



**DEVELOPMENT, CHARACTERIZATION AND
PHARMACOKINETIC STUDY OF SOLID DISPERSION
FORMULATION OF TELMISARTAN**

BY

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(Pharmaceutical Technology)**

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ABSTRACT

The drugs that belong to class II of Biopharmaceutical Classification System face several challenges in their dissolution and bioavailability due to their poor water solubility. Solid dispersion is an effective method to enhance the solubility of poorly water-soluble drug. Telmisartan is an antihypertensive drug with poor dissolution and poor bioavailability because of its low aqueous solubility. To enhance the solubility of telmisartan solid dispersion using freeze-drying method was carried out to formulate telmisartan with PVP K30 as carrier and Na_2CO_3 as alkalizer, and complete characterization using *in vitro* dissolution in different pH dissolution medium, FTIR, DSC, XRD and SEM was performed. Short term stability study in accelerated and ambient conditions on solid-dispersed telmisartan powders was carried out for two months. *In vivo* study in a rat model was performed to determine the bioavailability of solid-dispersed formulations compared to raw drug and marketed telmisartan tablet. From the results, it was found that the solid dispersion formulations presented higher *in vitro* drug release rate in different pH media (pH 1.2, 6.8 & 7.5) compared to raw and marketed telmisartan tablet. Solid-dispersed formulations containing drug: PVP K30: Na_2CO_3 at a weight ratio of 1:1:2, 1:2:2 and 1:3:2 were selected as the most suitable formulations based on the higher dissolution and low amount of excipients. Based on the results of FTIR, there was no physical incompatibility between telmisartan and excipients in the dry state. The DSC and SEM results described the absence or reduction of telmisartan crystallinity. The XRD results confirmed that the crystallinity of telmisartan was significantly reduced and it was changed to amorphous form after solid dispersion. There was no change in *in vitro* drug release rate and physical nature of dry powder of the selected solid-dispersed formulations after two months of stability study. The pharmacokinetic studies in the rat model were performed after oral administration of selected solid-dispersed formulations (drug: PVP K30: Na_2CO_3 at a weight ratio of 1:1:2 and 1:2:2), raw drug and marketed telmisartan tablet. The highest C_{max} and $\text{AUC}_{0-\text{inf}}$ recorded for the two tested solid-dispersed formulations (drug: PVP K30: Na_2CO_3 at a weight ratio of 1:1:2, 1:2:2) were 0.611 ± 0.303 , 1.363 ± 0.229 $\mu\text{g/ml}$ and 4.876 ± 0.556 , 5.564 ± 0.63 $\mu\text{g h/ml}$ respectively. In addition, K_{el} and $T_{1/2}$ of two solid-dispersed formulations 1:1:2, 1:2:2 were 0.198 ± 0.11 , 0.241 ± 0.031 h^{-1} and 4.802 ± 3.619 , 2.91 ± 0.39 h respectively, and there was no significant difference ($p > 0.05$) in K_{el} and $T_{1/2}$ between two solid-dispersed formulations and marketed telmisartan tablet. Moreover, the relative bioavailability of the above mentioned solid dispersion formulations were 246.15 ± 28.04 and $280.88 \pm 31.80\%$, respectively with respect to marketed telmisartan tablet. The overall results indicate that reduction of telmisartan crystallinity and the presence of alkalizer promote higher *in vitro* dissolution in all mediums in case of solid dispersion formulations of telmisartan. The *in vivo* relative bioavailability study also indicates better systemic absorption of telmisartan from freeze-dried solid dispersion formulations. It can be concluded that freeze-dried solid dispersion formulations of telmisartan containing PVP K30 as carrier and Na_2CO_3 as alkalizer have the potential of overcoming poor solubility and bioavailability issues of telmisartan.

خلاصة البحث

تواجه الأدوية التي تنتمي إلى نظام التصنيف الصيدلاني البيولوجي من الدرجة الثانية عدة تحديات في تحللها وتوافرها البيولوجي بسبب ضعف قابليتها للذوبان في الماء. يعتبر التبعثر الصلب طريقة فعالة لتعزيز القابلية للذوبان. التلميسارتان دواء خافض للضغط، ضعيف في الانحلال وفي التوافر الحيوي بسبب قلة قابليته للذوبان في الماء. لتعزيز قابلية ذوبان التلميسارتان في الماء، تم تنفيذ التبعثر الصلب باستخدام طريقة التحفيف بالتجميد للتلميسارتان مع PVP K30 كحامل و صوديوم كربونات كعامل قلوي، وتم دراسة مواصفات التبعثر الصلب للتلميسارتان باستخدام الإنحلال في المختبر و FTIR و DSC و XRD و SEM. كما تم دراسة الإستقرار على مساحيق التبعثر الصلب للتلميسارتان لمدة شهرين في استقرار متسارع وأيضا في درجة حرارة الغرفة. من جهة أخرى تم تنفيذ الدراسة على الجسم الحي للفئران من اجل تحديد التوافر الحيوي للتبعثر الصلب للتلميسارتان ومقارنتها مع التلميسارتان الخام والتجاري. وقد تبين من النتائج أن صيغ التبعثر الصلب قد أظهرت تحسن في إنحلال التلميسارتان في كل الأوساط الحمضية (1.2، 6.8، 7.5) مقارنة مع التلميسارتان الخام والتجاري. لذلك تم اختيار الصيغ التي تحتوي على التلميسارتان و PVP K30 و صوديوم كربونات بنسب وزنية: 1:1:2، 1:2:2، 1:3:2 كأفضل الصيغ بسبب ارتفاع نسبة إنحلالها واحتوائها على كمية منخفضة من السواغات الغير فعالة. إستنادا إلى نتائج FTIR لم يكن هناك عدم توافق بين التلميسارتان والسواغات. من جهة اخرى، وصفت نتائج DSC و SEM غياب أو تقليل بلورات التلميسارتان وأكدت نتائج XRD أن بلورة التلميسارتان انخفضت بشكل كبير وتغيرت إلى شكل غير متبلور بعد التبعثر الصلب. كذلك لم يحدث اي تغير في إنحلال صيغ التبعثر الصلب المختارة ولا في خواصها الفيزيائية وظلت مستقره خلال فترة الاستقرار. تم أيضا إجراء دراسات الحرائك الدوائية في الفئران بعد تناولها عن طريق الفم لصيغ التبعثر الصلب التي تحتوي على التلميسارتان و PVP K30 و صوديوم كربونات بنسب وزنية: 1:1:2، 1:2:2 وايضا التلميسارتان الخام والتجاري. وقد كانت أعلى C_{max} و AUC_{0-inf} في صيغ التبعثر الصلب 1:1:2 و 1:2:2 حيث كانت 0.611 ± 0.303 ، 1.363 ± 0.229 ميكروجرام/مل وايضا 4.876 ± 0.556 ، 5.564 ± 0.63 ميكروجرام كل ساعه/مل، على التوالي. علاوة على ذلك، كان التوافر الحيوي النسبي لصيغ التبعثر الصلب المذكوره سابقا 246.15 ± 28.04 و 280.88 ± 31.80 %، على التوالي مقارنة مع التلميسارتان التجاري.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master in Pharmaceutical Sciences (Pharmaceutical Technology)

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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LIST OF ABBREVIATIONS

AC	Accelerated Stability Study
AED	Animal Equivalent Dose
AMB	Ambient
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
ARB	Angiotensin Receptor Blocker
ATR-FTIR	Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy
AUC _{0-inf}	Areas under the plasma-concentration–time curve from time zero to infinity
AUC _{0-t}	Areas under the plasma-concentration–time curve from time zero to the last measurable TEL sample time.
BCS	Biopharmaceutical Classification System
CC	Calibration Curve
C _{max}	Maximum concentration
conc.	Concentration
Cu-K α	Copper K-Alpha Emission
DSC	Differential Scanning Calorimetry
Eq	Equation
et al.	and others
etc.	and so on
FDA	Food and Drug Administration
HPLC	High Performance Liquid Chromatography
HQC	High Quality Control
ICH	International Council for Harmonisation
IS	Internal Standard
K _{el}	Elimination rate constant
K _m	Correction factor
LCMS	Liquid Chromatography Mass Spectrometry
LOD	Limit of Detection
Log P	Partition coefficient for determining lipophilicity

LOQ	Limit of Quantification
LQC	Low Quality Control
MQC	Mid Quality Control
MSNs	Mesoporous Silica Nanoparticles
PEG	Polyethylene glycol
pH	A measure of hydrogen ion concentration
pH _M	Microenvironmental pH
pK _a	Acid dissociation constant
PM	Physical mixture
PTFE	polytetrafluoroethylene
<i>p</i> -value	Statistical significance testing value
PVP	Polyvinylpyrrolidone
QC	Quality Control
RH	Relative Humidity
RSD	Relative Standard Deviation
S.D.	Standard Deviation
SD	Solid Dispersion
SDs	Solid Dispersions
SEM	Scanning Electron Microscopy
SNEDDS	Self-nanoemulsifying drug delivery system
T _{1/2}	Elimination half-life
TEL	Telmisartan
T _g	Glass transition temperature
T _{max}	Time to reach the maximum concentration
TPGS	Tocopherol polyethylene glycol 1000 succinate
USP	United States Pharmacopeia
UV-VIS	Ultraviolet or visible light
vs	Versus
w.r.t	With respect to
XRD	X-ray Powder Diffraction

LIST OF SYMBOLS

Å	angstrom
$^{\circ}\text{C}$	degree Celsius
θ	diffraction angle
λ	wavelength
cm	centimeter
cps	Counts per second
g	gram
h	hour
hrs	hours
kV	kilovolt
L	liter
μg	microgram
μm	micrometer
M	Molarity
mA	milliamperage
mAU	milli absorbance unit
mbar	millibar
mg	milligram
min	minute
ml	milliliter
N	Normality
nm	nanometer
R^2	linear correlation coefficient
rpm	rotation per minute
v	volume
w	weight

LIST OF EQUATIONS

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3.3	Cumulative drug release %	38
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3.5	Animal equivalent dose (AED; mg/kg)	45
3.6	Relative bioavailability	47
4.1	Henderson-Hasselbalch (H-H)	59
4.2	Similarity Factor (f_2)	71

CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Poor bioavailability of drug is the major challenge while designing the oral dosage form. Lipophilic molecules having poor aqueous solubility and poor dissolution profile, poses a great challenge to the formulation of oral drug. According to Biopharmaceutical Classification System, BCS class II drugs exhibit low solubility and high permeability. The dissolution is the rate limiting step in this class for its oral absorption, which results in poor oral bioavailability (Kawabata et al., 2011). Therefore, the rate and extent of absorption of these compounds are highly dependent on the performance of the formulation.

Several approaches are applied to enhance the drug solubility such as modification of the crystal habit, reduction of the particle size, solid dispersions, solid solutions, salt formation, and miscellaneous methods, namely, supercritical fluid process and use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients (Savjani et al., 2012). Solid dispersion technique is one of the strategies that is used to improve the solubility of poor water-soluble drug. Solid dispersion technique have many advantages in enhancing the solubility and dissolution rate of the poorly water-soluble drug by reducing the particles size, improved wettability & porosity and changing the drug crystalline state into a more preferable amorphous state (Vasconcelos et al., 2007). The choice of polymer has a remarkable impact on the success of this solid dispersion formulation. The polymer should be inert (safe) and stable, remain chemically and physically stable upon storage and preparation method (Baghel et al., 2016). Solid dispersion is mainly prepared by

two methods: heat based method, such as hot-melt extrusion, melt granulation and melt mixing and solvent based method, such as spray-drying and lyophilization. Each method has its own advantages and limitations, for instance: the thermal instability of drugs and selection of suitable carriers in the melting method, the use of organic solvent in the solvent evaporation method. These problems must be kept in mind while selecting the proper manufacturing method. Current advances in formulation, preparation and characterization of solid dispersions can overcome some of the limitation of solid dispersion products. Moreover, the careful selection of the solid dispersion formulation, such as polymer excipients and polymer/drug ratio, as well as processing parameter, is of critical importance in order to achieve the stable solid dispersion products at storage temperature and to create the favourable dissolution profile (Huang & Dai, 2014).

In the present study, the drug of interest is Telmisartan (TEL), which is an angiotensin II type I receptor blocker (ARB), useful in the treatment of hypertension (Kumar et al., 2010). TEL belongs to class II in Biopharmaceutical Classification System. The solubility of TEL is strongly pH-dependent, with maximum solubility observed only at high or low pH and it is poorly soluble in the pH range of 3-9 (Wienen et al., 2000). The poor solubility of TEL in intestinal medium obstructs its oral bioavailability. In this study, TEL was solid-dispersed in a suitable water-soluble polymer with the presence of alkalizer to enhance solubility and bioavailability. Both *in vitro* and *in vivo* studies had been carried out to evaluate the dissolution and bioavailability improvement.

1.2 STATEMENT OF THE PROBLEM

Bioavailability of orally administered TEL is reported to be low (approximately 40%). One of the main reasons is low aqueous solubility of TEL, followed by poor dissolution in intestinal medium. TEL belongs to BCS class II which means it possesses low solubility but high permeability.

TEL has pH-dependent solubility, it is soluble in high acidic and basic pH and it is practically insoluble in water and pH range 3-9. In spite of the solubility of TEL is high in gastric medium, its absorption in gastric medium is very low. In contrast, the solubility of TEL in intestine is very low which is considered the main site for TEL absorption. Also, the fraction of TEL which is soluble in gastric medium, is precipitated when reaches to intestinal medium like all BCS class II as reported by some researchers (Carlert et al., 2012; Tsume et al., 2013).

Enose et al. (2016) and Marasini et al. (2013) have formulated TEL as solid dispersion by melt extrusion involving heat and low melting point polymer and spray-drying involving organic solvents or complicated process. Tran et al. (2008) and Phuong et al. (2011) also have developed the solid-dispersed TEL using melt and solvent evaporation methods involving organic solvent. However, freeze-drying to prepare TEL solid dispersion has not been adopted yet. This simple technique offers use of completely aqueous solvent instead of organic.

In addition to that, the amorphous solid dispersion has issue with stability during storage. If amorphous material recrystallizes, then the advantages of improved solubility and dissolution would be compromised. To maintain the amorphous structure of the drug, high amount of polymer is required to incorporate into the SD system, which reduces its acceptability in downstream processing. Use of pH modifier can reduce the required polymer amount.

1.3 RESEARCH HYPOTHESES

1. Solid dispersion of TEL can be prepared by freeze-drying, which will enhance its *in vitro* dissolution.
2. Solid dispersion of TEL prepared by freeze-drying containing polymer-alkalinizer mixture will enhance its *in vivo* absorption.

1.4 OBJECTIVES OF THE RESEARCH

The main aim of this research entitled “Development, Characterization and Pharmacokinetic Study of Solid Dispersion Formulation of Telmisartan” is to develop and characterize a solid-dispersed TEL formulation with enhanced dissolution and oral bioavailability. The following specific objectives would be met in order to achieve the goal.

- i. To develop and formulate TEL solid dispersion formulations by freeze-drying.
- ii. To characterize the solid dispersion by solid state characterization techniques and *in vitro* dissolution with reference to raw TEL and marketed TEL tablet.
- iii. To evaluate the stability of developed formulations in accelerated and ambient storage condition studies.
- iv. To determine the pharmacokinetic parameters and oral bioavailability of TEL in SD formulations by *in vivo* pharmacokinetic study in rat model with reference to raw TEL and marketed TEL tablet.

CHAPTER TWO

LITERATURE REVIEW

2.1 PROBLEM WITH POORLY SOLUBLE DRUGS

The advent of new techniques in drug discovery has led to the discovery of many drug candidates (Robertson et al., 2015) but more than 40% of these drug candidates are poorly water-soluble (Takagi et al., 2006). The poorly soluble drug candidates face formulation problems, as they cannot be produced using conventional methods and also have numerous performance issues associated with formulation. Additionally, the poor aqueous solubility of the drugs result in poor dissolution rate in body and eventually, low bioavailability. In orally administered drugs, compounds with less than 100 µg/ml aqueous solubility exhibit restricted absorption due to poor dissolution (Hörter & Dressman, 2001). One way to address the problem regarding the improvement of the drug bioavailability in poorly soluble drugs, would be dose escalation to achieve therapeutic drug concentration range. However, this is undesirable especially in orally administered drugs, as it may cause topical toxicity in the gastrointestinal tract, which may lead to poor patient compliance such as nonsteroidal anti-inflammatory drugs (diclofenac, flurbiprofen & aceclofenac) (Varshney & Chatterjee, 2012). In addition, the use of large amounts of the active pharmaceutical ingredient would be needed in developing and manufacturing the drug product to achieve the desired therapeutic effect, that leads to increasing the costs of manufacturing (Kawabata et al., 2011). In summary, poorly water-soluble drugs present several issues from patient compliance and safety to cost effectiveness. The biopharmaceutical classification system (BCS) is a useful tool for decision-making regarding the development of drug formulation based on their solubility and intestinal

permeability (Amidon et al., 1995). Drugs can be categorized into four classes according to United State Food and Drug Administration (FDA, 2000) as illustrated in Figure 2.1. Class I and III drugs with high solubility but variable permeability are formulated following simple methods, whereas class II and IV drugs with low solubility and variable permeability require more complicated formulation strategies to achieve desirable bioavailability following oral administration (Kawabata et al., 2011).

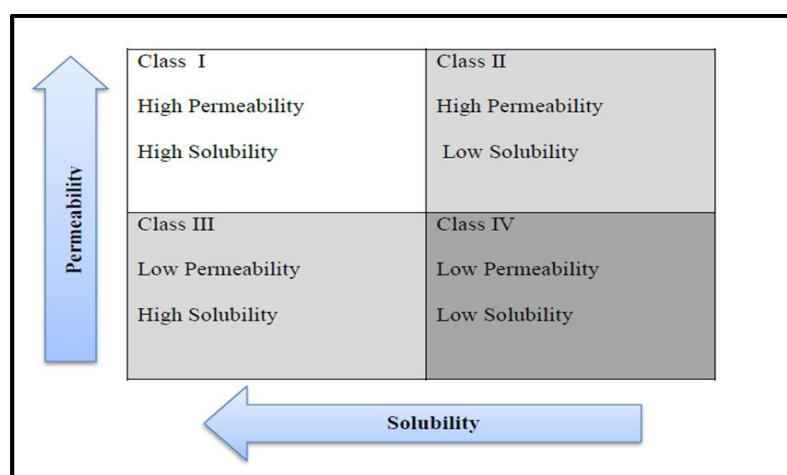


Figure 2.1 BCS Classification System of Pharmaceutical Drugs

2.2 THE DRUG OF INTEREST: TELMISARTAN (TEL)

TEL is a Class II drug with poor solubility and high permeability; thus it is a potential candidate for solubility improvement strategy.

2.2.1 Chemical Name and Physicochemical Properties of TEL

TEL is chemically described as [1,1-biphenyl]-2-carboxylic acid, 4-[(1,4-dimethyl-2-propyl[2,6-bi-1H-benzimidazol]-1-yl)methyl], the chemical structure of TEL is shown in Figure 2.2. It is a white crystalline powder with a molecular weight of 514.6 and a