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Systemic investigation of multiparticulate systems (MPS) for controlled release dosage forms employing Quality by Design (QbD) principles

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COMMITTEE DECISION

This Thesis (Systemic investigation of multiparticulate systems (MPS) for controlled release dosage forms employing Quality by Design [QbD] principles) was Successfully Defended and Approved on ----------

Examination Committee	Signature

Dedication

All praise to Allah, today we fold the days' tiredness and the errand summing up between the cover of this humble work. To the utmost knowledge lighthouse, to our greatest and most honoured prophet Mohamed - May peace and grace from Allah be upon him

To the Spring that never stops giving, to my mother who weaves my happiness with strings from her merciful heart... to my mother

To whom he strives to bless comfort and welfare and never stints what he owns to push me in the success way who taught me to promote life stairs wisely and patiently, to my dearest father

To whose love flows in my veins, and my heart always remembers them, to my brothers and sisters.

To those who taught us letters of gold and words of jewel of the utmost and sweetest sentences in the whole knowledge. Who reworded to us their knowledge simply and from their thoughts made a lighthouse guides us through the knowledge and success path, To our honored teachers and professors.

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List of Contents

Contents

List of Tables

Chapter three:

Chapter four:

Chapter five:

Chapter six:

List of Figures and Plates

Chapter one:

Chapter four:

Chapter five:

Chapter six:

List of Abbreviations

Critical Input parameters	CIP
Critical Quality Attributes	CQA
Cyclo-oxygenase	COX
Design of experiments	DOE
Dibasic calcium phosphate	DCP
Dissolution of coarse granules	DIS-C
Dissolution of fine granules	DIS-F
Distilled Water	DW
Ethylcellulose	ETH
European Medicines Agency	EMA
Experiment name	EN
Flowability of coarse granules	FLOW-C
Flowability of fine granules	FLOW-F
Fourier-transform infrared spectroscopy	FTIR
Gastro-Intestinal Tract	GIT
Gram	g
High Performance Liquid Chromatography	HPLC
Hydroxy propyl methyl cellulose	HPMC
Ibuprofen	IBU
International Conference of Harmonization	ICH
International unit	IU
Limit of detection	LOD
Limit of quantification	LOQ
Microgram	µg
Microcrystalline cellulose	MCC
Milligram	mg
Milliliter	ml
Minute	min
Multiparticulate system	MPS
Nanometer	nm
Non-steroidal anti-inflammatory drugs	NSAIDs
Number	NO
Polyvinyl-pyrrolidone	PVP
Quality by Design	QbD
Relative standard deviation	RSD
Run Order	RO
Scanning Electron Microscopy	SEM
Sodium lauryl sulphate	SLS
Sustained release	SR
The correlation coefficient	R^2
Ultra Violet	UV
Ultraviolet-visible Spectroscopy	UV\Vis
United State Pharmacopeia	USP
Variable importance plot	VIP
World Health Organization	WHO

الملخص

يعد برنامج تصميم الجودة نهج أساسي في تطوير الصناعة الدوائية والعديد من العمليات الصيدلانية، ركزت هذه الدراسة على تطبيق البرنامج لتطوير نظام الأشكال الصيدلانية المتعددة بشكل حبيبات للتحكم بعملية تحرر الدواء على فترة طويلة. تم استخدام دواء الأيبوبروفين كنموذج لتطوير هذه الأشكال الصيدلانية باستخدام طريقة التحبب الرطب. في بداية المشروع البحثي تم التحقق من عملية التحليل الكمي للايبوبروفين باستخدام الأشعة فوق البنفسجية والاعتماد على الإرشادات الدولية لتحديد الدقة والتقارب بالنتائج. ولكي يتحقق المشروع باستخدام هذا البرنامج بشكل فعال، تم القيام بدراسات أولية لتحديد العوامل المؤثرة على جودة وخصائص المنتج وتحديد الطريقة المثلى لإنتاج الأشكال الصيدلانية المتعددة. تضمنت الدراسة الأولية الاستعانة بالعديد من التقنيات التحليلية لتقييم جودة الحبيبات المنتجة مثل (تحليل حجم الحبيبات، اختبار الصلابة، تحليل نسبة الرطوبة، عملية الطلاء الخارجي، اختبار الانسيابية وسهولة حركة الحبيبات، ودراسات لكيفية تحرر الدواء). وتم بعد ذلك إجراء هذه التقنيات والاستفادة من مخرجاتها والحصول على النتائج واستخدامها للتعرف على العلاقة بين مدخلات المستحضرات المحببة واليات التصنيع ذات الأثر الأكبر على كفاءة المستحضر الصيدلاني والحبيبات، كالمكونات المستخدمة ومن ثم تم تحديد المدخلات التالية: نسبة كل من الايبوبروفين، ايثيل سيليلوز، والهيدروكسي بروبل ميثيل سليلوز كعوامل أساسية لتتضمن في البرنامج. وتم تحديد خصائص الاستجابة المستخدمة في البرنامج (القدرة على التدفق للحبيبات الكبيرة والصغيرة، سرعة التحلل للحبيبات الكبيرة والصغيرة، ونسبة الدواء في الحبيبات). ومن مخرجات تطبيق النظام تبين ان تركيز كلا من نسبة ايثيل سيليلوز وهيدروكسي بروبل ميثيل سليلوز له الأثر الأكبر في جودة وكفاءة الحبيبات.

Systemic investigation of multiparticulate systems (MPS) for controlled release dosage forms employing Quality by Design (QbD) principles

By

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Abstract

Quality by design (QbD) is a key approach in pharmaceutical process development. This study focused on the application of QbD principles to develop multiparticulate system (MPS) with controlled release profile. Model drug, ibuprofen, was employed to develop the controlled release MPS using wet granulation method. The project started with validation of quantitative analytical technique for ibuprofen using UV-spectrometry and based on the ICH guidelines in terms of specificity, accuracy, precision, linearity, limit of detection and limit of quantification. To enable effective QbD project, initial screening studies were conducted. The outcome of the screening studies set the boundaries for the QbD, where critical factors and product quality attributes were identified. Granulation process was optimized and a range of analytical techniques were investigated during screening process to assess the quality of the produced granules. Characterization included, granules size analysis, hardness test, moisture content analysis, coating process, flowability test, FTIR analysis and drug release studies. The results were used to establish the boundaries of the design of experiment (DOE) using MODDE software to detect the relationship between factors (HPMC, Ibuprofen, ethylcellulose concentrations) and the critical quality attributes/ responses (dissolution of coarse and fine MPS, content uniformity and flowability of coarse and fine MPS). The produced model was verified using multiple verification tools then the coefficient plots were used to understand the effect of factors on responses. The outcome of this study was the determination of design

space to specify the desirable range of input parameters for successful MPS. Ethylcellulose concentration of 0.25%- 0.5% and HPMC concentration of 15%- 30% were the key factors affecting MPS performance. The produced MPS could be further used to develop several dosage forms ranging from granules in sachets, capsules or compressed into orally disintegrating tablets which could be suitable for age specific population.