"Optimization of the Formulation of Certain Buccal Delivery System"

A thesis submitted in the partial fulfillment of the requirements for the Master Degree in Pharmaceutical Sciences (Pharmaceutics)

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Dedicated to

My Parents, My Husband, My Brother,

My Sister and My Lovely son Omayr

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List of Abbreviations

Analysis of variance	ANOVA
Area under the plasma concentration-time curve from time zero to 12 hours	AUC_{0-12}
British pharmacopeia	BP
Carbon dioxide	CO_2
Centimetre	cm
Coefficient of variance	C.V
Collision energy	CE
Collision exit potential	CXP
Cyclic guanosine monophosphate	cGMP
Cytochrome P450 2C9	CYP2C9
Cytochrome P450 3A4	CYP3A4
Dalton	Da
Declustering potential	DP
Degree celius	°C
Differential Scanning Calorimetery	DSC
Disintegration time	DT
Entrance potential	EP
Food and drug administration	FDA
Fourier transform infrared spectroscopy	FTIR
Gastrointestinal tract	GIT
Gram	g
Hour	h
Human immunodeficiency virus	HIV
Idiopathic pulmonary arterial hypertension	IPAH
Infra red	IR
Internal standard	IS
Kilovolt	kV
Lambda maximum	λ_{max}
Liquid chromatography/Mass-Mass spectrophotometer	LC-MS/MS
Litre	L
Magnesium stearate	Mg.stearate
Mass-to-charge ratio	m/z
Melting point	m.p.
Membrane coating granules	MCG

Metre	m
Microgram	µg
Microlitre	µl
Micrometre	µm
Milliampere	mA
Millibar	mbar
Milligram	mg
Milliliter	ml
Millimeter	mm
Millimetre mercury	mmHg
Minutes	min
Molar	M
Molecular weight	MW
Multiple reaction monitoring	MRM
Nano metre	nm
Nanogram	ng
Newton	N
Peak area ratio	PAR
Peak plasma concentration	C_{max}
Phosphodiestrase type 5	PDE5
Physical mixtures	PX
Polyethylene glycol	PEG
Polyethylene oxide	PEO
Polypropylene oxide	PPO
Polyvinylchloride	PVC
Polyvinylidene chloride	PVDC
Polyvinylpyrrolidine	PVP
pound-force per square inch	psi
Primary pulmonary hypertension	PPH
Pulmonary Arterial Hypertension	PAH
Pulmonary hypertension	PH
Rapid Expansion of Supercritical Solution	RESS
Relative degree of crystallinity	RDC
Revolutions per minute	rpm
Second	sec
Sildenafil citrate	SILD
Sodium starch glycolate	SSG
Solid dispersion	SD

Solid dispersion technique	SDT
Specific phosphodiesterase type 5	PDE5
Standard deviation	S.D
Sublingual tablets	STs
Sulphur dioxide	SO_2
Terminal elimination rate constant	λz
Time to reach peak plasma concentration	T_{max}
Ultraviolet	UV
United Kingdom	UK
United States	U.S.
United States of America	USA
United States Pharmacopeia	USP
Volt	V
Volume per volume	v/v
Weight	W
Weight per weight	w/w
World Health Organization	WHO
Xanthan gum	X.gum
X-ray powder diffraction analysis	XRPD

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Abstract

Sildenafil (SILD) was approved by the U.S. Food and Drug Adminstration (FDA) for pulmonary arterial hypertension (PAH) treatment. Sublingual tablets (STs) of SILD was supposed to overcome SILD first-pass effect consequently enhancing oral bioavailability, achieving rapid onset of action and minimizing oral side effects, together with being non-invasive and of good patient compliance. The oral cavity is water rich environment which requires adequate aqueous drug solubility. However SILD is of poor aqueous solubility that necessities enhancement before tablet preparation. This was planned to be achieved by two comparative techniques; solid dispersion and freeze drying technique.

In Solid dispersion technique (SDT), polyethylene glycol 4000 (PEG 4000), polyethylene glycol 6000 (PEG 6000), polyethylene glycol 8000 (PEG 8000) and poloxamer 188 were used as solid polymers for preparation of SILD solid dispersion (SDs) by fusion method. The SDs that showed the optimum results were incorporated into ST by direct compression using two superdisintegrants (Pharmaburst and sodium starch glycolate) in different concentrations. Results showed that SD enhanced SILD solubility and dissolution in comparison with their physical mixture (PX) counterparts and plain drug. SDs containing poloxamer 188 and PEG 8000 showed the best evaluation results and therefore were selected for tablet compression. The physicochemical and solid state properties, as well as the dissolution behavior of the tablets were evaluated. The results revealed