

Synthesis and Structure-property Evaluation of Novel Cellulosic Polymers as Amorphous Solid Dispersion Matrices for Enhanced Oral Drug Delivery

Haoyu Liu

Dissertation submitted to the faculty of the Virginia Polytechnic Institute and State University in
partial fulfillment of the requirements for the degree of

Doctor of Philosophy

In

Macromolecular Science and Engineering

Kevin J. Edgar, Chair

Richey M. Davis

Maren Roman

Lynne S. Taylor

S. Richard Turner

December 2, 2013

Blacksburg, VA

Keywords: cellulose ω -carboxyesters, amorphous solid dispersion, amphiphilicity, structure-property relationship, oral drug delivery

Copyright © 2013 by Haoyu Liu

CHAPTER 2 (Figure 2.4 Lipid digestion models for *in vitro* assessment of lipid-based formulations, reprinted from Dahan, A.; Hoffman, A. *J Control Release* 2008, 129, (1), 1-10. Used with permission of Elsevier, 2008.



RightsLink®

Home Account Info Help



Title: Rationalizing the selection of oral lipid based drug delivery systems by *in vitro* dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs
Author: Arik Dahan, Amnon Hoffman
Publication: Journal of Controlled Release
Publisher: Elsevier
Date: 2 July 2008
 Copyright © 2008, Elsevier

Logged in as:
 Haoyu Liu
 Account #: 3000704130
 LOGOUT

Order Completed

Thank you very much for your order.

This is a License Agreement between Haoyu Liu ("You") and Elsevier ("Elsevier"). The license consists of your order details, the terms and conditions provided by Elsevier, and the [payment terms and conditions](#).

[Get the printable license.](#)

License Number	3307330771612
License date	Jan 13, 2014
Licensed content publisher	Elsevier
Licensed content publication	Journal of Controlled Release
Licensed content title	Rationalizing the selection of oral lipid based drug delivery systems by <i>in vitro</i> dynamic lipolysis model for improved oral bioavailability of poorly water soluble drugs
Licensed content author	Arik Dahan, Amnon Hoffman
Licensed content date	2 July 2008
Licensed content volume number	129
Licensed content issue number	1
Number of pages	10
Type of Use	reuse in a thesis/dissertation
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
Format	both print and electronic
Are you the author of this Elsevier article?	No
Will you be translating?	No
Title of your thesis/dissertation	Synthesis and Structure-property Evaluation of Novel Cellulosic Polymers as Amorphous Solid Dispersion Matrices for Enhanced Oral Drug Delivery
Expected completion date	Jan 2014
Estimated size (number of pages)	200
Elsevier VAT number	GB 494 6272 12
Permissions price	0.00 USD
VAT/Local Sales Tax	0.00 USD / 0.00 GBP
Total	0.00 USD

ORDER MORE... CLOSE WINDOW

Copyright © 2014 Copyright Clearance Center, Inc. All Rights Reserved. [Privacy statement](#). Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 2 (Figure 2.7 Ibuprofen release with physical blends of CMCAB and microcrystalline cellulose (MC), reprinted from Posey-Dowty, J. D.; Watterson, T. L.; Wilson, A. K.; Edgar, K. J.; Shelton, M. C.; Lingerfelt, L. R. *Cellulose* **2007**, 14, (1), 73-83. Used with permission of Springer, 2006.

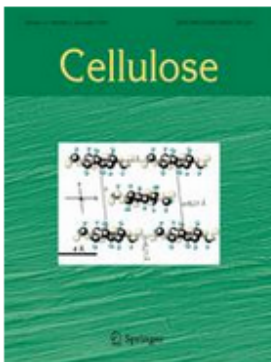


RightsLink[®]

Home

Account Info

Help



Title: Zero-order release formulations using a novel cellulose ester
Author: Jessica D. Posey-Dowty
Publication: Cellulose
Publisher: Springer
Date: Jan 1, 2006
 Copyright © 2006, Springer Science+Business Media B.V.

Logged in as:
 Haoyu Liu
 Account #:
 3000704130

LOGOUT

Order Completed

Thank you very much for your order.

This is a License Agreement between Haoyu Liu ("You") and Springer ("Springer"). The license consists of your order details, the terms and conditions provided by Springer, and the [payment terms and conditions](#).

[Get the printable license.](#)

License Number	3307331344297
License date	Jan 13, 2014
Licensed content publisher	Springer
Licensed content publication	Cellulose
Licensed content title	Zero-order release formulations using a novel cellulose ester
Licensed content author	Jessica D. Posey-Dowty
Licensed content date	Jan 1, 2006
Volume number	14
Issue number	1
Type of Use	Thesis/Dissertation
Portion	Figures
Author of this Springer article	No
Title of your thesis / dissertation	Synthesis and Structure-property Evaluation of Novel Cellulosic Polymers as Amorphous Solid Dispersion Matrices for Enhanced Oral Drug Delivery
Expected completion date	Jan 2014
Estimated size(pages)	200
Total	0.00 USD

CLOSE WINDOW

Copyright © 2014 [Copyright Clearance Center, Inc.](#) All Rights Reserved. [Privacy statement](#). Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 2 (Figure 2.8 Comparison of Fexofenadine HCl release from a compression tablet of a physical blend of CMCAB/drug with capsule containing amorphous formulation, reprinted from Shelton, M. C.; Posey-Dowty, J. D.; Lingerfelt, L. R.; Kirk, S. K.; Klein, S.; Edgar, K. J. *Polysaccharide Materials: Performance by Design* 2009. Used with permission of American Chemical Society, 2010.



RightsLink®

Home

Account Info

Help



ACS Publications
High quality. High impact.

Book: Polysaccharide Materials: Performance by Design
Chapter: Enhanced dissolution of poorly soluble drugs from solid dispersions in carboxymethylcellulose acetate butyrate matrices
Author: Michael C. Shelton, Jessica D. Posey-Dowty, Larry Lingerfelt et al.
Publisher: American Chemical Society
Date: Feb 8, 2010
Copyright © 2010, American Chemical Society

Logged in as:
Haoyu Liu
Account #:
3000704130

LOGOUT

PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

If credit is given to another source for the material you requested, permission must be obtained from that source.

BACK

CLOSE WINDOW

Copyright © 2014 [Copyright Clearance Center, Inc.](#) All Rights Reserved. [Privacy statement.](#) Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 2 (Table 2.1 Properties of cellulose esters used in pharmaceutical formulation, reprinted from Edgar, K. J. *Cellulose* **2007**, 14, (1), 49-64. Used with permission of Springer, 2006.

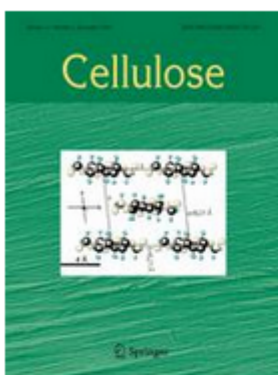


RightsLink[®]

Home

Account Info

Help



Title: Cellulose esters in drug delivery
Author: Kevin J. Edgar
Publication: Cellulose
Publisher: Springer
Date: Jan 1, 2006
 Copyright © 2006, Springer Science+Business Media, Inc.

Logged in as:

Haoyu Liu

Account #:
3000704130

LOGOUT

Order Completed

Thank you very much for your order.

This is a License Agreement between Haoyu Liu ("You") and Springer ("Springer"). The license consists of your order details, the terms and conditions provided by Springer, and the [payment terms and conditions](#).

[Get the printable license.](#)

License Number	3307331140249
License date	Jan 13, 2014
Licensed content publisher	Springer
Licensed content publication	Cellulose
Licensed content title	Cellulose esters in drug delivery
Licensed content author	Kevin J. Edgar
Licensed content date	Jan 1, 2006
Volume number	14
Issue number	1
Type of Use	Thesis/Dissertation
Portion	Figures
Author of this Springer article	No
Title of your thesis / dissertation	Synthesis and Structure-property Evaluation of Novel Cellulosic Polymers as Amorphous Solid Dispersion Matrices for Enhanced Oral Drug Delivery
Expected completion date	Jan 2014
Estimated size(pages)	200
Total	0.00 USD

CLOSE WINDOW

Copyright © 2014 Copyright Clearance Center, Inc. All Rights Reserved. [Privacy statement](#). Comments? We would like to hear from you. E-mail us at customer@copyright.com

CHAPTER 3

Adapted with permission from Kar, N.; Liu, H.; Edgar, K. J. *Biomacromolecules*, **2011**, 12, 1106-1115. Copyright 2011 American Chemical Society.



RightsLink®

Home

Account
Info

Help



ACS Publications
High quality. High impact.

Title: Synthesis of Cellulose Adipate Derivatives

Author: Nilanjana Kar, Haoyu Liu, and Kevin J. Edgar

Publication: Biomacromolecules

Publisher: American Chemical Society

Date: Apr 1, 2011

Copyright © 2011, American Chemical Society

Logged in as:

Haoyu Liu

Account #:
3000704130

LOGOUT

PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

BACK

CLOSE WINDOW

Copyright © 2013 [Copyright Clearance Center, Inc.](#) All Rights Reserved. [Privacy statement.](#)
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 4

Adapted with the permission from: Liu, H.; Kar, N.; Edgar, K. J. *Cellulose*, **2012**, 19:1279–1293.

Copyright 2012 Springer Science and Business Media.

Home Account Info Help



Title: Direct synthesis of cellulose adipate derivatives using adipic anhydride
Author: Haoyu Liu
Publication: Cellulose
Publisher: Springer
Date: Jan 1, 2012
Copyright © 2012, Springer Science+Business Media B.V.

Logged in as:
Haoyu Liu
Account #: 3000704130
[LOGOUT](#)

Order Completed

Thank you very much for your order.

This is a License Agreement between Haoyu Liu ("You") and Springer ("Springer"). The license consists of your order details, the terms and conditions provided by Springer, and the [payment terms and conditions](#).

[Get the printable license.](#)

License Number	3307381100434
License date	Jan 13, 2014
Licensed content publisher	Springer
Licensed content publication	Cellulose
Licensed content title	Direct synthesis of cellulose adipate derivatives using adipic anhydride
Licensed content author	Haoyu Liu
Licensed content date	Jan 1, 2012
Volume number	19
Issue number	4
Type of Use	Thesis/Dissertation
Portion	Full text
Number of copies	1
Author of this Springer article	Yes and you are a contributor of the new work
Title of your thesis / dissertation	Synthesis and Structure-property Evaluation of Novel Cellulosic Polymers as Amorphous Solid Dispersion Matrices for Enhanced Oral Drug Delivery
Expected completion date	Jan 2014
Estimated size(pages)	200
Total	0.00 USD

[CLOSE WINDOW](#)

Copyright © 2014 [Copyright Clearance Center, Inc.](#) All Rights Reserved. [Privacy statement](#).
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 5

Adapted from: Liu, H.; Ilevbare, G. A.; Cherniawski, B. P.; Ritchie E. T.; Taylor L. S.; Edgar K. J. *Carbohydrate Polymers*, **2014**, 100, 116-125. Copyright 2014, with permission from Elsevier.

Home Account Info Help



Title: Synthesis and structure–property evaluation of cellulose ω -carboxyesters for amorphous solid dispersions

Author: Haoyu Liu, Grace A. Ilevbare, Benjamin P. Cherniawski, Earl T. Ritchie, Lynne S. Taylor, Kevin J. Edgar

Publication: Carbohydrate Polymers

Publisher: Elsevier

Date: 16 January 2014

Copyright © 2014, Elsevier

Logged in as:
Haoyu Liu
Account #: 3000704130

LOGOUT

Order Completed

Thank you very much for your order.

This is a License Agreement between Haoyu Liu ("You") and Elsevier ("Elsevier"). The license consists of your order details, the terms and conditions provided by Elsevier, and the [payment terms and conditions](#).

[Get the printable license.](#)

License Number	3307381352548
License date	Jan 13, 2014
Licensed content publisher	Elsevier
Licensed content publication	Carbohydrate Polymers
Licensed content title	Synthesis and structure–property evaluation of cellulose ω -carboxyesters for amorphous solid dispersions
Licensed content author	Haoyu Liu, Grace A. Ilevbare, Benjamin P. Cherniawski, Earl T. Ritchie, Lynne S. Taylor, Kevin J. Edgar
Licensed content date	16 January 2014
Licensed content volume number	100
Number of pages	10
Type of Use	reuse in a thesis/dissertation
Portion	full article
Format	both print and electronic
Are you the author of this Elsevier article?	Yes
Will you be translating?	No
Title of your thesis/dissertation	Synthesis and Structure-property Evaluation of Novel Cellulosic Polymers as Amorphous Solid Dispersion Matrices for Enhanced Oral Drug Delivery
Expected completion date	Jan 2014
Estimated size (number of pages)	200
Elsevier VAT number	GB 484 6272 12
Permissions price	0.00 USD
VAT/Local Sales Tax	0.00 USD / 0.00 GBP
Total	0.00 USD

[ORDER MORE...](#) [CLOSE WINDOW](#)

Copyright © 2014 Copyright Clearance Center, Inc. All Rights Reserved. [Privacy statement](#).
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 6

Adapted from with permission from:

Ilevbare, G. A.; Liu, H.; Edgar, K. J.; Taylor, L. S. *Crystal Growth & Design* **2012**, *12*, 3133-3143.

Copyright 2012 American Chemical Society.



RightsLink®

Home

Account Info

Help



ACS Publications
High quality. High impact.

Title: Understanding Polymer Properties Important for Crystal Growth Inhibition—Impact of Chemically Diverse Polymers on Solution Crystal Growth of Ritonavir

Author: Grace A. Ilevbare, Haoyu Liu, Kevin J. Edgar, and Lynne S. Taylor

Publication: Crystal Growth and Design

Publisher: American Chemical Society

Date: Jun 1, 2012

Copyright © 2012, American Chemical Society

Logged in as:

Haoyu Liu

Account #:
3000704130

LOGOUT

PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

BACK

CLOSE WINDOW

Copyright © 2013 [Copyright Clearance Center, Inc.](#) All Rights Reserved. [Privacy statement.](#)
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 6

Adapted from with permission from:

Ilevbare, G. A.; Liu, H.; Edgar, K. J.; Taylor, L. S. *Crystal Growth & Design* **2012**, *12*, 6050-6060.

Copyright 2012 American Chemical Society.



RightsLink®

Home

Account
Info

Help



ACS Publications
High quality. High impact.

Title: Effect of Binary Additive
Combinations on Solution
Crystal Growth of the Poorly
Water-Soluble Drug, Ritonavir
Author: Grace A. Ilevbare, Haoyu Liu,
Kevin J. Edgar, and Lynne S.
Taylor
Publication: Crystal Growth and Design
Publisher: American Chemical Society
Date: Dec 1, 2012
Copyright © 2012, American Chemical Society

Logged in as:
Haoyu Liu
Account #:
3000704130

LOGOUT

PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

BACK

CLOSE WINDOW

Copyright © 2013 Copyright Clearance Center, Inc. All Rights Reserved. [Privacy statement](#).
Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 6

Adapted from with permission from:

Ilevbare, G. A.; Liu, H.; Edgar, K. J.; Taylor, L. S. *Crystal Growth & Design* **2013**, *13*, 740-751.

Copyright 2013 American Chemical Society.



RightsLink®

Home

Account Info

Help



ACS Publications
High quality. High impact.

Title: Maintaining Supersaturation in Aqueous Drug Solutions: Impact of Different Polymers on Induction Times

Author: Grace A. Ilevbare, Haoyu Liu, Kevin J. Edgar, and Lynne S. Taylor

Publication: Crystal Growth and Design

Publisher: American Chemical Society

Date: Feb 1, 2013

Copyright © 2013, American Chemical Society

Logged in as:

Haoyu Liu

Account #:

3000704130

LOGOUT

PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

BACK

CLOSE WINDOW

Copyright © 2013 [Copyright Clearance Center, Inc.](#) All Rights Reserved. [Privacy statement.](#) Comments? We would like to hear from you. E-mail us at customercare@copyright.com

CHAPTER 6

Adapted from with permission from:

Ilevbare, G. A.; Liu, H.; Edgar, K. J.; Taylor, L. S. *Molecular Pharmaceutics* **2013**, *10*, 2381-2393.

Copyright 2013 American Chemical Society.



RightsLink®

Home

Account
Info

Help



ACS Publications
High quality. High impact.

Title: Impact of Polymers on Crystal Growth Rate of Structurally Diverse Compounds from Aqueous Solution
Author: Grace A. Ilevbare, Haoyu Liu, Kevin J. Edgar, and Lynne S. Taylor
Publication: Molecular Pharmaceutics
Publisher: American Chemical Society
Date: Jun 1, 2013
Copyright © 2013, American Chemical Society

Logged in as:
Haoyu Liu
Account #:
3000704130

LOGOUT

PERMISSION/LICENSE IS GRANTED FOR YOUR ORDER AT NO CHARGE

This type of permission/license, instead of the standard Terms & Conditions, is sent to you because no fee is being charged for your order. Please note the following:

- Permission is granted for your request in both print and electronic formats, and translations.
- If figures and/or tables were requested, they may be adapted or used in part.
- Please print this page for your records and send a copy of it to your publisher/graduate school.
- Appropriate credit for the requested material should be given as follows: "Reprinted (adapted) with permission from (COMPLETE REFERENCE CITATION). Copyright (YEAR) American Chemical Society." Insert appropriate information in place of the capitalized words.
- One-time permission is granted only for the use specified in your request. No additional uses are granted (such as derivative works or other editions). For any other uses, please submit a new request.

BACK

CLOSE WINDOW

Copyright © 2013 [Copyright Clearance Center, Inc.](#) All Rights Reserved. [Privacy statement.](#)
Comments? We would like to hear from you. E-mail us at customercare@copyright.com