



A Formulation And Evaluation Of Gastro Retentive Floating Tablets Of Pindolol

KVSS ANNAPURNA¹, D.S.PHANI SURYA², M.ASHA JYOTHI², N.VENU KUMARI²

1. Asst.professor, Department of Pharmacy, Lydia college of Pharmacy,Nh-5, Ethakota,East Godavari, Ravulapalem, Andhra Pradesh 533238.
2. Department of Pharmacy, Lydia college of Pharmacy,Nh-5, Ethakota,East Godavari, Ravulapalem, Andhra Pradesh 533238.

INTRODUCTION:

BIOLOGICAL ASPECTS OF GRDFs:

Role of GI tract:

Stomach

The stomach is a J-shaped organ located in the upper left-hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hypochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very, little absorption takes place from the stomach. It provides a barrier to the delivery of drugs to small intestine.

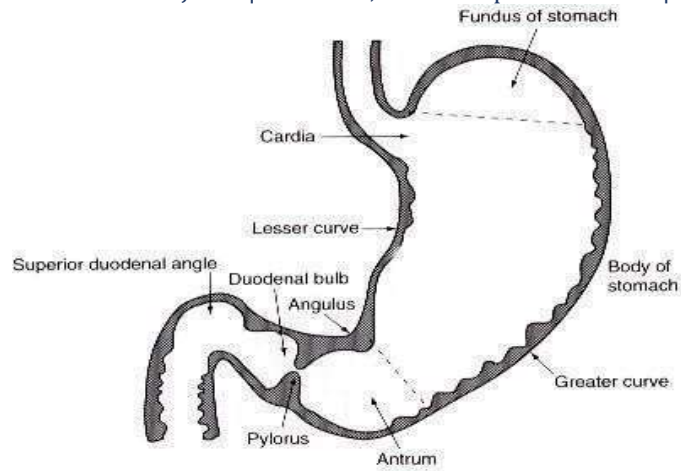


Fig 1.1: Anatomy of Stomach

The stomach is divided into three anatomical regions. I) Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consists of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states.

The GI tract is always in a state of continuous motility. There are two modes of motility pattern. The digestive mode and inter digestive mode. In case of fasted state an inter digestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as inter digestive my electric cycle.

Phase I	:	Period of no contraction.
Phase II	:	Period of intermittent contraction.
Phase III	:	Period of regular contractions at the maximal frequency that migrate distally.
Phase IV	:	Period of transition between phase III and phase I.

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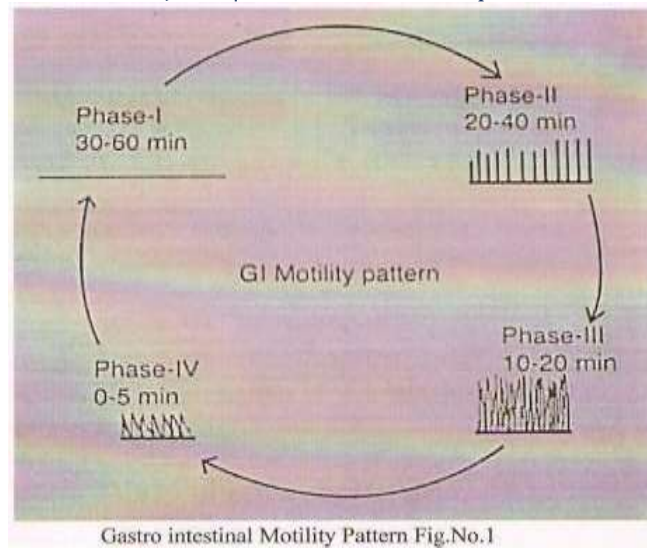


Fig1.2: Gastro intestinal motility pattern

PHASE I: The quiescent period, lasts from 30 to 60 mins and is characterized by a lack of secretory, electrical and contractile activity.

PHASE II: Exhibits intermittent activity for 20-40 min, during which the contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of phase II and throughout phase III.

Phase III: Has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the housekeeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle.

PHASE IV: Is the transition period of 0-5 mins between Phase III & I.

1.2 REQUIREMENTS FOR GASTRO RETENTION

From the discussion of the physiological factors in the stomach, to achieve gastro retention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease.

1.3 APPROACHES TO GASTRIC RETENTION

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: Floating systems, Bio adhesive systems, swelling and expanding systems, High density systems, Modified systems etc.

Fig1.3: Classification of gastro retentive drug delivery system



1.3.1 Buoyant/ Floating Systems:

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non- effervescent and effervescent systems.

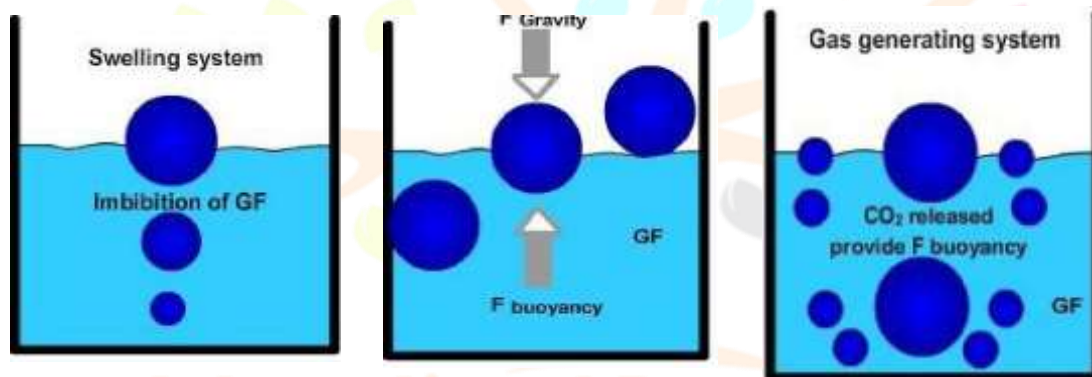


Fig 1.4: Mechanism of floating system

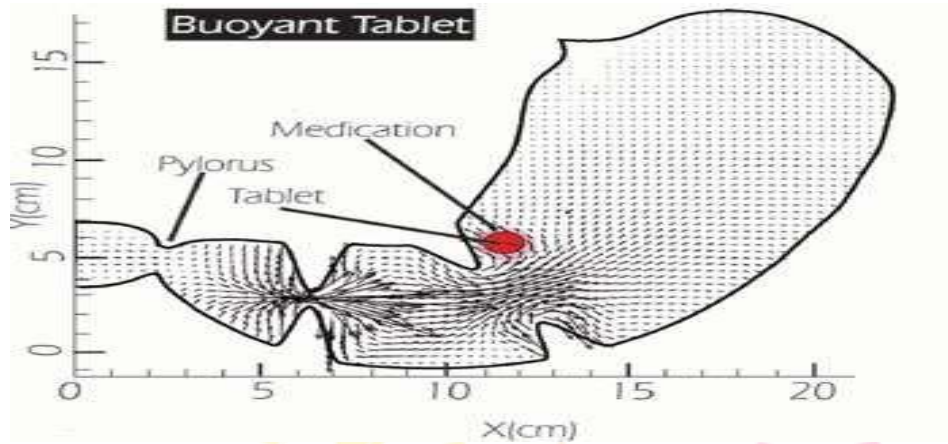


Fig 1.5: Graphic of Buoyant tablet, which is less dense than the stomach fluid and therefore remains in the fundus.

1.3.2 Bio/Muco-adhesive Systems:

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery systems in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three broad categories: –

1. Hydration-mediated adhesion.
2. Bonding-mediated adhesion.

3. Receptor-mediated adhesion.

1.3.3 Swelling and Expanding Systems:

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “*plug type system*”, since they exhibit the tendency to remain lodged at the pyloric sphincter if they exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for a prolonged period.

1.3.4 High Density Systems:

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of $2.6\text{-}2.8 \text{ g/cm}^3$ acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulfate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of the stomach as shown in Fig. 6.

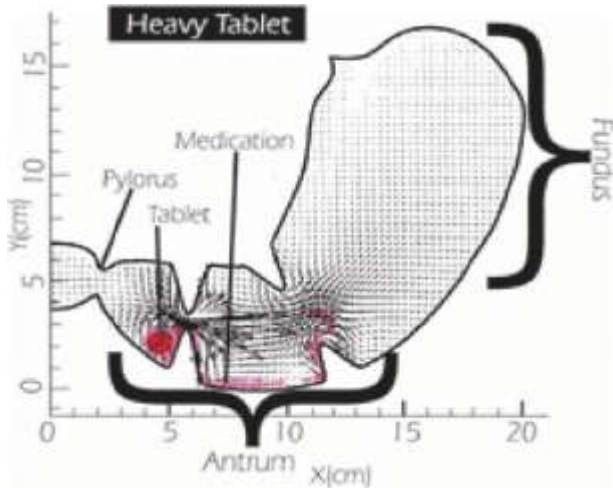


Fig1.6: Graphic of heavy tablet, which is denser than the stomach fluid and therefore sinks to the antrum.

1. IN-VITRO BUOYANCY STUDIES:

The in vitro buoyancy was determined by floating lag time and total floating time as per the method described by Roy.*et.al*. The tablets (N=3) were placed in a thousand ml of 0.01N HCl in USB Type II dissolution apparatus ($37 \pm 0.5^{\circ}\text{C}$, 50 rpm).

2. IN VITRO DISSOLUTION TESTING:

The in vitro dissolution studies were performed using USP type II dissolution apparatus at 50 rpm. Dissolution test was carried out for a total period of 1hr using water and other respectable dissolution liquids (900 ml) as dissolution medium at $37 \pm 0.5^{\circ}\text{c}$. An aliquot (5ml) sample was withdrawn at specific time intervals and replaced with fresh medium to maintain a constant volume. The samples were filtered, and analyzed by UV spectrophotometer at respective wavelengths. The concentration was calculated using standard calibration curve



Figure: 3.2 Dissolution apparatus

TABLE 3.3 Different type of Dissolution apparatus

S.NO	Apparatus	Dosage forms	Medium (ml)	Rotating speed (RPM)	Reciprocating amplitude
1	Basket	Capsules, tablets	500-4000	25-50	Not activity
2	Paddle	Capsules, tablets	500-4000	25-150	Not activity
3	cylinder	Capsules, tablets, suspensions, granulates	250		9.9 to 10%
4	Flow through cell	Capsules, Tablets	Up to 3 lit	Not activity 25-150	Not activity
5	Paddle over disc	Transdermal, patches	500-4000	25-150	Not activity
6	Reciprocating cylinder	Non disintegrating tablets	Up to 3 lit	Not activity	Not activity

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3. KINETIC MODELING OF DRUG RELEASE:

To analyze the mechanism of drug release from the floating tablets, the *in vitro* dissolution data of the formulations were fitted to the zero order, first order, Higuchi model and Korsmeyer- Peppas model as per the method described by Dash *et al.*

Kinetic Studies:

Zero Order Release Equation: The equation for zero order release is

$$Q_t = Q_0 + K_0 t$$

Where, Q_0 = initial amount of drug, Q_t = cumulative amount of drug release at time “t”, K_0 = zero order release constant, t = time in hours

It describes the systems where the drug release rate is independent of its concentration of the dissolved substance.

A graph is plotted between the time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives a straight line.

A.First Order Release Equation: The first order release equation is

$$\text{Log } Q_t = \text{Log } Q_0 + Kt / 2.303$$

Where, Q_0 = initial amount of drug, Q_t = cumulative amount of drug release at time “t”, K = first order release constant, t = time in hours.

Here, the drug release rate depends on its concentration

A graph is plotted between the time taken on x-axis and the log cumulative percentage of drug remaining to be released on y-axis and it gives a straight line.

Floating Time of Pindolol



Figure 4.6: Floating of tablet after 45 sec hrs



Figure 4.7: Floating of tablet after 10 hrs

Dissolution Profile Studies:

All formulations were subjected to dissolution profile studies in 0.1N HCL as per the following conditions:

Apparatus: USP Type II Dissolution Medium: 900 ml, 0.1N HCL RPM: 50 rpm

Temperature: $37^{\circ} \pm 5^{\circ}\text{C}$

Time points (hrs): 1,2,4,6,8,10.

5 ml of sample was withdrawn at each time point, suitably diluted and absorbance was measured at 219nm. The % drug dissolved was calculated by The 5

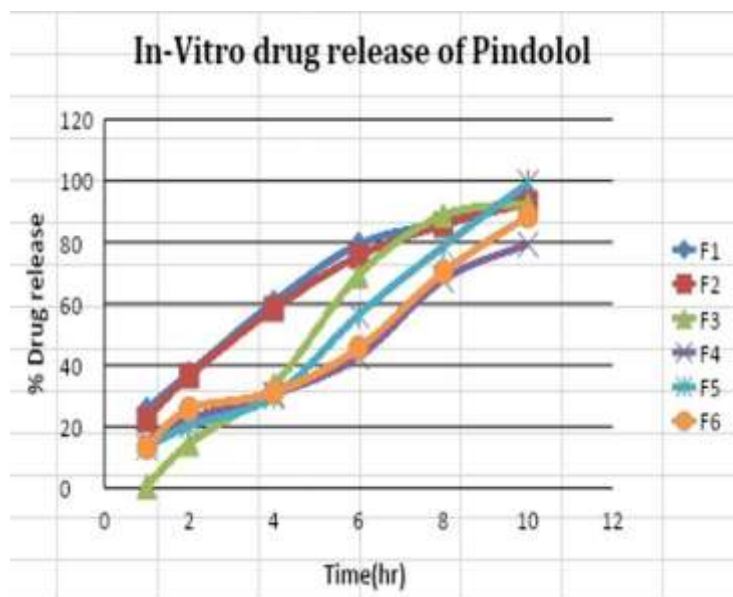
ml sample withdrawn was replaced with fresh 5 ml 0.1NHCL. The mean % drug dissolved (mean of n= 6 samples) for all formulations is recorded in Tables 7.5.

In-vitro drug release:

The tablets were evaluated for in-vitro drug release and the cumulative %drug release was calculated. The formulations (F1, F3, F5, F7, F8 & F9) containing combination of polymers like NaHCO₃, HPMC K4M, in the different ratios F1-1:2, F3- 1:3, F5-1:4, 1:1, and The formulation (F2, F4, F6,)containing combination of polymers like NaHCO₃, HPMC K100M in the ratio of F2-1:2, F4- 1:3, F61:4, and F9-1:2 release the drug before residence time. The formulations F8 in 1:1ratio NaHCO₃, HPMC K4M and NaHCO₃, HPMC K100M shows the release of drug in 69.3.The formulations F5 containing combination of polymers like NaHCO₃, HPMC K4M in the ratio of 1:4 release 99.3% of drug, 2:1 release 96.5% of drug, 1.5:1.5 release 98.72% of drug at 10 hours. The results were shown in the tables 6.5 and the graph plot between time and %drug release was shown in 7.3

Table.4.5 In-vitro drug release of Pindolol floating tablets

Time (hr)	F1	F2	F3	F4	F5	F6
1	25.6	22.3	10.8	12.8	15.2	13.2
2	37.2	36.4	14.5	22.3	20.3	25.6
4	60.8	58.2	33.6	30.5	29.7	31.2
6	79.4	75.4	69.2	42.8	56.4	45.8
8	95.3	92.8	92.5	67.9	78.5	70.3
10	-	-	-	79.2	99.3	88.5

Figure 4.8 Graph for In-vitro Drug release of Pindolol**Permeation study:****In-vitro drug permeation:**

The optimized Formulation F5 also evaluated for in-vitro drug permeation and the cumulative percentage drug permeated was calculated. The optimized formulation have shown 99.3% of drug permeation in 10hr, The result of in-vitro drug permeation profile is shown in table 7.6

The drug permeation data were analyzed for the rate and mechanism of drug permeation using Zero order, First order, Higuchi and Peppas models. The r^2 values for Zero order, First order, Higuchi and Peppas are shown in table and Figure 7.9 to 7.12

Table 4.6 In-vitro Kinetic Release of Pindolol

Formulation code	Zero order	First order	Higuchi model	Korsmeyer peppas	
F5	R2	R2	R2	R2	N
	0.98	0.70	0.89	0.94	0.8

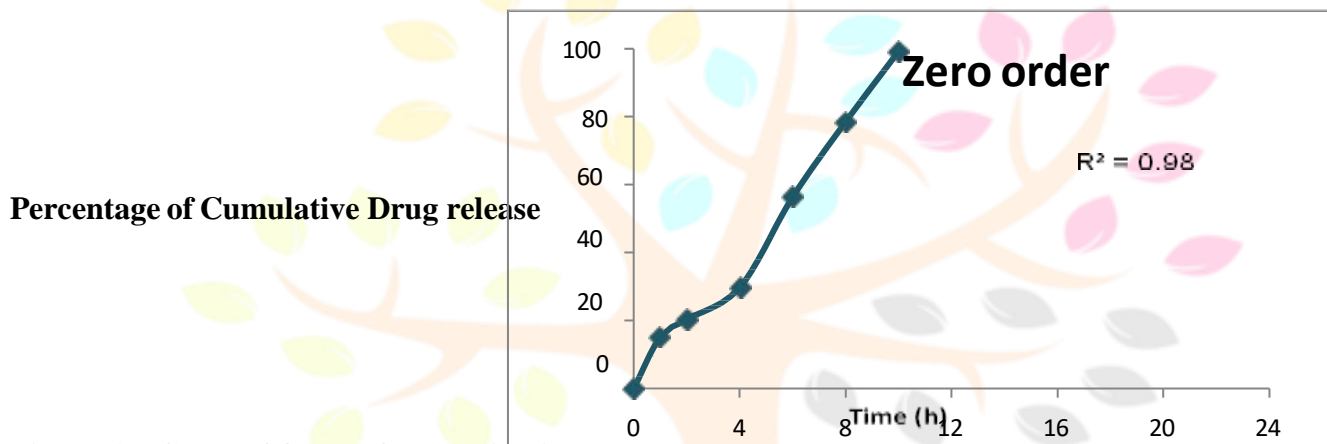
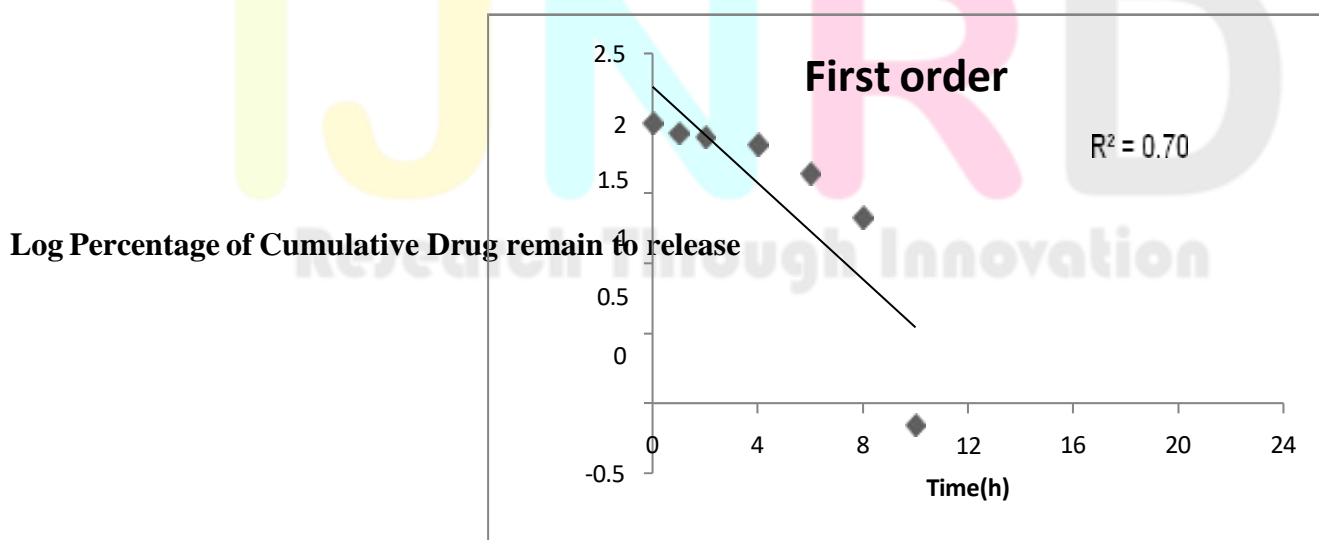


Figure 4.9 Graph Of Zero Order Kinetics

Figure 4.10 Graph Of First Order Kinetics



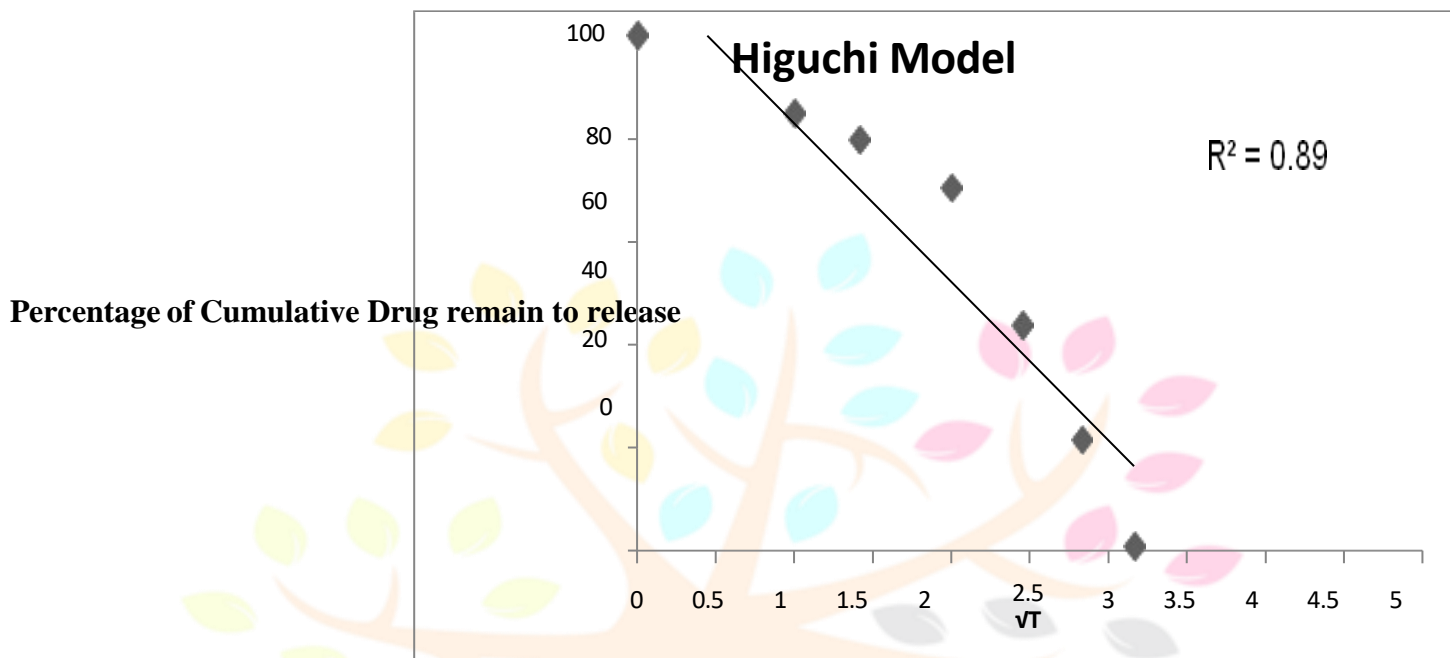
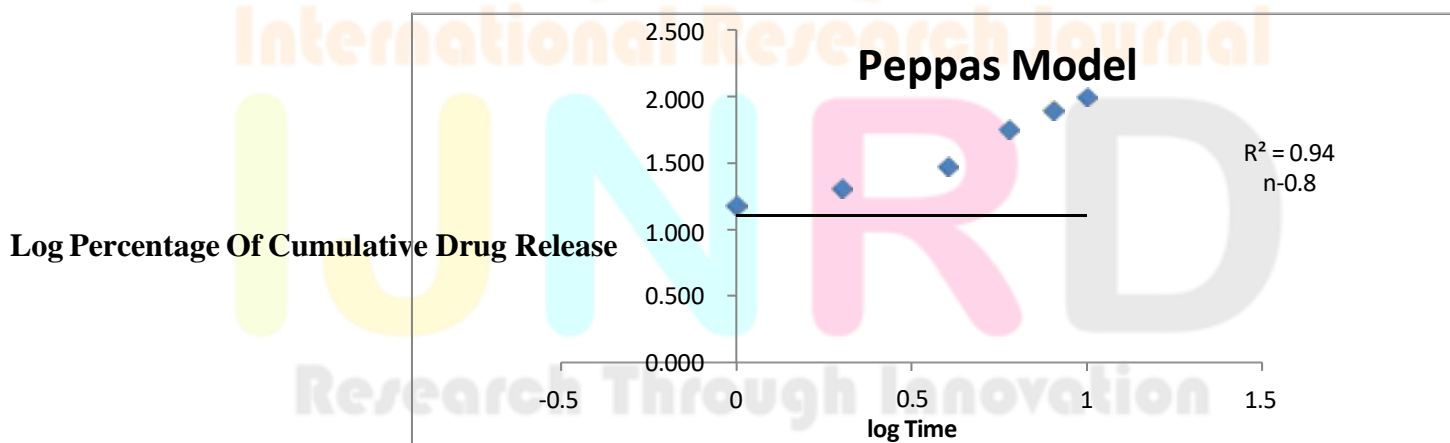


Figure 4.11 Graph Of Higuchi Model



5.1 Figure 4.12 Graph Of Poppas Model

CONCLUSION:

The literature survey on the Floating drug delivery system reveals that this drug delivery system gives promising results for the drugs which have low molecular weight, low dose and undergo extensive first-pass metabolism. Pindolol is an anti- hypertensive agent. Good biphasic solubility and extensive first-pass metabolism, which makes it a very suitable drug candidate for incorporating it into the floating drug delivery

system.

Literature surveys on the HPMC, Sodium bicarbonate and DCP polymers have strongly suggested that they have total floating time and log time properties. The purity of the drug was confirmed by the FT-IR and DSC. There was no any interaction between the drug and polymers.

The floating tablets of Pindolol were prepared by wet granulation method based on an effervescent approach. HPMC and DCP were used as the polymers and sodium bicarbonate was used as a gas generating approach. It was seen that changing the concentration of polymers (HPMC K4M and DCP) delayed the drug release profile. However, there was no effect on drug release profile upon changing the viscosity grades of HPMC (K4M to K100M). Increasing the amount of HPMC K4M and sodium bicarbonate increased the floating lag time. But the amount of sodium bicarbonate did not have any effect on the total floating time of formulations. Changing the concentrations of sodium bicarbonate and citric acid had no significant effect on drug release profile. Hence from the present study, it can be concluded that hypromellose (HPMC K4M) and DCP in appropriate concentration can be used to develop controlled release floating tablets of Pindolol by incorporating appropriate concentration of sodium bicarbonate for gas generation. Such systems can remain buoyant for more than 10 hours along with the sustained drug release for the same duration.

Results of in vitro permeation study have suggested that the selected tablets (F5) followed zero order kinetics and the drug transport mechanism was found to be non-Fickian diffusion. It has shown good in vitro drug permeation.

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