UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.
Petitioner

v.

SUMITOMO DAINIPPON PHARMA CO., LTD.
Patent Owner

U.S. Patent No. 9,555,027

Title: Pharmaceutical Composition

Inter Partes Review Case No. Unassigned

DECLARATION OF SCOTT BENNETT, Ph.D.
13 April, 2017

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I, Scott Bennett, hereby declare under penalty of perjury:

I. INTRODUCTION

1. I have personal knowledge of the facts and opinions set forth in this declaration, I believe them to be true, and if called upon to do so, I would testify competently to them. I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both.

2. I am a retired academic librarian working as a Managing Partner of the firm Prior Art Documentation LLC at 711 South Race Street, Urbana, IL, 61801-4132. Exhibit 1005 is a true and correct copy of my Curriculum Vitae describing my background and experience. Further information about my firm is available at www.priorartdocumentation.com.

3. I have been retained by Latham & Watkins LLP to authenticate and establish the dates of public accessibility of certain documents in an *inter partes* review proceeding for U.S. Patent No. 9,555,027 (Exhibit 1001, "the '027 Patent"). For this service, I am being paid my usual hourly fee of $88/hour. My compensation in no way depends on the substance of my testimony or the outcome of this proceeding.

II. BACKGROUND AND QUALIFICATIONS

4. I was previously employed as follows:

- University Librarian, Yale University, New Haven, CT, 1994-2001;

- Director, The Milton S. Eisenhower Library, The Johns Hopkins University, Baltimore, MD, 1989-1994;
- Assistant University Librarian for Collection Management, Northwestern University, Evanston, IL, 1981-1989;
- Instructor, Assistant, and Associate Professor of Library Administration, University of Illinois at Urbana-Champaign, Urbana, IL, 1974-1981; and
- Assistant Professor of English, University of Illinois at Urbana-Champaign, 1967-1974.

5. Over the course of my work as a librarian, professor of English, researcher, and author of nearly fifty scholarly papers and other publications, I have had extensive experience with cataloging records and online library management systems built around Machine-Readable Cataloging (MARC) standards. I also have substantial experience in authenticating printed documents and establishing the date when they were accessible to researchers.

6. In the course of more than fifty years of academic life, I have myself been an active researcher. I have collaborated with many individual researchers and, as a librarian, worked in the services of thousands of researchers at four prominent research universities. Members of my family are university researchers. Over the years, I have read some of the voluminous professional

literature on the information seeking behaviors of academic researchers. And as an educator, I have a broad knowledge of the ways in which students in a variety of disciplines learn to master the bibliographic resources used in their disciplines. In all of these ways, I have a general knowledge of how researchers work.

III. PRELIMINARIES

7. *Scope of this declaration*. I am not a lawyer and I am not rendering an opinion on the legal question of whether any particular document is, or is not, a "printed publication" under the law.

8. I am, however, rendering my expert opinion on the authenticity of the documents referenced herein and on when and how each of these documents was disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, could have located the documents before 26 May 2005.

9. *Materials considered*. In forming the opinions expressed in this declaration, I have reviewed the documents and attachments referenced herein. These materials are records created in the ordinary course of business by publishers, libraries, indexing services, and others. From my years of experience, I am familiar with the process for creating many of these records, and I know these records are created by people with knowledge of the information in the record. Further, these records are created with the expectation that researchers

and other members of the public will use them. All materials cited in this declaration and its attachments are of a type that experts in my field would reasonably rely upon and refer to in forming their opinions.

10. *Persons of ordinary skill in the art*. I am told by counsel that the subject matter of this proceeding relates to pharmaceutical compositions.

11. I have been informed by counsel that the "person of ordinary skill in the art at the time of the invention" is a hypothetical person who is presumed to be familiar with the relevant field and its literature at the time of the invention. This hypothetical person is also a person of ordinary creativity, capable of understanding the scientific principles applicable to the pertinent field.

12. I am told by counsel that a person of ordinary skill in this art as of May 26, 2005, would be a formulator with a Ph.D. in pharmaceutics, or in a drug delivery-relevant field of a related discipline such as physical chemistry, or could have a bachelor's degree in pharmaceutics or in a related field, plus two to five years of relevant experience in developing solid oral drug formulations. This description is approximate, and a higher level of education or skill might make up for less experience, and vice versa. This person of ordinary skill may also consult with others from an interdisciplinary team, such as a clinician with experience in treating and/or dosing schizophrenic patients.

13. It is my opinion that such a person would have been engaged in advanced research starting at least in university or graduate school, learning though study and practice in the field and possibly through formal instruction from the bibliographic resources relevant to his or her research. In the 1990s and 2000s such a person would have had access to a vast array of long-established print resources in pharmacology as well as to a rich and fast changing set of online resources providing indexing information, abstracts, and full text services for pharmacology.

14. *Library catalog records*. WorldCat is the world's largest public online catalog, maintained by the Online Computer Library Center, Inc., or OCLC, and built with the records created by the thousands of libraries that are members of OCLC. WorldCat records appear in many different catalogs, including the Statewide Illinois Library Catalog.

15. When an OCLC participating institution acquires a document for which it finds no previously created record in OCLC, or when the institution chooses not to use an existing record, it creates a record for the document using OCLC's Connexion, the bibliographic system used by catalogers to create catalog records.

16. Once the MARC record is created by a cataloger at an OCLC participating member institution, it becomes available to other OCLC participating members in Connexion and to the public in WorldCat.

17. When a book has been cataloged, it will normally be made available to readers soon thereafter—normally within a few days or (at most) within a few weeks of cataloging.

18. *Periodical publications*. A library typically creates a catalog record for a periodical publication when the library receives its first issue. When the institution receives subsequent issues/volumes of the periodical, the issues/volumes are checked in (often using a date stamp), added to the institution's holdings records, and made available very soon thereafter—normally within a few days of receipt or (at most) within a few weeks of receipt.

19. The initial periodicals record will sometimes not reflect all of the subsequent changes in publication details (including minor variations in title, etc.).

20. *Internet Archive.* The Internet Archive is a non-profit digital library founded in 1996.

21. The Internet Archive maintains an archive of webpages collected from the Internet using software called a crawler. Crawlers automatically create a snapshot of webpages as they existed at a certain point in time. The Wayback Machine is an application created by the Internet Archive to search its archive of

Web pages and to represent, graphically, the date of each crawler capture. The Internet Archive, now with about 50 petabytes of data, collects only Web material that is publicly available. Some sites are "not archived because they were password protected, blocked by robots.txt, or otherwise inaccessible to our automated systems. Site owners might have also requested that their sites be excluded from the Wayback Machine" (Internet Archive Frequently Asked Questions – The Wayback Machine, https://archive.org/about/faqs.php#The_Wayback_Machine (last visited April 5, 2017)) (Attachment 5).

22. Many Internet Archive captures made by the Wayback Machine have a banner at the top with the capture date prominently displayed. Other dates when captures of the same URL have been made are indicated to the right and left of the date provided in the banner. Some captures may lack this banner. In any case, the URL for the capture begins with the identification of the Internet Archive (e.g., http://web.archive.org/web/) followed by information that dates and time stamps the capture as follows: year in yyyy, month in mm, day in dd, time code in hh:mm:ss (e.g., 20041208081749, or 8 December 2004 at 8:17:49 a.m.). These elements are then followed by the URL of the original capture site.

23. Internet Archive captures often include links to other, related documents. Sometimes these links have become inactive. Where they remain

active, the Wayback Machine is programmed to produce the archived file with the closest available date (not the closest available prior date) to the page upon which the link appeared and was clicked.

24. *Indexing*. A researcher may discover material relevant to his or her topic in a variety of ways. One common means of discovery is to search for relevant information in an index of periodicals and other publications. Having found relevant material, the researcher will then normally obtain it online, look for it in libraries, or purchase it from the publisher, a bookstore, a document delivery service, or other provider. Sometimes, the date of a document's public accessibility will involve both indexing and library date information. Date information for indexing entries is, however, often unavailable. This is especially true for online indices.

25. Indexing services use a wide variety of controlled vocabularies to provide subject access and other means of discovering the content of documents. The formats in which these access terms are presented vary from service to service.

26. Online indexing services commonly provide bibliographic information, abstracts, and full-text copies of the indexed publications, along with a list of the documents cited in the indexed publication. These services also often provide lists of publications that cite a given document. A citation of a document

is evidence that the document was publicly available and in use by researchers no later than the publication date of the citing document.

27. Prominent indexing services include:

28. Scopus. Produced by Elsevier, a major publisher, Scopus is the largest database of abstracts and citations of peer-reviewed literature. Its scope includes the social sciences, science, technology, medicine, and the arts. It includes 60 million records from more than 21,500 titles from some 5,000 international publishers. Coverage includes 360 trade publications, over 530 book series, more than 7.2 million conference papers, and 116,000 books. Records date from 1823.

29. Science Direct. Science Direct, provided by Elsevier, is a database of abstracts and articles in the physical sciences and engineering, the life and health sciences, and the social sciences and humanities. It has over 12 million items from 3,500 journals and 34,000 books.

30. Google Scholar. Google Scholar indexes the texts and metadata of scholarly publications across a wide range of disciplines. It includes most peer-reviewed online academic journals, conference papers, theses, technical reports, and other material. Google does not publish the size of the Google Scholar database, but researchers have estimated that it contained approximately 160 million items in 2014. Enrique Oduña-Malea et al., *About the Size of Google*

Scholar: Playing the Numbers, 18 EC3 WORKING PAPERS 1 (Jul. 2014), *available at* https://arxiv.org/ftp/arxiv/papers/1407/1407.6239.pdf (Attachment 4).

IV. OPINIONS REGARDING INDIVIDUAL DOCUMENTS

Document 1. K.P.R. Chowdary & N. Rama Rao, *Formulation and Evaluation of Dispersible Tablets with Pregelatinized Starch*, 35 INDIAN DRUGS 368 (1998)

1. Authentication

31. Document 1 is a research paper by K. P. R. Chowdary and N. Rama Rao published in the June 1998 issue of Indian Drugs.

32. Attachment 1a is a true and correct copy of Document 1 (along with the volume cover, contents pages, and a page listing other IDMA publications) from the National Library of Medicine. Attachment 1b is a true and correct copy of the National Library of Medicine catalog record for Indian Drugs, showing the holdings for volume 35, no. 4 through volume 37, no. 6 issues of this periodical, including therefore volume 35, no. 6, in which Document 1 was published.

33. Attachment 1a is in a condition that creates no suspicion about its authenticity. Specifically, Document 1 in Attachment 1a is not missing any intermediate pages of the article's text, the text on each page appears to flow seamlessly from one page to the next, and there are no visible alterations to the document. Attachment 1a was found within the custody of a library—a place where, if authentic, it would likely be found.

34. Attachment 1c is a true and accurate copy of the Scopus index record for Document 1, showing the many keywords under which Document 1 might be found.

35. Attachment 1d is a true and accurate copy of the entry for Indian Drugs from Ulrichsweb, the most complete, authoritative, and commonly used online directory of periodical publications. This record reports an International Standard Serial Number (ISSN) of 0019-462X, the same as the ISSN number on the cover of Indian Drugs in Attachment 1a and in the Attachment 1b catalog record for Indian Drugs.

36. I have compared Attachment 1a, a copy of Document 1 from the National Library of Medicine, with Exhibit 1011, a copy of Document 1 provided by counsel. I find them to be substantively the same document.

37. I conclude, based on finding Document 1 in a library and on finding library catalog records and an online index record for Document 1, that Attachment 1a and Exhibit 1011 are authentic copies of Document 1.

2. Public Accessibility

38. Attachment 1e is a true and correct copy of the Statewide Illinois Library Catalog record for Indian Drugs, showing this periodical was first published in 1963 and is held by 22 libraries world-wide. Researchers would have had no difficulty finding copies of Indian Drugs.

39. Attachment 1a, from the National Library of Medicine, includes a library date label indicating that the June 1998 issue of Indian Drugs was processed on 3 December 1998. Based on my experience, I affirm this date label has the general appearance of date labels that libraries have long affixed to periodicals in processing them. I do not see any indications or have any reason to believe this date label was affixed by anyone other than library personnel on or about the date indicated by the label.

40. Allowing for some time between affixing the date label of 3 December 1998 and the appearance of the June 1998 issue of Indian Drugs on library shelves, where it would be publicly available, it is my opinion that Document 1 was publicly available at least by January 1999.

3. Conclusion

41. Based on the evidence presented here—publication in periodical, ISSN number, library processing and cataloging, online indexing—**it is my opinion that Document 1 is an authentic document that was publicly available to researchers by January 1999.**

Document 2. Colorcon, *Starch 1500: Partially Pregelantinized Maize Starch* (1999)

1. Authentication

42. Document 2 is a product description brochure copyrighted by Colorcon in 1999.

43. Attachment 2a is a true and correct copy of an Internet Archive capture with a banner date of 07 December 2004, as explained in paragraphs 22 and 23 above. Attachment 2a shows various documents relating to Starch 1500® available from Colorcon. The Sales Brochure listed here is available in 7 languages. I obtained Attachment 2b, the English language version of the Sales Brochure, from the Internet Archive at http://web.archive.org/web/20041208081749/http://www.colorcon.com/pharma/excipients/starch/lit/sales_brochures/english.pdf. I note that the URL for Attachment 2b indicates it was captured by the Wayback Machine on 8 December 2004, as explained in paragraphs 22 and 23, above.

44. Attachment 2c is a true and correct copy of another Internet Archive capture of Document 2, which I obtained at https://web.archive.org/web/20050501004036/http://www.colorcon.com/pharma/excipients/starch/lit/sales_brochures/english.pdf. I note that the URL for Attachment 2c indicates it was captured by the Wayback Machine on 4 May 2005, as explained in paragraphs 22-23 above.

45. I have examined Attachments 2b and 2c and find them to be substantively identical to one another. For instance, the design elements and text blocks are the same in Attachments 2b and 2c; both Attachments bear the same 1999 copyright date and the same printing abbreviation, EX/STAR/PB1199. I

conclude there is no evidence of any substantive change to Document 2 between 8 December 2005 and 4 May 2005.

46. I have compared Attachments 2b and 2c with Exhibit 1025, a copy of Document 2 provided by counsel. I find them to be substantively the same document.

47. Based on these findings, I have confirmed that Attachments 2b and 2c and Exhibit 1025 are authentic copies of Document 2.

2. Public Accessibility

48. As discussed in Paragraph 43 and Paragraphs 21-23 above, Document 2 is accessible through the Internet Archive webcrawlers at least as early as 8 December 2004. Further, it is self-evident that Colorcon would have wished to make Document 2 readily available to customers. Therefore, the reasonable conclusion is that (1) internet search engines circa 2004 would have been able to find and index Document 2, and (2) a person of ordinary skill in the art in 2004 using typical internet search tools would have readily found a copy of Document 2.

49. Attachment 2a lists a number of other documents related to Starch 1500® as being available on the banner date of this capture, 07 December 2004. Included are Attachment 2d, a poster reprint relating to Low Dose Drugs presented at the November 2000 AAPS meeting; Attachment 2e, an article by two

Colorcon authors relating to Moisture Sensitive Drugs published in the May 2001 issue of Pharmaceutical Technology Europe; and Attachment 2f, a poster reprint relating to Moisture Sensitive Drugs presented at the October 2001 AAPS meeting. I conclude from these supporting Colorcon documents that various attributes of Starch 1500® were well documented before 26 May 2005.

3. Conclusion

50. Based on the evidence presented here—Internet Archive captures—**it is my opinion that Document 2 is an authentic document that was publicly available to researchers by at least 8 December 2004.**

Document 3. PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN 136 (Michael E. Aulton ed., 1988)

1. Authentication

51. Document 3 is a book by Michael Aulton published by Churchill Livingston in 1988. Attachment 3a is a true and accurate copy of the book's title page, title page verso, table of contents, and Chapters 9, 13, 18, and 39 from the Rutgers University Library. Attachment 3b is a true and accurate copy of that library's catalog record, in MARC format, for Document 3.

52. Attachment 3a is in a condition that creates no suspicion about its authenticity. Specifically, Chapters 9, 13, 18, and 39 in Document 3 are not missing any intermediate pages, the text on each page appears to flow seamlessly from one page to the next, and there are no visible alterations to the document

(other than a few highlighted items in Chapters 13 and 39). Attachment 3a was found within the custody of a library – a place where, if authentic, it would likely be found.

53. I have compared Attachment 3a, a copy from the Rutgers University Library, with Exhibit 1009, a copy of Document 3 provided by counsel. I find them to be substantively the same document.

54. I conclude, based on finding Document 3 in a library and on finding library catalog records for Document 3, that Attachment 3a and Exhibit 1009 are authentic copies of Document 3.

2. Public accessibility

55. Attachment 3c is a Statewide Illinois Library Catalog record for Document 3, showing that Document 3 is held by 88 libraries world-wide and was cataloged or indexed in a meaningful way—including being cataloged by subject. In Attachment 3c, the date of entry, corresponding to the MARC Field 008, subfield a, indicates that Document 3 was first cataloged on 12 September 1986, well before the publication of Document 3. This was a cataloging-in-publication record, as evident from the verso of the title page in Attachment 3a, which displays cataloging-in-publication information from both the British Library and the Library of Congress. I conclude from this catalog record that Document 3 was bibliographically identifiable by 12 September 1986.

56. In Attachment 3b, the Rutgers University Library catalog record for Document 3, the MARC Field 040 indicates this record was created jointly by the National Library of Medicine and the Library of Congress (OCLC codes = DNLM and DLC). The MARC Field 008, subfield 8, indicates this record was created on 3 February 1988.

57. Attachment 3d is a true and accurate copy of a second Statewide Illinois Library catalog record for Document 3, showing the book is held by another 10 libraries world-wide. The date of entry in Attachment 3d, corresponding to the MARC Field 008, indicates this catalog record was created on 17 February 1988.

58. Given this cataloging evidence, it is my opinion that Document 3 was sufficiently accessible to the public interested in the art; and an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of Document 3 in at least one library by March 1988.

59. Attachment 3e is a true and accurate copy of a Google Scholar list of publications citing Document 3. One document citing Document 3 is by Hak-Kim Chan & Igor Gondoa, *Serendipitous Preparation of Crystals of Methotrexate and Attempts to Modify its Crystal Habit*, 94 JOURNAL OF CRYSTAL GROWTH 488 (1988). Attachment 3f is a true and accurate copy of the Science Direct record for the Chan and Gondoa paper; it shows that the paper was received by the Journal

of Crystal Growth on 15 September 1988 and that Document 3 is the fifth item in its list of references.

3. Conclusion

60. Based on the evidence presented here—book publication, library cataloging, and citations—**it is my opinion that Document 3 is an authentic document that was bibliographically identifiable by 12 September 1986 and was publicly available in at least one library at least by March 1988**. The citation evidence presented here indicates that Document 3 was in actual use by researchers at least by September 1988.

V. ATTACHMENTS

61. The attachments attached hereto are true and correct copies of the materials identified above. Helen Sullivan is a Managing Partner in Prior Art Documentation Services LLC (*see* http://www.priorartdocumentation.com/helen-sullivan/ **)**. One of her primary responsibilities in our partnership is to secure the bibliographic documentation used in attachments to our declarations.

62. Ms. Sullivan and I work in close collaboration on the bibliographic documentation needed in each declaration. I will sometimes request specific bibliographic documents or, more rarely, secure them myself. In all cases, I have carefully reviewed the bibliographic documentation used in my declaration. My

signature on the declaration indicates my full confidence in the authenticity, accuracy, and reliability of the bibliographic documentation used.

63. Each Attachment has been marked with an identifying label on the top of each page. No alterations other than these noted labels appear in these attachments. All attachments were created on 11 January 2017 – 5 April 2017 and all URLs referenced in this declaration were available 28 March 2017.

VI. CONCLUSION

64. In summary, I conclude that Documents 1, 2, and 3 discussed above are all authentic documents that were publicly accessible before 26 May 2005.

65. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner or its expert(s) may raise and to take into account new information as it becomes available to me.

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 13th day of April, 2017 in Urbana, Illinois.

Scott Bennett

ATTACHMENT 1a

ISSN 0019-462X

INDIAN DRUGS

SCIENTIFIC AND RESEARCH PUBLICATION FROM
INDIAN DRUG MANUFACTURERS' ASSOCIATION

Vol. 35 No. 6 JUNE 1998

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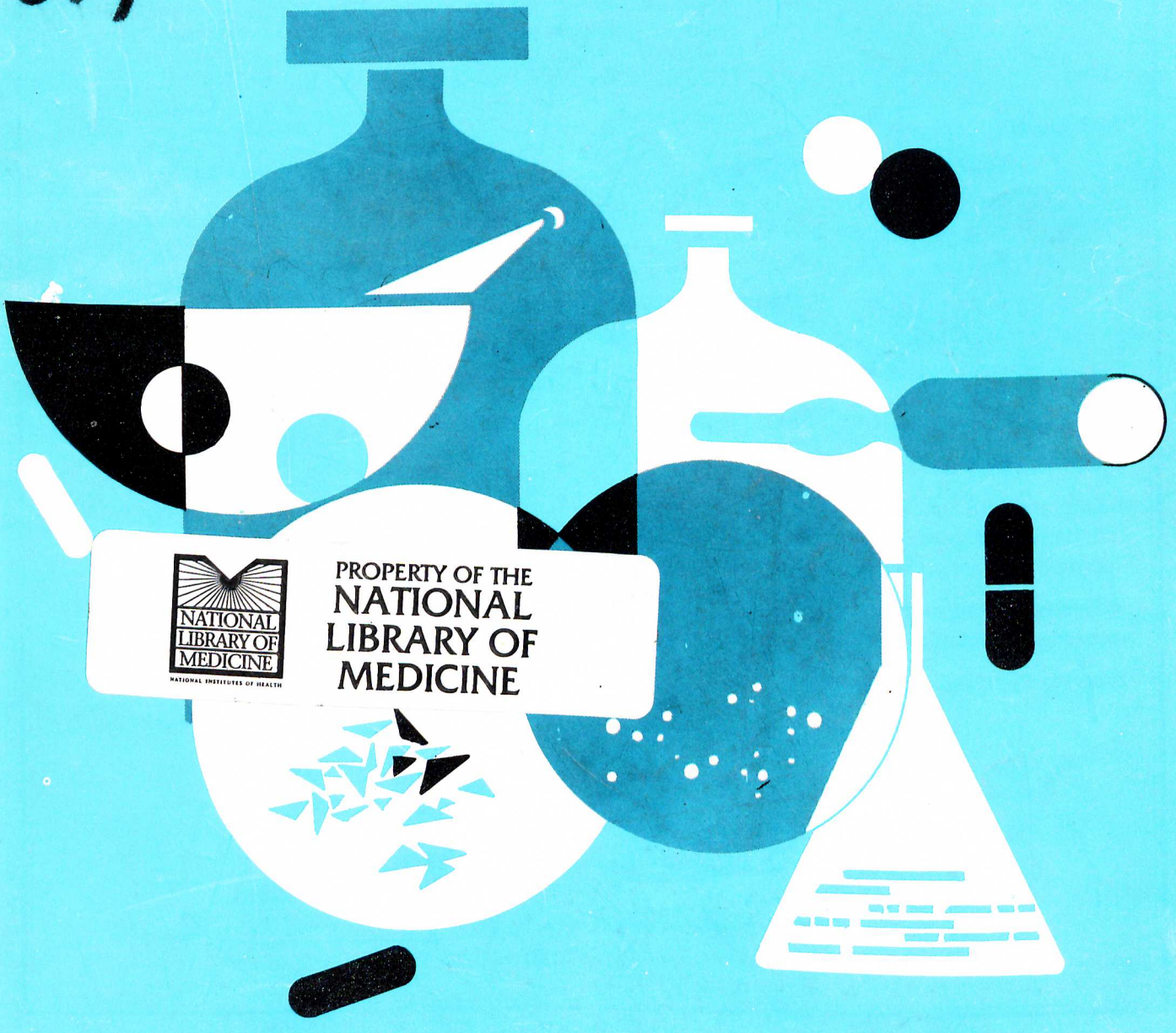

INDIAN DRUGS

Scientific Publication from the Indian Drug Manufacturers' Association
102–B, Poonam Chambers, Dr. A.B. Road, Worli, Mumbai – 400 018

Vol. 35 | No. 6 | JUNE 1998

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Tel. : 497 4308/494 4624 Fax : 022-495 0723
e-mail : idma@giasbm01.vsnl.net.in

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FORMULATION AND EVALUATION OF DISPERSIBLE TABLETS WITH PREGELATINIZED STARCH

K.P.R. Chowdary and N. Rama Rao

(Received 27 January 1998)

INTRODUCTION

Dispersible tablets of norfloxacin, paracetamol and piroxicam formulated with pregelatinized starch (PGS) fulfilled the official (I.P.) requirements of dispersible tablets and gave fast and rapid dissolution of the contained medicament when compared to conventional tablets.

Pregelatinized starch (PGS) is a modified starch that has been modified chemically or mechanically processed to rupture all on part of the starch granules. It is used in oral capsule and tablet formulations as a diluent[1] and disintegrant[2]. Though many modified starches have been studied[3-7] widely for their pharmaceutical applications, PGS has not been investigated throughly. PGS was reported to enhance the dissolution rate of salicylic acid[8] and acetaminophen[9] from tablet formulations. We have been working on the pharmaceutical applications of PGS. The objective of the present study is to evaluate PGS for its application in the formulation of dispersible tablets. Dispersible tablets of norfloxacin (NF), paracetamol (PA) and piroxicam (PY) were formulated employing PGS and were evaluated. The results are reported here.

METHODS

Materials: Norfloxacin, U.S.P., Paracetamol, I.P., Pirxociam, U.S.P., Pregelatinized starch (prepared from potato starch in the laboratory by a known method[10]), polyvinyl pyrrolidone (Mol.Wt. 40,000), Lactose, I.P., Talc, I.P. and Magnesium stearate, I.P. were used.

Norbid (Norfloxacin 100mg, Cipla), Norflox (Norfloxacin 200mg, Cipla), Tyfy (Paracetamol 125mg, Legend), Metacin (Paracetamol 500mg, Themis), Pirox DT (Piroxicam 200mg, Cipla) and Suganril (Piroxicam 20mg, SG Pharma) were procured from local market and were used.

Preparation of dispersible tablets

Dispersible tablets of (i) NF (100mg) (ii) PA (125mg) and (iii) PY (20mg) were prepared as per formulae given in Table-1 by conventional wet granulation method. Tablet granulations were compressed into tablets to a hardness of 5-6Kg/Sq.cm on "Cadmach" single punch tablet machine.

Disintegration times were determined in "Thermonic" tablet Disintegration Test Machine, U.S.P. standard using distilled water as the fluid. Hardness of the tablets was tested using "Monsanto" Hardness Tester. Friability of the tablets was determined in Roche Friabilator. All the tablets were tested for uniformity of dispersion as per I.P. test[11]. Known spectrophotometric methods were used for the estimation of NF[12], PA[13] and PY[14].

Dissolution rate study

This dissolution rate of NF, PA and PY from

*For correspondence
Siddhartha College of Pharmaceutical Sciences
Vijayawada - 10, A.P.

Table 1: Formulae of dipsersible tablets prepared

Ingredient (mg/Tablet)	Formulation														
	NF1	NF2	NF3	NF4	NF5	PY1	PY2	PY3	PY4	PY5	PA1	PA2	PA3	PA4	PA5
1. Norfloxacin	100	100	100	100	100	-	-	-	-	-	-	-	-	-	-
2. Piroxicam	-	-	-	-	-	20	20	20	20	20	-	-	-	-	-
3. Paracetamol	-	-	-	-	-	-	-	-	-	-	125	125	125	125	125
4. Lactose	122.5	110	85	60	10	202.5	190	165	140	90.	97.5	85	60	35	-
5. PGS	12.5	25	50	75	125	12.5	25	50	75	125	12.5	25	50	75	125
6 PVP	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
7. Talc	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
8. Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Total Weight:	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250

dispersible tablets prepared as well as commercial dispersible and conventional tablets was studied using USP XXI Dissolution Rate Test Apparatus employing paddle stirrer. Acetate buffer of pH 4.0 (750 ml), phosphate buffer of pH 7.8 (900 ml) and 0.1 N hydrochloric acid (900 ml) were used as dissolution fluids for NF, PA and PY respectively. In each test one tablet, a speed of 100 rpm and a temparature of 37° ± 1°C were employed. A 5 ml aliquot of dissolution medium was withdrawn through a filter at different time intervals, suitably diluted and assayed spectrophotometrically at 278 nm for NF, 249 nm for PA and 333 nm for PY. Dissolution efficiency (D.E.) values were calculated from the dissolution date as suggested by Khan[15].

RESULTS AND DISCUSSION

Pregelatinized starch, prepared from potato starch by a known method, was used in the present study. The PGS prepared fulfilled the official (XXIII) identification tests and test for absence of oxidising substances. The PGS prepared was insoluble and easily dispersible in purified water. The pH of a 10% W/V slurry in water was 7.2.

All the tablets were found to contain the medicament within 100 ± 5 percent of the labelled claim. Hardness of the tablets was found to be within the range of 5-6 Kg/Sq.cm and was satisfactory. Friability of all the tablets was less than 1%. All the dispersible tablets disintegrated within 3 minutes fulfilling the official (I.P.) requirement for dispersible tablets. In the test for uniformity of dispersion, all dispersible tablets containing PGS at 10% and above concentration fulfilled the official requirement. The dispersion produced in water passed through mesh No. 22. Whereas conventional tablets did not pass this test and about 15-25 percent of the total mass was retained on mesh No. 22.

With all the three medicaments dispersible tablets

Table 2 : Disintegration and dissolution characteristics of various tablets

Tablet	D.T. (min)	Hixson–Crowell's Dissolution Rate ($mg^{1/3}$ min^{-1}) (±SD)	Dissolution efficiency (%)
		Norfloxacin	
C	4.0	0.034 ± 0.015	65.33
DF1	1.0	0.115 ± 0.018	88.00
DF2	1.5	0.140 ± 0.009	90.22
DC	1.0	0.144 ± 0.008	90.66
		Paracetamol	
C	9.5	0.035 ± 0.019	80.26
DF1	1.5	0.077 ± 0.014	90.80
DF2	1.5	0.085 ± 0.023	92.10
DC	2.5	0.058 ± 0.007	90.50
		Piroxicam	
C	11.0	0.036 ± 0.098	36.68
DF1	1.5	0.077 ± 0.009	79.83
DF2	1.5	0.085 ± 0.006	84.26
DC	1.5	0.059 ± 0.012	75.67

C : Conventional; DF1: Dispersible formulated (PGS 10%);
DF2: Dispersible formulated (PGS 20%); DC : Dispersible commercial.

both prepared with PGS and commercial gave very fast and rapid dissolution of the contained medicament when compared to the corresponding conventional tablets (Table-2). Dissolution efficiency was also high in the case of dispersible tablets. Dissolution of medicament from these tablets obeyed Hixson-Crowell's cube root equation.

Thus dispersible tablets of NF, PA and PY could be formulated employing pregelatinized starch. A concentration of 10-20% of PGS in the formula is optimum for formulation of dispersible tablets.

ACKNOWLEDGEMENTS

The authors are grateful to Siddhartha Academy of General and Technical Education, Vijayawada for providing necessary facilities.

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13. **Indian Pharmacopoeia**, 1996, Ministry of Health and Family Welfare, Govt. of India, Delhi, 1996, p. 556.

14. **The United States Pharmacopoeia,** 23rd Ed., U.S. Pharmacopoeial convention, Inc., Rockville, Md., 1995, p. 1235.

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MANAGING DIABETES AFTER MYOCARDIAL INFARCTION

This major randomised control trial confirmed and extended observations from smaller studies of the relation between diabetic control and the development of small vessel disease and neuropathy. However, no previous studies have argued convincingly for a relation between diabetic control and macrovascular disease, which remains the major cause of mortality in diabetic patients and makes a substantial contribution to morbidity.

Undoubtedly, insulin and insulin treatment of diabetes should become part of a more aggressive approach to managing diabetic patients after myocardial infarction. Attempts to improve management in this area have been bedeviled by an unjustified reluctance to translate evidence into practice or, perhaps with somewhat greater justification, to extrapolate from the non-diabetic situation. Thus, thrombolysis, probably the single most important measure and one that has been shown to almost halve mortality in hospital after infarction, is withheld because of vague fears of its impact on diabetic retinopathy; and other agents that have been shown to be of benefit in diabetic patients, such as β blockers, are not used because they alter the lipid profile or mask hypoglycaemic symptoms, minor considerations in both effect and importance when set against mortality. Angiotension converting enzyme inhibitors, aspirin, and cholesterol lowering drugs might also form part of this more aggressive package of care. Hopefully, the findings of this present study do not flounder on a reluctance on the part of either patients of doctors to introduce insulin.

Courtesy: M. Nattrass, BMJ, May 1997; 314: 1497.

ATTACHMENT 1b

Attachment 1b: National Library of Medicine catalog record for Indian Drugs

LocatorPlus
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Indian drugs.

Title: Indian drugs.
Description: v.
Publisher: Bombay : Indian Drug Manufacturers' Association
Related Name(s): Indian Drug Manufacturers' Association.
ISSN: 0019-462X
Electronic Links: http://www.indiandrugsonline.org/
NLM Unique ID: 0207670
Other ID Numbers: (DNLM)I08700000(s)
(OCoLC)01752855

Location: v. 12, no. 1-10 1974/1975 c.1 Shelved At General Collection
Call Number: W1 IN204C
Availability: v.6:no.1(1968)-v.6:no.7(1969),v.6:no.10(1969)-v.7:no.3(1969),v.7:no.5(1970)-v.11:no.3(1973),v.11:no.5(1974)-v.11:no.8(1974),v.11:no.10(1974)-v.12:no.10(1975),v.13:no.3(1975)-v.15:no.2(1977),v.15:no.5(1978)-v.21:no.1(1983),v.21:no.3(1983)-v.21:no.8(1984),v.21:no.10(1984)-v.26:no.4(1989),v.26:no.6(1989)-v.26:no.10(1989),v.26:no.12(1989)-v.28:no.7(1991),v.28:no.9(1991)-v.29:no.7(1992),v.29:no.9(1992)-v.29:no.15(1992),v.30:no.7(1993)-v.30:no.12(1993),v.31:no.7(1994)-v.35:no.2(1998),v.35:no.4(1998)-v.37:no.6(2000),v.37:no.8(2000),v.37:no.10(2000)-v.38(2001),v.39:no.2(2002)-v.40:no.4(2003),v.40:no.6(2003)-v.41:no.11(2004),v.42(2005)-v.43:no.6(2006),v.47:no.8(2010),v.48:no.3(2011)-v.49:no.2(2012),v.49:no.7(2012)-v.50:no.6(2013),v.50:no.8(2013)-
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ATTACHMENT 1c

Attachment 1c: Scopus index record for Document 1

Document details

Back to results | < Previous 3 of 3

Indian Drugs
Volume 35, Issue 6, June 1998, Pages 368-377

Formulation and evaluation of dispersible tablets with pregelatinized starch (Article)

Chowdary, K.P.R., Rama Rao, N.
Siddhartha Coll. Pharmaceutical Sci., Vijayawada - 10, A.P., India

View references (15)

Abstract

[No abstract available]

Indexed keywords

EMTREE drug terms: norbid; norflox; norfloxacin; oxyphenonium bromide; paracetamol; pirox dt; piroxicam; starch; suganril; tyfy; unclassified drug
EMTREE medical terms: article; drug formulation; drug solubility; tablet; tablet disintegration time; tablet hardness

Chemicals and CAS Registry Numbers: norfloxacin, 70458-96-7; oxyphenonium bromide, 14214-84-7, 50-10-2; paracetamol, 103-90-2; piroxicam, 36322-90-4; starch, 9005-25-8, 9005-84-9
Drug tradename: metacin, Themis,norbid, Cipla,norflox, Cipla,pirox dt, Cipla,suganril, SG Pharmaceuticals,tyfy, legend.
Manufacturers:Drug manufacturer: Cipla;legend;SG Pharmaceuticals;Themis.

ISSN: 0019462X **CODEN:** INDRB **Source Type:** Journal **Original language:** English
Document Type: Article
Publisher: Indian Drug Manufacturers' Association

References (15)

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Uekama, K., Hirashima, N., Horiuchi, Y., Hirayama, F., Ijitsu, T., Ueno, M.

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Symecko, C.W., Rhodes, C.T.

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Chowdary, K.P.R.; Siddhartha Coll. of Pharmaceut. Sci., India

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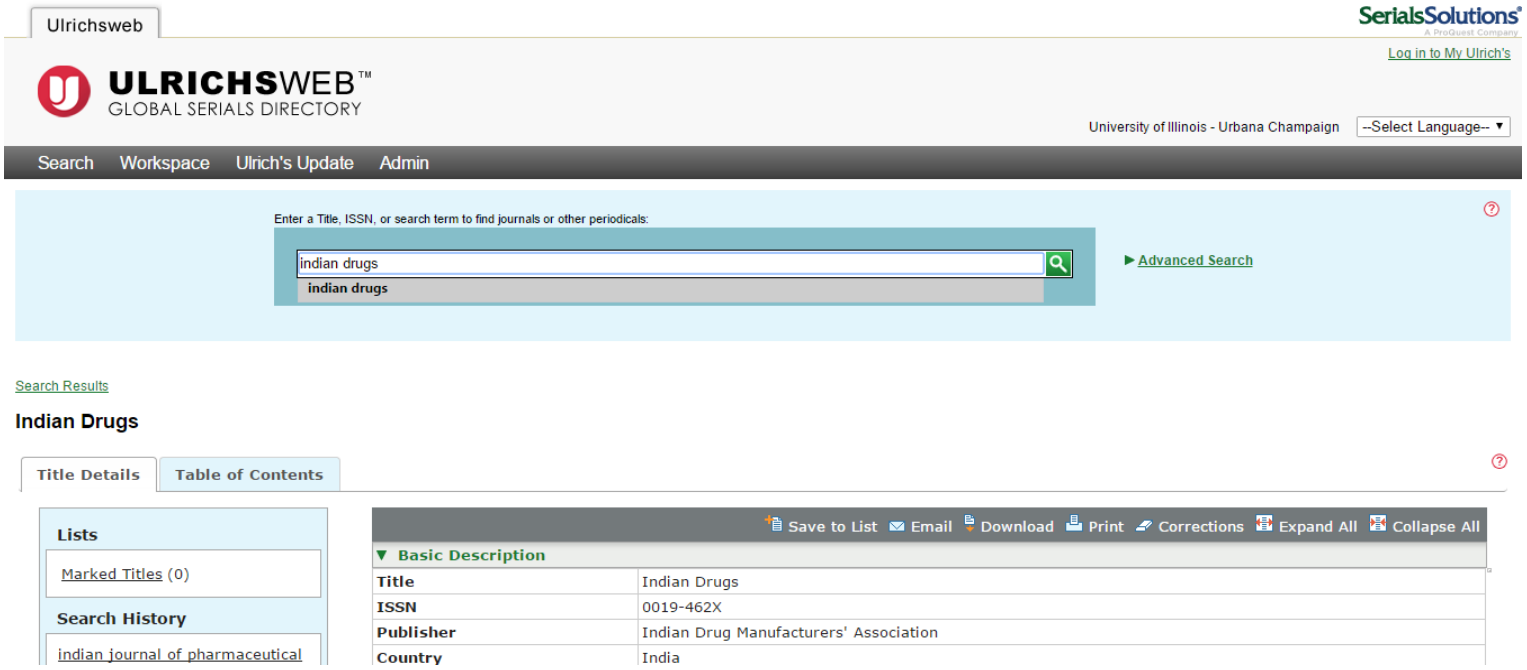
ATTACHMENT 1d

Attachment 1d: Ulrichsweb record for Indian Drugs



ATTACHMENT 1e

Attachment 1e: Statewide Illinois Library Catalog record for Indian Drugs

Statewide Illinois Library Catalog — UNIV OF ILLINOIS

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Title: Indian drugs **Author:** Indian Drug Manufacturers' Association **Accession Number:** 1752855

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US,MD	NATIONAL LIBR OF MED		NLM
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US,MI	UNIV OF MICHIGAN, TAUBMAN MED LIBR	(7)8 (1969-1970)	HJ8
US,MN	UNIV OF MINNESOTA, MINNEAPOLIS		MNU
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US,OH	THE AM CHEMICAL SOC THROUGH ITS CHEMICA		CAS
US,WA	UNIV OF WASHINGTON LIBR	v.6(1968/1969)-v.40(2...	WAU
US,WI	UNIV OF WISCONSIN, MADISON, EBLING LIBR	v.6-v.17(1968-1979,19...	GZH
US,WI	UNIV OF WISCONSIN, MADISON, GEN LIBR SYS	v.6-v.17(1968-1979/1980)	GZM
France	BIBLIOTHEQUE INTERUNIV DE PHARMACIE		FEP
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Germany	UNIV HANNOVER & TIB		UB#
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Title: **Indian drugs.**
Corp Author(s): Indian Drug Manufacturers' Association.
Publication: Bombay : Indian Drug Manufacturer's Association
Year: 1963-
Frequency: Monthly
Description: Began in 1963.; volumes : illustrations ; 24 cm
Language: English
Standard No: **ISSN:** 0019-462X; **CODEN:** INDRBA; **National Library:** 013724428; 639086-9; 0207670; I08700000; 009848267; **LCCN:** 78-900021
References: Chemical abstracts; 0009-2258

SUBJECT(S)

Descriptor: Pharmaceutical industry -- India -- Periodicals.
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Pharmaceutical industry.
Genre/Form: Periodicals.
Periodicals.

Geographic: India.
India.
Note(s): Official organ of: Indian Drug Manufacturers' Association.
Class Descriptors: **LC:** HD9672.I5; **Dewey:** 338.4/7/6151900954; **NLM:** W1; **NAL:** RM1
Other Titles: Indian drugs; Indian drugs
Material Type: Periodical (per)
Document Type: Serial
Entry: 19751101
Update: 20160224
Accession No: **OCLC:** 1752855
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ATTACHMENT 2a

Starch 1500® Literature

roduct literature is in .pdf format. In order to read them you need Adobe Acrobat Reader Version 4.0

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General

Article Reprints

Starch Contrasts. Cunningham, C. (Discusses differences between pregelatinized starches - morphology, particle size and the degree of modification effects on functionality)

Direct Compaction

Data Sheets

Ambroxol HCL (60 mg) Tablets
Fluid-Bed Method for Increasing the Compactability of Echinacea Purpurea Powder
Direct Compaction Formulation Used to Produce Aspirin (325 mg) Tablets
Direct Compaction Formulation Used to Product Theophylline (100 mg) Tablets

---

Wet Granulation

Poster Reprints

Fluid-Bed Granulation of Acetaminophen: Effect of Key Process Variables on Granule and Tablet Characteristics

Data Sheets

Wet Granulation of Acetaminophen
Fluid-Bed Method for Increasing the Compactability of Echinacea Purpurea Powder

---

Capsule Filling

Data Sheets

Starch 1500 Use on Tamp Capsule Filling Machine
Starch 1500 Use on Dosator-Type Filling Machine

Disintegrant

Poster Reprints

Evaluation of a Partially Pregelatinized Starch in Comparison with Superdisintegrants in a Direct Compression Hydrochlorothiazide Formulation

Data Sheets

Ambroxol HCL (60 mg) Tablets
Hydrochlorothiazide (50 mg) Tablets
Multivitamin Tablets

Flow Aid/Self Lubricant

Poster Reprints

Optimizing Lubricant Usage in a Direct Compression Hydrochlorothiazide Formulation Containing a Plastically Deforming Excipient

Data Sheets

Hydrochlorothiazide (50 mg.) Tablets

HPMC Matrix Formulations

Poster Reprints

Influence of Starch 1500 on Drug Release from HPMC Matrices
Influence of Fillers on Tableting and Drug Release from HPMC Matrices

Data Sheets

Chlorpheniramine Maleate (12 mg) Tablets - Extended Release
Dextromethorphan Hydrobomide (30 mg) Tablets - Extended Release
Diltiazem HCL (120 mg) Tablets - Extended Release
Promethazine HCL (25 mg) Tablets - Extended Release
Propranolol HCL (160 mg) Tablets - Extended Release

Article Reprint

Influence of Fillers, Compression Force, Film Coatings & Storage Conditions on Performance of Hypromellose Matrices, Levina

---

Attachment 2a: List of Colorcon publications relating to Starch 1500

Low Dose Drugs

Poster Reprints

Use of Starch 1500 ® to Improve the Uniformity of a Low Dose, Direct Compression Chlorpheniramine Formulation

Data Sheets

Chlorpheniramine Maleate (4 mg) Tablets

Article Reprint

Formulation of Low Dose Medicines - Theory and Practice, Ahmed & Shah

---

Moisture Sensitive Drugs

Article Reprint

Formulation of Acetylsalicylic Acid Tablets for Aqueous Enteric Film Coating

Poster Reprint

Effect of Starch 1500 on the Stability of Aspirin Tablets Stored Under Accelerated Conditions

Influence of Core Formulation, Film Coating Level and Storage Conditions on Stability of Ranitidine Tablets

ATTACHMENT 2b

STARCH 1500®

PARTIALLY PREGELATINIZED MAIZE STARCH

Flexibility for performance

Colorcon®

STARCH 1500®
PARTIALLY PREGELATINIZED MAIZE STARCH

THE SUPERIOR MULTIFUNCTIONAL EXCIPIENT FOR SOLID DOSAGE DEVELOPMENT

Starch 1500 is a unique pharmaceutical excipient combining several properties in a single product. Only Starch 1500 performs the multiple functions of a binder, disintegrant, flow-aid and self-lubricant. It is extremely versatile, being effective in a variety of processing methods for solid oral dosage forms. Starch 1500 also exhibits synergy, enhancing the functionality of other commonly used excipients in formulations.

MULTIFUNCTIONAL

Provides a unique range of functions:

- **Binder**
- **Disintegrant**
- **Flow-Aid**
- **Lubricant**

VERSATILE

Flexible performance in a variety of applications:

	DIRECT COMPACTION	WET GRANULATION	CAPSULE PLUG FORMATION
Binder	X	X	X
Disintegrant	X	X	X
Flow-Aid	X	X*	X
Lubricant	X	X*	X

*** In the extra granular phase**

COST-EFFECTIVE

Cuts process and material costs by reducing or eliminating:

- **Excess binders**
- **Superdisintegrants**
- **Additional lubricants and glidants**
- **Manufacturing steps**

MANUFACTURED FOR THE PHARMACEUTICAL INDUSTRY

- **Manufactured in modern cGMP facilities dedicated solely to the production of pharmaceutical excipients**

INDUSTRY LEADING TECHNICAL EXPERTISE

- **Worldwide manufacturing, distribution and technical service facilities**
- **Formulation and application development support**
- **Global regulatory assistance**
- **Innovative new product development**

DIRECT COMPACTION

Starch 1500 performs key functions in direct compaction formulations as a binder, disintegrant, flow-aid and self-lubricant. It also promotes formulation flexibility by complementing and enhancing the functionality of other excipients.

BINDER

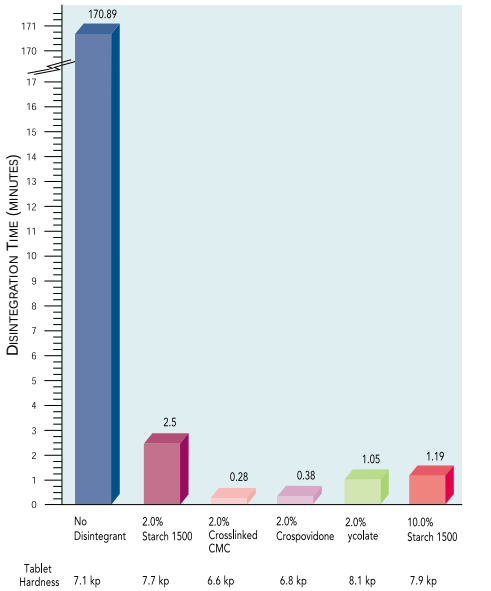
As a dry binder, it compresses well, predominately deforming plastically. Starch 1500 can be used with other excipients, such as microcrystalline cellulose, lactose, and dicalcium phosphate, to produce tablets with excellent hardness and low friability at compaction forces typically used in tableting operations.

DISINTEGRANT

Starch 1500 performs the actions of two disintegrants; maize starch and free amylose in dry processes. In some applications, 2% to 10% of Starch 1500 provides disintegrant action as effective as super disintegrants, greatly reducing costs. (See Figure 1)

Figure 1

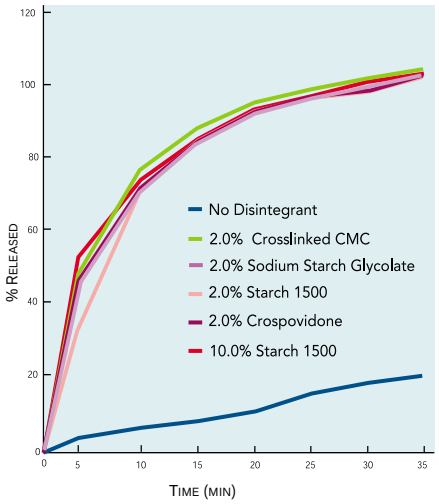
DISINTEGRATION PROFILE FOR HYDROCHLOROTHIAZIDE TABLETS, 50 MG **



The combination of maize starch and free amylose has a positive impact on drug dissolution. Supporting the tablet disintegration data in Figure 1, the resulting drug dissolution data in Figure 2 compares Starch 1500 with more costly disintegrants.

Figure 2

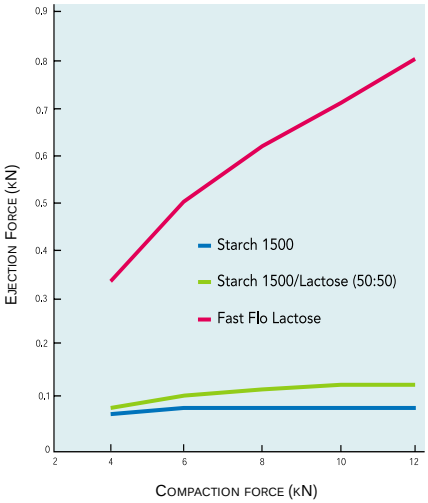
DISSOLUTION PROFILE FOR HYDROCHLOROTHIAZIDE TABLETS, 50 MG**



**** Tablets were formulated with 25% hydrochlorothazide, 0.25% magnesium stearate, and equal parts lactose and dicalcium phosphate. Equal portions of the lactose and dicalcium phosphate were substituted with 2% or 10% Starch 1500.**

Figure 3

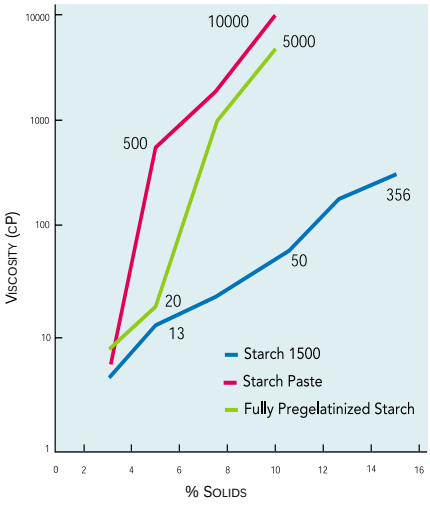
EJECTION FORCE VALUES FOR HYDROCHLOROTHIAZIDE TABLETS



Hydrochlorothiazide 25%, excipient 74.75%, 0.25% magnesium stearate as lubricant

Figure 4

CONCENTRATION DEPENDENT VISCOSITY PROFILES



Traditional starch paste at 85°C compared to Starch 1500 and a fully pregelatinized starch prepared in cold water

FLOW-AID

Starch 1500 provides excellent flow properties, demanded by today's high-speed tableting and capsule filling equipment; ensuring that manufacturers can produce tablets and capsules with consistent uniform weight and drug content.

SELF LUBRICANT

The high inherent lubricity of Starch 1500 enables the formulator to lower the levels of traditional lubricants, such as magnesium stearate. For example, magnesium stearate added in high levels, or when over-blended, can slow dissolution and cause problems with compaction (soft tablets) and film coating (poor film adhesion). Therefore, Starch 1500 enables lubricant levels and their potential problems to be reduced or eliminated. (See Figure 3)

WET GRANULATION

In wet granulation applications, Starch 1500 exhibits dual functionality as both binder and disintegrant as a result of partial cold water solubility. Starch 1500 allows process flexibility: it can be dry-blended with other ingredients before adding water, or a portion can be dispersed in cold water. A slurry of Starch 1500 in cold water provides effective binding properties at higher solids and lower viscosity than traditional starch pastes, which must be heated and prepared at lower concentrations. (See Figure 4) Processing costs are reduced by eliminating the time and expense of preparing traditional binder solutions. In addition, granulations using Starch 1500 as a binder give excellent tablet hardness and fast disintegration.

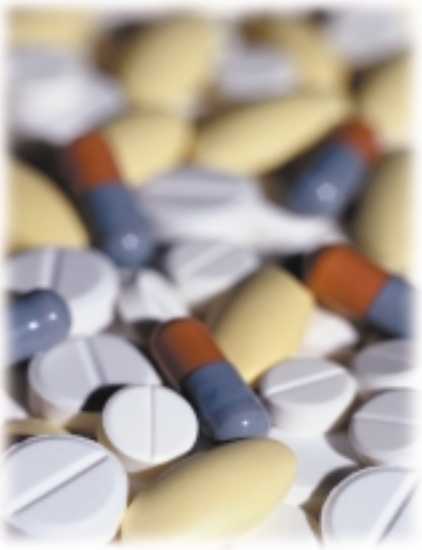
In fluid bed granulations, Starch 1500 alone can be used as both binder and disintegrant. For example, capsule-shaped acetaminophen tablets, 500mg, of excellent hardness and friability values of less than 0.19% were produced through the simple formulation of 85% acetaminophen and 15% Starch 1500 used as the wet granulation binder. In this formulation, Starch 1500 functioned as an exceptional disintegrant with disintegration time less than 1 minute. Dissolution was excellent. Test results showed 80% drug release within 5 minutes. In addition, the low viscosity of Starch 1500 in cold water allowed higher binder content solutions and faster spray times, resulting in reduced process times.

Capsule Plug Formation

Starch 1500, as a flow-aid, improves uniformity of capsule fill. As a binder, Starch 1500 facilitates plug formation in dosator-type equipment and reduces powder fallout when the plug is transferred. The inherent lubricity of Starch 1500 means a lower force to eject material into the capsule shell (compared to other excipients) and leads to reduced wear on dosator-type equipment.

Starch 1500 Product Range

Colorcon has made Starch 1500 even more versatile by developing a line of products for optimal performance applicable to a variety of formulations. The Starch 1500 product range is produced exclusively for the pharmaceutical industry under cGMP guidelines. Starch 1500 products are designed to meet regulatory needs worldwide. Specific products conform to the USP/NF, Ph.Eur, and JPE compendial monographs.



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SUPPLIER OF CHOICE

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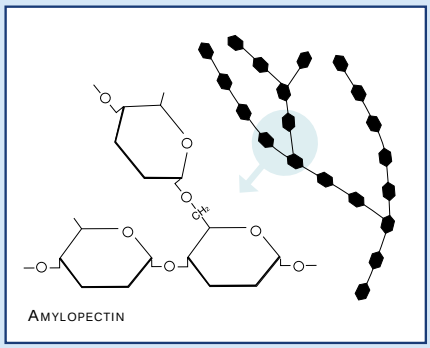
Colorcon's worldwide network of technical service laboratories and experts bring solutions to our customers when and where they are needed. These resources serve all aspects of customer projects including; formulation development, application development, scale-up support and regulatory information. We understand the impact of speed to market in the competitive fast paced pharmaceutical industry and support our customers in the production of highly effective formulations in reduced time frames.

Take advantage of our experience, technology and creativity; enhance your position in the marketplace. Make Colorcon your partner, your supplier of choice.

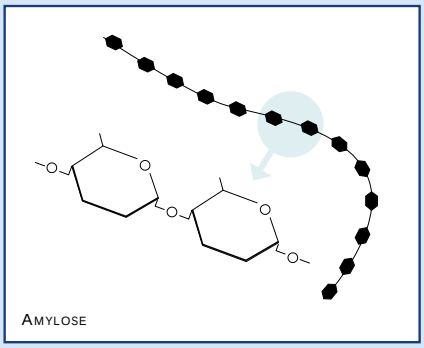
Unique Manufacturing Process

Starch 1500 is a partially pregelatinized maize starch manufactured exclusively for the pharmaceutical industry in dedicated cGMP facilities. The process involves a physical modification of the starch (no chemical additives or surfactants are used), resulting in the combined benefits of the soluble and insoluble functionality of Starch 1500.

Maize starch is composed of two polymers, amylose and amylopectin which are tightly bound in a specific spherocrystalline structure. Through partial pregelatinization, the bond between a portion of the two polymers is broken, providing Starch 1500 with its unique properties. The process results in partial solubility, increased particle size, improved flow properties and compactability.



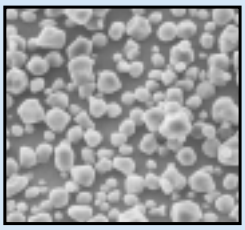
Amylopectin has a branched-chain molecular structure, which makes it readily soluble in cold water. Amylopectin functions as a binder in wet granulation processes.



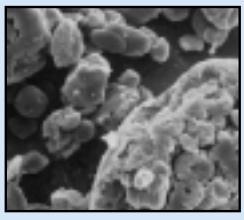
Amylose has a straight-chain molecular structure, which exhibits a very strong intermolecular bonding capability. Amylose swells significantly when wetted, giving it excellent disintegrating characteristics.

One Excipient, Multiple Functions

Starch NF



Starch 1500®



Colorcon's unique manufacturing process results in the most effective functional balance for Starch 1500, providing good cold water binding and granulation properties, yet retaining effective tablet disintegrant properties. The physical structure of Starch 1500 also imparts good compactability, flow and lubrication capabilities.

These multifunctional properties can be utilized in a variety of applications, including direct compaction, wet granulation, fluid bed granulation and capsule plug formation. The distinct benefits of Starch 1500 can bring significant process flexibility to solid dosage forms.

SEM photo of Starch 1500 shows individual starch grains along with aggregates bonded to the hydrolyzed starch. Starch 1500 has better flow characteristics than Starch NF and has much higher compactability. Photos shown at 10 microns.

STARCH 1500®

PARTIALLY PREGELATINIZED MAIZE STARCH

- Multifunctional for formulation versatility
- Flexibility for performance in a variety of applications
- Manufactured exclusively for the pharmaceutical industry
- Meets global regulatory requirements

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Modified Release Products
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Surelease® Aqueous Ethylcellulose Dispersion

Monogramming Inks
Opacode®
Opacode® WB

Excipients
Starch 1500® Partially Pregelatinized Maize Starch

Additional Products
Opaspray® Color Coating Dispersion
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Opaglos® Tablet Core Sealant Product
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Pigment Blends

Colorcon
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ATTACHMENT 2c

STARCH 1500®

PARTIALLY PREGELATINIZED MAIZE STARCH

Flexibility for performance

Colorcon®

STARCH 1500®
PARTIALLY PREGELATINIZED MAIZE STARCH

THE SUPERIOR MULTIFUNCTIONAL EXCIPIENT FOR SOLID DOSAGE DEVELOPMENT

Starch 1500 is a unique pharmaceutical excipient combining several properties in a single product. Only Starch 1500 performs the multiple functions of a binder, disintegrant, flow-aid and self-lubricant. It is extremely versatile, being effective in a variety of processing methods for solid oral dosage forms. Starch 1500 also exhibits synergy, enhancing the functionality of other commonly used excipients in formulations.

MULTIFUNCTIONAL

Provides a unique range of functions:

- **Binder**
- **Disintegrant**
- **Flow-Aid**
- **Lubricant**

VERSATILE

Flexible performance in a variety of applications:

	DIRECT COMPACTION	WET GRANULATION	CAPSULE PLUG FORMATION
Binder	X	X	X
Disintegrant	X	X	X
Flow-Aid	X	X*	X
Lubricant	X	X*	X

*** In the extra granular phase**

COST-EFFECTIVE

Cuts process and material costs by reducing or eliminating:

- **Excess binders**
- **Superdisintegrants**
- **Additional lubricants and glidants**
- **Manufacturing steps**

MANUFACTURED FOR THE PHARMACEUTICAL INDUSTRY

- **Manufactured in modern cGMP facilities dedicated solely to the production of pharmaceutical excipients**

INDUSTRY LEADING TECHNICAL EXPERTISE

- **Worldwide manufacturing, distribution and technical service facilities**
- **Formulation and application development support**
- **Global regulatory assistance**
- **Innovative new product development**

DIRECT COMPACTION

Starch 1500 performs key functions in direct compaction formulations as a binder, disintegrant, flow-aid and self-lubricant. It also promotes formulation flexibility by complementing and enhancing the functionality of other excipients.

BINDER

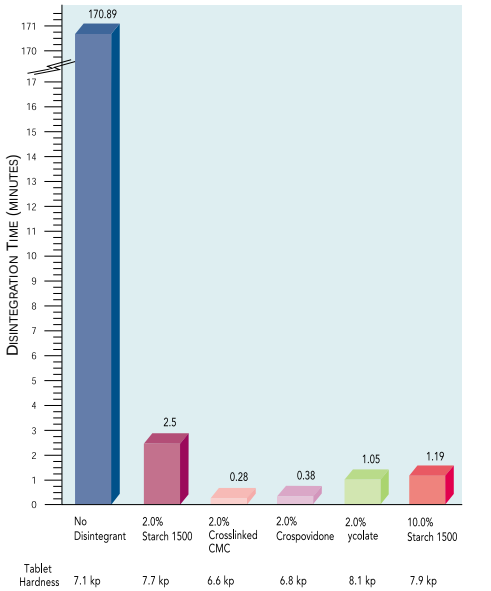
As a dry binder, it compresses well, predominately deforming plastically. Starch 1500 can be used with other excipients, such as microcrystalline cellulose, lactose, and dicalcium phosphate, to produce tablets with excellent hardness and low friability at compaction forces typically used in tableting operations.

DISINTEGRANT

Starch 1500 performs the actions of two disintegrants; maize starch and free amylose in dry processes. In some applications, 2% to 10% of Starch 1500 provides disintegrant action as effective as super disintegrants, greatly reducing costs. (See Figure 1)

Figure 1

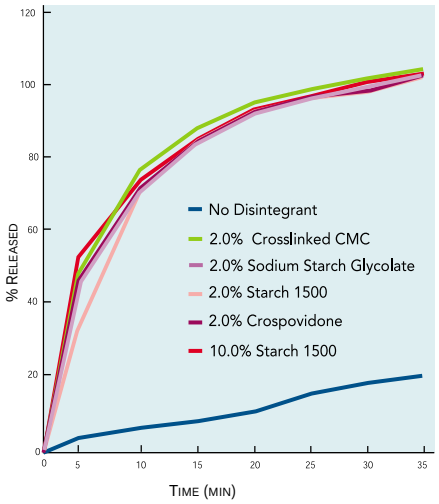
DISINTEGRATION PROFILE FOR HYDROCHLOROTHIAZIDE TABLETS, 50 MG **



The combination of maize starch and free amylose has a positive impact on drug dissolution. Supporting the tablet disintegration data in Figure 1, the resulting drug dissolution data in Figure 2 compares Starch 1500 with more costly disintegrants.

Figure 2

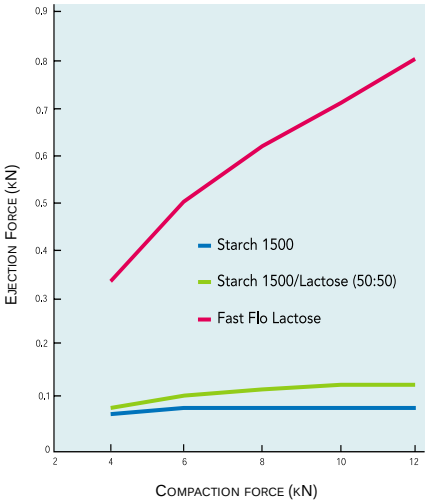
DISSOLUTION PROFILE FOR HYDROCHLOROTHIAZIDE TABLETS, 50 MG**



**** Tablets were formulated with 25% hydrochlorothazide, 0.25% magnesium stearate, and equal parts lactose and dicalcium phosphate. Equal portions of the lactose and dicalcium phosphate were substituted with 2% or 10% Starch 1500.**

Figure 3

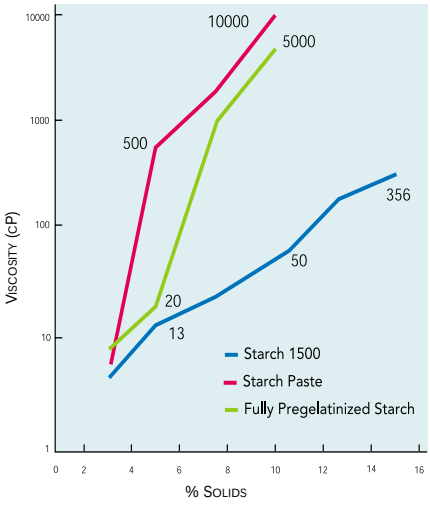
EJECTION FORCE VALUES FOR HYDROCHLOROTHIAZIDE TABLETS



Hydrochlorothiazide 25%, excipient 74.75%, 0.25% magnesium stearate as lubricant

Figure 4

CONCENTRATION DEPENDENT VISCOSITY PROFILES



Traditional starch paste at 85°C compared to Starch 1500 and a fully pregelatinized starch prepared in cold water

FLOW-AID

Starch 1500 provides excellent flow properties, demanded by today's high-speed tableting and capsule filling equipment; ensuring that manufacturers can produce tablets and capsules with consistent uniform weight and drug content.

SELF LUBRICANT

The high inherent lubricity of Starch 1500 enables the formulator to lower the levels of traditional lubricants, such as magnesium stearate. For example, magnesium stearate added in high levels, or when over-blended, can slow dissolution and cause problems with compaction (soft tablets) and film coating (poor film adhesion). Therefore, Starch 1500 enables lubricant levels and their potential problems to be reduced or eliminated. (See Figure 3)

WET GRANULATION

In wet granulation applications, Starch 1500 exhibits dual functionality as both binder and disintegrant as a result of partial cold water solubility. Starch 1500 allows process flexibility: it can be dry-blended with other ingredients before adding water, or a portion can be dispersed in cold water. A slurry of Starch 1500 in cold water provides effective binding properties at higher solids and lower viscosity than traditional starch pastes, which must be heated and prepared at lower concentrations. (See Figure 4) Processing costs are reduced by eliminating the time and expense of preparing traditional binder solutions. In addition, granulations using Starch 1500 as a binder give excellent tablet hardness and fast disintegration.

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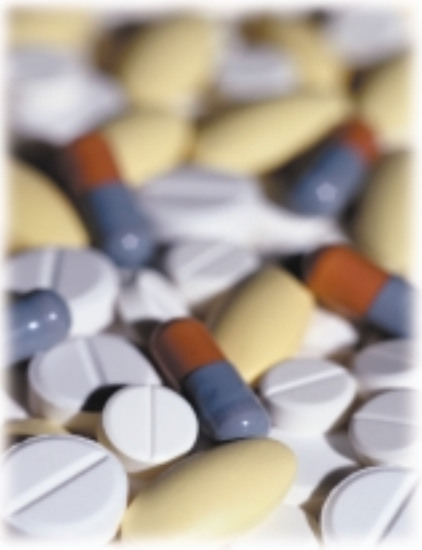

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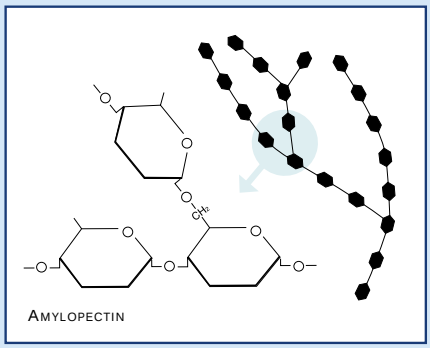

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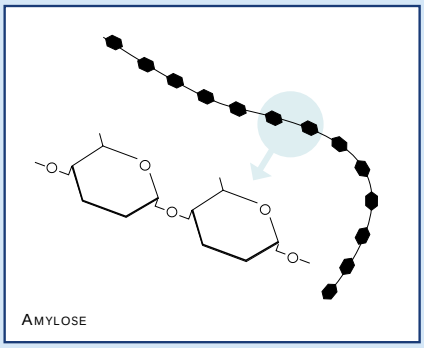

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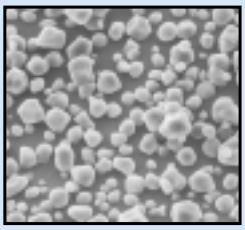
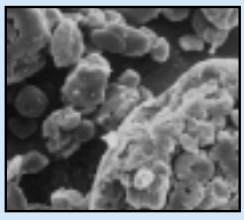
Starch NF



Starch 1500®



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ATTACHMENT 2d

T E C H N I C A L 

Use of Starch® 1500 to Improve the Uniformity of a Low Dose Direct Compression Chlorpheniramine Formulation

Charles R. Cunningham and Laura K. Scattergood
Colorcon, West Point, PA

Objectives:

Wet granulation has typically been used when preparing low dose formulations to ensure homogeneity of the drug substance. Direct compression methods can offer a simplified and more economical process if drug uniformity can be assured. This study examines the effect of Starch 1500 as an agent for pre-blending a low dose active to ensure good uniformity in a direct compression chlorpheniramine maleate (4mg) formulation.

Methodology:

Materials:

Chlorpheniramine maleate U.S.P. (CPM
Kongo Chemical Company Ltd.
Partially pregelatinized corn starch
Starch 1500®, Colorcon
Lactose monohydrate spray dried
Fast Flo®, Foremost
Microcrystalline cellulose
Emcocel® 50M, Penwest
Magnesium stearate N.F.
HyQual ®, Mallinckrodt
Stearic acid N.F.
Purified vegetable grade powder, Oleotec Ltd.
Fumed Silica
Cabosil ®, Cabot Corp.

Formulations:

Chlorpheniramine was used at 2.7% (w/w) in all formulations. Starch 1500, lactose, and microcrystalline cellulose were used in combination as diluents at a 94.3% level in each of the formulations.

All formulations included 0.75% fumed silica as a glidant and 0.25% magnesium stearate and 2.0% stearic acid as the lubricants

INGREDIENTS	PERCENTAGES					
CPM	2.70	2.70	2.70	2.70	2.70	2.70
Lactose	**47.15**	**47.15**	**47.15**			**47.15**
MCC	**47.15**		**47.15**	**47.15**	**47.15**	
Starch 1500		**47.15**		**47.15**	**47.15**	**47.15**
Cabosil	0.75	0.75	0.75	0.75	0.75	0.75
Stearic acid	2.00	2.00	2.00	2.00	2.00	2.00
Mg stearate	0.25	0.25	0.25	0.25	0.25	0.25
Total	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**

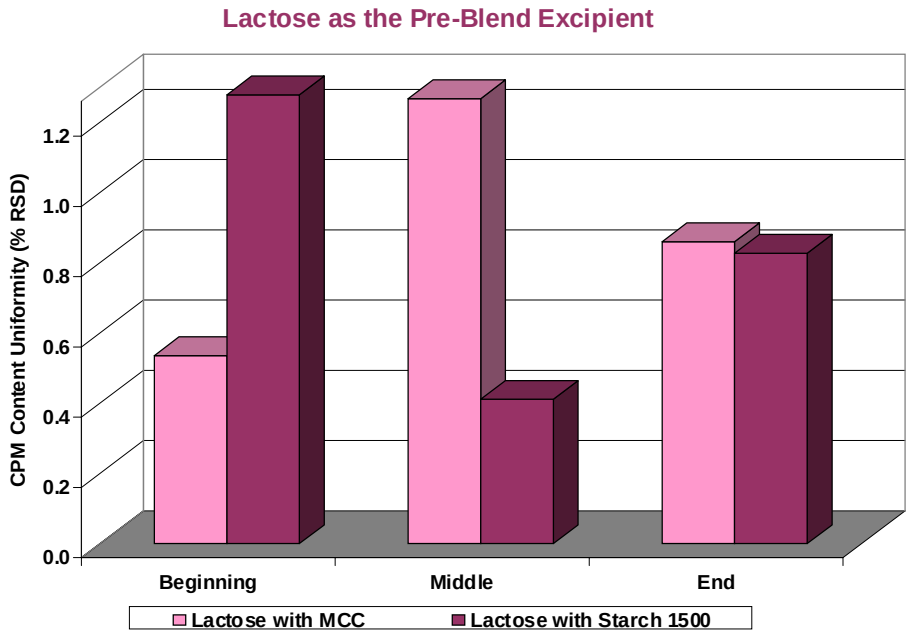
The excipient used to pre-blend the CPM for each batch is denoted in RED.

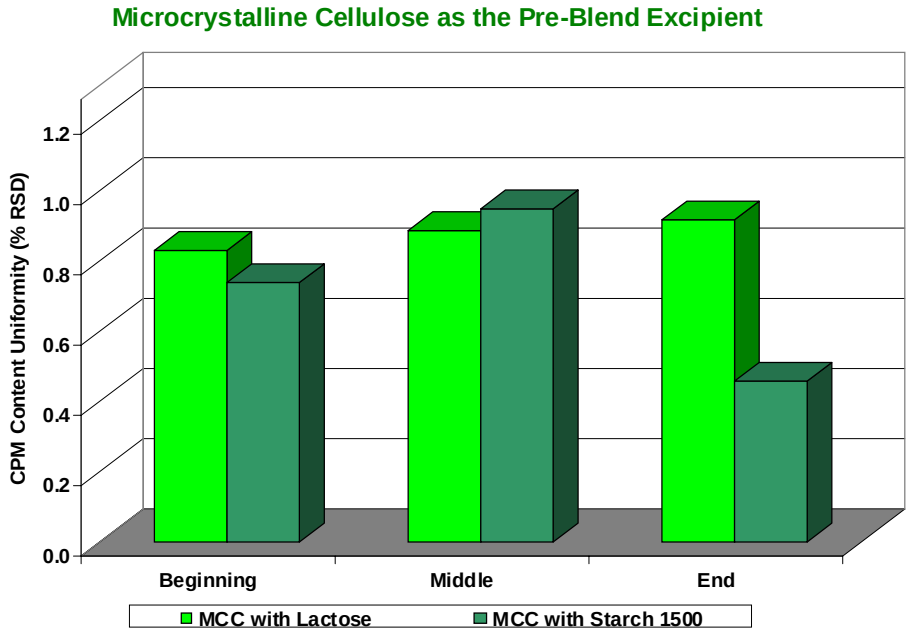
***Blending*:**
Blending was carried out in a twin shell blender. Each of the primary excipients was used alone to preblend the chlorpheniramine for 5 minutes prior to the addition of the remaining excipients. Upon addition of the remaining excipients, blending continued for 10 minutes. Magnesium stearate was then added and blended with each batch for an additional 5 minutes.

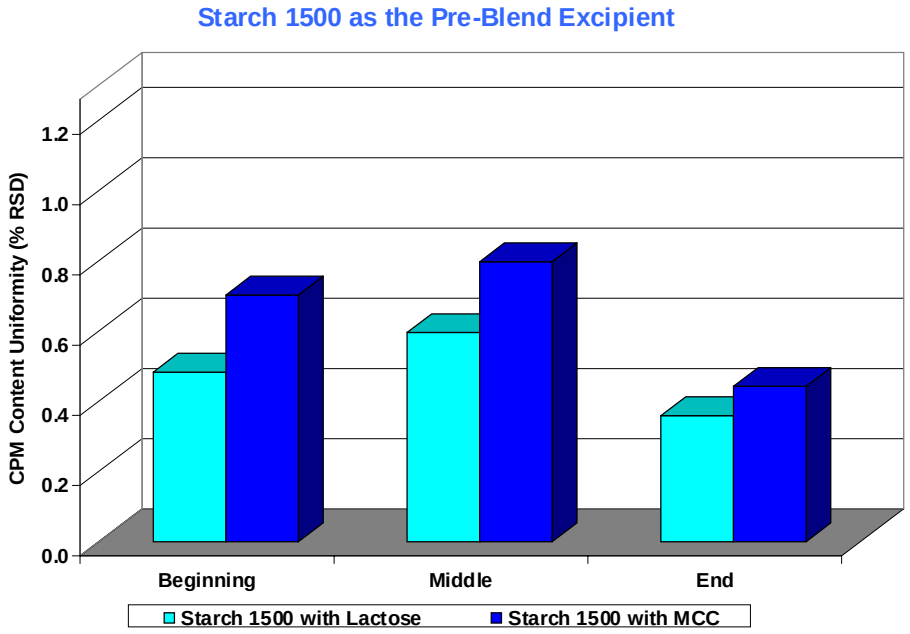
Compaction:
The powder blends were tabletted on a 10 station rotary tablet press using 5/16" flat-faced beveled edge tooling. The tablet weight was 150mg.
Tablet samples were taken at the beginning, middle and end of each batch.

Assay and Content Uniformity for
Chlorpheniramine Maleate According to USP 23:
Assay and content uniformity testing was conducted for Chlorpheniramine Maleate according to U.S.P. 23

Results:







Comparing the uniformity of CPM tablets collected from the beginning, middle, and end of the tableting run, the use of lactose as the excipient / drug pre-blend resulted in the highest overall relative standard deviations.

Batches with microcrystalline cellulose as the pre-blend had lower deviation both tablet to tablet or across the whole batch when compared to lactose.

Starch 1500, when used as the pre-blend excipient, showed the lowest relative standard deviations when compared to either lactose or MCC.

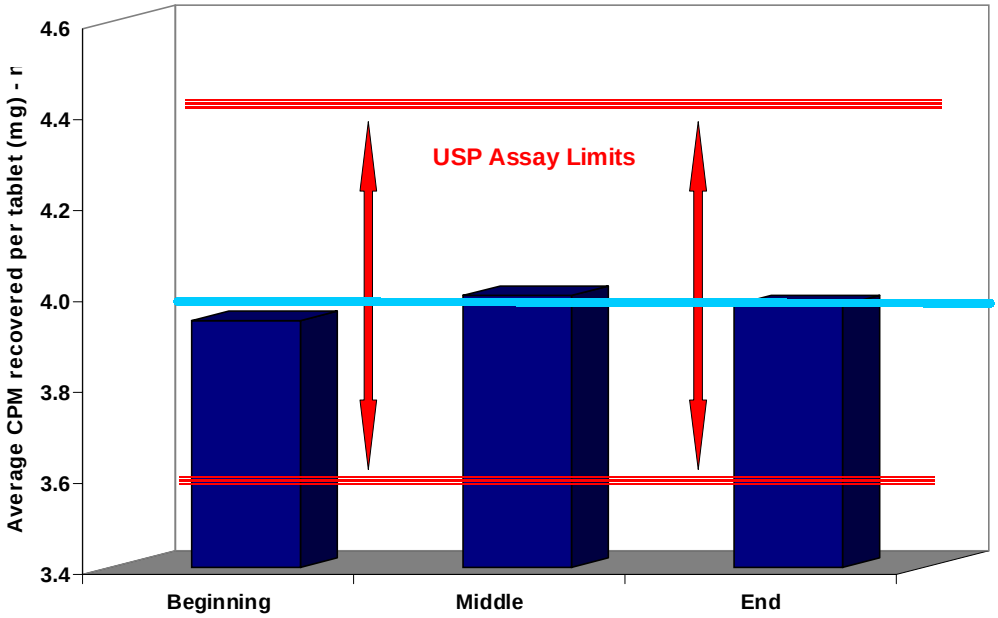
Confirmatory Trial:

A final formulation was developed with a slightly increased level of Starch 1500 to be used as the pre-blend along with MCC as the secondary filler.

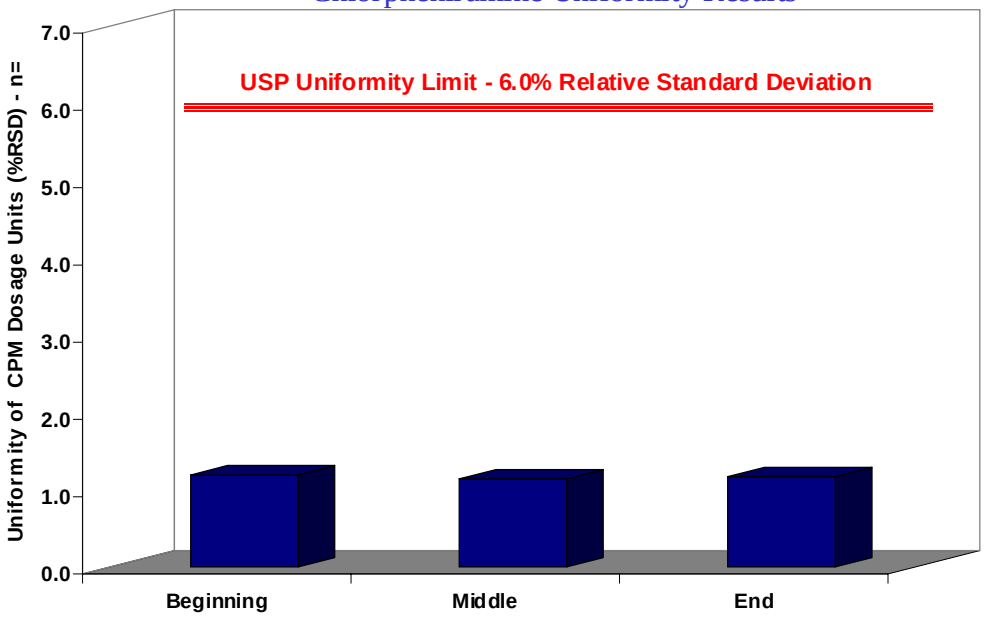
Final Formulation

Ingredients	Percent (w/w)
Chlorpheniramine maleate	2.70
Starch 1500	50.00
Microcrystalline cellulose	44.30
Stearic acid	2.00
Fumed silica	0.75
Magnesium stearate	0.25
Total	100.00

Chlorpheniramine Assay Results



Chlorpheniramine Uniformity Results



Starch 1500, when used as the pre-blend excipient, and combined with microcrystalline cellulose pro vided for drug assay and uniformity results that were well below the USP limits and showed little or no variation throughout the course of the tableting run.

Conclusions:

Starch 1500 was sucessfully used to uniformly disperse the chlorpheniramine and enable a switch to a more economical direct compression process from wet granulation.

The sphero-granular morphology of Starch 1500 may contribute to enhanced particle to particle homogeneity.

Further studies will examine the specific properties of Starch 1500 and their contribution to enhancing the uniformity of low dose actives in direct compression formulations.

Reprint of poster presented at AAPS, Indianapolis Nov. 2000.

ATTACHMENT 2e

Formulation of Acetylsalicylic Acid Tablets for Aqueous Enteric Film Coating

Image Colorcon

The goal of this study was to determine which combination of excipients would result in a tablet core that would be suitable for use in an aqueous enteric film-coating process. A relatively simple formulation of microcrystalline cellulose (MCC) and partially pregelatinized starch (P-PGS) was found to provide the necessary properties. MCC in the formulation provides the compactability needed to produce a tablet that will withstand the mechanical stresses of the film-coating process. P-PGS provides the dissolution characteristics and is responsible for the stability characteristics in this moisture sensitive, enteric film-coated application. It was also found that P-PGS could be used to reduce the deleterious effects of superdisintegrants in formulations.

Charles R. Cunningham* and Bruce R. Kinsey are global technical managers.

Laura K. Scattergood is an applications technologist.

All in global technical support at Colorcon, 415 Moyer Boulevard, West Point, Pennsylvania 19486, USA.
Tel: +1 215 699 7733
Fax: +1 215 661 2626.
ccunningham@colorcon.com
www.colorcon.com

*To whom all correspondence should be addressed.

In recent years, acetylsalicylic acid (ASA; also well known as aspirin) has been prescribed for a host of indications. In addition to its uses as an analgesic, anti-inflammatory and antipyretic agent, ASA is now indicated for use in the prevention and treatment of heart disease and stroke. Further studies are currently under way investigating the potential of ASA in bolstering the immune system, treating cognitive decline and lowering the risk of colon and ovarian cancer. A low daily dose, 75–81 mg, is commonly used in preventive ASA therapy. Historically, ASA has been regarded as a potential gastric irritant[1] and studies have shown that the incidence of gastric intestinal side-effects may increase with regular use.[2] Enteric coating of the tablets is therefore desirable for preventing stomach upset or irritation in those taking daily ASA therapy.

Aspirin is a moisture sensitive drug and can hydrolyse into acetic and salicylic acids when exposed to high humidity and elevated temperatures.[3] As the coating process will subject ASA tablets to both high temperatures and humidity, it is important that the formulation is resistant to moisture interaction. Mitrevej and Hollenbeck found that a hydrophilic field is generated around ASA crystals under high humidity conditions and that upon combining the ASA with certain hydrophilic disintegrants, condensation in the vicinity of the ASA crystal can occur.[4] The disintegrants studied were sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone and colloidal silica. During the aqueous film-coating process, Faroongsarng and Peck determined that depth of water penetration into the tablet core could be directly linked to the concentration and type of disintegrant used in the formulation.[5] Further work by Bashar Al-Taani studying aqueous coating solutions for ASA tablets confirmed that moisture penetration during the coating process was not only formulation dependent but could be directly linked

to the stability of the final coated ASA tablet.[6]

A review of ingredients contained in five commercially purchased ASA products found that, in most cases, the primary listed excipients were microcrystalline cellulose (MCC) and some form of starch. The use of additional excipients including disintegrants (such as CCS and SSG), lubricants and glidants varied. All five products were packaged in foil-sealed high density polyethylene (HDPE) bottles, three of which contained carbon/silica desiccant packs.

The goal of this study was to determine which combination of excipients, found in commercial ASA products, would result in a tablet core that would be suitable for use in an aqueous enteric film-coating process.

The goal of this study was to determine which combination of excipients, found in commercial ASA products, would result in a tablet core that would be suitable for use in an aqueous enteric film-coating process.

Materials and equipment

Aspirin 1040 (Aspirin USP 40-mesh crystals, Rhodia, Cranbury, New Jersey, USA) was used as the active material. The excipients used in the study were partially pregelatinized starch (P-PGS) (Starch 1500, Colorcon, West Point, Pennsylvania, USA); MCC (Emcocel 50M, Penwest, Patterson, New York, USA); SSG (Explotab, Penwest); CCS (Ac-Di-Sol, FMC, Princeton, New Jersey, USA) and stearic acid NF (purified vegetable grade powder, Oleotec Ltd, London, UK).

The packaging materials used were 85 mL foil-sealable HDPE bottles (Drug Plastics and Glass Co., Boyertown, Pennsylvania, USA) and desiccant packs (3964, Süd-Chemie Performance Packaging, Belen, New Mexico, USA). The coating materials used were an aqueous enteric coating system (Sureteric) and an aqueous film coating system (Opadry II), both manufactured by Colorcon.

Ingredients were dry blended in a 16-quart twin-shell blender (Patterson-Kelley Co., East Stroudsburg, Pennsylvania, USA). Tablets were compressed on an instrumented 10-station Piccola rotary press (Riva, Buenos Aires, Argentina). Tablet hardness was measured using a Multichek tester (Erweka, Milford, Connecticut, USA). A side-vented 15 in. coating pan (Labcoat II, O'Hara Technologies, Toronto, Canada) was used to apply the coatings. A dissolution test station (VK 7010, apparatus I, VanKel, Cary, North Carolina, USA) with a UV spectrophotometer (Varian, Palo Alto, California, USA) was used for drug release testing. An HPLC (high performance liquid chromatography) system (Alliance 2690, Waters Corp., Milford, Massachusetts, USA) was used to determine free salicylic acid concentration.

Methods

Blending and tablet preparation. Six formulations (see Table I), composed of constant levels of ASA and lubricant and varying levels of MCC, P-PGS, CCS and SSG, were each dry blended for 15 min in the twin-shell blender. The batch size of each blend was 5 kg.

Each of the six blends was then compressed on the 10-station rotary tablet press with 7.0 mm standard concave tooling. The target tablet weight was 162.0 mg and the compaction force was adjusted to produce tablets with a breaking force of 6.0–7.0 kp. The tablet coating was performed in a 15 in. side-vented pan equipped with one spray-gun. The pan load was 3 kg. A subcoat of Opadry II dispersed in water (15% w/w) was applied to obtain a theoretical 2% tablet weight gain to tablets from all of the six batches. The subcoat application was immediately followed by an enteric coat consisting of Sureteric dispersed in water (15% w/w) and applied to obtain a theoretical 10% weight gain. A topcoat of Opadry II dispersed in water (15% w/w) was then applied to the tablets to obtain a 2% theoretical weight gain. All six coating trials were conducted using the same recommended process temperatures, spray rates and operating conditions. In general, the use of a subcoat beneath the enteric coating is optional and largely depends on the quality of the tablet core. As the six batches contained varying ingredients, a subcoat was applied to all six batches so that the enteric layer would be unaffected by minor changes in the tablet surface. The use of a topcoat is optional as well but many commercial products have a topcoat applied to colour the core.

Dissolution and free salicylic acid testing. The dissolution and free salicylic acid tests for the uncoated tablets were performed according to the USP 23 monograph for ASA tablets. The coated tablets were tested according to the USP 23 monograph for delayed-release ASA tablets.

Tablet hardness testing. The uncoated tablets were tested for diametrical breaking force before and after storage at accelerated conditions. The average result was reported from 20 tablets tested.

Table I Study formulations

	Ingredients	Concentration (% w/w)					
		A	B	C	D	E	F
Constant	Aspirin	50.0	50.0	50.0	50.0	50.0	50.0
	Stearic acid	0.5	0.5	0.5	0.5	0.5	0.5
Study variables	Microcrystalline cellulose (MCC)	49.5	29.5	46.5	46.5	26.5	26.5
	Starch 1500 (P-PGS)	0.0	20.0	0.0	0.0	20.0	20.0
	Croscarmellose sodium (CCS)	0.0	0.0	3.0	0.0	3.0	0.0
	Sodium starch glycolate (SSG)	0.0	0.0	0.0	3.0	0.0	3.0

Packaging and stability. Samples of the uncoated tablets from each formulation were packaged in HDPE bottles (120 tablets per bottle). The coated tablets from each formulation were packaged in the same manner: one set of samples was packaged without desiccant; a second set of samples was packaged with a desiccant pack in each bottle. All bottles were induction (foil) sealed and stored under accelerated conditions — 40 °C/75% relative humidity [RH] — for 3 months.

Results and discussion

Uncoated ASA tablets. The dissolution testing conducted in acetate buffer (pH = 4.5) revealed that only batch A containing MCC alone as the excipient failed to achieve 80% drug release in less than 20 min. The dissolution results after storage under accelerated conditions showed little change from the initial tests (see Figure 1).

More significant were the results of the tablet mechanical strength after exposure to accelerated temperature and humidity conditions (see Figure 2). The tablets containing just ASA and MCC lost 8.57% in tablet hardness, whereas the tablets containing the MCC–P-PGS combination showed the least decrease in tablet hardness, with a 3.0% loss. The use of either CCS or SSG in combination with MCC resulted in a loss of more than 36.3% in tablet mechanical strength. Interestingly, when the same levels of CCS or SSG were used in the tablets that combined P-PGS and MCC, the loss in tablet hardness was less profound.

When comparing the levels of free salicylic acid in uncoated tablets, at the initial time point and after 3 months at 40 °C/75% RH, the results showed a similar trend to the tablet hardness results (see Figure 3).

The USP limit for free salicylic acid in uncoated ASA tablets is not more than 0.3%. After 3 months in accelerated conditions, the tablets containing just MCC as the excipient or MCC with either CCS or SSG exhibited significantly increased levels of free salicylic acid and failed to meet the USP requirements. The MCC–P-PGS combination showed virtually no degradation of the ASA with time in adverse storage conditions, and the increase in free salicylic acid was negligible.

It has been shown that the P-PGS used in this study has a lower propensity for moisture uptake than either CCS or SSG and will draw less moisture into a tablet under elevated humidity conditions.[7] This may account for some of the positive effects seen with its use in this formulation. The data also suggest that P-PGS may be able to trap or retain moisture within the formulation, thus retarding moisture interaction with the ASA.

Initial results for the coated ASA tablets. After coating, the tablets from all of the formulations had a good appearance. None of the tablets exhibited any signs of defects either during or after the coating trials. Tablets from all the batches passed the acid phase of dissolution testing with no release of ASA after 2 h in 0.1 N HCl. During the buffer phase of testing (pH = 6.8), as with the uncoated tablet dissolution results, only the tablets containing just MCC

Figure 1 Comparison of uncoated tablet dissolution profiles before and after 3 months of storage at 40 °C/75% RH.

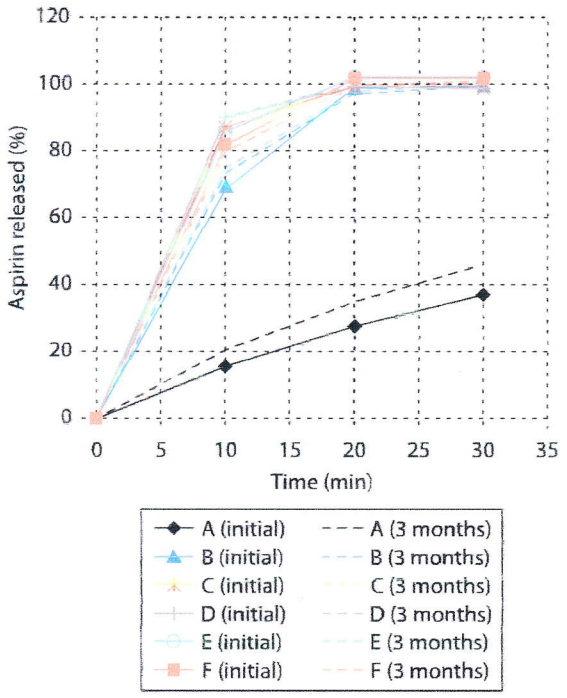


Figure 2 Comparison of breaking force of uncoated tablets before and after 3 months of storage at 40 °C/75% RH.

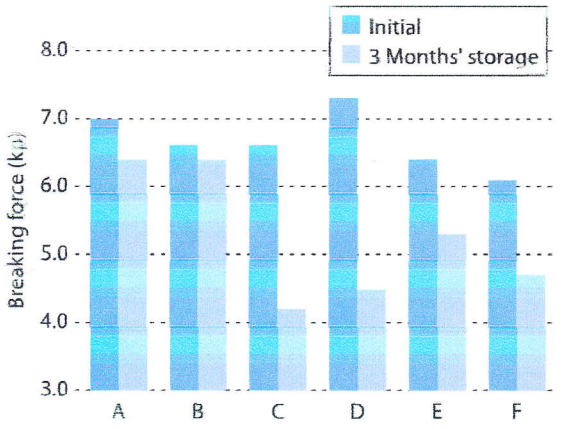
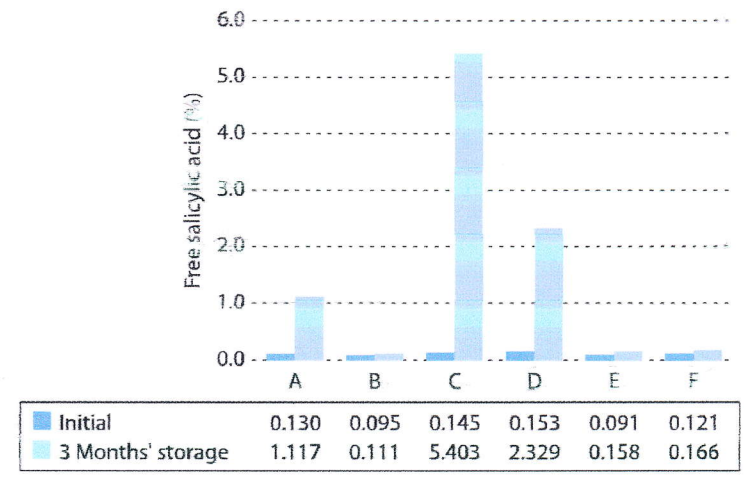


Figure 3 Comparison of free salicylic acid of uncoated tablets before and after 3 months of storage at 40 °C/75% RH (USP limit NMT 0.3%).



	A	B	C	D	E	F
Initial	0.130	0.095	0.145	0.153	0.091	0.121
3 Months' storage	1.117	0.111	5.403	2.329	0.158	0.166

After 3 months of storage ... some of the tablets containing CCS or SSG exhibited softening of the film coating and sticking of the tablets to one another within the HDPE bottles.

and ASA failed to meet the USP specification of not less than 80% ASA released in 90 min (see Figure 4). In fact, the other five formulations attained 80% ASA release in less than 20 min.

Coated tablet stability results. After 3 months of storage at 40 °C/75% RH, some of the tablets containing CCS or SSG exhibited softening of the film coating and sticking of the tablets to one another within the HDPE bottles (see Figure 5). This occurred in the samples that were packaged both with and without desiccant packs. Any tablets exhibiting signs of defects at this point were considered stability failures.

The free salicylic acid results for the coated tablets were very similar to those results obtained for the uncoated tablets. The USP limit for free salicylic acid in coated ASA tablets, 3.0%, is higher than the uncoated tablet specification. After 3 months in accelerated conditions, the tablets containing just MCC as the excipient exhibited higher, but acceptable, free salicylic acid levels (see Figure 6). The combination of the MCC with CCS or SSG resulted in substantial increases to more than 5.0% free salicylic acid overall, so failed to meet the USP requirements. Again, the most acceptable results were seen for tablets containing MCC and P-PGS as the excipients, which showed no increase in free

Figure 4 Initial delayed-release dissolution profiles of enteric-coated ASA tablets.

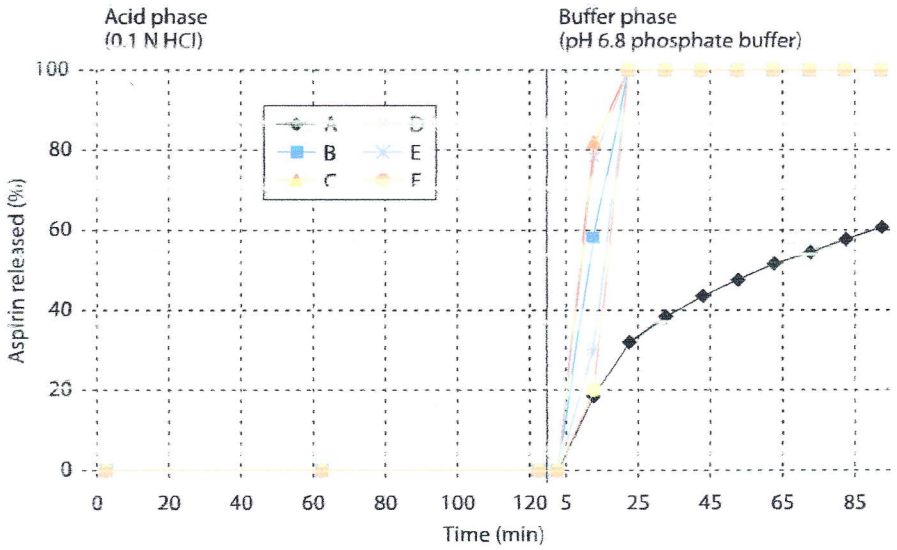
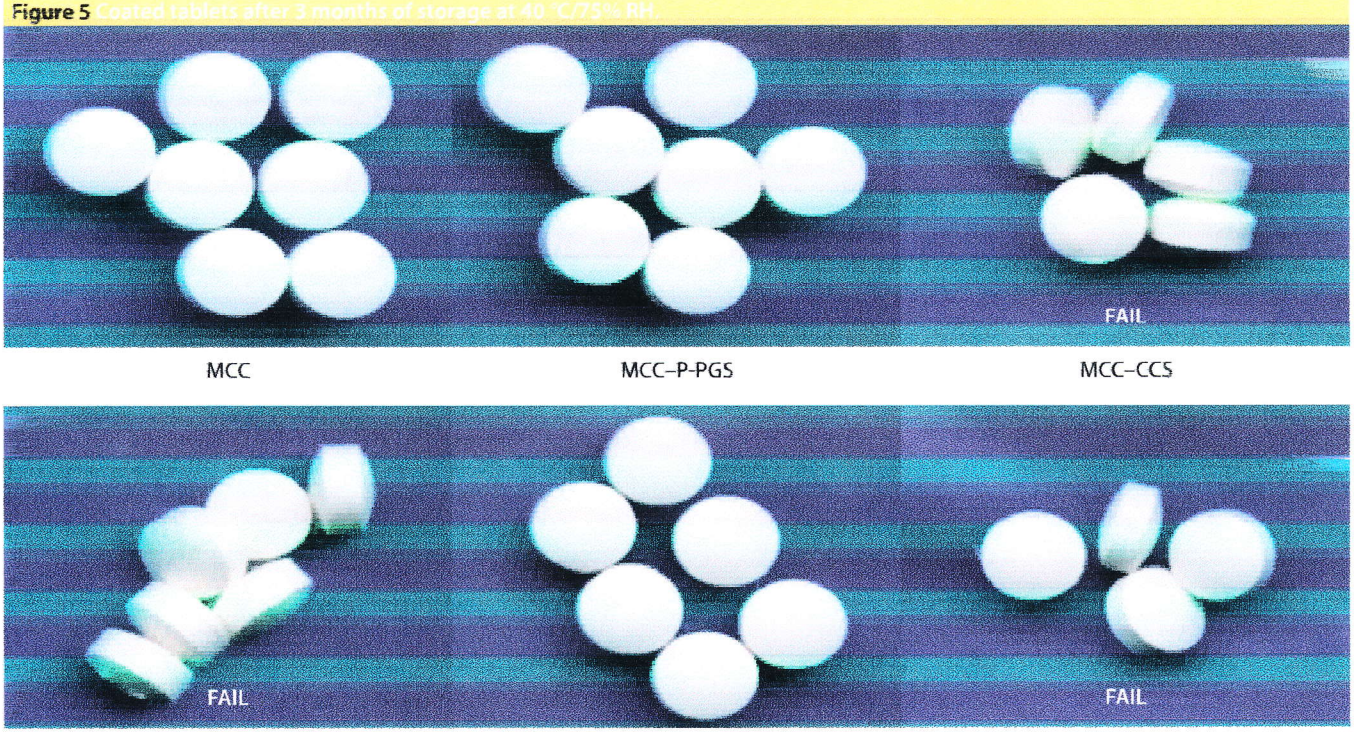


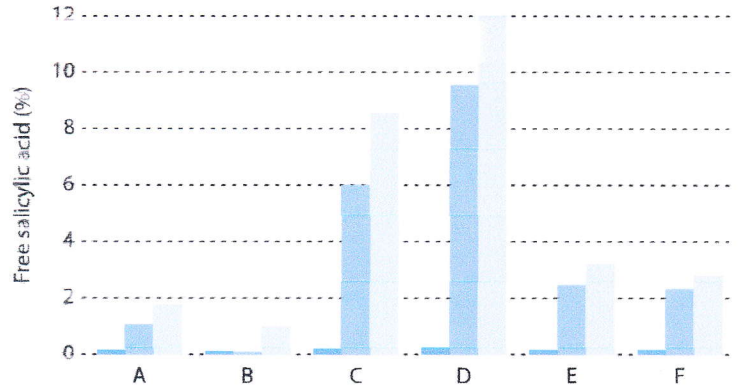
Figure 5 Coated tablets after 3 months of storage at 40 °C/75% RH.



MCC | MCC–P-PGS | MCC–CCS

MCC–SSG | MCC–P-PGS–CCS | MCC–P-PGS–SSG

Figure 6 Comparison of free salicylic acid levels from coated tablets before and after storage at 40 °C/75% RH (USP limit NMT 3.0%).



	A	B	C	D	E	F
Initial	0.11	0.06	0.16	0.19	0.10	0.12
3 Months with desiccant	1.01	0.04	5.97	9.52	2.38	2.26
3 Months no desiccant	1.73	0.97	8.52	12.00	3.19	2.78

used and only a 0.91% increase when packaged without desiccant. The addition of P-PGS substantially reduced the amount of ASA degradation in those tablets containing MCC combined with either SSG or CCS, which had unacceptable free salicylic acid levels.

It was interesting to note that the addition of desiccant packs to the bottles was not sufficient to eliminate, or even substantially reduce, the adverse effects of the superdisintegrants. Of the six formulations, the tablets containing MCC alone or the MCC–P-PGS excipient combination met the desired stability performance requirements of good appearance, acid resistance and acceptable free salicylic acid levels. The formulation with just MCC did not meet the delayed dissolution requirements for ASA release in buffer either initially or after

Table II Drug dissolution results for coated tablets made from formulation B (see Table I). Tablets were stored for 3 months at 40 °C/75% RH.

	Released (%) in 0.1N HCl after 2 h	$t_{80\%}$ in phosphate buffer (pH = 6.8)
Initial	0.0	<20 min
3 Months with desiccant	0.0	<20 min
3 Months no desiccant	0.0	<20 min

months of storage, in accelerated conditions. The tablets containing the MCC–P-PGS combination did exhibit excellent delayed release dissolution results initially and after 3 months at 40 °C/75% RH (see Table II).

Conclusions

The results obtained in this study have yielded a relatively simple ASA formulation utilizing a combination of MCC and P-PGS as the primary excipients. MCC in the formulation provides the compactability needed for producing a tablet that will withstand the mechanical stresses of the film-coating process. Starch provides the necessary dissolution characteristics to the formulation and was responsible for the stability characteristics in this moisture sensitive, enteric film-coated application. This formulation without the use of additional superdisintegrants would be well suited to the aqueous film-coating process, and the final coated tablets would not require the use of any specialized packaging materials. It was also found that P-PGS could be used to reduce the deleterious effects of superdisintegrants in formulations. This would also reduce raw material costs. The next phase of this study will focus on optimization of the necessary enteric coating levels and the scale-up of the enteric coating process.

Acknowledgements

The authors gratefully acknowledge Rhodia Inc. for the donation of the ASA used in this project. In addition, we thank Mr. David Ferrizzi of Colorcon for his analytical support.

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ATTACHMENT 2f

Poster Reprint

American Association of Pharmaceutical Scientists

October, 2001

The Effect of STARCH 1500® On The Stability of Aspirin Tablets Stored Under Accelerated Conditions

Charles R. Cunningham and Laura K. Scattergood; Colorcon, West Point, PA, USA

Objectives

Aspirin is a moisture sensitive drug and can hydrolyze into acetic and salicylic acids. Hydrophilic excipients can have adverse effects on aspirin under accelerated stability conditions. This study examines the effect of Starch 1500, partially pregelatinized starch, in combination with microcrystalline cellulose and two hydrophilic superdisintegrants on the stability of aspirin 81mg tablets.

Materials and Equipment

Aspirin 1040, (Aspirin USP 40-mesh crystals) from Rhodia was used in the study. The excipients included in the study were partially pregelatinized corn starch, Starch1500®, Colorcon; Microcrystalline Cellulose, Emcocel® 50m, Penwest; Sodium starch glycolate, Explotab®, Penwest; Croscarmellose sodium, Ac-Di-Sol®, FMC; Stearic acid N.F., Purified vegetable grade powder, Oleotec Ltd.

The tablets were packaged for stability using 85cc foil-sealable HDPE bottles, Drug Plastics and Glass Co.

The ingredients were dry blended in an 8-qt. twin-shell blender (Patterson-Kelley Co.). The tablets were compressed on an instrumented 10-station Piccola rotary press (Riva Co.) with 7.1mm standard concave tooling. Tablet Hardness was measured using a Multichek™ tester (Erweka). A Dissolution Test station, VK7010, apparatus I, (VanKel) with a UV spectrophotometer (Varian) was used for drug release testing. An Alliance 2690 HPLC (Waters Corp.) was used for free salicylic acid determinations.

Methods

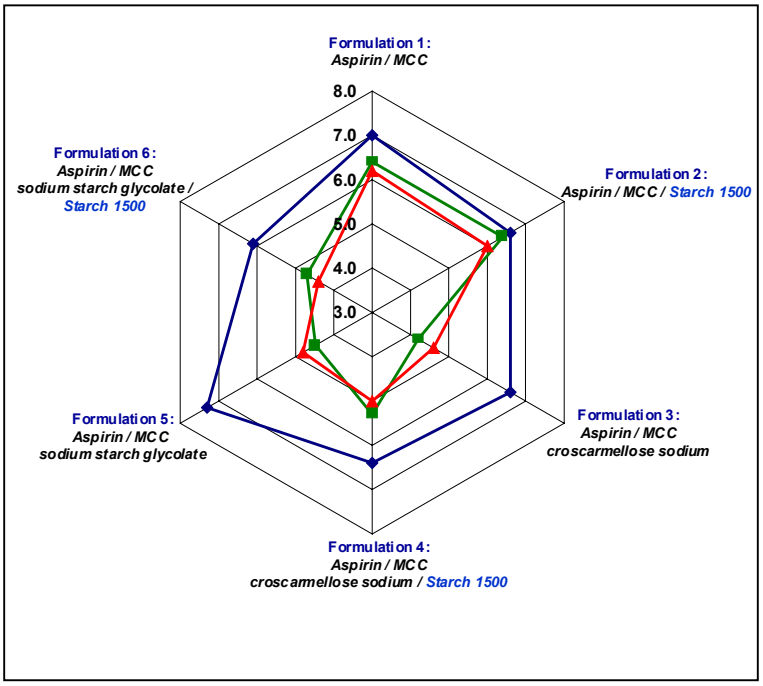
The following six formulations were dry blended for 15 minutes in the twin-shell blender. Each formulation was then compressed to 162.0 mg total tablet weight with a tablet breaking force target of 6 - 7 kp.

Ingredients	Formulations (% w/w)					
	1	2	3	4	5	6
Aspirin	50.0	50.0	50.0	50.0	50.0	50.0
Stearic acid	0.5	0.5	0.5	0.5	0.5	0.5
Microcrystalline cellulose	49.5	29.5	46.5	26.5	46.5	26.5
Starch 1500	-	20.0	-	20.0	-	20.0
Croscarmellose sodium	-	-	3.0	3.0	-	-
Sodium starch glycolate	-	-	-	-	3.0	3.0

Samples of the resultant tablets were packaged in foil-sealed HDPE bottles and stored in a 40 °C/75% RH chamber for six months.

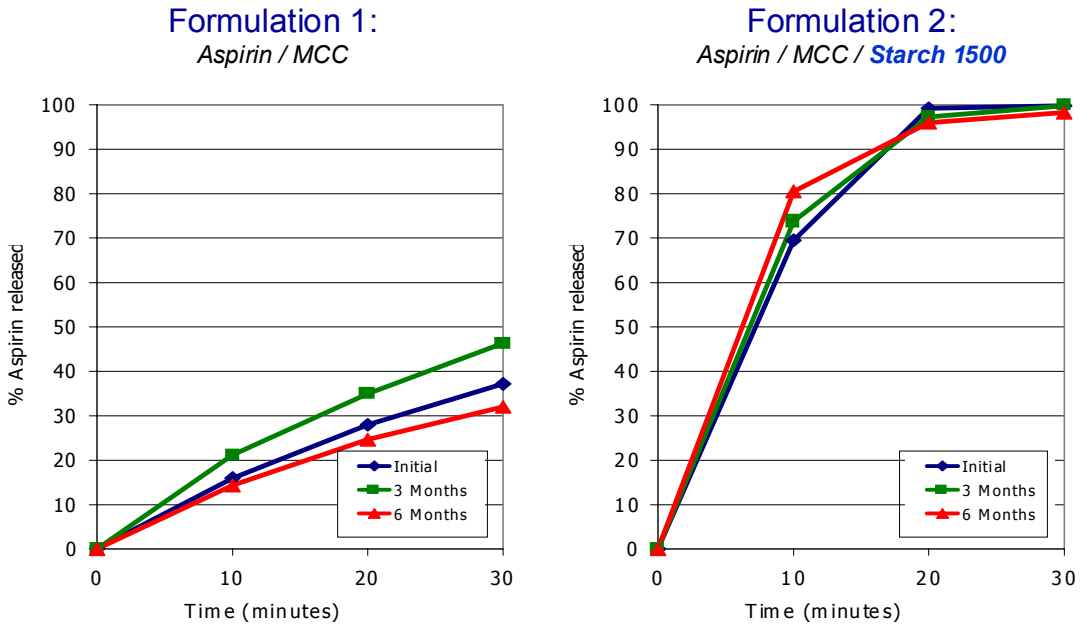
Stability Results

Tablet breaking force (kp)



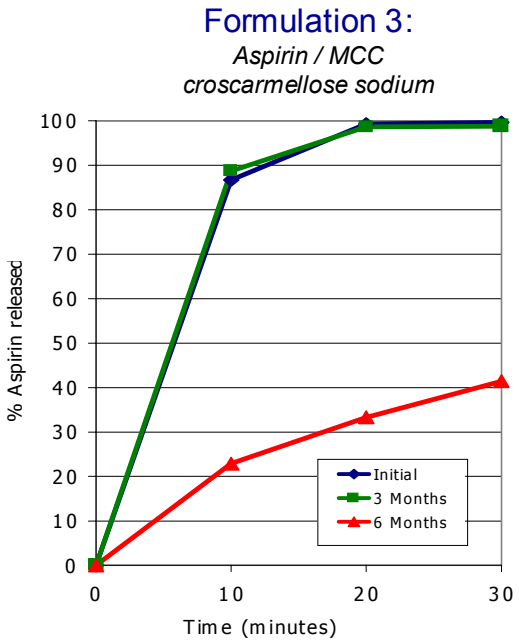
At six months, the tablets containing just aspirin and MCC lost 11.43% in tablet breaking force while the tablets containing the Starch 1500 / MCC combination showed the least decrease in breaking force with just a 9.0% loss. The use of either the croscarmellose sodium or sodium starch glycolate in combination with MCC resulted in a 30.3% and 34.24% loss in tablet mechanical strength respectively. When the same levels of superdisintegrant were used in the tablets that combined Starch 1500 and MCC, the % loss in tablet breaking force was reduced.

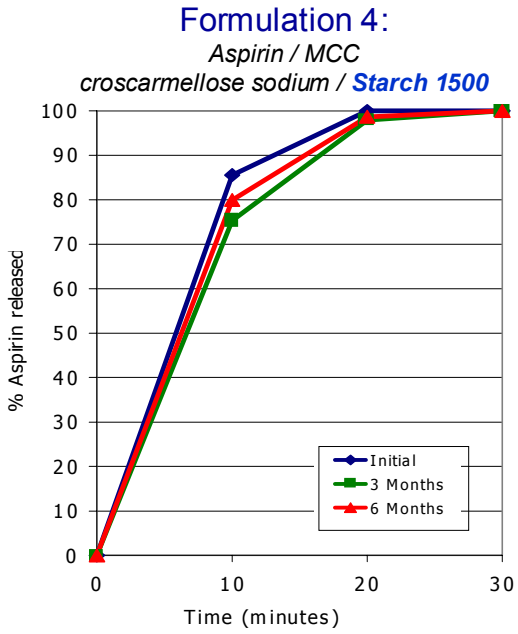
Dissolution Stability



The tablets containing only microcrystalline cellulose (MCC) and aspirin exhibited slow dissolution initially and at the three and six month time points. The tablets failed the USP release criteria of not less than 80% aspirin released in 30 minutes. No significant change in release characteristics was observed over the 6 month stability period.

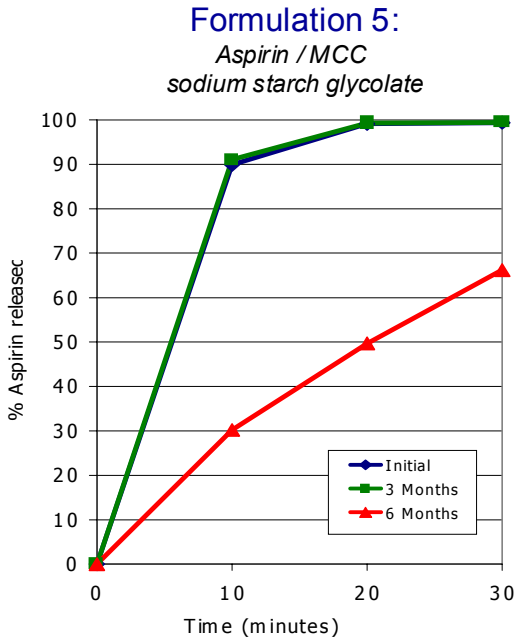
The addition of Starch 1500 to the formulation resulted in dissolution that exceeded the USP requirements at all time points.

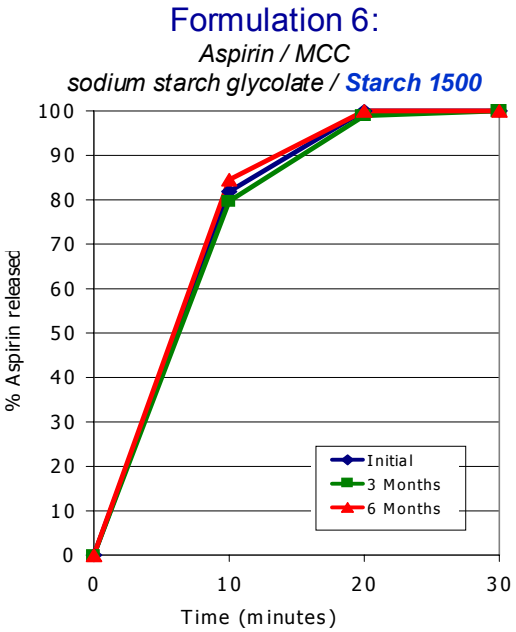




The tablets containing aspirin and MCC with croscarmellose sodium exhibited significantly slower release at six months compared to the initial and three month time points. Undispersed tablet fragments were found in the baskets upon completion of the dissolution test indicating a reduction in disintegrant effectiveness.

The addition of Starch 1500 to this formulation resulted in tablets that exhibited rapid release of aspirin independent of storage times or conditions.

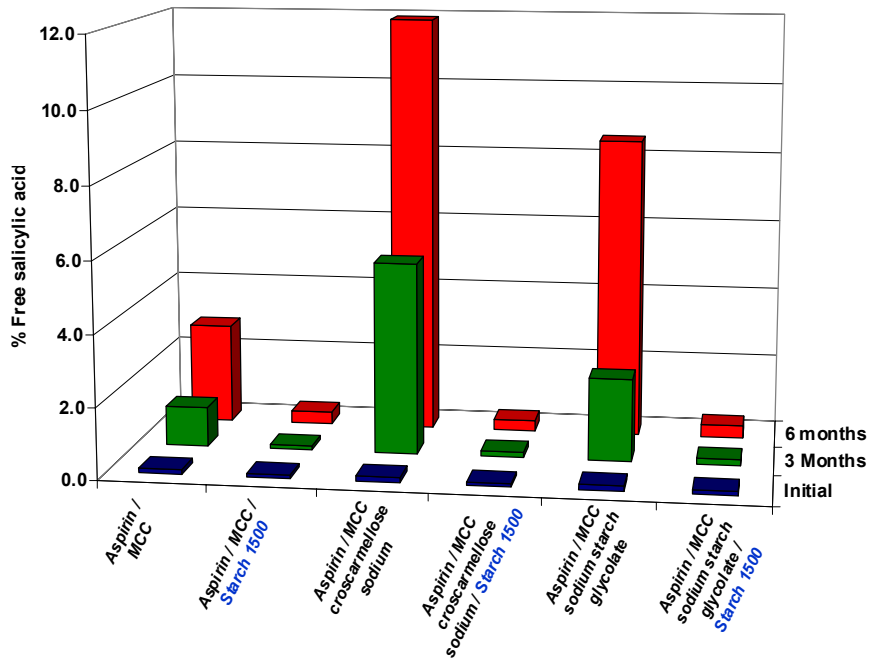




As with the tablets containing croscarmellose sodium, the tablets containing aspirin and MCC with sodium starch glycolate also exhibited rapid dissolution initially and at the three month time points. The release of aspirin from the tablets stored for six months was much slower and failed the USP release criteria. Again, undispersed tablet fragments were found in the baskets upon completion of the dissolution tests for the six month samples.

The addition of Starch 1500 to this formulation also resulted in tablets that exhibited rapid release of aspirin independent of storage times or conditions.

Free Salicylic Acid Stability



After 6 months, only the tablets that contained Starch 1500 in the formulation had acceptably low levels of free salicylic acid. The use of MCC alone with the aspirin or with either of the superdisintegrants resulted in substantial degradation.

Conclusions

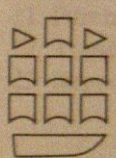
Starch 1500 has a lower propensity for moisture absorption than either croscarmellose sodium or sodium starch glycolate and does not rely solely on water uptake and swelling as a mechanism for disintegration. This may account for some of the positive effects seen with its use in these formulations. The data suggest that Starch 1500 may be inhibiting water activity within the formulation and retarding moisture interaction with the aspirin. The use of Starch 1500 provided for exceptional stability in this moisture sensitive application. Most noteworthy was the effect of Starch 1500 in reducing or eliminating the deleterious effects of other excipients in the study.

ATTACHMENT 3a

Pharmaceutics: The Science of Dosage Form Design

EDITED BY

Michael E. Aulton BPharm PhD MPS
Reader in Pharmacy, Leicester Polytechnic, Leicester, UK



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Factors influencing bioavailability: factors influencing drug absorption from the gastrointestinal tract

DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

The various factors which can influence drug release from dosage forms and absorption into the systemic circulation will be considered in this chapter by reference to the peroral (i.e. gastrointestinal) route of administration. This route is chosen as the example, since the majority of drugs are administered orally and the vast majority of orally administered drugs are intended to be absorbed from the gastrointestinal tract. Thus, a detailed consideration of the factors which can influence the absorption of drugs from this region is warranted.

In order that the reader may gain an insight into the numerous factors which can potentially influence the rate and extent of appearance of intact drug into the systemic circulation, a schematic illustration of the steps involved in the release and gastrointestinal absorption of a drug from a tablet is presented in Fig. 9.1. It is evident from this diagram that the rate and extent of appearance of intact drug into the systemic circulation depends

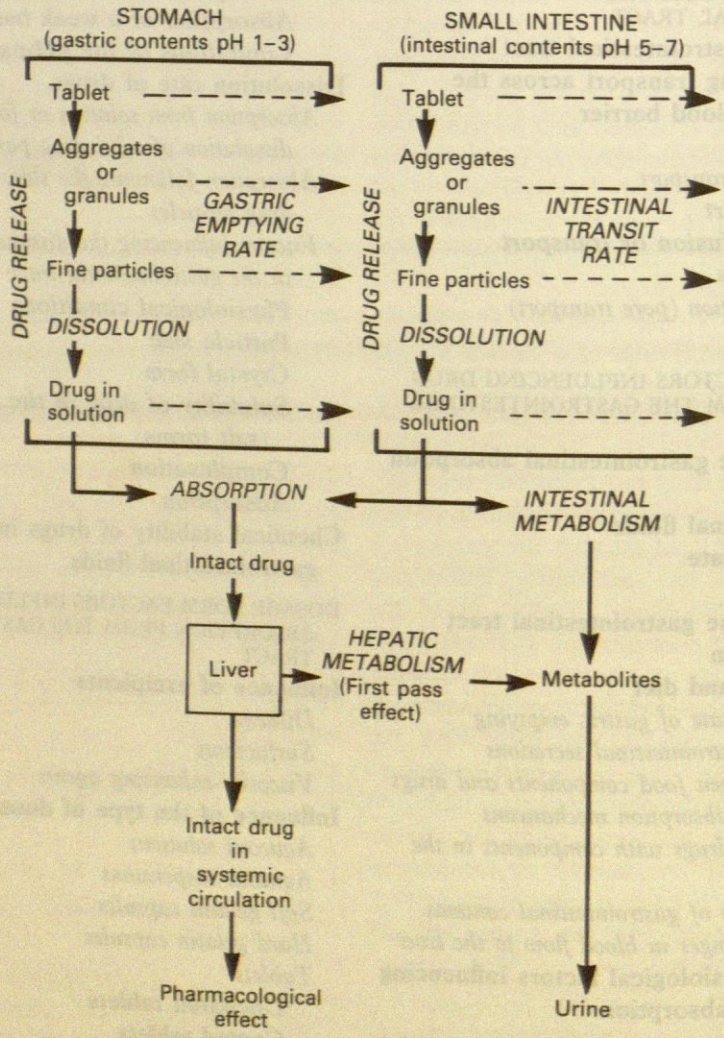

Fig. 9.1 Schematic illustration of steps involved in the appearance of intact drug in the systemic circulation following peroral administration of a tablet. Potential rate-limiting steps with respect to drug bioavailability are shown in italic capitals. (After Barr, 1972)

on a succession of rate (kinetic) processes. The slowest step in this series of rate processes, which is known as the rate-limiting step, will control the overall rate and extent of appearance of intact drug in the systemic circulation. The particular rate-limiting step may vary from drug to drug. Thus for a drug which exhibits a very poor aqueous solubility, the rate at which the drug dissolves in the gastrointestinal fluids is often the slowest step and therefore exhibits a rate-limiting effect on a drug bioavailability. In contrast, for a drug which has a high aqueous solubility, its dissolution rate will be rapid and the rate at which the drug crosses the gastrointestinal membrane may be the rate-limiting step. Other potential rate-limiting steps include the rate of release of the drug from the dosage form (especially important in the case of controlled released dosage forms), the rate at which the stomach empties the drug into the small intestine, the rate at which drug is metabolized by enzymes in the intestinal mucosal cells during its passage into the mesenteric blood vessels and the rate of metabolism of drug during its initial passage through the liver, i.e. the 'first pass' effect.

Structure of the gastrointestinal tract

The gastrointestinal tract consists of three major anatomical regions: the stomach, the small intestine and the large intestine (colon). The small intestine includes the duodenum, jejenum and ileum. As a drug descends through these regions of the gastrointestinal tract, it encounters different environments whth respect to pH, enzymes, electrolytes, fluidity and surface features, all of which can influence drug absorption (see later in this chapter).

The gastrointestinal tract is basically a hollow muscular tube composed of four concentric layers of tissue named from the innermost to the outermost as the mucosa (or mucous membrane), the submucosa, the muscularis externa and the serosa. These are shown diagrammatically in Fig. 9.2. Of these four layers, the mucosa is the most important with respect to the absorption of drugs

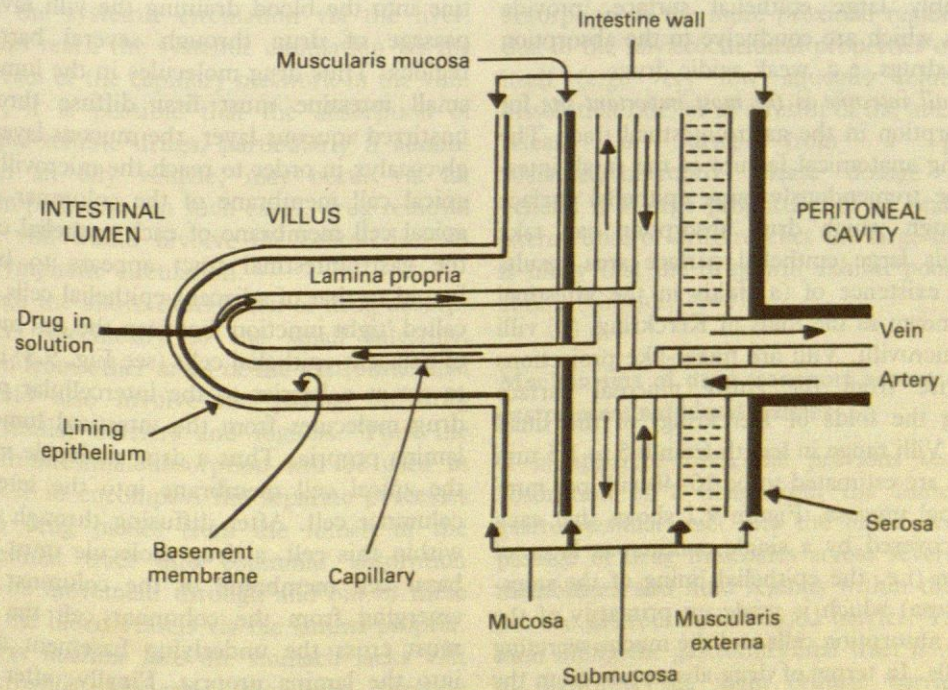

Fig. 9.2 Diagrammatic representation of the small intestine showing the absorption of a drug from the intestinal lumen into a blood capillary. (After Smith 1964)

from the lumen of the gastrointestinal tract. The mucosa contains the cellular membranes and regions through which a drug must pass in order to reach the blood (or lymph). Figure 9.2 shows that the mucosa, itself, consists of three layers: the lining epithelium, the lamina propria and the muscularis mucosa. The epithelium lining the lumen of the gastrointestinal tract comprises a single layer of columnar and some specialized secretory cells (e.g. mucus secreting goblet cells). Of these cells only the columnar cells are concerned with absorption. The layer underlying the epithelium is the lamina propria which contains connective tissue, blood and lymph vessels. The final layer comprising the mucosa is the muscularis mucosa which is a relatively thin layer of muscle fibres.

In *the stomach* the mucosa contains many folds which increase the total surface area over that afforded by a flat smooth lining. Although the stomach does not function primarily as an absorption organ, its excellent blood supply and the fact that a drug can potentially reside in the stomach for 30 minutes up to several hours in contact with a reasonably large epithelial surface, provide conditions which are conducive to the absorption of certain drugs, e.g. weak acidic drugs.

The *small intestine* is *the most important site* for drug absorption in the gastrointestinal tract. The outstanding anatomical feature of the small intestine is the tremendously large epithelial surface area through which drug absorption can take place. This large epithelial surface area results from the existence of (a) folds in the intestinal mucosa known as the folds of Kerckring, (b) villi and (c) microvilli. Villi are finger-like projections which arise from the entire mucosal surface (including the folds of Kerckring) of the small intestine. Villi range in length from 0.5 to 1.5 mm and there are estimated to be 10–40 villi per mm^2 of intestinal mucosa. Figure 9.2 shows that each villus is covered by a single continuous layer of epithelium (i.e. the epithelial lining of the intestinal mucosa) which is made up primarily of the columnar absorption cells and the mucus-secreting goblet cells. In terms of drug absorption from the small intestine the columnar cells are extremely important since it is the anatomical structure of the apical surface of each columnar cell (i.e. the cell surface facing the intestinal lumen) which further increases the epithelial surface area of the small intestine that is available for drug absorption. Figure 9.3 shows that the apical surface of each cell consists of numerous minute slender projections, approximately 1 μm long, known as microvilli. Microvilli appear to be microtubular projections of the apical cell membrane of each columnar cell. The microvilli (between 700 and 1000 per columnar cell), together with the villi and folds of Kerckring, are estimated to increase the surface area available for absorption by 600 times that which would be available if the inner surface of the small intestine was flat.

Intimately associated with the microvilli is a coating of fine filamentous material composed of mucopolysaccharides. This coating is known as the glycocalyx. In addition to the glycocalyx there are two further layers of material between the microvilli and the luminal contents of the small intestine, i.e. a layer of protective mucus secreted by the goblet cells and the so-called 'unstirred aqueous layer'. Figures 9.2 and 9.3 show that the absorption of a drug from the lumen of the intestine into the blood draining the villi involves the passage of drug through several barriers and regions. Thus drug molecules in the lumen of the small intestine must first diffuse through the unstirred aqueous layer, the mucous layer and the glycocalyx in order to reach the microvilli, i.e. the apical cell membrane of the columnar cell. The apical cell membrane of each epthelial cell lining the gastrointestinal tract appears to be tightly bound to that of adjacent epithelial cells. This so-called 'tight junction' between the cell membranes of adjacent epithelial cells (see Fig. 9.3) is thought to act as a barrier to the intercellular passage of drug molecules from the intestinal lumen to the lamina propria. Thus a drug molecule must cross the apical cell membrane into the interior of a columnar cell. After diffusing through the fluids within this cell, a drug molecule must cross the basal cell membrane of the columnar cell. On emerging from the columnar cell the molecule must cross the underlying basement membrane into the lamina propria. Finally, after diffusing through the tissue region of the lamina propria, drug molecules must cross the endothelium of one of the blood capillaries present in this region.

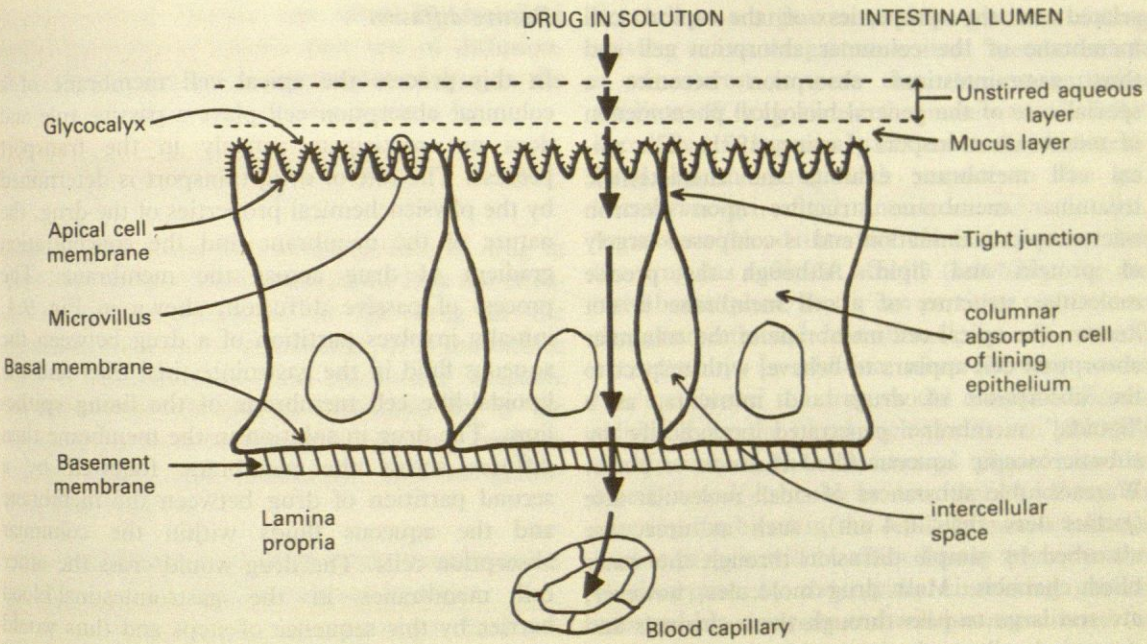

Fig. 9.3 Diagrammatic representation of intestinal columnar absorption cells in the lining epithelium showing a pathway of drug absorption from the intestinal lumen to a blood capillary lying in the lamina propria

Drug molecules would then be carried away in the blood to the systemic circulation via the liver. Most drugs reach the systemic circulation via the blood stream of the capillary metwork in the villi. However, it is possible that the absorption of highly lipid-soluble drugs, particularly if administered in an oily vehicle, may occur via fat absorption pathways. In such cases, drug removal from the villi would involve the central lacteals and the lymphatic circulation.

Although the above description of drug absorption refers specifically to the small intestine, absorption from other areas of the gastrointestinal tract would also involve the passage of drug through similar barriers and regions. Thus the term gastrointestinal absorption will be used in this chapter to encompass the separate processes by which drug passes from the lumen of the gastrointestinal tract into columnar absorption cells and its movement through and out of these cells into the blood vessels via the lamina propria.

The *large intestine* like the stomach lacks villi (and microvilli). However, the large intestine serves as a site for the absorption of drug which has not been completely absorbed in the more proximal regions of the gastrointestinal tract, i.e. the stomach and small intestine. Incomplete drug absorption in the more proximal regions may be due to the physicochemical properties of the drug itself (e.g. very low aqueous solubility and dissolution rate) or as a result of the intended slow release of drug from a prolonged/sustained/controlled release dosage form. In general if a large proportion of an orally administered dose of drug reaches the large intestine, it is likely that the drug will exhibit poor bioavailability (Gibaldi, 1984).

Mechanisms of drug transport across the gastrointestinal/blood barrier

It is apparent from the previous section that absorption of a drug from the lumen of the gastrointestinal tract into the blood involves the passage of drug molecules across several cellular membranes and fluid regions within the mucosa, i.e. the gastrointestinal/blood barrier. The epithelium lining the gastrointestinal tract is considered to constitute the main cellular barrier to the absorption of drugs from the gastrointestinal tract (Blanchard, 1975). The permeability characteristics of this epithelial layer appear to be directly