Chapter VII
Size Exclusion Technology
(Swelling)
Approach III

VII.1 INTRODUCTION

The expandable gastro retentive dosage forms (GRDFs) are usually based on three configurations:

- a small ('collapsed') configuration which enables convenient oral intake;
- expanded form that is achieved in the stomach and thus prevents passage through the pyloric sphincter; and
- finally another small form that is achieved in the stomach when retention is no longer required i.e. after the GRDF has released its active ingredient, thereby enabling evacuation.

The expansion can be achieved by swelling or by unfolding in the stomach. Swelling usually occurs because of osmosis. Unfolding takes place due to mechanical shape memory i.e. the GRDF is fabricated in a large size and is folded into a pharmaceutical carrier e.g. a gelatin capsule, for convenient intake. In the stomach, the carrier is dissolved and the GRDF unfolds or opens out, to achieve extended configuration. The unfolding occurs when polymeric matrices, known or designed to have suitable mechanical properties, are used with some emphasis on appropriate storage conditions of the GRDF. The formulation of such type of dosage form can not be prepared by conventional methods of compression and also the storage should maintain unfoldable properties for extended time spans. So, swelling controlled release dosage form was prepared using different polymers in a matrix unit dosage form.

Water-soluble polymers, such as hydroxypropyl methylcellulose, poly (ethylene oxide) (PEO), and poly (vinyl Pyrrolidone), are often used as a polymeric excipient in oral dosage formulations for controlling the rate of drug release. For water-soluble drugs, the drug-release rate from such an oral dosage formulation is controlled primarily by the diffusion of the drug through the hydrogel layer produced on the outer layer of a tablet. For water-insoluble drugs, the drug-release rate is determined chiefly by the erosion rate of the polymeric matrix. Thus; the swelling characteristics of the polymeric matrix may significantly affect the drug-release characteristics of an oral tablet containing that polymeric matrix. Additionally, for oral dosage formulations intended for sustained gastric-retention application, the swelling characteristics of such a formulation may affect the size expansion of such a device in the gastric system, which, in turn, could affect the drug-release characteristics of such a device.

A brief introduction of the various polymers selected is given below:

Polyethylene Oxide (Polyox) (PEO) (POLYOXTM water-soluble resins, 2005)

POLYOX™ Water-Soluble Resins, NF Grade are nonionic poly (ethylene oxide) polymers that meet all the specifications of the United States Pharmacopoeia—National Formulary. They are white, free-flowing hydrophilic powders supplied in a wide variety of molecular weight grades, ranging from one hundred thousand to seven million Daltons (Da). They are essentially tasteless, colorless, nonionic, and noncaloric. This unusual combination of

properties makes them useful in a surprisingly broad array of pharmaceutical formulations. They have a long history of successful applications in uses such as controlled release solid dose matrix systems, transdermal drug delivery systems, and mucosal bioadhesives.
POLYOX Resins are among the fastest-hydrating water soluble polymers used in pharmaceutical systems. They very quickly form hydrogels that initiate and regulate release of active ingredients. Systems using POLYOX Resins are often superior to others in approaching zero order release models.

Table VII. 1 SENTRY POLYOX water-soluble Resins NF for Pharmaceutical Applications

SENTRY POLYOX water-soluble Resin NF Product	Approximate Molecular Weight	Viscosity Range at 25°C, mPa x s		
		5% Solution	2% Solution	1% Solution
N10 NF	100,000	30 – 50		
N80 NF	200,000	55 – 90		
N750 NF	300,000	600 – 1200		
205 NF	600,000	4500 – 8800		
1105 NF	900,000	8800 – 17,600		
N12K NF	1,000,000		400 – 800	
N60K NF	2,000,000		2000 – 4000	
301 NF	4,000,000			1650 – 5500
COAG NF	5,000,000			5500 – 7500
303 NF	7,000,000			7500 – 10,000

PEO had been shown to exhibit excellent swelling characteristics in water, and it is the preferred polymeric excipient used in OROL system for delivering zero-order drug release.
Polyethylene oxides (PEOs) have recently been tested for their use as controlled release dosage forms, and hydrophilic matrix tablets as well as extrudates have been successfully produced (Kim, 1995, 1998; Maggi et al, 2000; Pinto et al, 2004; Apicella et al, 1993). These studies have shown release characteristics dependent on molecular mass and drug loading. The application of PEOs as tableting excipients is all the more desirable since PEO is nontoxic and biodegradable. It is a synthetically produced polymer, which results from the polymerization of ethylene oxide. Chemically this product is known as polyethylene glycol; however, products with a molecular mass of more than 20,000 Da are called PEO (Falbe et al, 1995; Koleske, 1996). The molecular mass can be as high as 8,000,000 Da. PEO molecules are produced with the aid of catalysts, such as red iron oxide and activated aluminum. In order to achieve PEOs of different molecular masses, the molecules which are produced are split while under the influence of UV irradiation.

The PEOs are partially crystalline (about 50% (Koleske ,1996), between 57 and 85% (Yang et al, 1996) and it must be noted that crystallinity decreases with increasing molecular mass (Koleske ,1996; Yang et al, 1996). The glass transition temperature (Tg) was determined to be –52°C for materials with a molecular mass of several million Da, the Tg was –17°C for a molecular mass of 6.000 Da and the melting point was determined at 65°C (Falbe et al, 1995; Koleske ,1996; Bailey et al, 2000). PEOs possess an excellent flowability (Yang et al, 1996; Efentakis et al, 2000), which is a main factor in high speed tablet production. Furthermore, they showed a high compressibility coupled with a high elastic recovery after tableting. According to (Yang

et al, 1996), no differences between different molecular masses (200,000–7,000,000 Da) could be determined using the Heckel analysis.

The swelling properties of POLYOX™ WSR are dependent on molecular weight of the various grades. Little if any swelling occurs with the relatively low molecular weight of 100,000.

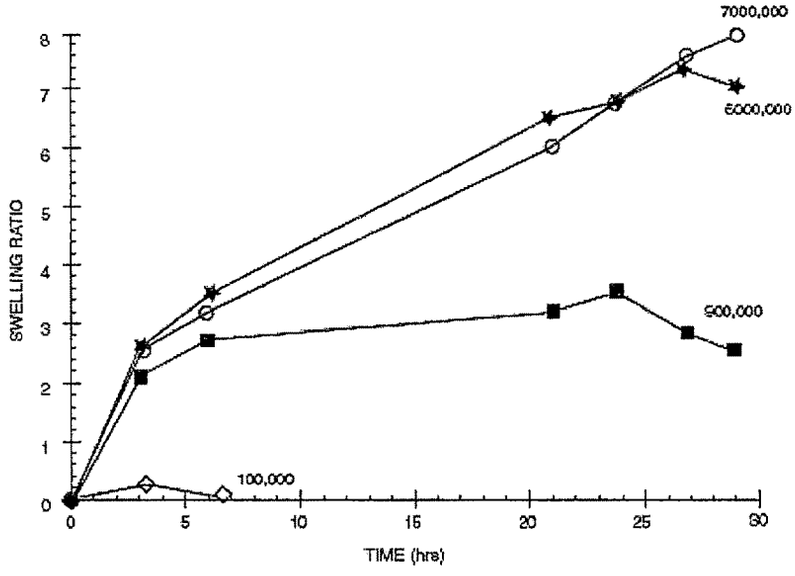


Figure VII. 1 Swelling Capacity of POLYOXTM Resins with Molecular Weight

Hydroxypropyl Methyl Cellulose (Methocel) (Technical Bulletin, 2000)

Of the available range of cellulosic controlled-release agents, hydroxypropyl methylcellulose (HPMC) is the most widely used. HPMC is a well-known excipient with an excellent safety record.

HPMC polymers are very versatile release agents. They are nonionic, so they minimize interaction problems when used in acidic, basic, or other electrolytic systems. HPMC polymers work well with soluble and insoluble drugs and at high and low dosage levels. METHOCEL products are available in two basic types: methylcellulose and hydroxypropyl methylcellulose. Both types of METHOCEL have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units. During the manufacture of cellulose ethers, cellulose fibers are treated with caustic solution, which in turn is treated with methyl chloride and/or propylene oxide. The fibrous reaction product is purified and ground to a fine powder.

To achieve controlled release through the use of a water-soluble polymer such as hypromellose, the polymer must quickly hydrate on the outer tablet surface to form a gelatinous layer. A rapid formation of a gelatinous layer is critical to prevent wetting of

the interior and disintegration of the tablet core. Once the original protective gel layer is formed, it controls the penetration of additional water into the tablet. As the outer gel layer fully hydrates and dissolves, a new inner layer must replace it and be cohesive and continuous enough to retard the influx of water and control drug diffusion. Although gel strength is controlled by polymer viscosity and concentration, polymer chemistry also plays a significant role. Evidence suggests that the chemistry of hypromellose encourages a strong, tight gel formation compared to other cellulosics. As a result, drug-release rates have been sustained longer with hypromellose than with equivalent levels of methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC) or carboxymethylcellulose (CMC). For these reasons, hypromellose is very often the polymer of choice over other cellulose derivatives.

Within the general scheme for categorizing powders, Hydroxypropyl methyl cellulose (METHOCEL™ Premium Products) would be classed as "very fine." It is essential that the powder be quite fine for it to function as a rate-controlling polymer. METHOCEL™ Cellulose Ethers, like many other very fine powders, flow satisfactorily but should not be considered free flowing. For those products most commonly used in controlled release, METHOCEL™ E Cellulose Ethers have somewhat better flow properties than METHOCEL™ K Cellulose Ethers. Depending on the particular components of a formulation, it may be necessary to improve the overall flow properties through the use of an appropriate granulation process.

The hydration rates of the various grades of METHOCEL™ Products differ because of varying proportions of the two chemical substituents, hydroxypropoxyl and methoxyl substitution, attached to the cellulose backbone of hypromellose. The hydroxypropoxyl substitution is relatively hydrophilic in nature and greatly contributes to the rate of hydration of METHOCEL™. The methoxyl substitution is relatively hydrophobic in nature and does not contribute significantly to the rate of hydration of METHOCEL™. K-chemistry METHOCEL™ Products usually establish the gel barrier the quickest among the product grades because K-chemistry has the highest ratio of hydroxypropoxyl to methoxyl substitution. Based on studies examining the effect of substitution on release rate from hydrophilic matrix tablets, K-chemistry results in the slowest release compared to other polymers of similar molecular weight (Nixon, 1997; Cheong et al, 1992).

Table VII. 2 Properties of selected METHOCEL products for use in pharmaceuticals

METHOCEL premium Product grade	-	K100 Premium LV	K4M Premium	K15M Premium	K100M Premium	E4M Premium	E10M Premium CR
Methoxyl, %	USP	19-24	19-24	19-24	19-24	28-30	28-30
Hydroxypropoxyl, %	USP	7-12	7-12	7-12	7-12	7-12	7-12
USP substitution type	USP/ EP	2208	2208	2208	2208	2910	2910
Chlorides, max. %	EP	0.5	0.5	0.5	0.5	0.5	0.5
Apparent viscosity, 2% in water at 20°C, cP	USP	80-120	3000-5600	11250-21000	80000-120000	3000-5600	7500-14000
Apparent viscosity, 2% in water at 20°C, mPas	EP	78-117 [98 Nom]	2308-3755 [2903 Nom]	6138-9030 [7382 Nom]	16922-19267 [18243 Nom]	2308-3755 [2903 Nom]	4646-7070 [5673 Nom]
ID Test A, B, C	USP	Pass	Pass	Pass	Pass	Pass	Pass
ID Test A, B, C, D, E, F	EP	Pass	Pass	Pass	Pass	Pass	Pass
Opalescence of solution	EP	Pass	Pass	Pass	Pass	Pass	Pass
Solution Color, yellowness, 1% in water	EP	Pass	Pass	Pass	Pass	Pass	Pass
pH, 1% in water	EP	5.5-8.0	5.5-8.0	5.5-8.0	5.5-8.0	5.5-8.0	5.5-8.0
Loss on drying, max. %	USP/ EP	5.0	5.0	5.0	5.0	5.0	5.0
Organic impurities, volatile	USP	Pass	Pass	Pass	Pass	Pass	Pass
Residue in ignition, max., %	USP	1.5	1.5	1.5	1.5	1.5	1.5
Ash, sulfated, max., %	EP	1.0	1.0	1.0	1.0	1.0	1.0
Heavy metals, as Pb.max., ppm	USP/EP	10	10	10	10	10	10

Polyvinyl Pyrrolidone (Kollidon)(PVP) (Volker Bühler,2002)

The soluble grades of Kollidon are obtained by free-radical polymerization of vinylpyrrolidone in water or isopropanol, yielding the chain structure of polyvinylpyrrolidone (Vieweg et al, 1971; Ullmanns, 1980).

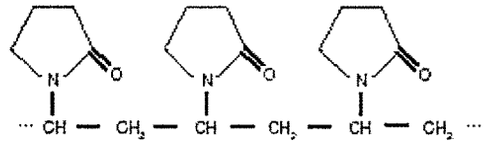


Figure VII. 2 The chemical structure of polyvinylpyrrolidone (povidone) Mr (111.1)x

The current range of soluble Kollidon grades consists of pharmaceutical grade products with the different K-values given in Table VII.3. The K-value indicates the average molecular weight and is included as part of the commercial product name.

Spray drying technology is used in the production of all the soluble Kollidon grades with the exception of Kollidon 90 F. Because of its very high average molecular weight, it has to be dried on a roller.

All the Kollidon grades are of pharmaceutical purity. They are free-flowing white or yellowish-white powders with different particle sizes. The typical odor of the individual products depends on their method of synthesis and is therefore not the same for all the grades of Kollidon. Kollidon 25 and Kollidon 30, for instance, always have a slight amine or ammonia odor, as ammonia is used for neutralization. All the soluble grades of Kollidon give aqueous solutions with very little taste.

Table VII. 3 Characteristic data of the soluble Kollidon grades

	Kollidon 12 PF*	Kollidon 17 PF*	Kollidon 25	Kollidon 30	Kollidon 90 F
Clarity and color (10% in water)	Clear and lighter than B6/BY6/R7	Clear and lighter than B6/BY6/R7	Clear and lighter than B6/BY6/R7	Clear and lighter than B6/BY6/R7	Clear and lighter than B6/BY6/R7
K-value	10.2-13.8	15.3 – 18.0	22.5-27.0	27.0-32.4	81.0-96.3
Nitrogen content (%)	11.5– 12.8	12.0 – 12.8	12.0 – 12.8	12.0 – 12.8	12.0 – 12.8
Water (k.Fischer, %)	≤5.0	≤5.0	≤5.0	≤5.0	≤5.0
pH value (5% in water)	3.0-5.0	3.0-5.0	3.0-5.0	3.0-5.0	4.0-7.0
Vinylpyrrolidone (ppm)	≤5	≤5	≤10	≤10	≤10
Sulfated ash (%)	≤0.1	≤0.1	≤0.1	≤0.1	≤0.1
Aldehyde (%)	≤0.05	≤0.05	≤0.05	≤0.05	≤0.05
Heavy metals (ppm)	≤10	≤10	≤10	≤10	≤10
Hydrazine (ppm)	≤1	≤1	≤1	≤1	≤1
Peroxides (ppm H_2O_2)	≤400	≤400	≤400	≤400	≤400
2-Pyrrolidone	≤1.0%	≤1.0%	≤3.0%	≤3.0%	≤1.0%
Formic acid	-	-	≤0.5%	≤0.5%	≤0.5%
2-Propanol	≤0.5%	≤0.5%	-	-	-
Microbial status	Passes Test	Passes Test	Passes Test	Passes Test	Passes Test
Bacterial endotoxins (Ph.Eur.)	≤6 I.U/ml (= ≤ 0.1 I.U./mg)	≤6 I.U/ml (= ≤ 0.1 I.U./mg)	Not tested	Not tested	Not tested

* PF = free of bacterial endotoxins

One of salient features of the soluble Kollidon grades is their universal solubility, which extends from extremely hydrophilic solvents, such as water, to hydrophobic liquids, such as butanol. Today, the use of organic solvents, such as methylene chloride or chloroform is severely restricted, but nevertheless, small quantities of organic solvents are still used by most pharmaceutical companies. The most commonly used are ethanol, isopropanol, propylene glycol or low-molecular polyethylene glycol, e. g. Lutrol® E 400. Soluble Kollidon is miscible in practically all proportions in these solvents and in water, though, above a certain concentration, the solution obtained has a high viscosity.

The viscosity of aqueous solutions of the soluble Kollidon grades depends on their average molecular weight. This can therefore be calculated from the viscosity, giving the viscosity-average molecular weight. Fig. VII.3 shows the very considerable differences in viscosity between solutions of the different Kollidon grades in water, as a function of their concentration. A 20 % aqueous solution of Kollidon 12 PF shows hardly any visible

difference to pure water, while a 20 % solution of Kollidon 90 F in water gives high viscosities between 6 and 25 Pa · s.

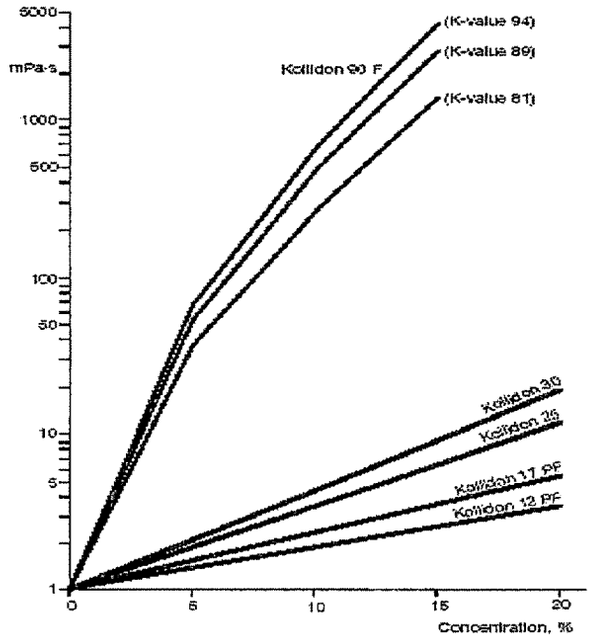


Figure VII. 3 Viscosity curves for the soluble Kollidon grades in water (capillary viscometer, 25 °C)

It was reported that most cations increase the viscosity and most of anions decrease the viscosity of povidone K 90 solutions (Paik, 1992). Some polymers such as carragheenan show a synergistic viscosity increasing effect with Kollidon 90 F.

It must be emphasized that the viscosity of Kollidon solutions is independent of their pH value over a wide range. Only in extreme cases does this rule not apply: concentrated hydrochloric acid increases their viscosity; strong alkali precipitates povidone. However, it usually re-dissolves on addition of water.

The soluble grades of Kollidon possess a number of very useful properties for which they are widely used in pharmaceuticals. Because of these properties, the products can perform different functions in different dosage forms.

Table VII. 4 General Properties of the soluble Kollidon grades in pharmaceuticals

Solubility in all conventional solvents
Adhesive and binding power
Film Formation
Affinity to hydrophilic and hydrophobic surfaces
Ability to form complexes
Availability in different average molecular weights
Thickening properties

VII.2 MATERIALS

Table VII. 5 List of Materials along with specifications and Manufacturer details

Sr. No.	Ingredients	Spec.	Manufacturer
1	Lactose Anhydrous	NF	DMV international
2	Hypromellose K 100M CR	USP	Dow Chemicals
3	Povidone K-90	USP	BASF
4	Povidone K-30	USP	BASF
5	Polyethylene oxide (Polyox WSR 303 NF)	NF	Dow Chemicals
6	Polyethylene oxide (Polyox N80)	NF	Dow Chemicals
7	Polyethylene oxide (Polyox N-10)	NF	Dow Chemicals
8	Microcrystalline Cellulose (Avicel PH 102)	NF	FMC Biopolymer
9	Dibasic calcium phosphate anhydrous	NF	Rhodia
10	Talc	USP	Luzinac
11	Colloidal Silicon dioxide	NF	Degussa
12	Magnesium Stearate	NF	Ferro
13	Isopropyl Alcohol	USP	Finar

VII.3 APPROACHES

Two approaches with combination of polymers were employed:

- With PEO (polyethylene oxide) and HPMC (hydroxypropyl methyl cellulose)
- With PVP (polyvinyl pyrrolidone) and HPMC (hydroxypropyl methyl cellulose)

VII.3.1 With PEO + HPMC

VII.3.1.1 METHOD

VII.3.1.1.1 Formulation with PEO alone (High viscosity grade)

Trials were taken with only Polyethylene oxide (high viscosity grade) with polymer concentration of 20% and 40%.

Non aqueous granulation with Isopropyl alcohol as solvent was used and as polyvinyl pyrrolidone is soluble in Isopropyl alcohol, it was used as binder. Brief description of the process used is as follows:

Step1. Alfuzosin Hydrochloride, Polyethylene oxide and Microcrystalline cellulose were mixed together in a high shear mixer (Rapid mixer granulator) after sifting through 30# sieve.
Step2. Binder solution was prepared by dispersing and dissolving PVP K30 in Isopropyl alcohol (IPA) while stirring.
Step3. Binder was slowly added to the dry mix of step 1, with impeller at slow speed and chopper off and then kneaded with impeller and chopper at fast speed.
Step4. The material of step 3 was dried in fluidized bed dryer and then sized through oscillatory granulator fitted with 1.0 mm sieve.
Step5. Colloidal silicon dioxide and Magnesium stearate were sifted through 60# sieve and blended with dried granules of step 4 in conta blender.
Step6. Lubricated blend of step 5 was compressed in 16 station compression machine fitted with 9.5 mm round punches and suitable dies.

VII.3.1.1.2 Formulation with PEO and HPMC combination

Two formulations with different combination of HPMC K100 MCR with Polyethylene oxide (N80 and N10) were formulated with process similar to that mentioned above.

VII.3.1.1.3 Evaluation of Compressed formulations

Physico -chemical characterization of compressed tablets was carried out. Tablets were evaluated for Average weight, Thickness, Diameter, Hardness, Friability, Assay, Content uniformity, Related impurities, Water by KF and Dissolution profile.

VII.3.1.1.4 Gastric Residence Time

In order to study the gastric retention time in healthy volunteers, dummy formulation of B. No 47 was prepared with tablet weight of 340 mg (excluding weight of Barium sulphate tablet).

VII.3.1.1.4.1 Preparation of Barium Sulphate tablets

Barium Sulphate tablets were prepared similar to method mentioned in size exclusion technology (non swelling (Chapter V)

B. No 47 was chosen for gastric retention study. In order to prepare dummy tablets, lubricated blend for each tablet was divided into two parts. One part i.e. 170 mg was filled in the die of compression machine and then two tablets of 40 mg of Barium Sulphate were placed over it at some distance apart and then the other half of the lubricated blend was filled and compressed manually.

VII.3.1.1.4.2 In vitro Evaluation of Tablet containing Barium Sulphate

In order to check how long Barium sulphate tablets will remain inside the matrix of swelling controlled formulation, an in-vitro study was done. Tablets were placed in 500 ml beaker containing simulated gastric media with pepsin and the media was stirred occasionally with glass rod and X-Ray exposures were taken at different intervals of time: 0, 0.30, 1.0, 2.0, 4.0, 6.0, 7.0 hrs.

VII.3.1.1.4.3 In vivo Evaluation of Tablet containing Barium Sulphate

Protocol for gastric residence time was followed the same as mentioned in gastric residence time for size exclusion tablet (non swelling) (Chapter V).
Gastric retention time study was carried out in 5 healthy volunteers (2 for fasted state and 3 for fed state).

VII.3.1.1.5 Bio Study

In order to know the effect of different release profiles in vivo, Bio study was performed with formulation of B. No. 16 and B. No. 47. Protocol for bio study was followed same as that mentioned in size exclusion technology (non –swelling) (Chapter V).

VII.3.1.1.6 Development of Biorelevant Discriminatory media

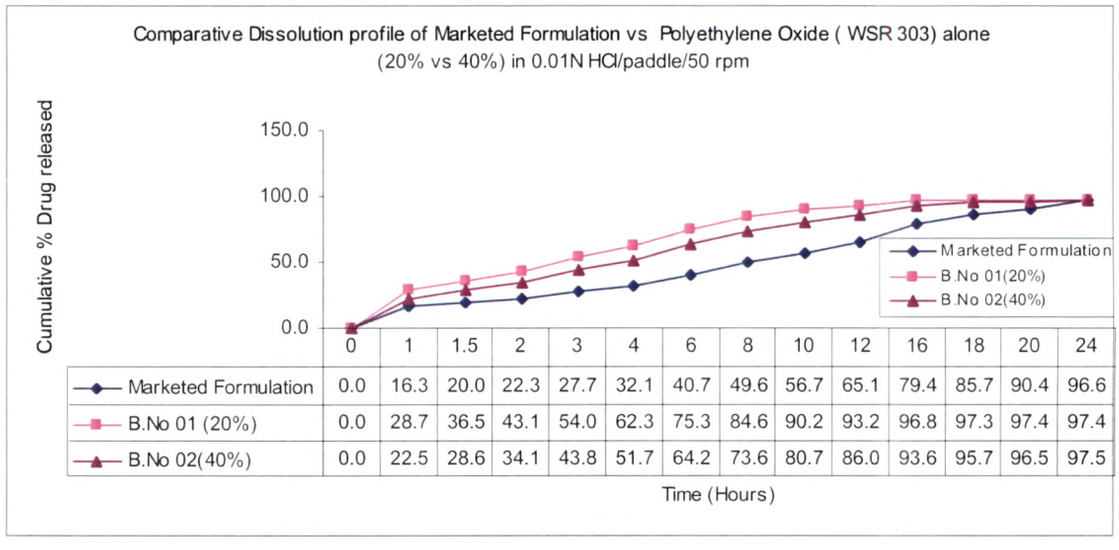
In order to establish an IVIVC, dissolution profile was carried out in different media and apparatus, at different conditions, with B. No 16 in comparison with Marketed Formulation.

VII.3.1.2 RESULTS

VII.3.1.2.1 Formulation with PEO alone (High viscosity grade)

Table VII. 6 Formulation composition with 20% (B.No 01) and 40% (B.No 02) Polyethylene Oxide

Sr. No	Ingredients	Function	B.N0. 01		B.No. 02	
			Qty / Tab. (In mg)	% w/w	Qty / Tab. (In mg)	% w/w
1	Alfuzosin HCL	Active	10.00	4.44	10.00	4.44
2	Polyethylene Oxide (Polyox WSR 303 NF)	Release controlling agent	45.00	20.00	90.00	40.00
3	Microcrystalline Cellulose (Avicel PH 102)	Diluent	160.30	71.24	115.30	51.24
4	Povidone K-30	Binder	6.25	2.78	6.25	2.78
5	Isopropyl Alcohol	Solvent	q.s	-	q.s	-
6	Colloidal Silicon Dioxide(Aerosil 200)	Glidant	1.20	0.53	1.20	0.53
7	Magnesium Stearate	Lubricant	2.25	1.00	2.25	1.00
	Core Tablet Weight		**225.00**		**225.00**	



	0	1	1.5	2	3	4	6	8	10	12	16	18	20	24
Marketed Formulation	0.0	16.3	20.0	22.3	27.7	32.1	40.7	49.6	56.7	65.1	79.4	85.7	90.4	96.6
B.No 01 (20%)	0.0	28.7	36.5	43.1	54.0	62.3	75.3	84.6	90.2	93.2	96.8	97.3	97.4	97.4
B.No 02(40%)	0.0	22.5	28.6	34.1	43.8	51.7	64.2	73.6	80.7	86.0	93.6	95.7	96.5	97.5

Figure VII. 4 Comparative Dissolution profile of Marketed Formulation vs B. No. 01 and B. No. 02 containing Polyethylene Oxide (WSR 303) alone (20% vs. 40%) in 0.01N HCl/paddle/50 rpm

Dissolution profile with High viscosity grade polyethylene oxide alone showed faster dissolution profile than marketed formulation and a significant difference was not observed even after doubling the polymer quantity (20% vs 40%). So a combination of PEO (low viscosity) and HPMC K100 (High viscosity grade) was tried.

VII.3.1.2.2 Formulation with Combination of HPMC and PEO

Table VII. 7 Formulation composition with HPMC K100 MCR (39.71%) and Polyethylene oxide (12.86%) (B. No 16) vs. HPMC K100 MCR (57.14%) and Polyethylene oxide (20.0%) (B. No 47)

Sr. No	Ingredients	Function	B.N0. 16		B.No. 47	
			Qty / Tab. (In mg)	% w/w	Qty / Tab. (In mg)	% w/w
1	Alfuzosin Hydrochloride	Active	10.00	2.86	10.00	2.86
2	Lactose Anhydrous	Diluent	113.00	32.29	----	----
3	Dibasic calcium phosphate	Diluent	20.00	5.71	----	----
4	Hypromellose K100M CR	Release controlling agent	139.00	39.71	200.00	57.14
5	Polyox N80	Release controlling agent	45.00	12.86	40.00	11.43
6	Polyox N-10	Release controlling agent	----	----	30.00	8.57
7	Povidone K30	Binder	15.00	4.29	19.00	5.43
8	Colloidal silicon dioxide	Glidant	1.33	0.38	1.00	0.29
9	IPA	Vehicle	q.s		q.s.	
		Extra granular				
10	Microcrystalline Cellulose (Avicel PH 102)	Diluent	----	----	43.33	12.38
11	Talc	Glidant	2.00	0.57	2.00	0.57
12	Colloidal silicon dioxide	Glidant	0.67	0.19	0.67	0.19
13	Magnesium stearate	Lubricant	4.00	1.14	4.00	1.14
	Total Weight		**350.00**	100	**350.00**	100

VII.3.1.2.2.1 Evaluation of Compressed formulations

Table VII. 8 Physico-Chemical parameters of B. No 16 and B. No. 47

S.No.		B. No 16	B. No 47
Physical Parameter			
1	Diameter (mm)	9.5 ± 0.05	9.5 ± 0.05
2	Thickness (mm)	4.40 (4.35-4.47)	4.51 (4.45-4.56)
3	Hardness (N)	78 (75-83)	131 (125-132)
4	Average weight (mg)	354 (352.8-354.8)	354.54 (352.5-356.1)
5	Friability (%)	0.04	0.06
Chemical Parameter			
6	Content Uniformity	98.2 ± 0.5	97.4 ± 1.40
7	Related Impurities (%) Single unknown Total Impurities	 0.02 0.11	 0.04 0.07
8	Assay (%)	99.2	98.4
9	Water By KF (% w/w)	3.35	3.34

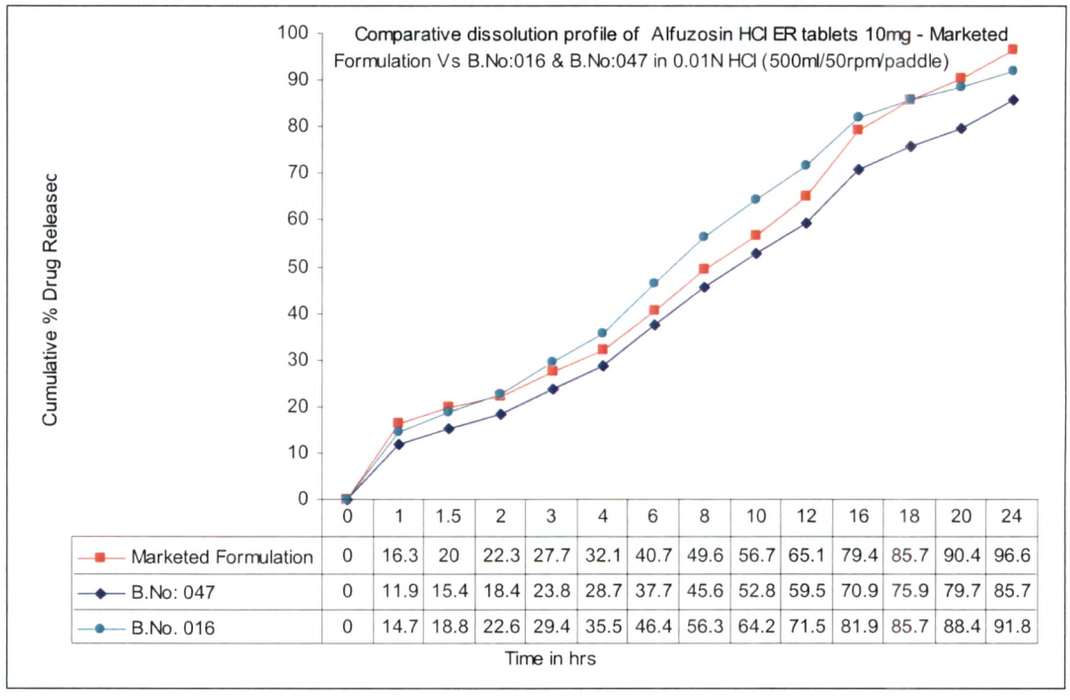
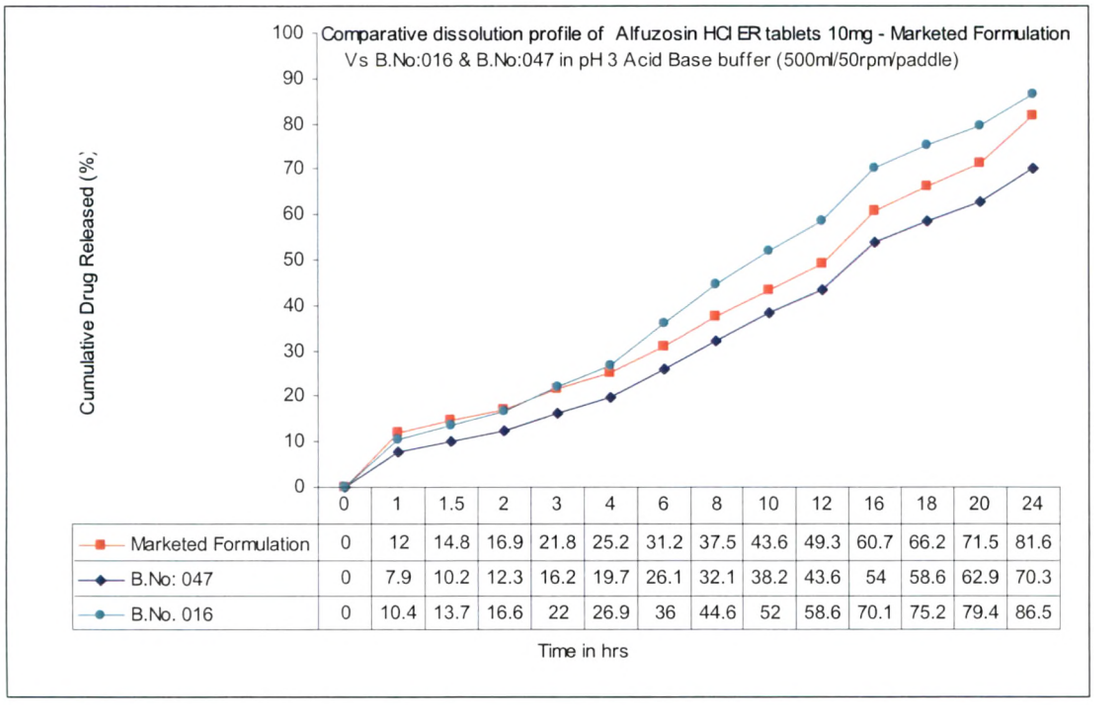
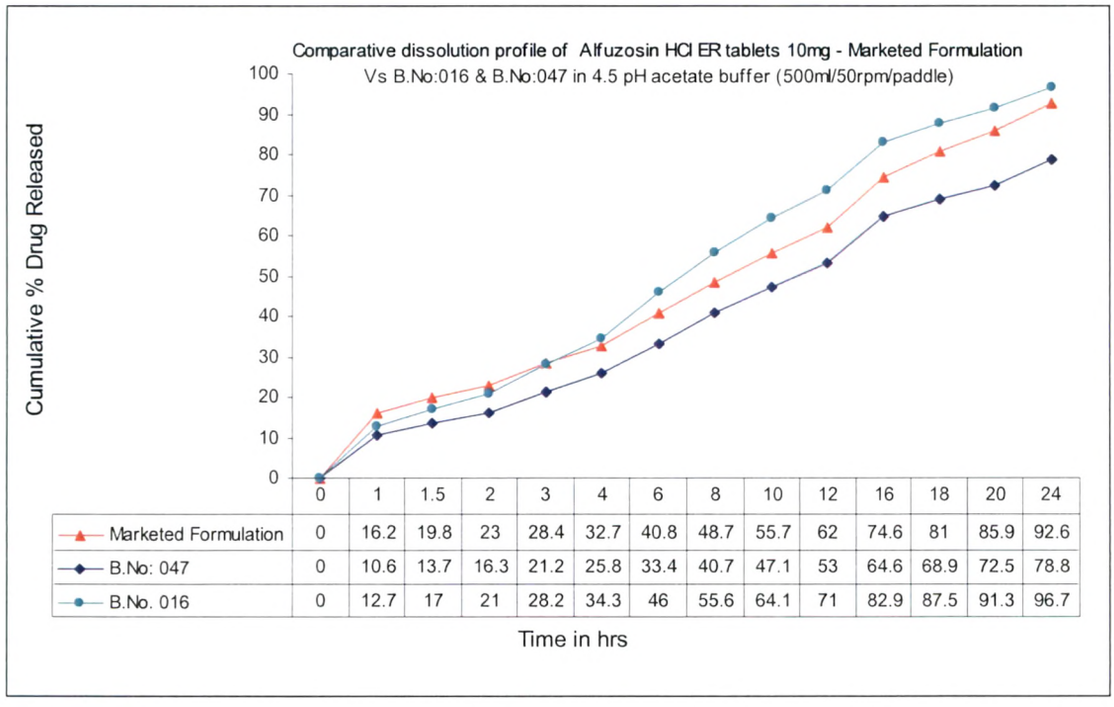


Figure VII.5 (A)



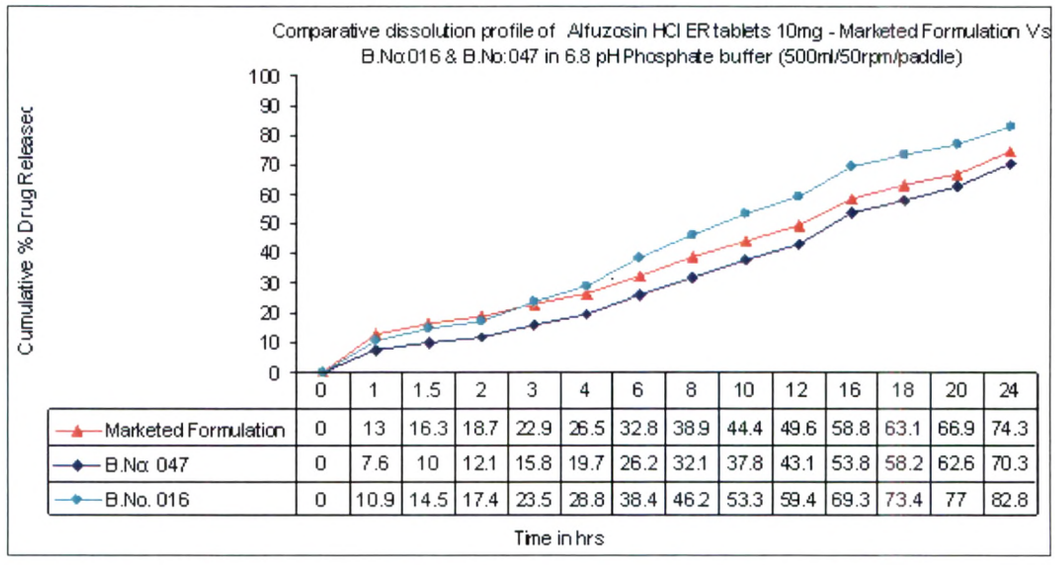
	0	1	1.5	2	3	4	6	8	10	12	16	18	20	24
Marketed Formulation	0	12	14.8	16.9	21.8	25.2	31.2	37.5	43.6	49.3	60.7	66.2	71.5	81.6
B.No: 047	0	7.9	10.2	12.3	16.2	19.7	26.1	32.1	38.2	43.6	54	58.6	62.9	70.3
B.No. 016	0	10.4	13.7	16.6	22	26.9	36	44.6	52	58.6	70.1	75.2	79.4	86.5

Figure VII.5 (B)



	0	1	1.5	2	3	4	6	8	10	12	16	18	20	24
Marketed Formulation	0	16.2	19.8	23	28.4	32.7	40.8	48.7	55.7	62	74.6	81	85.9	92.6
B.No: 047	0	10.6	13.7	16.3	21.2	25.8	33.4	40.7	47.1	53	64.6	68.9	72.5	78.8
B.No. 016	0	12.7	17	21	28.2	34.3	46	55.6	64.1	71	82.9	87.5	91.3	96.7

Figure VII.5 (C)



	0	1	1.5	2	3	4	6	8	10	12	16	18	20	24
Marketed Formulation	0	13	16.3	18.7	22.9	26.5	32.8	38.9	44.4	49.6	58.8	63.1	66.9	74.3
B.No: 047	0	7.6	10	12.1	15.8	19.7	26.2	32.1	37.8	43.1	53.8	58.2	62.6	70.3
B.No. 016	0	10.9	14.5	17.4	23.5	28.8	38.4	46.2	53.3	59.4	69.3	73.4	77	82.8

Figure VII.5 (D)

Figure VII. 5 Comparative Dissolution profile of B. No 16 and B. No 47 with Marketed Formulation in different media (0.01 N HCl, pH 3 acid base buffer, 4.5 pH acetate buffer, 6.8 pH phosphate buffer)

VII.3.1.2.2.2 Gastric Residence Time

VII.3.1.2.2.2.1 In vitro Evaluation of Tablet containing Barium Sulphate

In Vitro evaluation showed that although the tablet swelled over the period of time, matrix remained intact throughout the study and Barium Sulphate tablets remained within the swollen matrix throughout the time period i.e.7 hours. X-Ray slides (data not shown) showed distinct Barium Sulphate tablets, but as they were cut in round shape, they seemed merged with each other. So, for gastric residence time in human volunteers, it was decided to cut the Barium Sulphate tablets in uneven shape, so that two distinct tablets can be seen in X-Ray slides.

VII.3.1.2.2.2.2 In vivo Evaluation of Tablet containing Barium Sulphate

Table VII. 9 Gastric Residence time of Dummy formulation of B.No 47 in Fasted State

	Size Exclusion (Swelling Controlled)	
Time (min)	**PK-E-395**	**PK-E-428**
0	Stomach	Stomach
20	Stomach	Stomach
40	Stomach	Small Intestine
60	Small Intestine	Small Intestine
90	Small Intestine	Small Intestine
150	Colon	Small Intestine

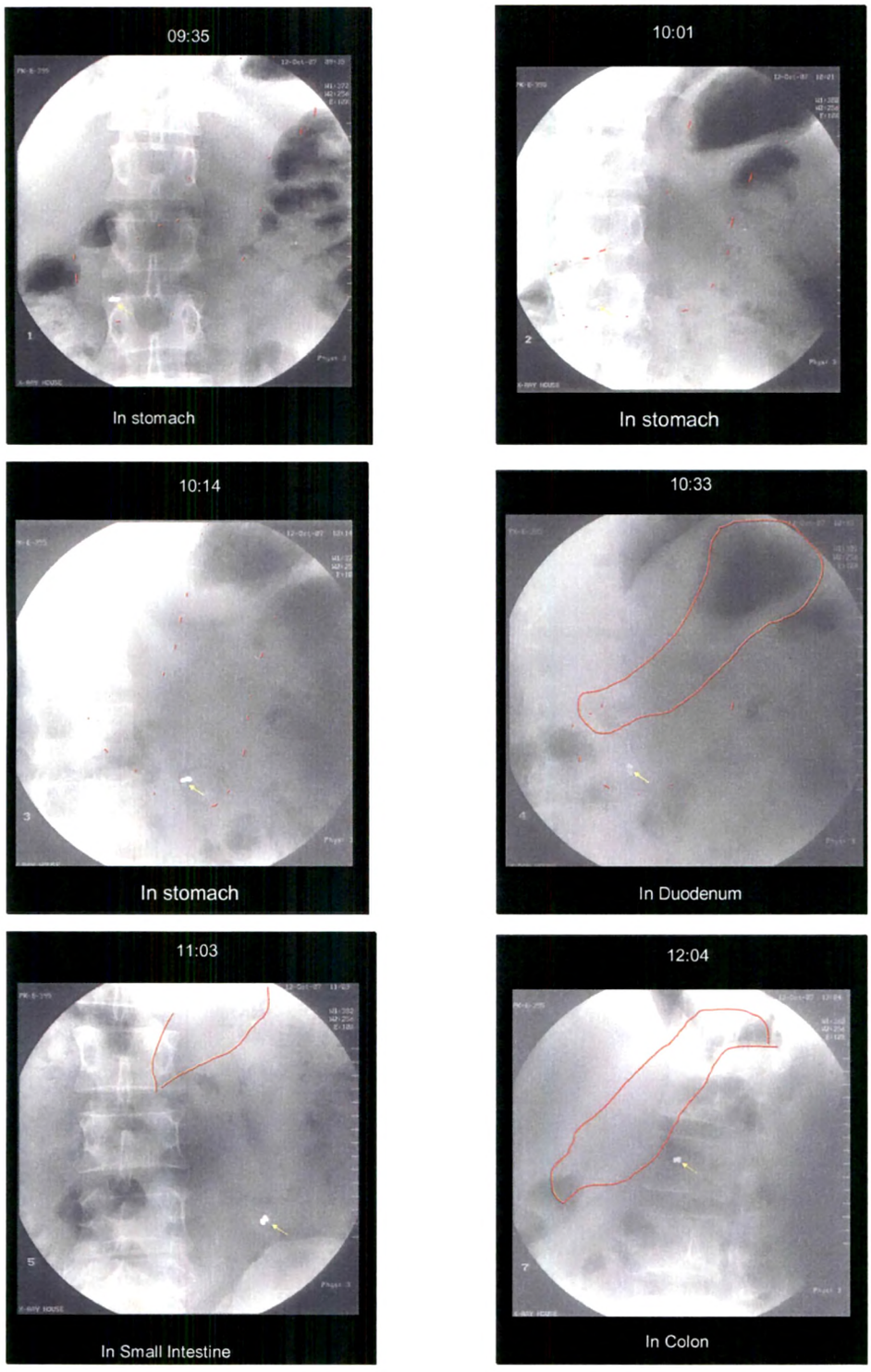


Figure VII. 6 Gastric Residence time of Dummy formulation of B.No 47 in Healthy Volunteer (PK-E-395) under Fasted State

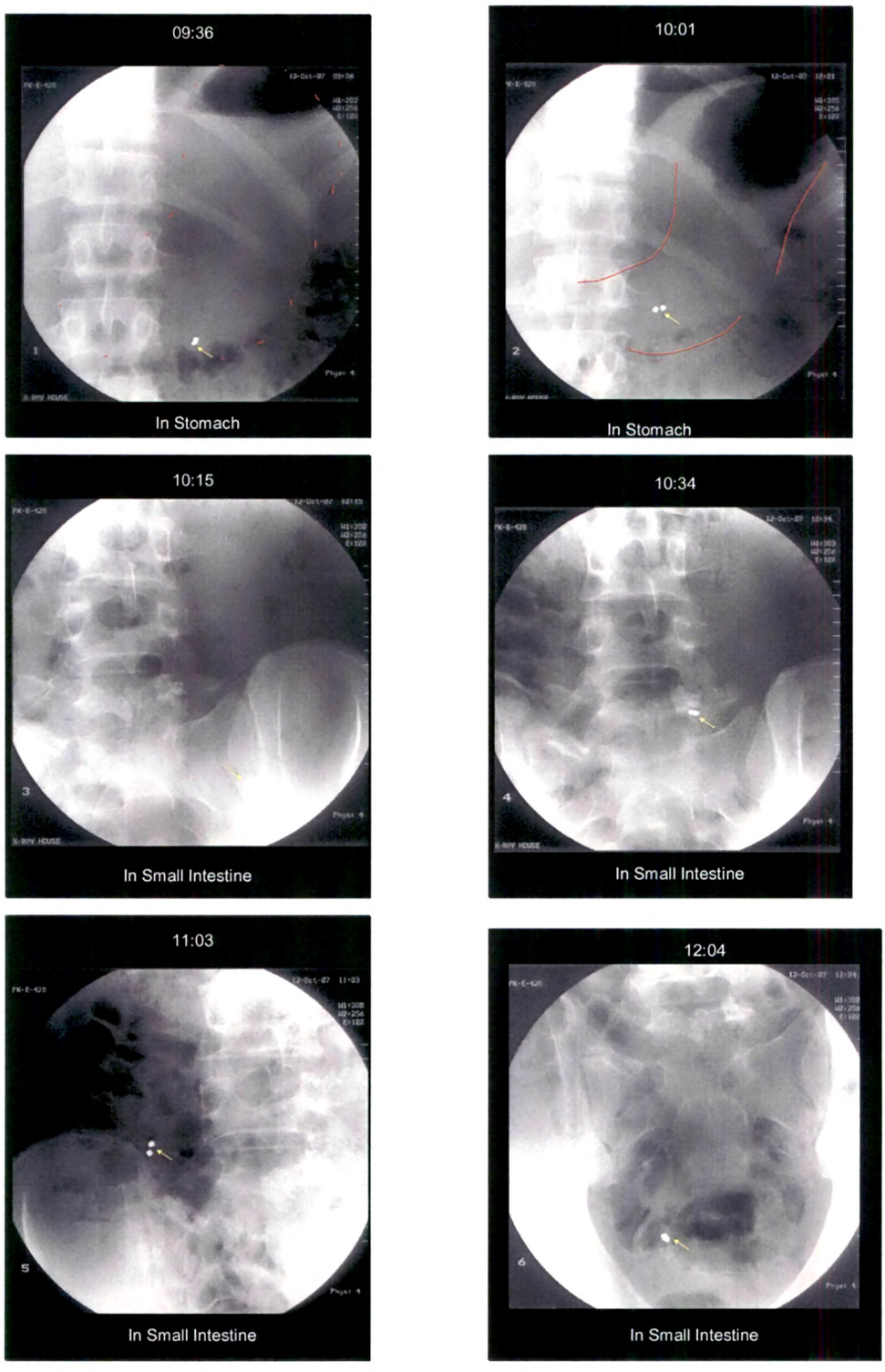
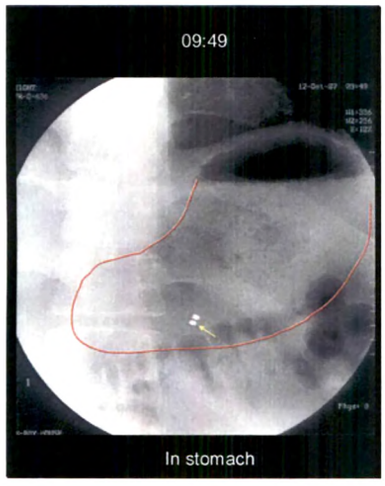
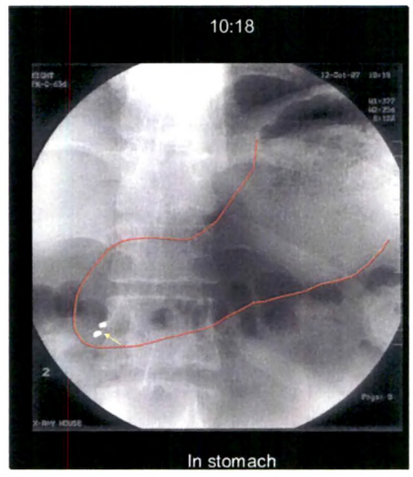


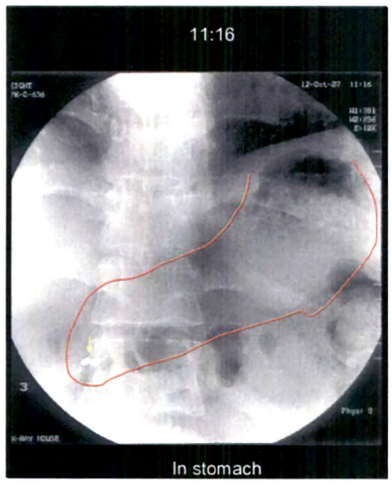
Figure VII. 7 Gastric Residence time of Dummy formulation of B.No 47 in Healthy Volunteer (PK-E-428) under Fasted State

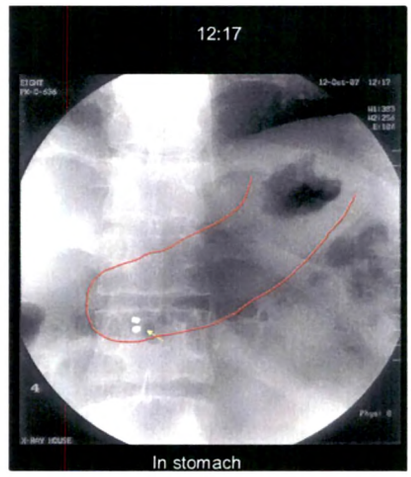
Table VII. 10 Gastric Residence time of Dummy formulation of B.No 47 in Fed State

	Size Exclusion (Swelling Controlled)		
Time (hr)	**PK-C-636**	**PK-E-018**	**PK-F-685**
0	Stomach	Stomach	Stomach
0.5	Stomach	Stomach	Stomach
1.5	Stomach	Stomach	Stomach
2.5	Stomach	Stomach	Stomach
2.6	Not Done	Not Done	Not Done
3.5	Small Intestine	Stomach	Stomach
4.5	Small Intestine	Stomach	Stomach
5.5	Caecum	Stomach	Stomach
6.5	Colon	Stomach	Stomach









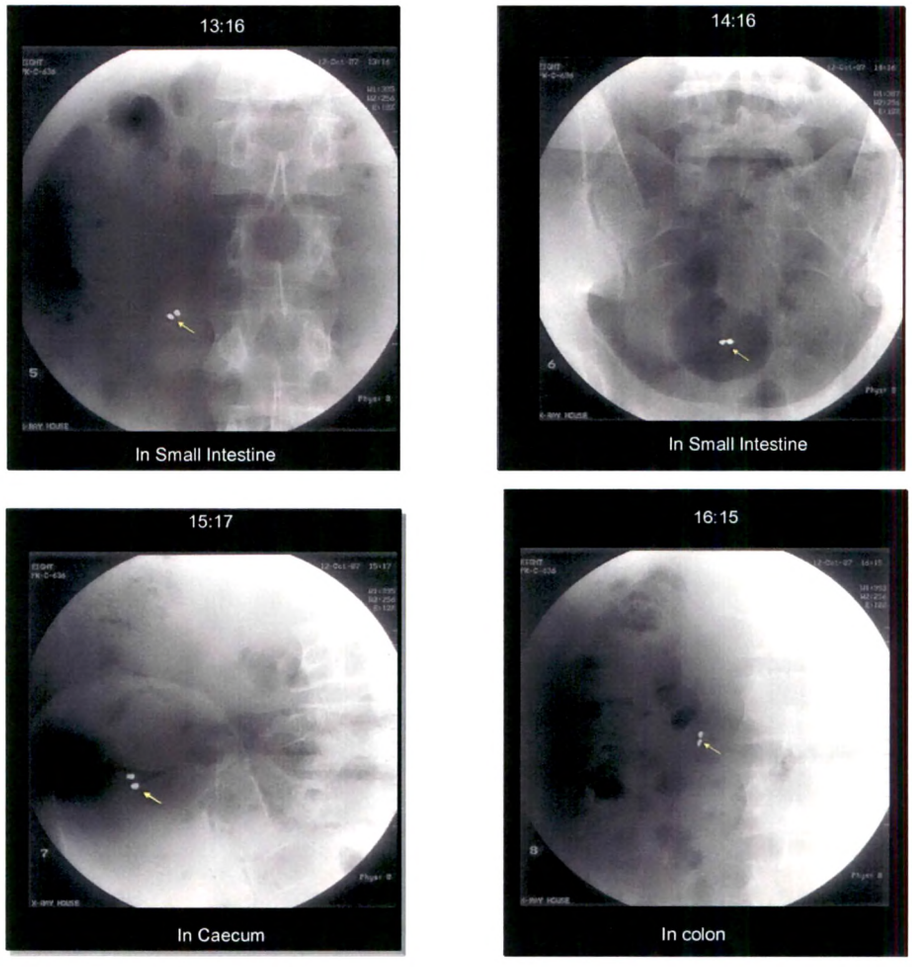
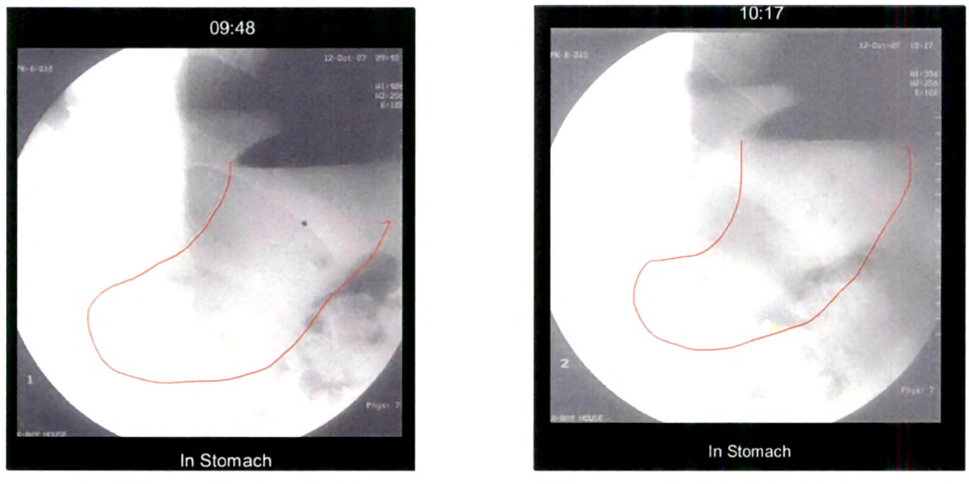


Figure VII. 8 Gastric Residence time of Dummy formulation of B.No 47 in Healthy Volunteer (PK-C-636) under Fed State



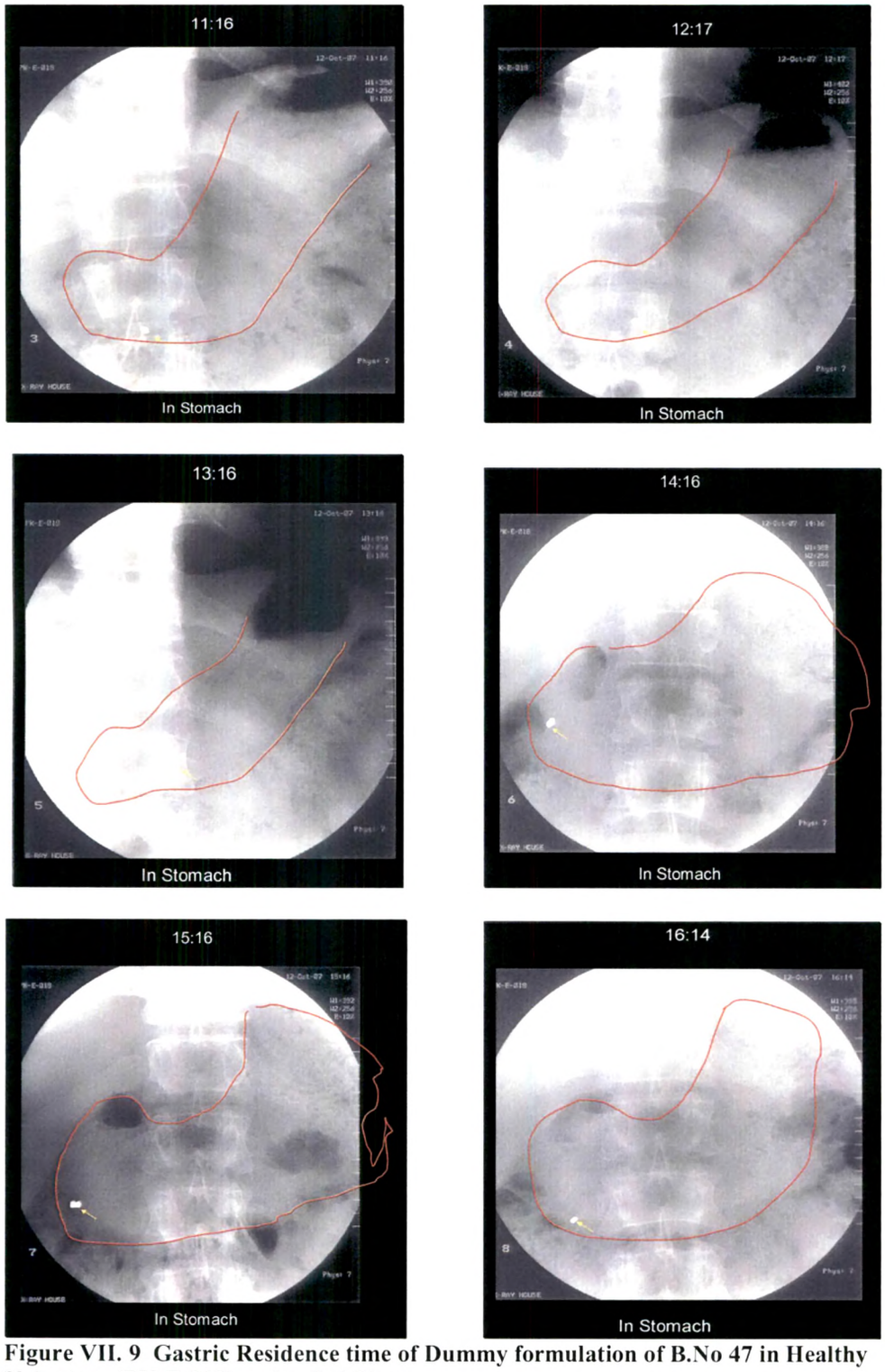
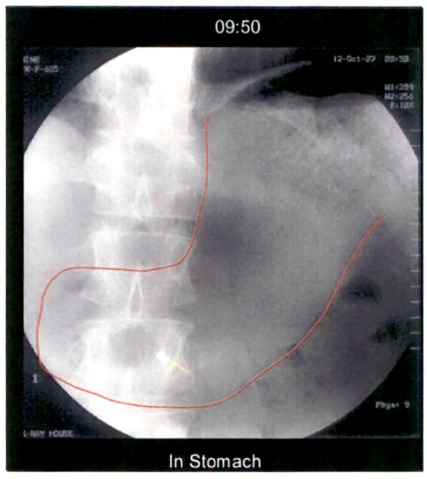


Figure VII. 9 Gastric Residence time of Dummy formulation of B.No 47 in Healthy Volunteer (PK-E-018) under Fed State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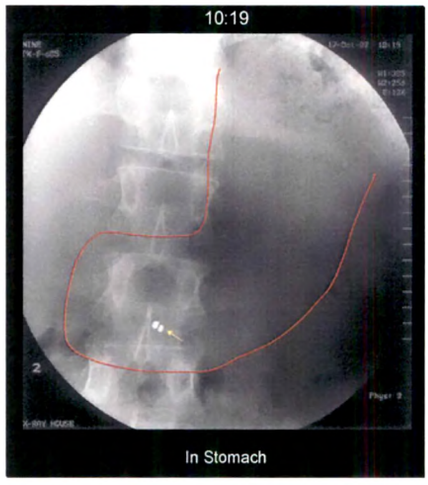
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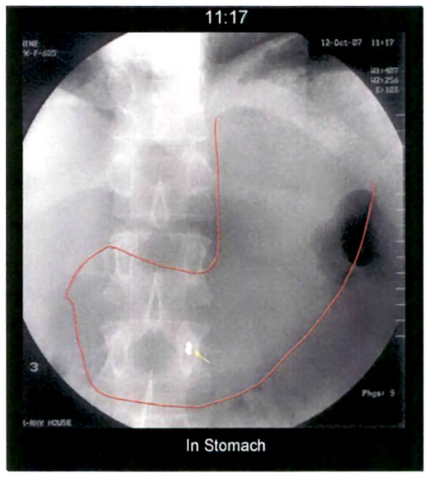
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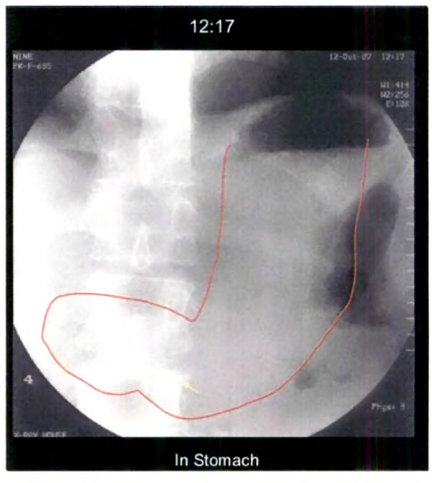
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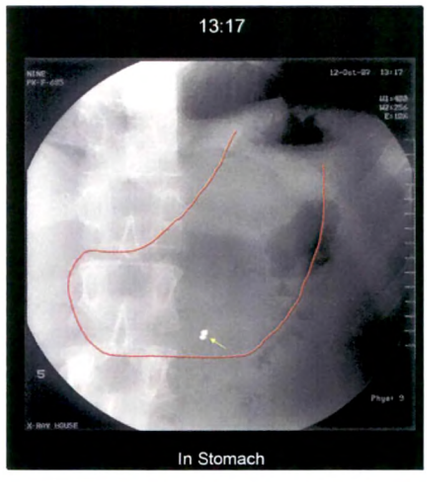
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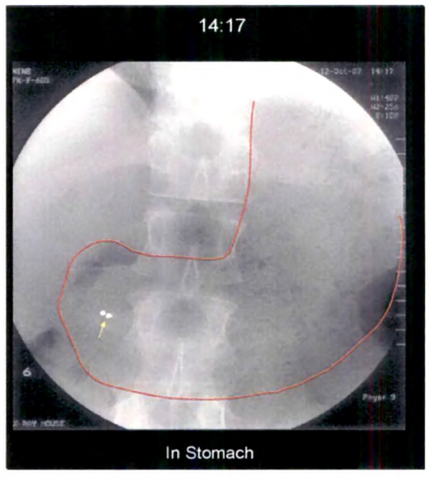
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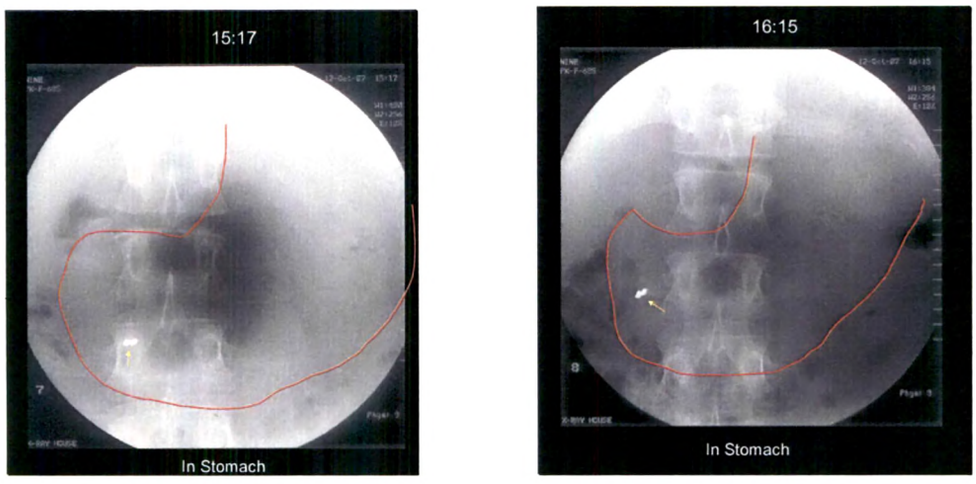


Figure VII. 10 Gastric Residence time of Dummy formulation of B.No 47 in Healthy Volunteer (PK-F-685) under Fed State

VII.3.1.2.2.3 Bio Study

Bio study of Batch no.16 and B. No. 47 was carried out along with Marketed Formulation with B. No 16 in Fed condition whereas B. No 47 was carried out in both Fed and Fasted condition.

VII.3.1.2.2.3.1 Statistical Evaluation of B. No 16 (Fed State)

Table VII. 11 BE limit of B. No 16 vs Marketed Formulation in Fed state

BE Limits:(n=11) Alfuzosin10mg Fed Study	90%CI		90%W.L.		AHpval	Power	Within Limits Y/N
	Lower	Upper	Lower	Upper			
Ln(Cmax)	168.1	273.5	Not Estimable	Not Estimable	0.9986	0.4444	N
Ln(AUCt)	108.2	171.87	37.63	162.37	0.745	0.4775	N
Ln(AUCinf)	108.13	165.34	43.07	156.93	0.7116	0.5384	N

Table VII. 12 Pharmacokinetic Parameters of B. No 16 vs Marketed Formulation in Fed State

Study Statistics:(n=11) Alfuzosin10mg Fed Study	Test			Reference			T/R of mean
	Mean	SD	CV%	Mean	SD	CV%	
Cmax	23.624	10.69	45.24	11.090	5.32	47.97	2.13
AUCt	237.086	105.96	44.69	187.836	110.70	58.93	1.26
AUCinf	242.369	104.53	43.13	193.694	108.39	55.96	1.25

Table VII. 13 Test/Reference ratio of Pharmacokinetic parameters in individual volunteers (B. No 16 vs Marketed Formulation)

Subject	T/R		
	Cmax	AUCt	AUCinf
1	1.38	1.16	1.15
2	1.72	0.85	0.85
3	1.44	1.16	1.15
4	4.68	1.64	1.62
5	1.45	0.74	0.81
6	5.10	3.08	2.99
7	2.15	1.49	1.53
8	1.57	0.85	0.84
9	1.85	1.84	1.76
10	3.40	2.35	1.77
11	2.18	1.61	1.61
Geometric Mean	2.19	1.39	1.36
Mean	2.45	1.52	1.46
SD	1.34	0.71	0.63

Table VII. 14 Pharmacokinetic Parameters of Test formulation (B.No 16) in fed state

	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-inf}	Residual Area#	K_{el}	TLIN	LQCT	$T_{1/2\ el}$	MRT_{0-t}	MRT_{0-inf}
	(ng/ml)	(h)	(ng.h/ml)	(ng.h/ml)	(%)	(h^{-1})	(h)	(h)	(h)	(h)	(h)
GEOMETRIC MEAN	21.702	5.69	214.72	221.10	1.77	0.10	13.84	39.73	6.71	11.24	12.16
MEAN	23.624	6.14	237.09	242.37	2.84	0.11	14.59	41.45	6.98	11.39	12.31
SD (±)	10.687	2.41	105.96	104.53	3.11	0.04	4.67	11.21	1.98	1.87	1.95
CV(%)	45.238	39.26	44.69	43.13	109.79	33.37	32.03	27.04	28.30	16.46	15.85
Range(min)	10.852	2.00	96.45	106.73	0.38	0.06	8.00	24.00	3.61	8.16	8.57
Range(max)	44.322	12.00	422.83	425.68	10.52	0.19	20.00	48.00	10.73	14.21	14.98
Median	20.403	6.00	217.19	224.05	1.71	0.10	16.00	48.00	7.02	11.50	11.97

Table VII. 15 Pharmacokinetic Parameters of Reference (Marketed Formulation) in fed state

	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-inf}	Residual Area#	K_{el}	TLIN	LQCT	$T_{1/2\ el}$	MRT_{0-t}	MRT_{0-inf}
	(ng/ml)	(h)	(ng.h/ml)	(ng.h/ml)	(%)	(h^{-1})	(h)	(h)	(h)	(h)	(h)
GEOMETRIC MEAN	9.923	4.56	154.61	162.99	2.39	0.10	12.62	39.73	6.86	12.87	14.43
MEAN	11.090	5.64	187.84	193.69	4.84	0.10	14.36	41.45	6.98	13.27	14.74
SD (±)	5.320	4.97	110.70	108.39	7.48	0.02	6.63	11.21	1.42	3.30	2.99
CV(%)	47.971	88.09	58.93	55.96	154.52	18.55	46.18	27.04	20.29	24.87	20.29
Range(min)	4.001	2.00	34.01	35.75	0.70	0.07	4.00	24.00	5.35	7.57	8.74
Range(max)	20.307	20.00	397.52	400.93	25.58	0.13	20.00	48.00	9.92	18.40	18.78
Median	10.690	4.00	163.09	167.42	2.04	0.10	20.00	48.00	6.65	13.48	14.46

Table VII. 16 Analysis of Variance Tables for Ln (C max), Ln (AUC0-t), Ln (AUCinf)

a) Ln (Cmax)

Cmax(ng/ml) Analysis-ANOVA for Ln(Cmax)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.3065	0.3065	3.19	0.1076
Subject(seq.)	9	2.9836	0.3315	3.45	0.0398
Period	1	3.3680	3.3680	35.05	0.0002
Formulation	1	0.2575	0.2575	2.68	0.1363
Residual	9	0.8648	0.0961	-	-
Intra-subject CV:31.76%			Inter-subject CV:34.31%		

b) Ln (AUC o-t)

AUC0-t(ng.h/ml) Analysis-ANOVA for Ln(AUC0-t)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.5629	0.5629	6.48	0.0314
Subject(seq.)	9	5.8482	0.6498	7.48	0.0031
Period	1	0.5933	0.5933	6.83	0.0281
Formulation	1	0.2198	0.2198	2.53	0.1465
Residual	9	0.7818	0.0869	-	-
Intra-subject CV:30.13%			Inter-subject CV:53.05%		

c) Ln(AUCinf)

AUC0-inf(ng.h/ml) Analysis-ANOVA for Ln(AUCinf)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.4579	0.4579	6.26	0.0337
Subject(seq.)	9	5.3979	0.5998	8.20	0.0022
Period	1	0.5113	0.5113	6.99	0.0267
Formulation	1	0.1375	0.1375	1.88	0.2036
Residual	9	0.6583	0.0731	-	-
Intra-subject CV:27.55%			Inter-subject CV:51.31%		

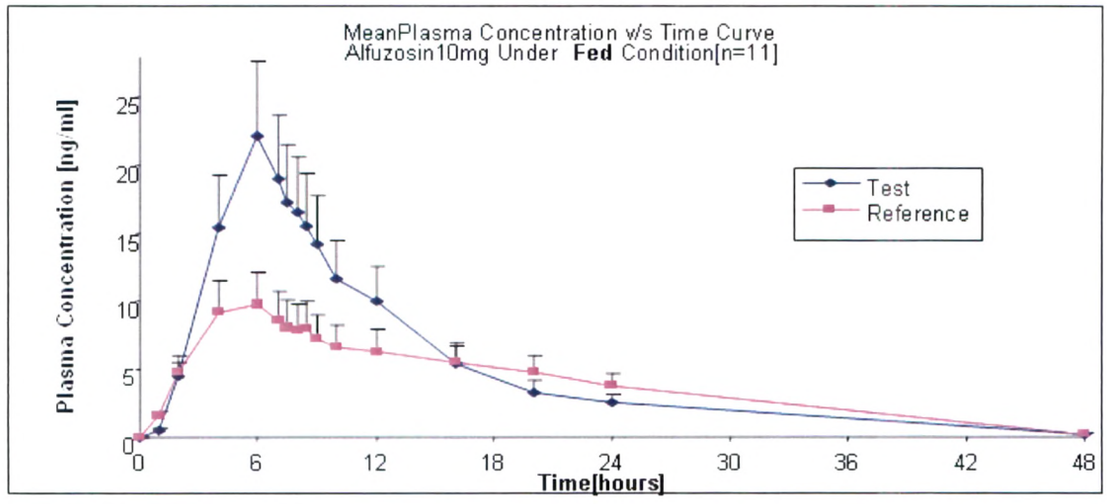


Figure VII. 11 Mean plasma concentration vs time curve of B.NO 16 (Test) vs Marketed formulation (Reference) in Fed state

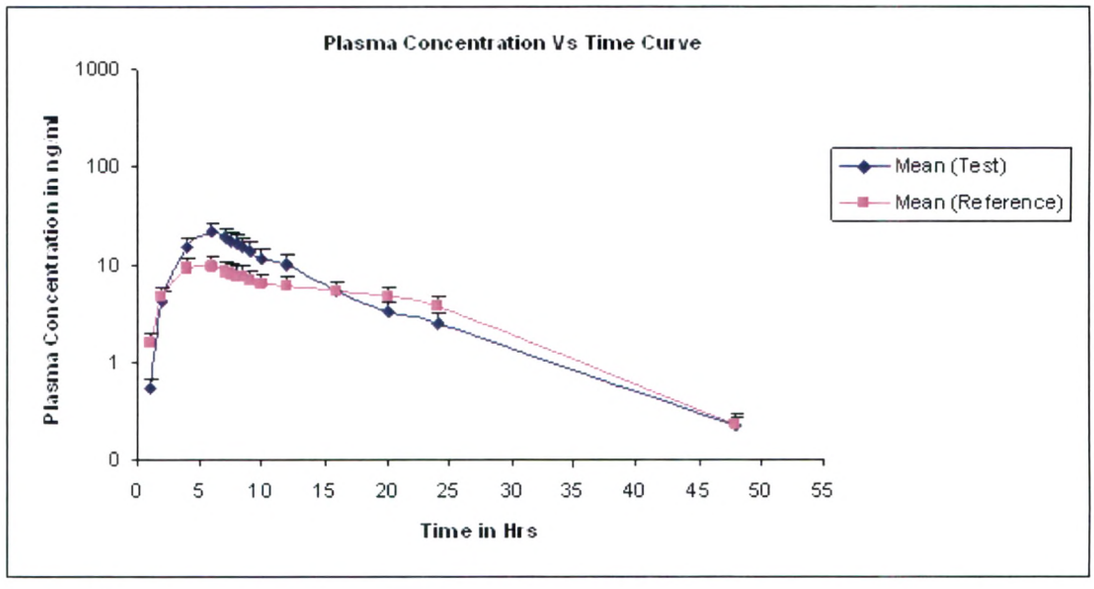


Figure VII. 12 Semi logarithmic plasma concentration vs time curve of B.NO 16 (Test) vs Marketed formulation (Reference) in Fed state

VII.3.1.2.2.3.2 Statistical Evaluation of B. No 47 (Fasted State)

Table VII. 17 BE limit of B.No 47 vs Marketed Formulation in Fasted State

BE Limits:(n=14) Alfuzosin 10mg Fasted Study	90%CI		90%W.L.		AHpval	Power	Within Limits Y/N
	Lower	Upper	Lower	Upper			
Ln(Cmax)	115.35	168.53	38.95	161.05	0.8376	0.6223	N
Ln(AUCt)	131.81	174.77	31.03	168.97	0.9848	0.8404	N
Ln(AUCinf)	124.86	173.93	32.83	167.17	0.949	0.7266	N

Table VII. 18 Pharmacokinetic Parameters of B.No 47 vs Marketed Formulation in Fasted State

Study Statistics:(n=14) Alfuzosin 10mg Fasted Study	Test			Reference			T/R of mean
	Mean	SD	CV%	Mean	SD	CV%	
Cmax	8.953	4.93	55.09	6.212	2.31	37.12	1.44
AUCt	119.690	46.35	38.72	81.839	39.81	48.65	1.46
AUCinf	136.305	48.87	35.86	95.011	39.59	41.67	1.43

Table VII. 19 Test/Reference ratio of Pharmacokinetic parameters in individual volunteers (B. No 47 vs Marketed Formulation)

Subject	T/R			
	Cmax	AUCt	AUCinf	Tmax
1	1.87	1.38	1.09	1.00
2	0.89	1.12	1.03	2.00
3	0.86	1.77	2.06	1.00
4	1.92	2.98	3.18	2.50
5	0.72	0.88	0.90	1.00
6	1.06	1.89	1.45	3.00
7	0.94	1.02	0.99	1.88
8	1.34	1.11	0.96	2.00
9	2.51	2.10	2.23	0.75
10	1.86	1.35	1.37	0.67
11	1.42	1.33	1.64	0.80
12	1.77	1.93	2.03	1.25
13	2.29	1.88	1.43	1.88
14	1.46	1.63	1.73	0.33
Geometric Mean	**1.39**	**1.52**	**1.47**	**1.23**
Mean	**1.49**	**1.60**	**1.58**	**1.43**
SD	**0.56**	**0.55**	**0.64**	**0.78**

Table VII. 20 Pharmacokinetic Parameters of Test formulation (B.No 47) in fasted state

	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-inf}	Residual Area#	K_{el}	TLIN	LQCT	$T_{1/2\ el}$	MRT_{0-t}	MRT_{0-inf}
	(ng/ml)	(h)	(ng.h/ml)	(ng.h/ml)	(%)	(h^{-1})	(h)	(h)	(h)	(h)	(h)
GEOMETRIC MEAN	8.130	5.88	111.65	128.16	8.71	0.08	11.63	29.26	8.16	11.04	14.43
MEAN	8.953	6.32	119.69	136.31	12.34	0.09	12.39	30.86	8.64	11.28	14.87
SD (±)	4.932	2.56	46.35	48.87	9.71	0.03	4.36	11.25	3.35	2.44	3.73
CV(%)	55.090	40.52	38.72	35.86	78.68	30.29	35.14	36.46	38.79	21.62	25.09
Range(min)	4.522	4.00	48.24	51.68	1.26	0.04	6.00	24.00	5.51	8.28	9.61
Range(max)	24.208	12.00	214.45	244.77	36.42	0.13	20.00	48.00	18.00	15.63	22.39
Median	7.281	6.00	110.40	130.76	9.83	0.09	12.00	24.00	7.69	10.75	14.92

Table VII. 21 Pharmacokinetic Parameters of Reference (Marketed Formulation) in fasted state

	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-inf}	Residual Area#	K_{el}	TLIN	LQCT	$T_{1/2\ el}$	MRT_{0-t}	MRT_{0-inf}
	(ng/ml)	(h)	(ng.h/ml)	(ng.h/ml)	(%)	(h^{-1})	(h)	(h)	(h)	(h)	(h)
GEOMETRIC MEAN	5.831	4.80	73.56	86.97	9.33	0.09	9.15	26.50	7.63	10.12	13.95
MEAN	6.212	5.43	81.84	95.01	14.64	0.10	10.86	27.43	8.23	10.33	14.60
SD (±)	2.306	2.87	39.81	39.59	11.53	0.04	6.16	8.72	3.49	2.20	4.54
CV(%)	37.123	52.95	48.65	41.67	78.72	36.88	56.76	31.77	42.38	21.33	31.09
Range(min)	3.151	2.00	34.86	44.20	1.09	0.04	4.00	24.00	4.23	7.34	8.48
Range(max)	10.864	12.00	159.23	160.98	39.58	0.16	20.00	48.00	15.95	14.15	25.12
Median	5.854	4.00	70.10	90.23	14.18	0.10	9.00	24.00	7.01	9.98	14.86

Table VII. 22 Analysis of Variance Tables for Ln (C max), Ln (AUC o-t), Ln (AUCinf)

a) Ln (Cmax)

Cmax(ng/ml) Analysis-ANOVA for Ln(Cmax)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.0000	0.0000	0.00	0.9885
Subject(seq.)	12	3.0678	0.2557	3.23	0.0262
Formulation	1	0.7733	0.7733	9.77	0.0088
Period	1	0.0570	0.0570	0.72	0.4118
Residual	12	0.9498	0.0791	-	-
Intra-subject CV:28.70%			Inter-subject CV:29.71%		

b) **Ln (AUC0-t)**

AUC0-t(ng.h/ml) Analysis-ANOVA for Ln(AUC0-t)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.0026	0.0026	0.06	0.8061
Subject(seq.)	12	4.2643	0.3554	8.11	0.0005
Formulation	1	1.2190	1.2190	27.82	0.0002
Period	1	0.1871	0.1871	4.27	0.0611
Residual	12	0.5258	0.0438	-	-
Intra-subject CV:21.16%			Inter-subject CV:39.47%		

c) **Ln (AUCinf)**

AUC0-inf(ng.h/ml) Analysis-ANOVA for Ln(AUCinf)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.0266	0.0266	0.44	0.5193
Subject(seq.)	12	3.5124	0.2927	4.84	0.0053
Formulation	1	1.0523	1.0523	17.40	0.0013
Period	1	0.1863	0.1863	3.08	0.1046
Residual	12	0.7257	0.0605	-	-
Intra-subject CV:24.97%			Inter-subject CV:34.08%		

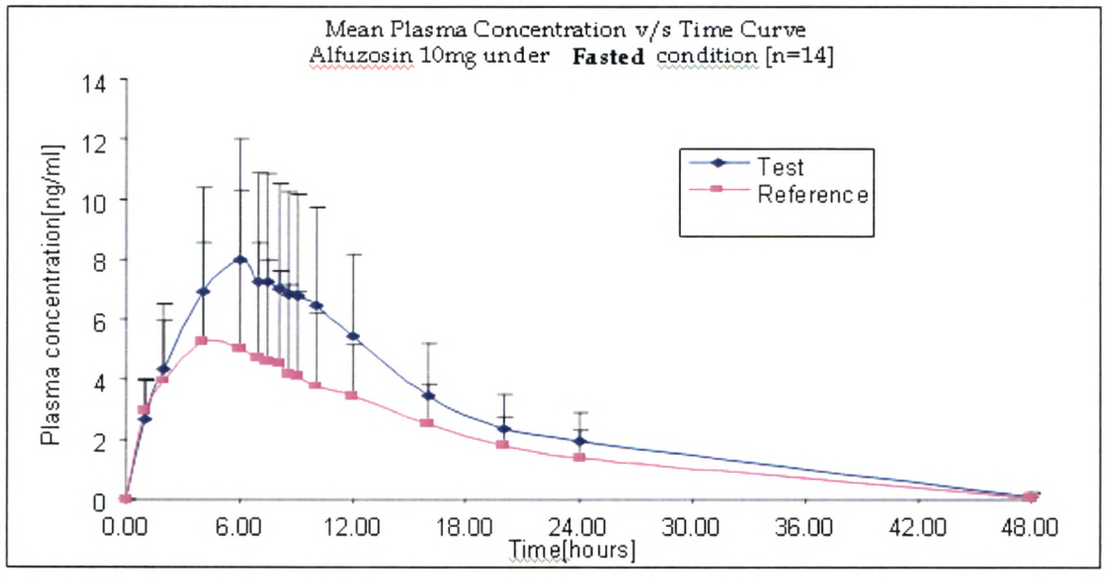


Figure VII. 13 Mean plasma concentration vs time curve of B.NO 47 (Test) vs Marketed formulation (Reference) in Fasted state

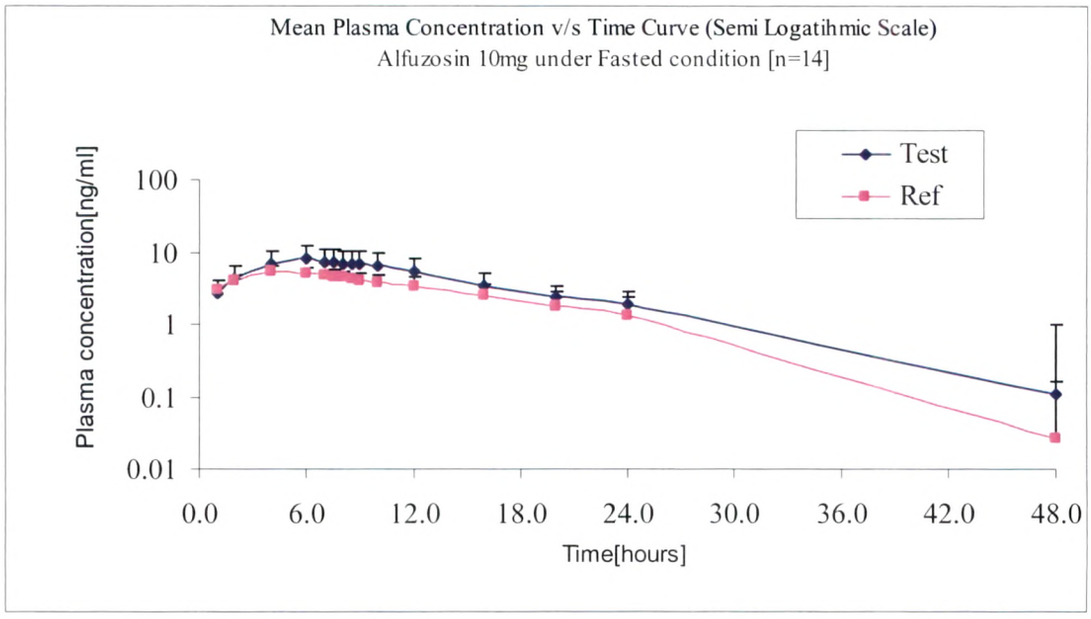


Figure VII. 14 Semi logarithmic plasma concentration vs time curve of B.NO 47 (Test) vs Marketed formulation (Reference) in Fasted state

VII.3.1.2.2.3.3 Statistical Evaluation of B. No 47 (Fed)

Table VII. 23 BE limit of B.No 47 vs Marketed Formulation in Fed state

BE Limits:(n=12) Alfuzosin 10mg Fed Study	90%CI		90%W.L.		AHpval	Power	Within Limits Y/N
	Lower	Upper	Lower	Upper			
Ln(Cmax)	126.1	236.04	Not Estimable	Not Estimable	0.9534	0.312	N
Ln(AUCt)	119.56	249.62	Not Estimable	Not Estimable	0.9272	0.2536	N
Ln(AUCinf)	120.06	250.25	Not Estimable	Not Estimable	0.9295	0.2532	N

Table VII. 24 Pharmacokinetic Parameters of B.No 16 vs Marketed Formulation in Fed State

Study Statistics:(n=12) Alfuzosin 10mg Fed Study	Test			Reference			T/R of mean
	Mean	SD	CV%	Mean	SD	CV%	
Cmax	14.544	8.78	60.37	7.365	2.44	33.11	1.97
AUCt	168.814	90.53	53.63	96.052	58.89	61.32	1.76
AUCinf	180.195	86.85	48.20	92.984	32.09	34.51	1.94

Table VII. 25 Test/Reference ratio of Pharmacokinetic parameters in individual volunteers (B. No 47 vs Marketed Formulation)

Subject	T/R			
	Cmax	AUCt	AUCinf	Tmax
1	0.83	0.93	0.96	1.50
2	1.76	1.28	1.22	1.00
3	1.45	2.63	2.90	1.17
4	3.27	1.06	-	0.29
5	1.50	1.40	1.37	1.00
6	1.84	1.29	1.25	1.75
7	2.40	1.70	1.56	0.78
8	1.50	0.96	1.00	0.67
9	1.46	4.11	3.72	10.00
10	0.62	0.74	0.80	0.50
11	1.83	3.54	3.33	1.88
12	6.08	6.73	5.32	1.75
Geometric Mean	1.73	1.73	1.75	1.18
Mean	2.05	2.20	2.13	1.86
SD	1.44	1.79	1.47	2.62

Table VII. 26 Pharmacokinetic Parameters of Test formulation (B.No 47) in fed state

	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-inf}	Residual Area#	K_{el}	TLIN	LQCT	$T_{1/2\ el}$	MRT_{0-t}	MRT_{0-inf}
	(ng/ml)	(h)	(ng.h/ml)	(ng.h/ml)	(%)	(h^{-1})	(h)	(h)	(h)	(h)	(h)
GEOMETRIC MEAN	12.076	6.36	145.59	162.19	4.89	0.11	12.04	30.24	6.46	11.54	14.07
MEAN	14.544	7.21	168.81	180.19	9.27	0.12	13.46	32.00	7.13	11.87	14.78
SD (±)	8.780	4.32	90.53	86.85	12.24	0.04	5.76	11.82	4.12	3.03	5.38
CV(%)	60.369	60.00	53.63	48.20	131.96	33.90	42.79	36.93	57.74	25.52	36.39
Range(min)	2.720	2.00	43.34	78.75	0.66	0.04	4.00	24.00	3.75	8.07	9.24
Range(max)	31.177	20.00	347.14	358.45	44.97	0.18	20.00	48.00	19.36	16.52	29.45
Median	10.846	7.00	144.32	149.34	5.20	0.12	16.00	24.00	6.00	10.64	13.94

Table VII. 27 Pharmacokinetic Parameters of Reference (Marketed Formulation) in fed state

	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-inf}	Residual Area#	K_{el}	TLIN	LQCT	$T_{1/2\ el}$	MRT_{0-t}	MRT_{0-inf}
	(ng/ml)	(h)	(ng.h/ml)	(ng.h/ml)	(%)	(h^{-1})	(h)	(h)	(h)	(h)	(h)
GEOMETRIC MEAN	7.000	5.37	84.27	87.96	8.79	0.09	10.71	27.22	7.46	10.97	13.78
MEAN	7.365	6.58	96.05	92.98	12.60	0.10	11.82	28.36	7.99	11.27	14.29
SD (±)	2.438	5.76	58.89	32.09	11.02	0.03	5.11	9.71	3.46	2.98	4.51
CV(%)	33.105	87.49	61.32	34.51	87.44	31.70	43.24	34.23	43.35	26.42	31.55
Range (min)	4.148	2.00	42.22	45.12	0.93	0.04	4.00	24.00	5.00	8.44	10.20
Range(max)	11.496	24.00	254.19	154.03	40.57	0.14	20.00	48.00	16.64	18.71	26.28
Median	6.564	5.00	78.94	98.18	10.06	0.10	10.00	24.00	6.70	10.31	13.52

Table VII. 28 Analysis of Variance for Ln (C max), Ln (AUC o-t), Ln (AUCinf)

a) Ln (Cmax)

Cmax(ng/ml) Analysis-ANOVA for Ln(Cmax)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	1.1283	1.1283	6.29	0.0310
Subject(seq.)	10	3.2468	0.3247	1.81	0.1828
Formulation	1	1.7849	1.7849	9.95	0.0103
Period	1	0.0987	0.0987	0.55	0.4766
Residual	10	1.7938	0.1794	-	-
Intra-subject CV:44.33%			Inter-subject CV:26.957%		

b) Ln (AUC0-t)

AUC0-t(ng.h/ml) Analysis-ANOVA for Ln(AUC0-t)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	1.3356	1.3356	5.40	0.0424
Subject(seq.)	10	2.7702	0.2770	1.12	0.4280
Formulation	1	1.7932	1.7932	7.25	0.0226
Period	1	0.1286	0.1286	0.52	0.4862
Residual	10	2.4734	0.2473	-	-
Intra-subject CV:52.97%			Inter-subject CV:12.18%		

c) Ln (AUCinf)

AUC0-inf(ng.h/ml) Analysis-ANOVA for Ln(AUCinf)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.4507	0.4507	2.06	0.1853
Subject(seq.)	10	1.7286	0.1729	0.79	0.6435
Formulation	1	1.7286	1.7286	7.90	0.0203
Period	1	0.0744	0.0744	0.34	0.5723
Residual	9	1.9692	0.2188	-	-
Intra-subject CV:49.46%			Inter-subject CV: not estimable		

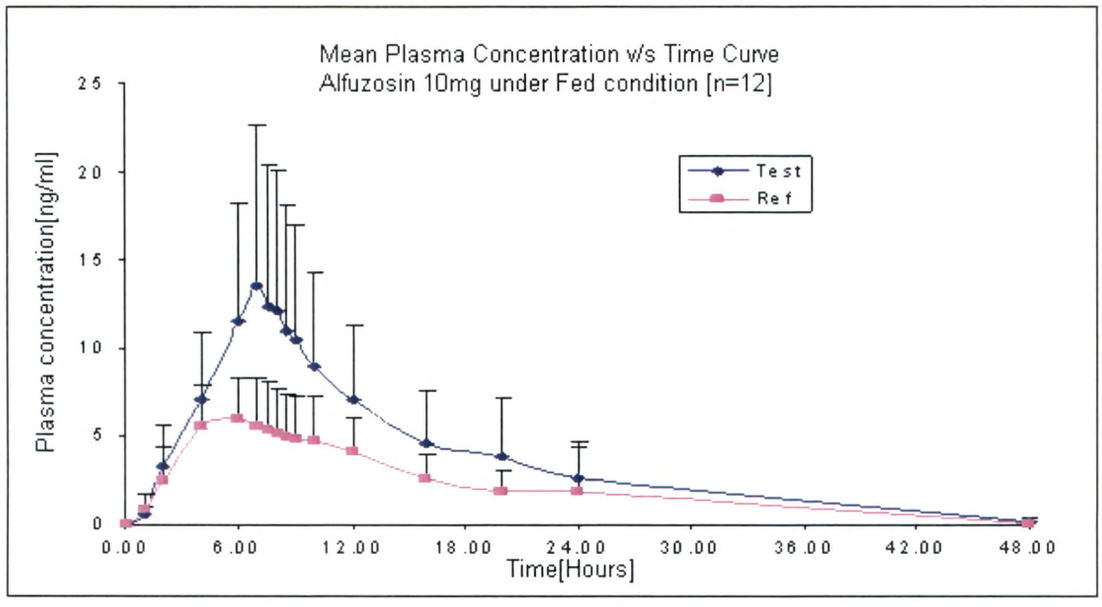


Figure VII. 15 Mean plasma concentration vs time curve of B.NO 47 (Test) vs Marketed formulation (Reference) in Fed state

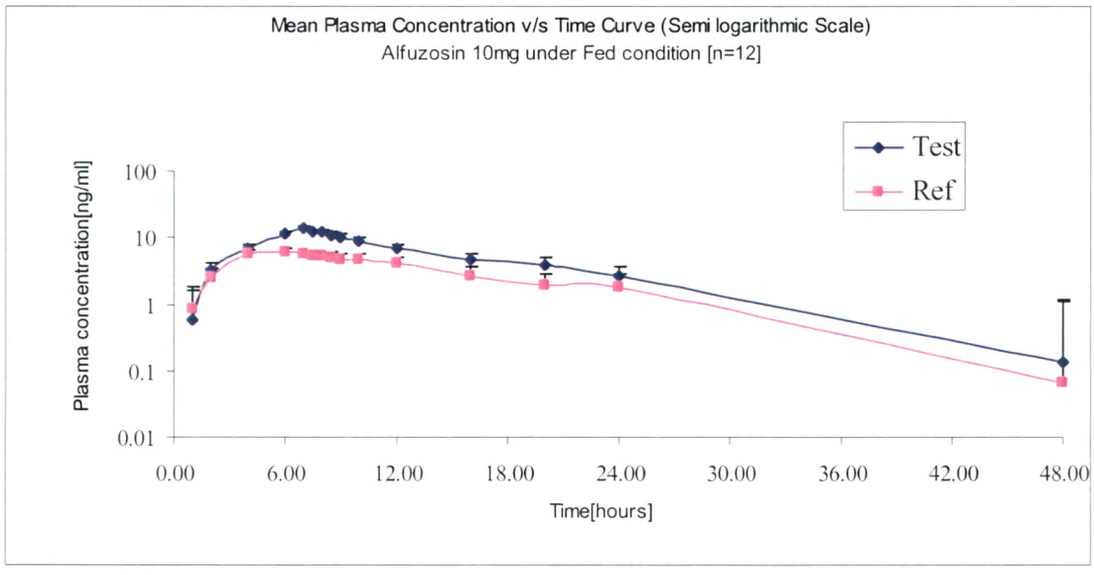
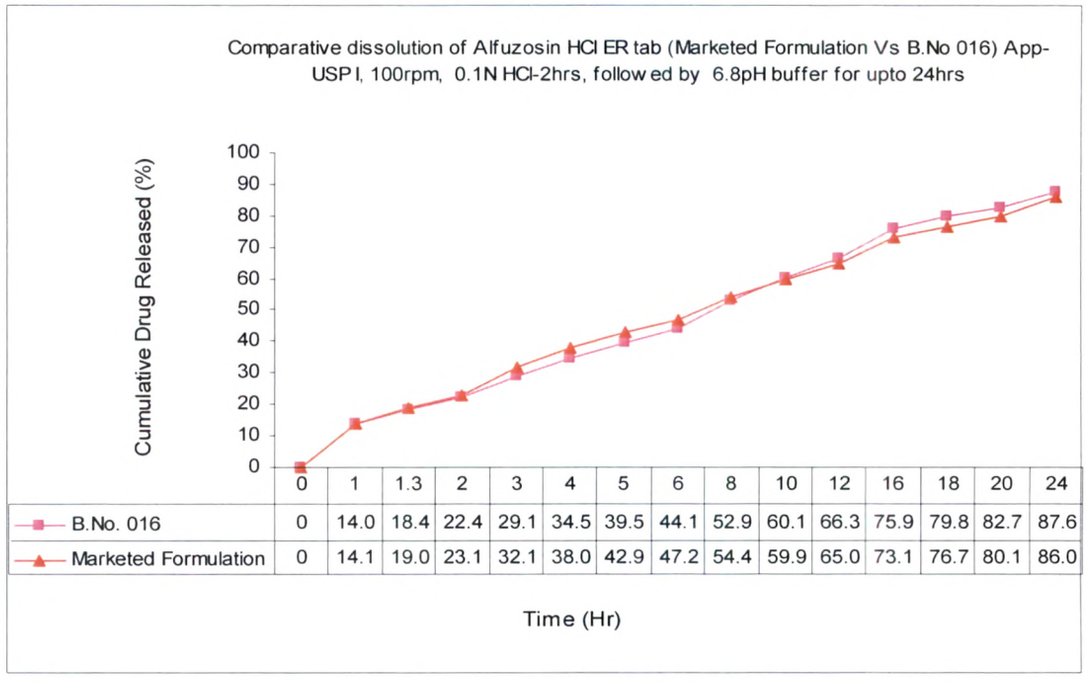


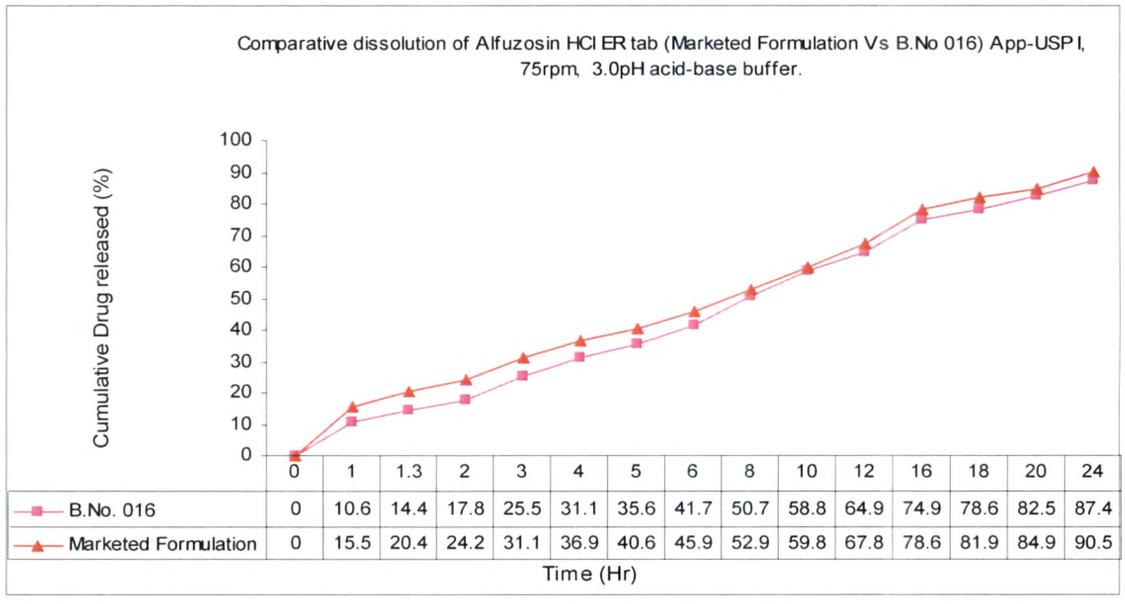
Figure VII. 16 Semi logarithmic plasma concentration vs time curve of B.NO 47 (Test) vs Marketed formulation (Reference) in Fed state

VII.3.1.2.2.4 Development of Biorelevant Discriminatory media



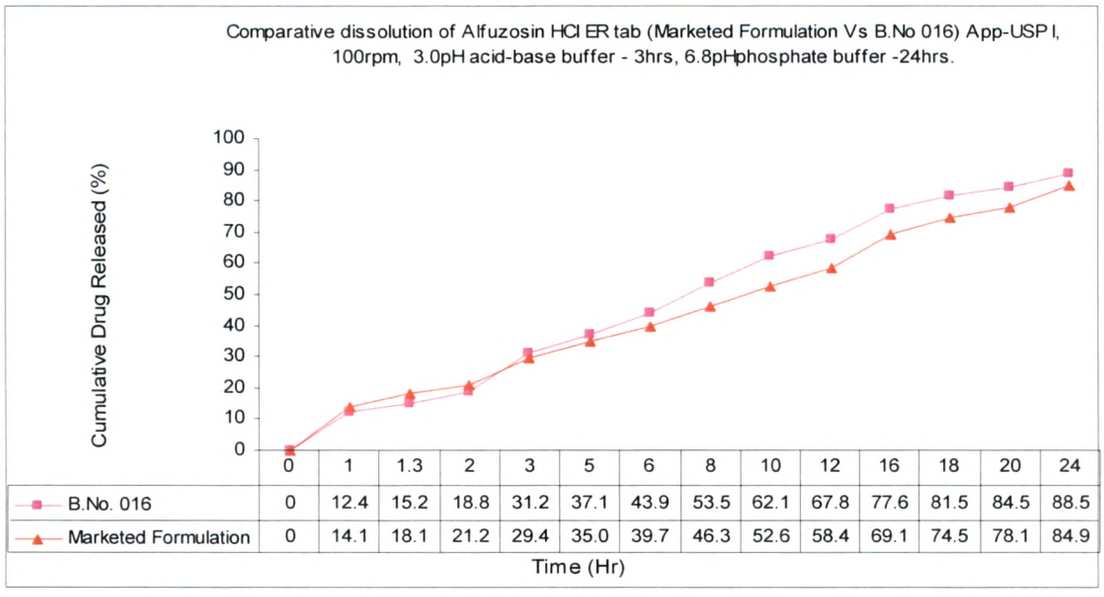
	0	1	1.3	2	3	4	5	6	8	10	12	16	18	20	24
B.No. 016	0	14.0	18.4	22.4	29.1	34.5	39.5	44.1	52.9	60.1	66.3	75.9	79.8	82.7	87.6
Marketed Formulation	0	14.1	19.0	23.1	32.1	38.0	42.9	47.2	54.4	59.9	65.0	73.1	76.7	80.1	86.0

Figure VII.12 (A)



	0	1	1.3	2	3	4	5	6	8	10	12	16	18	20	24
B.No. 016	0	10.6	14.4	17.8	25.5	31.1	35.6	41.7	50.7	58.8	64.9	74.9	78.6	82.5	87.4
Marketed Formulation	0	15.5	20.4	24.2	31.1	36.9	40.6	45.9	52.9	59.8	67.8	78.6	81.9	84.9	90.5

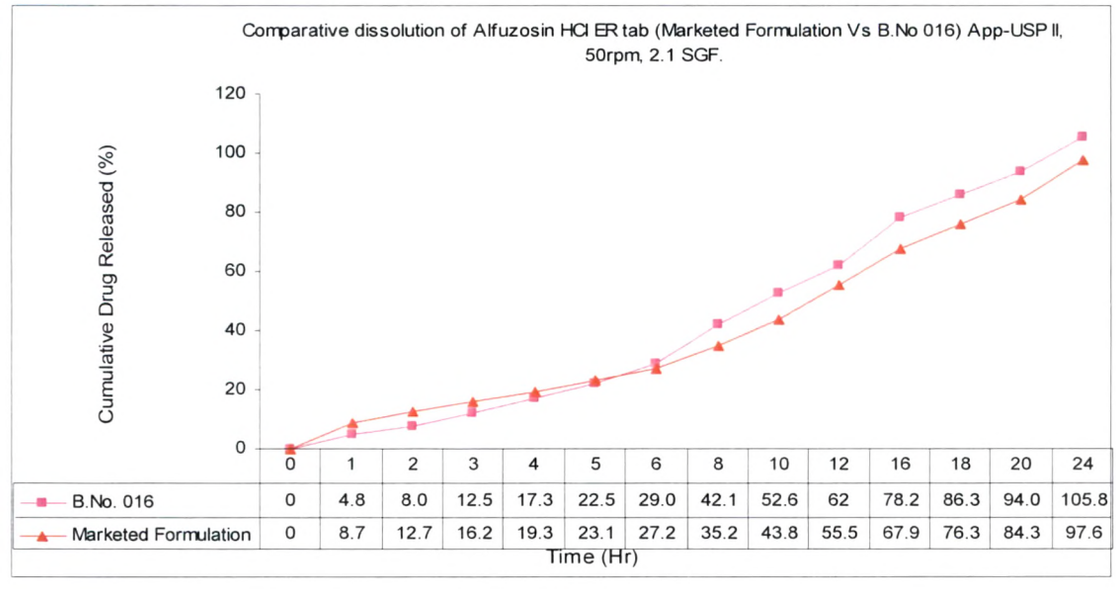
Figure VII.12 (B)



	0	1	1.3	2	3	5	6	8	10	12	16	18	20	24
B.No. 016	0	12.4	15.2	18.8	31.2	37.1	43.9	53.5	62.1	67.8	77.6	81.5	84.5	88.5
Marketed Formulation	0	14.1	18.1	21.2	29.4	35.0	39.7	46.3	52.6	58.4	69.1	74.5	78.1	84.9

Time (Hr)

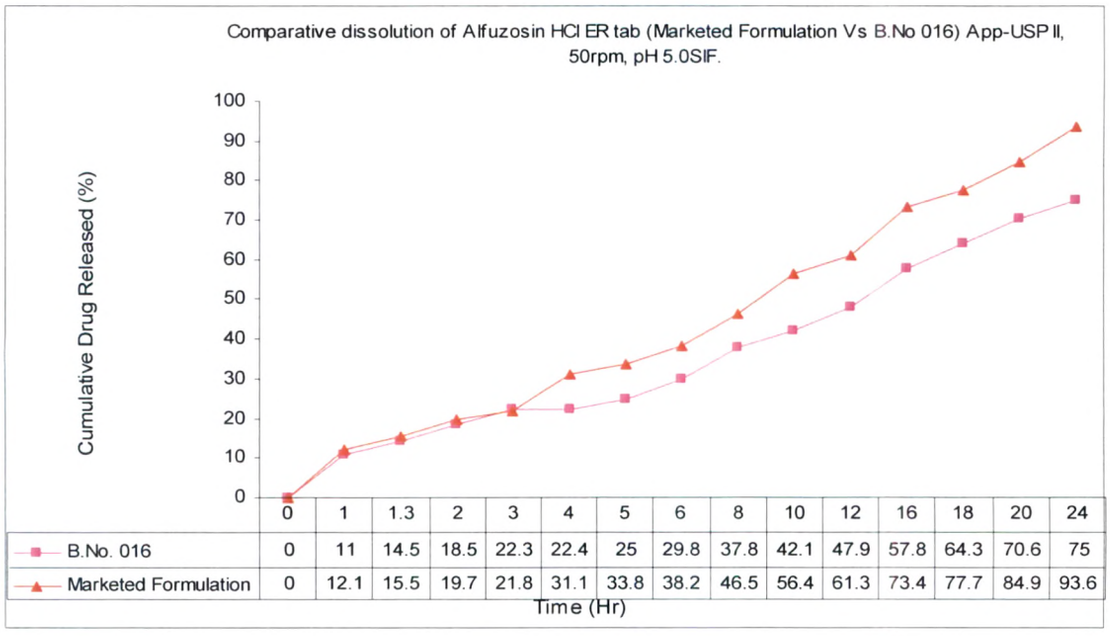
Figure VII.12 (C)



	0	1	2	3	4	5	6	8	10	12	16	18	20	24
B.No. 016	0	4.8	8.0	12.5	17.3	22.5	29.0	42.1	52.6	62	78.2	86.3	94.0	105.8
Marketed Formulation	0	8.7	12.7	16.2	19.3	23.1	27.2	35.2	43.8	55.5	67.9	76.3	84.3	97.6

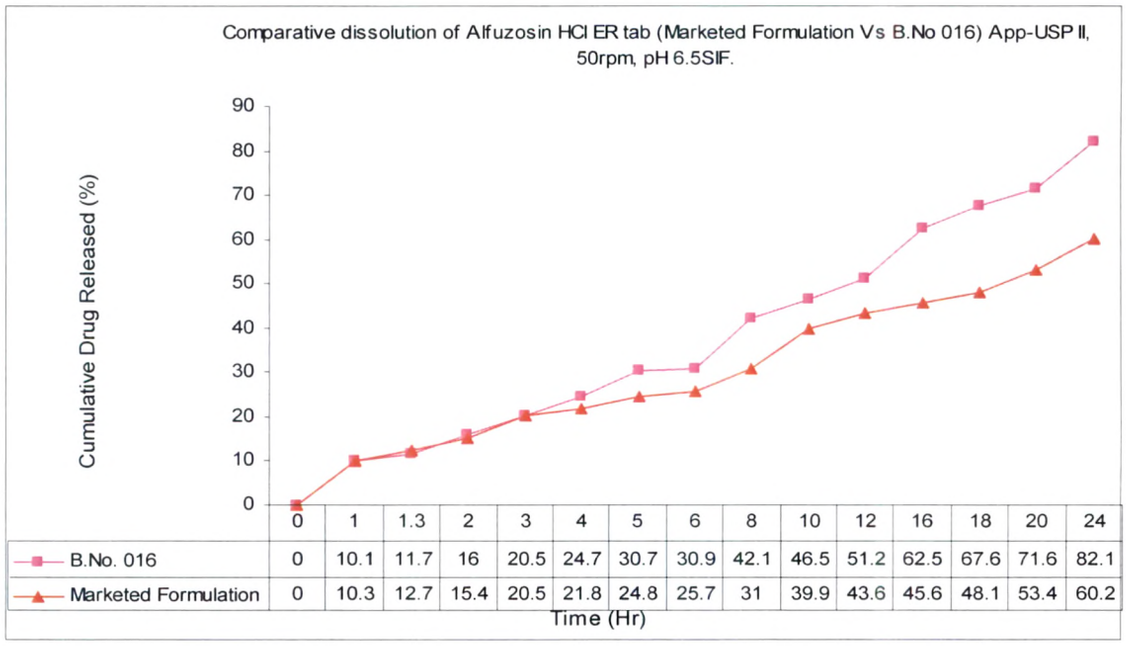
Time (Hr)

Figure VII.12 (D)



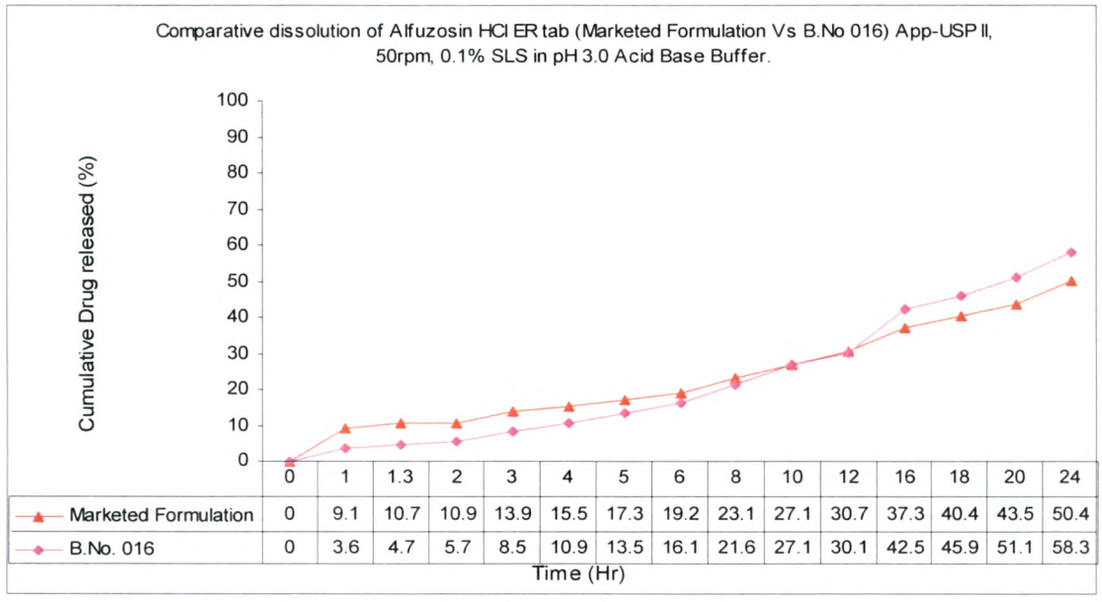
	0	1	1.3	2	3	4	5	6	8	10	12	16	18	20	24
B.No. 016	0	11	14.5	18.5	22.3	22.4	25	29.8	37.8	42.1	47.9	57.8	64.3	70.6	75
Marketed Formulation	0	12.1	15.5	19.7	21.8	31.1	33.8	38.2	46.5	56.4	61.3	73.4	77.7	84.9	93.6

Figure VII.12 (E)



	0	1	1.3	2	3	4	5	6	8	10	12	16	18	20	24
B.No. 016	0	10.1	11.7	16	20.5	24.7	30.7	30.9	42.1	46.5	51.2	62.5	67.6	71.6	82.1
Marketed Formulation	0	10.3	12.7	15.4	20.5	21.8	24.8	25.7	31	39.9	43.6	45.6	48.1	53.4	60.2

Figure VII.12 (F)



	0	1	1.3	2	3	4	5	6	8	10	12	16	18	20	24
Marketed Formulation	0	9.1	10.7	10.9	13.9	15.5	17.3	19.2	23.1	27.1	30.7	37.3	40.4	43.5	50.4
B.No. 016	0	3.6	4.7	5.7	8.5	10.9	13.5	16.1	21.6	27.1	30.1	42.5	45.9	51.1	58.3

Figure VII.12 (G)

Table VII. 29 Description of media and duration in USP Apparatus III

pH	TIME(HR)	DISSOLUTION PARAMETERS	
	0	APPARATUS	Bio-Disc (III)
2.1	1	DPM	15
3.0	2	pH	Medium
3.0	3	2.1	Simulated Gastric Fluid
3.0	4	3.0	Acid-Base Buffer
4.5	5	4.5	Acetate Buffer
5.0	6	5.0	Acetate Buffer
5.0	7	6.5	Phosphate Buffer
5.0	8	6.5	Phosphate Buffer
6.5	9	6.5	Phosphate Buffer
6.5	10	6.5	Phosphate Buffer

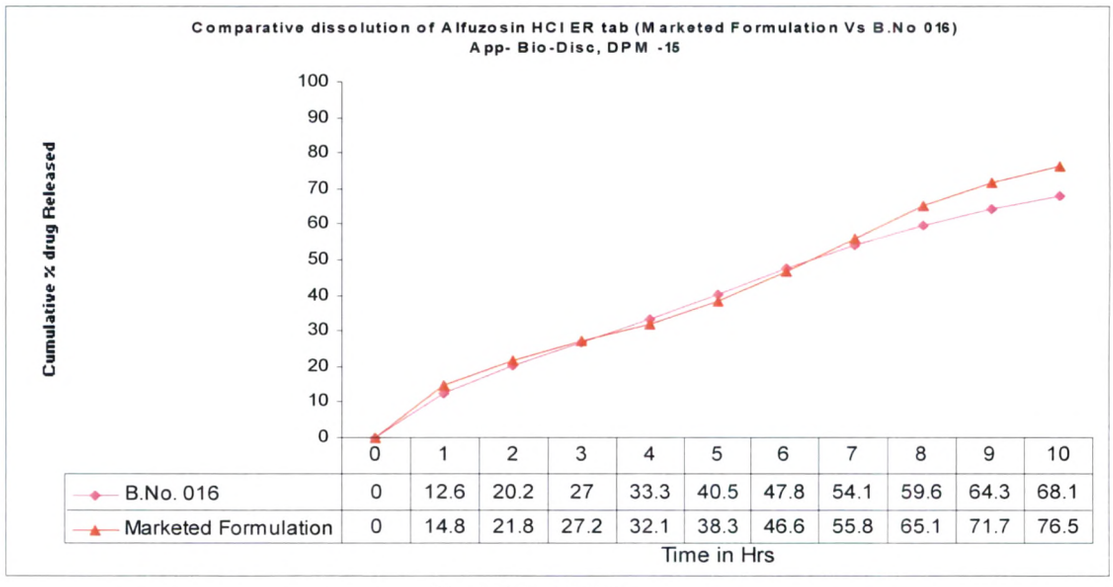
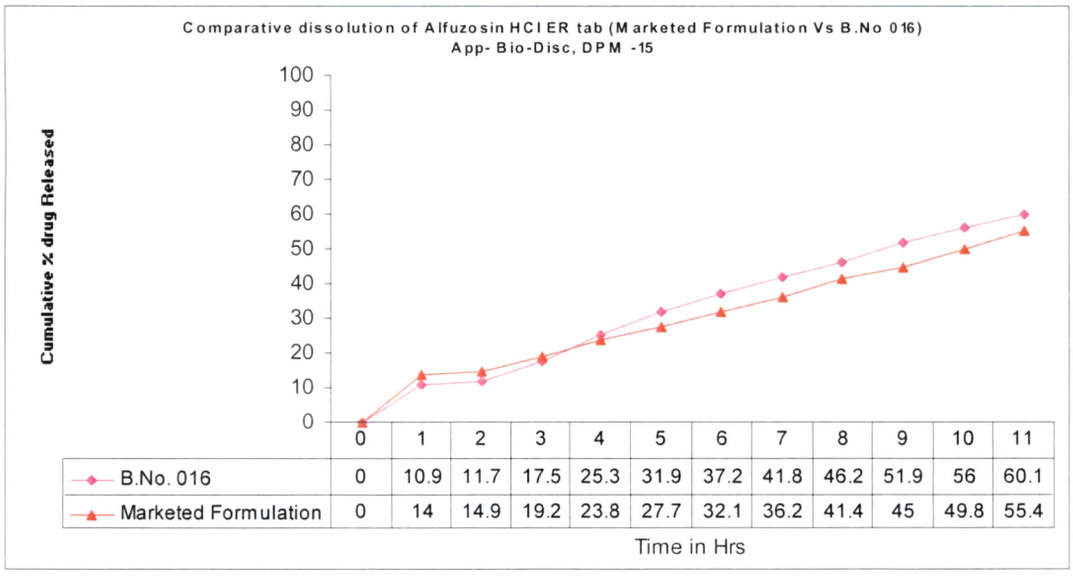


Figure VII.12 (H)

Table VII. 30 Description of media and duration in USP Apparatus III

pH	TIME(HR)	DISSOLUTION PARAMETERS	
	0	APPARATUS	Bio-Disc (III)
2.1	1	DPM	15
3.0	2	pH	Medium
3.0	3	2.1	Simulated Gastric Fluid
3.0	4	3.0	Acid-Base Buffer
5.0	5	5.0	FESSIF
5.0	6	5.0	FESSIF
5.0	7	5.0	FASSIF
5.5	8	5.0	FESSIF
6.0	9	5.0	FESSIF
6.0	10	5.0	FASSIF
6.0	11	5.0	FESSIF



	0	1	2	3	4	5	6	7	8	9	10	11
B.No. 016	0	10.9	11.7	17.5	25.3	31.9	37.2	41.8	46.2	51.9	56	60.1
Marketed Formulation	0	14	14.9	19.2	23.8	27.7	32.1	36.2	41.4	45	49.8	55.4

Figure VII.12 (I)

Table VII. 31 Description of media and duration in USP Apparatus III

pH	TIME	APPARATUS	Bio-Disc (USP Apparatus III)
1.2	1	DPM	15
2.0	2	**pH**	**Medium**
2.0	3	1.2	0.1N HCl
3.0	4	2.0	0.01N HCl
3.0	5	3.0	Acid-Base Buffer
4.5	6	4.5	Acetate Buffer
4.5	7	5.0	Acetate Buffer
5.0	8	6.0	Phosphate Buffer
5.0	9	6.0	Phosphate Buffer
6.0	10	6.0	Phosphate Buffer
6.0	11	6.0	Phosphate Buffer

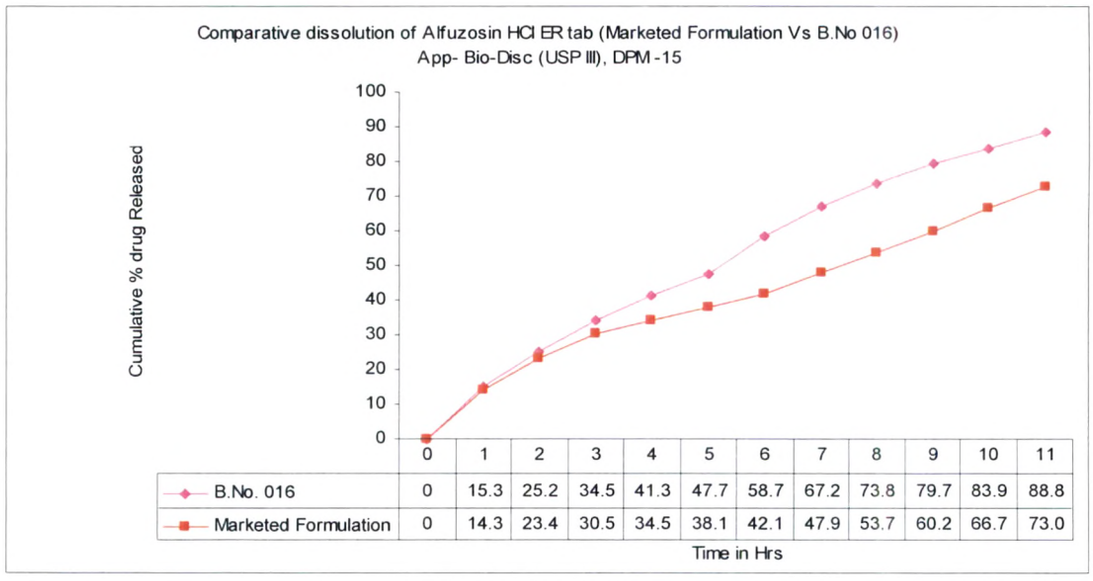


Figure VII.12 (J)

Figure VII. 17 Comparative dissolution profile of Alfuzosin HCl ER tablet (Marketed Formulation Vs B.No 016) in different media and with different rpm and apparatus

VII.3.1.3 DISCUSSION

Hydrophilic matrix systems have been proven for over four decades. Matrix controlled-release tablets are relatively simple systems that are more forgiving of variations in ingredients, production methods, and end-use conditions than coated controlled-release tablets and other systems. This results in more uniform release profiles with a high resistance to drug dumping. Matrix systems are relatively easy to formulate. The performance of many products is already well documented, providing a body of data to refer to and rely upon. This helps speed development work and can shorten approval times as well. Matrix systems are easy to produce. Tablets are manufactured with existing, conventional equipment and processing methods. This is true for almost any size tablet, whether it involves direct compression, dry granulation, or wet granulation.

Results of dissolution profile with pure high viscosity grade Polyethylene oxide showed that even after doubling the percentage of polymer, the release profile was faster than marketed formulation. 84.6% and 80.7% of the drug was released with 20% and 40% Polyethylene oxide in just 8 and 10 hrs respectively as compared to 79.4% of the marketed formulation in 16 hrs in 0.01 N HCl, whereas in formulations with combination of HPMC and PEO, release profile was much controlled. Cumulative percentage of drug released was 70.9%, 81.9% and 79.4% after 16 hours of B. No. 16, B.No 47 and marketed formulation respectively. So it was concluded that formulation alone with even high viscosity grade of PEO will not provide desirable release profile. A combination of HPMC and PEO is required for controlled release profile.

In general, dry core of polymer tablets is glassy and the drug contained in them cannot diffuse unless swelling takes place. On swelling, drug molecules dissolve in water and are released by diffusion. During swelling individual particles of the polymer swell and their macromolecular chains start disentangling, thus creating diffusional spaces that are controlled by the molecular weight and hydrophobic characteristics of the carrier polymers. Evidently the average distance between consecutive physical entanglements, tie junctions, or tie points in these physical networks is a most important molecular parameter that will control not only the integrity of the formed swollen network but also the diffusional characteristics of the drug diffusing through it and being released. This average distance is often called the "mesh size "and can be expressed either in units of molecular weight (Daltons) or in units of length (typically nm). From a thermodynamic point of view, the most important parameters that define the behavior of these swollen matrices and subsequently the release of the drug are the polymer volume fraction in the swollen state, the average molecular weight of the polymer chains between cross linked points and the associated mesh size.

Polyethylene oxide is a linear chain polymer and is among the fastest-hydrating water soluble polymers used in pharmaceutical systems. Given below (Fig.VII.18) is a comparative swelling capacity of polyethylene oxide vs Hydroxypropyl methyl cellulose (POLYOXTM water-soluble resins, 2005).

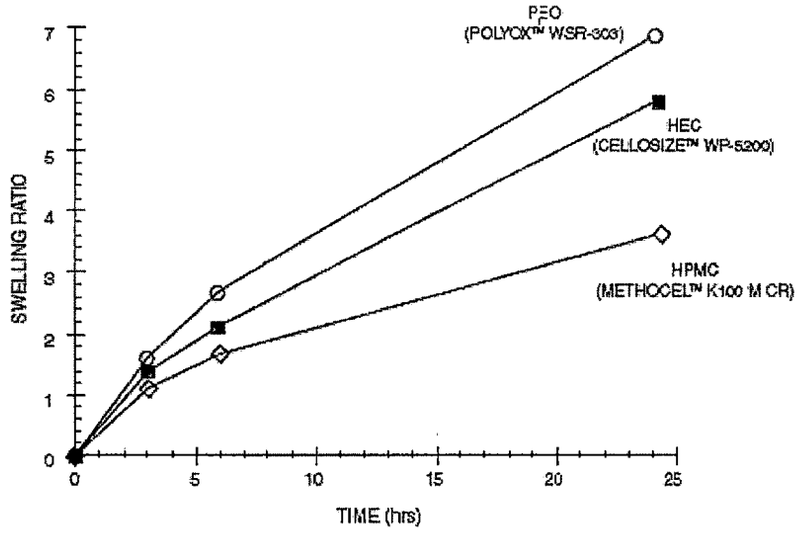


Figure VII. 18 Swelling Capacity of Non-Ionic Water Soluble Polymers

As Alfuzosin is a highly soluble drug, therefore due to faster hydration and swelling nature, these linear chain polyethylene oxide polymers might not be able to control the release profile. Similar observations have been made by other authors as given below.

Combination of hydroxypropylmethyl cellulose (HPMC) and poly (ethylene oxide) (PEO), two non ionic matrix tablets, has been shown to give a novel matrix tablet system that allows modification of the rate of drug release compared with pure HPMC. For example, the HPMC/PEO system can be used to increase the release rate at later times (Macrae and Smith, 1997). A possible mechanism by which drug release is modified is via a direct polymer: polymer interaction. Studies by Kondo et. al. have established that the primary hydroxyl group on cellulose and methylcelluloses can form a hydrogen bond to the ether oxygen in PEO (Kondo et al, 1994). This opens up the possibility of a similar interaction between PEO and the hydroxyl groups on hydroxypropyl methylcellulose.

*Maggi et al.*2000, in their study compared the performance of PEO and HPMC polymers when employed in the Geomatrix® technology, a versatile, well-known method to achieve extended release of drugs at a constant rate, and found that Diltiazem release rate from the matrices containing HPMC was slower compared to the release rate from PEO matrices. Their results of the swelling studies performed on the plain tablets made of pure polymer evidenced quite different morphological behavior of HPMCs and PEOs during hydration. In fact they found that HPMCs tablets showed a slow and continuous volume increase, up to four-fold (Methocel K4M) or six-fold (Methocel K100M) the volume of the dry tablet, after 20 hours in distilled water. On the other hand, tablets made of pure PEOs were found to swell rapidly (up to six-fold or two-fold in the case of Polyox WSR 303 or Polyox NF-60K tablets, respectively, after 8 hours), but these polymers formed a weaker gel, tend to be eroded much more quickly and the tablet volume decreased progressively.

Moreover *Maggi et al.*2000 found that the photomicrographs of the tablets made of pure HPMCs evidenced a slow hydration rate: after 20 hours a bulky glassy core could still be evidenced in both Methocel K4M and Methocel K100M tablets. Methocel K100M showed a stronger resistance to erosion compared to Methocel K4M, as evidenced by the presence of a gel layer characterized by a considerable thickness at the tablet surface. On the other hand, PEOs showed a faster hydration rate: after 15 hours in water only a small portion of the tablet made of Polyox WSR 303 was still in the glassy state, and the Polyox NF-60K tablet was completely gelled. After 20 h both polymers were fully gelled, but Polyox WSR 303 was eroded at a slower rate because it seemed to form a stronger gel compared to Polyox NF-60K. The volume of the Polyox WSR 303 tablet was about five-fold compared to that of the tablet made of PEO of lower viscosity after 20 hours in water. As expected by them, HPMC and PEO of higher viscosity grade were characterized by a slower hydration rate and by a stronger resistance to erosion compared to the corresponding polymers of lower viscosity. They concluded that PEOs appeared to be less efficient when compared to HPMCs in reducing the delivery rate of a soluble drug such as Diltiazem Hydrochloride, probably because they form a weaker gel layer than HPMCs of comparable viscosity. A softer gel can be more rapidly removed by the dissolution medium, and therefore, the matrix system is more easily susceptible to an erosion process.

In our study, results of dissolution profile with a combination of low viscosity PEO and high viscosity HPMC showed that by varying the % of PEO and HPMC, different release profiles could be achieved. So two different release profile, one nearly same as that of marketed formulation and the other a slower one was developed. This trend was noticed in all the media: 0.01 N HCL, 4.5 pH acetate buffer and 6.8 pH phosphate buffer.

In vitro gastric residence time showed that Barium Sulphate tablets remained within the matrix of B.No 47 throughout the study. This was due to highly viscous polymer HPMC K 100 MCR.

In vivo gastric retention study showed that gastric retention was for an average of 50 min in fasted state but in fed state, gastric retention was quite high, an average time of 6.5 hrs. In the fed state, out of three volunteers studied, in one of the volunteer (PK-C-636) retention time was between 2.5-3.5 hrs whereas in other two volunteers (PK-E-018 and PK-F-685), retention time was till the study period i.e. 6.5 hrs. Further study could not be carried out due to limitation of X-Ray exposures. Volunteer (PK –C-636) defecated twice during the study. As food emptied due to defecation, this might be the reason for variation observed with respect to other two volunteers studied in fed state. No discomfort was reported during and after the study in both fasted and fed condition indicating that the dosage form is safe to be administered.

In Vivo Bio results depict the following:

Table VII. 32 Bio-equivalence Limits of B.No 16 Vs B.No 47 under Fed condition

BE Parameter		BE Limit	Ln (Cmax)		Ln (AUCt)		Ln (AUCinf)	
			B.No 16	B.No 47	B.No 16	B.No 47	B.No 16	B.No 47
			No. of volunteers (11)	No. of volunteers (12)	No. of volunteers (11)	No. of volunteers (12)	No. of volunteers (11)	No. of volunteers (12)
90 % CI	Lower	80	168.1	126.1	108.2	119.56	108.13	120.06
	Upper	125	273.5	236.04	171.87	249.62	165.34	250.25
	AHpval	1.00	0.9986	0.9534	0.745	0.9272	0.7116	0.9295
	Power	1.00	0.4444	0.312	0.4775	0.2536	0.5384	0.2532

Above results showed that both the formulations B. No 16 and B. No 47 showed higher bioavailability (Area under curve) and peak plasma concentration (Cmax) as compared to marketed reference formulation in the fed state. B. No 47 depicted higher bioavailability and lower Cmax as compared to B. No 16.

Comparative results between fasted and fed state of B.No 47 depict the following:

Table VII. 33 Bio-equivalence Limits of B.No 47 (Fasted vs Fed State)

BE Parameter		BE Limit	Ln(Cmax)		Ln(AUCt)		Ln(AUCinf)	
			Fasted	Fed	Fasted	Fed	Fasted	Fed
90% CI	Lower	80	115.35	126.1	131.81	119.56	124.86	120.06
	Upper	125	168.53	236.04	174.77	249.62	173.93	250.25
	AHpval	1.00	0.8376	0.9534	0.9848	0.9272	0.949	0.9295
	Power	1.00	0.6223	0.312	0.8404	0.2536	0.7266	0.2532

From the results shown in Table VII.33, it was evident that fed state had higher bioavailability (41.04%) than fasted state .Literature also supports the data that with food enhances the bioavailability by 50% in comparison to fasted state (UroXatral® alfuzosin package insert, 2003).

Table VII. 34 Comparative Cmax, AUC and AUC inf values of B.No 16 and B.No 47 under Fasted and Fed condition

		Test	Ref	% increase
B. No 16 Fed	Cmax	23.624	11.090	113.021
	AUC	237.086	187.836	26.220
	AUC inf	242.369	193.694	25.130
B. No 47 Fed	Cmax	14.544	7.365	97.475
	AUC	168.814	96.052	75.753
	AUCinf	180.195	92.984	93.791
B. No 47 Fasted	Cmax	8.953	6.212	44.124
	AUC	119.690	81.839	46.251
	AUCinf	136.305	95.011	43.462

B. No 47 with slower release profile than marketed showed higher bioavailability than B. No 16 whose dissolution profile was comparable to that of marketed formulation. This is further confirmed from the greater mean residence time (MRT) as shown in table below.

Table VII. 35 Comparative Mean Residence Time (MRT) of B.No 16 and 47

	B.No 16	B.No 47	
	Fed	Fed	Fasted
Mean	11.39	11.87	11.28

As discussed in Chapter II, food can enhance absorption by various mechanisms. Here we have tried to propose a hypothesis responsible for an increase in absorption of Alfuzosin from extended release formulation after food intake.

1) Increased solubility due to:

a) Increased *GI Transit Time which can be due to* Inhibitory effects caused by Nervous reflexes or Harmonal feedback

Solubility enhancement due to increased residence time can be ruled out as earlier in pre-formulation study we had estimated solubility of Alfuzosin Hydrochloride at different pH and water and found it to be highly soluble at all pH (Chapter IV). Enhancement in absorption due to increased residence time of the dosage form from which drug slowly diffuses out does apply to this model drug (Alfuzosin Hydrochloride). As per the literature, food effect is insignificant in immediate release dosage form whereas in modified release dosage form the effect was found to be significant and our data with B.No 16 and B.No 47 also support this (UroXatral® alfuzosin package insert, 2003, Xatral® alfuzosin package insert, 2003). In immediate release dosage form, drug is immediately released in the biological fluid and as the drug is in the solubilized form, it passes along with the biological fluid through the open pylorus which remains slightly open even in the fed state (Tonzi et al, 2002). Therefore the completely solubilized drug gets absorbed through its absorption site irrespective of whether given in the fed or fasted state. Marketed preparation with it gemotrix technology, releases the drug slowly over a period of time. In fasted state, the marketed extended release formulation does not retain in the stomach for extended periods of time as compared to fed state and as the drug is slowly released from the matrix, only part of the drug that is released gets absorbed and rest of it passes out as such. In the fed state, due to slow release and greater retention time, the drug gets more absorbed than in the fasted state. Marketed extended release formulation is only 30% released in the stomach and rest of 40% and 30% is released in the small intestine and colon respectively. As Alfuzosin is preferentially absorbed from the ileum and route of absorption is paracellular, so more time is required by the drug for absorption. This might be the cause for lower drug bioavailability of marketed extended release formulation than immediate release formulation. In our case, B.No 16 and B.No 47 showed higher bioavailability in both fasted and fed state as compared to marketed

extended release formulation. This might be due to greater residence time of our formulations in the stomach than that of marketed formulation.

b) Bile induced solubilization
Food induced bile stimulation can lead to increased solubilization and thus increased absorption (refer Chapter II).

But Abdenour Haddouche et al., 1996 found that sodium taurocholate, the major bile salt in rat and man (Poelma et at., 1990a), had no effect at low concentration (0.1 mM) on tissular conductance and Alfuzosin passage in the ileum.

c) Increased Secretions
Food induced secretions do enhance the solubility of drugs which are solubility limited (refer Chapter II) but Alfuzosin Hydrochloride is not solubility limited instead it is permeability limited as discussed in preformulation study (Chapter II).

d) pH
As a general concept, weak acids solubility is increased at basic pH and vice versa .Alfuzosin Hydrochloride solubility is pH independent as confirmed in preformulation study (Chapter II).

2) Decreased first pass Metabolism
Food enhances the splanchic blood flow and may result in decreased first pass metabolism (refer Chapter II)

As per Abdenour Haddouche et al., 1996, Alfuzosin Hydrochloride does not undergo metabolism in gut. If increased splanchic blood flow would have been responsible for more bioavailability of Alfuzosin Hydrochloride, then in immediate release dosage form of marketed formulation also, bioavailability should have increased whereas this was not the case.

3) Physiological responses
Physiological responses to the sight and smell of food can enhance the bioavailability of drug (refer Chapter II).

If physiologic response should have been the case then it should have an impact on immediate release dosage form as well but this was not the case. It has been reported in literature that food does not have effect on immediate release dosage form (Xatral® alfuzosin package insert, 2003).

4) Formulation Factors
The release of drug from some formulations may also be affected by the concomitant intake of food.

Formulation factors do play the role. A slower release profile (B.No. 47) from high concentration of polymer resulted in greater retention and greater bioavailability than marketed preparation as well as B.No. 16.

5) Meal Effects on Drug Diffusivity

If meal induced slow diffusion would have been the case then it should have an impact on immediate release dosage form of marketed formulation as well but this was not the case.

6) Mixing Contractions (Segmentation Contractions)

Chyme is propelled through the small intestine by peristaltic waves. Contraction rate in the ileum is slower than in duodenum (refer Chapter II). Therefore, absorption time might be increased and also length of ileum is more than duodenum or jejunum giving more time for Alfuzosin absorption.

Thus increased residence time in stomach to achieve higher absorption in ileum is must to enhance the bioavailability of Alfuzosin Hydrochloride.

Various methodologies were applied for development a Biorelevant Discriminatory media in order to establish IVIVC. Even by using different medias, different rpm and different apparatus, not much discrimination in between the formulations i.e. B.No 16 and Marketed formulation in in- vitro conditions was obtained as compared to in vivo results. This might be due to neutral polymers, Hypromellose and PEO and pH independent highly soluble drug, Alfuzosin HCl which might be insensitive to the media and conditions applied by us to discriminate the two formulations.

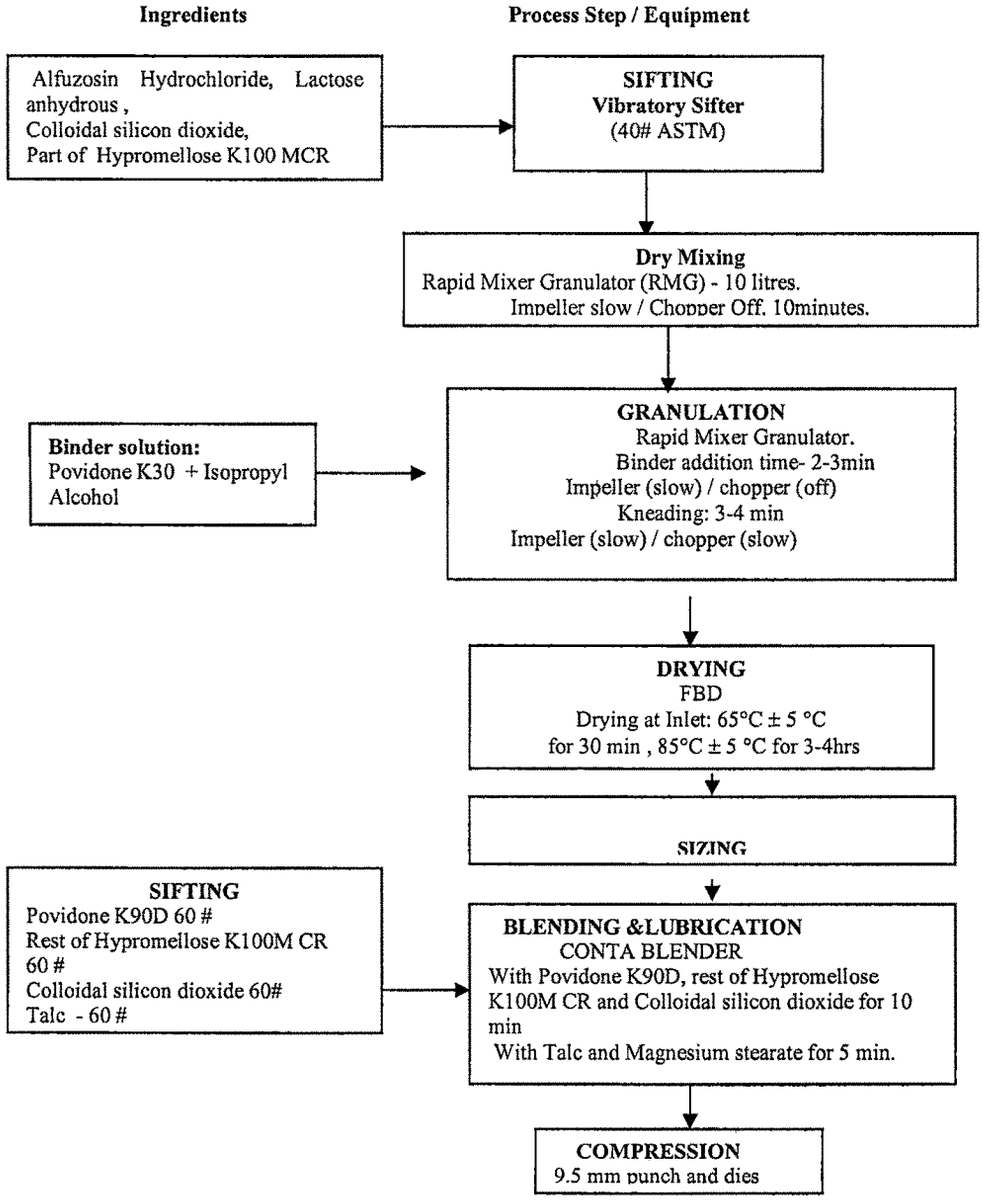
VII.3.2 With PVP and HPMC combination

VII.3.2.1 METHODS

Batches of Alfuzosin tablets were taken with Povidone K 90 in place of Polyethylene oxide and dissolution study was carried out. Povidone K 90 being a cross linked chain polymer as compared to Polyethylene oxide which is a linear chain polymer.
Non aqueous granulation with Isopropyl alcohol as solvent was used and as polyvinyl pyrrolidone is soluble in Isopropyl alcohol, it was used as binder. Brief description of the process is as follows:

Step1. Alfuzosin Hydrochloride, Lactose anhydrous, Colloidal silicon dioxide and part of Hydroxypropyl methyl cellulose K100MCR were mixed together in high shear mixer (Rapid mixer granulator) after sifting through 40# sieve.
Step2. Binder solution was prepared by dispersing and dissolving PVP K30 in Isopropyl alcohol (IPA) while stirring.
Step3. Binder was slowly added to the dry mix of step 1 with impeller at slow speed and chopper off and then kneaded with impeller and chopper at slow speed.
Step4. The material of step 3 was dried in fluidized bed dryer and then sized through oscillatory granulator fitted with 0.8 mm sieve.
Step5. Povidone K90, rest of Hydroxypropyl methyl cellulose K100MCR and Colloidal silicon dioxide were sifted through 60# sieve and mixed with sized material of step 4 in conta blender for 10 min.
Step6. Talc and Magnesium stearate were sifted through 60# and blended with material of step 5 in conta blender.
Step7. Lubricated blend was compressed in 16 station compression machine fitted with 9.5 mm round punches and suitable dies.

Process Flow Diagram



VII.3.2.1.1 Evaluation of Compressed formulations

Physico -chemical characterization of compressed tablets was carried out. Tablets were evaluated for Average weight, Thickness, Diameter, Hardness, Friability, Assay, Content uniformity, Related impurities, water by KF and Dissolution profile.

VII.3.2.1.2 Bio Study

In order to study the effect of different release profiles in vivo, Bio study was performed with formulation of B.No 147 and B.No. 158. Protocol for bio study was followed same as that mentioned in size exclusion technology (non swelling) (Chapter V). Bio study of B. no.147 and B.No. 158 were carried out in comparison with Marketed Formulation in both Fed and Fasted conditions.

VII.3.2.1.3 IVIVC

Over four decades ago Levy et al, 1965 reported a significant correlation between in vitro dissolution and in vivo bioavailability of aspirin tablets. A separate study by Wood, 1996 suggested that the drug absorption was very much dependent on dissolution rate. In 1973, Wagner et al demonstrated relationships between in vitro and in vivo pattern of various digoxin dosage forms (Wagner et al, 1973) which was confirmed by other reports (Lindenbaum et al, 1973; Johnson at al, 1973).

Since then many attempts have been carried out to study the in vitro in vivo correlation for various drugs and dosage forms. The studies have been conducted both in animal, such as rat, rabbit, dog and human. In these studies the possibility of developing different levels of correlation between in vitro dissolution parameters and in vivo pharmacokinetic parameters had been investigated.

In order to establish an IVIVC for Alfuzosin Hydrochloride, in vivo data of B.No 147 and B.No 158 were put to statistical evaluation.

VII.3.2.1.4 Process Optimization

A process scale up was taken for formulation with dissolution profile most near to marketed formulation i.e. B. No 147.

VII.3.2.1.5 Stability study

Stability study of B.No 147 was carried out at accelerated conditions according to ICH (International conference on Harmonization) guidelines in different packings.

VII.3.2.2 RESULTS

Table VII. 36 Formulation composition with 50% (B.No 158) vs 60% (B.No 159) vs 69% (B.No. 147) of HPMC K100MCR keeping 11% PVP K90 constant

Batch No	147	159	158
HPMC concentration	**69%**	**60%**	**50%**
Ingredients	**mg / Tab.**		
Intra Granular			
Alfuzosin Hydrochloride	10.00	10.00	10.00
Lactose Anhydrous	36.50	68.00	103.00
Hypromellose	139.00	139.00	139.00
Povidone K30	12.00	12.00	12.00
Colloidal silicon dioxide	1.00	1.00	1.00
Extra Granular			
Povidone K90D	38.50	38.50	38.50
Hypromellose K100 M CR	102.50	71.00	36.00
Talc	2.0	2.0	2.0
Colloidal silicon dioxide	3.50	3.50	3.50
Magnesium stearate	5.00	5.00	5.00
Total Weight	**350.00**	**350.00**	**350.00**

VII.3.2.2.1 Evaluation of Compressed formulations

Table VII. 37 Comparative physico-chemical parameters of B.No 147 and B.No. 158

S.No.		B.No 147	B.No 158
Physical Parameter			
1	Diameter (mm)	9.5 ± 0.05	9.5 ± 0.05
2	Thickness (mm)	4.40 (4.35-4.47)	4.25 (4.20-4.28
3	Hardness (N)	178 (157-193)	190 (175-208)
4	Average weight (mg)	351(349.9-350.9)	347.4(345.6-352.1)
5	Friability (%)	0.04	0.02
Chemical Parameter			
6	Content Uniformity	99.6 ± 1.03	98.5 ± 1.33
7	Related Impurities (%) Single unknown Total Impurities	 0.004 0.013	 0.02 0.04
8	Assay (%)	101.4	98.9
9	Water By KF (% w/w)	5.52	4.44

Table VII. 38 Dissolution profile of Formulations B.No 147 vs B.No 158 vs B.No 159 compared with the marketed formulation

Time in hrs	Cumulative % Drug release in 500 ml of 0.01N HCl at 100 rpm with paddle			
	B.No 158	**B.No 159**	**B.No 147**	**Market Formulation**
	50% HPMC	**60% HPMC**	**69% HPMC**	**NA**
1	14.6	12.5	11.80	16.3
3	29.1	25.7	23.50	28.6
6	44.3	39.9	37.20	41.4
12	68.2	62.4	58.50	66.3
20	86.7	82.1	78.30	89.6
24	91.5	89.3	86.10	94.8
30	96.4	95.3	94.20	97.2

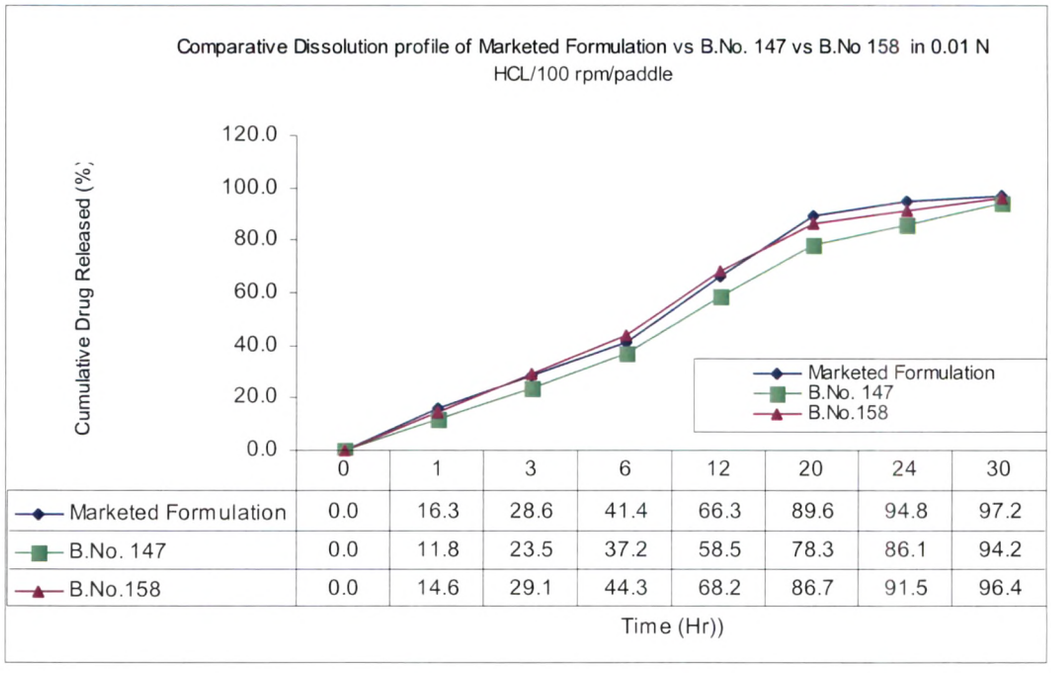
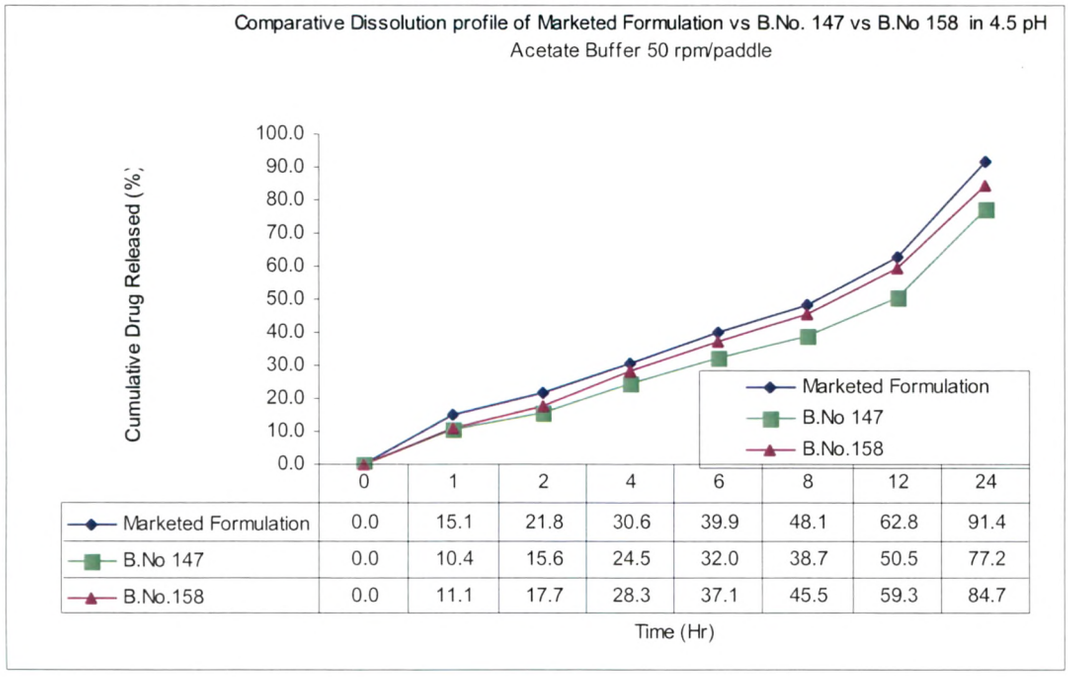
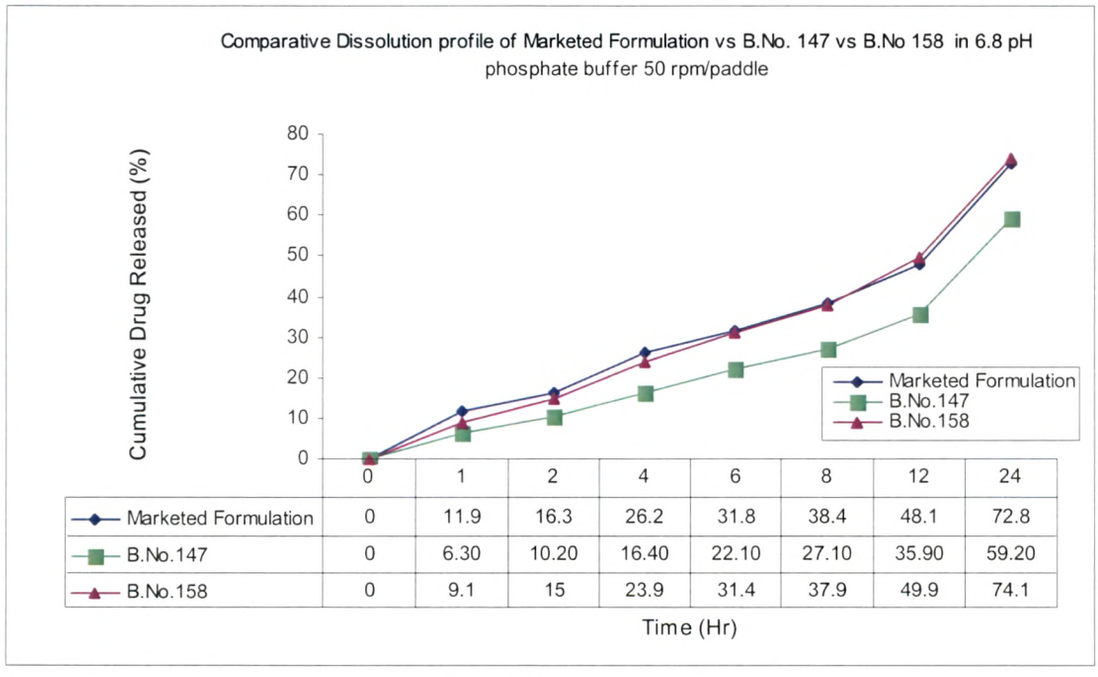


Figure VII.13 *(A)*



	0	1	2	4	6	8	12	24
Marketed Formulation	0.0	15.1	21.8	30.6	39.9	48.1	62.8	91.4
B.No 147	0.0	10.4	15.6	24.5	32.0	38.7	50.5	77.2
B.No.158	0.0	11.1	17.7	28.3	37.1	45.5	59.3	84.7

Figure VII.13 *(B)*



	0	1	2	4	6	8	12	24
Marketed Formulation	0	11.9	16.3	26.2	31.8	38.4	48.1	72.8
B.No.147	0	6.30	10.20	16.40	22.10	27.10	35.90	59.20
B.No.158	0	9.1	15	23.9	31.4	37.9	49.9	74.1

Figure VII.13 (C)

Figure VII. 19 Comparative Dissolution profile of B.No 147 and B.No 158 with Marketed Formulation in different media (0.01 N HCl, 4.5 pH acetate buffer, 6.8 pH phosphate buffer)

VII.3.2.2.2 Bio Study

VII.3.2.2.2.1 Statistical Evaluation of B.No 147 (Fasted State)

Table VII. 39 Pharmacokinetic Parameters of B.No 147 vs Marketed Formulation in Fasted State

Study Statistics: PK Parameters [N=17]	Test		Reference		T/R of Mean
	Mean	S.D.	Mean	S.D.	
Cmax	7.073	3.70	7.203	3.10	0.9820
AUC(0-t)	105.992	85.43	127.154	83.73	0.8336
AUC(0-Inf)	119.346	88.73	150.141	78.67	0.7949

Table VII. 40 BE limit of B.No 147 vs Marketed Formulation in Fasted state

BE Limit: PK Parameters [N=17]	90% CI		AHpval	Power	Within limits Y/N
	Lower	Upper			
Ln(Cmax)	81.2900	111.4800	0.0320	0.7604	Y
Ln(AUC(0-t))	64.7900	97.3400	0.5239	0.5672	N
Ln(AUC(0-Inf))	64.5200	85.3200	0.8202	0.8442	N

Table VII. 41 Test/Reference ratio of Pharmacokinetic parameters in individual volunteers (B. No 147 vs Marketed Formulation)

T/R Ratio (Alfuzosin ER 10mg; Fasted-State Study)			
Volunteer no.	Cmax	AUCt	AUCinf
1	0.85	0.45	0.48
2	2.47	1.68	1.46
3	1.76	0.90	0.55
4	0.69	0.32	0.46
5	0.80	0.98	1.20
6	1.18	1.05	1.09
7	0.69	0.70	0.61
8	0.94	0.48	0.60
9	0.94	0.92	0.87
10	0.56	0.60	0.61
11	1.03	1.06	1.07
12	1.10	0.80	0.80
13	0.78	0.57	0.38
14	0.93	1.26	1.13
15	1.41	2.38	1.15
16	0.72	0.67	0.58
17	0.70	0.60	0.70
N	17	17	17
(Normal Mean)	1.03	0.91	0.81
Geometric Mean	0.96	0.80	0.75
SD	0.48	0.51	0.32
CV%	46.02	55.92	39.25
MEDIAN	0.93	0.80	0.70
MIN	0.56	0.32	0.38
MAX	2.47	2.38	1.46

Table VII. 42 Pharmacokinetic Parameters of Test formulation (B.No 147) in Fasted State

	Tmax (hr)	Cmax (ng/mL)	AUCINF_obs (hr*ng/mL)	AUC_% Extrap_obs (%)	Lambda_z (1/hr)	Lambda_z_lower (hr)	Lambda_z_upper (hr)	HL_Lambda_z (hr)	MRTlast (hr)	MRTINF_obs (hr)
N	17	17	17	17	17	17	17	17	17	17
Mean	5.471	7.0732	119.5424	13.5543	0.0867	11.0000	29.7371	8.9319	11.3262	15.3905
SD	2.9393	3.69871	89.00842	8.86398	0.02888	5.53399	10.66118	3.16488	3.26632	4.00830
Min	2.000	2.9770	46.4069	1.6137	0.0430	5.0000	24.0000	4.7459	8.3583	9.5708
Median	5.000	6.2780	109.9764	10.0009	0.0915	10.0000	24.0000	7.5783	10.1691	15.6595
Max	12.000	18.3550	443.3196	31.8378	0.1461	20.0000	48.5600	16.1025	17.9853	21.4400
CV%	53.7	52.3	74.5	65.4	33.3	50.3	35.9	35.4	28.8	26.0
Geometric Mean	4.839	6.3887	103.1003	10.4833	0.0821	9.7292	28.3043	8.4417	10.9482	14.8810

Table VII. 43 Pharmacokinetic Parameters of Reference (Marketed Formulation) in Fasted State

	Tmax (hr)	Cmax (ng/mL)	AUClast (hr*ng/mL)	AUCINF_obs (hr*ng/mL)	AUC_%Extrap_obs (%)	Lambda_z (1/hr)	Lambda_z_lower (hr)	Lambda_z_upper (hr)	HL_Lambda_z (hr)	MRTlast (hr)	MRTINF_obs (hr)
N	17	17	17	17	17	17	17	17	17	17	17
Mean	4.706	7.2031	127.6003	150.6209	17.5417	0.0838	15.0588	32.6600	9.8360	12.6733	18.6417
SD	1.9610	3.09864	84.48895	79.44349	16.70196	0.02972	4.99338	12.08806	5.27197	2.80926	6.83913
Min	2.000	3.0330	50.8475	64.5823	1.5756	0.0269	5.0000	24.0000	5.0744	8.5640	10.1866
Median	5.000	6.1670	94.0650	126.8072	11.6598	0.0893	16.0000	24.0000	7.7634	11.5152	16.3497
Max	11.000	15.6000	394.8882	408.1059	55.3042	0.1366	20.0000	48.9000	25.7286	17.9557	38.8918
CV%	41.7	43.0	66.2	52.7	95.2	35.4	33.2	37.0	53.6	22.2	36.7
Geometric Mean	4.376	6.6689	110.6229	137.2861	9.9094	0.0778	14.0218	30.7722	8.9091	12.3934	17.7102

Table VII. 44 Analysis of Variance Tables for Ln (Cmax), Ln (AUC o-t), Ln (AUC o-∞)

a) Ln (Cmax)

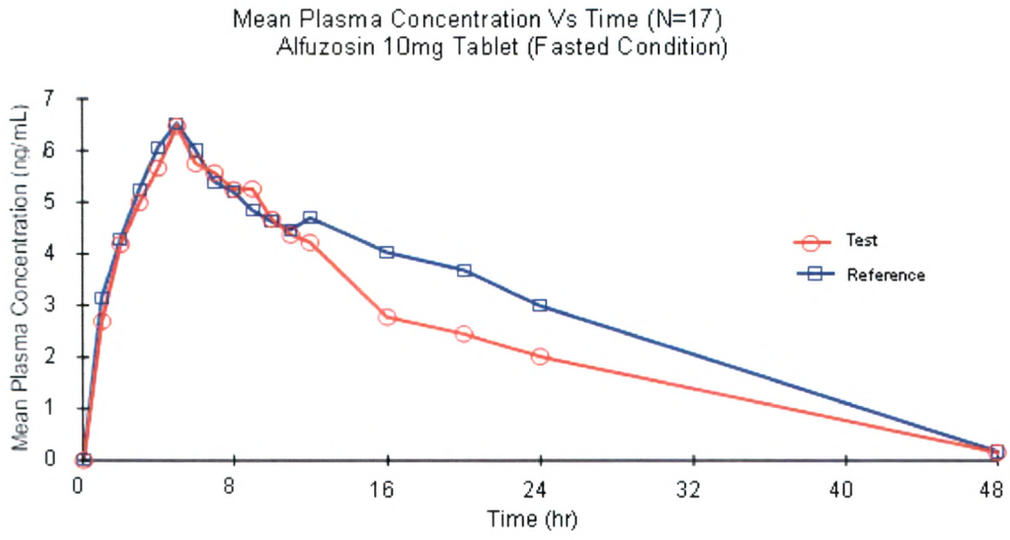
Source	df	SS	MSS	F value	p value
Sequence	1	0.015	0.015	0.05	0.8279
Sequence*Subject	15	4.5975	0.3065	4.46	0.0031
Formulation	1	0.0205	0.0205	0.3	0.5925
Period	1	0.0979	0.0979	1.43	0.251
Error	15	1.0304	0.0687		
Intra Subject CV	0.2666				
Inter Subject CV	0.3553				

b) Ln (AUC0-t)

Source	df	SS	MSS	F value	p value
Sequence	1	0.0934	0.0934	0.19	0.6671
Sequence*Subject	15	7.2747	0.485	4.22	0.0042
Formulation	1	0.4544	0.4544	3.95	0.0654
Period	1	0.2628	0.2628	2.28	0.1514
Error	15	1.7253	0.115		
Intra Subject CV	0.4507				
Inter Subject CV	0.3491				

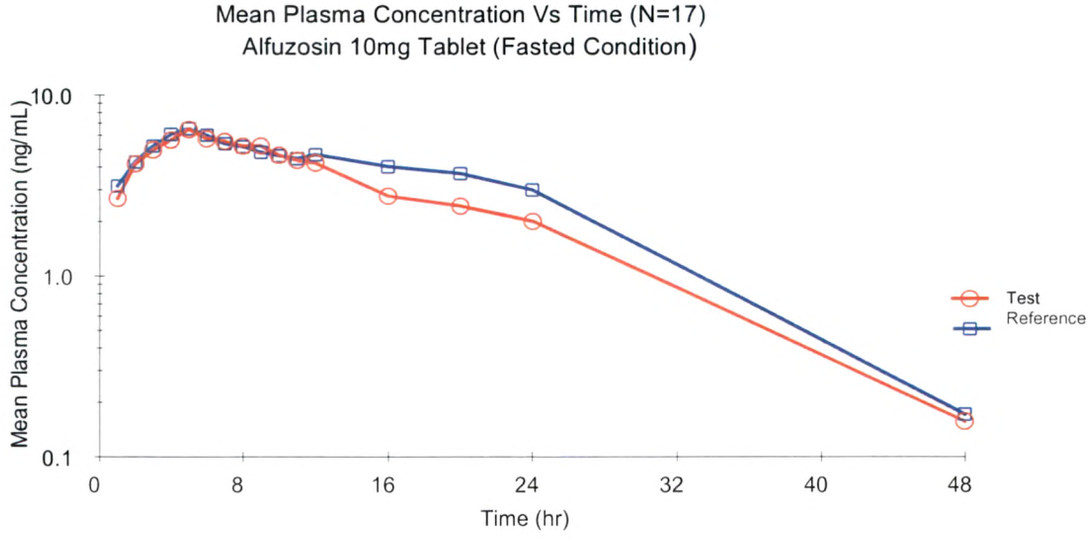
c) Ln (AUC0-inf)

Source	df	SS	MSS	F value	p value
Sequence	1	0.0089	0.0089	0.02	0.8792
Sequence*Subject	15	5.5796	0.372	6.86	0.0003
Formulation	1	0.7607	0.7607	14.04	0.0019
Period	1	0.4331	0.4331	7.99	0.0127
Error	15	0.8128	0.0542		
Intra Subject CV	0.2359				
Inter Subject CV	0.4149				



Row Scale

Figure VII. 20 Mean plasma Concentration vs Time curve of B.NO 147 (Test) vs Marketed formulation (Reference) in Fasted state



Ln Scale

Figure VII. 21 Semi logarithmic plasma Concentration vs Time curve of B.NO 147 (Test) vs Marketed formulation (Reference) in Fasted state

VII.3.2.2.2.2 Statistical Evaluation of B.No 147 (Fed State)

Table VII. 45 BE limit of B.No 147 vs Marketed Formulation in Fed state

BE Limit: PK Parameters [N=16]	90% CI		AHpval	Power	Within limits Y/N
	Lower	Upper			
Ln(Cmax)	88.0300	113.5800	0.00	0.90	Y
Ln(AUC(0-t))	79.1900	118.7400	0.04	0.57	N
Ln(AUC(0-Inf))	77.9700	120.1000	0.04	0.52	N

Table VII. 46 Pharmacokinetic Parameters of B.No 147 vs Marketed Formulation in Fed State

Study Statistics: PK Parameters [N=16]	Test		Reference		T/R of Mean
	Mean	S.D.	Mean	S.D.	
Cmax	15.161	8.232	15.157	7.623	1.0003
AUC(0-t)	292.929	174.657	281.914	136.479	1.0391
AUC(0-∞)	313.782	174.854	295.834	130.940	1.0607
Tmax	6.594 (2-12)	2.697	7.719	5.115 (2-24)	0.854
$t_{1/2}$	7.977	2.620	7.621	2.370	1.047

Table VII. 47 Test/Reference ratio of Pharmacokinetic parameters in individual volunteers (B. No 147 vs Marketed Formulation)

	T/R Ratio(Alfuzosin 10mg)		
Volunteer no.	Cmax	AUCt	AUCinf
1	1.20	1.24	1.24
2	0.84	1.17	1.18
3	0.88	0.80	----
4	0.84	0.87	1.16
5	1.09	1.00	1.06
6	1.03	0.90	0.88
7	0.46	0.92	0.94
8	1.04	1.75	1.25
9	1.10	1.17	1.20
10	0.77	1.24	0.80
11	1.22	1.30	1.30
12	1.54	1.72	2.08
13	1.26	0.94	0.94
14	1.30	0.76	0.75
15	1.07	1.02	1.01
16	0.90	0.23	0.23

Table VII. 48 Pharmacokinetic parameters of Alfuzosin ER following Single dose (10mg) administration of Test drug (B.No 147) under Fed condition

	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-inf}	Residual Area#	K_{el}	LQCT	TLIN	$T_{1/2\,el}$	MRT_{0-t}	MRT_{0-inf}
	(ng/ml)	(h)	(ng.h/ml)	(ng.h/ml)	(%)	(h^{-1})	(h)	(h)	(h)	(h)	(h)
GEOMETRIC MEAN	13.910	6.029	248.404	270.133	4.057	0.091	37.013	14.786	7.584	13.298	15.727
MEAN	15.161	6.594	292.929	313.782	7.529	0.096	39.000	15.562	7.977	13.855	16.277
SD (±)	8.232	2.697	174.657	174.854	9.437	0.034	12.000	4.718	2.620	3.855	4.037
CV(%)	67.765	7.274	30504.952	30573.813	89.063	0.001	144.000	22.262	6.864	14.861	16.296
Range(min)	8.69	2.00	87.99	89.44	0.95	0.05	24.00	8.00	3.74	7.35	7.70
Range(max)	42.98	12.00	761.81	769.09	34.05	0.19	48.00	20.00	14.03	18.85	22.53
Median	12.50	6.00	262.41	266.54	2.99	0.09	48.00	16.00	7.32	14.58	16.24

Table VII. 49 Pharmacokinetic parameters of Alfuzosin ER following Single dose (10mg) administration of Reference drug (Marketed Formulation) under Fed condition

	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-inf}	Residual Area#	K_{el}	LQCT	TLIN	$T_{1/2\,el}$	MRT_{0-t}	MRT_{0-inf}
	(ng/ml)	(h)	(ng.h/ml)	(ng.h/ml)	(%)	(h^{-1})	(h)	(h)	(h)	(h)	(h)
GEOMETRIC MEAN	13.894	6.603	252.024	270.101	3.692	0.095	37.013	13.309	7.302	13.563	15.838
MEAN	15.157	7.719	281.914	295.834	8.794	0.099	39.000	14.300	7.621	13.864	16.110
SD (±)	7.623	5.115	136.479	130.940	11.223	0.028	12.000	5.147	2.370	2.907	3.114
CV(%)	58.116	26.166	18626.444	17145.234	125.962	0.001	144.000	26.493	5.616	8.450	9.697
Range(min)	8.65	2.00	110.01	120.05	0.40	0.06	24.00	6.00	4.55	9.32	10.80
Range(max)	35.30	24.00	584.17	592.62	36.81	0.15	48.00	20.00	11.97	18.52	23.31
Median	12.05	6.00	236.97	259.08	4.11	0.10	48.00	16.00	7.13	14.37	15.27

Table VII. 50 Analysis of Variance Tables for Ln (Cmax), Ln (AUC o-t), Ln (AUC o-∞)

a) Ln (Cmax)

Cmax (ng/ml) Analysis-ANOVA for Ln(Cmax)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.1648	0.1648	0.59	0.454
Subject(seq.)	14	3.8884	0.2777	6.74	0.001
Formulation	1	0.0000	0.0000	0.00	0.999
Period	1	0.0009	0.0009	0.02	0.887
Error	14	0.5768	0.0412		
Intra subject CV = 20.50%					
Inter subject CV = 35.43%					

b) Ln (AUC o-t)

AUC o-t (ng.hr/ml) Analysis-ANOVA for Ln(AUC o-t)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.3354	0.3354	0.64	0.436
Subject(seq.)	14	7.2856	0.5204	5.00	0.002
Formulation	1	0.0075	0.0075	0.07	0.793
Period	1	0.1345	0.1345	1.29	0.275
Error	14	1.4575	0.1041		
Intra subject CV = 33.12%					
Inter subject CV = 43.10%					

c) Ln (AUC o-∞)

AUC o-∞ (ng.hr/ml) Analysis-ANOVA for Ln(AUC o-∞)					
Source	**df**	**SS**	**MSS**	**F value**	**p value**
Sequence	1	0.2579	0.2579	0.57	0.461
Subject(seq.)	14.323	6.4381	0.4495	4.04	0.008
Formulation	1	0.0080	0.0080	0.07	0.792
Period	1	0.0981	0.0981	0.88	0.364
Error	13	1.4453	0.1112		
Intra subject CV = 34.29%					
Inter subject CV = 42.93%					

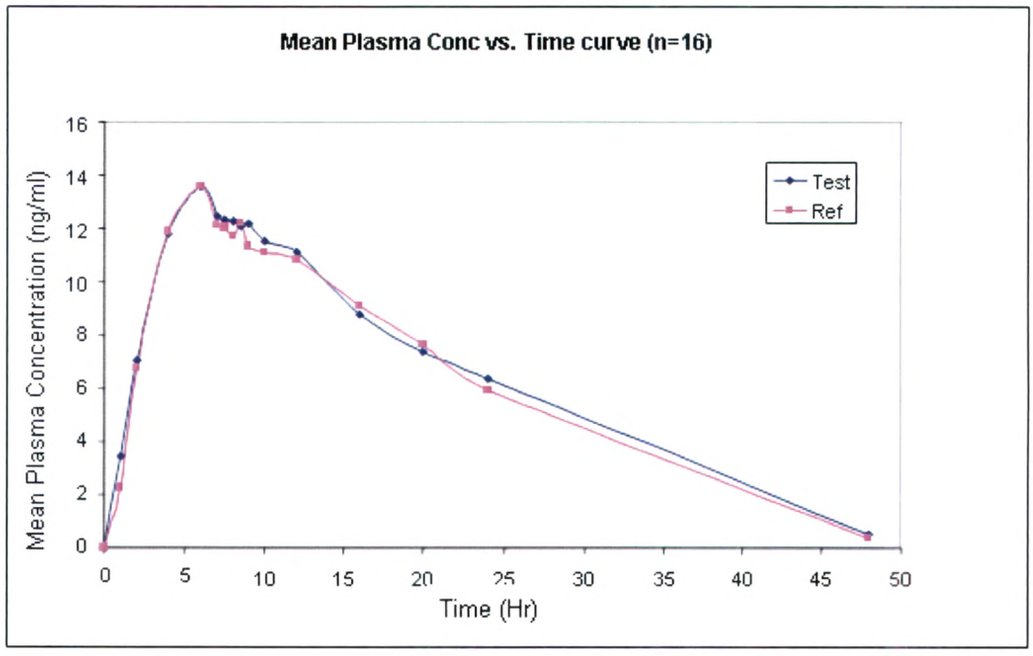


Figure VII. 22 Mean plasma Concentration vs Time curve of B.NO 147 (Test) vs Marketed formulation (Reference) in Fed state

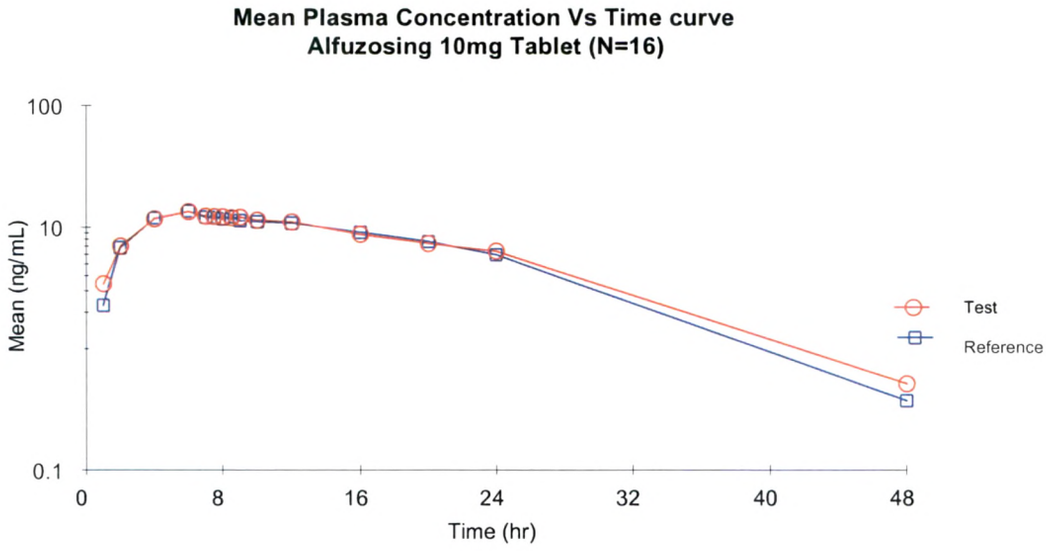


Figure VII. 23 Semi logarithmic plasma Concentration vs Time curve of B.NO 147 (Test) vs Marketed formulation (Reference) in Fed state

VII.3.2.2.2.3 Statistical Evaluation of B.No 158 (Fasted State)

Table VII. 51 Pharmacokinetic Parameters of B.No 158 vs Marketed Formulation in Fasted State

PK Parameters [N=15]	Test		Reference		T/R of Mean
	Mean	S.D.	Mean	S.D.	
Cmax	11.9602	4.89678	9.0469	3.49629	1.32
AUC(0-t)	139.7000	49.36926	129.3357	61.01088	1.08
AUC(0-Inf)	172.3084	62.68929	149.9338	62.93254	1.15
Tmax (hr)	4.7 (3-6)	0.8165	5.4 (2-11)	2.0976	0.87
t1/2 (hr)	12.1081	12.10847	8.2312	3.28101	1.47

Table VII. 52 BE Limits of B.No 158 vs Marketed Formulation in Fasted state

PK Parameters [N=15]	90% CI		AHpval	Power	Within limits Y/N
	Lower	Upper			
Ln(Cmax)	112.28	150.25	0.68	0.82	N
Ln(AUC(0-t))	91.27	131.09	0.10	0.66	N
Ln(AUC(0-Inf))	92.72	135.04	0.15	0.63	N

Table VII. 53 Test/Reference ratio of Pharmacokinetic parameters in individual volunteers(B. No 158 vs Marketed Formulation)

T/R Ratio(Alfuzosin 10mg Fasted BE Study)			
Subject	**Cmax**	**AUCt**	**AUCinf**
1	1.57	0.79	0.78
2	1.27	1.14	1.44
3	1.37	0.77	0.84
4	2.05	1.43	1.53
5	1.81	2.10	2.18
6	1.02	1.08	1.08
7	1.34	1.42	1.88
8	0.67	0.55	0.56
9	1.48	1.46	1.31
10	0.85	0.58	0.41
11	0.98	0.81	2.14
12	1.52	1.13	1.10
13	1.87	1.68	1.19
14	1.70	1.82	1.27
15	1.17	1.55	1.87
N	15	15	15
Normal Mean	1.38	1.22	1.31
Geo.Mean	1.32	1.13	1.18
SD	0.39	0.47	0.54
CV%	28.5	38.3	41.7
MEDIAN	1.37	1.14	1.27
MIN	0.67	0.55	0.41
MAX	2.05	2.10	2.18

Table VII. 54 Pharmacokinetic Parameters of Test formulation (B.No 158) in fasted state

	Tmax (hr)	Cmax (ng/mL)	AUClast (hr*ng/mL)	AUCINF_obs (hr*ng/mL)	AUC _%Extrapobs (%)	Lambda _z (1/hr)	Lambda _z_ lower (hr)	Lambda _z_ upper (hr)	HL_Lambda _z (hr)	MRTlast (hr)	MRTINF_ obs (hr)
N	15	15	15	15	15	15	15	15	15	15	15
Mean	4.667	11.960	139.7000	172.3084	16.5560	0.0816	11.5333	31.9093	12.1081	10.9542	18.7809
SD	0.8165	4.8967	49.36926	62.6893	17.3357	0.0341	6.1396	11.5804	12.1085	2.1350	14.1337
Min	3.000	6.4220	76.9345	84.0497	0.9311	0.0128	3.0000	24.0000	5.5092	8.1442	10.1717
Median	5.000	10.9230	135.5480	153.8359	10.6044	0.0978	11.0000	24.0000	7.0894	10.8796	13.7053
Max	6.000	22.3640	230.8022	320.9328	62.9399	0.1258	20.0000	48.2500	54.0379	14.8127	67.6488
CV%	17.5	40.9	35.3	36.4	104.7	41.8	53.2	36.3	100.0	19.5	75.3
Geometric Mean	4.597	11.1467	131.8408	162.3267	8.2771	0.0720	9.8095	30.1805	9.6309	10.7685	16.3606

Table VII. 55 Pharmacokinetic Parameters of Reference (Marketed Formulation) in fasted state

	Tmax (hr)	Cmax (ng/mL)	AUClast (hr*ng/mL)	AUCINF_obs (hr*ng/mL)	AUC_%Extrap_obs (%)	Lambda_z (1/hr)	Lambda_z_lower (hr)	Lambda_z_upper (hr)	HL_Lambda_z (hr)	MRTlast (hr)	MRTINF_obs (hr)
N	15	15	15	15	15	15	15	15	15	15	15
Mean	5.400	9.0469	129.3357	149.9338	14.0418	0.0942	13.8000	30.4013	8.2312	11.2178	15.4208
SD	2.0976	3.49629	61.01088	62.93254	13.24307	0.02797	5.07374	10.98802	3.28101	2.32085	4.28465
Min	2.000	4.6170	55.6670	58.7832	1.2172	0.0423	4.0000	24.0000	5.1718	8.5806	9.8227
Median	5.000	8.3120	126.3111	149.8116	9.8455	0.1067	16.0000	24.0000	6.4933	10.0817	14.7349
Max	11.000	15.7380	265.4195	269.0273	40.2745	0.1340	20.0000	48.0700	16.3719	15.8427	24.0148
CV%	38.8	38.6	47.2	42.0	94.3	29.7	36.8	36.1	39.9	20.7	27.8
GM	5.050	8.4427	116.3531	137.0411	7.9103	0.0896	12.6506	28.8734	7.7388	11.0143	14.9051

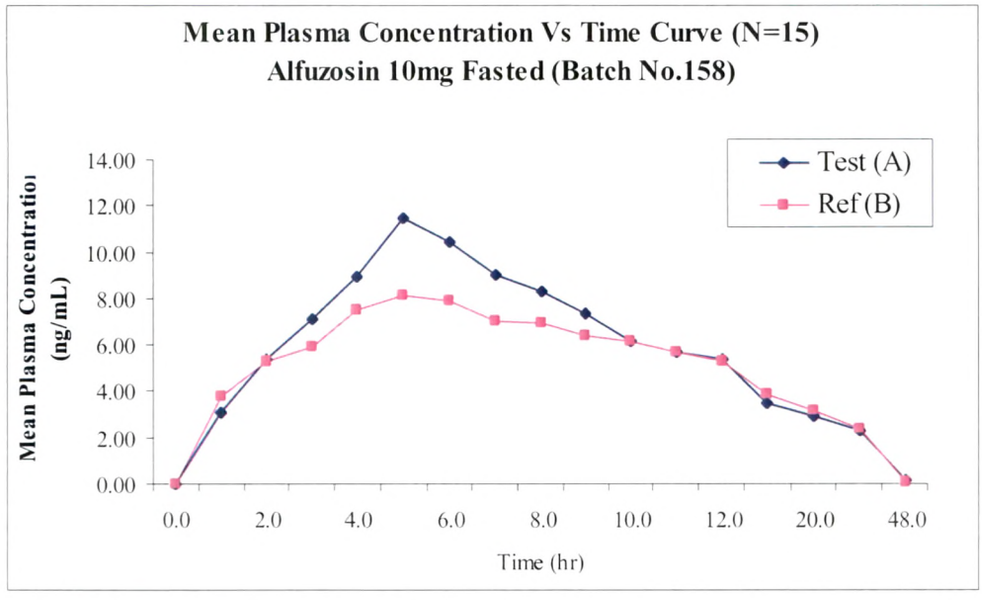


Figure VII. 24 Mean plasma concentration vs time curve of B.NO 158 (Test) vs Marketed formulation (Reference) in Fasted state

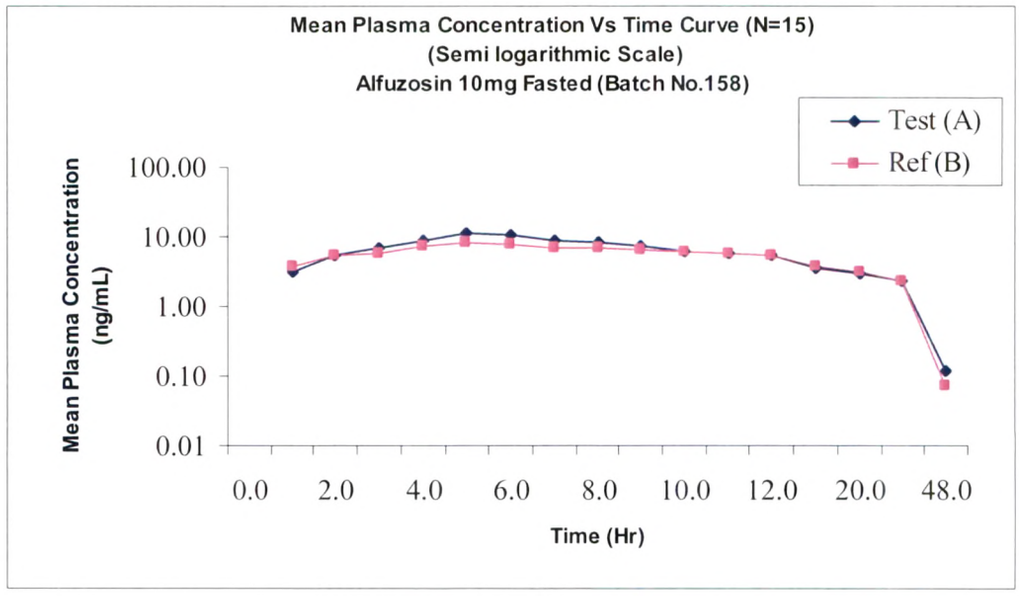


Figure VII. 25 Semi logarithmic plasma concentration vs time curve of B.NO 158 (Test) vs Marketed formulation (Reference) in Fasted state

VII.3.2.2.2.4 Statistical Evaluation of B.No 158 (Fed State)

Table VII. 56 Pharmacokinetic Parameters of B.No 158 vs Marketed Formulation in Fed State

PK Parameters [N=17]	Test		Reference		T/R of Mean
	Mean	S.D.	Mean	S.D.	
Cmax	15.2972	5.37517	11.6041	5.04224	1.32
AUC(0-t)	204.1080	63.81105	182.4020	82.51901	1.12
AUC(0-Inf)	219.7903	59.68277	199.9796	84.62370	1.10
tmax	6.176 (4-8.5)	1.3572	6.794 (2-16)	4.1005	
t1/2	7.1548	1.69872	8.3862	5.08644	

Table VII. 57 BE limit of B.No 158 vs Marketed Formulation in Fed state

PK Parameters [N=17]	90% CI		AHpval	Power	Within limits Y/N
	Lower	Upper			
Ln(Cmax)	120.55	149.76	0.87	0.96	N
Ln(AUC(0-t))	99.50	147.33	0.39	0.59	N
Ln(AUC(0-Inf))	95.49	145.46	0.31	0.54	N

Table VII. 58 Test/Reference ratio of Pharmacokinetic parameters in individual volunteers(B. No 158 vs Marketed Formulation) in fed state

T/R Ratio(Alfuzosin 10mg Tablet Fed BE Study)			
Subject	**Cmax**	**AUCt**	**AUCinf**
1	2.64	4.01	5.03
2	1.66	1.33	1.28
3	1.03	1.57	1.03
4	1.75	0.81	0.88
5	1.39	1.18	1.18
6	1.41	0.67	0.56
7	1.08	1.30	1.30
8	1.57	0.83	0.92
9	0.71	1.28	1.31
10	1.38	0.77	0.77
11	1.11	1.39	1.38
12	1.35	2.18	1.65
13	1.25	1.19	1.18
14	0.89	0.80	0.80
15	1.65	1.33	1.32
16	1.23	0.75	0.75
17	2.12	1.52	1.68
N	17	17	17
Normal Mean	1.42	1.35	1.35
Geo.Mean	1.36	1.21	1.18
SD	0.46	0.79	1.00
CV%	32.56	58.47	73.67
MEDIAN	1.38	1.28	1.18
IQR	0.54	0.57	0.45
MIN	0.71	0.67	0.56
MAX	2.64	4.01	5.03

Table VII. 59 Pharmacokinetic Parameters of Test formulation (B.No 158) in fed state

	Tmax (hr)	Cmax (ng/mL)	AUClast (hr*ng/mL)	AUCINF_obs (hr*ng/mL)	AUC_%Extrap_obs (%)	Lambda_z (1/hr)	Lambda_z_lower (hr)	Lambda_z_upper (hr)	HL_Lambda_z (hr)	MRTlast (hr)	MRTINF_obs (hr)
N	17	17	17	17	17	17	17	17	17	17	17
Mean	6.176	15.2972	204.1080	219.7903	7.6137	0.1012	14.5294	36.4765	7.1548	12.0451	14.1499
SD	1.3572	5.37517	63.81105	59.68277	7.98723	0.02052	5.37201	12.12568	1.69872	2.52530	2.63533
Min	4.000	7.9460	123.8666	125.4291	0.5018	0.0569	7.0000	24.0000	4.8303	9.4000	11.0511
Median	6.000	14.3300	203.5285	205.0312	3.2074	0.1026	16.0000	47.2300	6.7553	11.4521	13.9744
Max	8.500	27.6350	335.0849	337.9471	27.7957	0.1435	20.0000	47.8700	12.1915	17.1960	20.0802
CV%	22.0	35.1	31.3	27.2	104.9	20.3	37.0	33.2	23.7	21.0	18.6
Geometric Mean	6.029	14.4394	195.3538	212.2530	3.8491	0.0992	13.4815	34.4741	6.9906	11.8136	13.9358

Table VII. 60 Pharmacokinetic Parameters of Reference (Marketed Formulation) in fed state

	Tmax (hr)	Cmax (ng/mL)	AUClast (hr*ng/mL)	AUCINF_obs (hr*ng/mL)	AUC_%Extrap_obs (%)	Lambda_z (1/hr)	Lambda_z_lower (hr)	Lambda_z_upper (hr)	HL_Lambda_z (hr)	MRTlast (hr)	MRTINF_obs (hr)
N	17	17	17	17	17	17	17	17	17	17	17
Mean	6.794	11.6041	182.4020	199.9796	9.3658	0.0997	14.6176	37.6200	8.3862	12.8385	16.2644
SD	4.1005	5.04224	82.51901	84.62370	11.53332	0.03373	5.82969	12.27430	5.08644	3.51845	6.99663
Min	2.000	3.8590	35.4795	39.2169	0.3561	0.0277	2.0000	20.0000	4.5177	7.3943	9.3583
Median	6.000	10.2480	161.5340	166.8530	4.0478	0.1101	16.0000	47.4000	6.2957	13.0652	14.7111
Max	16.000	23.3970	337.6593	349.8257	35.9195	0.1534	20.0000	47.8700	24.9946	21.2313	40.1927
CV%	60.4	43.5	45.2	42.3	123.1	33.8	39.9	32.6	60.7	27.4	43.0
Geometric Mean	5.775	10.6255	161.6841	179.9323	3.7485	0.0925	12.6727	35.5013	7.4956	12.4011	15.3165

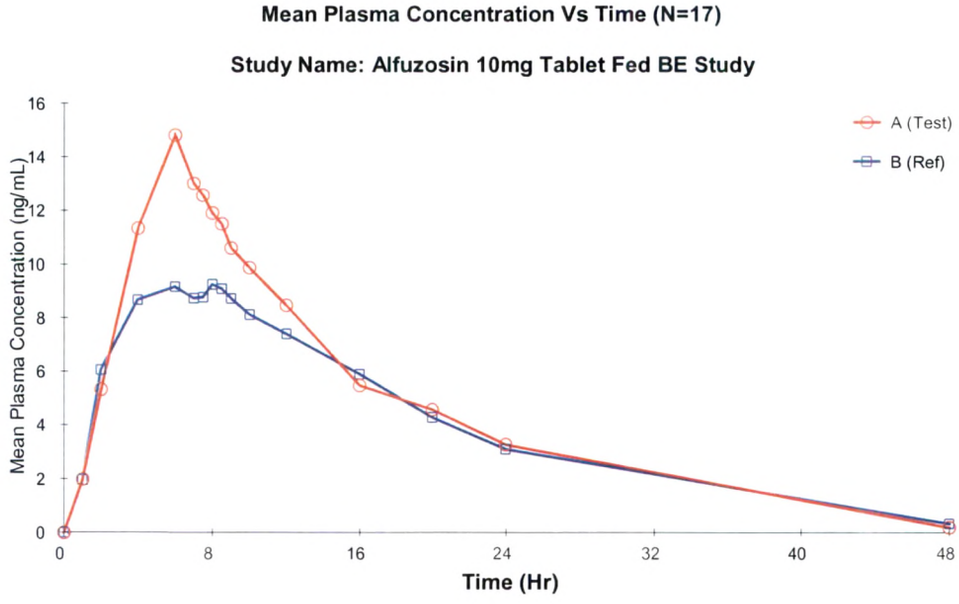


Figure VII. 26 Mean plasma concentration vs time curve of B.NO 158 (Test) vs Marketed formulation (Reference) in Fed state

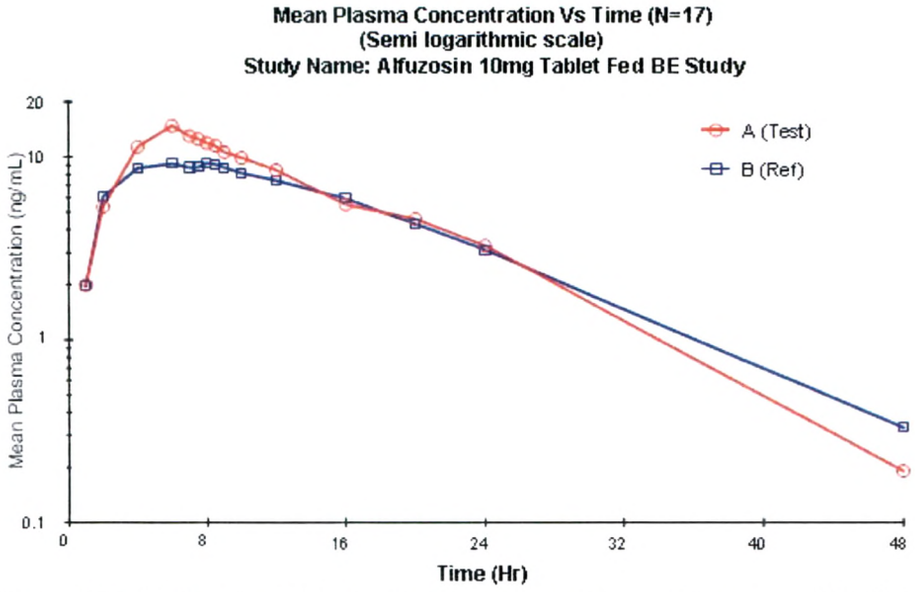


Figure VII. 27 Semi logarithmic plasma concentration vs time curve of B.NO 158 (Test) vs Marketed formulation (Reference) in Fed state

VII.3.2.2.3 IVIVC

An IVIVC (level B) correlation was established.

Table VII. 61 MRT (mean residence time) vs MDT (mean dissolution time) of B.No 147 and B.No 158 in fasted and Fed state

B.No	MDT (Hrs)	MRT(Fast) (Hrs)	MRT(Fed) (Hrs)
158	9.81	10.95	12.05
147	12.56	11.33	13.86

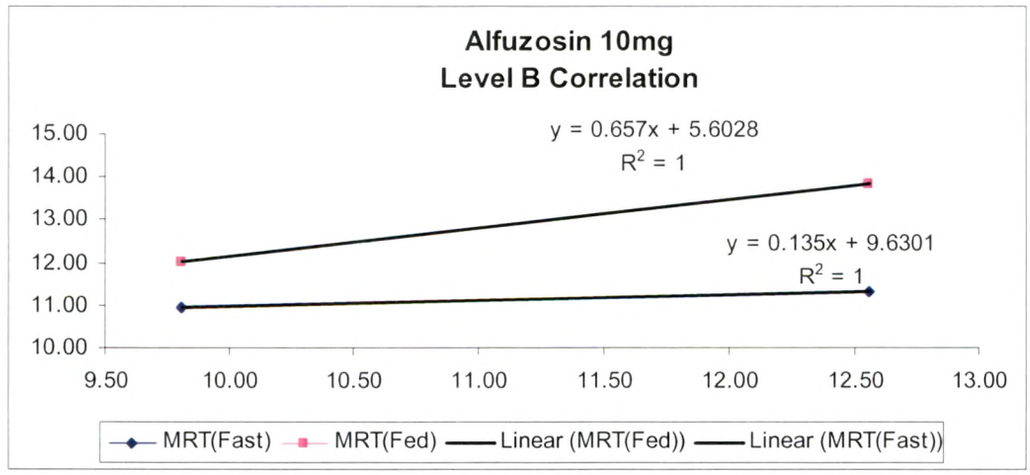


Figure VII. 28 Level B correlation of B.No 147 and B.No 158 in Fasted and Fed state

VII.3.2.2.4 Process Optimization

In order to optimize the process, following critical process parameters were identified in Alfuzosin HCL ER tablet manufacturing process and were studied for the optimization of manufacturing process to check robustness of formula.

1) Dry mixing: Blend uniformity
2) Drying : Residual solvent
3) Compression: Tablet hardness, Dissolution, Content uniformity.

VII.3.2.2.4.1 Dry mixing

It is an important parameter which is expected to alter the content uniformity of tablets. Therefore it was decided to challenge this parameter. Two different parameters were studied to observe the effect on blend uniformity analysis, trials was taken with slow impeller, chopper off and slow impeller, and slow chopper.
Dry mixing time was kept constant i.e. 10 min

Table VII. 62 Dry mix blend uniformity analysis at different mixing time points

Location	10min	10 min
Parameters	With slow impeller and chopper off	With slow impeller and slow chopper
S1	100.5	99.6
S2	97.5	99.2
S3	100.2	100.0
S4	95.5	99.8
S5	97.1	97.9
S6	96.3	99.6
S7	102.6	98.5
S8	98.0	99.3
S9	101.7	97.7
S10	93.3	99.6
Avg	**98.3**	**99.1**
Min	**93.3**	**97.7**
Max	**102.6**	**100.0**
% RSD	**3.0**	**0.8**

The blend uniformity result of dry mix was found satisfactory with slow chopper and slow impeller at 10 min from the Table above, as the RSD value was least as compared with value with slow impeller and chopper off.

VII.3.2.2.4.2 Drying

To control the Isopropyl alcohol content in tablets, drying temperature was monitored with respect to time and temperature, during Alfuzosin HCl ER tablet manufacturing process.

VII.3.2.2.4.2.1 Drying Temperature

In order to study the effect of drying temperature on IPA content of the granules, IPA content of the granules were analyzed at different temperature interval so as to optimize the drying temperature and IPA content in tablets.

Table VII. 63 IPA content at different temperature in granules

Dying time	Inlet Temp.	Product Temp.	L.O.D	O.V.I (IPA in µg/g)
3hrs	65°C	53°C	2.7%	12970
3hrs	75°C	71°C	1.0%	6643
3hrs	85°C	76° C	1.0%	3640

Increasing the inlet air temperature decreases the quantity of residual solvent (Isopropyl alcohol) in granules.

VII.3.2.2.4.2.2 Drying Time

In order to study the effect of drying time on IPA content of the granules, IPA content of the granules was analyzed at different time interval so as to optimize the drying time and IPA content in tablets.

Table VII. 64 IPA content at different time interval in granules

Dying time	Inlet Temp.	Product Temp.	L.O.D	O.V.I (IPA in µg/g)
2hr	85°C	76°C	0.40%	4690
3hr	85°C	75°C	0.43%	3640
4hr	85°C	76°C	1.0%	2401

Increasing drying time reduces the quantity of residual solvent content (IPA content) in granules.

VII.3.2.2.4.3 Tablet Hardness and content uniformity of tablets at different stages of compression

VII.3.2.2.4.3.1 Tablet hardness

In order to study the effect of different hardness on dissolution profile, tablets were compressed at different hardness and dissolution was performed in 0.01N HCl

Table VII. 65 Effect of different hardness on dissolution profile of Alfuzosin HCl ER Tablets

Parameter	% drug release in 0.01N HCl (Time in hrs) Paddle 500ml 100RPM						
	1	3	6	12	20	24	30
High Hardness (280N)	12.0	23.0	36.0	56.3	77.0	84.5	92.9
Low Hardness (140N)	12.9	24.5	37.5	57.1	77.8	85.1	92.9
Optimum Hardness (200N)	11.6	23.0	35.4	55.2	74.9	81.6	91.3

From above results it was found that impact of hardness on dissolution of profile of Alfuzosin Hydrochloride tablets was insignificant.

VII.3.2.2.4.3.2 Content uniformity

Being a low dose drug, content uniformity of compressed tablets was done at different time periods during compression.

Table VII. 66 Content uniformity of Alfuzosin hydrochloride ER tablets 10 mg

Location	1	2	3	4	5	6	7	8	9	10	Mean	RSD
Initial	98.9	97.7	100.4	99.1	100.1	99.5	97.7	99.6	98.2	98.3	**99.0**	**0.95**
Middle	99.3	100.7	99.4	99.4	99.6	99.7	100.3	99.4	99.4	98.9	**99.6**	**0.51**
End	100.1	99.4	99.5	100.6	99.1	100.5	99.7	99.7	99.4	99.5	**99.8**	**0.50**

From above results it was found that tablets content uniformity was uniform till the end of compression.

VII.3.2.2.5 Stability study

Stability study was carried out as per ICH (International conference on Harmonization) guidelines in temperature and humidity controlled chambers set at 60°C / 75% RH and 40 °C / 75% RH separately. The data is presented in the following table.

Table VII. 67 Stability Data of Alfuzosin Hydrochloride Extended Release Tablets 10 mg (B.No.147)

Packaging	Aging	Description	Water Content (%)	Assay (%)	Related impurities (%)	
					Single unknown	Total
PVDC	Initial	Complies	5.5	101.4	0.004	0.013
	60°C- 1M	Complies	4.3	99.6	0.031	0.031
	40°C/75%RH - 1M	Complies	6.4	100.9	0.039	0.039
	40°C/75%RH - 2M	Complies	6.7	99.7	0.051	0.051
	40°C/75%RH - 3M	Complies	7.8	98.6	0.065	0.084
HDPE with dessicant and rayon filler	60°C- 1M	Complies	6.9	99.1	0.036	0.069
	40°C/75%RH - 1M	Complies	6.6	99.2	0.021	0.027
	40°C/75%RH - 2M	Complies	6.0	98.6	0.051	0.051
	40°C/75%RH - 3M	Complies	5.7	98.9	0.062	0.082

Dissolution Profile of Alfuzosin Hydrochloride Extended Release Tablets 10 mg samples under stability study.

In order to assess the influence of aging at different conditions of temperature and humidity on the dissolution profile, samples under stability study were subjected to in-vitro dissolution study. The dissolution profiles of these samples are tabulated below.

Table VII. 68 Comparative dissolution profile at various stability conditions and in different packaging (B.No. 147)

	Aging	Cumulative % Drug release in 0.01n HCl at 100 rpm with paddle						
		Time in hrs						
		1	3	6	12	20	24	30
Packaging	Initial	11.8	23.5	37.2	58.5	78.3	86.1	94.2
PVDC	60°C- 1M	11.2	22.3	35.1	56.7	77.0	84.7	92.0
	40°C/75%RH - 1M	11.6	23.9	37.2	58.1	77.9	85.2	93.6
	40°C/75%RH - 2M	11.3	22.2	34.8	55.8	76.2	83.1	90.4
	40°C/75%RH - 3M	10.9	21.9	35.0	54.9	75.1	83.2	90.4
HDPE with dessicant and rayon filler	60°C- 1M	11.7	23.0	36.2	56.5	77.1	83.2	91.1
	40°C/75%RH - 1M	11.3	22.8	36.8	58.0	78.2	85.5	94.1
	40°C/75%RH - 2M	10.9	21.5	34.8	54.9	75.2	82.1	88.8

Results of 3 months accelerated stability data (40°C ± 2°C/75% RH ± 5% RH) and at 60°C presented above confirmed that the formulation was stable and the storage had no significant influence on the dissolution behavior.

VII.3.2.3 DISCUSSION

It was observed that by keeping PVP K90 constant i.e. 11%, and varying HMPC K100MCR concentration i.e. 50, 60 and 69%, different dissolution profiles were obtained in which B. No 158 release profile was similar to that of Marketed formulation and B. No 147 was a slower one than Marketed formulation in 0.01 N HCl. Release profile of B. No 159 was in between that of B. No 147 and B. No 158.This is in line with the fact that increasing the highly viscous polymer (HPMC K100 MCR), the release profile decreases although it was not very significant in all the media i.e. 0.01 N HCl, 4.5 pH acetate buffer and 6.8 pH phosphate buffer.

In vivo Bioavailability study showed that bioavailability was higher (as compared to marketed formulation) in fed condition then in fasted condition in both the batches, B. No 147 and B. No 158.

Table VII. 69 Bio-equivalence study of B. No 147 Vs B. No 158 under Fed condition

BE Parameter		BE Limit	Ln (Cmax) Formulation		Ln (AUCt) Formulation		Ln (AUCinf) Formulation	
			B.No 158	B.No 147	B.No 158	B.No 147	B.No 158	B.No 147
			No. of volunteers (17)	No. of volunteers (16)	No. of volunteers (17)	No. of volunteers (16)	No. of volunteers (17)	No. of volunteers (16)
90% CI	Lower	80	120.55	88.0300	99.50	79.1900	95.49	77.9700
	Upper	125	149.76	113.5800	147.33	118.7400	145.46	120.1000
	AHpval	1.00	0.87	0.00	0.39	0.04	0.31	0.04
	Power	1.00	0.96	0.90	0.59	0.57	0.54	0.52

The above results showed that B. No. 158 containing lower percentage of Hypromellose K 100 MCR (50%) had higher bioavailability than B. No. 147 containing 69% of Hypromellose K100MCR.

Table VII. 70 Bio-equivalence study of B. No 147 Vs B. No 158 under Fasted condition

BE Parameter		BE Limit	Ln(Cmax) Formulation		Ln(AUCt) Formulation		Ln(AUCinf) Formulation	
			B.No 158	B.No 147	B.No 158	B.No 147	B.No 158	B.No 147
			No. of volunteers (15)	No. of volunteers (17)	No. of volunteers (15)	No. of volunteers (17)	No. of volunteers (15)	No. of volunteers (17)
90% CI	Lower	80	112.28	81.2900	91.27	64.7900	92.72	64.5200
	Upper	125	150.25	111.4800	131.09	97.3400	135.04	85.3200
	AHpval	1.00	0.68	0.0320	0.10	0.5239	0.15	0.8202
	Power	1.00	0.82	0.7604	0.66	0.5672	0.63	0.8442

Above results indicate that B. No 158 containing lower percentage of Hypromellose K 100 MCR (50%) had higher bioavailability than B. No 147 containing 69% of Hypromellose K100MCR.

Table VII. 71 Comparative Cmax, AUC and AUC inf values

A comparative study of Cmax, AUC and AUCinf of B. No 147 and B. No 158 were made under fed and fasted conditions. Results are summarized as under;

		Test	Reference	% increase
B.No 147 Fed	Cmax	15.161	15.157	0.026
	Auc	292.929	281.914	3.907
	Aucinf	313.782	295.834	6.067
B.No 147 Fasted	Cmax	7.073	7.203	-1.805
	Auc	105.992	127.154	-16.643
	Aucinf	119.346	150.141	-20.511
B.No 158 Fasted	Cmax	11.960	9.047	32.202
	Auc	139.700	129.336	8.013
	Aucinf	172.308	149.934	14.923
B.No 158 Fed	Cmax	15.297	11.604	31.826
	Auc	204.108	182.402	11.900
	Aucinf	219.790	199.980	9.906

Here, B. No 147 with slower release profile than that of marketed formulation showed lower bioavailability than B. No 158 with comparable dissolution profile to that of marketed formulation. The results obtained were opposite that obtained with B. No 16 and B. No 47 formulated with a combination of HPMC and PEO where B.No 47 with slower release profile than marketed formulation had higher bioavailability than B.No 16 whose dissolution profile was comparable to that of marketed formulation.

Table VII. 72 Comparative Cmax, AUC and AUC inf values

A comparative study of Cmax, AUC and AUCinf of formulations B.No 16, B. No 47, B. No 147 and B. No 158 were made under fed and fasted conditions. Results are summarized as under;

		Test	Ref.	% increase	Remark
B.No 16 Fed	Cmax	23.624	11.090	113.021	HPMC +PEO
	Auc	237.086	187.836	26.220	
	Aucinf	242.369	193.694	25.130	
B.No 47 Fed	Cmax	14.544	7.365	97.475	HPMC +PEO
	Auc	168.814	96.052	75.753	
	Aucinf	180.195	92.984	93.791	
B.No 47 Fasted	Cmax	8.953	6.212	44.124	HPMC +PEO
	Auc	119.690	81.839	46.251	
	Aucinf	136.305	95.011	43.462	
B.No 147 Fed	Cmax	15.161	15.157	0.026	HPMC +PVP
	Auc	292.929	281.914	3.907	
	Aucinf	313.782	295.834	6.067	
B.No 147 Fasted	Cmax	7.073	7.203	-1.805	HPMC +PVP
	Auc	105.992	127.154	-16.643	
	Aucinf	119.346	150.141	-20.511	
B.No 158 Fasted	Cmax	11.960	9.047	32.202	HPMC +PVP
	Auc	139.700	129.336	8.013	
	Aucinf	172.308	149.934	14.923	
B.No 158 Fed	Cmax	15.297	11.604	31.826	HPMC +PVP
	Auc	204.108	182.402	11.900	
	Aucinf	219.790	199.980	9.906	

Results of Bio study showed that all Pharmacokinetic parameters of Test formulations are higher than reference (marketed Formulations), except in B.No 147 in fasted state.
Although Cmax values of test formulations are higher than Marketed formulations, they were well within the reported values ((UroXatral® alfuzosin package insert, 2003, Xatral® alfuzosin package insert, 2003) as shown in table below:

Table VII. 73 Comparative Pharmacokinetic parameters of Marketed formulation of extended release (ER) and immediate release (IR) formulation

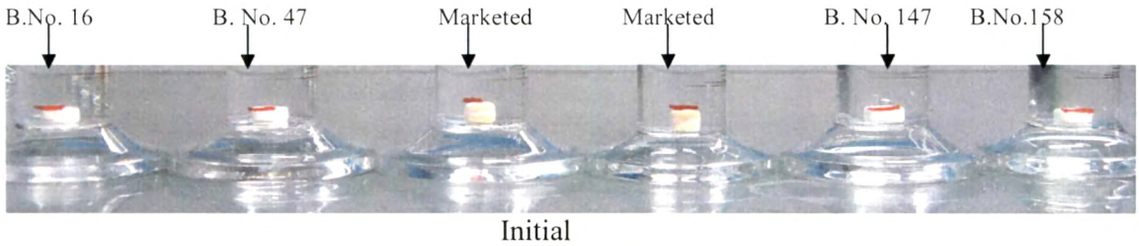
Parameter	10 mg ER	2.5 mg tid (IR)
C_{max}(µg/L)	16.6	20.2
AUC_{24} (µg.h/L)	238	233

This means that all test formulations lies below toxicity range.
Results show that Bioavailability followed the following order in fed state: B.No 47> B.No 16>B.No 158>B.No 147.

The reason for this was found out by studying the swelling properties of all the formulations in petri- dishes filled with water and measuring the tablet thickness over a period of time with digital vernier calipers.

Table VII. 74 Comparative swelling properties of B.No 16 vs B.No 47 vs B.No 147 vs B.No 158

Time	B.No.			
(Hr.)	16	47	158	147
0	4.42	4.52	4.30	4.39
1	6.03	6.36	5.71	5.21
2	7.93	8.71	7.32	5.83
4	8.89	9.17	9.91	9.45
6	9.94	10.36	11.09	10.78
8	10.91	10.94	12.32	10.97
10	12.30	11.75	13.14	11.20
12	13.06	13.41	13.44	13.77
24	15.48	14.82	14.63	14.17
26	17.51	16.79	14.93	16.07



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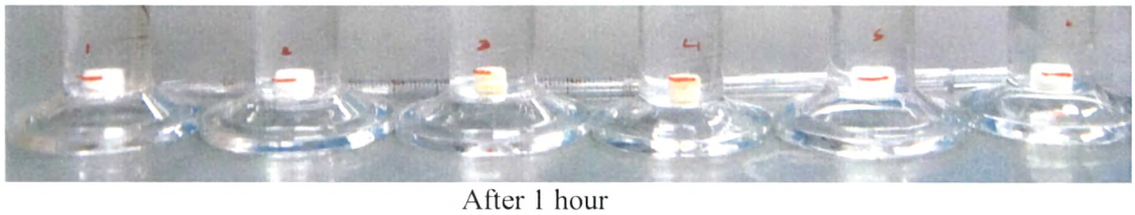
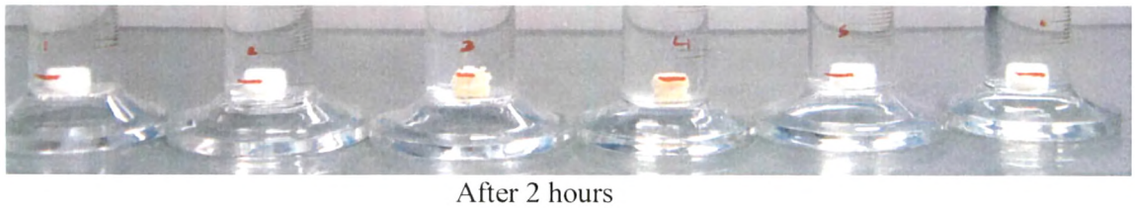
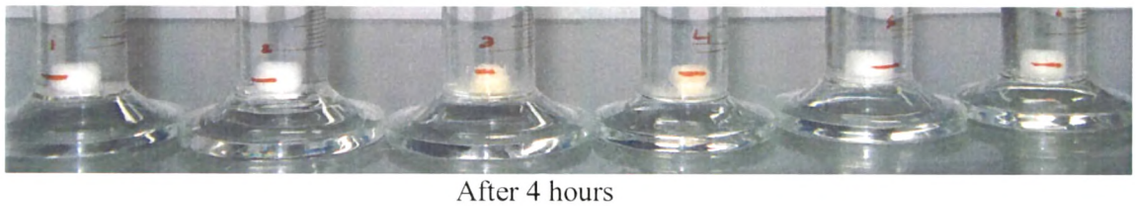


After 1 hour



After 2 hours

After 3 hours



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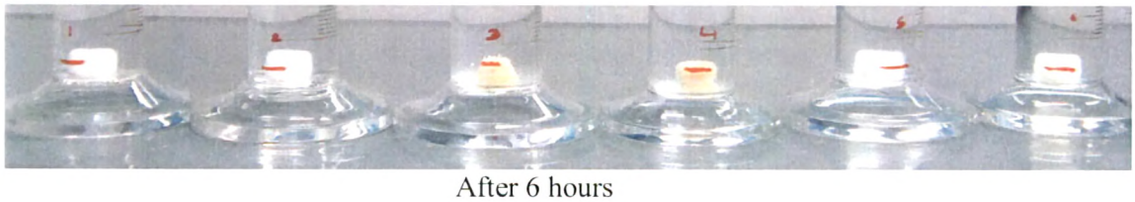
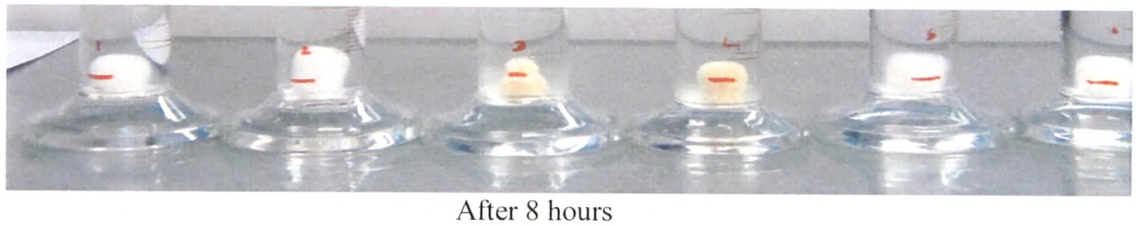
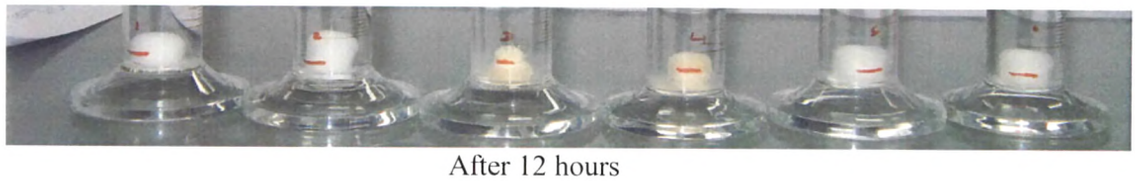


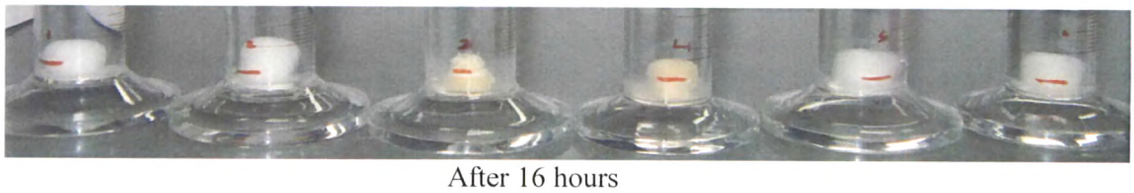
After 6 hours



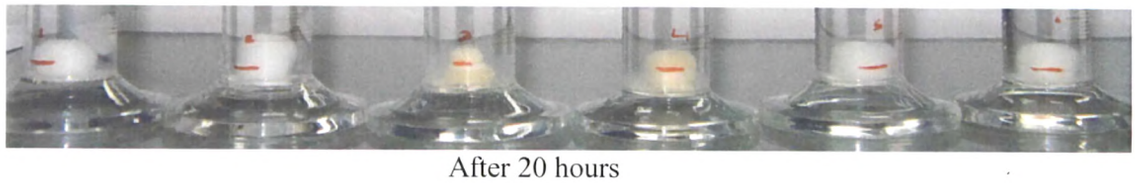
After 8 hours



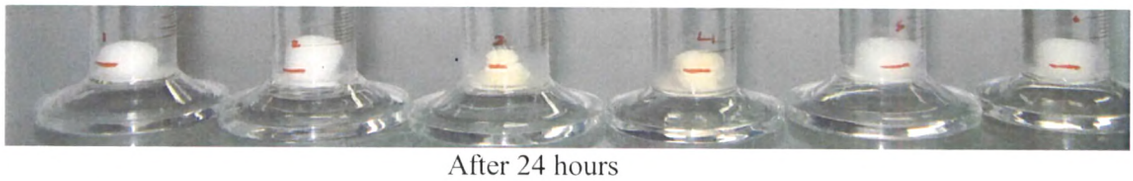
After 12 hours



After 16 hours



After 20 hours



After 24 hours

Figure VII. 29 Comparative characterization of swelling nature of Batch No. 16 Vs Batch No. 47 Vs Marketed formulation Vs Batch No. 147 Vs Batch No. 158 at different time intervals.

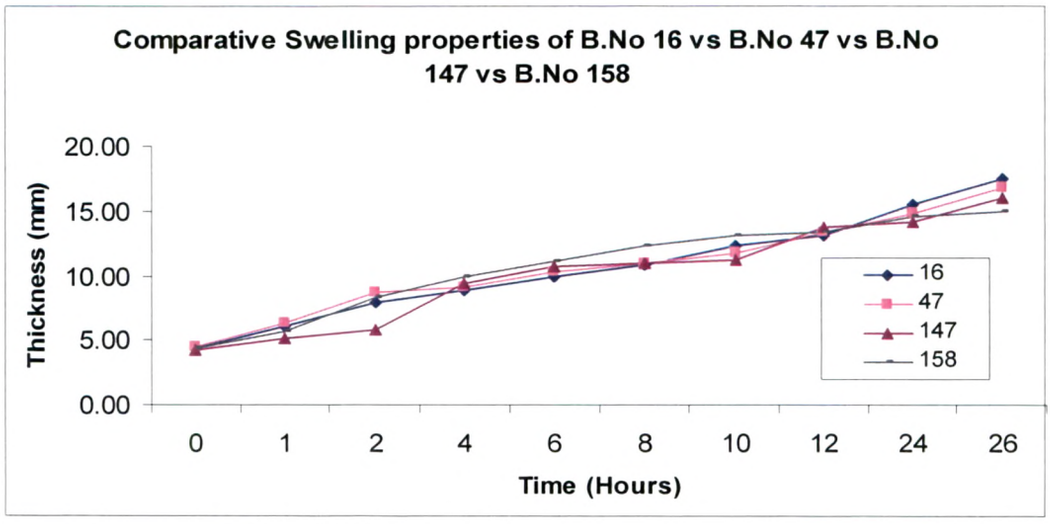


Figure VII. 30 Comparative Swelling properties of B.No 16 vs B.No 47 vs B.No 147 vs B.No 158

Table VII.74 and Fig VII.30 chart clearly showed that swelling followed following order: B.No 47>B.No 16 > B.No 158>B.No 147 and similar trend was observed in Bio results.

As discussed earlier about the work of Maggi et al.2000 that the results of the swelling studies performed on the plain tablets made of pure polymer showed quite different morphological behavior of HPMCs and PEOs during hydration. In fact, HPMCs tablets showed a slow and continuous volume increase, up to four-fold (Methocel K4M) or six-fold (Methocel K100M) the volume of the dry tablet, after 20 hours in distilled water. On the other hand, tablets made of pure PEOs swelled rapidly (up to six-fold or two-fold in the case of Polyox WSR 303 or Polyox NF-60K tablets, respectively, after 8 hours).

This might be the reason for higher bioavailability with PEO and HPMC combination compared with PVP and HPMC combination. PVP and HPMC combination showed slower hydration rate than PEO and HPMC combination which might have resulted in lesser retention time. Although studies with gastric residence time were done with B. No 47 but it should have been done for B.No 158 also. Shorter retention time of B. No 147 was further indicated by low bioavailability than marketed and other test formulations (B.No. 16, 47,158) in fasted sate.

A faster hydration rate is the prerequisite for greater retention time in the stomach. Therefore greater retention time and a release profile where drug release rate is equivalent to drug absorption rate is required for enhancing the bioavailability of Alfuzosin HCl.

Another reason for higher bioavailability of test formulations (B.No. 16, 47,158) than marketed formulation is due to the fact that the marketed formulation releases 30% in 6 hrs in stomach; 40% for another 6 hrs in intestine and another 30% in the colon for 8 hrs.

As discussed earlier in preformulation study, absorption through ileum was at a faster rate than in duodenum, so greater residence time along with slower release profile may have provided greater bioavailability for the test formulation.
Based on two test formulations, B. No 147 and 158, a level B correlation was established. Although it is desirable to establish an IVIVC at level A, but as no significant difference in in- vitro release profiles were obtained, level B correlation was established. In order to check the validity of the correlation established, a bio study with B. No 159 (with 60% HPMC and 11 % PVP K 90; formula mentioned above, Table VII.38) was done in fasted and fed state and following parameters were obtained:

Table VII. 75 MRT vs MDT of B.No 147, B.No 159 and B.No 158 in Fasted and Fed state

B.No.	MDT (Hrs)	MRT(Fast) (Hrs)	MRT(Fed) (Hrs)
158	9.81	10.95	12.05
159	11.33	11.05	12.83
147	12.56	11.33	13.86

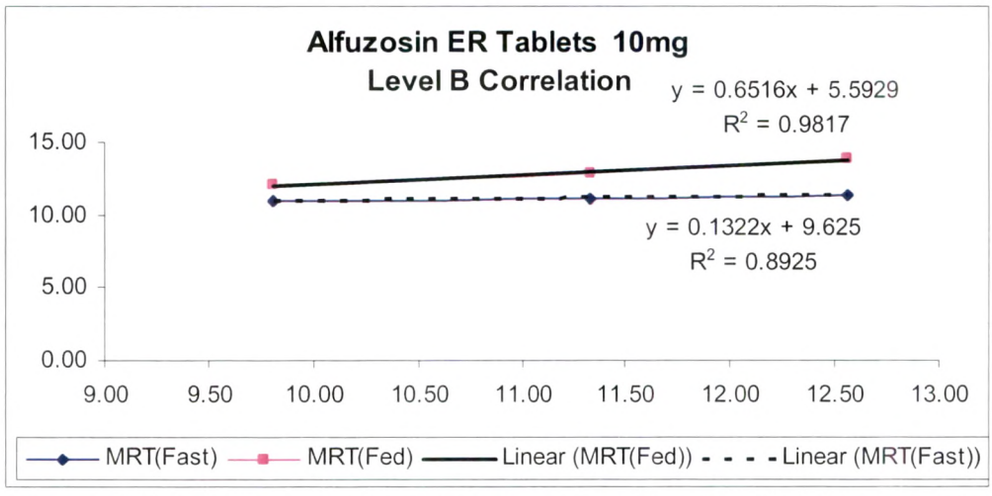


Figure VII. 31 Level B correlation of B. No 147, B. No 159 and B. No 158 in fasted and Fed state

Results of the study showed, that a perfect linear correlation was established.

Results of stability study showed that the formulation (B.No. 147) was stable even under accelerated condition in both the packings.

VII.3.2.4 CONCLUSION

The results investigated into current research have brought into light the fact that proper choice of polymer is necessary to get the desired bioavailability. Here, we have found that although in vitro dissolution profile of B. No 16 and B. No 47 (combination of HPMC and PEO) was similar and slower than marketed formulation respectively and similar trend was observed with B. No 158 and B. No 147 (combination of HPMC and PVP), their behavior in-vivo was quite different. Formulations with PEO and HPMC combination had higher bioavailability than with PVP and HPMC combination. Results of swelling indicate that higher swelling in initial time periods is necessary for better retention in the stomach. Therefore greater retention time and a release profile where drug release rate is equivalent to drug absorption rate is required for enhancing the bioavailability of Alfuzosin HCL.

The results of the study also showed that development of discriminatory media for drugs with high solubility formulated in swelling controlled release matrix is quite difficult. Also establishment of Level A is not possible but here we were able to develop Level B correlation.

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