FORMULATION AND EVALUATION OF GASTRO RETENTIVE FLOATING MICROBALLOONS OF IMIDAPRIL HCl

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ABSTRACT: The aim of the present study is to develop floating microballons of Imidapril HCl, an oral anti-hypertensive drug and also used in the treatment of chronic heart failure belongs to ACE inhibitor. It is rapidly and completely absorbed from the gastrointestinal tract but having low bioavailability due to first pass metabolism. Single unit dosage form of drug causes gastric irritation and when converted to multiple unit dosage like microballons causes no gastric irritation and maintains a constant drug concentration in the blood plasma for a longer period of time as drug is rapidly absorbed and eliminated from the body. Floating microballons were prepared by non-aqueous solvent evaporation method by using polymers like ethyl cellulose, HPMC and solvents like ethanol, dichloromethane and tween 80. Floating microballons are evaluated for drug entrapment efficiency, percentage yield, floating buoyancy, particle size, shape and surface morphology by SEM and *in vitro* drug release studies. Results show that as the concentration of polymer increases, the particle size, percentage yield, *in vitro* buoyancy and drug release from microballons varies. Percentage drug release at the end of 12 hrs was found to be 99.2 % for formulation F2. Microballons that are prepared by HPMC exhibited excellent drug release when compared with ethyl cellulose due hydrophilicity and viscosity. The SEM photographs revealed that the formulated floating Microballons were spherical in shape, smooth textured and having 500 µm sizes.

Key Words: Ethyl Cellulose, Floating Microballons, Hydroxy Propyl Methyl Cellulose (HPMC), Imidapril HCl.

I. INTRODUCTION

1.1. Gastro retentive drug delivery system

Gastro retentive drug delivery systems can remain in the stomach for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged the gastric retention improves bioavailability, reduces the drug waste (Chien YW ET AL., 1990). Their application can be advantageous in the case of drugs absorbed mainly from the upper part of GIT or unstable in the alkaline medium (Vyas, SP et al, 2002). GRDDS can be used as carriers for drugs having narrow absorption windows. Microballoons are solid spherical particles having central hollow space (Jain, NK et al, 2002). Floating microballons are non effervescent multiple unit systems, floated on gastric fluid by low density (Gattani YS et al, 2010).

1.1.1. Floating Microballoons

Floating microballoons are gastro-retentive drug delivery systems based on non-effervescent approach. Microballoons are in strict sense, spherical empty particles without core. These microballoons are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometer (Saniya Jawed et al, 2017). Solid biodegradable microballoons incorporating a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs (Ravindra A, 2006). Gastro-retentive floating microballons are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention, reduced fluctuations in plasma drug concentration (Lenkalapally Matsyagiri et al, 20139.

1.1.1.1.Advantages of floating Microballoons

- It has lower potential for dose dumping and it minimizes the risk of local irritation.
- It has shorter floating lag time and greater gastric retention.
- It distributes more uniformity of drug in GIT.
- It has very low particle size.
- Improve drug absorption.
- Decreasing dosing frequency and cost of the drug
- Avoiding first pass metabolism
- Better patient compliance by reducing repeated administration.
- It was also filled into hard gelatin capsules or compressed into tablets.

The purpose of this research work was to formulate and evaluate gastro retentive floating microballons of Abacavir sulphate using different concentrations of ethyl cellulose (Barhate1 Shashikant D et al, 2009). The floating microballons prepared by non-aqueous solvent evaporation technique. To study the effect of various factors like drug polymer ratio of different polymers on the parameters like percentage of floating buoyancy, drug entrapment efficiency and *in vitro drug* release study (Maryam Kouchak et al, 2007).

Abacavir sulphate is a nucleoside reverse transcriptase inhibitor with antiretroviral activity against HIV. It is administered alone or in combination therapy with other. It is well absorbed following oral administration. It's solubility in stomach pH is higher than intestinal pH (De Clercq E et al, 2002).

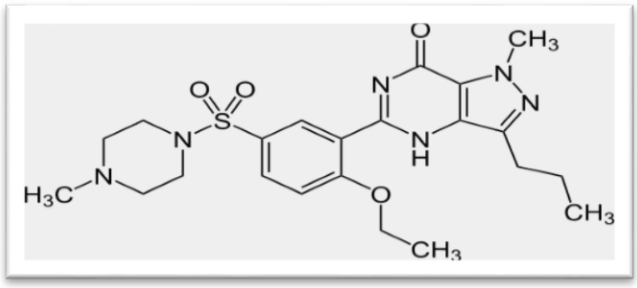

Figure 1.1: Structure of Imidapril HCl

II. MATERIALS AND METHODS

2.1. Materials

Imidapril HCl was obtained as a gift sample from Wintac Ltd., (Bangalore). HPMC (Rohm Pharma GmbH, Germany), Ethyl Cellulose were used as polymers. Light Liquid Paraffin (SD Fine Chemicals) served as dispersing medium. Dichloromethane (DCM), ethanol served as solvent mixture was also obtained from CDH, New Delhi. All other chemicals/reagents were of analytical grade and were used without further purification.

2.2. Methods

2.2.1. Drug-excipient compatibility study: FTIR spectroscopy

Compatibility studies were carried out to know the possible interactions between Imidapril HCl and excipients used in the formulation (Peeyush Bhardwaj et al, 2010).

2.2. 2Determination of absorption maximum (λ_{max}) of Imidapril HCl

From the UV spectrophotometric analysis it was conclude that the drug, Imidapril HCl showed a λ_{max} at 213 nm. Therefore the observed λ_{max} was used for further work to analyze the test samples.

2.2.3.Calibration curve

The calibration curves for Imidapril HCl in 0.1 N HCl, phosphate buffer pH 6.8, pH 7.8 was developed spectrophotometrically at 213 nm (Lenkalapally Matsyagiri et al 2013).

2.2.4.Preliminary Solubility studies Imidapril HCl

The equilibrium solubility of Imidapril HCl was measured in 0.1M hydrochloric acid (pH of 1.2), phosphate buffer of pH 6.8 and phosphate buffer of pH 7.8 respectively in order to determine its solubility. Excess amount of the drug were added to 50 mL-stoppered conical flasks (n=3). The flasks were shaken mechanically at 37°C±0.5°C for 24 hrs, in a horizontal shaker. After 2 days of equilibrium, aliquots were withdrawn and filtered (0.22 µm pore syringe filter). Then, the filtered samples were assayed by UV-spectrophotometer (Lenkalapally Matsyagiri et al, 2019).

2.2.5.Preparation of Floating Microballoons

Floating Microballoons containing Imidapril HCl as a core material were prepared by the non-aqueous solvent evaporation method11. Briefly, the polymer was dissolved in the 1:1 ratio of solvent mixture of dichloromethane and ethanol to this mixture drug was added. The solution of drug and polymer mixture was poured drop by drop into light liquid paraffin while being stirred at 600 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature12. The stirred was continued for two hours (2 hrs) to allow to solvents (Dichloromethane, Ethanol) to evaporate completely and the formed microspheres were collected by filtration. The microspheres were washed repeatedly with petroleum ether until free from oil. The collected microspheres were dried at room temperature for 24 hours then store in desiccators (Anand Panchakshari Gadad et al, 2016).

2.2.6.Evaluation of floating microballoons of Imidapril HCl

Physico chemical properties and floating properties of Imidapril HCl microballoons

Floating microballons were evaluated for physicochemical properties of all batches by measuring the angle of repose (Salomy Monica Diyya A et al 2015), and Carr's index (Ganesan.V et al, 2013), mean particle size (Senthilkumar SK et al, 2019) and floating properties like drug entrapment efficiency (Gholap SB et al, 2010), percentage yield [19], and floating buoyancy (Singh Bandana et al, 2010).

2.2.7.*In vitro* drug release studies

Drug release tests on each batch of the microballoons were carried out using a USP type-II dissolution rate test apparatus (DISSO 2000, Lab India). Microballoons equivalent to 300 mg of Imidapril HCl were spread over dissolution medium containing 900 ml of 0.1 N HCl (pH 1.2) and stirring speed of 75 rpm and temperature of 37 ± 0.5ºC. A 5ml quantity of the dissolution medium was sampled at predetermined time intervals, and fresh dissolution medium was simultaneously used to replenish to maintained sink conditions. The sample was filtered through filter disc and the filtrate was diluted with fresh dissolution medium if necessary. The samples were analyzed using UV-visible double beam spectrophotometer against an appropriate blank. From this percentage drug release was calculated and plotted against function of time to study the pattern of drug release (Navneet Kumar Verma et al, 2015).

III. RESULTS AND DISCUSSION

The formulations of Imidapril HCl loaded microballoons were prepared using different ratio of cellulose polymers (HPMC and Ethyl Cellulose) and solvent (Ethanol and Dichloromethane) by non- aqueous solvent evaporation technique.

Table 3.1: Formulation of Imidapril HCl floating Microballoons

Batch code	Drug (mg)	HPMC (mg)	EC (mg)	DCM: Ethanol	Dispersion medium (ml)
F1	10	10	-	1:1	250
F2	10	20	-	1:1	250
F3	10	30	-	1:1	250
F4	10	-	10	1:1	250
F5	10	-	20	1:1	250
F6	10	-	30	1:1	250

HPMC - Hydroxy Propyl Methyl Cellulose, **EC** - Ethyl Cellulose, **DCM** - Dichloro methane, **Dispersion medium** - Light Liquid Paraffin, **Speed** - 600 rpm.

Table 3.2: Data of standard Graph of Imidapril HCl in pH 1.2 (0.1 N HCl) at 213 nm

Sl. No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.149
3	4	0.261
4	6	0.373
5	8	0.476
6	10	0.591
7	12	0.689
8	14	0.781
9	16	0.891
10	18	0.991
11	20	1.099

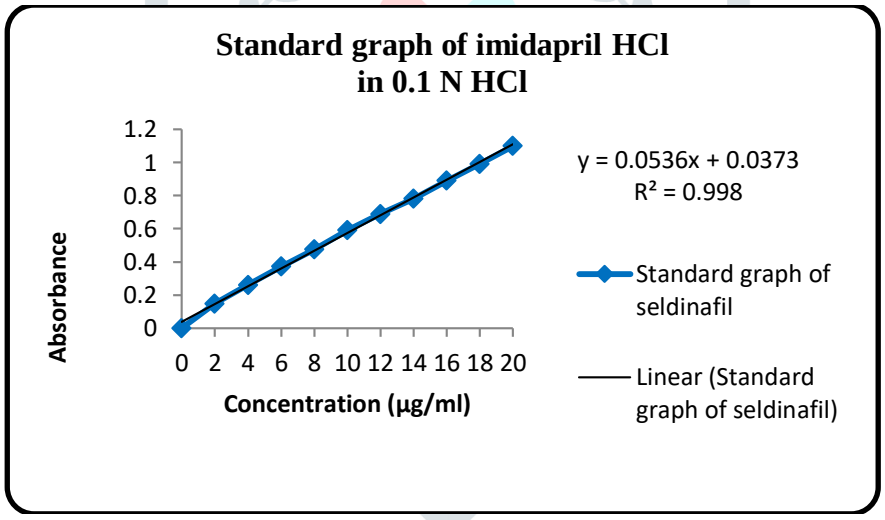

Figure 3.1: Standard Graph of Imidapril HCl in pH 1.2 (0.1 N HCl) at 213 nm

Table 3.3: Micromeritic properties of floating Microballoons

Batch Code	Angle of repose* (^{0})	Loose Bulk density* (gm/cm^3)	Tapped bulk density* (gm/cm^3)	Carr's Index* (%)	Hauser's Ratio*
F1	19º79 ± 2.40	2.769 ± 0.04	2.6 ± 0.004	11.7 ± 7.03	0.962 ± 0.03
F2	19º73 ± 1.20	5.0 ± 0.06	4.9 ± 0.012	14.0 ± 2.12	0.98 ± 0.02
F3	20º21 ± 0.60	3.0 ± 0.07	2.8 ± 0.008	12.0 ± 6.04	0.933 ± 0.01
F4	20º14 ± 2.31	2.8 ± 0.05	1.8 ± 0.057	11.8 ± 3.08	0.892 ± 0.01
F5	21º61 ± 0.40	2.0 ± 0.06	1.0 ± 0.014	11.0 ± 2.23	0.8 ± 0.02
F6	19º74 ± 3.52	1.0 ± 0.08	1.6 ± 0.023	11.6 ± 3.06	0.7 ± 0.03

*The mean ± SD, n = 3

Flow properties of batches were evaluated by measuring the angle of repose and Carr's index. In the evaluation of flow properties of dry solid ,the substances shows excellent flow properties of performance, when the angle of repose have the value less than 22^0 while when Carr's index has value below 14.0, the Hausner's ratio was below 1, no aid is needed for enhancing the flow properties of power. Thus, angle of repose and compressibility index are indicates of good flow properties of floating microspheres, showing no need for addition of

glidant to enhance flow properties. The better flow properties of Microballoons indicate that the microballoons produced were non-aggregated.

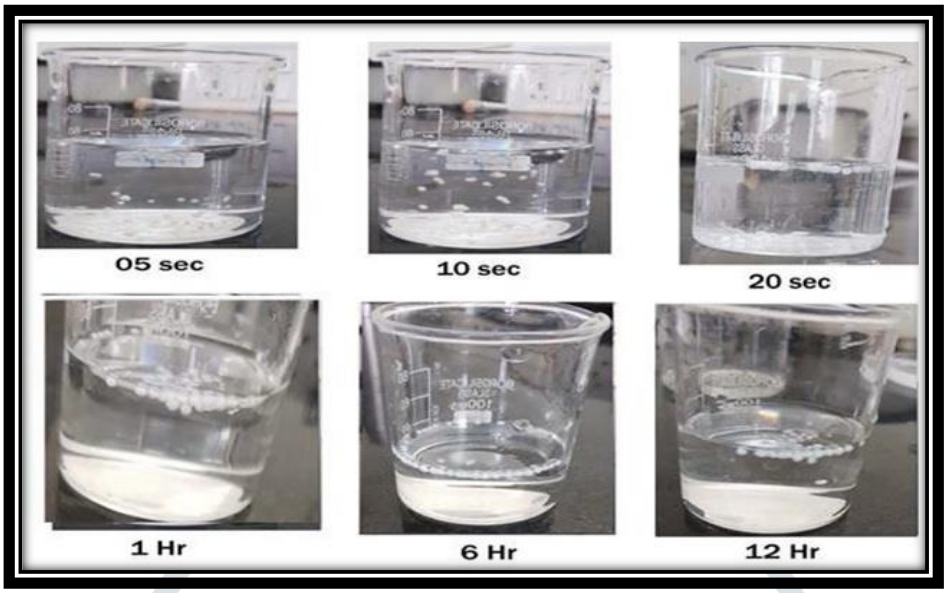

Figure 3.2: Floating microballons of optimized batch (F2)

Table 3.4: Floating properties Microballoons

Batch Code	Yield* (%)	Drug Entrapment Efficient* (%)	Percentage Floating Buoyancy*
F1	71.7 ± 4.68	92.1 ± 3.75	94.8 ± 1.84
F2	89.5± 4.72	94.5 ± 4.62	96.48 ± 3.64
F3	80.8 ± 3.81	96.84 ± 3.84	92.10 ± 2.82
F4	94.8 ± 1.64	98.28 ± 4.65	93.54 ± 3.31
F5	89.7 ± 4.38	97.7 ± 5.45	94.6 ± 4.57
F6	85.6 ± 3.62	99.24 ± 4.51	94.2 ± 5.73

*The mean ± SD, n = 3

3.1.Characteristics of floating microballoons of Imidapril HCl

The prepared floating microballons were evaluated for various parameters such as Particle shape, percentage of yield, drug entrapment efficiency, percentage of buoyancy; *in vitro* drug release studies and its results were given below.

3.1.1.Percentage yield of Microballoons

The yields of the individual formulations were calculated and a bar graph represents the yield of various formulations. The yield was high for the F4 amounting of 94.8 % and the yield of F1 was low amount among all formulations to 71.7 %.

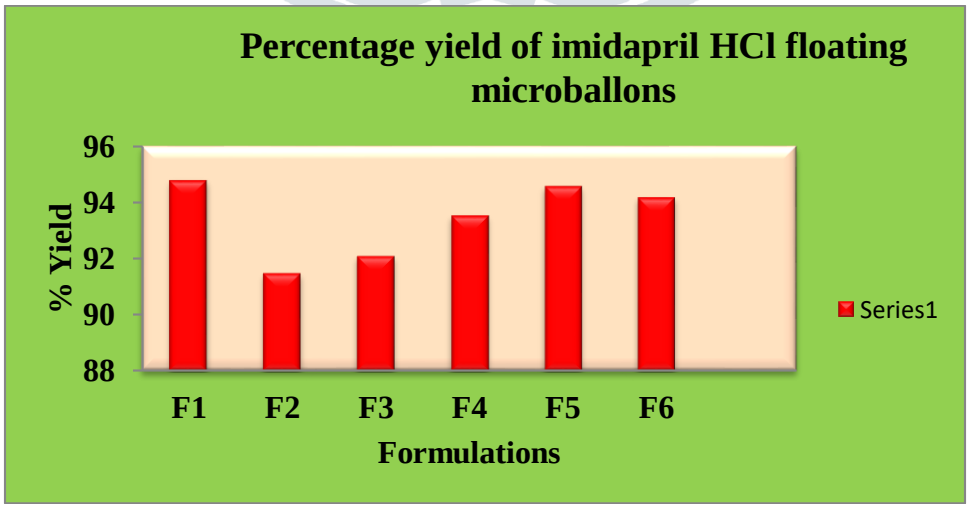

Figure 3.3: Percentage yield of F1-F6 formulations

3.1.2.Drug entrapment efficiency (DEE)

The drug entrapment efficiency was higher for F6 formulation (99.24 %) and it was lower for F1 (92.1%). The results obtained clearly indicated that the drug entrapment efficiency increased as the drug to polymer ratio increased. This may be attributed to the availability of more coat material per drug molecule.

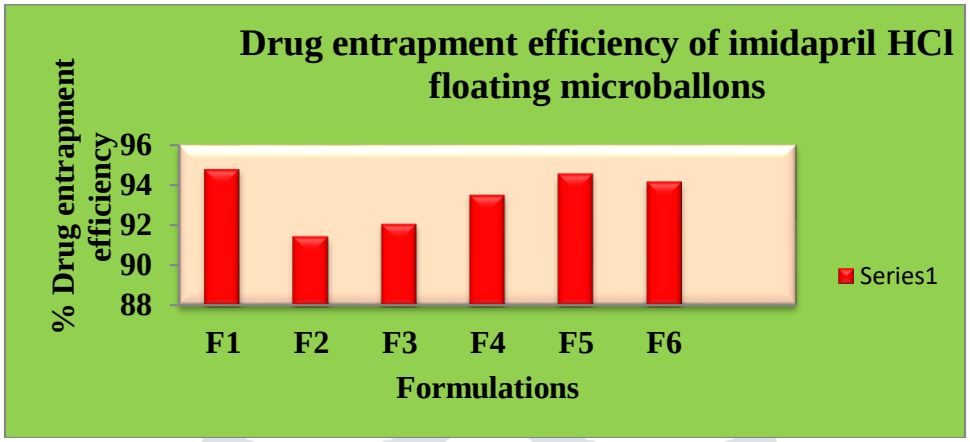

Figure 3.4: Drug entrapment efficiency of F1-F6 formulations

3.1.3.Percentage of floating buoyancy

The *in vitro* floating ability of formulated floating microspheres were evaluated. The floating ability was higher for F2 (96.48 %) and it was lower for F3 (92.10 %). The floating ability was decreased with increase the particle size by increasing viscosity of polymer due to as the size was small, the mass to volume ratio (density) may be more leading to early settling of the microsperes. Here using ethyl cellulose is low density polymer as floating on dissolution medium during the *in vitro* drug release study.

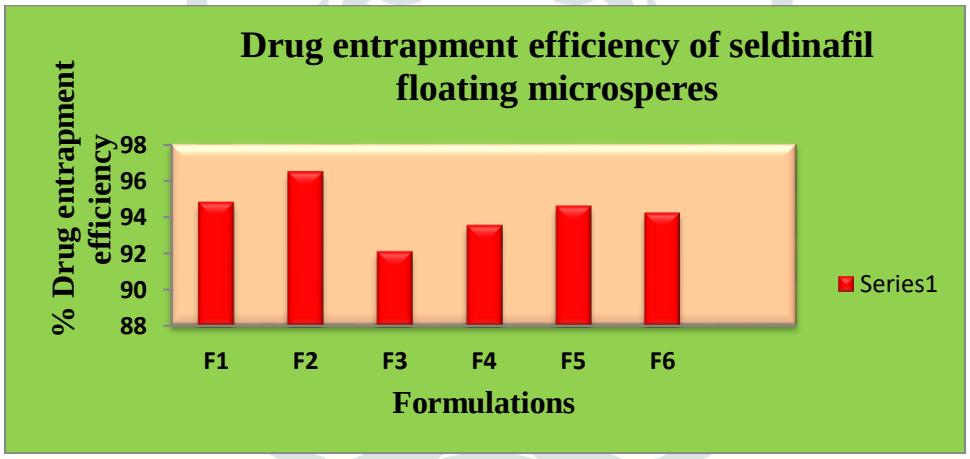

Figure 3.5: Percentage of floating buoyancy of F1-F6 formulations

Table 3.5: *In vitro* drug release of Imidapril HCl in pH 1.2

Time (hrs)	F1	F2	F3	F4	F5	F6
0.5	32.48	29.77	28.95	40.68	30.31	27.77
1	38.4	33.56	30.18	48.82	34.91	30.62
1.30	43.43	37.28	35.85	56.53	38.9	34.1
2	45.78	41.92	38.17	62.31	45.91	42.3
3	58.91	49.9	40.21	70.14	49.02	46.34
4	60.83	56.72	48.19	83.08	53.97	49.2
6	68.97	60.9	50.77	98.48	59.05	50.34
8	75.34	68.73	55.37	-	64.33	52.75
10	88.2	79.07	65.79	-	75.06	61.9
11	90.31	82	76.45	-	79	64
12	-	99.2	80.21	-	82	70

3.1.4.*In vitro* drug release studies

The results of the *in vitro* drug release studies were given in the tables11, and figures 23, 24. From the obtained dissolution data following inferences were made. The drug release of Imidapril HCl by using HPMC is 28.95 - 99.2 % at the end of 12 hrs, and using ethyl cellulose is 27.77- 98.48 % at the end of 12 hrs. This may be due to the more effective of viscosity of HPMC for sustained release of drug so finally

the maximum drug release is 99.2 % at the end of 12 hr and the all formulations should be float on the dissolution medium during the dissolution study so as it is consider as optimized batch (F2) when compared with all formulations of the microspheres. The percentage of drug release for F1 formulation was up to 11 hrs, the percentage of drug release for F4 formulation was up to 6 hrs. The volume of the dissolution media (900 ml) to which the microspheres were exposed could be one of the factor influencing the faster release of the drug. On increasing the drug to polymer ratio, the drug release could be prolonged.

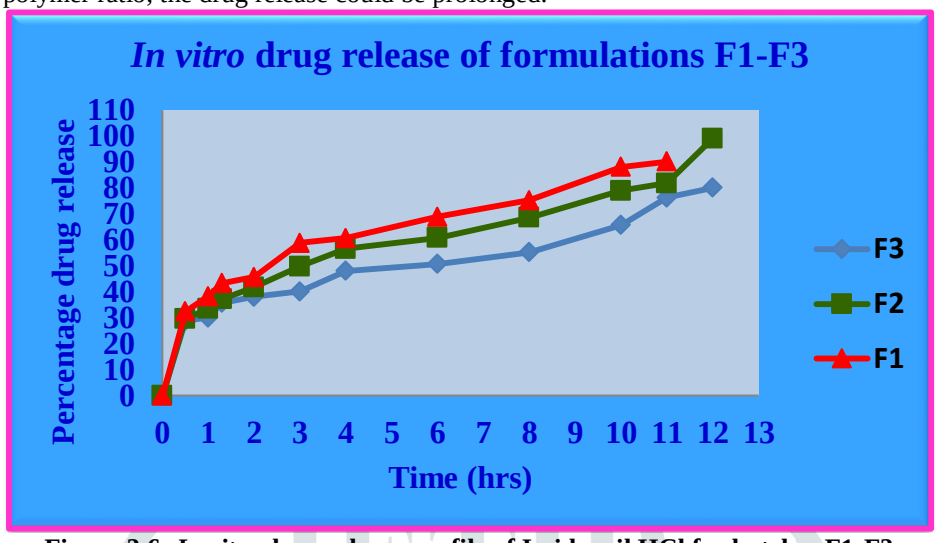

Figure 3.6: *In vitro* drug release profile of Imidapril HCl for batches F1-F3

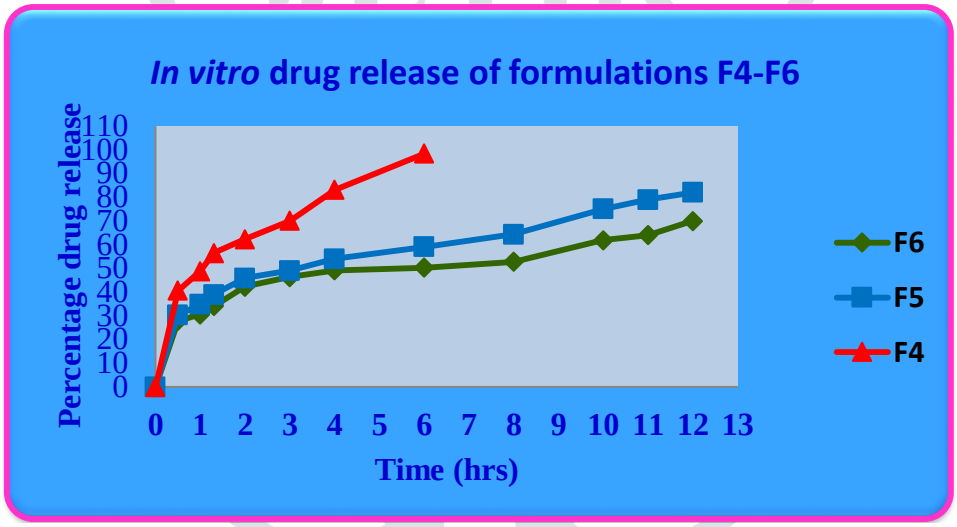

Figure 3.7: *In vitro* drug release profile of Imidapril HCl for batches F4-F6

IV. CONCLUSION

From the results it can be concluded that the drug release from the floating microballons matrix was sustained by the polymer. When the polymer proportion in the formulation was increased with increased drug loading, drug release was decreased significantly. It was also observed that the release of drug was increased significantly with increasing polymer concentration. The drug release of Imidapril HCl by using HPMC is 28.95 - 99.2 %, and using ethyl cellulose is 27.77- 98.48 % at the end of 12 hrs. This may be due to the more effective of viscosity of HPMC for sustained release of drug so finally the maximum drug release is 99.2 % so as it is consider as optimized batch (F2) when compared with all formulations of the Microballoons. All formulations should be float on the dissolution medium during the dissolution study.

V. Acknowledgments

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