Call for South Initiatives 2014

Format for the project proposals

The format below is to be followed strictly when drafting a project proposal for a South Initiative. Project proposals exceeding 6 pages (without annexes) will not be accepted. All compulsory fields have to be completed within the format, not in annex.

GENERAL INFORMATION (max. 2 pages)

A. Country and region of the project (+ name of the research platform - only for Uganda)

Hanoi, Vietnam

B. Project title

Development and application of dry coating technology to prepare tablets containing berberin for colon targeting

C. Project duration (max. 2 years)

Two years

D. Expected date of project start (not before April 2014)

October 2014

E. Applying partner institute (leading partner)

- Name institute
  Department of Pharmaceutics, Hanoi University of Pharmacy, Vietnam
- Website of the institute
  www.hup.edu.vn
- Name of the local promoter
  Address, phone, fax and e-mail address of the local promoter

  Associate Prof. Dr. Pham Thi Minh Hue

  Department of Pharmaceutics

  Hanoi University of Pharmacy, 13-15 Le Thanh Tong, HoanKiem, VIETNAM

  Tel.: +84-38264990

  Mobile: +84-982152969

  e-mail: hueptm@hup.edu.vn
- Name of the authority of the institute (e.g. Rector, Vice-Chancellor)
  Associate Prof. Dr. Nguyen Dang Hoa
  Rector of Hanoi University of Pharmacy
  hoanguyendang@hup.edu.vn
- Private or public institute?
  Public university

F. Involvement of other partner institute(s) (supporting partner(s)) (if applicable)

G. Applying Flemish university/ university college

- University/ University college, faculty, department
  Department of Pharmaceutical and Pharmacological Sciences, Catholic University of Leuven
- Name of the promoter
  Address, phone, fax and e-mail address of the promoter
  Prof. Dr. G. Van den Mooter

  Drug Delivery and Disposition

  Department of Pharmaceutical and Pharmacological Sciences

  University of Leuven; Campus Gasthuisberg O+N2; Herestraat 49 b921

  3000 Leuven; BELGIUM

  Tel.: +32 16 330 304 fax: +32 16 330 305

  Mobile: +32 473 356 132

  e-mail: guy.vandenmooter@pharm.kuleuven.be

- Name of the copromoter (if applicable)
  Not applicable
  Address, phone, fax and e-mail address of the copromoter (if applicable)
- Name of the person who is responsible for the implementation of the project (if different from promoter or copromoter)
  Address, phone, fax and e-mail address of the person who is responsible for the execution of the project (if different from promoter or copromoter)
- Financial/ administrative project officer (if applicable)
  Address, phone, fax and e-mail address of the financial/ administrative project officer (if applicable)

H. Involvement of other Flemish universities/ university colleges (if applicable)

Not applicable

I. Total budget requested from VLIR-UOS (in € for the full duration of the project) (in principle max. € 75.000)

- Total indicative budget (indicative): € 74802
- Budget divided over the different budget lines
  A. Investment costs (max. 25% of the budget): € 17500
  B. Operational costs: € 19000
  C. Personnel costs (max. 25% of the budget): € 14500
  D. Scholarship costs: € 17000
  E.1. Coordination costs for Flemish institution (5% lump sum from A to D): € 3401
  E.2. Coordination costs for local partner institution(s) (5% lump sum from A to D): € 3401

J. Signature of the local promoter Signature of the Flemish promoter

DETAILED INFORMATION

1. DESCRIPTION OF THE PROJECT CONTEXT (max. 2 pages)

1.1. Background of the project

In Vietnam,colon inflammation is one of the most occuring diseases which cause many inconveniences for patients. Berberine, a plant alkaloid with a long history of medical use in Vietnam, has shown many advantages in the treatment of colon inflammation. However, this drug is mainly prepared in conventional tablets which requires a very high dose to obtain a local effect in colon. Consequently, development of berberin colon targeting tablets is a suitable solution to reduce the drug dose and increase the drug local effect. Among the ways to prepare colon delivery systems, coating technology for delaying drug release is a useful approach.

Application of film coating technology in the formulation of pharmaceutical dosage forms is popular. However, development of (organic) solvent-free coating methods is attracting the attention of scientists because of safety and environmental reasons. Dry coating technology is emerging as an effective way in overcoming the many disadvantages associated with traditional film coating; however, application of dry coating in colon drug targeting systems in Vietnam and Belgium is still in its infancy.

Therefore, the purpose of this project is to develop and apply dry coating technology for berberin colon targeting tablets to increase the residence time and drug concentration in the colon and increase the therapeutic effect. Based on the historical relationship between HUP and KU Leuven, we know about “Call for South Initiatives 2014”. Hopefully, through funding from “Call for South Initiatives 2014” for this project, we can make a modest contribution to development of health care system in Vietnam.

1.2. Presentation of the project partners

1.2.1. The leading partner institution (university/ university college; faculty/ department/ unit/ ...) (if applicable)

- Local project team (promoter and copromoter(s), research and administrative assistants, etc.)
  Promoter: Associate Prof. Dr. Pham Thi Minh Hue
  Copromoter: Dr. Nguyen Thach Tung
  Researcher: Nguyen Van Lam
- Major (project related) activities
  1. Review related papers and develop idea by Prof. Hue and Dr. Tung
  2. Preformulation study will be determined simultaneously by researchers in HUP and KU Leuven
  3. Preparation of colon-specific drug delivery tablets containing berberin by dry coating technique will be conducted in the Department of Pharmaceutics, Hanoi University of Pharmacy. The effect of coating components on the drug release pattern will be determined.
  4. Phase behavior of polymer-plasticizer coating will be done by Vietnamese researchers in the Department of Pharmaceutical and Pharmacological Sciences under the guidance of Prof. G. Van den Mooter.Experiments such as DSC, MDSC, PXRD, and FTIR will be conducted for this purpose.
  5. In-vivo studies in animal model including determination of drug concentration in blood plasma and lumen will be carried out with the collaboration of National Institute of Bioequivalence, Vietnam.
  6. Scientific papers will be written by Dr. Tung, and Mr. Lam and revised by Prof. Guy and Prof. Hue

- Capacities (strengths and weaknesses as they relate to the proposed project/ discipline)
  Strengths:
  +Experience in coating technique including: film coating, sustained release coating,
  +Eager for conducting innovative ideas.
  Weaknesses:
  +Not enough facilities and funding to conduct specialized experiments such as: AFM, NMR, Caco-2 cells experiments, non-invasive fluorescence imaging, and pharmacodynamic tests of oral drug delivery systems.
  +Limited knowledge in physical chemistry to explain in depth data of DSC, PXRD, FT-IR, NMR…
  +Limited experience in conducting and writing a high quality international paper
- Background promoter
  Experience in development of different drug delivery systems (DDS): solid dispersion, sustained release systems (pellet, tablet), orally disintegrating tablet, liposome.

  Principal investigator of one national project and 10 smaller projects (see CV)

  Author of many domestic papers and some international papers

1.2.2. The Flemish institution (university/ university college; faculty/ department/ unit/ ...)

- Project team (promoter and copromoter(s), lecturers, research and administrative assistants, etc.)
  Promoter: Prof. Dr. G. Van den Mooter

- Capacities and strategic interest in relation to the proposed project
  State of the art facilities (DSC, MTDSC, XRD, FTIR…) and experience to carry out experiments concerning phase behavior of polymer-drug coating, polymer-plasticizer, polymer-polymer of coating layer including:
  +Recognized as expert in thermal analysis (MDSC) and PXRD
  +Experience in studying molecular interactions between polymer, drug and plasticizer by FTIR, NMR
  +Experience in surface morphology studies of coating by SEM and AFM
- Background promoter
  Significant experience in solid dispersions, solid state analysis (DSC, MTDSC, XRD, FTIR), polymorphism, formulation and preformulation, micro emulsions. Prof. G. Van den Mooter has a background in development of colon drug delivery systems (biodegradable azopolymers)

  Author of more than 190 peer-reviewed papers, inventor on 7 patents

1.2.3. Other actor(s) involved (if applicable)

1.3. Link with the VLIR-UOS country strategy

If accepted, this project can make a contribution to Vietnamese development in terms of 4 aspects: human care, environment, technology innovation and international cooperation.
Human development:This project offers potential in reduction of colon inflammation rate which will improve health state of Vietnamese people. Besides, this project also creates favourable conditions to improve the quality of lecturers/researchers through joint research and co-organising training courses.
Environment: Dry coating process is considered as a “green” technology because of avoidance of organic solvents such as dichloromethane, acetone, methanol…which can cause serious problems for soil, air and water pollution and which are used in traditional film coating
Technology innovation: Besides avoidance of the usage of organic solvents, dry coating technology is also very economical and convenient. This technology does not require huge investment in terms of facilities, plant and human training. In Vietnam, this technology is completely new, and it has been

applied or studied before in universities or pharmaceutical companies. Successful development of the colon targeting tablets by dry coating will offer high potential in effectively delivering many kinds of drugs (not only berberin) to the colon: colitis, Crohn's disease, anti-cancer,etc.

International cooperation:Through this project, the two departments (Department of Pharmaceutics, HUP and Department of Pharmaceutical and Pharmacological Sciences, KU Leuven) will exchange professional research activities to strengthen collaboration for development of dry coating technology.

At higher levels, this project also opens realistic opportunities for cooperation of 2 universities (HUP and KULeuven) in pharmaceutical technology.

1.4. Link with other initiatives (complementarity/ synergy)

1.5. Beneficiaries

Scientists in HUP will make use of overwhelming source of berberin in Vietnam and primarily evaluate the therapeutic potential of this drug.

Dry coating technology has not been applied in Vietnam; therefore, this free-organic solvent technology offers potential benefit to the community instead of the traditional film coating technique.

Lecturers/ researchers in Department of pharmaceutics, HUP will have the opportunity to approach new manufacturing techniques and techniques necessary for the evaluation of solid state dosage forms.

Successful development of this project will help researchers in KU Leuven to develop various drug targeting systems to the colon for treatment ofcolitis, Crohn's disease, etc.

Published data of this project will also help other scientists to get insight into the effect of dry coating technique, and the phase behaviour of dry coating powders

Patients who are suffering from colon in ammation will get the opportunity to have access to a novel therapeutic solution.Accordingly, usage of berberin colon targeting tablets will reduce the rate of in ammatory bowel disease in Vietnam.

The two universities (HUP and KU Leuvein) will establish a framework for future collaboration projects in different fields: pharmacokinetics, biotechnology....

The results obtained can be transferred to pharmaceutical companies thus contributing to the development of Vietnamese pharmaceutical industry.

2. DESCRIPTION OF THE PROJECT (max. 1 page)

Problems: Dry coating technology can overcome many of the disadvantages associated with film coating in pharmaceutical coating (e.g., solvent exposure, solvent disposal, and residual solvent in the final product). However, application of dry coating for to colon targeting tablets in Vietnam faces some difficulties:

+There is no proper coating equipment for the dry coating process in Hanoi University of Pharmacy.

+In depth evaluation of coating properties including phase behavior of polymer-plasticizer is hardly conducted in HUP

+The effect of colon targeting tablets manufactured by dry coating needs to be carefully evaluated during *in-vivo* studies

Objectives:

+Develop a dry coating process for colon targeting tablets containing berberin

+Investigate phase behavior of polymer-plasticizer coating

+Determine the concentration in the plasma of berberin, and in the lumen of the gastrointestinal tract

Methods:

+Preparation:

a. Core tablets containing berberin will be prepared by wet granulation.

b.Coating of tablet: Colon targeting tablets are developed by dry coating technology.
+Evaluation:

a. In vitro drug release testing in media that mimic the gastrointestinal tract

b. Study of the phase behavior of the coatings (made up of polymer blendsand plasticizer). The effect of storage time, temperature and relative humidity will be determined as a stability indicating tool. For this purpose solid state analytical methodology will be applied (MDSC, PXRD, FTIR)

c.Study of the berberinconcentration in the plasma and in the lumen of the gastrointestinal tract

Content and predicted results

+Development of a dry coating process using pan coating equipment.

+The influence of coating components on drug release kinetics in vitro and in vivo will become available. Prediction of drug release will be possible.

+The interaction of coating components through phase behavior study will enable to predict stability and drug release

3. FEASIBILITY AND SUSTAINABILITY OR FOLLOW-UP TO BE GIVEN TO THE PROJECT (max. 1 page)

3.1. Describe and analyze in sufficient detail the pre-conditions and factors external to the project that may influence the accomplishment of the specific objectives and results (feasibility)

+ Facilities: Even HUP has a sugar coating machine; however, the modification of this machine for dry coating caused many difficulties for manufacturing purposes; especially coating uniformity and yield. Therefore, if being properly invested in terms of dry coating machine and coating evaluation machine, researchers at HUP can have an exact observation about effect and properties of dry coating technique. With the fund from this project, HUP can purchase a suitable dry coating machine. Given coating evaluation tests such as in vitro release testing, DSC, MTDSC, XRD, FTIR; Prof. Dr. G. Van den Mooter in KU Leuven (Belgium) can support HUP through this collaboration project.

+Experiences: Dry coating process for colon targeting tablet is a novel technology in Vietnam. Therefore, during the first period of the project Vietnamese research team will face with many difficulties to develop a manufacturing process. Besides, solid state analysis of coating components by specific techniques like DSC, MDSC and FTIR also has not been carried out properly in HUP. This fact is also barrier for Vietnamese scientists to get insight into the mechanism of coating formation. Fortunately, Prof G. Van den Mooter in KU Leuven has a strong background in solid state analysis necessary to investigate the phase behavior of polymer-plasticizer coating. Moreover, he has a lot of experience in developing colon specific drug delivery systems based on biodegradable polymers.

+Other: Dry coating using pan coating equipment is a new method in Vietnam; therefore, potential hurdles will show up during the research period. Participants from Vietnam do not have any experience in conducting a collaborative project; especially working in a multi-disciplinary environment. Therefore, project progress may be slower than expectation. However, Prof. Van den Mooter has experience in collaboration with foreign countries as he was one of the project leaders (pharmaceutical part) of a project with the university “Marta Abreu" de Las Villas in Santa Clara, Cuba.

Both HUP and KU Leuven are eager to develop this bilateral project, which will pave the way for future collaboration projects. Both universities always create all favorable conditions for participants to develop this project.

3.2. Describe the opportunities and challenges regarding the possibility of the benefits of the project to be sustained after the VLIR-UOS-funding (sustainability).

Opportunities:

+Research: After finishing this project, HUP will use the facilities of this project to develop different delivery systems to the colon (e.g. anti-cancer drugs, anti-inflammatory drugs to treat colitis, Crohn's disease). Besides, obtained skills from this project will be applied to other projects such as: project management, data analysis, writing papers.

+Collaboration: This project also opens up opportunities for collaboration between HUP and KU Leuven in different fields such as: pharmacokinetics, organic synthesis…

+The experience acquired during this project will help HUP tocontinue to obtain the necessary funding from other collaboration projects which will help HUP to gradually become equipped with modern research facilities and techniques.

Challenges:

Beside advantages, development of dry coating technology in Vietnam may face withsome difficulties:

Materials: Even berberin is massively available in Vietnam; however, the source of this material is unstable and diversified. Consequently, results of the experiments have to be carefully controlled to avoid unpredicted errors.

Technology: Dry coating technology is a novel method; therefore, its scaling in industrial level is obviously not easy. Problems such as coating yield, coating uniformity, or labor cost have to be highly monitored when conducting this project in research or pilot scale.

4. ANNEXES TO BE ADDED

4.1. Logical Framework Matrix (LFM) and Indicative Operational Plan (IOP) (cfr. format)

4.2. Budget proposal (cfr. format)

4.3. Written confirmation of copromotership by the local and Flemish copromoter(s) (if applicable)

4.4. Brief CV (max. 2 pages) of the local and Flemish (co)promoters

4.5. Declaration for promoters or co-promoters who are not only affiliated to a Flemish university or university college but also to an institution within which DGD funding is or can be provided on a project or structural basis (if applicable)

4.6. Checklist ICOS

4.7. General overview of the proposals per Flemish association