate, sodium palmitoleate, sodium oleate, sodium ricinoleate, sodium linoleate, sodium stearate, sodium lauryl sulfate, sodium tetradecyl sulfate, sodium laryl sarcosine, sodium dioctyl sulfosuccinate, sodium cholate, sodium taurocholate, sodium

glycocholate, sodium deoxycholate, sodium taurodeoxycholate, sodium glycodeoxycholate, sodium ursodeoxycholate, sodium chenodeoxycholate, sodium taurochenodexoycholate, sodium glycol chenodesoxycholate, sodium cholylsarcosine, sodium *N*-methyl taurocholate, sodium tauro-24,25-dihydrofusidate, disodium polyoxyethylene-10 oleyl ether phosphate, esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride, ether carboxylates, succinylated monoglycerides, sodium stearyl fumarate, steaoryl propylene glycol hydrogen succinate, mono/diacetylated tartaric acid esters of mono- and diglycerides, citric acid esters of mono- and diglycerides, glyceryl-lacto esters of fatty acids, lactylic esters of fatty acids, alginate salts, ethoxylated alkyl sulfates, alkyl benzene sulfones, α-olefin sulfonates, acyl isethionates, acyl taurates, alkyl glyceryl ether sulfonates, octyl sulfosuccinates disodium, disodium undecylenamideo-MEA-sulfosuccinate, phosphatidic acid, phosphatidyl glycerol, polyacrylic acid, hyaluronate sodium, glycyrrhetinic acid, ethylene diamine tetraacetate and sodium citrate.

Cationic permeation enhancers include ammonium and pyridinium salts. For simplicity, chloride conterion is shown for cationic permeation enhancers, which is not limiting and includes any other biocompatible counterion that is currently known to the skilled in the art or will be discovered in the future. Specifically, preferred cationic permeation enhancers include chitosan, trimethyl chitosan, poly-*L*-arginine chitosan, poly-*L*-lysine chitosan, aminated gelatin, hexadecyl triammonium chloride, decyl trimethylammonium chloride, cetyl trimethylammonium chloride, alkyl benzyldimethylammonium chloride, diisobutyl phenoxyethoxydimethyl benzylammonium chloride, ethyl pyridinium chloride, isopropyl pyridinium chloride, *N*-lauryl,N,N-dimethylglycine, *N*-capryl,N,N-diethylglycine,

polyoxyethylene-15 coconut amine, poly-*L*-lysine, poly-*L*-arginine.

Zwitterionic permeation enhancers include naturally occurring and synthetic compounds that exhibit simultaneous positive and negative charges at the site of administration. Specifically, preferred zwitterionic permeation enhancers include lecithin, lysolecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, didecanoyl-L-α-phosphatidylcholine, laurolylcarnitine, acylcarnitine, palmitoyl-D,L-carnitine.

Concentration of these enhancers varies significantly from compound to compound, however, they are preferably used in concentration from about 0.01 to about 60%, and more preferably from about 10 to about 15%.

Non-ionizable glycol ether derivative is a polyoxyethylene alkyl ether, ester or a glycol derivative with glycerol ester represented by a compound selected from the group consisting of polyoxyethylene alkyl ether such as, for example, polyoxyethylene lauryl ether, polyoxyethylene monooleyl ether and ethoxydiglycol, polyoxyethylene alkyl phenol, such as, for example polyoxyethylene nonylphenol and polyoxyethylene octylphenol ether, polyoxyethylene sterol, such as, for example polyoxyethylene cholesterol ether and polyoxyethylene soya sterol ether and cyclodextrins, such as, for example, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, dimethyl-β-cyclodextrin, methylated-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin and sorbitol.

Non-ionizable glycol ester derivative is a polyoxyethylene glycol ester, polyoxyethylene glycerol fatty acid ester, polyoxyethylene glycerol fatty acid ester, polyoxyethylene glyceride or polyoxyethylene vegetable or hydrogenated oil, said derivative represented by a compound selected from the group consisting of polyoxyethylene glycol ester, such as, for example, polyoxyethylene monooleate,

polyoxyethylene dilaurate, polyoxyethylene mono and dioleate, polyoxyethylene glycerol fatty acid ester, such as, for example, polyoxyethylene glyceryl laurate and polyoxyethylene glyceryl oleate, polypropylene glycol fatty acid ester, such as, for example, propylene glycol oleate and propylene glycol stearate, polyoxyethylene glyceride, such as, for example, polyoxyethylene sorbitan monooleate and polyoxyethylene tristearate, polyoxyethylene vegetable or hydrogenated oil, such as, for example, polyoxyethylene hydrogenated castor oil, polyoxyethylene almond oil, polyoxyethylene apricot kernel oil, polyoxyethylene caprylic or capric glyceride and lauroyl macrogol glyceride.

Non-ionizable glycol derivative with glycerol ester is represented by glycol derivative with glycerol ester, such as, for example, polyoxyethylene oleate and polyoxyethylene glyceryl stearate.

In polymer compositions used for formation of foam or films according to the invention, the variable or non-ionizable enhancers are present in an amount from about 0.01 to about 60%, preferably from about 5 to about 25%, most preferably from about 10 to about 15%, by weight.

The most preferred non-ionizable glycol derivative is ethoxydiglycol, also known as TRANSCUTOL®, commercially available from Gattefosse, Westwood, N.J.

c. Release Modifiers

In order to achieve desirable drug release from the mucosal, transmucosal, labial, translabial, scrotal, or transscrotal foam or film compositions, the pharmacological agent is optionally incorporated into a vehicle or carrier for which the drug has low affinity and which promote a drug release from the foam or film or which can modify a rate of such release. Hence, lipophilic drugs are incorporated into hydrophilic modifiers and lipophilic drugs are incorporated into hydrophilic carriers.

Hydrophilic modifiers include polyethylene glycol 200,

polyethylene glycol 8000, poloxamer, polyoxyethylene glycerylcocoate and carbopol.

Hydrophobic modifiers include Suppocire AS2, Suppocire AS2X, suppocire CM, Witepsol H15, Witepsol W25, mineral oil, corn oil, paraffin oil, canola oil, castor oil, cottonseed oil, lecithin, peanut oil, sesame oil, soybean oil and hydrogenated vegetable oil.

Release modifiers may be present in the composition in the amounts from about 5% to about 70% by weight.

d. Additional Excipients and Additives

1. Solubilizing Agents

Solubilizing agents are used to increase the solubility of an agent in a formulation during the production of a device or, alternatively, to increase the solubility of an agent in fluids of tissue during the use of a device.

Any pharmaceutically acceptable solubilizing agent may be used. Preferred solubilizing agents are polyethylene glycol (PEG), cyclodextran, glycofurol, propylene glycol, propylene carbonate and surfactants.

Solubilizing agents are typically added in amount from about 5% to about 30%.

2. Buffering Agents

Buffering agents are used for control of the pH of the immediate environment of the device in order to control or enhance the release of an agent. Any pharmaceutically acceptable buffering agent or a mixture thereof may be used for the purposes of this invention. Exemplary buffering agents are potassium metaphosphate, potassium phosphate, monobasic sodium acetate, sodium carbonate, sodium bicarbonate, boric acid, tartaric acid, tris citrate and triethanolamine.

Buffering agents are typically added in amount from about 1% to about 10%.

3. Fillers

Fillers are inert ingredients used to increase the size

or improve the usability of a device. Any pharmaceutically acceptable filler may be conveniently used for the purposes of this invention. Exemplary fillers are calcium carbonate, silicon dioxide, titanium dioxide, paraffin, stearic acid, talc, wax and zinc stearate.

Fillers are typically added in amount from about 5% to about 15%.

4. Preservatives

Preservatives are used to prevent the growth of microorganisms during storage. All pharmaceutically suitable preservatives may be used. The preferred preservatives are benzalkonium chloride, propyl paraben, benzyl alcohol, sorbic acid, phenol, phenylethyl alcohol, BHA and BHT.

Preservatives are typically added in amounts from about 0.01% to about 5%.

5. Plasticizers

Plasticizers are compounds used to soften the film or foam. Exemplary plasticizers are glycerin, water, polyethylene glycol, propylene glycol, sorbitol and triacetin, to name a few.

Plasticizers are typically added in amount from about 5% to about 25%.

6. Surfactants

Surfactants, such as Tween 80, sodium lauryl sulfate and Brij, may be advantageously added as needed in amount from 0.01% to about 5%.

7. Antioxidants

Antioxidants suitable to be used for foams and films are selected from ascorbic acid, BHA, BHT, sodium bisulfite, vitamin E, sodium metabisulphite and propyl gallate and may be added in amounts from 0.1% to about 3%.

D. Pharmacological Agents

Foam or film compositions of the invention are suitable for topical or transepithelial delivery of any

pharmacological agent or a mixture of two or more agents which asserts a therapeutic effect when delivered locally to vaginal, nasal, buccal, labial or scrotal epithelium or can be delivered to the systemic circulation through the vaginal, nasal, buccal, labial or scrotal epithelium.

a. Representative Pharmacological Agents

Representative pharmacological agents which may be conveniently delivered using foams or films of this invention are groups of anti-inflammatory agents, calcium or potassium channel antagonists, β-adrenergic agonists, vasodilators, topical anesthetics, cyclooxygenase inhibitors, antimicrobial, antiviral, antipsychotic, anti-epileptic, antifungal, anti-osteoporotic, anti-migraine, anti-HIV, anti-neurodegenerative, anti-cancer agents, opioid analgesics, and biotechnology-derived pharmacological agents, such as proteins and peptides. Non-limiting representative examples of these drugs are nonsteroidal anti-inflammatory drugs which include aspirin, ibuprofen, indomethacin, diclofenac, phenylbutazone, bromfenac, fenamate, sulindac, nabumetone, ketorolac, and naproxen.

Examples of calcium channel antagonists include diltiazem, israpidine, nimodipine, felodipine, verapamil, nifedipine, nicardipine, and bepridil.

Examples of potassium channel blockers include dofetilide, almokalant, sematilide, ambasilide, azimilide, tedisamil, sotalol, piroxicam, and ibutilide.

Examples of β-adrenergic agonists include terbutaline, salbutamol, metaproterenol, and ritodrine.

Vasodilators include nitroglycerin, isosorbide dinitrate and isosorbide mononitrate.

Examples of cyclooxygenase (COX) inhibitors are acetylsalicylic acid, naproxen, ketoprofen, ketorolac, indomethacin, fenamate, ibuprofen, diclofenac, tenoxicam, bromfenal, celecoxib, nabumetone, phenylbutazone, rofecoxis, sulindac, meloxicam and flosulide.

Examples of local anesthetics include lidocaine, mepivacaine, etidocaine, bupivacaine, 2-chloroprocaine hydrochloride, procaine, and tetracaine hydrochloride.

Examples of anti-osteoporotic drugs are bisphosphonates selected from the group consisting of alendronate, clodronate, etidronate, pamidronate, tiludronate, ibandronate, alpadronate, residronate, neridronate and zoledronic acid.

Examples of antifungal, antimicrobial drugs are miconazole, terconazole, isoconazole, fenticonazole, fluconazole, nystatin, ketoconazole, clotrimazole, butoconazole, econazole, metronidazole, clindamycin, 5-fluoracil, acyclovir, AZT, famovir, penicillin, tetracycline, erythromycin, amprenavir, amividine, ganciclovir, indivaris, lapinavis, nelfinavir, rifonavir and saguinar.

Examples of anti-migraine drugs are almotriptan, eletriptan, flavotriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, ergotamine, dihydroergotamine, bosentan and lanepitant.

Examples of anti-neoplastin or chemotherapeutic drugs are vincristine, cisplastin, doxorubicin, daunorubicin, actinomycin D, colchicin, digoxin, etoposide, topotecan, irinotecan, paclitaxel, docetaxel, cyclophosphamide, methotrexate, gemcitabine, mitoxantrone, topotecan, teniposide, vinblastine and mytomycin C.

Examples of anti-HIV drugs are saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, lopinavir and ganciclovir.

Examples of antinausea drugs are aprepitant, cyclizine, dolasetron, domperidone, dronabinol, levonantradol, metoclopramide, nabilone, ondansetron, prochlorperazine, promethazine and tropisetron.

Examples of opioid analgesics are buprenorphine, dynorphin A, fentanyl, Met-enkaphalin, morphine, naloxone,

pentazosine and spiradoline.

Examples of antiepileptic drugs are carbamazepine, clonazepam, phenobarbital, phenytoin, primidone, and valproate.

Examples of anti-psychotic drugs for treatment of neurogenerative diseases are bromocriptine, carbidopa, galantamine, memantine, pergolide, selegiline, tacrine and trihexyphenidyl.

Examples of drugs for treatment of psychiatric disorders are alprazolam, amitriptyline, amoxapine, bupropion, buspirone, chlordiazepoxide, chlorpromazine, clozapine, diazepam, fluoxetine, fluphenazine, haloperidol, imipramine, loxapine, metrotiline, oxazepam, paroxetine, perephenazine, phenelzine, pimozide, prazepam, protriptyline, risperidone, selegiline, sertraline, thoridazine and trazodone.

Examples of antinausea drugs are aprepitant, cyclizine, dolasetron, domperidone, dronabinol, levonantradol, metoclopramide, nabilone, ondansetron, prochlorperazine, promethazine and tropisetron.

Examples of biotechnology-derived drugs are insulin, calcitonin, somatostatin, vasopressin, luprolide, oxytocin, bivalirudin, integrilin, natrecor, abarelix, gastrine G17 peptide, ziconotide, cereport, interleukins, humanized antibodies and growth hormone.

b. Doses of Pharmacological Agents

Pharmacological agents are added in amount which is therapeutically effective locally or systemically. Typically, the drug will be added in amount from about 0.01 to about 2000 mg as shown below. Occasionally, the dose may exceed 2000 mg range up to 20,000 mg, particularly when there is a repeated administration.

Calcium channel antagonists: bepridil (50-1600 mg), diltiazem (30-1500 mg), felodipine (1-50 mg), israpidine (1-20 mg), nicardipine (30-600 mg), nifedipine (15-650 mg),

nimodipine (100-1400 mg), verapamil (100-1500 mg).

Potassium channel blockers: almokalant, ambasilide, azimilide, dofetilide (0.2-5 mg), ibutilide (0.3-5 mg), sematilide, sotalol, (80-1300 mg), tedisamil.

β-Adrenergic agonists: metaproterenol (20-240 mg), ritodrine (100-2000 mg), salbutamol (0.1-5 mg), terbutaline (1-60 mg).

Vasodilators: isosorbide dinitrate (10-500 mg), isosorbide mononitrate (10-250 mg), nitroglycerin (2-150 mg).

Cyclooxygenase inhibitors: acetylsalicylic acid (5-8000 mg), bromfenac, celecoxib (100-2400 mg), diclofenac (50-800 mg), fenamate, flosulide, ibuprofen (600-6,000 mg), indomethacin (30-600 mg), ketoprofen (50-1200 mg), ketorolac (5-200 mg), meloxicam (2-60 mg), nabumetone (500-4,000 mg), naproxen (100-3000 mg), phylbutazone, rofecoxib (5-200 mg), sulindac, tenoxicam.

Local anesthetics: 2-chloroprocaine (50-2400 mg), bupivacaine (50-1600 mg), etidocaine, lidocaine (10-150 mg), mepivacaine (25-1600 mg), procaine (150-3,000 mg), tetracaine.

Anti-osteoporotic drugs: alendronate (2-160 mg), alpadronate, clodronate (1-3200 mg), etidronate (2-1400 mg), ibandronate (0.01-100 mg), neridronate (0.1-200 mg), pamidronate (1-3,000 mg), residronate (0.05-50 mg), tiludronate (0.02-400 mg), zoledronic acid (0.05-150 mg).

Antimicrobial drugs: acyclovir (100-4,000 mg), amprenavir (150-7,200 mg), amivudine (10-1200 mg), butoconazole, clindamycin (75-20,000 mg), clotrimazole (5-200 mg), econazole (2-100 mg), erythromycin (100-16,000 mg), famovir, fenticonazole, fluconazole (50-1600 mg), ganciclovir (250-12,000 mg), indinavir (400-9,600 mg), isoconazole, ketoconazole (1-6400 mg), lopinavir (50-2000 mg), metronidazole (100-10,000 mg), miconazole (600-15,000 mg), nelfinavir (300-10,000 mg), nystatin (0.5-12 Mio U),

penicillin VK (100-8000 mg), ritonavir (150-4800 mg), saquinavir (300-15,000 mg), terconazole (2-400 mg), tetracycline (300-16,000 mg).

Antimigraine drugs: almotriptan (2-100 mg), bosentan (50-1000 mg), dihydroergotamine (1-20 mg), eletriptan (1-400 mg), ergotamine, flavotriptan, lanepitant, naratriptan (0.5-20 mg), rizatriptan (2-120 mg), sumatriptan (10-800 mg), zolmitriptan (0.5-40 mg).

Antineoplastic/Chemotherapeutic drugs: actinomycin D, cisplatin (5-400 mg/m^2), colchicin (0.1-50 mg), cyclophosphamide (50-800 mg), daunorubicin, docetaxel, doxorubicin (50-2,500 mg/m^2), etoposide, gemcitabine (70-4,000 mg/m^2), irinotecan, methotrexate (0.2-40 mg), mitoxantrone (0.05-2 mg/m^2), mytomycin C, paclitaxel, teniposide, topotecan, vinblastine, vincristine (1-200 mg).

Biotechnology-derived drugs: abarelix, bivalirudin (0.5-1000 mg), calcitonin (100-20,000 IU), cereport, gastrine G17 peptide, growth hormones, humanized antibodies, insulin, integrilin (0.1-1400 mg), interleukins, luprolide, natrecor (0.001-2 mg), oxytocin (0.01-10,000U), somatostatin, vasopressin (0.1-40,000U), ziconotide.

Antinausea drugs: aprepitant (40-600 mg), cyclizine, dolasetron (25-400 mg), domperidone, dronabinol (1-60 mg/m^2), levonantradol, metoclopramide (10-200 mg), nabilone, ondansetron (4-75 mg), prochlorperazine (5-600 mg), promethazine (5-200 mg), tropisetron.

Opioid analgesics: buprenorphine (0.5-2000 mg), dynorphin A, fentanyl (0.1-10 mg), met-enkephalin, morphine (30-1000 mg), naloxone (0.1-3000 mg), pentazocine (50-1500 mg), spiradoline.

Antiepileptic drugs: carbamazepine (100-9,600 mg), clonazepam (3-60 mg), phenobarbital (15-800 mg), phenytoin (150-1200 mg), primidone (5-3000 mg), valproate (350-12,000 mg)

Drugs in neurodegenerative diseases: bromocriptine

(0.5-400 mg), carbidopa (5-400 mg), galantamine (4-100 mg), memantine, pergolide (0.02-20 mg), selegiline (2-40 mg), tacrine (20-650 mg), trihexypehenidyl (0.5-40 mg)

Drugs in psychiatric disorders: alprazolam (0.2-40 mg), amitriptyline (5-400 mg), amoxapine (25-1200 mg), bupropion (25-1800 mg), buspirone (5-250 mg), chlordiazepoxide (5-1200 mg), chlorpromazine (10-3200 mg), clozapine (5-1200 mg), diazepam (1-200 mg), fluoxetine (5-350 mg), fluphenazine (0.2-40 mg), haloperidol (0.5-400 mg), imipramine (10-1200 mg), loxapine (10-1000 mg), maprotiline (10-1000 mg), oxazepam (20-600 mg), paroxetine (5-250 mg), perphenazine (10-300 mg), phenelzine (20-400 mg), pimozide (0.5-40 mg), prazepam, protriptyline (10-300 mg), risperidone (0.1-20 mg), selegiline (2-40 mg), sertraline (10-800 mg), thoridazine, trazodone (50-1200 mg.

c. Uniformity and Release of Pharmacological Agents from the Foam or Film Composition

In order to determine whether the foam or film of the invention is efficacious for the drug delivery and thus suitable for therapeutic purposes, release of the drug from the foam or film and its uniformity was determined.

Uniformity, expressed as % of recovery and release of pharmacological agents from the foam was determined using lyophilized foam rods comprising ketorolac tromethamine in alginic acid sodium salt.

The uniformity of the distribution of the ketorolac in the foams prepared according to Example 5 was measured by a UV absorbance method. A standard curve for ketorolac in deionized water was developed by measuring the UV absorbance at 322.5 nm (path length 12.31 mm) for alginic acid alone, for ketorolac solutions comprising ketorolac (7.4%) and alginic acid, sodium salt (92.6%), and ketorolac (3.8%), alginic acid (48.1%) and hydroxypropyl methylcellulose (48.1%) mixture. Alginic acid solution alone without the drug serving as a control had a negligible absorbance.

For this study, three foam rods A, B and C prepared from the mixture containing 7.4% ketorolac and 92.6% alginic acid, were selected for analysis. About 2 mm of irregular material was trimmed from both ends of the foam rods. Using a razor blade, each foam rod was divided into 5 shorter cylindrical sections of length 9 mm. The weight of each section was recorded. Each section was dispersed into 200 ml deionized water using a high intensity mixer. The UV absorbance at 322.5 nm was recorded for each solution.

From the standard curve, the ketorolac concentration in ug/ml of solution was calculated from the following relationship: absorbance = 0.051 X Concentration + 0.0001.

For each foam section, the concentration multiplied by 200 ml gives the weight (μg) of ketorolac in that section. For each section, the ketorolac weight is divided by the weight of the foam section to yield the ketorolac weight per section in μg ketorolac per mg of foam. Finally, the obtained result is divided by the ideal value from the formulation (73.4 ug/mg of foam) to give the % ketorolac recovered for each foam section.

Results are seen in Table 2.

Table 2

Ketorolac Recovery (%)

	Foam Rod A	Foam Rod B	Foam Rod C
Foam Section #			
1	99.7	98.6	96
2	100	97.3	97.3
3	92.1	96.7	95.8
4	91.8	99.5	99
5	96	94.7	97.7
Mean	95.9	97.4	97.2

Standard Deviation	3.95	1.85	1.31
High/Low Ratio	1.09	1.04	1.03
High/Low Ratio, All Data	1.09		

Ideal, 100 %, recovery of ketorolac is 73.4 ug of ketorolac per 1 mg of foam.

Alginic acid sodium salt (AA) solution concentration contained 2.5 g of alginic acid per 100 g water.

Concentration of ketorolac tromethamine represented 7.43% of foam weight. Ratio of ketorolac:AA was 2:25.

As seen in Table 2, mean recovery for all three rods were very close to 100%, namely 95.7, 97.4 and 97.7%, respectively. Results show that almost 100% release of ketoroloc can be achieved from the foam prepared from alginic acid sodium salt when the drug is present in about 2:25 ratio of the drug to the polymer.

The above study was further expanded for release of ketorolac tromethamine from alginic acid sodium salt/HPMC foams in pH 4.22 phosphate buffer. For that study, ketorolac concentration was 7.4%, normalized to 120 mg foam. The foam was prepared from alginic acid sodium salt/HPMC mixture.

Results are seen in Figure 1 which shows that the foam prepared from a mixture of ketorolac, alginic acid and HPMC has slower more controlled release of ketorolac than the one prepared from ketorolac and alginic acid only.

Results seen in Figure 1 show that the foams prepared from mixtures of ketorolac, alginic acid sodium salt, and HPMC have slower more controlled release than the one prepared from ketorolac and alginic acid sodium salt only.

As seen in Figure 1, approximately 93% of ketorolac was released from the alginic acid foam at 2 hours, while

approximately 54% of the drug was released at the same time from the 50:50 AA:HPMC foam.

These results illustrate the point of a slow versus fast release of the drug from the foam. The speed of the release may be conveniently controlled and regulated by changing the substrate or by combining the substrate materials and varying their proportions relative to each other or relative to the drug.

The data further show that the distribution of ketorolac in the lyophilized alginic acid or alginic acid/HPMC mixture is extremely uniform.

As seen in Figure 1, approximately 93% of ketorolac was released from the alginic acid foam at 2 hours, while approximately 54% of the drug was released at the same time from the alginic acid/HPMC foam (50:50).

These results illustrate the point of a slow versus fast release of the drug from the foam. The speed of the release may be conveniently controlled and regulated by changing the substrate or by or combining the substrate materials and varying their individual proportions relative to each other or relative to the drug.

The data further show that the distribution of ketorolac in the lyophilized alginic acid or alginic acid/HPMC mixture is extremely uniform.

The same type of experiment was performed for a film composition where the ketorolac release from the alginic acid film into a synthetic vaginal fluid at pH 4.2 was determined.

As seen in Figure 2, at two hours interval, approximately 55% of ketorolac was released from the film prepared from a film prepared from a solution consisting of 96.2 % alginic acid (sodium salt) and 3.8% of ketorolac. The film was prepared according to Example 7.

The same type of experiment was performed for a film composition where the ketorolac release from the alginic

acid film into a synthetic vaginal fluid at pH 4.2 was measured. As seen in Figure 2, after 2 hours approximately 55% of the ketorolac was released from a film prepared from a solution consisting of 96.2% alginic acid sodium salt and 3.8% of ketorolac. The film was prepared according to Example 7.

d. Drug Release from the Foam

Drug release from the foams or films of the inventions is controllable and may be changed by design. Specifically, certain polymers permit a fast water uptake into the foam or gel resulting in faster release of the drug, other polymers or mixtures, particularly those containing hydroxypropyl methyl cellulose contribute to a decreased rate of the drug release.

To determine a water uptake and drug release from the foam, microcrystalline cellulose (AVICEL), HPMC, alone or in combination in various concentrations was tested. Foam prepared for this study were according to Examples 4-6.

Results of this study are shown in Figure 3. Figure 3 clearly shows that the foam prepared from the AVICEL/HPMC mixture (95.2%/4.8%) takes up water much faster and in larger amounts than the foam prepared from AVICEL/HPMC mixture containing the same amount of each (50%/%50%) or foam prepared solely from HPMC.

Figure 3 demonstrates that for foam prepared from AVICEL/HPMC mixtures, the water uptake depends on a proportion of microcrystalline cellulose (AVICEL). Faster water uptake is observed when the proportion relative to HPMC is higher. HPMC slows down the water uptake.

e. Modifying Drug Release

To fabricate foam or film layers with rapid release properties of the pharmacologically active agent, the polymer or mixture of polymers is selected to enhance solubility of the drug in the hydrated polymer layer. For high-solubility drugs, hygroscopic polymers such as

cellulose derivatives are used alone or in combination with excipients that decrease viscosity, such as, for example, surfactants. Alternatively, dissolution of low-solubility drugs can be accelerated by incorporation of small fractions of hydrophobic polymers such as polyethylene or polypropylene and the use of solubility enhancers and/or surfactants.

Controlled or sustained release is achieved by incorporating polymers that increase viscosity upon hydration or polymers that decrease solubility of the drug. Incorporation of drug particles of different physical forms such as amorphous vs. crystalline can also delay the release of the drug from the foam or film device. Balanced approaches that include a combination of rapid with sustained release layers will achieve pulsed release that may be beneficial for the therapy of the disease.

The topical foams, films, and sprays typically contain a mucoadhesive agent in the amount of about 0.5% to about 10% concentration by weight, about 1% to about 10% penetration enhancer, and about 1% to about 10% buffering agent, wherein the drug to polymer ratio is from about 1-15 to about 85-99.

The transmucosal, translabial or transscrotal foams and films typically contain a mucoadhesive agent in the amount of about 0.5% to about 25% concentration by weight, about 5% to about 25% penetration enhancer and about 1% to about 10% buffering agent, wherein the drug to polymer ratio is about 1-15 to about 85-99.

Topical foams or films of the invention comprise at least of a hydrophilic or hydrophobic polymer, preferably a polymer which has a mucoadhesive properties and a pharmacological agent. If the mucoadhesive properties of the polymer are slight or if the polymer has no mucoadhesive properties, then the mucoadhesive agent is added.

Transmucosal drug delivery permits transport of the

drug into the systemic circulation directly through the nasal, buccal, vaginal, labial or scrotal epithelium, thereby avoiding invasive intravenous or less effective oral administration.

II. Therapeutic Compositions

Therapeutical compositions of the invention are either topical nasal, buccal, vaginal, labial or scrotal compositions or transepithelial compositions delivering the drug to the systemic circulation through the nasal, buccal or vaginal mucosa or through the labial or scrotal epithelium.

d. Topical Nasal, Buccal, Vaginal, Labial or Scrotal Foams or Films

Topical foams or films of the invention comprise at least of a hydrophilic or hydrophobic polymer, preferably a polymer which has a mucoadhesive properties and a pharmacological agent. If the mucoadhesive properties of the polymer are slight or if the polymer has no mucoadhesive properties, then the mucoadhesive agent is added.

B. Transepithelial Compositions

Transepithelial drug delivery permits transport of the drug into the systemic circulation directly through the nasal, buccal and vaginal mucosa or through labial or scrotal epithelium, thereby avoiding invasive intravenous or less effective oral administration.

Transmucosal or trans-epithelial foams or films of the invention typically comprise at least of a hydrophilic or hydrophobic polymer substrate, preferably a polymer which has a mucoadhesive properties, penetration enhancer or sorption promoter and a pharmacological agent. If the mucoadhesive properties of the polymer are slight or if the polymer substrate has no mucoadhesive properties, then the additional mucoadhesive agent is added.

C. Specific Exemplary Foam or Film Compositions

Specific and preferred topical, and transepithelial

foam or film compositions are those comprising a polymer, preferably mucoadhesive polymer or a mixture of polymers formulated for rapid or slow drug delivery. These compositions and also include empty foams or films which can be conveniently incorporated with a drug solution or powder. Also included are compositions wherein the foam or film is used for coating of conventional devices, such as tampons and, depending on the polymer(s) used for regulation of drug release form such devices, depending on their use.

Thus, for rapid drug release for topical use the composition contains mostly AVICEL-like polymers in combination with an appropriate mucoadhesive agent while for a slow release the composition will primarily contain HPMC-like polymers which may have mucoadhesive properties but primarily regulate the release of the drug.

Foam or film compositions of the invention consist essentially of a combination of an effective amount of a pharmacological agent from about 0.01 mg to about 2000 mg and occasionally higher, said agent selected from the group of agents exemplarily listed above in section D or any other drug suitable for transmucosal delivery, incorporated into a foam or film prepared from a polymer or mixture thereof and preferably containing at least one or several penetration enhancers and/or a release modifier and/or additional mucoadhesive agent and/or additional nontoxic pharmacologically acceptable biocompatible excipient.

Said composition is typically formulated as a foam or film suitable for insertion into a nasal, buccal or vaginal cavity or in a shape suitable for placement on the labia or scrotum, said composition further optionally incorporated into a nasal, buccal, vaginal, labial or scrotal device or covering such device.

Specific representative compositions are listed in Table 3.

Table 3

FOAM AND FILM FORMULATIONS

	Ex.A Wt/g	Wt%	Ex.B Wt/g	Wt%	Ex.C Wt/g	Wt%	Ex.D Wt/g	Wt%	Ex.E Wt/g	Wt%	Ex.F Wt/g	Wt%	Ex.F-1 Wt/g	Wt%
Material														
AA	1.2503	46.3	2.5023	92.6	2.5	96.2								
HPMC	1.2507	46.3					1	4.8	5.0014	50	5.0002	100	5.0044	20
Ktr	0.2015	7.46	0.2002	7.41	0.1	3.8								
Avicel							20.192	95.2	5.005	50			20.0017	80
Water	100		100		50		79		90		95		75	
Form	Foam		Foam		Film		Foam		Foam		Foam			
	Ex.5		Ex.6		Ex.7		Ex.8		Ex.9				Ex.10	

AA = Alginic Acid, Sodium Salt (Sigma)

HPMC = Hydroxypropylmethyl Cellulose USP (Dow Chemical)

Ktr = Ketorolac Tromethamine USP (Quimica Sintetica)

Avicel = Avicel NF, Ph-101 (FMC Biopolymer), nominal particle size 50 microns

Wt% = Weight % of dry components in the foam

In a general method for preparing the transmucosal or trans-epithelial compositions of the invention, 0.01 to 2000 mg of the drug is dissolved in a solvent, aqueous or non-aqueous, depending on the nature of the drug and combined with a polymer or polymer mixture used for foam or film preparation and subjected to appropriate process to fabricate foams and films as described above, preferably lyophilization, aeration, spray-drying or drying as described above. Other additives, as described, may or may not be added. Resulting foam or film may be formed as a stand alone device or incorporated into a device, such as an intravaginal tampon, foam suppository, foam tablet, foam pessary, etc., or molded into a buccal dissolvable tablet, strip or patch or incorporated into a foam capsule, gel capsule or another form suitable for buccal, nasal insertion and suitable for these applications, or as described above, may be incorporated into or used for coating of an independent non-foam, non-film device.

Typically, for transepithial vaginal, labial and scrotal delivery, the composition will contain higher percentage of the mucoadhesive agent and penetration enhancer than for nasal or buccal transmucosal delivery as the barrier properties of the nasal and buccal mucosa are less restrictive and blood supply is closer to the mucosal surface than in the vaginal mucosa. For labial or scrotal use, the foam or film will contain the higher amount of the mucoadhesive agent and amount of penetration enhancer will also be generally higher as these compositions have to cross non-cornified or cornified non-mucosal epithelium.

The foam or film according to the invention compositions are useful for delivery of drugs by permeation through the vaginal, nasal, buccal, labial or scrotal epithelium directly to the systemic circulation. The mucoadhesive polymer enhances adhesion of the foam or film to the covering epithelia and the glycol derivative

optimally present in these compositions enhances permeation through the mucosa, particularly of the drugs which would otherwise not be able to cross the nasal, oral, vaginal, labial or scrotal epithelial barrier.

Moreover, the drug compounds solubilized with a glycol derivative in combination with an appropriate mucoadhesive agent allow a prolonged contact of the drug with the mucosal surface, thereby further enhancing the efficiency of delivery of the compound.

III. Formulations and Devices

Each foam or film composition of the invention is formulated for its specific use, namely for the use as topical or transepithial vaginal, nasal, buccal or labial, translabial, scrotal or transscrotal foam or film.

A. Formulations

Formulations are prepared specifically for the intended use of delivery route.

Thus, for nasal transepithelial administration, the composition is formulated as a foam or film, preferably sprayable foam or gellable film.

For buccal transepithelial delivery, the composition is formulated as a foam tablet or capsule or gel foam or spray or is microincorporated into a device insertable into the buccal space, such as a buccal patch, strip, permeable pad or bag, etc.

For vaginal transmucosal delivery, the composition is formulated as a foam tampon, foam ring, foam pessary, foam suppository or foam sponge. Each of these may be conveniently incorporated into an intravaginal device, such as, for example, a conventional tampon, vaginal ring, pessary, suppository or vaginal sponge.

For labial transepithelial delivery, the foam or film will take on the structure conveniently attachable to labia, such as strip, pillow, pad, butterfly bandage, etc.

For scrotal transepithelial delivery, the composition

is preferably formulated as a liquid or semi-liquid which is conveniently sprayed or otherwise applied to scrotum.

For transepithelial scrotal delivery, the foam or film is formulated as strip, attachable or sprayed on as a gellable film.

For a low release, bioadhesive foam tablets, strips, pads, or films consist essentially of hydroxypropyl cellulose and polyacrylic acid. These foams or films release drugs for up to five days once they are placed on or in close proximity of labial or scrotal epithelium.

For all these transmucosal administrations, the drug can also be first formulated as a solution, suspension, cream, lotion, paste, ointment or gels which can be incorporated into the foam or film and applied to the nasal or buccal cavity or vagina, labia or scrotum.

The choice of additional suitable additives and excipient depends on the exact nature of the particular transmucosal delivery route and the form in which the drug is delivered. Thus, the actual formulation depends on the properties of the pharmacological agent and on whether the active ingredient(s) is/are to be formulated into a foam or film or indirectly into a cream, lotion, foam, ointment, paste, solution, or gel, which is then incorporated into the foam or film, as well as on the identity of the active ingredient(s).

2. Devices

A therapeutic foam or film according to the invention can be a stand alone device or it may become a part of a more complex assembly comprising as one component the foam or film and as a second component a device or formulation made of a different material than foam or film described herein. Such other device may be in the form of, for example, a structural device such as a strip, pad, sphere, pillow, tampon, tampon-like device, vaginal ring, sponge

or pessary, or it may be in a form of a formulation, such as a tablet, paste, suppository, bioadhesive tablet, bioadhesive microparticles, cream, lotion, ointment, or gel.

The structural device such as the tampon can be completely or partially coated or covered with the foam or film or the foam or film may be inserted inside of the device or into certain part of the device in any convenient arrangement.

In the alternative, the drug could be incorporated into the non-foam, non-film device and an empty foam or film composition could be used for coating or covering such device solely for the purpose of control of release rate.

IV. Routes of Delivery

The present invention concerns a polymer foam or film for delivery of therapeutic agents to and through nasal, oral or vaginal mucosal epithelium as well as through the cornified or noncornified epithelium of labia and scrotum. In particular, the invention concerns a solid, semi-solid or liquid polymeric foam or film having a therapeutic agent incorporated therein wherein said agent is released from said foam or film upon placement of said foam or film on the surface of nasal, buccal or vaginal mucosa, labia or scrotum. The foam of the invention has a controllable rate of gelling, swelling and degradation.

Treatment of various diseases, such as osteoporosis, inflammation, pain, prostate cancer and other neoplastic growths, fungal, bacterial, viral or parasitic infections and other medical conditions using a method of invention involves contacting the nasal, buccal, vaginal, labial or scrotal epithelium directly with a therapeutic agent suitable for treatment of such condition. Such direct contact permits an immediate, continuous and efficacious treatment of various diseases or medical conditions. Systemic drug delivery using transepithelial route

eliminates inactivation of the agent by gastrointestinal tract or by liver metabolism. Such direct treatment also permits use of only such a dosage of the agent as is therapeutically required for treatment of the affected tissue.

For each of these treatments, the drug is formulated differently, as described. Briefly, the active drug is formulated to adhere to and directly cross or be transported through the mucosal, labial or scrotal epithelium. For transepithelial delivery to the general circulation, if necessary and appropriate for the properties of the drug, the additives which promote adhesion to transport and penetration of the drug through the nasal, buccal, vaginal, labial or scrotal epithelium are added.

A. Vaginal Delivery

The vaginal drug delivery system provides a sustained delivery of the drug to the vaginal epithelium for the treatment of various conditions including dysmenorrhea, osteoporosis, neoplastic growth, migraine, neurodegenerative diseases, vaginal or systemic infections, among others.

The vaginal delivery may be achieved by the foam device or film having a drug incorporated therein or it can be a solid object delivery system such as a conventional vaginal tampon, ring, pessary, tablet or suppository, for example, coated with or containing the foam or film. Alternatively, it can be a paste or gel incorporated into the foam or film having a sufficient thickness to maintain prolonged vaginal epithelium contact. Alternatively, the foam or film can provide a coating on a suppository wall or a sponge or other absorbent material impregnated with a liquid drug containing solution, lotion, or suspension of bioadhesive particles, for example. Any form of drug delivery system which will effectively deliver the treatment agent to the vaginal epithelium is intended to be included within the scope of this invention.

Intravaginal topical delivery comprises contacting the vaginal epithelium and mucosa with a foam or film composition comprising a therapeutically effective agent alone or in admixture with a carrier, mucoadhesive agent, sorption enhancer or penetration promoter.

Intravaginal delivery is achieved either directly by delivering the foam or film composition of the invention to the vagina or by delivering the composition of the invention to the vagina incorporated into a vaginal device, as described above. The foam or film composition or the device, coated or incorporated therewith, is placed into a close contact with or into a close proximity of the vaginal epithelium wherein the agent is either released from the composition or device or released from the foam or film device and either directly or through the action of the mucoadhesive compound it comes into a contact with or adheres to the vaginal epithelium and mucosa where it penetrates the vaginal wall and is delivered to the uterus and/or to the blood circulation by being absorbed or transported through vaginal mucosa.

Delivery of the drugs through the vaginal mucosa using the current foams or films significantly improves systemic bioavailability and greatly increases concentrations of these drugs in the plasma.

B. Buccal Delivery

Transepithelial foam or film for buccal delivery of drugs permits transport of the drug into the systemic circulation directly through the nasal mucosa, thereby avoiding invasive intravenous or less effective oral administration.

In one embodiment, this invention concerns buccal delivery systems that are designed to interact with the epithelium lining the oral cavity wherein drug released from these devices may act topically on the buccal mucosa or successfully traverse the barrier of the buccal epithelium

and reach mucosal and submucosal areas where they gain access to the systemic circulation for distribution to targets distinctly separated from the site of administration.

Drug delivery via the buccal route is applicable to patients of both genders, achieves high compliance since it is non-invasive and offers easy access to the site of administration. The buccal mucosa is rich in blood vessels facilitating access to systemic circulation. Furthermore, drug absorbed from the buccal mucosa will avoid hepatic first-pass metabolism similar to the vaginal route.

C. Nasal Delivery

In yet another embodiment, this invention also concerns administration of foam and film drug delivery devices to the nasal mucosa where incorporated drug may be released to the nasal epithelium or permeates the epithelial barrier to reach deeper mucosal tissue, where it may gain access to the systemic circulation for distribution. The nasal route has the advantage of providing rapid absorption with little or no degradation of drugs that have systemic targets since blood drainage from the nasal cavity also bypasses hepatic first-pass metabolism. This route is well-received by patients due to ease in administration of nasal preparations. Of particular interest are nasal delivery approaches for biotechnology-based drugs such as proteins that are designed to interact with the body immune system and boost immune defense (i.e., vaccines). Access to the immune system through the nose is provided only a few cell layers below the epithelium in form of the nasal-associated lymphatic tissue (NALT).

D. Labial Delivery

The current invention concerns delivery through the external non-cornified mucosal labial epithelium.

The foam or film the invention comprises administration of therapeutic and/or palliative anti-inflammatory,

analgesic, chemotherapeutic, antineoplastic, antiosteoporotic, antifungal, antibacterial, antiviral or parasiticidal drugs to the non-cornified labial epithelium or through this barrier to deliver the pharmacologically active agents directly to the systemic circulation.

The foam or film composition or the medicated device is applied once, twice or several times a day, as needed, or according to a treatment regimen. The device, or its active part, such as for example a pad containing or covered with the foam or film composition, is typically provided in dry or wet form or may be wetted prior insertion.

The foam or film female device for drug delivery through labial epithelium is typically an insert, such as a tape, small pillow, minipad, small preferably rectangular pad or combination of two tapes or pads connected in butterfly-like fashion or one or two of these inserts attached to labia may be held in place with vaginal insert. The advantage of labial administration is that two devices and/or both sides of the device, be it the pad or the tape, can be medicated and two of these inserts may be applied at the same time along each side of clitoris.

One embodiment of the invention is a female foam or film device having a design of a labial butterfly pad, a pair of labial pads or a combination of a labial butterfly with a vaginal insert to hold the labial device in place. Both above devices are modified for containment of, or to accept, include or be impregnated with, a pharmacological agent formulated as a cream, lotion, foam, ointment, microparticles, nanoparticles, microemulsions, solution, or gel incorporated within said device.

Alternatively, the drug can be incorporated into a coating on a foam pad or sponge, or included within the foam pad as a suppository, sponge, tablet or other absorbent material may be impregnated with a liquid, drug containing solution, lotion, or suspension of bioadhesive particles,

shaped into a pad may be used.

The female device for drug delivery through labia is generally any structure which can be attached or applied to labia. Device may be stand alone or attached to some structural support, such as a slip.

Typically, additionally to the devices described above, the female device may be a foam tape, adhesive tape, bandage, pad, pouch or bag which can be attached to the labia directly or is mounted into some structural support, such as a slip or strap, etc.

The device may optionally include a battery powered heating device to enhance blood flow and/or promote drug release and delivery. The battery is either attached to the pad or may be attached to the waistband of the slip or strap.

E. Scrotal Delivery

The foam or film of the invention permits administration of therapeutic anti-inflammatory, analgesic, chemotherapeutic, antiosteoporotic, antineoplastic, antifungal, antibacterial, antiviral or parasiticidal pharmacological agents to the cornified scrotal epithelium or through this barrier to deliver the pharmacologically active agent to prostate, testes or directly to the systemic circulation for systemic drug delivery.

The invention concerns a discovery that many of the problems noted with systemic delivery could be overcome by focusing the delivery of drug therapy directly to the non-mucosal scrotal epithelium using a topical composition or a device comprising a specially formulated therapeutical agent. The specially formulated foam or film composition promotes adhesion of the drug released from the device to the scrotum for transscrotal delivery. Optionally, such composition comprises additional components that enhance drug penetration and absorption through scrotal epithelium.

The method for transscrotal treatment encompasses a

typical topical treatment comprising contacting the lightly cornified scrotal epithelium directly with the drug or with the device comprising the drug, for extended periods of time for as long as needed, by providing a topical foam or film composition or a device comprising a topical composition comprising the drug formulated in combination with at least a mucoadhesive agent to promote adherence of the drug to the scrotal epithelium and, optionally, with penetration enhancer.

One embodiment of the invention concerns a male device made of or coated with foam or film for delivery of a pharmacological agent through non-mucosal lightly cornified scrotal tissue. The device provides a continuous contact with the scrotal epithelium thereby asserting a therapeutic effect of the composition of the invention incorporated therein.

Typically, the male device is a foam or film tape, adhesive tape, bandage, pad, or set of tapes, bandages or pads, pouch or bag which can be attached to the scrotum directly or is mounted into some structural support, such as a strap, athletic supporter, suspender, etc., but it may also be a foam or film gel sprayed on the scrotum.

The foam or film compositions or the foam or film coated devices are administered or applied to the nasal, oral or vaginal cavity or to labia or scrotum once, twice or several times a day, as needed, or according to a treatment regimen. It may be applied once and left on the covering epithelium for several hours or days or it may be applied repeatedly in various intervals. The device, or its active part, such as for example a stand-alone foam or film coated pad or pad containing the composition is typically provided in dry or wet form or may be wetted prior to emplacement into the nasal, oral or vaginal cavity or labia or scrotum.

EXAMPLE 1

Ketoconazole Foam

This example illustrates preparation of the foam containing ketoconazole.

Polyethylene glycol 400 was obtained from Fluka Chemika, alginic acid sodium salt was obtained from Sigma-Aldrich, and ketoconazole (USP 24, micronized) was obtained from Quimica Sintetica S.A.

Ketoconazole was dissolved in polyethylene glycol (PEG) 400 to form a homogeneous 10 mg/mL solution. Alginic acid sodium salt was dissolved in distilled water to produce a 5.0 w/w% solution. Forty-five milliliters (45.0 mL) of the alginic acid solution was combined with 5.0 mL of the ketoconazole/PEG 400 solution, and these solutions were mixed together at 70°C for 15 minutes. Five milliliter (5.0 mL) aliquots of this solution were poured into 5.0 mL plastic syringes and frozen at -80°C. Frozen cylindrical samples were subsequently removed from the syringe molds and lyophilized using a Virtis Unitop 1000L shelf lyophilizer. Cylindrical ketoconazole-containing polymeric foams resulted.

EXAMPLE 2

Preparation of Drug-Containing Foam for Vaginal Delivery

This example describes a process for preparation of a foam for topical vaginal delivery of ketoconazole.

Ketoconazole (USP 24, micronized) was obtained from Quimica Sintetica S.A. Hydroxypropyl methylcellulose (Methocel@ K, HPMC K15M), was obtained from Dow Chemical, Midland, Michigan. Polysorbate 80 (Tween@ 80) was obtained from Spectrum Chemical Manufacturing Corp., Gardena, California.

Foams were prepared by adding 1.0 gm of Tween 80 to 100.0 mL of distilled water in a beaker. The solution was heated to 80°C and 2.5 gm of Methocel were subsequently added. Mechanical stirring was used to prepare a homogenous

solution. The solution was cooled to 60°C and 2.0 gm ketoconazole was added. Mechanical stirring was used to completely mix the resulting formulation.

Eighteen 5.0 mL plastic syringes were filled with the drug-containing solution and placed into a freezer at -80°C for one hour. Frozen cylinders of the solution were then expelled from the syringes and placed in a Virtis Unitop 1000L lyophilizer. The cylinders were subsequently lyophilized to produce cylindrical ketoconazole-containing foam samples.

EXAMPLE 3

Preparation of Drug-Containing Foam for Topical Vaginal Delivery

This example describes a process for preparation of a foam for transvaginal delivery of ketoconazole.

Ketoconazole (USP 24, micronized) was obtained from Quimica Sintetica S.A. Hydroxypropyl methylcellulose (Methocel@ K, HPMC K15M) was obtained from Dow Chemical, Midland, Michigan. Polysorbate 80 (Tween@ 80) was obtained from Spectrum Chemical Manufacturing Corporation, Gardena, California. All other chemicals were obtained from Sigma Aldrich, St. Louis, Missouri.

A citric acid/phosphate buffer solution (pH=5.0) was prepared using a 0.1 molar citric acid solution and a 0.2 molar disodium phosphate solution. One hundred milliliters of the solution was prepared by adding 49.0 mL of the citric acid solution to 51.0 mL of the disodium phosphate solution.

Foams were prepared by adding 1.0 gm of Tween to 80 to 100.0 mL of the citric acid/phosphate buffer solution in a beaker. The solution was heated to 80°C and 2.5 gm of Methocel were subsequently added. Mechanical stirring was used to prepare a homogenous solution. The solution was cooled to 60°C and 2.000 mg ketoconazole was added. Mechanical stirring was used to completely mix the resulting formulation.

Eighteen 5.0 mL plastic syringes were filled with the drug-containing solution and placed into a freezer at -80°C for one hour. Frozen cylinders of the solution were then expelled from the syringes and placed in a Virtis Unitop 1000L lyophilizer. The cylinders were subsequently lyophilized to produce cylindrical ketoconazole-containing foam samples.

EXAMPLE 4

Preparation of Drug-Containing Foam for Transvaginal Delivery

This example describes a process for preparation of a foam for transvaginal delivery of ketoconazole.

Foams were prepared by adding 2.5 gm of Methocel to 100.0 mL of distilled water and heating the solution to 80°C. Mechanical stirring was used to prepare a homogenous solution. The solution was cooled to 60°C and 2.0 gm ketoconazole was added.

Eighteen 5.0 mL plastic syringes were filled with the drug-containing solution and placed into a freezer at -80°C for one hour. Frozen cylinders of the solution were then expelled from the syringes and placed in a Virtis Unitop 1000L lyophilizer. The cylinders were subsequently lyophilized to produce cylindrical ketoconazole-containing foam samples.

EXAMPLE 5

Ketorolac Containing Foam

This example describes preparation of the ketorolac containing foam using alginic acid/hydroxypropyl methylcellulose substrates.

A solution was prepared by mixing 0.2015 g ketorolac tromethamine with 100.0 ml deionized water at 70-80 C with stirring, followed by adding 1.2507 g hydroxypropyl methylcellulose followed by 1.2503 g alginic acid with continued stirring. The warm solutions were dispensed into 10 ml plastic syringes in 10 ml aliquots. The samples were

frozen at -80°C for 18 hr. After brief warming at room temperature, the samples were ejected from the syringes onto a metal pan precooled to -40°C. The samples were converted to foams by freeze-drying under vacuum at -20°C for 117 hr, followed by warming to ambient temperature for 5 hr while under vacuum. The resulting foams were stored under dry conditions.

EXAMPLE 6

Alginic Acid Foam Containing Ketorolac

This example describes preparation of alginic acid foam containing ketorolac tromethamine.

A solution was prepared by mixing 0.2002 g ketorolac tromethamine with 100.0 ml deionized water at 70-80°C with stirring, followed by adding 2.5023 g alginic acid with continued stirring.

The warm solutions were dispensed into 10 ml plastic syringes in 10 ml aliquots. The samples were frozen at -80°C for 18 hr. After brief warming at room temperature, the samples were ejected from the syringes onto a metal pan precooled to -40°C. The samples were converted to foams by freeze-drying under vacuum at -20°C for 117 hr, followed by warming to ambient temperature for 5 hr while under vacuum. The resulting foams were stored under dry conditions.

EXAMPLE 7

Alginic Acid Film Containing Ketorolac

This example describes preparation of alginic acid film containing ketorolac tromethamine.

A solution was prepared by mixing 2.5 g alginic acid with 50.0 ml deionized water at 80°C with stirring. After cooling to room temperature, 100 mg of ketorolac was added and stirred for 1 hr. The solution was poured into 4-inch diameter molds and was allowed to dry at room temperature for 70 hr. The resulting films were stored under dry conditions.

EXAMPLE 8

Hydroxypropyl Methylcellulose-Avicel Foam

This example describes preparation of foam using hydroxypropyl methylcellulose and microcrystalline cellulose derivative as a substrate.

A solution was prepared by mixing 1.0046 hydroxypropylmethyl cellulose and 20.0192 g avicel PH-101 microcrystalline cellulose with 79.0 g deionized water at about 70°C with stirring. The warm solution was dispensed into 5 ml plastic syringes in 5 ml aliquots. After cooling to room temperature, the samples were frozen at -80°C for 2 hr. After brief warming at room temperature, the samples were ejected from the syringes onto a metal pan precooled to -20°C. The samples were converted to foams by freeze-drying at -20°C for 90 hr and -10°C for 2 hr. The samples were then warmed to ambient temperature under vacuum for 22 hr. The resulting foam rods were stored under dry conditions.

EXAMPLE 9

Hydroxypropyl Methylcellulose Foam

This example describes preparation of foam using hydroxypropyl methylcellulose and microcrystalline cellulose derivative as a substrate.

A solution was prepared by mixing 5.0014 Hydroxypropylmethyl Cellulose and 5.0050 g Avicel PH-101 microcrystalline cellulose with 90.0 g deionized water at about 70°C with stirring. The warm solution was dispensed into 5 ml plastic syringes in 5 ml aliquots. After cooling to room temperature, the samples were frozen at -80°C for 2 hr. After brief warming at room temperature, the samples were ejected from the syringes onto a metal pan precooled to -20°C. The samples were converted to foams by freeze-drying at -20°C for 90 hr and -10°C for 2 hr. The samples were then warmed to ambient temperature under vacuum for 22 hr. The resulting foam rods were stored under dry

conditions.

EXAMPLE 10

Hydroxypropyl Methylcellulose Foam

This example describes preparation of foam using hydroxypropyl methylcellulose and microcrystalline cellulose derivative as a substrate.

A solution was prepared by mixing 5.0044 hydroxypropylmethyl cellulose and 20.0017 g avicel PH-101 microcrystalline cellulose with 75.0 g deionized water at about 70°C with stirring. The warm solution was dispensed into 5 ml plastic syringes in 5 ml aliquots. After cooling to room temperature, the samples were frozen at -80°C for 2 hr. After brief warming at room temperature, the samples were ejected from the syringes onto a metal pan precooled to -20°C. The samples were converted to foams by freeze-drying at -20°C for 90 hr and -10°C for 2 hr. The samples were then warmed to ambient temperature under vacuum for 22 hr. The resulting foam rods were stored under dry conditions.

EXAMPLE 11

Alginic Acid-HPMC Foams Containing Transcutol and Ketorolac Tromethamine

This example describes preparation of alginic acid/HPMC foams containing penetration enhancer transcutol and ketorolac tromethamine.

A solution was prepared by mixing 0.20 g ketorolac tromethamine with 100.0 ml deionized water at 70-80°C with stirring, followed by adding 1.25 g hydroxypropyl methylcellulose followed by 1.25 g Alginic Acid with continued stirring. The warm solutions were dispensed into 10 ml plastic syringes in 10 ml aliquots. The samples were frozen at -80°C for 18 hr. After brief warming at room temperature, the samples were ejected from the syringes onto a metal pan precooled to -40°C. The samples were converted

to foams by freeze-drying under vacuum at 20°C for 117 hr, followed by warming to ambient temperature for 5 hr while under vacuum. Foam rods, cut to about 4 cm length and weighing about 160 mg, were sprayed with about 1.0 ml of 1.6% transcutol tromethamine in methylene chloride. The methylene chloride was evaporated using gentle heat, leaving about 16 mg of transcutol tromethamine in the foam rod. The resulting foams were stored under dry conditions.

EXAMPLE 12

HPMC Foams Containing Cyclodextrin B

This example describes preparation of HPMC foams containing Cyclodextrin B.

Composition:

	Foam #1	Foam #2	Foam #3
HPMC	2.4992 g (95.21%)	2.5100 g (91.0%)	2.4906 g (83.2%)
Beta-Cyclodextrin	0.1258 g (4.79%)	0.2940 g (9.02%)	0.5015 g (16.8%)
Water	97.5 g	97.5 g	
BCD:HPMC Ration	1:20	1:10	1:5

Solutions were prepared by mixing hydroxypropylmethyl cellulose, β-gyclodextrin, and deionized water at about 70°C with stirring. The warm solution was dispensed into 5 ml plastic syringes in 5 ml aliquots. After cooling to room temperature, the samples were frozen at -80°C for 35 min. After brief warming at room temperature, the samples were ejected from the syringes onto a metal pan precooled to -20°C. The samples were converted to foams by freeze drying at -20°C for 17 hr and -10°C for 49hr. The samples were then warmed to ambient temperature under vacuum for 4.5 hr. Soft white foam rods were produced in all cases. The foam rods were stored under dry conditions.

EXAMPLE 13

Alginic Acid Film

This example describes preparation of alginic acid film.

Alginic acid sodium salt was obtained from Sigma-Aldrich and dissolved in distilled water to produce a 5.0 w/w% solution. The alginic acid and water were mixed for at least 2 hours at 80°C using a magnetic stir bar to form a homogeneous solution. Layers of this viscous alginic acid solution, with thicknesses ranging from 300 mm to 2.0 mm, were coated onto glass plates (20 x 20 cm^2) using a manual thin layer chromatography (TLC) plate coater (CAMAG, Switzerland). The layers of solution were allowed to dry for 24 hours at 25°C, and the resultant polymer films were removed from the glass plates. Clear, flexible, hydrophilic alginic acid films resulted.

EXAMPLE 14

Alginic Acid Alendronate Sodium Film

This example describes preparation of alginic acid film comprising alendronate.

Alginic acid sodium salt was obtained from Sigma-Aldrich and dissolved in distilled water to produce a 5.0 w/w% solution using the above described method. Alendronate sodium (Lot #ASFPGO04) was obtained from Albany Molecular Research, Albany, New York, and 50.6 mg was added to 25.0 mL of the alginic acid solution. The solution was agitated at 25°C for at least one hour in a plastic 50 mL conical tube using a wrist action shaker to form a clear, homogeneous solution. The viscous alginic acid alendronate sodium solution was coated onto glass plates (20 x 20 cm^2) in layers approximately 1.0 mm thick using a manual thin layer chromatography (TLC) plate coater (CAMAG, Switzerland). The layers of solution were allowed to dry for 24 hours at 25°C, and the resultant polymer films were removed from the glass plates. Clear, flexible, hydrophilic

alginic acid alendronate sodium films resulted.

EXAMPLE 15

Alginic Acid Metoclopramide Hydrochloride Film

This example describes preparation of alginic acid film comprising metoclopramide.

Alginic acid sodium salt was obtained from Sigma-Aldrich and dissolved in distilled water to produce a 5.0 w/w% solution using the above described method. Metoclopramide hydrochloride was obtained from ICN Biomedicals, Inc., Aurora, Ohio, and 51.6 mg was added to 25.0 mL of the alginic acid solution. The solution was agitated at 25°C for at least one hour in a plastic 50 mL conical tube using a wrist action shaker to form a clear, homogeneous solution. The viscous alginic acid metoclopramide hydrochloride solution was coated onto glass plates (20 x 20 cm^2) in layers approximately 1.0 mm thick using a manual thin layer chromatography (TLC) plate coater (CAMAG, Switzerland). The layers of solution were allowed to dry for 24 hours at 25°C, and the resultant polymer films were removed from the glass plates. Clear, flexible, hydrophilic alginic acid/metoclopramide hydrochloride films resulted.

EXAMPLE 16

HPMC/Alendronate Sodium Film

This example describes procedure used for preparation of alendronate containing film.

Hydroxypropyl methylcellulose (HPMC) was obtained from The Dow Chemical Company (Methocel K15M) and dissolved in distilled water to produce a 2.5 w/w% solution using the above described method. Alendronate sodium (Lot #ASFPG004) was obtained from Albany Molecular Research, Albany, New York, and 49.0 mg was added to 25.0 mL of the HPMC solution. The solution was agitated at 25°C for at least one hour in a plastic 50 mL conical tube using a wrist action shaker to form a clear, homogeneous solution. The viscous

HPMC/alendronate sodium solution was coated onto glass plates (20 x 20 cm^2) in layers approximately 1.0 mm thick using a manual thin layer chromatography (TLC) plate coater (CAMAG, Switzerland). The layers of solution were allowed to dry for 24 hours at 25°C, and the resultant polymer films were removed from the glass plates. Clear, flexible, hydrophilic HPMC/alendronate sodium films resulted.

EXAMPLE 17

HPMC/Metoclopramide Hydrochloride Film

This example describes procedure used for preparation of film containing metoclopramide.

Hydroxypropyl methylcellulose (HPMC) was obtained from The Dow Chemical Company (Methocel K15M) and dissolved in distilled water to produce a 2.5 w/w% solution using the above described method. Metoclopramide hydrochloride was obtained from ICN Biomedicals, Inc., Aurora, Ohio, and 50.8 mg was added to 25.0 mL of the HPMC solution. The solution was agitated at 25°C for at least one hour in a plastic 50 mL conical tube using a wrist action shaker to form a clear, homogeneous solution. The viscous HPMC/metoclopramide hydrochloride solution was coated onto glass plates (20 x 20 cm^2) in layers approximately 1.0 mm thick using a manual thin layer chromatography (TLC) plate coater (CAMAG, Switzerland). The layers of solution were allowed to dry for 24 hours at 25°C, and the resultant polymer films were removed from the glass plates. Clear, flexible, hydrophilic HPMC/metoclopramide hydrochloride films resulted.

EXAMPLE 18

Preparation of Foams or Films Containing Pharmacological Agent

This example describes the preparation of foams or films for mucosal, transmucosal, scrotal, transscrotal, labial or tarns-labial delivery of various pharmacological agents.

A foam or film prepared according to any of the

Examples 1 through 17 for mucosal, transmucosal, labial, translabial, scrotal or transscrotal administration of each one of the following drugs at the indicated dose: aspirin (975 mg), piroxicam (20 mg), indomethacin (50 mg), fenamate (500 mg), sulindac (200 mg), nabumetone (750 mg), detorolac (10 mg), ibuprofen (200 mg), phenylbutazone (50 mg), bromfenac (50 mg), naproxen (550 mg), lidocaine (100 mg), mepivacaine (0.2 mg), etidocaine (200 mg), bupivacaine (100 mg), 2-chloroprocaine hydrochloride (100 mg), procaine (200 mg), tetracaine hydrochloride (20 mg), diltiazem (60 mg), israpidine (10 mg), nimodipine (30 mg), felodipine (450 mg), nifedipine (90 mg), nicardipine (30 mg), ritodrine (150 mg), bepridil (300 mg), dofetilide (1 mg), almokalant (1 mg), sematilide (1 mg), ambasilide (1 mg), azimilide (1 mg), tedisamil (100 mg), sotalol (240 mg), ibutilide (1 mg), terbutaline (5 mg), salbutamol (1 mg), piroxicam (20 mg), metaproterenol sulphate (20 mg), nitroglycerin (3 mg), isosorbide dinitrate (40 mg), isosorbide mononitrate (120 mg). Other drugs, in amounts as described above in Section D, may be formulated in the same fashion.

The quantity of the drug dosage needed to deliver the desired dose depends on the concentration of the active ingredient in the composition and the amount of the penetration enhancer or mucoadhesive agent. The therapeutic dosage range for vaginal transmucosal administration of the compositions of the present invention will vary with the size of the patient.

EXAMPLE 19

Preparation of Film Solution Containing Ketorolac for Transmucosal Nasal Delivery

This example describes the preparation of a transmucosal ethoxydiglycol-containing nasal composition.

Using a high-shear mixer, 1 g ketorolac tromethamine, 1.5 g Tween 80, 1.0 g polycarbophil, 0.05 g sodium chloride, and 2.5 g sorbitol were dispersed in 44 g deionized water.

The solution is sterilized by passing it through a 0.2 micron Millipore filter. The resulting translucent mixture was suitable for spraying or spreading onto nasal tissue.

EXAMPLE 20

Preparation of a Transmucosal Foam Gel Composition Containing Ketorolac

This example describes the preparation of a transmucosal gel composition containing ketorolac for transvaginal delivery.

Ketorolac tromethamine (1 g), Tween 80 (5 g), propylene glycol (10 g), and ethoxydiglycol (Transcutol P) (15 g) were added to deionized water (44 g) heated to 70 - 80°C in a 200 ml beaker while mixing with a high-shear mixer. Triacetin (20 g) and hydroxypropyl methylcellulose (5 g) were added gradually while maintaining the temperature and mixing. Upon cooling, the viscosity increased until the mixture had the consistency of a gel.

EXAMPLE 21

Preparation of Pamidronate Containing Buccal Foam Pad

This example describes preparation of pamidronate containing buccal pad.

The dose of unlabeled pamidronate, commercially available from Sigma, St. Louis, MO, was 0.2 mg/kg body weight. The pamidronate buccal pad is prepared by soaking the cotton, hydroxypropyl methyl cellulose or foam pad in the solution of pamidronate prepared similarly as described in Example 4.

EXAMPLE 22

Mucoadhesive Buccal Film

This example describes the preparation of a mucoadhesive buccal film containing the peptide drug salmon calcitonin as the hydrophilic drug for transmucosal delivery.

Salmon calcitonin (MW = 3.4 kD) was purchased from Bachem (Torrance, CA). 50:50 Poly(D,L-lactide-co-glycolide)

was obtained from Boehringer Ingelheim (Ingelheim, Germany). Chitosan glutamate salt, medical grade (MW = 150 kD) was received from Pronova Biochemical AS (Oslo, Norway). Methanol, dichlormethane, and glycerol were purchased from Sigma Chemical (St Louis, MO). An oil-in-water emulsion was formed by dropping 5 g of a solution prepared with 0.5 mL of 2% (w/w) salmon calcitonin in methanol and 4.5 mL of 20% (w/w) poly(D,L-lactide-*co*-glycolide in chloroform into a chitosan aqueous solution (2%, w/w) with 0.5% (w/w) glycerol under stirring (9500 rpm) at 15°C. The mixture was maintained under stirring for 20 minutes, spread as a thin layer onto a glass plate using a CAMAG TLC plate coater, and kept at 30°C to allow solvent evaporation.

WHAT IS CLAIMED IS:

1. A polymer foam or film composition for delivery of pharmacologically effective agents topically to nasal, buccal, vaginal, labial or scrotal epithelium or through nasal, buccal, vaginal, labial or scrotal epithelium into a systemic circulation, said composition comprising at least one substrate polymer or a mixture of substrate polymers and a pharmacologically effective agent.

2. The composition of claim 1 wherein said substrate polymer is hydrophilic, hydrophobic or a mixture of both.

3. The composition of claim 3 wherein said substrate polymer is selected for the group consisting of hydropropyl methylcellulose, gelatin, alginic acid, alginic acid sodium salt, polyethyleneglycol, pectin, collagen, poloxamer, carbopol, microcrystalline cellulose, polyacrylic acid, polyethylene glycol, polypropylene glycol, divinyl glycol, polyethylene oxide, polypropylene oxide, carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, polylactide, polyglycolide, polymethacrylic acid, poly-γ-benzyl-L-glutamate, polypropylene fumarate, poly-ε-caprolactone, poly-butylene terephthalate, polyvinyl alcohol, polyvinyl ether, poly-1-vinyl-2-pyrrolidinone, 2,5-dimethyl-1,5-hexadiene, divinyl benzene, polystyrene-divinyl benzene, polybis*p*-carboxy-phenoxypropane-*co*-sebacic acid, poly-β-hydroxybutyrate, poly-β-butyrolactone, tetraethylorthosilicate and dimethyldiethoxysilane.

4. The composition of claim 2 wherein the polymer is hydropropyl methylcellulose, gelatin, alginic acid, alginic acid sodium salt, polyethyleneglycol, pectin, collagen, poloxamer, carbopol or microcrystalline cellulose.

5. The composition of claim 4 further comprising a penetration enhancer, sorption promoter, mucoadhesive agent, hydrophilic or hydropholic release modifier, or a mixture thereof.

6. The composition of claim 5 wherein said mucoadhesive agent is selected form the consisting of hydroxypropyl methylcellulose, carboxymethylcellulose, polylactide-coglycolide, chitosan, chitosan ester or trimethylene chloride chitosan, sodium alginate, poloxamer, carbopol, pectin, polyacrylic acid, hyaluronic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polycarbophil and carbopol,

wherein said penetration enhancer is selected from the group consisting of sodium caproate, sodium caprylate, sodium caprate, sodium laurate, sodium myristate, sodium palmitate, sodium palmitoleate, sodium oleate, sodium ricinoleate, sodium linoleate, sodium stearate, sodium lauryl sulfate, sodium tetradecyl sulfate, sodium laryl sarcosine, sodium dioctyl sulfosuccinate, sodium cholate, sodium taurocholate, sodium glycocholate, sodium deoxycholate, sodium taurodeoxycholate, sodium glycodeoxycholate, sodium ursodeoxycholate, sodium chenodeoxycholate, sodium taurochenodexoycholate, sodium glycol chenodesoxycholate, sodium cholylsarcosine, sodium *N*-methyl taurocholate, sodium tauro-24,25-dihydrofusidate, disodium polyoxyethylene-10 oleyl ether phosphate, esterification product of fatty alcohols, fatty alcohol ethoxylate with phosphoric acid or anhydride, ether carboxylate, succinylated monoglyceride, sodium stearyl fumarate, steaoryl propylene glycol hydrogen succinate, mono/diacetylated tartaric acid ester of mono- and diglycerides, citric acid esters of mono- and diglycerides, glyceryl-lacto esters of fatty acids, lactylic ester of fatty acids, alginate salt, ethoxylated alkyl sulfate, alkyl benzene sulfone, α-olefin sulfonate, acyl isethionate, acyl taurate, alkyl glyceryl ether sulfonate, octyl sulfosuccinate disodium, disodium undecylenamideo-MEA-sulfosuccinate, phosphatidic acid, phosphatidyl glycerol, polyacrylic acid, hyaluronate sodium, glycyrrhetinic acid,

ethylene diamine tetraacetate, sodium citrate, chitosan, trimethyl chitosan, poly-*L*-arginine chitosan, poly-*L*-lysine chitosan, aminated gelatin, hexadecyl triammonium chloride, decyl trimethylammonium chloride, cetyl trimethylammonium chloride, alkyl benzyldimethylammonium chloride, diisobutyl phenoxyethoxydimethyl benzylammonium chloride, ethyl pyridinium chloride, isopropyl pyridinium chloride, *N*-lauryl,N,N-dimethylglycine, *N*-capryl,N,N-diethylglycine, polyoxyethylene- coconut amine, poly-*L*-lysine, poly-*L*-arginine, lecithin, lysolecithin, hydroxylated lecithin, lysophosphatidylcholine, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, didecanoyl-L-α-phosphatidylcholine, laurolycarnitine, acylcarnitine, palmitoyl-D,L-carnitine, polyoxyethylene lauryl ether, polyoxyethylene monooleyl ether, ethoxydiglycol, polyoxyethylene nonylphenol polyoxyethylene octylphenol ether, polyoxyethylene cholesterol ether, polyoxyethylene soya sterol ether, α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, dimethyl-β-cyclodextrin, methylated-β-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin, sorbitol, polyoxyethylene glycol ester, polyoxyethylene glycerol fatty acid ester, polyoxyethylene glycerol fatty acid ester, polyoxyethylene glyceride, polyoxyethylene vegetable or hydrogenated oil, polyoxyethylene monooleate, polyoxyethylene dilaurate, polyoxyethylene mono and dioleate, polyoxyethylene glyceryl laurate, polyoxyethylene glyceryl oleate, propylene glycol oleate, propylene glycol stearate, polyoxyethylene sorbitan monooleate, polyoxyethylene tristearate, polyoxyethylene hydrogenated castor oil, polyoxyethylene almond oil, polyoxyethylene apricot kernel oil, polyoxyethylene caprylic glyceride, polyoxyethylene capric glyceride, lauroyl macrogol glyceride, and

wherein said release modifier is selected from the group consisting of polyethylene glycol 200, polyethylene

glycol 8000, poloxamer, polyoxyethylene glycerylcocoate, carbopol, suppocire AS2X, suppocire CM, Witepsol H15, Witepsol W25, mineral oil, corn oil, paraffin oil, canola oil, castor oil, cottonseed oil, lecithin, peanut oil, sesame oil, soybean oil and hydrogenated vegetable oil.

7. The composition of claim 6 wherein said mucoadhesive agent is present in from about 0.5% to about 10% by weight, wherein said penetration enhancer is present in amount from about 0.1% to about 60% by weight, wherein said release modifier is present in amount from about to about 5% to about 70% by weight.

8. The composition of claim 7 further comprising pharmacologically acceptable additives or excipients.

9. The composition of claim 8 wherein said additives or excipients are solubilizing agents, buffering agents, fillers, preservatives, plasticizers, surfactants or anti-oxidants.

10. The composition of claim 9 wherein the substrate polymer, alone or in combination, is further combined with a pharmacologically effective agent selected from the group consisting of an anti-osteoporotic, non-steroidal anti-inflammatory, calcium channel antagonist, local anesthetic, potassium channel antagonists, β-adrenergic agonist, vasodilator, cyclooxygenase inhibitor, anti-fungal, antiviral, antimicrobial, antiparasitic, anti-epileptic, anti-migraine, anti-HIV, anti-neurodegenerative, anti-psychotic, chemotherapeutic or anti-neoplastic and opioid analgesic agent.

11. The composition of claim 10 wherein said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin, ibuprofen, indomethacin, phenylbutazone, bromfenac, fenamate, sulindac, nabumetone, ketorolac, and naproxen;

wherein said calcium channel antagonist is selected from the group consisting of diltaizem, israpidine, nimodipine, felodipine, verapamil, nifedipine, nicardipine, and bepridil;

wherein said potassium channel blocker is selected from the group consisting of dofetilide, almokalant, sematilide ambasilide, azimilide, tedisamil, sotalol, piroxicam and ibutilide;

wherein said β-adrenergic agonist is selected from the group consisting of terbutaline, salbutamol, metaproterenol, ritodrine;

wherein said COX-2 or COX-1 inhibitor is selected from the group consisting of naproxen, ketoprofen, ketorolac, indomethacin, diclofenac, teroxicam, celecoxib, meloxicam and flosulide;

wherein said vasodilator is selected from the group consisting of nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate;

wherein said bisphosphonate is selected from the group consisting of alendronate, clodronate, etidronate, pamidronate, tiludronate, ibandronate, zoledronate, alpadronate, residronate and neridronate;

wherein said antifungal agent selected from the group consisting of miconazole, terconazole, isoconazole, fenticonazole, tioconazole, fluconazole, nystatin, ketoconazole, clotrimazole, butoconazole, econazole, metronidazole and itraconazole;

wherein said antibacterial agent is selected from the group consisting of metronidazole, clindamycin, tetramycin, erythromycin, doxicycline, lumefloxacin, norfloxacin, afloxam, ciproflaxin, azitromycin, cefltoxime and doxicycline;

wherein said selected parasiticidal agent is metronidazole and clotrimazole;

wherein said antiviral agent is acyclovir or AZT;

wherein said anti-migraine agent is almotriptan, eletriptan, flovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, ergotamine, dihydroergotamine, bosentan and lanepitant;

wherein said anti-cancer agent is vincristine, cisplastin, doxorubicin, daunorubicin, etoposide, topotecan, irinotecan, paclitaxel, docetaxel, cyclophosphamide, methotrexate, and gemcitabine;

wherein said anti-HIV agent is saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, lopinavir and ganciclovir; and

wherein said biotechnology-derived protein or peptide is insulin, calcitonin, vasopressin, luprolide, somatostatin, oxytocin, bivalirudin, integrilin, natrecor, abarelix, gastrine G17, peptide, ziconotide, cereport, interleukin, humanized antibodies and growth hormone.

12. The composition of claim 11 administered to a surface of a nasal, buccal, vaginal, labial or scrotal device.

13. The composition of claim 12 formulated as a foam.

14. The composition of claim 13 wherein the foam has a variable shape and size.

15. The composition of claim 14 wherein the foam is preformed into a device shaped as a sheet, tube, tampon, cylinder, pillow, strip, pad, sphere, tablet, ring, or bead.

16. The composition of claim 12 formulated as a film.

17. The composition of claim 16 wherein the foam has a variable thickness and size.

18. The composition of claim 12 wherein the film is used as a coating for a nasal, buccal, vaginal or labial device.

19. The composition of claim 18 wherein said foam or film is prepared by lyophilization or by aeration.

20. A device comprising a polymer foam or film composition of claims 1-18, said device suitable for delivery of therapeutically effective agents topically to a nasal, buccal, vaginal or labial cavity wherein said device is either coated with said composition or said composition is incorporated into said device.

21. The device of claim 19 wherein the device is a tampon, tampon-like device, ring, sponge, pessary, suppository, pillow, pad, strip, cylinder, sphere or bead and wherein the composition is a foam or film coating or a foam or film incorporated into said device.

22. A method for topical or systemic delivery of drugs to or through nasal, buccal, vaginal, labial or scrotal epithelium said method comprising a step of contacting the vaginal, nasal, buccal, labial or scrotal epithelium with a foam or film composition consisting essentially of a substrate polymer and a pharmacologically effective agent.

23. The method of claim 22 wherein pharmacologically effective agent is selected from the group consisting of an nonsteroidal anti-inflammatory, anti-prostaglandin, prostaglandin inhibitor, cyclooxygenase inhibitor, calcium channel blocker, potassium channel blockers, β-adrenergic agonists, vasodilator, antibiotic, antimycotic, bisphosphonate, anti-nausea, anti-psychotic, anti-migraine, anti-HIV, anti-cancer, chemotherapeutic, a biotechnology derived protein or peptide, anti-epileptic, opioid analgesic,

wherein the amount of said pharmacological agent in the said composition administered to the mucosa is sufficient to deliver a therapeutically effective dose from about 0.01 to about 2000 mg of the pharmacological agent to the systemic circulation.

24. The method of claim 23 wherein said nonsteroidal anti-inflammatory drug is selected from the group consisting of aspirin, ibuprofen, indomethacin, phenylbutazone,

bromfenac, fenamate, sulindac, nabumetone, ketorolac, and naproxen;

wherein said calcium channel antagonist is selected from the group consisting of diltaizem, israpidine, nimodipine, felodipine, verapamil, nifedipine, nicardipine, and bepridil;

wherein said potassium channel blocker is selected from the group consisting of dofetilide, almokalant, sematilide ambasilide, azimilide, tedisamil, sotalol, piroxicam and ibutilide;

wherein said β-adrenergic agonist is selected from the group consisting of terbutaline, salbutamol, metaproterenol, ritodrine;

wherein said cyclooxygenase inhibitor is selected from the group consisting of naproxen, ketoprofen, ketorolac, indomethacin, diclofenac, teroxicam, celecoxib, meloxicam and flosulide;

wherein said vasodilator is selected from the group consisting of nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate;

wherein said bisphosphonate is selected from the group consisting of alendronate, clodronate, etidronate, pamidronate, tiludronate, ibandronate, zoledronate, alpadronate, residronate and neridronate;

wherein said antifungal agent selected from the group consisting of miconazole, terconazole, isoconazole, fenticonazole, tioconazole, fluconazole, nystatin, ketoconazole, clotrimazole, butoconazole, econazole, metronidazole and itraconazole;

wherein said antibacterial agent is selected from the group consisting of metronidazole, clindamycin, tetramycin, erythromycin, doxicycline, lumefloxacin, norfloxacin, afloxam, ciproflaxin, azitromycin, cefltoxime and doxicycline;

wherein said selected parasiticidal agent is

metronidazole and clotrimazole;

wherein said antiviral agent is acyclovir or AZT;

wherein said anti-migraine agent is almotriptan, eletriptan, flovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, ergotamine, dihydroergotamine, bosentan and lanepitant;

wherein said anti-cancer agent is vincristine, cisplastin, doxorubicin, daunorubicin, etoposide, topotecan, irinotecan, paclitaxel, docetaxel, cyclophosphamide, methotrexate, and gemcitabine;

wherein said anti-HIV agent is saquinavir, ritonavir, indinavir, amprenavir, nelfinavir, lopinavir and ganciclovir; and

wherein said biotechnology-derived protein or peptide is insulin, calcitonin, vasopressin, luprolide, somatostatin, oxytocin, bivalirudin, integrilin, natrecor, abarelix, gastrine G17, peptide, ziconotide, cereport, interleukin, humanized antibodies and growth hormone.

25. The method of claim 24 wherein said composition is delivered through vaginal epithelium.

26. The method of claim 24 wherein said composition is delivered through nasal mucosa.

27. The method of claim 24 wherein said composition is delivered through buccal mucosa.

28. The method of claim 24 wherein said composition is delivered through scrotal epithelium.

FIG. 1

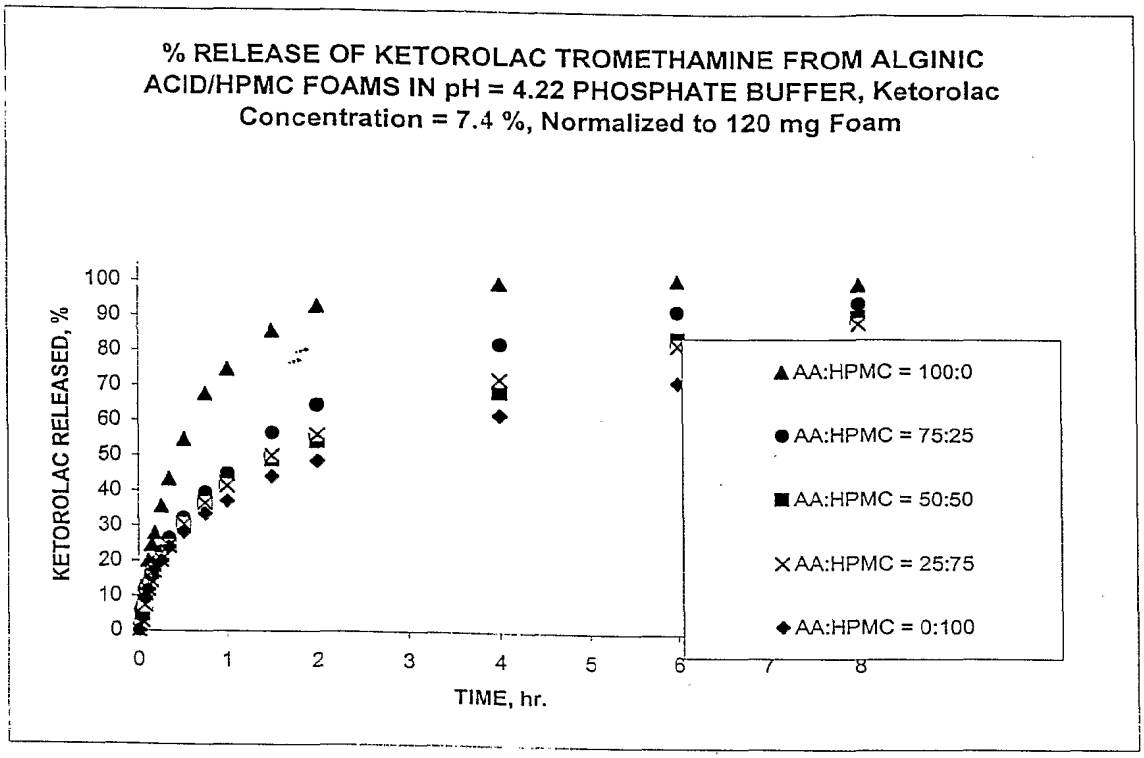

% RELEASE OF KETOROLAC TROMETHAMINE FROM ALGINIC ACID/HPMC FOAMS IN pH = 4.22 PHOSPHATE BUFFER, Ketorolac Concentration = 7.4 %, Normalized to 120 mg Foam
KETOROLAC RELEASED, %
TIME, hr.
AA:HPMC = 100:0
AA:HPMC = 75:25
AA:HPMC = 50:50
AA:HPMC = 25:75
AA:HPMC = 0:100

FIG. 2

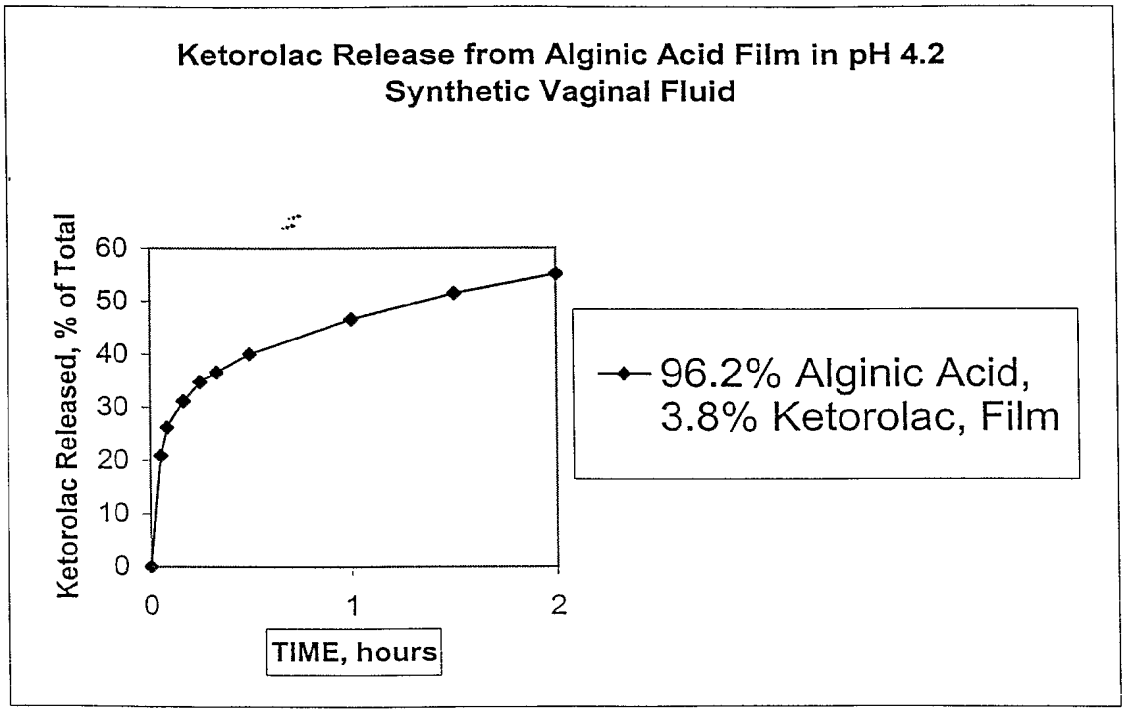
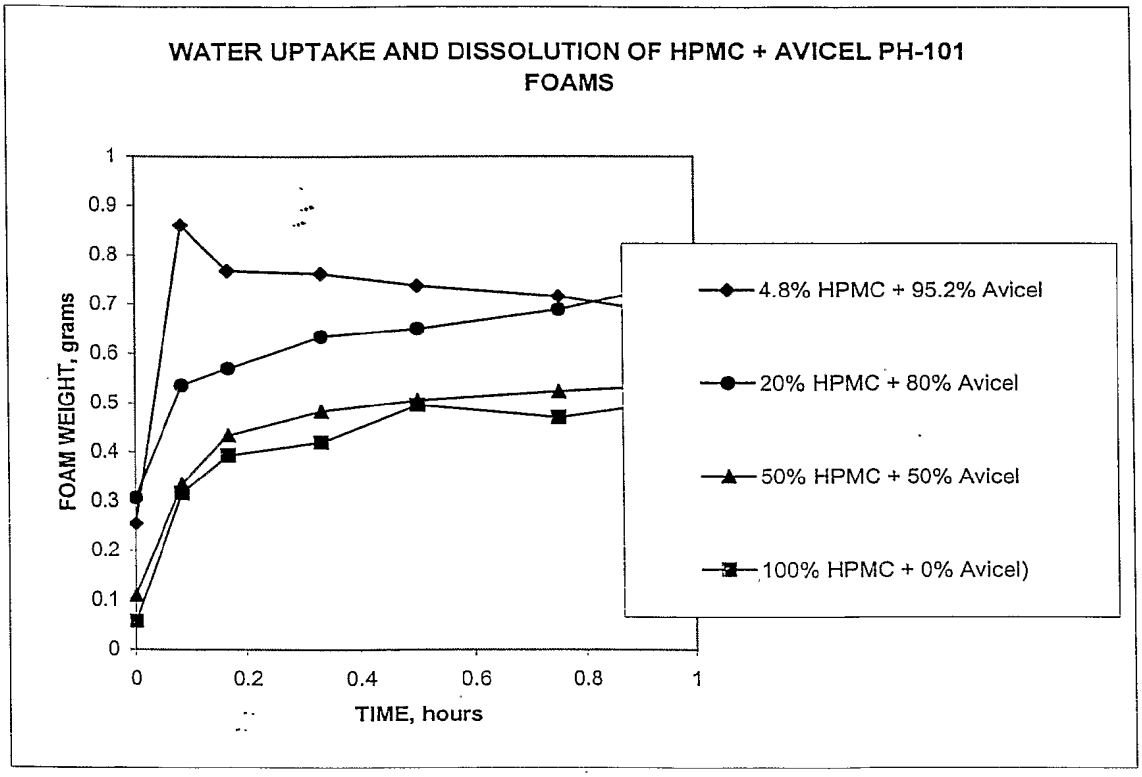

Ketorolac Release from Alginic Acid Film in pH 4.2
Synthetic Vaginal Fluid
Ketorolac Released, % of Total
60
50
40
30
20
10
0
0
1
2
TIME, hours
96.2% Alginic Acid,
3.8% Ketorolac, Film

FIG. 3


WATER UPTAKE AND DISSOLUTION OF HPMC + AVICEL PH-101 FOAMS
FOAM WEIGHT, grams
TIME, hours
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
0.2
0.4
0.6
0.8
4.8% HPMC + 95.2% Avicel
20% HPMC + 80% Avicel
50% HPMC + 50% Avicel
100% HPMC + 0% Avicel)

Electronic Acknowledgement Receipt

EFS ID:	18217484
Application Number:	13969724
International Application Number:	
Confirmation Number:	6392
Title of Invention:	BENDAMUSTINE PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Jason Edward Brittain
Customer Number:	46347
Filer:	Stephanie A. Lodise/Lynn Brown-Fischer
Filer Authorized By:	Stephanie A. Lodise
Attorney Docket Number:	CEPH-4604/CP391D US
Receipt Date:	17-FEB-2014
Filing Date:	19-AUG-2013
Time Stamp:	14:28:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	102085_004604_SIDS_1449-02 1714.PDF	135093 7072824a3592ea84e51cdaf326ae469da6b 745a2	no	3
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Information:					
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Warnings:					
Information:					
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