Preface

Ischemic cardiovascular diseases are one of the leading reasons for morbidity as well as mortality in the 21st century. The formation of thrombi in blood vessels due to the disruption of atherosclerotic plaques is considered as the major reason that triggers their onset. Thrombosis plays a pivotal role in the creation of various cardiovascular events, such as ischemic cardiovascular disease and venous thromboembolism. Thrombosis is defined as localized blood clotting regulated by an activated coagulation cascade due to a myriad of abnormal physiological conditions. In other words, this disease mainly occurs due to the deposition of blood clots in vessels (thrombus) that obstruct blood flow in the circulatory system. A thrombus is an end product of the hemostatic process, resulting from aggregated platelet plugs and activated clotting factors involved in the coagulation pathway. It plays a dual role; physiological in the case of vascular damage and pathological in the case of thrombotic events. Currently, for the treatment of thrombosis, rapid revascularization is available as the best emergent therapy, by angioplasty and surgical interventions of the occluded vessel. But it is a time taking process involving the transfer of the patient to a specialized hospital where cardiac surgery can be performed. Clinically, intravenous and oral administration of various anti-thrombotic drugs like anticoagulants, anti-platelets, and thrombolytic agents is also a treatment option for arterial and venous thrombosis for cardiac patients. Many of these anti-thrombotic drugs have short half-lives, require high doses, have poor targeting capability, have low therapeutic windows, require constant monitoring, and can easily induce hemorrhage and other side effects. Therefore, effective and safe delivery of these anti-thrombotic agents at the target site is the primary objective of anti-thrombotic treatment. Hence, in order to minimize side effects and maximize targeting efficiency, various approaches have been exploited, such as formulating drug-loaded nanoparticles, liposomes, micelles, nano-vectors, etc. with the addition of targeting

peptides on their surface or by using different external forces like a magnetic field, ultrasound, heat, light, etc.

The present study includes the development of mesoporous silica nanoparticles (MSN) for the efficient delivery of abciximab (ABX) for targeted and improved antithrombotic activity and targeted rutin-loaded liposomes for site-specific antithrombotic effects. The prepared nanoformulations were characterized through a variety of characterization parameters, including particle size, zeta potential, percent entrapment efficiency, morphological characterization (scannining electron microscopy, and transmission electron microscopy) encapsulation, drug release, hemolysis, targeting capability, platelet binding fluorescence imaging study, hemolysis, clot lysis, blood clot assay, tail bleeding, clotting time, ferric chloride-induced thrombosis study, pharmacokinetic study, and histopathological study.

Firstly, ABX decorated MSN was synthesized and the physicochemical characterization confirms the successful loading of ABX by X-ray photoelectron spectroscopy, transmission electron microscopy, and Bradford assay. Activity based analysis suggest the therapeutic effect of ABX remains same after conjugation. *In-vitro* imaging study suggest the potent affinity of MSN-ABX towards activated platelets. *In-vivo* analysis demonstrated the enhancement of therapeutic effect with no bleeding risk over clinical ABX injection. Furthermore, biosafety evaluations presented its *in-vitro* safety in human blood.

Moreover, we proposed novel liposomal formulation, which was loaded with RUT, and the surface of these vesicles was conjugated with tripeptide RGD and ABX (monoclonal antibody) as a targeting moiety (antagonist of GPIIb/IIIa receptor) to target the thrombus site were characterized for their physicochemical properties confirms satisfiable data related to size, shape, zeta potential,crystallinity, thermal stability and surface chemistry. The non-targeted and targeted liposomal formulations showed good stability, satisfiable

hemocompatibility, better *in-vitro* and *in-vivo* efficacy as compared to pure drug. In comparison with RUT, RUT-LIPO solved the solubility, bioavailability, and short half-life problem of RUT, but minimized related side effects as well. Moreover, an *in-vitro* assessment carried out with human blood showed the more credible antithrombotic potential of ABX-RUT-LIPO over RGD-RUT-LIPO due to its crucial binding to human integrin receptors. *In-vivo* evaluations demonstrated that RUT-LIPO, RGD-RUT-LIPO, and ABX-RUT-LIPO liposomal formulations maintained the antithrombotic function of RUT, prolonged the coagulation time in both intrinsic and extrinsic pathways. The histopathological examination demonstrated better safety in Sprague Dawley rats as compared to RUT.