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FORMULATION AND EVALUATION OF BILAYER FLOATING TABLETS OF ATORVASTATIN AND RAMIPRIL

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Abstract:

The aim of the present study is to formulate and evaluate the bilayer tablets of Atorvastatin and Ramipril using different media, to know the release studies in which media the release of the drug is in controlled manner. The bilayer tablets of Atorvastatin matrix floating and Ramipril immediate release tablets were prepared. Bi-Layer tablets consists of two layers i.e.,immediate release layer containing of disintegrant sodium starch glycollate and controlled release layer containing HPMCK100M, POLY0X WSR 303 and sodium alginate as retard layer. Combination of Atorvastatin and ramipril prepared by direct compression and wet granulation method which consists of various disintegrants and polymer in different ratios The tablets were evaluated for various parameters like weight variation, thickness, hardness and friability. The release studies were carried out using different media using USP dissolution testing apparatus II (paddle type) for 12hrs.

Keywords: *Bilayer tablets, Atorvastatin, Ramipril polymer.*

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INTRODUCTION:

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres[1] Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.[38] from the system. After release of drug, the residual system is emptied from the stomach[2]. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form.

Bilayer tablets are composed of two layers of granulation compressed together. They have appearance of a sandwich because the edges of each layer are exposed. They have the appearance of a sandwich because the edges of each layer are exposed. Bi-layer tablets are prepared with one layer of drug for immediate release with second layer design to release drug, later, either as second dose or in an extended release manner[3].Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two or three layers. More are possible but the design becomes very special[4-9].

Ramipril is a prodrug belonging to the angiotensin-converting enzyme (ACE) inhibitor class of medications[10]. It is metabolized to ramipril at in the liver and, to a lesser extent, kidneys. Ramiprilat is a potent, competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS). Ramipril may be used in the treatment of hypertension, congestive heart failure, nephropathy, and to reduce the rate of death, myocardial infarction and stroke in individuals at high risk of cardiovascular events. Atorvastatin (Lipitor) is a member of the drug class known as statins. It is used for lowering cholesterol. Atorvastatin is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme in cholesterol biosynthesis via the mevalonate pathway. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate. Atorvastatin acts primarily in the liver. Decreased hepatic cholesterol levels increases hepatic uptake of cholesterol and reduces plasma cholesterol levels.

MATERIALS AND METHODS

Ramipril and Atrovastatin a gift sample from Alkem pvt Ltd, Mumbai , HPMC K100M from colorcon chemicals Asia Pvt.Ltd, sodium alginate ,polyox wsr 303, croscarmellosesodium,L-HPC, microcrystallinecellulose, PVP-K30, Sodium Starch Glycolate Commercially procured from Loba chemie, Mumbai, menthol and lactose Commercially procured from Sd Fine –Chem Pvt, Mumbai.

PREPARATION OF BILAYER FLOATING TABLETS:

Bilayer floating tablets were prepared by direct compression using different super disintegrants (like sodium starch glycolate, Croscarmellose Sodium and L-HPC) and HPMC K100M and Sodium Alginate and POLYOX WSR 303 as the release controlling polymers, and sodium bicarbonate as a gas generating agent. The optimum concentrations of the above ingredients were determined under experimental conditions and on the basis of trial preparation of the tablets. Preparation of bilayer floating tablets had two steps:

Preparation of Immediate Layer of Ramipril by Direct Compression Method

Drug and super disintegrant (Sodium starch glycolate, Croscarmellose sodium and L-HPC) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.

Preparation of Floating matrix Layer of Atrovastatin by Wet Granulation Method

Drug and polymer (HPMC K100M, Sodium Alginate and Polyox WSR 303) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes. Binder (PVPK-30) dissolved in isopropyl alcohol which is used as a granulating agent. Above drug-polymer blend is granulated by using binder solution. Dry the prepared granules in the tray dryer for not more than 20 min at 60^0C. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min. Compressed the above lubricated blend by using suitable punches shown in table-1.

Drug-Excipients Compatibility Studies by FT-IR

For this study, potassium bromide (KBr) pellet method was employed. The samples were thoroughly mixed with dry powdered potassium bromide. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The

application of infra-red spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixtures and as a tool in establishment of the structure. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds shown in fig-1-3.

PRE COMPRESSION PARAMETERS [11]

Angle of Repose: Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The angle of repose is determined by funnel method. The funnel is fixed at a particular height (2.5cm) on a burette stand. The powder sample was passed through the funnel allowing it to form a pile. No more granules are added as the pile touches the tip of the funnel. This region is encircled to measure radius. The same procedure is done for triplicate, the average value is taken. The angle of repose is calculated by using equation

$$\text{Angle of repose } (\theta) = \text{Tan}^{-1} (h/r)$$

Where, h=height of pile r=radius of the base of the pile θ =angle of repose

Bulk Density Determination: Weighed quantity of the powder (W) is taken in a graduated measuring cylinder and volume (V_0) is measured and bulk density is calculated using the formula.

$$\text{Bulk density (BD)} = \text{Weight of the powder/Volume of powder}$$

Tapped Density Determination: Weighed quantity of powder taken in a graduated cylinder and the volume is measured (V_0). The graduated cylinder was fixed in the 'Tapped Densitometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The final reading was denoted by (V_f). The volume of blend was used to calculate the tapped density, Hausners's ratio and Carr's Index.

$$\text{Tapped density (TD)} = W/V_f \text{ g/ml}$$

Carr's Index or Compressibility index: Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics**.**

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100

Hausner's ratio: It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Hausner ratio = Tapped density/Bulk density

All the parameters are shown in table-2

EVALUATION OF TABLETS (POST COMPRESSIONAL PARAMETERS)

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, Weight, Hardness, Friability, Floating log time and invitro-dissolution characters shown in table-3.

Weight variation: The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the table.

Hardness Test : Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling and transportation. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and analyzed for hardness. The mean values were calculated

Friability: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Content uniformity: Ten tablets were selected randomly and crushed, from that average weight of one tablet was dissolved using 20ml methanol and 20ml of 0.1N HCl until drugs get dissolved then added the dissolution media (0.1N HCl) to make volume 100ml, 0.45µ membrane filter. Standard also performed with the same concentration then this would read at 210 nm, 242 nm by UV spectroscopy.

$$\text{Amount of drug} = \frac{\text{Sample absorbance}}{\text{Std.absorbance}} \times \frac{\text{Std.dilution}}{\text{Sample dilution}} \times \text{Conversion factor} \times 100$$

Conversion factor for Ramipril = Molecular wt of Ramipril

Conversion factor Atrovastatin = Molecular wt of Atrovastatin

$$\% \text{ Purity} = \frac{\text{Amount}}{\text{Label claim}} \times 100$$

Label Claim = 5 mg (Ramipril) and 40 mg (Atrovastatin)

In vitro buoyancy studies: In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were placed in a 100ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

In-Vitro Dissolution Studies: The dissolution conditions used for studying the drug release from Floating bilayered tabletsrepresented in tables 4&5,figures 4&5:

The samples were withdrawn at predetermined time points, and were analyzed spectrophotometrically at 210 nm and 242 nm

Apparatus	**USP apparatus II (Paddle)**
Agitation speed (rpm)	50rpm
Medium	0.1N HCl (1.2 pH)
Volume	900 ml
Temperature	37.0 ± 0.5 ^{0}C
Time:	5, 10, 15, 30, 45, 60 min (for immediate layer of Ramipril) and 1, 2, 4, 6, 8 and 12 hrs (for Floating matrix layer of Atrovastatin).
Wavelengths	210 nm and 242 nm

RESULTS AND DISCUSSION

FT-IR studies were carried out for pure drug alone and final optimized formulation. FTIR spectrum of pure Ramipril and Atrovastatin was shown in the **Figure 1&2.** Similarly FTIR spectra of optimized formulation were shown in **Figures**. Characteristic peaks were not affected and prominently observed in FTIR spectra given in Figures 1 and 2. This indicates that there is no interaction between Ramipril, Atrovastatin and polymers and the drug was compatible with the formulation components.

All Formulations tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of the formulation was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Among all formulations, R4 shows better drug release when compared with all other formulations. So formulation R4 selected as optimized formula consider as “R” in bilayer formulation.

Among all formulations, RA9 shows better drug release when compared with all other formulations. So formulation RA9 selected as optimized formula.
Kinetic studies for optimized formulation:

CONCLUSION

The aim of the present study was to develop an optimized formula for bilayer tablet containing Ramipril and Atrovastatin for the management of hyperlipidemia.

Ramipril was planned to design as the sustained release part and Atrovastatin as the immediate release part. After pre-formulation studies it was decided to prepare Ramipril part by direct compression and Atrovastatin by wet granulation method. For sustained release portion different polymers were used in granulation stage and also extragranularly. In the formulation of immediate release sodium starch glycolate, Croscarmellose Sodium and L-HPC were used as super disintegrants. Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner’s ratio. The compressed bilayer tablets were also evaluated for weight variation, hardness, friability, drug content, Floating lag time and invitro drug release.

In the above studies RA9 formulation showed promising results. It was further supported by FTIR analysis which showed that RA9 had no interaction with excipients. The stability studies were carried out for the optimized batch RA9 for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug release.

So RA9 formulation was considered as the optimized formulation.

Table:1 Formulation of Bi layer Tablets

S.NO.	INGREDIENTS	RA1 (mg)	RA2 (mg)	RA3 (mg)	RA4 (mg)	RA5 (mg)	RA6 (mg)	RA7 (mg)	RA8 (mg)	RA9 (mg)
1	Ramipril	20	20	20	20	20	20	20	20	20
2	Croscarmellose sodium	10	10	10	10	10	10	10	10	10
3	Microcrystalline cellulose	67	67	67	67	67	67	67	67	67
4	yellow iron oxide	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
5	Aerosil-200	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
6	Megnesium stearate	2	2	2	2	2	2	2	2	2
	Total wt	100	100	100	100	100	100	100	100	100
7	Atrovastatin	40	40	40	40	40	40	40	40	40
8	HPMC K100	20	40	--	--	--	--	20	20	--
9	POLY0X WSR 303	--	--	20	40	--	--	--	20	20
10	SODIUM ALGINATE	--	--	--	--	20	40	20	--	20
11	Sodium bicarbonate	30	30	30	30	30	30	30	30	30
12	Microcrystalline Cellulose	140	120	140	120	140	120	120	120	120
13	PVP K-30	5	5	5	5	5	5	5	5	5
14	Iso Propyl Alchol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
15	Magnesium Stearate	3	3	3	3	3	3	3	3	3
16	Talc	2	2	2	2	2	2	2	2	2
	Total Wt	350	350	350	350	350	350	350	350	350

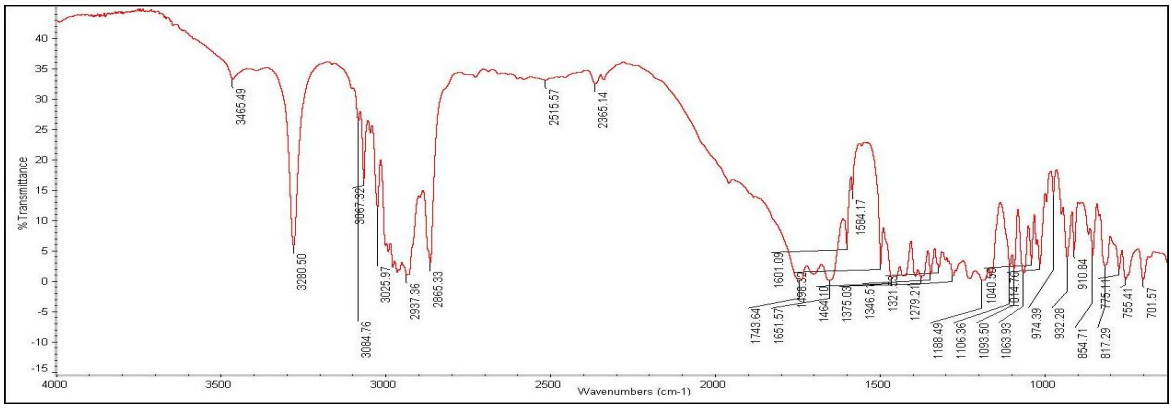

Fig 1: FT-IR graph for Ramipril Pure drug

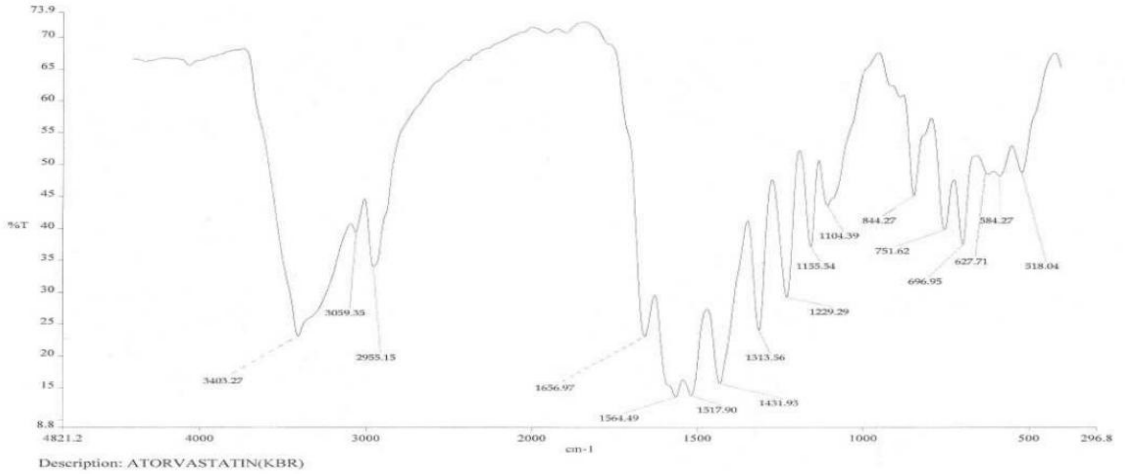

Fig 2: FT-IR graph for Atrovastatin Pure drug

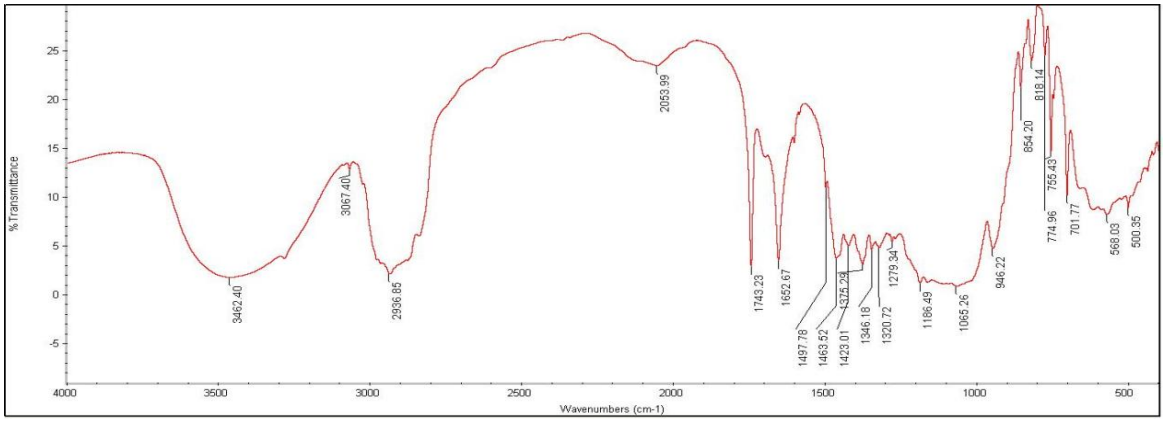

Fig 3: FT-IR graph for optimized formulation

Table 2: List of Micromeritic properties of Atrovastatin granules:

parameter	A1	A2	A3	A4	A5	A6	A7	A8	A9
Angle of repose	$26^0 35'$	$27^o 31'$	$28^o 33'$	$27^0 85'$	$26^0 62'$	$25^0 71'$	$27^o 35'$	$22^0 53'$	$25^0 62'$
Bulk density	0.46	0.61	0.47	0.60	0.46	0.55	0.63	0.42	0.57
Tapped density	0.51	0.69	0.52	0.64	0.51	0.63	0.66	0.53	0.63
%Compressibility	10.86	13.11	10.63	6.66	10.86	14.54	4.76	26.19	10.52
Hausner's ratio	1.10	1.13	1.10	1.06	1.10	1.14	1.047	1.15	1.10

Table 3 Post Compressional parameters of Bi layer tablets

parameter	RA 1	RA 2	RA 3	RA 4	RA 5	RA 6	RA 7	RA 8	RA 9
Weight variation	350±0.4	349±0.3	348±0.7	350±0.1	349±0.3	350±0.2	349±0.9	350±0.8	350±0.1
Thickness (mm)	2.5±0.4	2.6±0.4	2.3±0.4	2.6±0.4	2.5±0.4	2.5±0.3	2.5±0.2	2.5±0.1	2.5±0.2
Hardness (kg/cm^2)	6.9±1.4	6.4±1.2	6.2±1.2	6.9±0.9	6.4±1.9	6.1±1.7	6.2±1.5	6.3±1.6	6.2±1.4
Friability (%)	0.12±0.2	0.16±0.23	0.15±0.19	0.15±0.26	0.15±0.22	0.12±0.1	0.15±0.4	0.10±0.5	0.13±0.7
Floating lag time (Sec)	89	92	74	69	59	54	61	49	44
Assay of Ramipril	98.56	96.22	98.34	97.48	98.23	98.88	98.56	98.35	99.58
Assay of Atrovastatin	99.12	97.44	99.42	98.57	98.37	99.55	99.12	99.44	99.74

Table 4: In-vitro dissolution Profiles for Ramipril Immediate layer at 210 nm in 0.1N HCl

Time (Mins)	R1	R2	R3	R4	R5	R6
0	0	0	0	0	0	0
5	25.92	32.67	28.67	34.57	22.61	26.61
10	39.36	57.53	54.91	59.63	49.96	53.56
15	68.21	81.24	74.91	86.35	68.65	78.62
30	87.92	94.72	88.72	96.29	81.44	88.83
45	98.52	98.72	94.78	99.59	92.83	94.26

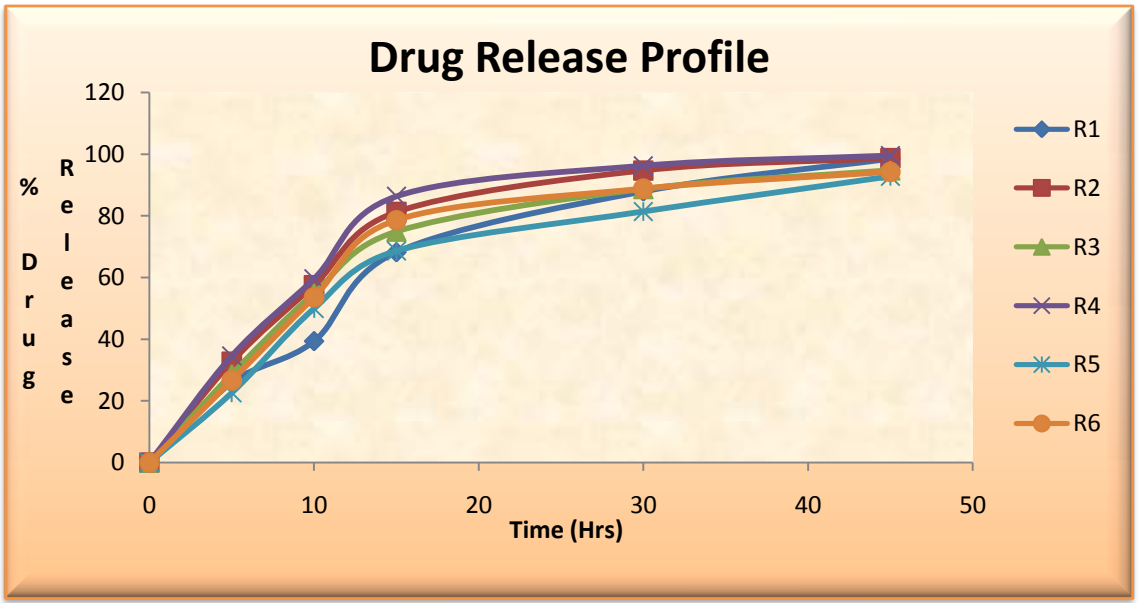

Fig 4: In-vitro dissolution Profiles for Ramipril Immediate layer at 210 nm in 0.1N HCl

Table 5: In-vitro dissolution Profiles for Atrovastatin Floating matrix layer in 0.1N HCl at 242 nm

Time (Hrs)	RA1	RA2	RA 3	RA 4	RA 5	RA 6	RA 7	RA 8	RA 9
0	0	0	0	0	0	0	0	0	0
1	36.28	31.54	38.41	30.61	42.57	35.61	28.43	26.67	23.41
2	52.51	48.51	57.53	50.24	62.63	56.56	45.54	51.67	46.89
4	74.44	66.92	72.73	69.62	79.35	76.62	62.65	60.24	59.72
6	87.38	83.84	87.49	79.83	90.29	87.83	78.37	73.72	68.47
10	98.72	94.58	96.58	93.26	98.21	95.26	89.47	86.61	84.21
12	99.39	99.66	99.82	99.49	99.73	99.87	98.28	98.72	97.29

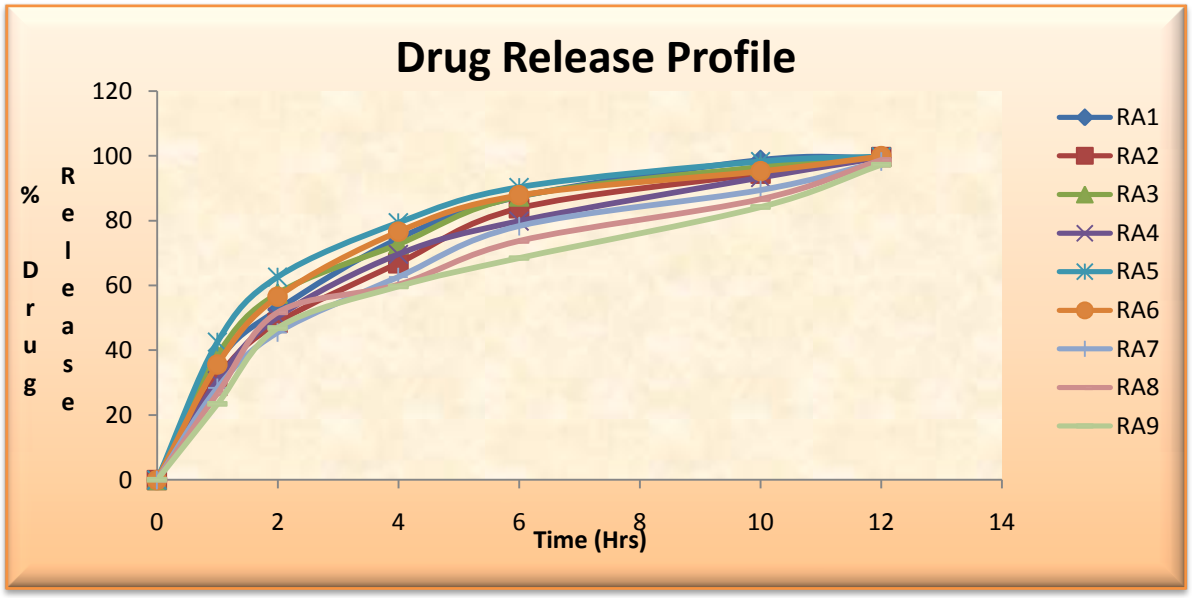

Fig 5: In-vitro dissolution Profiles for Atrovastatin Floating matrix layer in 0.1N HCl at 242 nm

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