รายงานวิจัยฉบับสมบูรณ์

โครงการ **การพัฒนายาเม็ดลอยตัวไรโบฟลาวินที่ประกอบด้วยผงโฟมความหนาแน่นต่ำเตรียมโดยเทคนิคการหลอมด้วยความร้อนและอัดรีด (MRG6080046)**

โดย **ผู้ช่วยศาสตราจารย์ ดร.วรวุฒิ เกรียงไกร**

ตุลาคม 2562

สัญญาเลขที่ MRG6080046

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คณะเภสัชศาสตร์ มหาวิทยาลัยนเรศวร

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัยและต้นสังกัด

บทคัดย่อ

รหัสโครงการ: MRG6080046

ชื่อโครงการ: การพัฒนายาเม็ดลอยตัวไรโบฟลาวินที่ประกอบด้วยผงโฟมความหนาแน่นต่ำเตรียมโดยเทคนิคการหลอมด้วยความร้อนและอัดรีด

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ระยะเวลาโครงการ: 2 ปี (4 เมษายน 2560 - 3 มีนาคม 2562)

การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อศึกษาและเปรียบเทียบคุณสมบัติทางเคมีกายภาพของยาเม็ดลอยตัวที่เตรียมโดยวิธีการหลอมด้วยความร้อนและอัดรีด หรือการตอกโดยตรง เพื่ออธิบายความสามารถในการลอยตัวและอัตราการปลดปล่อยตัวยา ยาเม็ดลอยตัวไรโบฟลาวิน 5'-ฟอสเฟต (R5P-FTs) ได้ถูกเตรียมขึ้นอย่างสมบูรณ์โดยกระบวนการผลิตทั้งสองวิธี พอลิเอทิลีนออกไซด์ (PEO) ถูกใช้เป็นสารก่อเมทริกซ์พอลิเมอร์ ผงโฟมพอลิโพรไพลีนถูกนำมาใช้เพื่อลดความหนาแน่นของระบบ ผลการทดลองแสดงให้เห็นว่าการเพิ่มปริมาณของผงโฟมจากร้อยละ 20 ถึง 50 โดยน้ำหนัก ทำให้ความหนาแน่นของเม็ดยาลดลงอย่างเห็นได้ชัดทันที ยาเม็ดลอยตัวที่เตรียมโดยวิธีการหลอมด้วยความร้อนและอัดรีดสดงการลดเวลาในการลอยตัวจนมีค่าเท่ากับศูนย์จากการใช้ร้อยละ 50 ของผงโฟมในตำรับ กล่าวคือ ยาเม็ดสามารถลอยตัวได้ทันทีเมื่อสัมผัสกับตัวกลาง ส่วนยาเม็ดลอยตัวที่เตรียมโดยวิธีการตอกโดยตรงปริมาณร้อยละ 40 ของผงโฟมเพื่อทำให้เม็ดยาลอยในทันที ยาเม็ดลอยตัวมีระยะเวลาลอยตัวนานกว่า 8 ชั่วโมง ยาเม็ดลอยตัวที่เตรียมโดยวิธีการตอกโดยตรงมีความหนาแน่นของเม็ดยาต่ำกว่าการเตรียมโดยวิธีหลอมด้วยความร้อนและอัดรีด ผงโฟมในยาเม็ดเมทริกซ์ทำให้โครงสร้างมีความพรุนเพิ่มขึ้นและความหนาแน่นของยาเม็ดลอยตัวลดลง การเพิ่มปริมาณของสารที่ไม่ละลายในกระบวนการหลอมด้วยความร้อนและอัดรีดทำให้ความดันหลอมละลายและความแข็งของเม็ดยาเพิ่มขึ้นอย่างมีนัยสำคัญ อัตราการปลดปล่อยตัวยาไรโบฟลาวินของยาเม็ดลอยตัวที่เตรียมโดยวิธีหลอมด้วยความร้อนและอัดรีดสูงกว่าอัตราการปลดปล่อยตัวยาจากยาเม็ดลอยตัวที่เตรียมโดยวิธีการตอกโดยตรงอย่างชัดเจน การใส่และเพิ่มขึ้นของผงโฟมในตำรับทำให้การปลดปล่อยตัวยาไรโบฟลาวินช้าลงเนื่องจากความไม่ชอบน้ำของผงโฟม เทคนิคราแมนอิมเมจิ้งถูกใช้เพื่อระบุสถานะของไรโบฟลาวินในยาเม็ดลอยตัว ยาเม็ดลอยตัวที่เตรียมโดยวิธีหลอมด้วยความร้อนและอัดรีดมีการกระจายไรโบฟลาวินอยู่ในสารก่อเมทริกซ์พอลิเมอร์

คำหลัก : วิธีการหลอมด้วยความร้อนและอัดรีด การตอกโดยตรง ยาเม็ดลอยตัว ไรโบฟลาวิน เทคนิคราแมนอิมเมจิ้ง

Abstract

Project Code: MRG6080046

Project Title: Development of riboflavin floating tablet containing foam powder prepared by hot-melt extrusion

Investigator: Worawut Kriangkrai, PhD

E-mail Address : wg.kriangkrai@gmail.com

Project Period: 2 years (4 April 2017 – 3 March 2019)

The aim of the present study was to determine and compare the physicochemical properties of floating tablets prepared by either hot-melt extrusion (HME) or direct compression (DC) to explain the floating ability and drug release rate. The riboflavin-5-phosphate floating tablets (R5P-FTs) was successfully prepared by the two techniques. Polyethylene oxide (PEO) was used as a matrix-forming polymer. Polypropylene foam powder was used to lower the density of the system. The result demonstrated that increasing the amount of foam powder from 20%-50% w/w resulted in an immediately noticeable reduction in the density of the tablet. The tablet prepared by HME exhibited decreasing the time-to-float to zero, meaning immediate buoyancy, at 50% w/w of foam powder. The tablet prepared by DC used 40% w/w of foam powder to achieve the floatation. The floating tablets had floating duration longer than 8 h. The tablets prepared by a DC method demonstrate the tablet density lower than those prepared by the HME method. The foam powder in the matrix tablet caused the porosity of the structure to increase, and the density of the tablet to decrease. Adding a higher amount of insoluble substance into HME process, the foam powder, led to a significant increase in melting pressure and the hardness of the tablet. The release rate of riboflavin from HME floating tablets was clearly higher than those from DC floating tablets. Incorporation and increasing amount of foam powder retarded the riboflavin release rate due to hydrophobicity of the foam powder. Raman imaging technique has been successfully used to determine the state of R5P in the floating tablets. The HME tablets exhibited R5P distributed in a matrix-forming polymer.

Keywords : hot-melt extrusion, direct compression, floating tablet, riboflavin, raman imaging technique

Executive Summary

(เนื้อหางานวิจัย)

ความสำคัญ / ความเป็นมา

Floating tablets, gastro-retentive delivery systems, had several advantages, not only extending the duration of drug release but also prolonging gastric retention time. These are currently utilized to overcome the limitation of some group of APIs including (i) APIs which have an absorption window in the upper small intestine, (ii) poorly soluble or unstable APIs in the intestinal fluid, and (iii) the APIs that act locally in the proximal part of the gastrointestinal tract.

Direct compression (DC) is the simplest methods of production of a pharmaceutical tablet. The prime advantage of DC is economic since it requires fewer unit operations. This method also is suitable for moisture and heat sensitive APIs. However, the poorly soluble API has been a major obstacle for the development of more efficient drug delivery methods. Dissolution is the rate limiting step in absorption in the case of tablets. To overcome this problem, Hot-melt extrusion (HME) is currently used to prepare solid dispersions for the improvement of solubility and dissolution rates of poorly soluble APIs. The solid dispersion can inhibit the formation and growth of the drug crystal nucleus through the hydrogen bond and complexation between the carrier molecule and the drug. Additionally, HME is a continuous manufacturing process, solvent-free, robust, quick and cost-effective for the production of a wide variety of pharmaceutical dosage forms.

The objectives of this study were to determine the physicochemical properties of riboflavin floating tablets (R5P-FTs) prepared by either DC or HME to explain the drug release mechanism. Polyethylene oxide (PEO) was a drug carrier due to its broad processing window for HME and PEO has been used in solubility enhancement. Polypropylene foam powder (Accurel® MP) were used to produce the tablets to provide the floating ability for the system. The influence of variable formulation on floating ability, drug release rate, and the physicochemical properties of the tablets was studied.

วัตถุประสงค์ของโครงการ

The aim of the present study was to determine and compare the physicochemical properties of floating tablets prepared by either HME or DC to explain the floating ability and drug release rate.

ผลการวิจัย (สั้น ๆ ที่บ่งชี้ประเด็นข้อค้นพบ กระบวนการ ผลผลิต และการเรียนรู้)

Floating tablets were successfully prepared by hot-melt extrusion (HME) and direct compression (DC). The tablets contained R5P as a poorly water soluble drug, PEO as a matrix-forming polymer and polypropylene foam powder as low-density substance. The foam powder in the matrix tablet caused the porosity of the structure to increase, and the density of the tablet to decrease. To achieve the immediate floatation, tablet prepared by HME used 50% w/w of foam powder and tablet prepared by DC used 40% w/w of foam powder. The tablets prepared by a DC demonstrate the tablet density lower than those prepared by the HME. The floating tablets had floating duration longer than 8 h.

Adding a higher amount of foam powder into HME process, led to a significant increase in melting pressure and the hardness of the tablet. Raman imaging technique has been successfully used to determine the state of R5P in the floating tablets. The results revealed that R5P could homogenously dispersed in to the PEO matrix for the floating tablets prepared by HME. These caused HME tablet released R5P faster than DC tablet. Incorporation and increasing amount of foam powder retarded the riboflavin release rate due to hydrophobicity of the foam powder. During the dissolution, HME tablet showed higher medium absorption and swelling, while the tablet prepared by DC demonstrated a lower swelling. These results were confirmed by the water content and erosion studies. Increasing particle size of FP substantially increased R5P release from tablets prepared by both DC and HME. This could be attributed to the relatively high porosity of tablets containing bigger sized FP particles as compared to the more compact of the tablets containing smaller sized FP particles. Different molecular weights of PEO slightly affected on R5P release from the DC tablets. In contrast, in the case of HME tablets, R5P release strongly depended on the grades of PEO. The R5P release noticeably increased with decreasing molecular weight of PEO. The DC tablets provided a constant swelling behavior for longer than 8 h, whereas higher tablets erosion was found in HME tablets. In order to investigate the importance of drug solubility, different drugs were selected to prepare the floating tablets. These were diltiazem, verapamil, propranolol and R5P (solubility in 0.1 N HCl: 588, 392, 220 and 5.9 mg/ml). The DC method clearly showed an increasing drug release when increased the solubility of the drugs. The HME method exhibited rapid drug release for the tablets containing diltiazem, verapamil and propranolol. In contrast, the release of the R5P, the low-solubility drug, could be effectively and simultaneously controlled by the erosion of PEO. These findings indicate that drug is not only predominantly released by erosion of the matrix polymer, but also by diffusion through the water-filled polymer.

Output จากโครงการวิจัยที่ได้รับทุนจาก สกว.

1. ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ (ระบุชื่อผู้แต่ง ชื่อเรื่อง ชื่อวารสาร ปี เล่มที่ เลขที่ และหน้า) หรือผลงานตามที่คาดไว้ในสัญญาโครงการ

☑ **ยังไม่มีการนำไปใช้** (โปรดกรอกในกรอบถัดไป)

Output จากโครงการวิจัยที่ได้รับทุนจาก สกว.

2. การนำผลงานวิจัยไปใช้ประโยชน์

☑ ยังไม่มีการนำไปใช้

ผลงานวิจัยมีศักยภาพในการนำไปใช้ประโยชน์ เชิงวิชาการ (มีการพัฒนาการเรียนการสอน/สร้างนักวิจัยใหม่)

ข้อเสนอแนะเพื่อให้ผลงานถูกนำไปใช้ประโยชน์

- นำองค์ความรู้ที่ได้จากงานวิจัยที่ ตีพิมพ์ในวารสารระดับนานาชาติ เป็นประโยชน์ทางวิชาการ นำไปสู่กระบวนการเรียนการสอน เป็นต้นแบบของการศึกษา
- รศ.ดร.สาธิต พุทธิพิพัฒน์ขจร ภาควิชาเภสัชอุตสาหกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยมหิดล – ร่วมกันนำผลงานวิจัยไปศึกษาต่อยอด
- ศาสตราจารย์ ดร.พรศักดิ์ ศรีอมรศักดิ์ คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร – ร่วมกันนำผลงานวิจัยไปศึกษาต่อยอด
- Professor Dr. Jürgen Siepmann, Univ. Lille, Inserm, CHU Lille, U1008 - Controlled Drug Delivery Systems and Biomaterials, F-59000, Lille, France – ร่วมกันนำผลงานวิจัยไปศึกษาต่อยอด

Output จากโครงการวิจัยที่ได้รับทุนจาก สกว.

3. อื่น ๆ (เช่น ผลงานตีพิมพ์ในวารสารวิชาการในประเทศ การเสนอผลงานในที่ประชุมวิชาการ หนังสือ การจดสิทธิบัตร)

ผลงานวิจัยที่นำเสนอในที่ประชุมวิชาการ (Proceedings)

- **Kriangkrai W**, Puttipipatkhachorn S, Sriamornsak P, Siepmann F, Siepmann J, Sungthongjeen S. Preparation and comparison of floating tablets manufactured by hot-melt extrusion and direct compression. In: Shuwisitkul D, editors. Pharmaceutical Sciences and Technology 2018; 2018 Jan 24-25; Bangkok, Thailand: Thai Industrial Pharmacist Association, Society of Pharmaceutical Education & Research, Silpakorn University; 2018 Jan. p. 109-12.

การนำเสนอในงานประชุมวิชาการระดับนานาชาติ

- การนำเสนอผลงาน (โปสเตอร์) “Preparation and comparison of floating tablets manufactured by hot-melt extrusion and direct compression” ใน งานประชุมวิชาการ International Conference on Pharmaceutical Sciences and Technology 2018 (PST 2018); 2018 Jan 24-25; at Ambassador Bangkok Hotel, Bangkok, Thailand
- การนำเสนอผลงาน (โปสเตอร์) “Physicochemical properties and drug release from floating tablets manufactured by hot-melt extrusion and direct compression” ใน งานประชุมวิชาการ สำนักงานกองทุนสนับสนุนงานวิจัย (สกว.): นักวิจัยใหม่ พบ เมธีวิจัยอาวุโส (TOAC2019) วันที่ 9-11 มกราคม 2562 ณ โรงแรมเดอะรีเจ้นท์ ชะอำ บีช รีสอร์ท จังหวัดเพชรบุรี ประเทศไทย

ภาคผนวก

ผลงานวิจัยที่นำเสนอในที่ประชุมวิชาการ (Proceedings)

- **Kriangkrai W**, Puttipipatkhachorn S, Sriamornsak P, Siepmann F, Siepmann J, Sungthongjeen S. Preparation and comparison of floating tablets manufactured by hot-melt extrusion and direct compression. In: Shuwisitkul D, editors. Pharmaceutical Sciences and Technology 2018; 2018 Jan 24-25; Bangkok, Thailand: Thai Industrial Pharmacist Association, Society of Pharmaceutical Education & Research, Silpakorn University; 2018 Jan. p. 109-12.

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- การนำเสนอผลงาน (โปสเตอร์) “Preparation and comparison of floating tablets manufactured by hot-melt extrusion and direct compression” ใน งานประชุมวิชาการ International Conference on Pharmaceutical Sciences and Technology 2018 (PST 2018); 2018 Jan 24-25; at Ambassador Bangkok Hotel, Bangkok, Thailand
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A comparative evaluation of hot-melt extrusion and direct compression methods for formulation of riboflavin floating tablets

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Abstract

The aim of the present study was to determine and compare the physicochemical properties of floating tablets prepared by either hot-melt extrusion (HME) or direct compression (DC) to explain the floating ability and drug release rate. The riboflavin-5-phosphate floating tablets (R5P-FTs) was successfully prepared by the two techniques. Polyethylene oxide (PEO) was used as a matrix-forming polymer. Polypropylene foam powder was used to lower the density of the system. The result demonstrated that increasing the amount of FP from 20%-50% w/w resulted in an immediately noticeable reduction in the density of the tablet. The tablet prepared by HME exhibited decreasing the time-to-float to zero, meaning immediate buoyancy, at 50% w/w of FP. The tablet prepared by DC used 40% w/w of FP to achieve the floatation. The floating tablets had floating duration longer than 8 h. The tablets prepared by a DC method demonstrate the tablet density lower than those prepared by the HME method. The FP in the matrix tablet caused the porosity of the structure to increase, and the density of the tablet to decrease. Adding a higher amount of insoluble substance into HME process, the FP, led to a significant increase in melting pressure and the hardness of the tablet. The release rate of riboflavin from HME floating tablets was clearly higher than those from DC floating tablets. Incorporation and increasing amount of FP retarded the riboflavin release rate due to hydrophobicity of the FP. Raman imaging technique has been successfully used to determine the state of R5P in the floating tablets. The HME tablets exhibited R5P distributed in a matrix-forming polymer.

1 Introduction

Floating tablets, gastro-retentive delivery systems, had several advantages, not only extending the duration of drug release but also prolonging gastric retention time. These are

currently utilized to overcome the limitation of some group of APIs including (i) APIs which have an absorption window in the upper small intestine, (ii) poorly soluble or unstable APIs in the intestinal fluid, and (iii) the APIs that act locally in the proximal part of the gastrointestinal tract [1-3].

Direct compression (DC) is the simplest methods of production of a pharmaceutical tablet. The prime advantage of DC is economic since it requires fewer unit operations. This method also is suitable for moisture and heat sensitive APIs. However, the poorly soluble API has been a major obstacle for the development of more efficient drug delivery methods. Dissolution is the rate limiting step in absorption in the case of tablets. To overcome this problem, Hot-melt extrusion (HME) is currently used to prepare solid dispersions for the improvement of solubility and dissolution rates of poorly soluble APIs [4-7]. The solid dispersion can inhibit the formation and growth of the drug crystal nucleus through the hydrogen bond and complexation between the carrier molecule and the drug. Additionally, HME is a continuous manufacturing process, solvent-free, robust, quick and cost-effective for the production of a wide variety of pharmaceutical dosage forms.

The objectives of this study were to determine the physicochemical properties of riboflavin floating tablets (R5P-FTs) prepared by either DC or HME to explain the drug release mechanism. Polyethylene oxide (PEO) was a drug carrier due to its broad processing window for HME and PEO has been used in solubility enhancement. Polypropylene foam powder (Accurel® MP) were used to produce the tablets to provide the floating ability for the system. The influence of variable formulation on floating ability, drug release rate, and the physicochemical properties of the tablets was studied.

2 Materials and methods

2.1 Materials

The following chemicals were obtained from commercial suppliers and used as received: riboflavin-5-phosphate (DSM, Basel, Switzerland); diltiazem hydrochloride (diltiazem HCl; VWR, Fontenay-sous-Bois, France); verapamil hydrochloride (verapamil HCl, Knoll AG, Ludwigshafen, Germany); propranolol hydrochloride (propranolol HCl, Salfic-Alcan, Puteaux, France); polypropylene foam powder (Accurel® MP, Membrana GmbH, Obernburg, Germany): Accurel® MP1002 (particle size: < 200 µm), Accurel® MP1004 (particle size: 200-400 µm) and Accurel® MP1x1 (particle size: 1000 µm); polyethylene oxide (PEO; Sentry Polyox® WSR LEO NF, Dow Chemicals, Midland, USA, provided by Colorcon, Dartford, UK): Polyox® WSR N-80 (200 kDa), Polyox® WSR N-60K (2000 kDa), and Polyox® WSR-303 (7000 kDa); polyvinyl acetate/polyvinylpyrrolidone (Kollidon® SR, BASF, Ludwigshafen Minden, Germany)

Abbreviations Used: riboflavin-5-phosphate (flavin mononucleotide) will be referred to as R5P, Accurel® MP1002, MP1004 and MP1x1 will be referred to as FP200, FP400 and FP1000, respectively.

2.2 Preparation of the riboflavin floating tablets

The floating tablets were prepared with 10% drug loading (riboflavin-5-phosphate). The FP was used as the low-density agent. PEO was a drug carrier due to its broad processing window for HME and PEO has been used in solubility enhancement. Dry powders were mixed in a Turbula T2A Turbula® Shaker-Mixer (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland) at 98 rpm for 10 min until homogeneously mixed. The blends were prepared with the two comparative methods; HME and DC methods. The influence of

variable formulation on floating ability, drug release rate, and the physicochemical properties of the tablets was studied.

2.2.1 Hot-melt extrusion method

The blend powders (batch size, 250 g) were then fed into a twinscrew extruder (NANO 16 from Leistritz, Nuremberg, Germany), which was equipped with a co-rotating twin screw (diameter = 16 mm, 4 heating zones, kneading elements in zones 1 and 2, diameter of the die orifice = 4 mm). The process temperatures were applied to the 4 heating zones of the barrel: 90°C -95°C -97°C -100°C (zone 1 - zone 2 - zone 3 - die). The rotational screw speed was kept at 30 rpm and the feeding rate was fixed at 3 cm^3/min. The extrudates were left to cool down at room temperature and manually cut into tablets (4 mm in diameter and 5 mm thick).

2.2.2 Direct compression method

DC floating tablets were manufactured on a single punch press machine (Korsch EKO/DMS, Berlin, Germany) with flat punches (diameter 5.0 mm).

2.3 Evaluation of floating tablet

2.3.1 Appearance of floating tablets

Macroscopic pictures of the surface and cross-section morphology were taken using an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan) equipped with an Axiocam ICc1 camera (Axiovision software; Carl Zeiss Micro Imaging, Jena, Germany).

2.3.2 Physical properties of floating tablets

The floating tablets were evaluated for weight variation, thickness, diameter, hardness and density. The thickness and diameter of the tablets were measured with a thickness tester (Micrometer Caliper, Model 7301 Series 7, Mitutoyo, Kawasaki, Japan), and the hardness measured with a texture analyzer (TA.XT.plus, Stable Micro Systems, Godalming, UK). The weight of the tablets was measured using an analytical balance. The apparent density was calculated from Equation 1 as follows:

$$\rho_a = \frac{W}{\pi(\frac{d}{2})^2 h} \qquad (1)$$

where ρ_a is the apparent density of the tablets, W is the tablet weight, π is the circular constant, d is the tablet diameter and h is the tablet height.

The porosity (ε) of the tablet was calculated using Equation 2:

$$Porosity\ (\varepsilon) = (1 - \rho_a / \rho_t) \times 100 \qquad (2)$$

The true volume of the tablet was calculated by determining the volume of helium displaced by the tablet during the test using a pycnometer (Pycnometer 1330, Micromeretics, Nercross, Georgia, USA). The true density (ρ_t) of the tablet was then calculated by dividing the weight of the tablet by the true volume. All calculations were performed in triplicate. The apparent density (ρ_a) of the tablet was directly calculated from the mass and volume of the tablet.

2.3.3 Scanning electron microscopy (SEM)

The tablets were fixed on a double-sided adhesive carbon ribbon positioned on a stub and then coated with a fine carbon layer. The surface and cross-section morphology of the

tablets was studied using an Hitachi S-4000 scanning electron microscope (Hitachi High-Technologies Europe, Krefeld, Germany).

2.3.4 Raman Mapping

Raman investigations were carried out using a Renishaw InVia Raman spectrometer (Renishaw plc, Wottonunder-Edge, Gloucestershire, UK), composed of a single-grating spectrograph coupled with an optical Leica microscope (Leica microsyst`emes, SAS, Nanterre, France). The 514.5-nm line of a ModuLaser (Modu-Laser, Centerville, UT) argon laser was used for excitation. Focusing the laser beam via a ×80 long-working distance objective, a test area of about 6,400 μm^2 was systematically analyzed. The spectra were collected in the 240–660 cm^{-1} spectral range. The spectrometer was controlled by PC with instrument-control software

2.3.5 Floating properties

Time-to-float is the time period starting at the immersion of the tablet until it is floating buoyantly on the surface of the acidic medium. Floating duration time is the duration of time that the tablet continues to float on the surface of the medium before sinking. The time-to-float and floating duration time were measured using the USP dissolution apparatus II (Sotax AT7; Aesch, Switzerland) (900 mL of 0.1 N HCl, 37.0 ± 0.5°C, 50 rpm). Each test was carried in triplicate.

2.3.6 Drug release studies

Our drug release studies were performed using 900 mL of 0.1 N HCl as the dissolution medium in USP dissolution apparatus II at 37 ± 0.5°C and 50 rpm. At predetermined time points, 3 mL samples were withdrawn and replaced with fresh medium to

compensate for loss due to sampling. The R5P content was determined by UV/visible spectrophotometer (UV-1800, Shimadzu, Kyoto, Japan) at a wavelength of 267 nm. At least three replicates were carried out for each formulation.

2.3.7 Water content and erosion studies

The Water content of the tablets upon exposure to the medium was studied under the same experimental conditions as for the drug release studies just described. At predetermined time points the tablets with the pre-weighed (W_0) mesh were withdrawn from the acidic medium and excess test liquid was gently removed with absorbent tissue (Goma-Camps, La Riba, Spain). The samples were weighed (W_1) and dried to constant weight on glass slides in an oven at 60°C (W_2). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. The water content (%), erosion (%) and remaining mass (%) were calculated by the following formulae, derived from the previous studies [8, 9].

$$\% \text{ water content} = (W_1 - W_2) / W_1 \times 100 \quad (4)$$

$$\% \text{ erosion} = [(W_0 - W_2) / W_0] \times 100 \quad (5)$$

$$\% \text{ remaining} = 1 - \% \text{ erosion} \quad (6)$$

3 Results and discussion

The tablets consisted of R5P, FP, and PEO. .R5P was the model drug in this study because it's poorly soluble and unstable in the basic condition [10, 11]. Additionally, R5P is highly absorbed at the proximal part of gastrointestinal tract [12, 13]. The FP that was used to lower the density of the tablet is a polypropylene powder (Accurel® MP) with a highly porous structure normally used as a drug carrier or low-density substance [14-20]. PEO was a drug carrier due to its broad processing window for HME and PEO has been used in solubility enhancement. Figures 1 shows macroscopic pictures of the floating tablets prepared by the two methods. The tablets were an orange color due to the natural color of the R5P.

3.1 Physical and floating properties of the floating tablets

The effect on physical and floating properties of the floating tablets of the various formulation variables was investigated and is summarized in Table.1. Increasing the amount of FP from 20%-50% w/w resulted in an immediately noticeable reduction in the density of the tablet. The DC tablets demonstrated the tablet density lower than those prepared by HME because the structure components of HME tablet was changed by high temperature and high pressure. PEO was melted and homogeneously mixed in HME while PEO powder was packed with compression in case of DC tablet (Fig 2). and the porosity of the structure to increase. The FP in the matrix caused the density of the tablet to decrease. The increasing amount of FP in DC method exhibited the decreasing the hardness of the tablet due the rising of porosity. However, adding a higher amount of insoluble substance into the HME, the FP, led to a significant increase in melting pressure and the hardness of the tablet. These results are in good agreement with earlier findings by Maggi, et al. [21] who demonstrated that extrudates made of pure polymer were harder than those containing the drug and other excipients, while maintaining slightly higher porosity. In contrast, addition and increasing amounts of FP led to increasing porosity and decreasing density of the tablet. These results were obtained upon increasing of foam particle size. The obstruction of HME was observed in the biggest size of foam.

The DC tablet started to float at 20% w/w of FP while the HME tablet required 40% w/w of FP to get buoyancy. The increasing amount of FP from 20%-50% w/w led to decreasing the time-to-float to zero, meaning immediate buoyancy, at 50% w/w, and floating duration for up to 8 h. The good floating properties were in good agreement with the result obtained in physical properties.

3.2 Raman Mapping

Raman spectroscopy is a useful tool for investigation of drug-polymer stage on pharmaceutical product. Floating tablets prepared by DC and HME were compared (Fig. 3). in the floating tablet. Under optical image, the R5P was observed as yellowish area due to its' color. However, the area of PEO and FP could not identify. Raman studies in the fingerprint region can be used to investigate the area of each component. The area of R5P, PEO and FP are present in green, red and blue, respectively. DC tablet exhibited the areas of each component separately. This result was in good agreement with the SEM. Interestingly, HME tablet exhibited the same areas between R5P and PEO. This suggested that R5P could homogenously dispersed in to the PEO matrix.

3.3 The influence of amount of foam powder on drug release

Our observations indicate that the amount of FP not only influences the time-to-float of the tablets, but also retards the drug release. In the case of floating tablets prepared by DC, incorporation of FP into the tablets significantly retarded R5P release as presented in Fig 4. The result revealed that R5P release from tablets without FP was rapid with essentially complete release approximate at 3 h due to complete erosion of tablets. Furthermore, an increasing level of FP also reduced R5P release. This was due to R5P release of floating tablet being related to dissolution medium permeability into tablet. The decrease of R5P release be explained by the hydrophobic diffusional barrier offered by the FP. The hydrophobicity of the tablets upon exposure to the dissolution medium increased with an increase in the FP level. This resulted in lower penetration of the dissolution medium into the tablets to dissolve the R5P.

As illustrated in Fig. 4., after incorporation of FP into the tablets prepared by HME, R5P release from the tablets containing higher level of FP (40-50%) was slower than demonstrated with the lower FP level of 0-30%. After 40%w/w of FP the sustained release profile was observed. The porous structure of the tablets created by incorporating the FP created a longer diffusional pathway for releasing the drug. The dissolved drug molecules need to diffuse out via the tortuosity of the FP in the tablet matrix. This result is consistent with a previous studies [18, 22]. The more tortuous the pore network of the tablets, the less accessible is the dissolved drug throughout the swelling matrix.

Additionally, Optical images of floating tablet prepared by DC and HME in difference time interval of dissolution test. are presented in Fig. 5. The tablets were basically an orange color due to the natural color of the R5P. Upon contact with the dissolution medium, the tablet

prepared by HME showed higher medium absorption and swelling, while the tablet prepared by DC demonstrated a lower swelling. The cross-section surfaces of tablet prepared by DC, the orange particles of R5P obviously distributed over the entire matrix tablet after exposure to 0.1 N HCl at 8 hr, whereas R5P appeared only inside the tablet prepared by HME. These results indicated that R5P remained in the tablets prepared by DC greater than those prepared by HME, resulting in lower R5P release. These results were confirmed by the water content and erosion studies as illustrated in Fig.6. The tablets formed by HME method showed higher water uptake and erosion than those formed by DC method, leading to higher R5P release.

3.4 The influence of particle size of foam powder on drug release

In addition to the amount of FP, the effect of FP particle size was evaluated on drug release. In this study, three different particle sizes, MP1002 (particle size < 200 µm), MP1004 (particle size 200 - 400 µm) and MP1x1(particle size 1000 µm), were used to lower the density of the tablets. The results presented that incorporating foam power into the tablets significantly retarded R5P release. Clearly, increasing particle size of FP substantially increased R5P release from tablets prepared by both DC and HME as shown in Fig. 7. This could be attributed to the relatively high porosity of tablets containing bigger sized FP particles as compared to the more compact of the tablets containing smaller sized FP particles. In addition, in the dissolution process, tablets containing bigger sized FP particles disintegrated faster than those tablets with the smaller particles. The tablets with the biggest size particles (1000 µm) showed the roughest surface from all tablets investigated in our study. Additionally, the hardness of the tablets dramatically decreased with increasing FP particle size, which can be explained by the increasing FP particle size causing discontinuities in the network of the PEO matrix. This resulted in high penetration of dissolution medium into tablets to dissolve the R5P and consequently provide a high R5P release.

3.5 The influence of PEO grade on drug release

In order to evaluate the impact of different grades of PEO according to the molecular weight or the polymer viscosity, floating tablets with 40% (w/w) MP1002 and 10% (w/w) R5P were prepared. The impact of the molecular weight of PEO on the R5P release of the tablets is shown in Fig. 8. The results revealed that using different molecular weight of PEO slightly affected on R5P release from tablets prepared by DC. In contrast, in the case of tablets manufactured by HME, R5P release strongly depended on the grades of PEO**.** The R5P release noticeably increased with decreasing viscosity of PEO in the following order: 7000 kDa < 2000 kDa < 200 kDa. The R5P release was greater with the lower molecular weight of PEO (200 kDa) due to less entanglement, less gel strength and a higher degree of polymer erosion. In contrast, the higher molecular weight of PEO (7000 kDa) produce highly viscous gels surrounding the tablet upon contact with dissolution medium, resulting in delayed medium diffusion into the tablets, which promoted retardation of the drug release from these tablets. Similar findings regarding faster drug release from low viscosity tablet over high viscosity tablets were reported [23, 24]. The high molecular weight of the PEO, with increasing gel strength around the tablet as a result of its molecular weight slowing the diffusion of the medium into the tablet, and thereby slowing the drug release

In addition, these higher R5P release observed in tablets prepared with PEO of a lower molecular weight or using HME method could be explained by the swelling behavior (Fig. 9) and the results of water content and erosion of tablets (Fig. 10). The tablets prepared by a DC method demonstrate the swelling behavior of tablet greater than those prepared by HME. The tablets prepared by a DC method provided a constant swelling behavior for longer than 8 h, whereas higher tablets erosion was found in tablets prepared by HME method as presented in Fig 9.

The tablets formed by PEO 200 kDa showed the lowest water content and the highest erosion, corresponding to its lower viscosity grade. On the other hand, increase of water content and a decrease in erosion were obtained in tablets formed by PEO 7000 kDa. This can be explained from other studies, where high viscosity polymers have resulted in a more tortuous gel layer and higher gel strength which decreased matrix erosion.

3.6 The influence of drug solubility on drug release

In order to investigate the importance of drug solubility, different drugs were selected to prepare the floating tablets. These were diltiazem, verapamil, propranolol and R5P (solubility in 0.1 N HCl: 588, 392, 220 and 5.9 mg/ml). Fig. 11 shows drug release from floating tablets consisted of 10% drug, 40% PEO (200 kDa) and 50% MP1002 (particle size < 200 μm) loaded with various types of drugs. The percentage of drug release were rapid from the tablets containing the high-solubility drugs, diltiazem, verapamil and propranolol. In contrast, the release of the R5P, the low-solubility drug, could be effectively and simultaneously controlled by the erosion of PEO (as discussed above). These findings indicate that drug is not only predominantly released by erosion of the matrix polymer, but also by diffusion through the water-filled polymer.

4 Conclusions

R5P loaded floating matrix tablets can be successfully prepared by HME. The optimum formulation and conditions for this system is tablet containing 50% w/w of FP and PEO 200 kDa, tabletd at the temperature of 100°C. The addition of FP causes a reduction in

the density of the tablet resulting in immediate buoyancy when coming into contact with the medium. The high FP level not only enhanced the floating properties of the exturdate but also its sustained-release property. The floating properties and drug release from the floating tablets were dependent on the amount of FP and the FP particle size, the PEO molecular weight, and the ratio of Kollidon® SR to PEO. The FP created a more tortuous tablet structure and hydrophobicity leading to lower water content and slower erosion rate. Physicochemical studies proved that the R5P partially melted into the PEO.

Riboflavin-5-phosphate loaded floating matrix tablets can be successfully prepared by two methods. The HME gave higher tablet's density than the DC at the same ratio of FP. The optimum formulation for this system is tablet containing 50% w/w of FP. The addition of FP causes a reduction in the density of the tablet resulting in immediate buoyancy when coming into contact with the medium.

5 Acknowledgements

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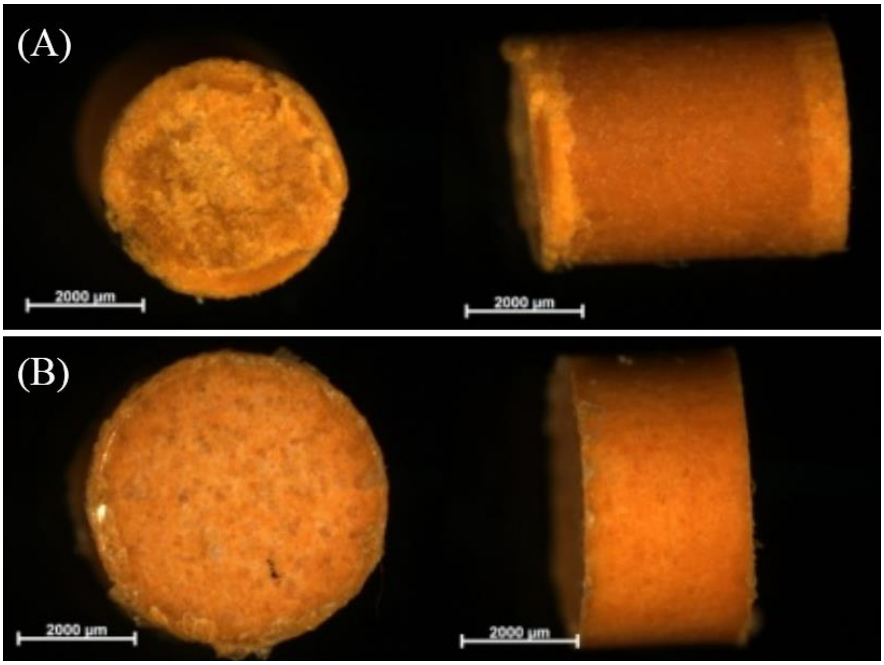
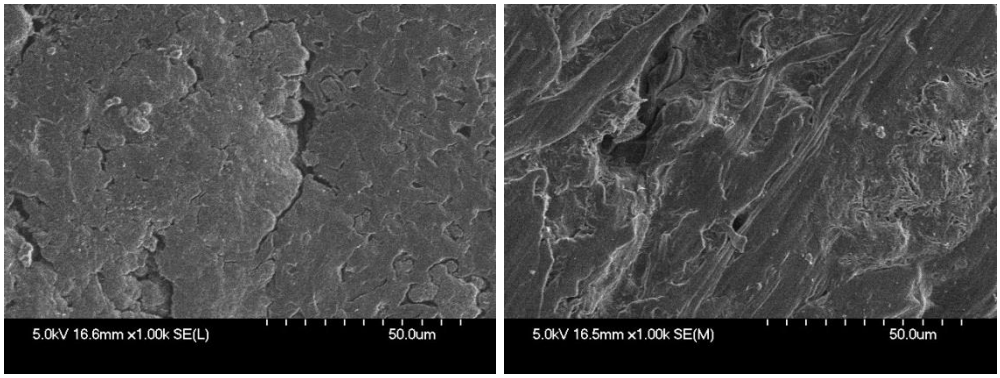


425

426 Figure 1 Appearance of floating tablets prepared by hot-melt extrusion (A) and direct
427 compression (B) containing riboflavin-5-phosphate, 50% PEO (200 kDa) and 40% foam
428 powder (particle size < 200 µm)

429

(A)



(B)

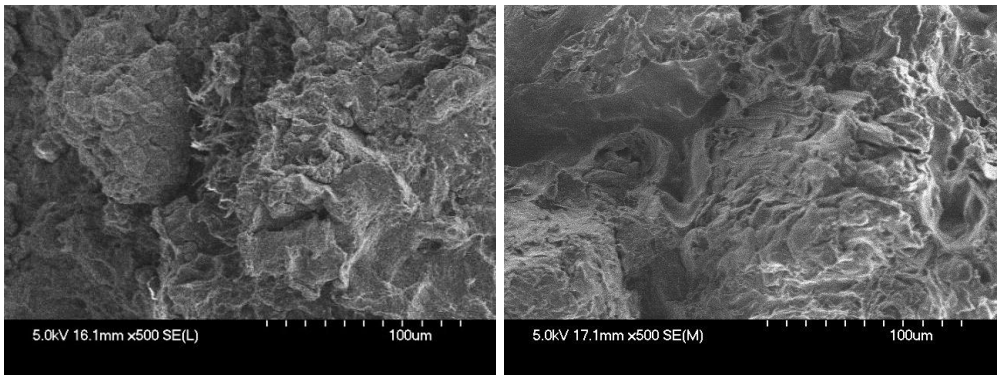


Figure 2 SEM images of floating tablet surfaces (A) and cross-section (B) (10% riboflavin-5-phosphate, 50% MP1002 and 40% Polyethylene oxide) prepared by direct compression (left) and HME (right)

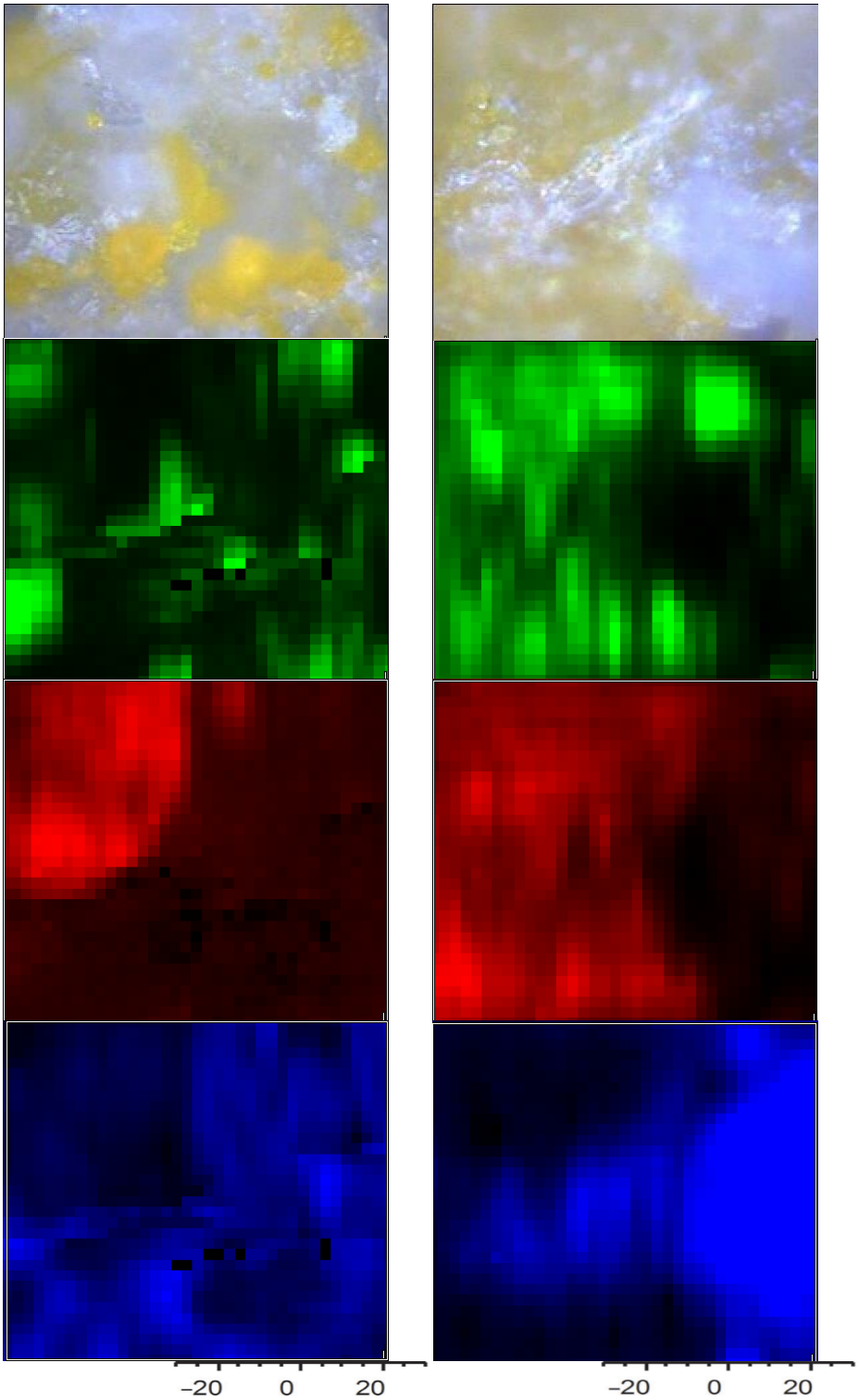
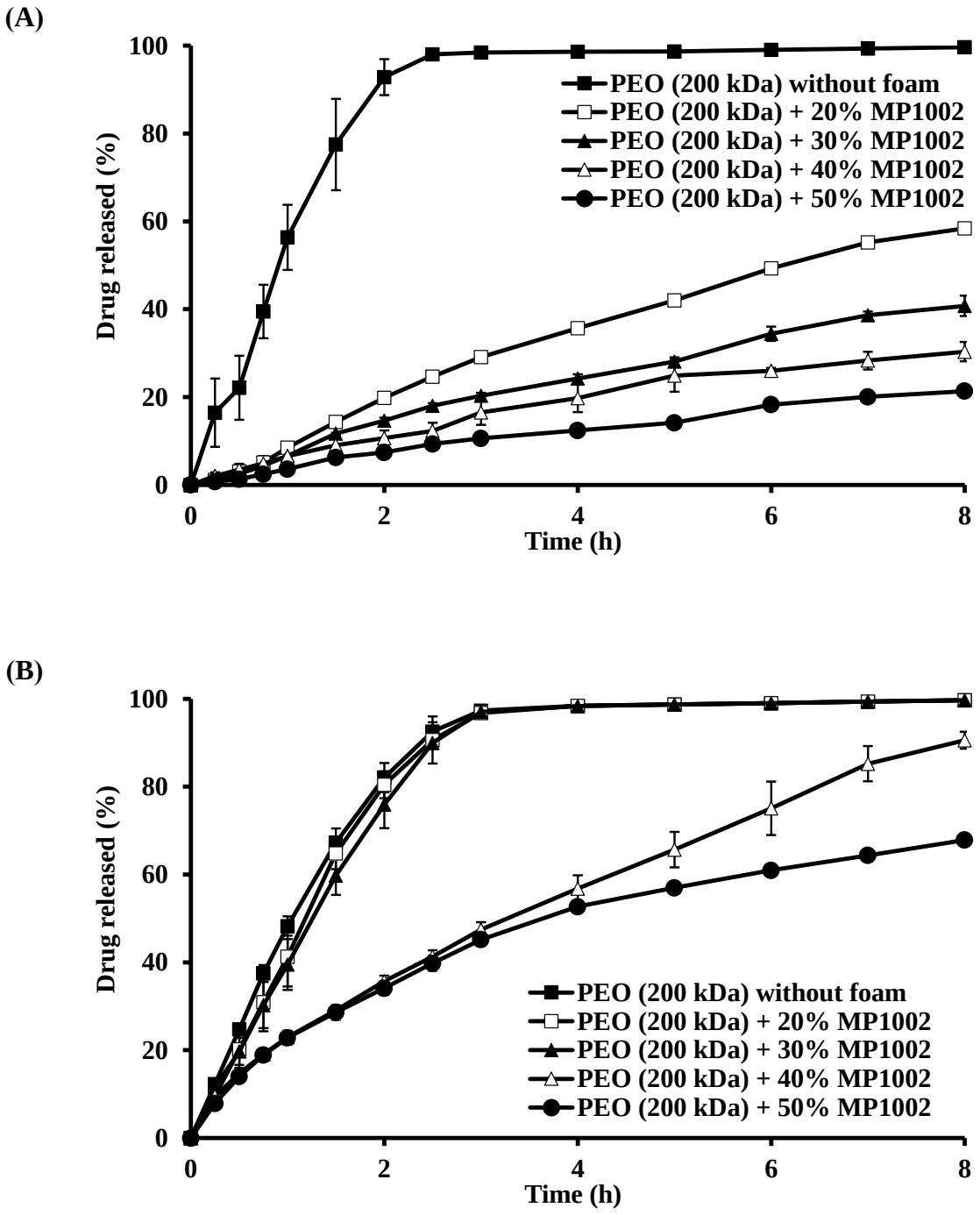


Figure 3 Panel of images from the raman imaging of cross-section floating tablets prepared by direct compression (left) and HME (right)



441 Figure 4 Effect of amount of foam particles on riboflavin released of floating tablets prepared

442 by DC (A) and HME (B) in 0.1 N HCl (n = 3)

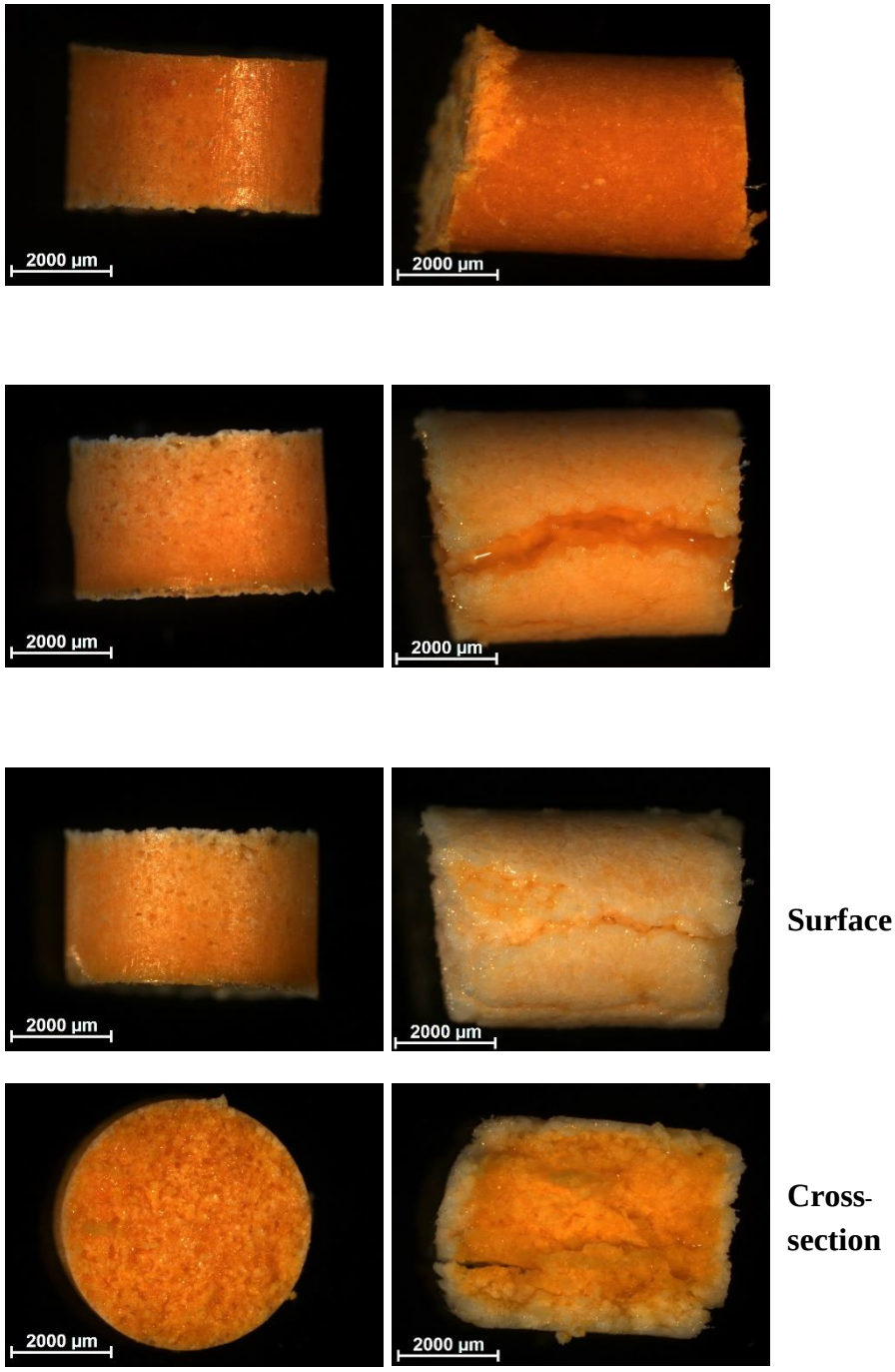
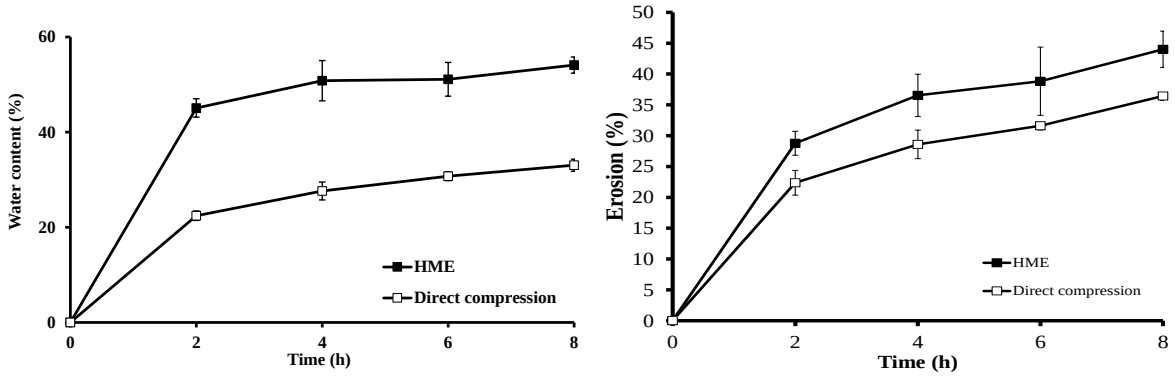
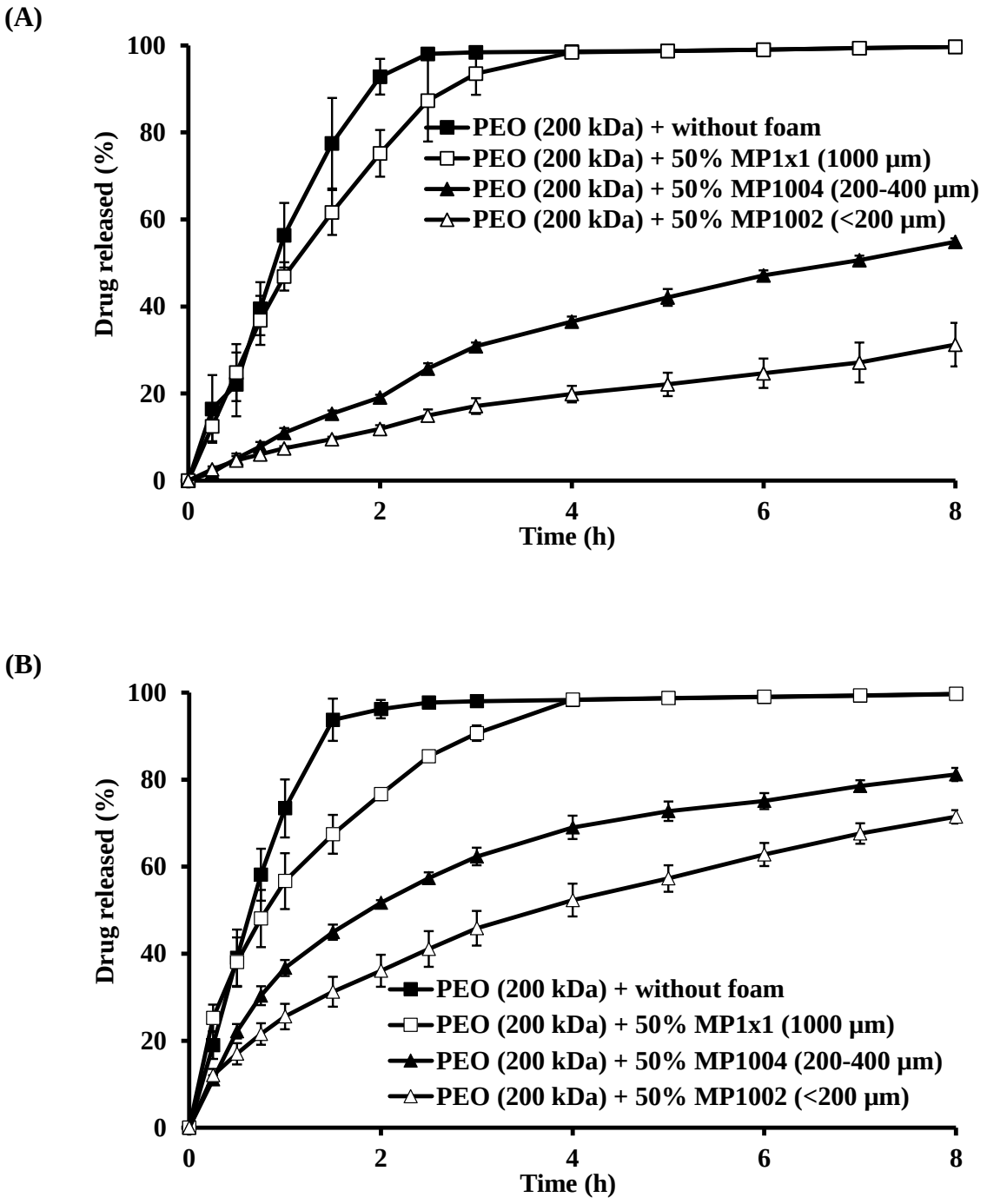


Figure 5 Optical images of floating tablet (10% riboflavin-5-phosphate, 50% MP1002 and 40% Polyethylene oxide) prepared by direct compression (left) and HME (right) in dissolution media (900 ml of 0.1 N HCl)

455 

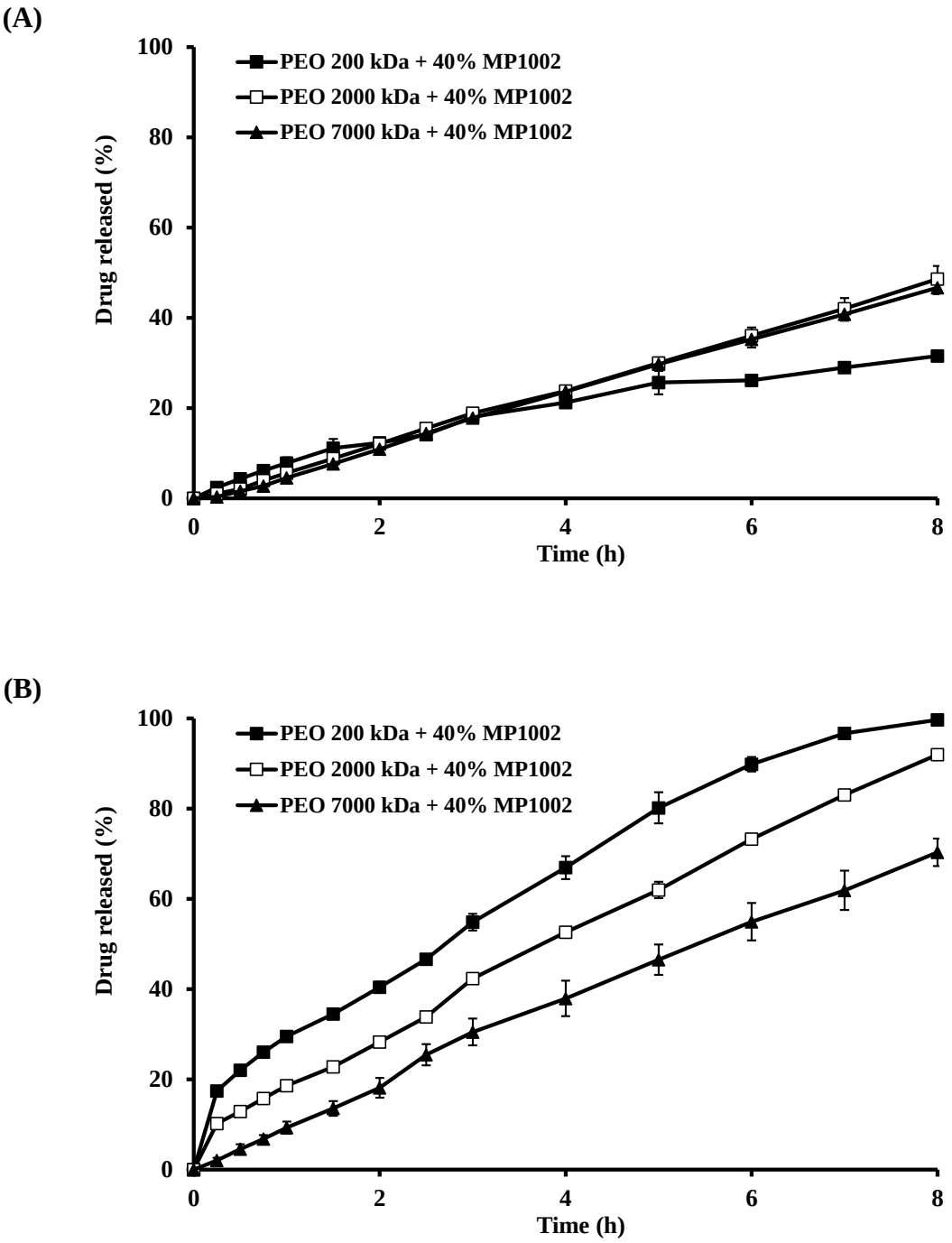
456 Figure 6. Effect of size of foam on drug release of floating tablets (10% riboflavin-5-
457 phosphate, 50% MP1002 and 40% Polyethylene oxide 200 kDa) prepared by HME in 0.1 N
458 HCl.

459



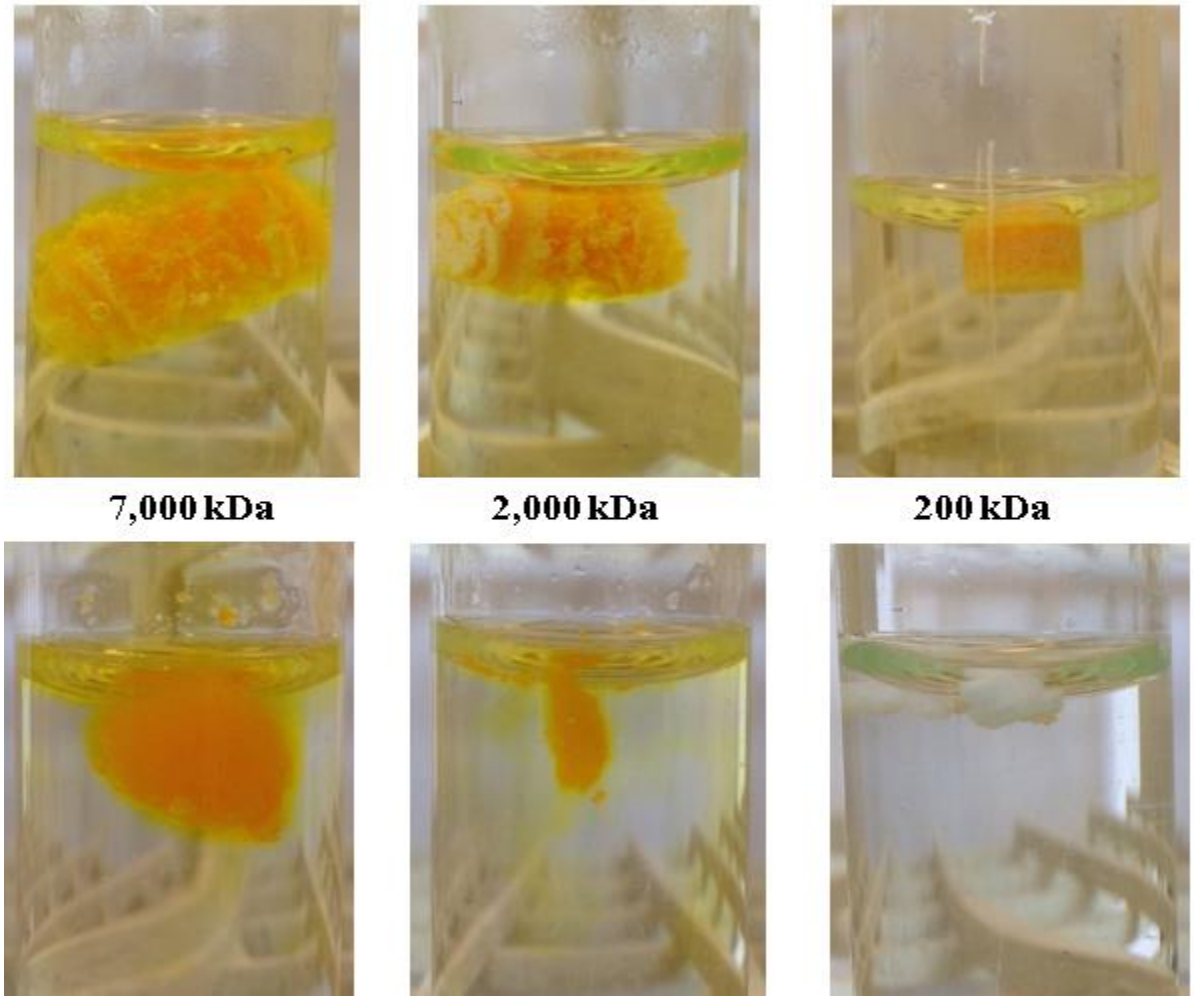
460 Figure 7 Effect of foam particles size (50% of foam) on riboflavin released of floating tablets
461 prepared by direct compression (A) and HME (B) in 0.1 N HCl

462



463 Figure 8 Effect of PEO grades on riboflavin released of floating tablets (40% MP1002)
464 prepared by direct compression (left) and HME (right) in 0.1 N HCl

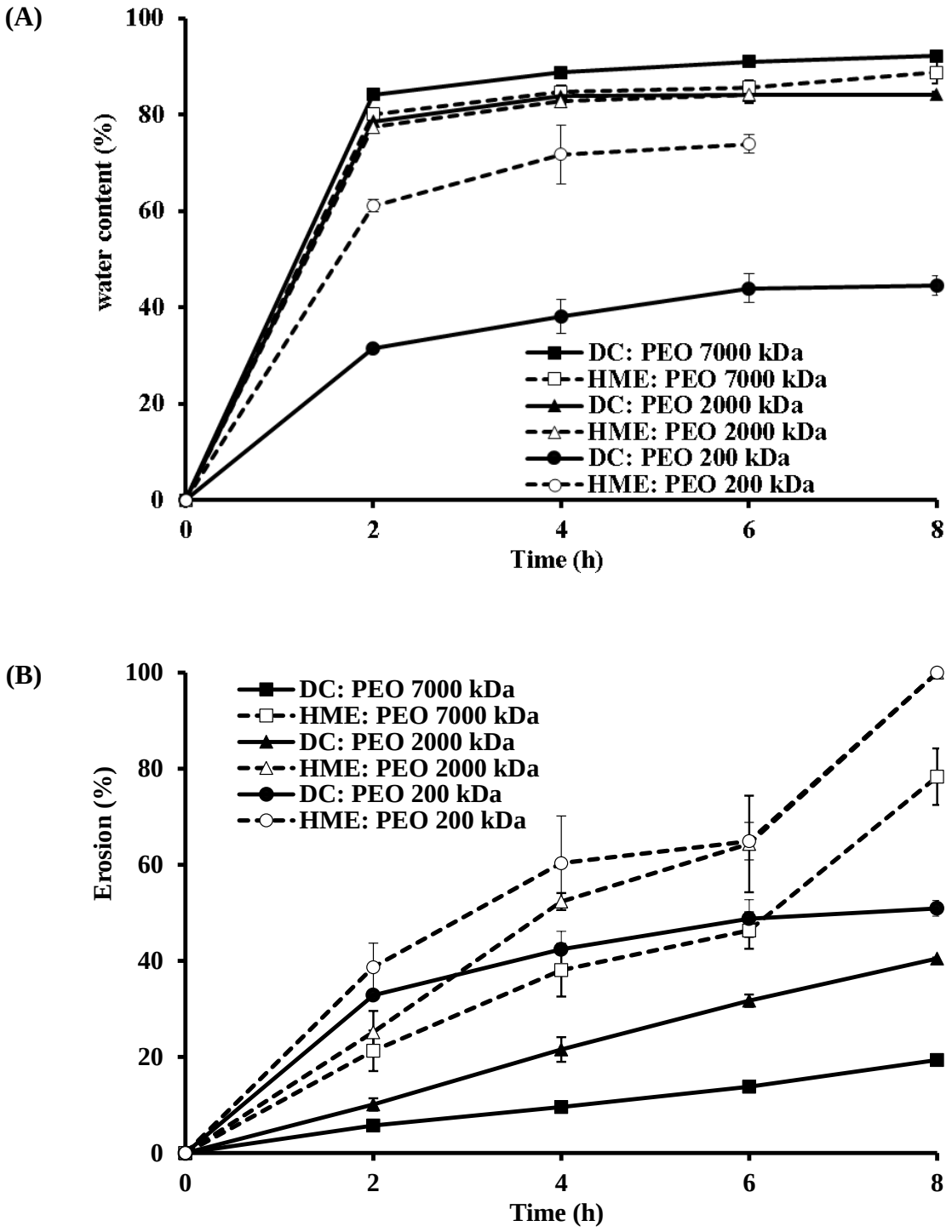
465



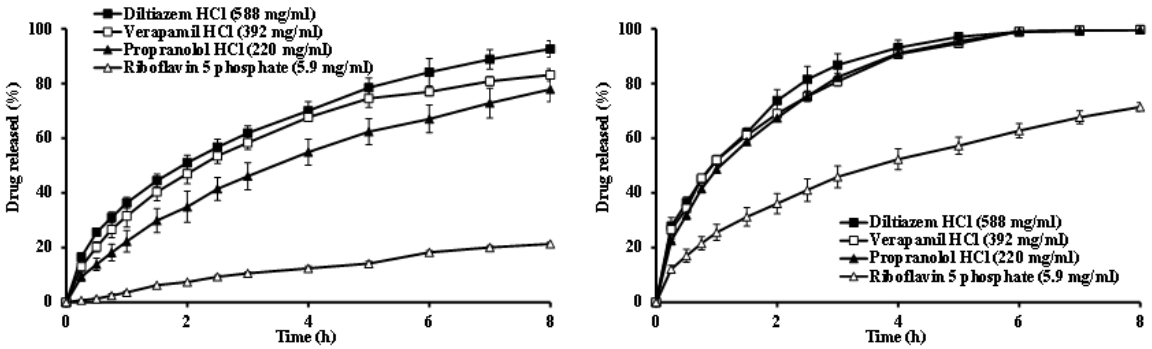
466

467 Figure 9 Effect of PEO grades on swelling behavior (at 8 h dissolution) of floating tablets
468 (40% MP1002) prepared by direct compression (top) and HME (bottom) in 0.1 N HCl

469



470 Figure 10 Effect of PEO grades Percentage on water content and percentage erosion of floating
471 tablets prepared by direct compression and HME in 0.1 N HCl



472

473 Figure 11 Effect of drug solubility on the drug released of floating tablets prepared by DC

474 and HME in 0.1 N HCl

475

476 Table 1. Key properties of the floating tablets based on 10% drug loading

Formulations	HME condition	Physical properties					Floating properties	
	Melt pressure (bar)	Weight (mg)	Surface area (mm^2)	Density (mg/mm^3)	Porosity (%)	Hardness (N)	Time to float (min)	Floating (h)
Direct compression								
PEO (200 kDa) without foam powder		72.39 ± 0.32	82.59 ± 1.73	1.13 ± 0.04	12.02 ± 0.53	128.27 ± 1.4	NF	NF
PEO (200 kDa) + 20% MP1002		63.77 ± 1.03	79.48 ± 0.96	1.06 ± 0.01	12.09 ± 4.78	111.55 ± 7.24	18.33 ± 2.52	> 8
PEO (200 kDa) + 30% MP1002		60.27 ± 1.72	79.27 ± 1.18	1.01 ± 0.01	12.06 ± 3.35	102.28 ± 0.54	10.17 ± 2.02	> 8
PEO (200 kDa) + 40% MP1002		56.58 ± 2.47	80.60 ± 2.51	0.92 ± 0.01	19.10 ± 7.60	92.57 ± 0.85	1.33 ± 2.31	> 8
PEO (200 kDa) + 50% MP1002		55.84 ± 0.6	79.22 ± 0.33	0.93 ± 0.02	20.74 ± 3.82	105.28 ± 4.39	IF	> 8
Hot-melt extrusion								
PEO (200 kDa) without foam powder	10	79.74 ± 5.26	85.18 ± 2.57	1.15 ± 0.02	7.95 ± 1.36	176.68 ± 17.93	NF	NF
PEO (200 kDa) + 20% MP1002	20	72.86 ± 1.69	94.01 ± 0.96	1.02 ± 0.02	9.68 ± 3.48	145.38 ± 13.41	NF	NF
PEO (200 kDa) + 30% MP1002	25	68.37 ± 1.43	91.94 ± 1.01	1.02 ± 0.01	9.17 ± 2.46	158.09 ± 1.09	NF	NF
PEO (200 kDa) + 40% MP1002	55	68.34 ± 2.65	93.24 ± 1.99	1.00 ± 0.01	14.81 ± 1.94	177.25 ± 3.64	14.33 ± 0.58	> 8
PEO (200 kDa) + 50% MP1002	75	67.97 ± 3.78	95.76 ± 2.02	0.96 ± 0.04	14.90 ± 2.44	179.73 ± 4.04	IF	> 8

477 NF = non-floating, IF = immediately floated

478 NF = non-floating, IF = initially floated, *Obstruction at the beginning

479

480

◀ **Full proceeding: PPT 33** ▶

Preparation and comparison of floating tablets manufactured by hot-melt extrusion and direct compression

Worawut Kriangkrai[1], Satit Puttipipatkhachorn[2], Pornsak Sriamornsak[3], Jürgen Siepmann[4], Florence Siepmann[4], Srisagul Sungthongjeen[1*]

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***Abstract*—The aim of the present study was to determine and compare the physical properties of floating tablets prepared by either hot-melt extrusion or direct compression to explain the floating behavior. The riboflavin-5-phosphate loaded floating tablet was successfully prepared by the two techniques. Polyethylene oxide (PEO) was used as matrix forming polymer. Polypropylene foam powder was used to lower the density of the system. The result demonstrated that increasing the amount of foam powder from 20%-50% w/w resulted in an immediately noticeable reduction in the density of the tablet. This led to decreasing the time-to-float to zero for tablet prepared by hot-melt extrusion, meaning immediate buoyancy, at 50% w/w, while the tablet prepared by direct compression process used 40% w/w of foam powder. The floating tablets had floating duration longer than 8 h. The tablets prepared by a direct compression method demonstrate the tablet density lower than those prepared by the hot-melt extrusion method. The foam powder in the matrix tablet caused the density of the tablet to decrease, and the porosity of the structure to increase. Adding a higher amount of insoluble substance into the hot-melt extrusion, the foam powder, led to a significant increase in melting pressure and the hardness of the tablet. These results indicate that 50% w/w of foam powder is an appropriate amount to use in the preparation of floating tablets for these two methods.**

***Keywords*—Floating tablets, Hot-melt extrusion, Direct compression, Physical properties, Polypropylene foam powder**

I. INTRODUCTION

Hot-melt extrusion has become a valuable and versatile process for manufacturing drug delivery systems . Hot-melt extrusion is a continuous manufacturing process, solvent-free, robust, quick and cost-effective for the production of a wide variety of pharmaceutical dosage forms including orally administered tablets, topical films, implants and ophthalmic inserts [1-4] . As oral drug delivery systems are an important method for delivering medication to chronically ill and poly-medicated patients, considerable research efforts have been directed towards the use of polymers that provide practical, safe and controlled long-term delivery of drugs . The major aspect of controlled oral drug delivery systems is the control that they allow in the release of the drugs over time, as well as the reduction in the frequency of administration by more effective release, and the amount of drugs being released, which reduces the amount of the drug necessary for effective treatment. Polyethylene oxide (PEO) is a non-ionic, hydrophilic, linear, semi-crystalline homo-polymer, with a low glass transition temperature that is easily processed via hot-melt extrusion and its hydrophilic chains ensure solubility enhancement for drugs with poor water-solubility .

While hot-melt extrusion has been widely used in the pharmaceutical manufacturing of controlled oral drug delivery systems, frequent problems with the oral dosage form have been encountered . Fast gastric emptying time and poor bioavailability of certain drugs due to incomplete absorption and degradation in the gastrointestinal tract are the two main problems encountered . To overcome these obstacles, gastro-retentive drug delivery syetems (GRDDSs) have been developed . Floating drug delivery systems (FDDSs) are classified in the group of GRDDSs as having the ability to float in and be retained in the gastric medium for prolonged intervals . Several approaches have been used to encourage buoyancy of the dosage form in the stomach [5] . Low-density foam powder is one technique that can be used in an FDDS, and floats on the stomach contents immediately on ingestion [6,7] . However, very few FDDSs are currently manufactured by hot-melt extrusion. This, therefore, was the focus of the present study: to develop

floating tablets prepared by hot melt extrudates extrusion using a polypropylene foam powder as the low-density substance allowing longer gastric retention time. The effects of formulation variables on floating behavior the floating tablets were investigated. In addition, the physical properties were also studied.

II. Materials and Methods

Materials

The following chemicals were obtained from commercial suppliers and used as received: riboflavin-5-phosphate(DSM, Basel, Switzerland); polypropylene foam powder Accurel® MP, Membrana GmbH, Obernburg, Germany :(Accurel® MP1002(< 200 μm); poly(ethylene oxide) (PEO; Sentry Polyox® WSR LEO NF, Dow Chemicals, Midland, USA, provided by Colorcon, Dartford, UK :(Polyox® WSR N-80, 200 kDa).

Methods

Preparation of floating tablets containing foam powder. The floating tablets were prepared with 10% w/w drug loading (riboflavin-5-phosphate). The floating tablets containing foam powder prepared by hot-melt extrusion was developed and compared with that prepared by direct compression .For the floating tablet prepared by hot-melt extrusion, the hot-melt extrusion processing was optimized e.g .temperature, screw speed, and feed rate .A dry blend of each sample drug, together with the PEO and the foam powder, was processed using a Turbula T2A (Willy A .Bachofen Maschinenfabrik, Muttenz, Switzerland) for 10 minutes until homogeneously mixed .The blends were then hot melt extruded using a twinscrew extruder, NANO 16 from Leistritz, Nuremberg, Germany, which was equipped with a co-rotating twin screw (diameter = 16 mm, 4 heating zones, kneading elements in zones 1 and 2, diameter of the die orifice =4 mm).The process temperatures were 90°C- 95°C -97°C- 100°C (zone 1 - zone 2 - zone 3 – die) .After the temperature was set and stabilized, the screw speed and feeding rate were kept constant at 30 rpm and 3 cm^3/min .The cylindrical extrudates were air-cooled and manually cut into tablets, 4 mm in diameter. In case the floating tablet prepared by direct compression method, the mixture was compressed into tablets (diameter, 3.95 mm; flat face) using a single punch tableting machine (Korsch EKO/DMS, Berlin, Germany).

Appearance of floating tablets. Macroscopic pictures of the surface and cross-section morphology were taken using an optical image analysis system (Nikon SMZ-U; Nikon, Tokyo, Japan) equipped with an Axiocam ICc1 camera (Carl Zeiss Micro Imaging, Jena, Germany.

Physical properties of floating tablets. The floating tablets were evaluated for weight variation, thickness, diameter, hardness, friability, and porosity . The thickness and diameter of tablets were measured by thickness tester) Micrometer Caliper, Model 7301 Series 7, Mitutoyo, Kawasaki, Japan, Micrometer Caliper .Hardness of tablets was measured by texture analyzer (TA. XT. plus, Stable Micro Systems, Godalming, UK .(Friability of tablets was determined by using friability test apparatus .The porosity of the floating tablet was calculated from true density of the tablet which was determined by helium displacement device (Pycnometer 1330, Micromeretics, Norcross, Georgia, USA).

Floating properties of floating tablets. Time-to-float is the time period starting at the immersion of the tablet until it is floating buoyantly on the surface of the medium .Floating duration time is the duration of time that the tablet continues to float on the surface of the medium before sinking . The time-to-float and floating duration time were measured using the USP dissolution apparatus II(Sotax AT7; Aesch, Switzerland) 900 mL of 0.1 N HCl, 37.0 ± 0.5°C, 50 rpm .Each test was carried in triplicate.

Statistical analyses. Data were reported as the mean ± standard deviation (SD). The difference in average of data was compared by analysis of variance (one-way ANOVA) or independent sample t test. The significance of the difference was determined at 95% confident limit (α=0.05).

III. Results and Disscusion

Preparation of floating tablets containing foam powder. The tablets consisted of riboflavin-5-phosphate, the low-density polypropylene foam powder, and a matrix forming polymer, PEO . The foam powder that was used to lower the density of the extrudate is a polypropylene powder (Accurel® MP) with a highly porous structure normally used as a drug carrier or low-density substance. In the present study, we first focused on reducing the tablet to a density of 1 g/cm^3 or less to achieve buoyancy on initial contact with the dissolution medium, given that tablet with no foam powder and with a density of 1. 2 g/ cm^3 would immediately sink.

Appearance. Figures 1 shows macroscopic pictures of the floating tablets prepared by the two methods. The tablets were an orange color due to the natural color of the riboflavin-5-phosphate.

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TABLE 1. KEY PROPERTIES OF THE TABLETS BASED ON 10% DRUG LOADING

Formulations	HME condition	Physical properties					Floating properties	
	Melt pressure (bar)	Weight (mg)	Surface area (mm^2)	Density (mg/mm^3)	Porosity (%)	Hardness (N)	Time to float (min)	Floating (h)
Direct compression								
PEO (200 kDa) without foam powder		72.39 ± 0.32	82.59 ± 1.73	1.13 ± 0.04	12.02 ± 0.53	128.27 ± 1.4	NF	NF
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NF = non-floating, IF = immediately floated

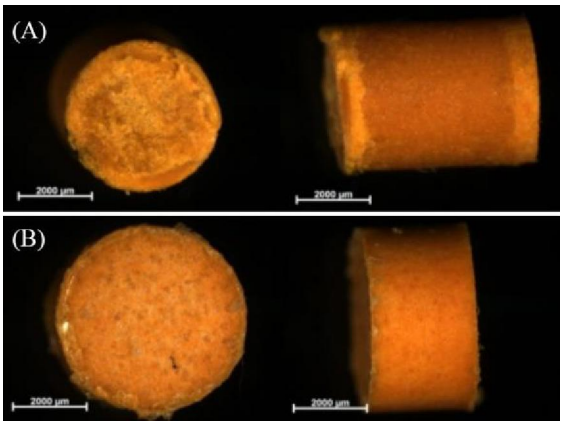

Fig. 1. Appearance of floating tablets prepared by hot-melt extrusion (A) and direct compression (B) containing riboflavin-5-phosphate, 50% PEO (200 kDa) and 40% foam powder (particle size < 200 µm)

Physical properties. The effect on the floating and physical properties of the floating tablets of the various formulation variables was investigated and is summarized in Table. 1 . Increasing the amount of foam powder from 20-% 50 % w/ w resulted in an immediately noticeable reduction in the density of the tablet . The tablets prepared by a direct compression method demonstrate the tablet density lower than those prepared by HME . The foam powder in the matrix caused the density of the tablet to decrease, and the porosity of the structure to increase . The increasing amount of foam powder in the direct compression preparation exhibited the decreasing the hardness of the tablet due the rising of porosity.

However, adding a higher amount of insoluble substance into the hot-melt extrusion, the foam powder, led to a significant increase in melting pressure and the hardness of the tablet .These results are in good agreement with earlier findings by Maggi, et al .[8] who demonstrated that extrudates made of pure polymer were harder than those containing the drug and other excipients, while maintaining slightly higher porosity.

Floating properties. The tablets manufactured by direct compression started to float at 20% w/w of foam powder while the tablet prepared by hot-melt extrusion required 40% w/w of foam powder to get buoyancy. The increasing amount of foam powder from 20%-50% w/w led to decreasing the time-to-float to zero, meaning immediate buoyancy, at 50% w/w, and floating duration for up to 8 h. The good floating properties were in good agreement with the result obtained in physical properties.

IV. CONCLUSIONS

Riboflavin-5-phosphate loaded floating matrix tablets can be successfully prepared by two methods . The hot-melt extrusion gave higher tablet's density than the direct compression at the same ratio of foam powder. The optimum formulation for this system is extrudate containing 50 %w/w of foam powder. The addition of foam powder causes a reduction in the density of the tablet resulting in immediate buoyancy when coming into contact with the medium.

ACKNOWLEDGMENTS

This work was financially supported by the Thailand Research Fund (Grant no. MRG6080046).

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Preparation and Comparison of Floating Tablets Manufactured by Hot-Melt Extrusion and Direct Compression

Worawut Kriangkrai[1], Satit Puttipipatkhachorn[2], Pornsak Sriamornsak[3], Juergen Siepmann[4], Florence Siepmann[4], Srisagul Sungthongjeen[1,*]

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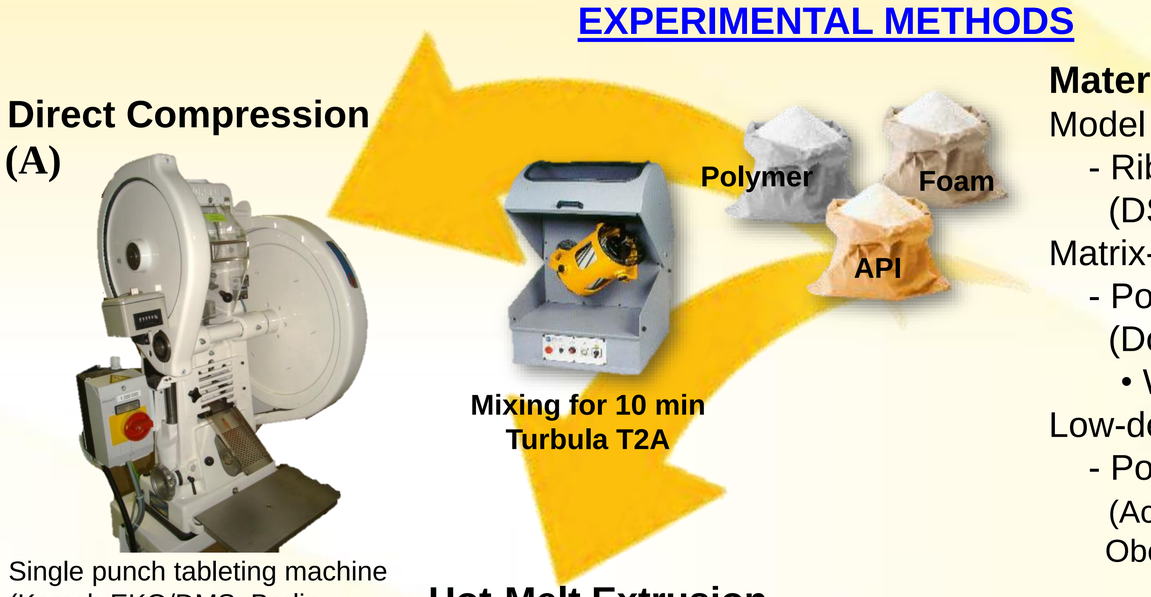
INTRODUCTION

Hot-melt extrusion is a continuous manufacturing process, solvent-free, robust, quick and cost-effective for the production of controlled oral drug delivery [1, 2]. However, fast gastric emptying time and poor bioavailability of certain drugs due to incomplete absorption and degradation in the gastrointestinal tract are the two main problems encountered. Floating drug delivery systems (FDDSs) were develop to overcome these obstacles [3]. Using low-density foam powder is one principle that can be used in an FDDS, and floats on the stomach contents immediately on ingestion [4, 5]. Only few FDDSs are currently manufactured by hot-melt extrusion. This, therefore, was the focus of the present study: to develop floating tablets prepared by hot melt extrusion using a polypropylene foam powder as the low-density substance allowing longer gastric retention time. The effects of formulation variables on floating behavior the floating tablets were investigated. In addition, the physical properties were also studied.

EXPERIMENTAL METHODS



Single punch tableting machine (Korsch EKO/DMS, Berlin, Germany)

Twinscrew extruder (NANO 16 from Leistritz, Nuremberg, Germany)
- The process temperatures were 90°C -95°C -97°C -100°C

Fig. 1: Design of the floating tablets prepared by direct compression (A) and hot-melt extrusion (B)

Materials

Model drug
- Riboflavin-5-phosphate (DSM, Basel, Switzerland)

Matrix-forming polymer
- Poly (ethylene oxide), PEO (Dow Chemicals, Midland, USA)
  - WSR N80, 200 kDa

Low-density compound
- Polypropylene foam powder (Accurel® MP1002 Membrana GmbH, Obernburg, Germany)

Tablet properties

The floating tablets were evaluated for weight variation, thickness, diameter, hardness, friability, and porosity.

Micrometer Caliper, Model 7301

Pycnometer 1330, Micromeretics

TA.XT.plus, Stable Micro Systems

Appearance of floating tablets.
- Nikon SMZ-U with Axiocam ICc1 camera

Floating properties

The time-to-float and floating duration time were measured using the USP dissolution apparatus II (900 mL of 0.1 N HCl, 37.0 ± 0.5°C, 50 rpm).

(Sotax AT7, Aesch, Switzerland)

RESULTS AND DISCUSSION

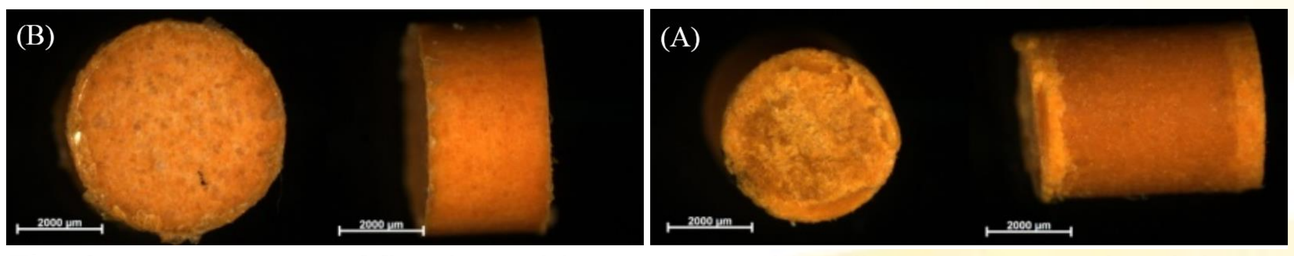


Fig. 2: Appearance of floating tablets prepared by direct compression (A) and hot-melt extrusion (B) containing riboflavin-5-phosphate, 50% PEO (200 kDa) and 40% foam powder (particle size < 200 µm).

Table 1. Key properties of the floating matrix tablets based on 10% drug loading

Formulations	HME condition	Physical properties					Floating properties	
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NF = non-floating, IF = immediately floated

CONCLUSIONS

Riboflavin-5-phosphate loaded floating matrix tablets can be successfully prepared by two methods. The hot-melt extrusion gave higher tablet's density than the direct compression at the same ratio of foam powder. The optimum formulation for this system is extrudate containing 50% w/w of foam powder. The addition of foam powder causes a reduction in the density of the tablet resulting in immediate buoyancy when coming into contact with the medium.

ACKNOWLEDGEMENTS

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Physicochemical properties and drug release from floating tablets manufactured by hot-melt extrusion and direct compression

Worawut Kriangkrai[1], Satit Puttipipatkhachorn[2], Pornsak Sriamornsak[3], Juergen Siepmann[4], Florence Siepmann[4], Srisagul Sungthongjeen[1,*]

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INTRODUCTION

Hot-melt extrusion (HME) is a continuous manufacturing process, solvent-free, robust, quick and cost-effective for the production of controlled oral drug delivery [1, 2]. However, fast gastric emptying time and poor bioavailability of certain drugs due to incomplete absorption and degradation in the GI tract are the two main problems encountered. Floating drug delivery systems (FDDS) were develop to overcome these obstacles [3]. Using low-density foam powder is one principle that was effectively used in an FDDS [4, 5]. Thus, floating tablet prepared by HME is the interesting area for research. The aim of the present study was to determine and compare the properties of floating tablets prepared by two techniques, hot-melt extrusion and direct compression. Raman spectroscopy was performed to characterize the physicochemical properties of 2 manufacturing processes. In addition, effect of formulation variables on floating behavior and drug release of the floating tablets were investigated.

EXPERIMENTAL METHODS

Direct Compression (A)

Single punch tableting machine (Korsch EKO/DMS, Berlin, Germany)

Materials

Low-density compound
- Polypropylene foam powder (Accurel® MP1002 Membrana GmbH, Obernburg, Germany)

Matrix-forming polymer
- Poly (ethylene oxide), PEO (Dow Chemicals, Midland, USA)
  • WSR N80, 200 kDa

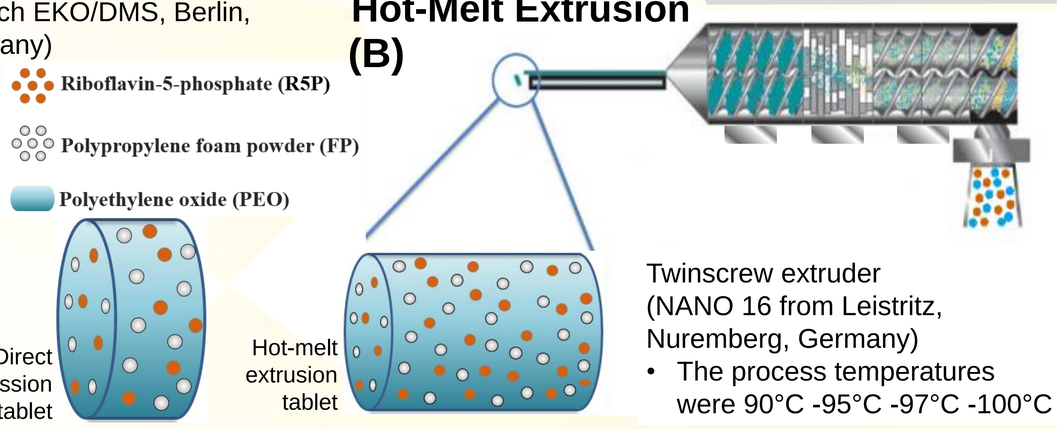
Model drug
- Riboflavin-5-phosphate (DSM, Basel, Switzerland)

Mixing for 10 min Turbula T2A

Physical properties

The floating tablets were evaluated for appearance, weight variation, thickness, diameter, hardness, friability, and porosity.

Hot-Melt Extrusion (B)



Twinscrew extruder (NANO 16 from Leistritz, Nuremberg, Germany)
- The process temperatures were 90°C -95°C -97°C -100°C

Physicochemical characterizations

DSC: 30°C–320°C, 10°C/min (Mettler Toledo, Germany)

PXRD: Cu X-ray tube ($\lambda_{CuK\alpha}$ = 1.54 Å) (PANalytical, Netherlands)

Raman imaging : Renishaw inVia Raman spectrometer (Renishaw plc, Wottonunder-Edge, UK)

Fig. 1: Design of the floating tablets prepared by direct compression (A) and hot-melt extrusion (B)

The experiments were perform with USP dissolution apparatus II (900 mL of 0.1 N HCl, 37°C, 50 rpm) (Sotax AT7, Aesch, Switzerland)

Floating properties and drug release

RESULTS AND DISCUSSION

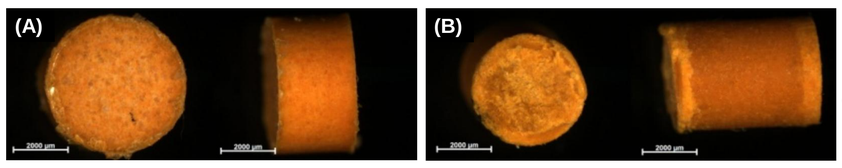


Fig. 2: Appearance of floating tablets prepared by direct compression (A) and hot-melt extrusion (B) containing riboflavin-5-phosphate, 50% PEO (200 kDa) and 40% foam powder (particle size < 200 µm)

8 h dissolution

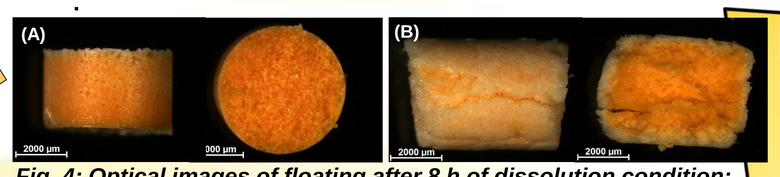
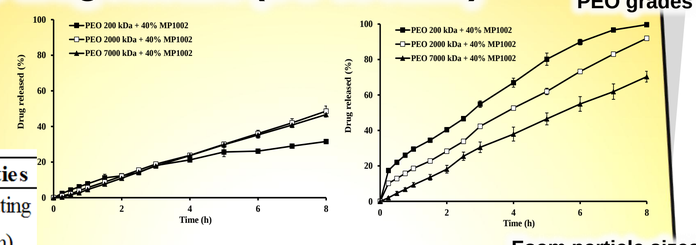


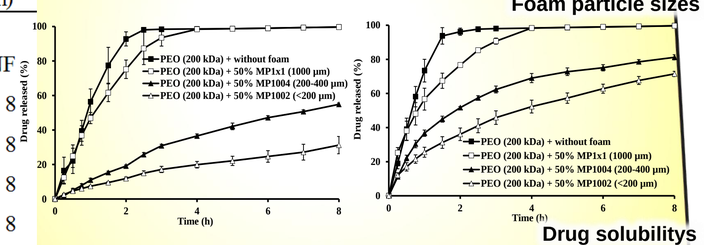
Fig. 4: Optical images of floating after 8 h of dissolution condition; surface (left) and cross-section (right) morphology

Effect of formulation variables on *In vitro* drug release (DC vs HME)

PEO grades



Foam particle sizes



Drug solubilitys

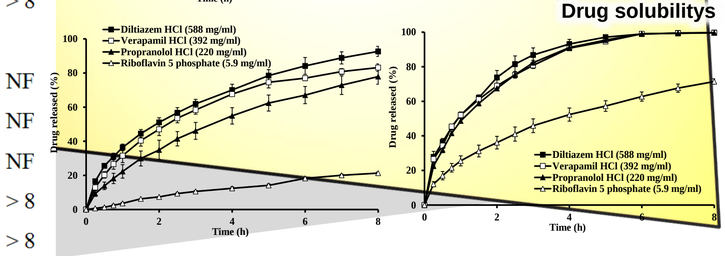


Table 1. Key properties of the floating matrix tablets based on 10% drug loading

Formulations	HME condition	Physical properties					Floating properties	
	Melt pressure (bar)	Weight (mg)	Surface area (mm^2)	Density (mg/mm^3)	Porosity (%)	Hardness (N)	Time to float (min)	Floating (h)
Direct compression								
PEO (200 kDa) without foam powder		72.39 ± 0.32	82.59 ± 1.73	1.13 ± 0.04	12.02 ± 0.53	128.27 ± 1.4	NF	NF
PEO (200 kDa) + 20% MP1002		63.77 ± 1.03	79.48 ± 0.96	1.06 ± 0.01	12.09 ± 4.78	111.55 ± 7.24	18.33 ± 2.52	> 8
PEO (200 kDa) + 30% MP1002		60.27 ± 1.72	79.27 ± 1.18	1.01 ± 0.01	12.06 ± 3.35	102.28 ± 0.54	10.17 ± 2.02	> 8
PEO (200 kDa) + 40% MP1002		56.58 ± 2.47	80.60 ± 2.51	0.92 ± 0.01	19.10 ± 7.60	92.57 ± 0.85	1.33 ± 2.31	> 8
PEO (200 kDa) + 50% MP1002		55.84 ± 0.6	79.22 ± 0.33	0.93 ± 0.02	20.74 ± 3.82	105.28 ± 4.39	IF	> 8
Hot-melt extrusion								
PEO (200 kDa) without foam powder	10	79.74 ± 5.26	85.18 ± 2.57	1.15 ± 0.02	7.95 ± 1.36	176.68 ± 17.93	NF	NF
PEO (200 kDa) + 20% MP1002	20	72.86 ± 1.69	94.01 ± 0.96	1.02 ± 0.02	9.68 ± 3.48	145.38 ± 13.41	NF	NF
PEO (200 kDa) + 30% MP1002	25	68.37 ± 1.43	91.94 ± 1.01	1.02 ± 0.01	9.17 ± 2.46	158.09 ± 1.09	NF	NF
PEO (200 kDa) + 40% MP1002	55	68.34 ± 2.65	93.24 ± 1.99	1.00 ± 0.01	14.81 ± 1.94	177.25 ± 3.64	14.33 ± 0.58	> 8
PEO (200 kDa) + 50% MP1002	75	67.97 ± 3.78	95.76 ± 2.02	0.96 ± 0.04	14.90 ± 2.44	179.73 ± 4.04	IF	> 8

NF = non-floating, IF = immediately floated

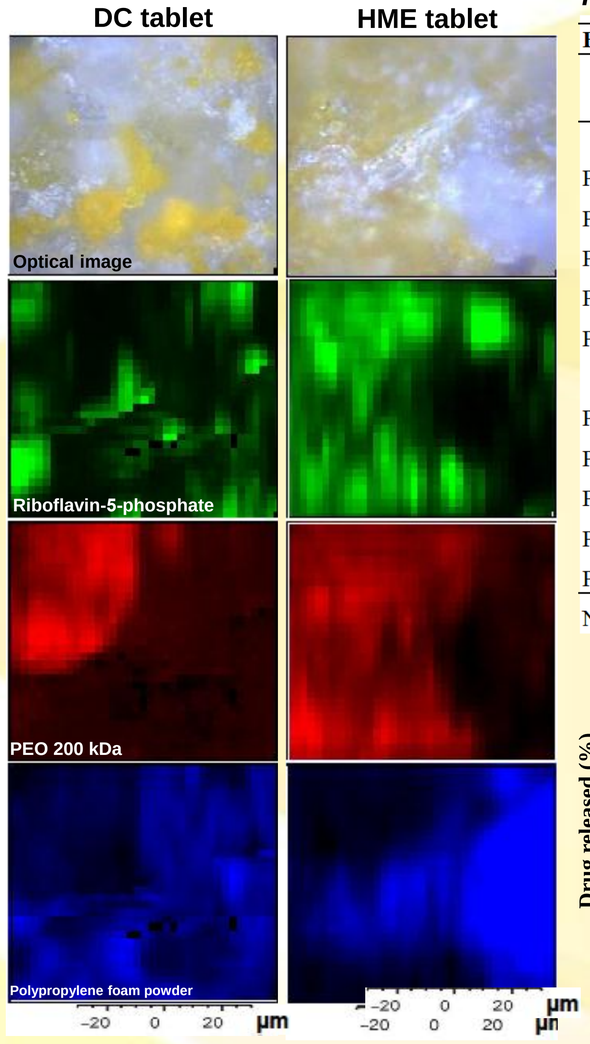


Fig. 3: Panel of images from the raman imaging of cross-section floating tablets

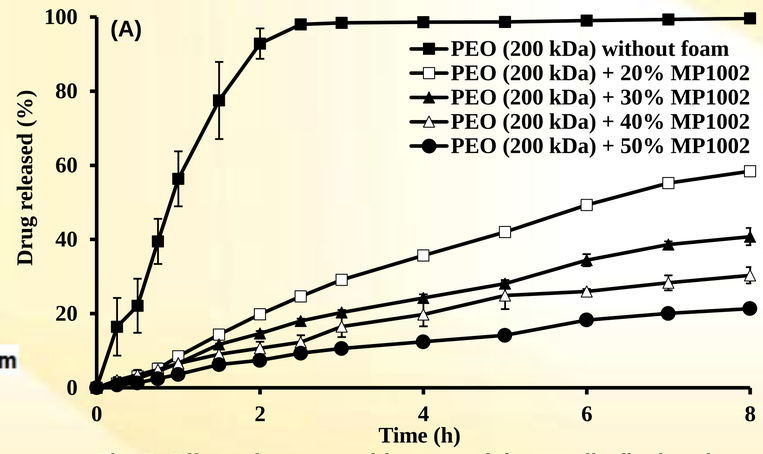


Fig. 5: Effect of amount of foam particles on riboflavin released of floating tablets prepared by direct compression (A) and HME (B) in 0.1 N HCl

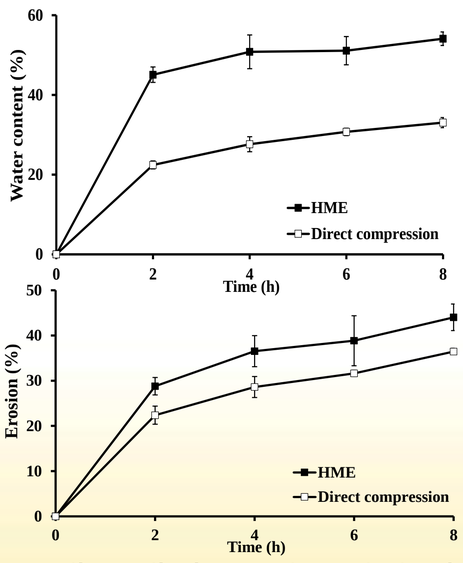


Fig. 6: Effect of preparation method on a water content and erosion of floating tablet (10% R5P, 50% FP200 and 40% PEO) in dissolution media (900 ml of 0.1 N HCl)

CONCLUSIONS

The production of FDDS by HME technique exhibited advantages the capacity to produce solid dispersion for improving the drug release of riboflavin-5-phosphate. The HME tablet need a high amount of foam powder to achieve the immediate buoyancy due to its high density and low porosity. The floating tablets had floating duration longer than 8 h. The sustained release effect was found due to the incorporation of foam powder. Its' hydrophobicity caused the lower penetration of the acidic medium into the system. Several variables, such as the PEO grade and size of form particle could modify the drug release from the floating tablet.

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Université Lille Nord de France
Pôle de Recherche et d'Enseignement Supérieur

รายงานสรุปการนำผลงานวิจัยไปใช้ประโยชน์

สัญญาเลขที่..... MRG6080046.....**ชื่อโครงการ**..การพัฒนายาเม็ดลอยตัวไรโบฟลาวินที่ประกอบด้วยผงโฟมความหนาแน่นต่ำเตรียมโดยเทคนิคการหลอมด้วยความร้อนและอัดรีด

หัวหน้าโครงการ ผศ.ดร.วรวุฒิ เกรียงไกร **หน่วยงาน** ภาควิชาเทคโนโลยีเภสัชกรรม คณะเภสัชศาสตร์ มหาวิทยาลัยนเรศวร

โทรศัพท์ 055-961880 **โทรสาร** 055-963731 **อีเมล์** WG.Kriangkrai@gmail.com

สถานะผลงาน ☐ ปกปิด ☑ ไม่ปกปิด

ความสำคัญ / ความเป็นมา

Floating tablets, gastro-retentive delivery systems, had several advantages, not only extending the duration of drug release but also prolonging gastric retention time. These are currently utilized to overcome the limitation of some group of APIs including (i) APIs which have an absorption window in the upper small intestine, (ii) poorly soluble or unstable APIs in the intestinal fluid, and (iii) the APIs that act locally in the proximal part of the gastrointestinal tract. . Direct compression (DC) is the simplest methods of production of a pharmaceutical tablet. The prime advantage of DC is economic since it requires fewer unit operations. This method also is suitable for moisture and heat sensitive APIs. However, the poorly soluble API has been a major obstacle for the development of more efficient drug delivery methods. Dissolution is the rate limiting step in absorption in the case of tablets. To overcome this problem, Hot-melt extrusion (HME) is currently used to prepare solid dispersions for the improvement of solubility and dissolution rates of poorly soluble APIs. The solid dispersion can inhibit the formation and growth of the drug crystal nucleus through the hydrogen bond and complexation between the carrier molecule and the drug. Additionally, HME is a continuous manufacturing process, solvent-free, robust, quick and cost-effective for the production of a wide variety of pharmaceutical dosage forms.

The objectives of this study were to determine the physicochemical properties of riboflavin floating tablets (R5P-FTs) prepared by either DC or HME to explain the drug release mechanism. Polyethylene oxide (PEO) was a drug carrier due to its broad processing window for HME and PEO has been used in solubility enhancement. Polypropylene foam powder (Accurel® MP) were used to produce the tablets to provide the floating ability for the system. The influence of variable formulation on floating ability, drug release rate, and the physicochemical properties of the tablets was studied.

วัตถุประสงค์ของโครงการ

The aim of the present study was to determine and compare the physicochemical properties of floating tablets prepared by either HME or DC to explain the floating ability and drug release rate

ผลการวิจัย (สั้น ๆ ที่บ่งชี้ประเด็นข้อค้นพบ กระบวนการ ผลผลิต และการเรียนรู้)

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คำสืบค้น (Keywords) hot-melt extrusion, direct compression, floating tablet, riboflavin, raman imaging technique

การนำผลงานวิจัยไปใช้ประโยชน์ (ดูคำจำกัดความ และตัวอย่างด้านหลังแบบฟอร์ม)

☐ **ด้านนโยบาย** **โดยใคร** (กรุณาให้ข้อมูลเจาะจง).....

มีการนำไปใช้อย่างไร .....

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☐ **ด้านวิชาการ** (กรุณาให้ข้อมูลเจาะจง).....

มีการนำไปใช้อย่างไร .....

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(กรณีที่ยังไม่มีการใช้ประโยชน์) ผลงานวิจัยมีศักยภาพในการนำไปใช้ประโยชน์

☐ ด้านนโยบาย ☐ ด้านสาธารณะ ☐ ด้านชุมชนและพื้นที่ ☐ ด้านพาณิชย์ ☑ ด้านวิชาการ

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- ศาสตราจารย์ ดร.พรศักดิ์ ศรีอมรศักดิ์ คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร – ร่วมกันนำผลงานวิจัยไปศึกษาต่อยอด
- Professor Dr. Jürgen Siepmann, Univ. Lille, Inserm, CHU Lille, U1008 - Controlled Drug Delivery Systems and Biomaterials, F-59000, Lille, France – ร่วมกันนำผลงานวิจัยไปศึกษาต่อยอด

การเผยแพร่/ประชาสัมพันธ์ (กรุณาให้รายละเอียด พร้อมแนบหลักฐาน)

1. สิ่งพิมพ์ หรือสื่อทั่วไป

☐ หนังสือพิมพ์ ☐ วารสาร ☐ โทรทัศน์ ☐ วิทยุ ☐ เว็บไซต์ ☐ คู่มือ/แผ่นพับ ☐ จัดประชุม/อบรม ☐ อื่น ๆ

.....

2. สิ่งพิมพ์ทางวิชาการ (วารสาร, การประชุม ให้ระบุรายละเอียดแบบการเขียนเอกสารอ้างอิง เพื่อการค้นหาซึ่งควรประกอบด้วย

ชื่อผู้แต่ง ชื่อเรื่อง แหล่งพิมพ์ ปี พ.ศ. (ค.ศ.) ฉบับที่ หน้า)

ผลงานวิจัยที่นำเสนอในที่ประชุมวิชาการ (Proceedings)

Kriangkrai W, Puttipipatkhachorn S, Sriamornsak P, Siepmann F, Siepmann J, Sungthongjeen S. Preparation and comparison of floating tablets manufactured by hot-melt extrusion and direct compression. In: Shuwisitkul D, editors. Pharmaceutical Sciences and Technology 2018; 2018 Jan 24-25; Bangkok, Thailand: Thai Industrial Pharmacist Association, Society of Pharmaceutical Education & Research, Silpakorn University; 2018 Jan. p. 109-12.

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- การนำเสนอผลงาน (โปสเตอร์) “Physicochemical properties and drug release from floating tablets manufactured by hot-melt extrusion and direct compression” ใน งานประชุมวิชาการ สำนักงานกองทุนสนับสนุนงานวิจัย (สกว.): นักวิจัยใหม่ พบ เมธีวิจัยอาวุโส (TOAC2019) วันที่ 9-11 มกราคม 2562 ณ โรงแรมเดอะรีเจ้นท์ชะอำ บีช รีสอร์ท จังหวัดเพชรบุรี ประเทศไทย

คำอธิบายและตัวอย่างการนำไปใช้ประโยชน์ในแต่ละด้าน

1. การใช้ประโยชน์ด้านนโยบาย

คำจำกัดความ : การนำความรู้จากงานวิจัยไปใช้ในกระบวนการกำหนดนโยบาย ซึ่งนโยบายหมายถึง หลักการ แนวทาง กลยุทธ์ ในการดำเนินงานเพื่อให้บรรลุวัตถุประสงค์ อาจเป็นนโยบายระดับประเทศ ระดับภูมิภาค ระดับจังหวัด ระดับท้องถิ่น หรือระดับหน่วยงาน นโยบายที่ดีจะต้องประกอบด้วยวัตถุประสงค์ แนวทาง และกลไกในการดำเนินงานที่ชัดเจน สอดคล้องกับปัญหาและความต้องการ การใช้ประโยชน์ด้านนโยบายจะรวมทั้งการนำองค์ความรู้ไปสังเคราะห์เป็นนโยบายหรือทางเลือกเชิงนโยบาย (policy options) แล้วนำนโยบายนั้นไปสู่ผู้ใช้ประโยชน์

2. การใช้ประโยชน์ด้านสาธารณะ

คำจำกัดความ : การดำเนินงานเพื่อนำผลงานวิจัยและนวัตกรรม ไปใช้ในวงกว้างเพื่อประโยชน์ของสังคม และประชาชนทั่วไป ให้มีความรู้ความเข้าใจ เกิดความตระหนัก รู้เท่าทันการเปลี่ยนแปลง ซึ่งนำไปสู่ การเปลี่ยนวิธีคิด พฤติกรรม เพื่อเพิ่มคุณภาพชีวิตของประชาชน สร้างสังคมคุณภาพ และส่งเสริมคุณภาพสิ่งแวดล้อม

3. การใช้ประโยชน์ด้านพาณิชย์

คำจำกัดความ : การนำนวัตกรรม เทคโนโลยี ผลิตภัณฑ์ใหม่ พันธุ์พืช พันธุ์สัตว์ ไปสู่การผลิตในเชิงพาณิชย์ การสร้างมูลค่าเพิ่มของผลิตภัณฑ์ การแปรรูป การสร้างตราสินค้า การเพิ่มประสิทธิภาพในกระบวนการผลิต และการลดต้นทุนการผลิต การสร้างอาชีพ และทางเลือกให้กับผู้ประกอบการ เกษตรกรหรือผู้ประกอบอาชีพอื่น ๆ

4. การใช้ประโยชน์ด้านชุมชนและพื้นที่

คำจำกัดความ : การนำกระบวนการ วิธีการ องค์ความรู้ การเปลี่ยนแปลง การเสริมพลัง อันเป็นผลกระทบที่เกิดจากการวิจัยและพัฒนาชุมชน ท้องถิ่น พื้นที่ ไปใช้ให้เกิดประโยชน์การขยายผลต่อชุมชนท้องถิ่นและสังคมอื่น

5. การใช้ประโยชน์ด้านวิชาการ

คำจำกัดความ : การนำองค์ความรู้จากผลงานวิจัยที่ตีพิมพ์ในรูปแบบต่าง ๆ เช่น ผลงานตีพิมพ์ในวารสารระดับนานาชาติ ระดับชาติ หนังสือ ตำรา บทเรียน ไปเป็นประโยชน์ด้านวิชาการ การเรียนรู้

การเรียน การสอน ในวงนักวิชาการและผู้สนใจด้านวิชาการ รวมถึงการนำผลงานวิจัยไปวิจัยต่อยอด หรือ การนำไปสู่ product และ process ไปใช้ในการเสริมสร้างนวัตกรรม และเทคโนโลยี