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GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEM CONTAINING ANTIHYPERTENSIVE DRUG – AN OVERVIEW

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ABSTRACT

The purpose of writing this review on gastro retentive floating drug delivery system was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. Hypertension is one of the world's major diseases.It currently affects an estimated143 million people worldwide and the number is growing rapidly. Research is directed towards overcoming physiological adversities such as short gastric residence time (GRT) & unpredictable gastric emptying time (GET). These systems will be very much useful to deliver 'narrow absorption window' drugs. Four technologies have involved a substantial number of human clinical trials: floating, mucoadhesion, density modification, and expansion. The floating drug delivery system can remain in the gastric region for several hours via float on the gastric contents and hence significantly prolong the gastric residence time of drugs.In the recent years, scientific and technological advancement have been made in the research and developed of novel drug delivery system. By overcoming physiological troubles such as short gastric residence time and unpredictable gastric emptying times, oral route is the most preferable route of administration but it has certain limitation for those drugs which absorb from upper part of GI tract or having narrow absorption window. The bioavailability of these drugs by increasing the residence of the dosage form in the stomach. The gastric residence time of the dosage form can be improved by formulating them as floating drug delivery system. The current and recent development of stomach specific antihypertensive drug formulated as floating drug delivery system is discussed in this review.

Key words : Gastric residence time, floating drug delivery system, Antihypertensive drugs, narrow absorption window.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing Controlled release systems for better absorption and enhanced bioavailability[1]. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal- tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa[1]. Thus small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized. Gastroretentive systems can remain in the Gastric- region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric-retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro- retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric-retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion[2, 3] flotation[4] sedimentation, [5, 6] expansion, [7, 8] modified shape Systems, [9, 10] or by the simultaneous administration of pharmacological agents that delay gastric emptying. They Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/ in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drug with bioavailability problems.

Mechanism of floating systems

When floating drug delivery system (FDDS) are administered orally, they retained in the stomach for a prolonged period of time by virtue of their floating properties, which can be acquired by several means. One of the basic mechanisms

beside the floatation can be explained by the concept of density. Mathematically density may be defined as: [11]

Density (ρ) = mass (m) / volume (v) (1)

In case of effervescent floating dosage form which is composed of gas generating agents and swellable polymers when come in contacts with acidic content of the stomach, CO_2 is liberated and is trapped in jellified hydrocolloid, which creates upward motion of dosage form and thus reducing the density of system and making it float on gastric content. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased GRT and a better control of the fluctuations in plasma drug concentration[12].

Factors affecting FDDS

Density

GRT is a function of dosage form buoyancy which is dependent on density.

Size

Dosage form units with a diameter more than 7.5 mm are reported to increase GRT Compared with those with a diameter of 9.9mm.

Shape

Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo Pounds per square inch (KSI) are reported to exhibit a better GRT and 90%–100% retention at 24 hours compared with other shapes[13, 14].

Single or multiple unit formulations

Multiple unit formulations exhibit a more predictable release profiles and insignificant impairment of performance due to unit failures, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety with regard to dosage form failure compared with single unit dosage forms.

Fed or fasted state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.[15]

Nature of the meal

Consumption of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus reducing the gastric emptying rate and prolonging drug release[16].

Caloric content

Gastric retention time can be increased by 4 to 10 hour with a meal that is high in proteins and fats[17].

Frequency of feeding

The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC Gender: Mean ambulatory GRT in males (3.4 ± 0.6 h) is less compared with age and race matched females (4.6 ± 1.2 h), regardless of the weight, height and body surface area.

Age

Elderly people, especially those over 70, have a significantly longer GRT.

Posture

GRT can vary between supine and upright ambulatory patient states.

Concomitant drug administration

Anti-cholinergic, like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride, affect the FDDS.

Biological factors

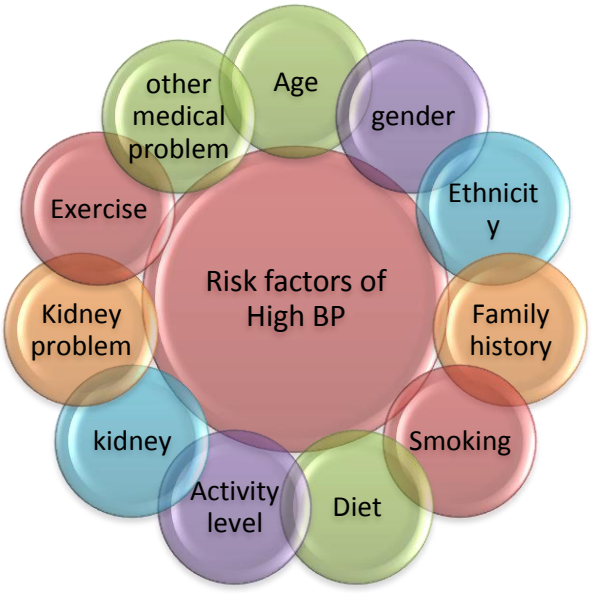
Diabetes and Crohn's disease, also affect the FDDS.

Antihypertensive Drugs

It is a common & usually progressive disease, which if not effectively treated, results in a greatly increased probability of coronary arterial disease, thrombosis, strokes & renal failure .it is a most common cardiovascular disease. Keeping the blood pressure below 140/90 mmHg (systolic /diastolic) reduces morbidity & mortality of these patients significantly. Antihypertensive therapy seeks to prevent complication of high BP such as stroke and myocardial information. Evidence suggest that reduction of the blood pressure by 5mmhg can decrease the risk of stroke by 34% of ischemic heart disease by 21% and reduce the likelihood of dementia , heart failure and mortality from cardiovascular. Most widely used drugs are Thiazides diuretics, ACE inhibitors, calcium channel blockers, beta blockers, and antagonist, 2 receptor antagonists or ARB'S[18].

WHO hypertension facts

Globally, nearly 1 billion people have high BP of these two third are developing countries. Hypertension is one of the most important cause of premature death worldwide & the problem is growing; in 2025. Hypertension kill nearly 8 million people every year worldwide & nearly 1.5 million people each year in the south east Asia, approximately one third of adult population in the south east Asia region has high Blood pressure[19]



Top 10 risk factors of high blood pressure:

Managing the medications

The right medications matched to the patient's characteristics can do wonders to control BP levels.

Diuretics: "water pill "1st

medication chosen, these drugs help control BP by ridding the body of excess salt & water.

Beta blockers

They lower BP by showing the heart rate & reducing the force of the heart rate & reducing the force of the heart beat, easing the heart's work load.

Ca channel blockers

Calcium channel blockers can decrease the heart pumping strength & release blood levels

ACE Inhibitors

They interfere with the body's production of Angiotensin- 2, a chemical that causes the arteries to narrow.

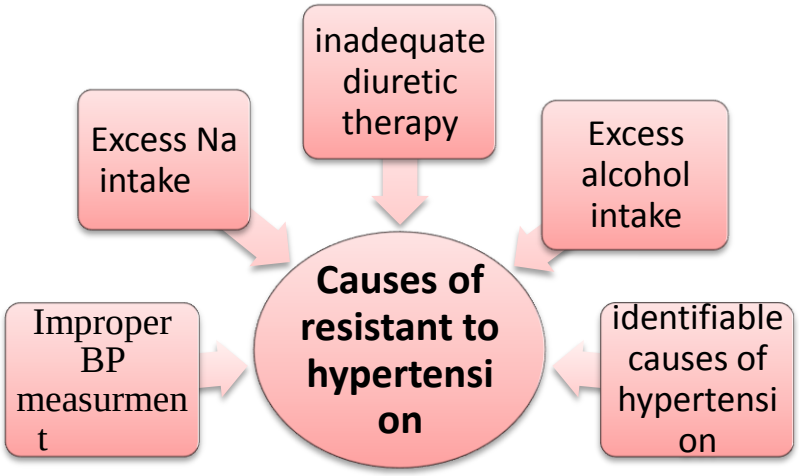
ARBs

They block effects of Angiotensin 2

Vasodilators

They can cause the muscle in blood vessel walls to release allowing the vessel to wider.

Causes of resistant to hypertension



CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS[21-23]

A Diuretics, helps the kidney eliminate excess salt and water from the body tissue and blood.

1. Loop diuretics include bumetanide, etacrynic acid, furosemide, and torsemide.
2. A Thiazides diuretic includes epithizide, hydrochlorothiazide and chlorothalidon, bendroflumethazides.
3. Thiazides like diuretics include Indapamide, chlorothalidon, and andmetalazone.
4. Potassium sparing diuretics includes amiloride, trimeterene, and Spironolactone

B. Adrenergic receptor antagonist

1. Beta blockers includes Atenolol, metaprolol, nadolo, oxprenolo, nebiuolol, pindolol, Propranolol, tremolol
2. Alpha blockers included oxazosin, phentolamine, indoramin, prazosin, terazosin, tolazoline and phenoxybenzamine.

C. Calcium channel blockers they block the entry of calcium into muscles cells in artery walls.

1. Dihydropyridines includes Amlodipine, clinidipine, felodipine, lercanidipine, isradipine, Nifedipine, Nicardipine, nimodipine and nitrendipine
2. Non Dihydropyridines includes DiltiazemHCl, Verapamil

D. Renin inhibitors include Renin comes one level higher than Angiotensin converting enzyme in the Renin Angiotensin system. Aliskiren (developed by Novartis) is a Renin inhibitor which has been approved by the US FDA for the treatment of hypertension.

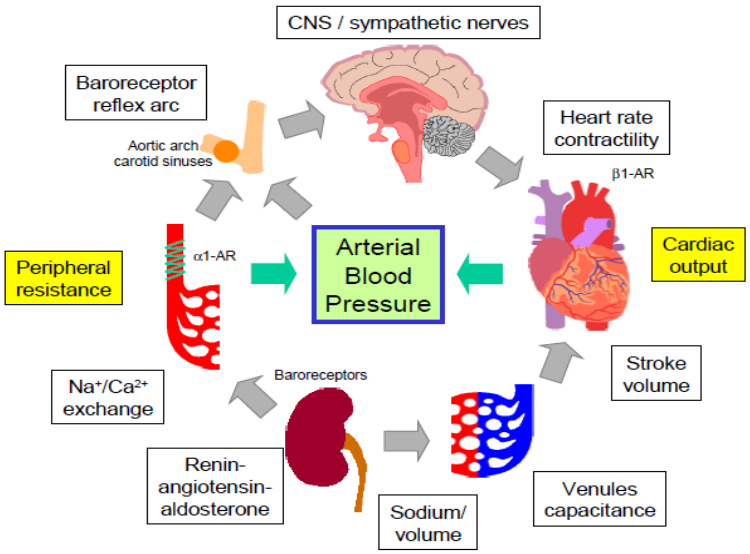
1. ACE Inhibitor they inhibits the activity of ACE an enzyme responsible for the conversion of Angiotensin one into Angiotensin two a potent vasoconstrictor They include drugs Captopril, Lisinopril, perindopril, quinapril, ramipril, trandolapril, benazepril
2. Angiotensin 2 receptor antagonist worked by antagonizing the activation of Angiotensin receptor includes drugs are candesartan, Losartan, eprosartan, olmesartan, Telmisartan, Valsartan, irbesartan, eprosartan

E Vasodilators includes Sodium Nitroprusside and Hydralazine

Table 4. Classification of Blood Pressure Readings[20, 21]

Category	Systolic BP (mmHg)	Diastolic BP (mmHg)
Optimal blood pressure	<120	<80
Normal blood pressure	<130	<85
High-normal blood pressure	130–139	85-89
Grade 1 hypertension (mild)	140–159	90–99
Grade 2 hypertension (moderate)	160–179	100–109
Grade 3 hypertension (severe)	180	110
Isolated systolic hypertension (Grade 1)	140–159	<90
Isolated systolic hypertension (Grade 2)	160	<90

$$BP = CO \times PVR$$



Hypertension and Pregnancy

The use of anti-hypertensive in pregnancy must consider foetal well-being. Treating uncomplicated Stage

1 hypertension is often not necessary in otherwise low-risk women with normal renal function and no other target organ disease. These women should be closely followed during pregnancy. Pre-eclampsia or other pregnancy-induced hypertension should be treated by a physician experienced in managing these diseases. Women considering pregnancy, who are hypertensive and require treatment, should be on anti-hypertensive medication ideally three to six months prior to conception. Medications for treating significant hypertension during pregnancy, in order of preference are 1) Methyldopa – the drug with the longest experience and probably still most commonly used. Problems

with this UMHS Hypertension Guideline, February 2009 13 medication includes frequent side effects and the need to dose multiple times a day.

2 Beta-blocker with or without diuretic (avoiding Atenolol, which may be associated with intrauterine growth retardation) – are relatively popular and the first choice of some.

3 Labetalol

4 Calcium channel blockers

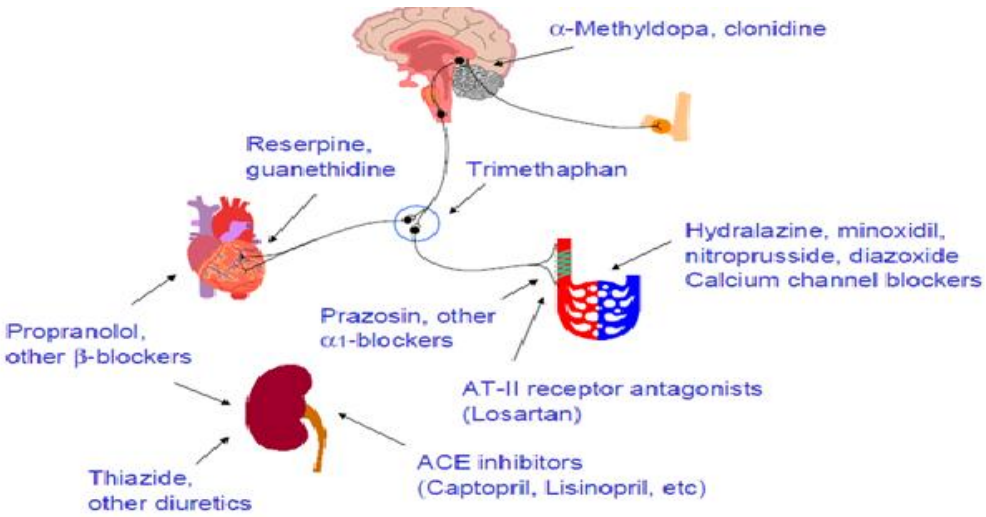
5 Diuretics are also acceptable to use

6 Contraindicated in pregnancy are ACE inhibitors, ARBs, and Renin inhibitors.

People can be done to prevent & compelling high BP

1. Reduce & manage mental stress through yoga, meditation other relaxation techniques
2. Healthy diet
3. Limit intake salt
4. Physically active
5. Don't use tobacco
6. Limit alcohol use
7. Regular check use
8. Treat high BP
9. Maintain a healthy weight
10. Prevent & manage other medical conditions such as diabetes

Mechanism of Antihypertensive drug



Compelling indications for individual drug classes[39,40]:

Sr No	Compelling indications	Initial drug options
1	Heart failure	Thiazides (THAIZ), Beta blockers (BB), Angiotensin receptor blockers (ARB), Altosterone antagonist (ALDO ANT) Angiotensin converting enzyme inhibitor (ACEI),
2	Post myocardial infarction	Beta blockers (BB), Altosterone antagonist (ALDO ANT) Angiotensin converting enzyme inhibitor (ACEI),
3	High cardiovascular disease risk	Thiazides (THAIZ), Beta blockers (BB),Calcium channel blockers (CCB) Angiotensin converting enzyme inhibitor (ACEI)
4	Chronic kidney disease	Angiotensin receptor blockers (ARB), Angiotensin converting enzyme inhibitor (ACEI),
5	Diabetes	Thiazides (THAIZ), Beta blockers (BB), Calcium channel blockers (CCB Angiotensin converting enzyme inhibitor (ACEI), Angiotensin receptor blockers (ARB)
6	Recurren stroke prevention	Thiazides (THAIZ), Angiotensin converting enzyme inhibitor (ACEI)

Doses of Antihypertensive drug along with brand name[30, 41]:

Class	generic names	daily dose (mg)	common brand names	tablets size in (mg)	Half life $t^{1/}_{2}$ (Hrs)	Bioavailability (%)
ACE Inhibitor	Captopril	50-150	Capoten Capozide Captopril	25,50 ,50 ,25,50	2	70
	Enalapril	2.5-40	Renetec Co-renetec Ezapril	10,20 10,20 10,20	11	50
	Lisinopril	10-40	Zestril Zestoretic	5,10,20,20	12	25
	Ramipril	2.5-20	Tritace Tritace comp Tritace comp LS	1.25,2.5,5,10 5 2.5	8-48	60
	Perindopril	2-8	Conversyl	2,4	25-30	66-95
	Benazepril	5,10,20,40	Lotensin	5,10,20,40	10-12	37
	Quinapril	10,20,40	Accupril	10,20,40	2	60
	Fosinopril	10,20,40	Monopril	10,20,40	12	30
	Trandolapril	1,2,4	Mavik	1,2,4	4-6	70
	Moexipril	7.5,15	Univasc	7.5,15	3	50
	Benazepril/HCTZ	5/6.25	Lotensin/HCTZ	5/6.25	–	–
	Fosinopril/HCTZ	10/12.5 20/12.5	Monopril/HCTZ	10/12.5	–	–
Angiotensin receptor blockers	Losartan	25-100	Cozaar Hyzaar Losartan Fortzar	50 50 50 100	2	33
	Valsartan	80-320	Tarea Co-tarea Co-diovan	100 80,160 80,160	6-9	23
	Candesartan	4-32	Atacand	8	8-12	15
	Telmisartan	20-80	Micardis	40,80	24	Depends

						on dosage
	Olmesartan	20,40	Benicar	20,40	12	26
	Irbesartan	150,300	Avapro	150,300	12	60-80
	Eprosartan	400,600	Tenveten	400,600	_	_
	Eprosartan/HCTZ	600/12.5, 600/25	Tenventen/HCTZ	600/12.5,600/25	_	_
	Olmesartan/HCTZ	20/12.5,40/12.5, 40/25	BenicarHCT	20/12.5,40/12.5, 40/25	_	_
	Losartan/ HCTZ	50/12.5,100/ 25	Hyzaar	50/12.5,100/25	_	_
	Eprosartan	400,600	Tenveten	400,600	_	_
	Eprosartan/HCTZ	600/12.5, 600/25	Tenventen/HCTZ	600/12.5,600/25	_	_
	Olmesartan/HCTZ	20/12.5,40/12.5, 40/25	BenicarHCT	20/12.5,40/12.5, 40/25	_	_
	Losartan/ HCTZ	50/12.5,100/ 25	Hyzaar	50/12.5,100/25	_	_
Diuretics	Hydrochlorothiazide	2.5-50	Hydrex, aldactazides, miodiuretic	25 25 25	5.6	50-60
	Indapamide	1.25-5	Natrilix, NatrilixSR	2.5 1.5		
	Chlorothalidon	25-50	Hygrotone	50	40	Rapidly absorbed
	Furosemide	20-400	Lasix	40	2	60
	Bumetanide	1-4 or more	Burinex	1		
	Amiloride	5-50	Amiloride/ HCTZ	5	6-9	Rapidly absorbed
	Triametrene	37.5/25	Triametrene/HCTZ	37.5	4.25	<50
	Spironolactone	25/25	Spironolactone/HCTZ	25	10	100
Renin Inhibitor	Aliskriren	150,300	Tekturma	150,300		
	Torsemide	5,10	Demadex	5,10		
Beta adrenergic blockers	Atenolol	25-100	Tenormin Blockium BlockiumDiu	50,100 50,100 50	6-7	50
	Metaprolol	50-200	Beta loc	100	3-7	50
	Bisoprolol	2.5-10	Concor Concorsplus	5-10 5	9-12	>80
Calcium channel antagonist	Verapamil	120-480	Isoptinretard Tarka	240 120	2.8-7.4	90
	DiltiazemHCl	90-240	Tildium Altiazem Delaytiazem	60 60 90,120,180	3-4.5	Absorbed GIT
Nifedipine	20-80	Adalatretard Epilatretard	20 20	6-10	40-50	
Amlodipine	2.5-10	Norvasc Anilo	5,10 5	30-50	64-90	

Literature survey of Antihypertensive drug using FDDS [42-191]

Sr no	Author name	Drug category	Drug name	Dosage form	Method & polymer used	Published by
1	Londhe S et al	Calcium channel blocker	Verapamil	Floating tablets	Method:Direct compression,HPMC K15,Carbopol934S, Starch gycolate	Journal of pharmaceutical science & Technology,vol2(11), 2010
2	Jiamiaowang et al	Calcium channel blocker	Nitrendipine	Floating microballons	Ethyl cellulose, acrylic acid resin,eudragit S100 Method: Emulsion solvent diffusion method	Asian journal of pharmaceutical science,vol 3(4),2003
3	Ajay kumar patil et al	Calcium channel blocker	Nitrendipine	Floating tablets	Method: wet granulation, Eudragit RSPO & HPMCK15 &K4.	International journal of pharmaceutical technology and research,vol3(2),2010
4	Dubey vivek et al	Calcium channel blocker	Amlodipine besylate	Floating tablets	Method: Direct compression, HPMC K100, Carbopol934.	Journal of pharmaceutical & scientific innovations,vol1(4) 2012
5	Mahesh molke et al	Calcium channel blocker	Verapamil HCl	Floating tablets	Method: direct compression,HPMCK100LV & compritol ATO888	Research journal of p'eutical, biological& chemical science,vol 1(3),2010
6	Suresh karudumpala et al	Calcium channel blocker	Nifedipine	Floating tablets	Method: direct compression,HPMCK4 & K15	American journal of advance drug delivery, vol 1 (3),2013
7	T.S. Keerthi et al	Angiotensin receptor blockers	Losartan potassium	Floating microspheres	Method :solvent evaporation method,span80,sodium alginate	International bulletin of drug research, vol 1(2),2011
8	Sallem M.A et al	Angiotensin receptor blockers	Valsartan	Floating beads	Method: inotropic gelation method	International research journal of pharmaceutical, vol 3 (6),2012
9	Jain C.P. et al	Angiotensin receptor blockers	Valsartan	Floating tablets	Method: direct compression, microcrystalline cellulose & starch gycolate	International journal of pharmaceutics & pharmaceutical science,vol 1 (1),2009
10	Manish jaimini et al	Angiotensin receptor blockers	Losartan	Floating tablets	Method: wet granulation, methocel K15 & K100	International current pharmaceutical journal,vol2 (1),2012
11	Nirav.P. et al	Angiotensin receptor blockers	Valsartan	Floating tablets	Method: direct compression,HPMCK100M,Ethyl cellulose	Der Pharmacia sinica,vol 4 (5), 2013
12	Swetha konda et al	Angiotensin receptor blockers	Irbesartan	Floating microspheres	Method: orifice ionic gelation,HPMCK100M,carbopoL934p,sodium alginate	Journal. of Advance. Pharmacy, Education & research, vol 3(4),2013

13	Sanjit Kr. Roy et al	AT_1 receptor	Losartan potassium	Floating tablets	Method: Direct compression, HPMC-K4M & carbopol 934P	World Journal of Pharmaceutical Research, vol2 (3),2013
14	Lodhiya DJ et al	Beta adrenergic blocker	Atenolol	Floating tablets	Method: direct compression,HPMCK15 M & Carbopol934p	International Journal .of Pharma tech research, vol 1(4),2009
15	Rabik K Panigrah y et al	Beta adrenergic blocker	Metoprolol	Floating tablets	Method: direct compression,carbopol 934p,Nacmc,	International journal of pharmacy & p'eutical science,vol 3(2),2011
16	Rangasa my et al	Beta adrenergic blocker	Atenolol	Floating tablets	Method: wet granulation,HPMCK4M, K100MK,K15m,lactose, pvpk30	Inter Journal .of recent adv. In p'ceutical, vol3(2),2011
17	Verma M. et al	Beta adrenergic blocker	Atenolol	Floating tablets	Method: direct compression,carbopol 934P,HPMCk100cps, lactose	Inter J. P'eutical & chemical science, vol 1(2),2012
18	Singh ajay et al	Beta adrenergic blocker	Atenolol	Floating tablets	Method: direct compression,HPMCK15 M,Nacmc	Pharma research Journal, vol 5(1),2011
19	Chaudhar i Shilpa et al	Alpha & beta adrenergic blockers	carvedilol	Bilayer floating tablets	Method: direct compression,HPMC K100M and Microcrystalline cellulose	Journal of Drug Delivery & Therapeutics,2(5),2012
20	Hemlata kaurav et al	ACE inhibitor	Ramipril	Mucoad hesive microsp heres	Method: inotropic gelation HPMC K15 & Eudragit S100	International journal of drug research and innovation, vol4(2),2012

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