Available online at www.pharmacie-globale.info ISSN 0976-8157

Research Article

PHARMACIE GLOBALE

INTERNATIONAL JOURNAL OF COMPREHENSIVE PHARMACY

COMPARATIVE STUDY OF ANTIHYPERTENSIVE ACTIVITY OF TELMISARTAN WITH TELMISARTAN-HYDROXYPROPYL-β-CYCLODEXTRIN INCLUSION COMPLEXES

Shashikant N Dhole*[1] and Bhanudas S Kuchekar[2]

[1]Head, Department of Pharmaceutics, Modern college of Pharmacy, Moshi, Pune, Maharashtra, India.
[2]Principal, MAEER's, Mahrashtra Institute of Pharmacy, Kothrud, Pune, Maharashtra, India.

Received: 8 August 2011; Revised: 22 September 2011; Accepted: 29 September 2011; Available online: 5 October 2011

ABSTRACT

Telmisartan is an angiotensin II receptor antagonist used in the treatment of hypertension. According to BCS, (biopharmaceutical classification system) telmisartan belongs to class II drug, and it is practically insoluble in water and it shows low dissolution profile and poor absorption and reduced oral bioavailability. The aim of work was to develop telmisartan-hydroxypropyl-β-cyclodextrin inclusion complexes in order to improve its water solubility and bioavailability. The complexes were prepared by the physical mixture, spray drying and freeze-drying techniques. The improvement in the solubility and bioavailability was evaluated by virtue of comparison of antihypertensive activity of the plain telmisartan (1 mg/kg) with the inclusion complexes equivalent to (1 mg/kg) of telmisartan using two kidney one clip (2K1C) induced renal hypertension model. The results showed that the inclusion complexes of the telmisartan were more significant in reducing the mean arterial blood pressure of the hypertensive rats as compared to the plain telmisartan showing the enhanced solubility and bioavailability of the drug by virtue of the complexes.

Keywords: Telmisartan, hydroxypropyl-β-cyclodextrin, antihypertensive activity, solubility, inclusion complexes.

INTRODUCTION

Cardiovascular diseases account for 12 million deaths, annually worldwide and are known to be number one group of 'killer disease'. Hypertension is one of the leading causes of disability, mortality, and morbidity along the populace. It is the most common chronic illness among the world faces.[1,2] Hypertension is the most common cardiovascular diseases and constituents a major factor for several cardiovascular pathologies including atherosclerosis, coronary artery disease, myocardium infract heart failure, renal insufficiency, stroke and dissecting aneurysm of aorta.[3] An elevated arterial pressure is an important public health issue in developed countries. Although it is common, asymptomatic and readily detectable but it can often lead to lethal complication, if left untreated. Because of high incidence and morbidity, various drugs and regimes have been advocated for the control of hypertension. Many new drugs have been introduced which may demonstrate better efficacy but posses side effects. Recently attention has been focused towards herbal and mineral preparations which are traditionally used as potential therapeutic agents in the prevention and management of cardiovascular diseases.[4]

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure through the actions of angiotensin-II (vasoconstriction, aldosterone secretion, renal sodium reabsorption and nor epinephrine release) and thus is an appropriate target for therapeutic intervention in hypertension.[5,6] Inhibitors of the RAS would be effective for the treatment of hypertension and congestive heart failure. On the other hand, angiotensin-II (the primary effector component of the RAS) receptor antagonists block the RAS at the angiotensin-II receptor level and are expected to be more specific and effective agents than angiotensin converting enzyme (ACE) inhibitors.

Angiotensin-II receptor blockers (ARBs) provide complete blockade of the renin-angiotensin system (RAS) by specifically inhibiting the actions of AII at the level of the angiotensin-II type 1 (AT 1) receptor.[7] Because another class of antihypertensive agents targeting the RAS, angiotensin-converting enzyme inhibitors, may cause a dry cough, ARBs are increasingly used for the treatment of hypertension. Among them, irbesartan, candesartan, valsartan, telmisartan, tasosartan and olmesartan are on the market.

Telmisartan is a new, orally active, non-peptide antagonist of the AT 1 receptor, which has been developed for the treatment of hypertension**.** Telmisartan is an ARB that is highly selective for the AT 1 receptor. In addition to its vasodilatory properties telmisartan appears to exert a further antihypertensive effect by directly modulating renal excretory function.[8] The drug has also been shown to promote the renal excretion of water, sodium (Na+) and chloride (Cl–) without affecting potassium (K+) excretion in normotensive anaesthetised rats and normotensive conscious dogs after intravenous or oral administration.[9,10]

***Corresponding Author:**
Shashikant N Dhole
Head Department of Pharmaceutics,
Modern college of Pharmacy, Moshi, Pune, Maharashtra, India.
Contact no: +96-9922007322; Email: shashikant_dhole@yahoo.com

Telmisartan is a potent, long-lasting, nonpeptide antagonist of the AT 1 receptor that is indicated for the treatment of essential hypertension. It selectively and insurmountably inhibits stimulation of the AT 1 receptor by angiotensin II without affecting other receptor systems involved in cardiovascular regulation. Very high lipophilicity, a unique feature of telmisartan, coupled with a high volume of distribution; indicate that the compound offers the clinically important advantage of good tissue penetration.

Telmisartan is not a prodrug and has a longer terminal elimination half-life than other commercially available sartans (24 h), making it suitable for once-daily dosing.[11] The compound is not metabolized by cytochrome P450 isoenzymes and has a low risk for P450-based drug interactions. In animal models, telmisartan exhibits pronounced cardio and reno-protective effects in animals with severe, essential hypertension. In clinical studies, telmisartan shows comparable antihypertensive activity to members of other major antihypertensive classes, such as ACE inhibitors, beta blockers and calcium antagonists. These trials have confirmed the placebo-like safety and tolerability of telmisartan in hypertensive patients. Based on these data, telmisartan offers advantages over other sartans and represents an important new treatment option for hypertension.[12]

According to the Biopharmaceutics Classification System (BCS) aqueous solubility and permeability are the most important variables affecting drug bioavailability. Telmisartan is classified as Class II, that is drugs that have low solubility and high permeability characteristics after oral administration as telmisartan is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base. Bioavailbility of telmisartan is also poor about 45%, which due to extensive first pass hepatic metabolism.[13]

Numerous studies have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. The use of cyclodextrins (CDs) is one of the pharmaceutical strategies available to circumvent these drawbacks, as they can be used as complexing agents to increase the aqueous solubility of hydrophobic drugs and to increase their bioavailability and stability.[14-16]

CDs are cyclic oligosaccharides containing six (α-CD), seven (β-CD) or eight (γ-CD) α-1, 4-linked glycopyranose units, with a hydrophilic hydroxyl group on their outer surface and a hydrophobic cavity in the center. CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or some part of it, into the cavity. They also have ability to alter their physical, chemical, and biological properties of guest molecules by formation of inclusion complex. In the pharmaceutical industry CDs have mainly used as complexing agents to increase the aqueous solubility of poorly soluble drugs and to increase the bioavailability and stability.[17] Hydroxypropyl-β-cyclodextrin acts as safe excipient in pharmaceutical formulations. Its advantages are quick onset of action, reduces drug side effects, increases shelf life, and reduction of toxicity.[18]

In the present investigation an attempt was made to increase the antihypertensive efficacy of the plain telmisartan by preparing different inclusion complexes namely physical mixture, spray dried and freeze dried complexes of telmisartan with solubility enhancer hydroxypropyl-β-cyclodextrin and the change in the antihypertensive efficacy of these complexes was evaluated by comparing the antihypertensive activity of plain telmisartan with that of the complexes using two kidney one clip (2K1C) induced renal hypertension model.

MATERIALS AND METHODS

Drugs and chemicals

Telmisartan was supplied as gift sample from Sun Pharmaceuticals Ltd, India. Hydroxypropyl-β-cyclodextrin was supplied as gift sample from Signet Chemical Corporation, India. Urethane, ethanol and heparin (Thromboparin injection, Charls Pharma Inc) were procured from local market. All other chemicals and solvents used were of analytical grade.

Experimental model

Wistar rats weighing 200-250 g were used. They were caged in a room under standard laboratory conditions (temperature 23±1°C, relative humidity 55±5% and lighting 08:00-20:00 h). The rats were fed on a pelleted diet (Amrut feed, Pune, India) and water ad libitum. The rats were transferred to the laboratory at least 1h before the start of the experiment. The experiments were performed during day (08:00- 16:00 h).

Ethical clearence

All the studies were carried out in accordance with the guidelines given by the Indian Council for Medical Research and the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi (India) and the Institutional Animal Ethical Committee approved the study (Approval No. 1036/a/07/CPCSEA/IAEC/2010/B-1).

Preparation of Inclusion Complexes

The inclusion complex of telmisartan with hydroxypropyl-β-cyclodextrin by different techniques i.e spray drying and freeze drying technique and physical mixture were prepared.

Physical mixture[19]:

Physical mixtures of telmisartan with hydroxypropyl-β-cyclodextrin 1:1 molar ratio were prepared by simple blending in a ceramic mortar.

Spray dried complex[20]:

Spray-drying was performed in Labultima LU 222 mini spray dryer. Telmisartan was dissolved in 50 ml of methanol. Hydroxypropyl-β-cyclodextrin was dissolved in 50 ml of distilled water on a magnetic stirrer, to it previously prepard telmisartan solution was added (Ratio of telmisartan to hydroxypropyl-β-cyclodextrin is 1:1 M). The clear solution was obtained and it was subjected to spray-drying. The drying conditions were as follows, inlet temperature 60°C, feed pump 90 ml/h and aspiration speed 40.

Freeze dried complex[21]:

Hydroxypropyl-β-cyclodextrin was dissolved in 50 ml of distilled water on a magnetic stirrer to it telmisartan was added. The solution is frozen at -7°C and freeze dried in Martin Christ alpha 1-2 LD plus freeze drier.

Experimental Protocols

Surgical procedure for induction of hypertension in rats: Hypertension in rats was induced by clipping the left renal artery (LRA), as previously described.[22] 30 healthy wistar rats weighing were anesthetized with ketamine (80 mg/kg, i.p.). Fur on the back was shaved and skin was

disinfected with alcohol (70 % v/v). An incision was made in the left lumbar area parallel to long axis of the rat. Renal pedicel was exposed with the kidney retracted to abdomen. Left renal artery (LRA) was isolated, cleaned and tied with the help of surgical silk suture (4.0). The left kidney was placed in position and skin incisions were closed by surgical absorbable suture. After recovery the rats were placed in clean cages and maintained under standard food pellets and 1% sodium chloride solution instead of water for four weeks.[23]

Determination of antihypertensive activity[23,24]***:*** After 4 weeks the rats were divided into six groups with six animals each. Group I served as normal control group without LRA ligation, Group II served as induction control group with LRA ligation. Group III, IV, V and VI served as LRA ligated test groups and received plain telmisartan (1 mg/kg), freeze dried complex of telmisartan with hydroxypropyl-β-cyclodextrin (1 mg/kg), physical mixture of telmisartan with hydroxypropyl-β-cyclodextrin equivalent to (1 mg/kg) of telmisartan and spray dried complex of telmisartan with hydroxypropyl-β-cyclodextrin equivalent to (1 mg/kg) of telmisartan respectively by oral route for four consecutive days. On 4th day, 01 hour after the respective treatments, the rats were anaesthetized with urethane (1.25 g/kg, i.p.) and blood pressures were recorded respectively.

Measurement of Mean Arterial Pressure (MAP): Anaesthetized rats were injected with heparin (100 IU/ml) to prevent the coagulation of blood in the catheter. The left carotid artery was exposed and cannulated with the catheter PE-50 (polyethylene-50) prefilled with heparinized 0.85% NaCl solution, for the measurement of the MAP. The catheter (PE-50) was connected to the blood pressure transducer which was connected with the Four Channel Data Acquisition System (BIOPAC System, Inc, MP35). After half hour of cannulation, when the arterial blood pressure reaches to stabilised condition (equilibrium), blood pressure was noted down. (Table **1**)

Table 1. Arterial blood pressure (MABP) (mmHg) of different groups

S No	Normal Control	Induction control	Plain (1 mg/kg)	Freeze dried complex (1 mg/kg)	Physical mixture (1 mg/kg)	Spray dried complex (1 mg/kg)
1	100	162.23	152.12	135.00	139.36	141.14
2	102	166.02	150.35	141.12	145.56	135.00
3	99	167.14	146.00	142.34	142.98	137.24
4	104	162.56	152.76	147.31	147.00	133.10
5	102	168.21	145.00	138.76	144.02	138.00
6	98	170.96	151.10	140.29	143.05	140.18
Mean	**100.83**	**166.18**	**149.55**	**140.80**	**143.66**	**137.44**
±SEM	**0.9098**	**1.374**	**1.332**	**1.662**	**1.068**	**1.243**

Statistical analysis

The results are expressed as mean ±SEM. Comparison between the groups was made by one way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test *, #, @-P<0.05, **, ##, @@-P<0.01, ***, ###, @@@-P<0.001; *-Comparison of induction control against normal control group; #-Comparison of test groups against Induction control group; @-Comparison of freeze dried complex, physical mixture and spray dried complex of telmisartan with telmisartan only group. Instat Graph Pad software was used for statistical analysis.[25] (Table **2**)

Table 2. Comparison of antihypertensive activity of telmisartan-Hydroxypropyl-β-cyclodextrin inclusion complexes with plain telmisartan

Groups	Arterial blood pressure (MABP) (mmHg) Mean±SEM
Normal Control	100.83±0.9098
Induction control	166.18±1.374***
Plain (1 mg/kg)	149.55±1.332###
Freeze dried complex (1 mg/kg)	140.80±1.662###@@@
Physical mixture (1 mg/kg)	143.66±1.068###@
Spray dried complex (1 mg/kg)	137.44±1.243###@@@

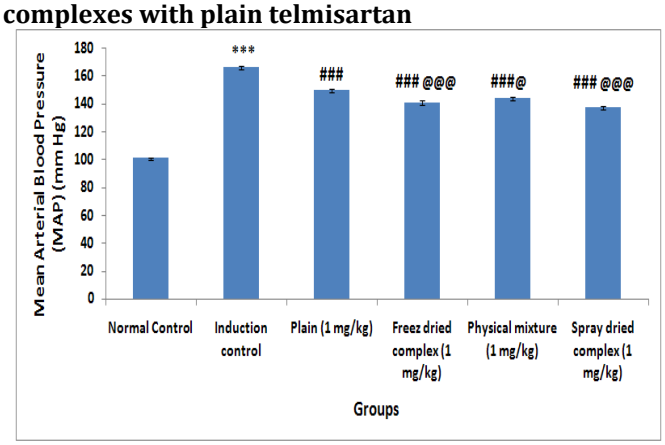
*The results are expressed as mean ± SEM. Comparison between the groups was made by one way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test *, #, @-P<0.05, **, ##, @@-P<0.01, ***, ###, @@@-P<0.001; *-Comparison of induction control against normal control group; #- Comparison of test groups against Induction control group; @- Comparison of freeze dried complex, physical mixture and spray dried complex of telmisartan with plain telmisartan group.*

RESULTS AND DISCUSSION

The mean arterial blood pressures of groups I, II III, IV, V and VI were 100.83±0.909, 166.18±1.374, 149.55±1.332, 140.80±1.662, 143.66±1.068, 137.44±1.243 respectively. LRA ligation significantly (P<0.001) increased MAP compared to non-ligated control rats. Pretreatment with all the test groups produced a significant (P<0.001) reduction in MAP. But when comparison was done between the plain telmisartan group and remaining three test groups it was found that freeze dried and spray dried complexes of telmisartan were more significant (P<0.001) than plain telmisartan in reducing the MAP. Physical mixture also showed more significant activity (P<0.05) than plain telmisartan but was less than the freeze dried and spray dried complexes.

The results are expressed as mean ±SEM. Comparison between the groups was made by one way analysis of variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test *, #, @-P<0.05, **, ##, @@-P<0.01, ***, ###, @@@-P<0.001; *-Comparison of induction control against normal control group; #- Comparison of test groups against Induction control group; @- Comparison of freeze dried complex, physical mixture and spray dried complex of telmisartan with plain telmisartan group.

Figure 1. Comparison of antihypertensive activity of telmisartan- Hydroxypropyl-β-cyclodextrin inclusion complexes with plain telmisartan



2K1C is very commonly used model for renal hypertension. In renovascular hypertension, Renin Angiotensin Aldosterone System (RAAS) plays an important role in control of cardiovascular homeostasis affecting both blood pressure and fluid volume and is one of the most important etiological candidates in

hypertension.[26,27] Experimentally the renal hypertension is produced by renal artery constriction, which activates RAAS and sympathetic nervous system. A number of factors like decreased blood volume may lead to sympathetic stimulation in this model. Renin is secreted by kidney when sympathetic activity is increased. Renin converts angiotensinogen to angiotensin-I. Angiotensin-I is converted to angiotensin-II by angiotensin converting enzyme (ACE). Angiotensin-II is a potent vasoconstrictor and increase BP. Angitensin-II also causes release of aldosterone leading to salt and water retention resulting in increased blood volume and hypertension.[28]

In two kidneys one clip hypertension the ligature is applied to artery of one kidney and contralateral kidney is left untouched.[29] This results in a sustained increase on BP due to increased plasma renin activity (PRA), which in turn increases the circulating angiotensin-II, a potent vasoconstrictor. However there is no salt and water retention because of the other normal kidney being intact. Thus the resultant hypertension at this stage is renin angiotensin dependent. After about 6 weeks, the increased angiotensin-II releases aldosterone from adrenal cortex leading to a gradual retention of salt and water which decreases the renin production. From this stage onwards, hypertension is volume dependent. Hence salt and water balance is critically involved in pathogenesis of renovascular hypertension.[30,31]

In our study the main purpose of the investigation was the comparison between the already established angiotensin II (AT1) blocker antihypertensive drug telmisartan with three new formulations i.e. physical mixture, freeze dried and spray dried complexes of telmisartan with hydroxypropyl-β-cyclodextrin in order to compare their efficacy as antihypertensive formulations with that of the plain telmisartan.

In a previous investigation, repeated oral administration of 1 mg/kg telmisartan over a period of 4 days resulted in significant and sustained reductions in mean arterial blood pressure of 35 to 60 mmHg[32] and as per this study the doses of all the test groups was decided. The results revealed that all the complexes were more efficient as compared to plain telmisartan. The spray dried and freeze dried complexes showed a much greater efficacy than plain telmisartan in reducing the MAP in LRA ligated animals whereas physical mixture showed less efficacy than former two complexes.

The increased efficacy of these complexes can be attributed to enhanced solubility by the inclusion of solubility enhancer hydroxypropyl-β-cyclodextrin in these complexes which lead to reduced duration of onset of action. The study proves that formulation of the drug with different techniques using solubility enhancer such as hydroxypropyl-β-cyclodextrin increases the efficacy and these complexes can be as an alternative to the plain drug to obtain better results.

CONCLUSION

From the present study it can be concluded that the solubility, biavailablity, physicohemical properties and antihypertensive efficacy of telmisartan can be enhanced by complexing it with hydroxypropyl-β-cyclodextrin which can be helpful in decreasing the frequency of dose administration, preventing nocturnal attack and improving patient compliance.

REFERENCES

1. Akinkigbe O; Current epidemiology of hypertension in Nigeria, In the achieves of Ibadan Medicine. *Int J Med Sci.* 2001; 1:1.
2. Schutte A, Van R J, Huisman H et al. Dietary risk markers that contribute to the etiology of hypertension in black South African childerens, The THUSA BAMMA study. *J Hum Hypertens.* 2003; 17:29-35.
3. Oparil S; Treating multiple risk hypertensive populations. *Am J Hypertens.*1999; 2:121-129.
4. Bhatt J D, Panchakshari U D, Hemavathi K G et al. Effect of Abana, an ayurvedic preparation on ethinyl estradiol induced hypertension in rats. *Indian J Pharmacol.* 1998; 30:399-403.
5. Naka T, Inada Y; Heterocyclic compounds, their production and use. *Eur. Pat. 520423, 1993; Chem Abstr.* 1993; 119:49388x.
6. Ferrario C M; The renin-angiotensin system: Importance in physiology and pathology. *J Cardiovasc Pharmacol.* 1990; 15b(3);S1-S5.
7. Böhm M, Lee M, Kreutz R et al. Angiotensin II receptor blockade in TGR (mREN2)27: Effects of renin-angiotensin-system gene expression and cardiovascular functions. *J Hypertens.* 1995; 138:891-899.
8. Carini D J, Duncia J V, Aldrich P E, Chiu A T et al. Nonpeptide angiotensin II receptor antagonists: The discovery of series of N- (Biphenylmethyl) imidazoles as potent, orally active antihypertensive. *J Med Chem.* 1991; 34:2525.
9. Wexler R R, Greenlee W J, Irvin J D et al. Nonpeptide angiotensin II receptor antagonists: The next generation in antihypertensive therapy. *J Med Chem.*1996; 39:625-656.
10. Sharpe M, Jarvis B, Goa K L; Telmisartan: a review of its use in hypertension. *Drugs.* 2001; 61:1501-1529.
11. Karlberg B E, Lins L E, Hermansson K; Efficacy and safety of telmisartan, a selective AT1 receptor antagonist, compared with enalapril in elderly patients with primary hypertension. *J Hypertens*. 1999; 17:293-302.
12. Lacourcière Y, Lenis J, Orchard R et al. A comparison of the efficacy and duration of action of the angiotensin II receptor blocker telmisartan to amlodipine. *Blood Press Monit.* 1998; 3:295-302.
13. Kothawade S N, Kadam N R, Aragade P D et al. Formulation and characterization of telmisatan solid dispersions. *Int J of PharmTech Res.* 2010; 2(1):341-347.
14. Loftsson T, Masson M, Brewster M E; Self-association of cyclodextrins and cyclodextrin complexes. *J Pharm Sci.* 2004; 93:1091-1099.
15. Loftsson T, Brewster M E; Pharmaceutical applications of cyclodextrins 1. Solubilization and stabilization. *J Pharm Sci.* 1996; 85:1017-1025.
16. Rajewski R A, Stella A J; Pharmaceutical applications of cyclodextrins 2. *In-vivo* drug delivery. *J Pharm Sci.* 1996; 85; 1142-1168.
17. Parikh B N, Patel D M, Patel C N et al. Formulation optimization and evaluation of immediate release tablet of telmisartan. *J Global Pharma Tech.* 2010; 2(2):79-84.
18. Patil J S, Kadam D V, Marapur S C et al. Inclusion

complex system: A novel technique to improve the solubility and bioavailability of poorly soluble drugs. *Int J Pharma Sci.* 2010; 2(2);29-34.

19. Fernandesa C M, Vieira M T, Francisco J B; Physicochemical characterization and in vitro dissolution behavior of nicardipine–cyclodextrins inclusion compounds. *Euro J Pharm Sci.* 2002; 15:79-88.
20. Ranpise N S, Kulkarni N S; Improvement of water solubility and in vitro dissolution rate of aceclofenac by complexation with beta-cyclodextrin and hydroxypropyl-β-cyclodextrin. *Pharm Dev Technol*. 2010; 15(1):64-70.
21. Vavia P R, Adhage N A; Inclusion complexation of nimesulide with beta-cyclodextrins. *Drug Dev Ind Pharm.* 1999; 25(4):543-545.
22. Kharin S N, Krandycheva V V, Shmakov D N; Depolarization pattern of ventricular epicardium in two-kidney one-clip hypertensive rats. *Exp Physiol.* 2005; 90:621-626.
23. Nandkumar K, Singh R, Bansal S K et al. Antihypertensive effect of newly synthesized acyl amino substituted propanolamine derivatives, DPJ890 and DPJ 955in rats. *Indian J Pharmacol.* 2004; 36(6):381-384.
24. Badyal D K, Lata H, Dadhich A P; Animal models of hypertension and effect of drugs. *Indian J Pharmacol* 2003; 35:349-362.
25. Graph Pad Instat- 3.01., Windows 95, Graph Pad Software Inc, 5755, San Diego, California, USA.
26. Sharifi A M, Darabi R, Akbarloo N. Investigation of antihypertensive mechanism of garlic in 2K1C hypertensive rats. *J Ethnopharmacol.* 2003; 86:219-224.
27. Christiaans J A M, Timmerman H. Cardiovascular hybrid drug: Combination of more than one pharmacological property in one single molecule. *European J Pharma Sci.* 1996; 4:1-22.
28. Gupta S K, Vyawahare N S, Kagathara V G et al. Assessment of antihypertensive activity of novel synthetic hybrid compound on 2K1C induced hypertensive rats. *Pharmacologyonline.* 2009; 2:273-280.
29. Mok J S L, Kong M L, Hutchinson J S; Cardiovascular effects of central & peripheral administration of dopamine in hypertensive & normotensive rats. *Indian J Pharmacol*. 1985; 17:192-196.
30. Guyton A C, Hall J E, editors. Textbook of medical physiology 9th edition, Noida: WB Saunders Company, 1998.
31. Sealy J E, Laragh J H; The rennin-angiotensin-aldosterone system for normal regulation of blood pressure and sodium and potassium homeostasis. In: Laragh J H, Brenner B M, eds. Hypertension: pathophysiology, diagnosis and management, 2nd ed. Raven Press, New York, NY, 1995:1763-1796.
32. Wienen W, Entzeroth M, Jacobus C A et al. A Review on Telmisartan: A novel, long acting angiotensin II-receptor antagonist. *Cardiovascular Drug Reviews*. 2000; 18(2):127-154.