Table of content

List of Figures	ix
List of Tables	xiii
Abbreviations	xiv
Preface	xvi
1.0 Introduction	1-19
1.1 Causes of Cerebral Stroke	2
1.2 Epidemiology	2
1.3 Clinical diagnosis.	3
1.4 Types of cerebral ischemia	4
1.5 Animal models of focal cerebral ischemic stroke	7
1.6 Role of platelets in focal cerebral ischemic stroke.	8
1.7 Current guideline for the treatment of ischemic stroke	9
1.8 Possible treatment strategy for ischemic stroke	13
1.9 Origin of thesis.	16
1.10 Hypothesis	16
1.11 Objectives of thesis	19
2.0 Pharmacokinetic and Brain Penetration Study of Piracetam in Focal Cerebral Ischemic	
Rats	20-42
2.1 Abstract	20
2.2 Introduction.	21
2.3 Hypothesis.	24
2.4 Materials and methods	24
2.5 Results.	31
2.6 Discussion.	38
3.0 Pharmacological effect of Barium Containing Bioactive Glass (BaBG) & Silver Containing	
Bioactive Glass (AgBG) for the treatment of Cerebral Ischemic Reperfusion Injury	43-86
3.1 Abstract	43
3.2 Introduction.	44
3.3 Hypothesis.	46
3.4 Materials and methods	47
3.5 Results.	58
3.6 Discussion.	82
4.0 Acute and Subacute Toxicity Studies of BaBG & AgBG in Wistar Rats	87-114
4.1 Abstract	87
4.2 Introduction.	88
4.3 Materials and methods	90
4.4 Results.	94
4.5 Discussion.	110

5.0 Pharmacological effect of Barium Containing Bioactive Glass in Ischemic and other			
Gastro-Duodenal Ulcers			
5.1 Abstract			
5.2 Introduction.			
5.3 Materials and methods			
5.4 Results.			
5.5 Discussion.			
6.0 Summary and Conclusion			
References			
List of publication from thesis			

List of Figures

Figure No.	Description	Page No.
Figure 1.1	Proposed hypothesis	18
Figure 2.1	Proposed hypothesis	24
Figure 2.2	Chemical structure of piracetam	25
Figure 2.3	Schematic representation of the experimental design	26
Figure 2.4	Plasma log concentration-time curve of piracetam in control group rats and ischemic stroke group rats after oral administration of piracetam (200 mg/kg)	32
Figure 2.5	Plasma log concentration-time curve of piracetam in control group rats and ischemic group rats after intravenous administration of piracetam (75 mg/kg)	32
Figure 2.6	Represent the effects of piracetam on infarct volume in middle cerebral artery occlusion rats after 24 h post-dose	37
Figure 3.1	Proposed hypothesis	47
Figure 3.2	Schematic representation of the experimental design	48
Figure 3.3	FTIR transmittance spectral analysis of BaBG and 45S5 samples	59
Figure 3.4	(A) SEM images and (B) Energy-dispersive X-ray spectroscopy of BaBG	60
Figure 3.5	FTIR transmittance spectral analysis of AgBG and 45S5 samples	61
Figure 3.6	(A) SEM images and (B) Energy-dispersive X-ray spectroscopy of AgBG	62
Figure 3.7	(A) shows representative aggregation curve, (B) In- vitro dose-response inhibition curves of BaBG on ADP-induced platelet aggregation in healthy rat PRP	63
Figure 3.8	Ex-vivo effects of BaBG on ADP induced platelet aggregation in ischemic rat PRP	64
Figure 3.9	(A) shows representative aggregation curve, (B) In- vitro dose-response inhibition curves for AgBG inhibitory actions on ADP-induced platelet aggregation in healthy rat PRP	65
Figure 3.10	Ex-vivo effects of AgBG on ADP induced platelet aggregation in ischemic rat PRP	66
Figure 3.11	Bars represent the effect of BaBG on carrageenan induced tail thrombosis	66
Figure 3.12	Bars represent the effect of AgBG on carrageenan induced tail thrombosis	67
Figure 3.13	Bars represent the effect of BaBG on changes in mean CBF in MCAO rats	68
Figure 3.14	Bars represent the effect of AgBG on changes in mean CBF in MCAO rats	69
Figure 3.15	Bars represent the effect of BaBG on EEG changes in MCAO rats	70
Figure 3.16	Bars represent the effect of AgBG on EEG changes in MCAO rats	71
Figure 3.17	Effect of BaBG on brain infarct volume in MCAO rats	72

Figure 3.18	Effect of AgBG on brain infarct volume in MCAO	73
Figure 3.19	Bars represent the effect of BaBG on changes in behavioral test in MCAO rats	75
Figure 3.20	Bars represent the effect of AgBG on changes in behavioral test in MCAO rats	76
Figure 3.21	Effects of BaBG on cortex of the ischemic brain	78
Figure 3.22	(A) SEM images and (B) Energy-dispersive X-ray spectroscopy of cortex of the ischemic brain at the dose of 1.0 mg/kg BaBG on the last day of the experimentin MCAO rats	78
Figure 3.23	Effects of AgBG on cortex of the ischemic brain	79
Figure 3.24	(A) SEM images and (B) Energy-dispersive X-ray spectroscopy of cortex of the ischemic brain at the dose of 5.0 mg/kg AgBG on the last day of the experiment	80
Figure 3.25	Bars represent the effects of BaBG on VEGF level in MCAO rats	80
Figure 3.26	Bars represent the effects of AgBG on VEGF level in MCAO rats	81
Figure 4.1	Schematic representation of the experimental design	91
Figure 4.2	Effect of 28 days daily intravenous administration of BaBG at dose of 1, 10, and 50 mg/kg in histology stained with (H.E., haematoxylin and eosin) of highly perfused organ including kidney, liver, lung, spleen, stomach, brain, heart and bone marrow in rats	106
Figure 4.3	Effect of 28 days daily intravenous administration of AgBG at dose of 5, 10, and 50 mg/kg in histology stained with (H.E., haematoxylin and eosin) of highly perfused organ including kidney, liver, lung, spleen, stomach, brain, heart and bone marrow in rats	108
Figure 4.4	Deposition of BaBG in liver. Liver image A was captured at magnification of 200X shows presence of particle, while image B shows particle present on the liver specimen have barium and silica peaks that confirm the particles are of BaBG	109
Figure 4.5	Deposition of AgBG in liver. Liver image (A) was captured at magnification of 200X shows presence of particle, while image (B) shows particle present on the liver specimen have silver and silica peaks that confirm the particles are of AgBG	109
Figure 5.1	pH behavior after immersion of the BaBG and 45S5 samples in SBF. Data are expressed as means \pm SEM (n=3). ap < 0.05 and bp < 0.05 compared with the 45S5 group on day 6 and 7 respectively	126
Figure 5.2	Bars represent the effect of BaBG on gastric blood flow	127
Figure 5.3	Bars represent the effect of BaBG on gross damage index in CAO rats	127
Figure 5.4	Bars represent the effect of BaBG on VEGF level on ischemic gastric mucosal tissue in CAO rats	128
Figure 5.5	Control group rats of ethanol-induced ulcer model have no disruption of the surface epithelium (A & G). Rats in the vehicle group have severe disruption of the	129

	surface epithelium, and extensive oedema of the submucosal layer and leukocyte infiltration are present (B & H). Rat in BaBG 0.3 mg/kg has disruption of the surface epithelium, and there is submucosal oedema (C & I). BaBG 1.0 mg/kg rat has moderate disruption of the surface epithelium with oedema of the submucosal layer (D & J). Rats in BaBG 3 mg/kg showed a mild disruption of the surface epithelium (E & K). The gastric mucosa in animals pretreated with omeprazole showed a mild disruption of the surface epithelium (F & L). Macroscopic damage indices were quantified (M)	
Figure 5.6	(A-D) shows the SEM images of gastric epithelial cells. (A) shows image of the sham group of the ethanol-induced model with normal gastric epithelial cell. (B) shows image of vehicle group and white arrow indicates severe damage in gastric epithelial cell. (C) shows image of treatment (1.0 mg/kg) group and white arrow indicate the formation of BaBG protective layer over the damaged gastric epithelial cell. Further image (D) clearly shown binding of BaBG at the erosive part of the stomach	130
Figure 5.7	Control group rats of pylorus ligation induced ulcer model have no disruption of the surface epithelium (A & G). Rats in the vehicle group have severe disruption of the surface epithelium, and extensive oedema of the submucosal layer and leukocyte infiltration are present (B & H). Rat in BaBG 0.3 mg/kg has disruption of the surface epithelium, and there is submucosal oedema (C & I). BaBG 1.0 mg/kg rat has moderate disruption of the surface epithelium with oedema of the submucosal layer (D & J). Rats in BaBG 3 mg/kg showed a mild disruption of the surface epithelium (E & K). The gastric mucosa in animals pretreated with omeprazole showed a mild disruption of the surface epithelium (F & L). Macroscopic damage indices were quantified (M)	132
Figure 5.8	Rats in the control group of aspirin-induced gastric ulcers model have no disruption of the surface epithelium (A). Rats in the vehicle group have severe disruption of the surface epithelium (B). Rat in BaBG 0.3 mg/kg has disruption of the surface epithelium (C). BaBG 1.0 mg/kg rat has moderate disruption of the surface epithelium (D). Rats in BaBG 3 mg/kg showed a mild disruption of the surface epithelium (E). The gastric mucosa in animals pretreated with omeprazole showed a mild disruption of the surface epithelium (F). Macroscopic damage indices were quantified (G)	134
Figure 5.9	Rats in the control group of acetic acid-induced chronic gastric ulcers model have no disruption of the surface epithelium (A). Rats in the vehicle group have severe disruption of the surface epithelium (B). Rat in BaBG 0.3 mg/kg has disruption of the surface	136

	epithelium (C). BaBG 1.0 mg/kg rat has moderate	
	disruption of the surface epithelium (D). Rats in	
	BaBG 3 mg/kg showed a mild disruption of the	
	surface epithelium (E). The gastric mucosa in animals	
	pretreated with omeprazole showed a mild disruption	
	of the surface epithelium (F). Macroscopic damage	
	indices in rats were quantified (G)	
Figure 5.10	Bars represent the macroscopic damage indices in rats	137
	SEM images (A-D) and EDS analysis (E) of the	
	intestine of cysteamine-induced duodenal ulcer	
	models at 3 mg/kg BaBG dose confirm the binding of	
	BaBG onto the surface of the intestine. Duodenum	
	images A, B, C and D were captured at a	
	magnification of 200, 500, 1000 and 5000×. Lower	
Figure 5.11	magnification (A and B) shows microvilli of the	137
0	intestine while the same images at higher	
	magnification (C and D) show BaBG particle	
	adsorbed at the surface of the microvilli. Image E	
	shows particle adsorbed at the surface of the intestinal	
	villi have barium and silica peaks that confirm the	
	particles are of BaBG	
F: (1	Proven hypothesis. " –" denotes inhibition and "+"	1 45
Figure 6.1	denotes activation	147

List of Tables

Table No.	Description	Page No.
Table 1.1	Available treatment of ischemic stroke as per American Stroke Association and their shortcomings	10
Table 1.2	Piracetam versus acetylsalicylic acid in secondary stroke prophylaxis	13
Table 1.3	Bioglass [™] or 45S5 composition	14
Table 2.1	Pharmacokinetic parameters of piracetam in control and ischemic stroke rats	33
Table 2.2	Brain Penetration data of piracetam in control and ischemic stroke rats after oral administration at 200 mg/kg dose	34
Table 2.3	Exposure of Piracetam in control and ischemic stroke rats at 200 mg/kg oral and 75 mg/kg intravenous doses	35
Table 4.1	Effect of BaBG treatment on feed consumption, water consumption and changes in body weight	95
Table 4.2	Effect of AgBG treatment on feed consumption, water consumption and changes in body weight	96
Table 4.3	Effect of BaBG treatment on organ weight / body weight coefficients	97
Table 4.4	Effect of AgBG treatment on organ weight / body weight coefficients	97
Table 4.5	Effect of BaBG on ECG parameters and blood pressure	98
Table 4.6	Effect of AgBG on ECG parameters and blood pressure	99
Table 4.7	Effect of BaBG on hematological parameters	100
Table 4.8	Effect of AgBG on hematological parameters	102
Table 4.9	Effect of BaBG in surface blood flow of highly perfused organ	104
Table 4.10	Effect of AgBG in surface blood flow of highly perfused organ	105
Table 5.1	Effect of BaBG on cell proliferation of stomach in pylorus-ligated rats (data are mean \pm S.E.M., n=6 in each group).	131
Table 5.2	Effect of BaBG on gastric pH in rats	134
Table 5.3	Effect of BaBG on gastric fluid volume in rats	135