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ORIGINAL ARTICLE **OPEN ACCESS**

A Study on Development and Evaluation of Floating Drug Delivery System in Non-Selective Adrenergic in Beta – Antagonists

Sunil Mekala[1], Ch.Suresh[2], M.Saranya Vasavi Kumari[2], Ch Lokeswari[2], V Lakshmi Prasanna Devi[2], B Koteswaramma[2], N Mahima Kumari[2]

1. Professor, Department of Pharmaceutics, Vishwabharathi College of Pharmaceutical Sciences, Perecherla, Guntur, Andhra Pradesh, Pin-522601.

2. Department of Pharmaceutics, Vishwabharathi College of Pharmaceutical Sciences, Perecherla, Guntur, Andhra Pradesh, Pin-522601.

ABSTRACT

Pindolol is a Non-Selective Beta Blocker (Adrenergic Beta -Antagonists) used in treating Hypertension. The purpose of this study was to develop a Sustained release tablet for pindolol because of its short biological half-life. Different formulas of 20mg pindolol were prepared as Oral floating matrix tablets by wet granulation technique, using polymers such as Hydroxy Propyl Methyl Cellulose (HPMC K4M, K100M), Poly Vinyl Pyrrolidone (PVP), alone or in combination and other standard excipients. Sodium bicarbonate as gas - generating agent. Floating Drug Delivery System (FDDS) with a view to improve the Bioavailability, patient compliance and reduce the side effects. The prepared tablets were evaluated for Hardness, Friability, Floating lag time, and Total floating time, in vitro drug release studies. The data obtained in the in vitro drug release studies were fitted into various kinetic equations like Zero order, Kore- Meyer peppas equation. Formulation F5 shows good floating lag time (10hrs), Good in vitro drug release. The kinetic data shows the values were best fit for Kores Meyer peppas equation, the 'n' value was found to be 0.8, so it follows non-fickion transport of the drug from tablets was confirmed.

***Key Words**: Pindolol,Gas-generating agent, FDDS, In-vitro Drug Release, Non-fickion transport.*

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INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine) [1]. The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS).

MATERIAL AND METHODS

FT-IRSPECTROPHOTOMETRIC ANALYSIS:

The samples of Pindolol prepared in the form of KBr pellets and subjected for scanning from 4000 cm^{-1} to 400 cm^{-1} using FT- IR spectrophotometer (FT-IR-8400, Shimadzu, Japan).

UV PECTROSCOPY:

The first step is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in ultraviolet wavelengths (190-390 nm), since they are generally aromatic or contain double bonds. 100 mg of Pindolol was accurately weighed on an electronic balance and dissolvedin100 ml alcohol. Alcohol is UV-transparent and a good solvent for most polar drugs. Since this is anhydrous, potential hydrolysis is prevented and can serve as a stock solution. 1 ml of this solution was diluted with 100 ml of HCL, NaOH, phosphate buffer and methanol and scanned on a UVscanner 219 nm. The maxima obtained in the graph were considered as λ_{max} for the Pindolol at respective buffers.

STANDARD CALIBRATION CURVE FOR PINDOLOL BY 0.1N HCL :

100 mg of was dissolved in small amount of pindolol by 0.1N HCland volume was made up to 100ml using the same. From the stock solution serial dilutions were done to obtain solutions in the conc. Ranging from 0, 4, 8, 12, 16 and 20 µg/ml. The absorbance of the solution was measured at 219 nm using UV-visible spectrophotometer. A graph of conc. V/s absorbance was plotted.

WET GRANULATION PROCESS:

Different Tablet formulations (F1-F9) were prepared by Wet Granulation Technique. Required quantities of Pindolol, (Hydroxy propyl methyl cellulose) HPMCK4M, HPMCK100M, Sodium bicarbonate, Di calcium phosphate was mixed uniformly and passed through 40 no Mesh. Add Dissolved with poly vinyl pyrolidone (PVP) in alcohol as granulating fluid mixer to form a damp mass. This damp mass is passed through mesh no 8 to obtain granules.The granules were dried in Oven and later passed through mesh no 16. Talc and Magnesium sterate was added as a Anti fixenal agent to the uniformly sized granules these were compressed using a compressed machine [2-6].

FORMULATION DESIGN:

Table No 1: Formulation Design

Ingredients (mg/tab)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pindolol	20	20	20	20	20	20	20	20	20
HPMC K4M	40	-	60	-	80	-	20	30	40
HPMCK 100M	-	40	-	60	-	80	20	30	40
NaHCO3	20	20	20	20	20	20	20	20	20
Citric acid	8	8	8	8	8	8	8	8	8
PVP in alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
DCP	106	106	86	86	66	66	106	86	66
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200	200

TESTING PROCEDURE FOR POWDERS:

ANGLE OF REPOSE:

The frictional force within the powders can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powders are added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The powders were carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

The angle of repose (θ) was calculated using the following formula

$$\mathbf{Tan\ \theta = h/r}$$

Where; θ = Angle of repose, h = Height of the cone in cms, r = Radius of the cone base in cms

Values for angle of repose ≤ 30^0 usually indicate a free flowing material and angles ≥ 40^0 suggest a poorly flowing material. 25- 30 showing excellent flow properties,31-35 showing good flow properties,36-40 showing fair flow properties,41-45 showing passable flow properties

2.BULK DENSITY:

Density is defined as weight per unit volume. Bulk density (D_b), is defined as the mass of the powders divided by the bulk volume and is expressed as gm/cm^3. The bulk density of the powders primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

The bulk density and tapped density were determined by using bulk density apparatus. Apparent bulk density was determined by pouring the powders into a graduated cylinder. The bulk volume (V_b) and weight of the granules (M) was determined. The bulk density was calculated using the formula.

$D_b = M/V_b$

Where, M is the mass of the powders and $V_b$is bulk volume of the granules.

3.TAPPED DENSITY:

The measuring cylinder containing a known mass of powders was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the powders was measured. The tapped density was calculated using the formula [7].

$D_t = M/V_t$

Where, M is the mass of the powders,$V_t$is tapped volume of the powder

COMPRESSIBILITY INDEX:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder/ granules to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. In a free-flowing powder/ granules, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poor flowing materials, there are frequently greater interparticulate interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:+

CI (%) = [(Tapped density – Bulk density) / Tapped density] x100

The value below 15% indicates a powder/granules which usually gives rise to good flow characteristics, where as above 25% indicates poor flowability. 1-10 showing excellent flow properties, 11-15 showing good flow properties, 16-20 showing fair to passable, 21-25 showing passable.

5. HAUSNER'S RATIO :

Hausner's ratio is an indirect index of ease of powder/granule flow. It is calculated by the following formula.

Hausner's Ratio=Tapped density (ρ_t) / Bulk density (ρ_b)

Where ρ_t is the tapped density and ρ_b is the bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones, between 1.25 to 1.5 showing moderate flow properties and more than 1.5 poor flow [8, 9].

TESTING PROCEDURE FOR TABLETS:

WEIGHT VARIATION:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula[95].

% Deviation = (Individual weight – Average weight / Average weight) × 100

TABLE 2: Specifications of % weight variation allowed in tablets as per BP.

S. No	Average Weight of tablet	% Deviation
1.	80 mg or less	10
2	More than 80 but less than 250 mg	7.5
3	250 or more	5

THICKNESS:

Tablet thickness is an important characteristic in reproducing appearance. Twenty tablets were taken and their thickness was recorded using vernier caliper and the average thickness is calculated.

FRIABILITY:

It is measured of mechanical strength of tablets. Roche friabilator (Electrolab, Mumbai, India) was used to determine the friability by following procedure. Pre weighed tablets (20 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were reweighed [6].

Loss in the weight of tablet is the measure of friability and is expressed in percentage by using below equation.

% Friability = [(W_1 – W_2) / W_1] × 100

Where, W_1=Initial weight ,W_2= Final weight. Limits for Friability are usually less than 1%

TENSILE STRENGTH:

A non-compendial method of measuring the mechanical strength of tablets that is now widely used is the tensile strength. This is the force required to break a tablet in a diametral compression test. The radial tensile strength, T, of the tablets can be calculated from the equation [7].

T or T_o = 2F/πDh

Where, T or T_o = tensile strength of tablet without or with centre hole respectively, F = diametric compression load needed to break the tablet, D = tablet diameter,h = tablet thickness.

DRUG CONTENT:

Drug content was determined by accurately weighing 5 tablets and crushing them in mortar with the help of a pestle. Then an accurately weighed quantity of powder equivalent to 100 mg of drug was transferred to a 100 ml volumetric flask. 50 ml of Diluent was added and shaken. Volume was made up to 100 ml with Diluent. The solution was filtered through Whatmann filter paper. First few ml of the filtrate was discarded. 10 ml of the filtrate was diluted to 100 ml with Diluent. From the above solution 1ml was taken and diluted to 10 ml with Diluent. The absorbance of the resulting 10 μg/ml solution was recorded at 243nm and 273nm. Content uniformity was calculated using formula.

% Purity = 10 C (Au / As)

Where, C = concentration, Au and As are absorbance obtained from standard preparation and assay preparation respectively [8]

SWELLING STUDIES *:*

For conducting the swelling study, the tablet was weighed (W_O) and placed in a petri dish containing 2% agar gel (pH 6.8)and incubate for 8 hours at 37^0C. After that, the tablets were taken out from the petri dish at regular 1hr time intervals and excess water was removed carefully by using filter paper and weighed again (W_t). The swelling index was calculated using the following formula

$$SI = (W_t - W_O) / W_O \times 100$$

Where, SI = Swelling index, W_t = Weight of tablets after time (t), W_O = Weight of tablet before placing in the Petri dish

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 thousand ml of 0.01N HCl in USB Type II dissolution apparatus (37+_0.5°C,50 rpm). The time required for the tablets to rise the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface was determined as the total floating time.

***IN VITRO* DISSOLUTION TESTING:**

The in vitro dissolution studies were performed using USP type II dissolution apparatus at 50rpm. 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 ± 0.5°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 analysed by UV spectrophotometer at respective wavelengths. The concentration was calculated using standard calibration curve.

TABLE 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, suspensions	500 – 4000	25 – 150	Not activity
3	Reciprocating cylinder	Capsules, tablets, suspensions, granulates	250	-	9.9 to 10 %
4	Flow through cell	All	Up to 3liters	Not activity	Not activity
5	Paddle over disk	Transdermal patches	500 – 4000	25 – 150	Not activity
6	Cylinder	Transdermal patches	500 – 4000	-	Not activity
7	Reciprocating holder	Non disintegrating tablets	Variable	Not activity	2

KINETIC MODELLING 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:

A. 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.

B. 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.

STABILITY STUDIES:

FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human life.The ICH tripartite guidelines have established long term stability testing to be done at 25^0C/60%RH for 12 months. Accelerated stability testing should be done at 40^0 C/75%RH for 6 months and stability testing at intermediate storage conditions should be done at 30^0C/65%RH. The following table shows different storage conditions and period of stability testing.

RESULTS AND DISCUSSION

FT-IR spectroscopy:

A study of the pindolol structure based on infrared spectroscopy and natural bond orbital (NBO) theory is the main aim of the present research. FTIR spectra of the solid pindolol were recorded from 4000 to 400cm (-1), at temperatures between 25 and -170 degrees

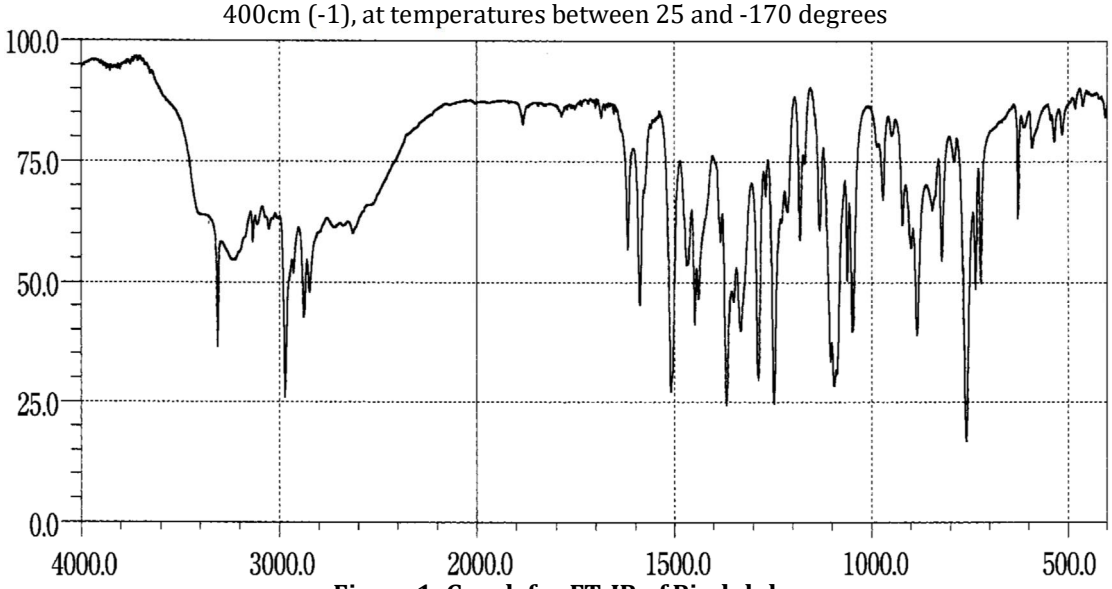

Figure 1: Graph for FT-IR of Pindolol

DSC of pure pindolol:

Differential scanning calorimetry (DSC) Fusion gives rise to overlapped curves, which were analysed by peak-fitting on temperature and heat flow. The polymorphs were identified as the clusters formed with the values obtained for T (peak) of the component curves.

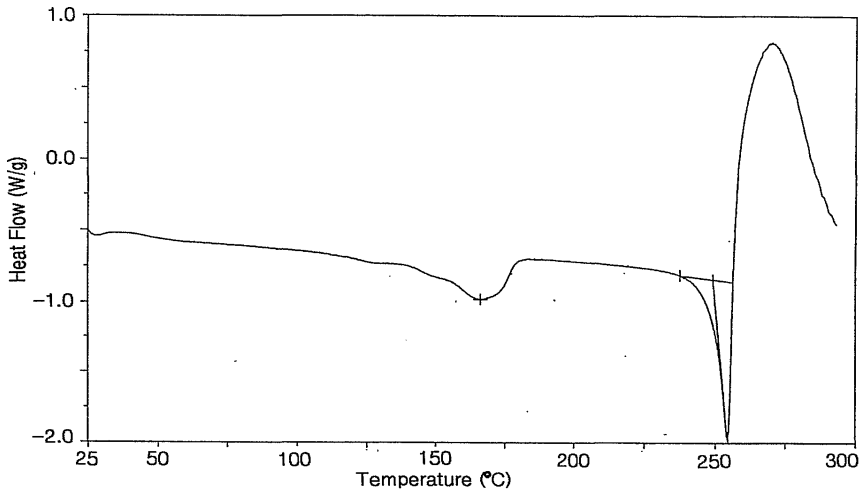

Figure 2: Graph for DSC of Pindolol

GRANULES CHARECTERISTICS:

The dried granules for all batches were evaluated as per the method described in Chapter 5 and the values are recorded in Table 4:

Table 4: Flow properties of pindolol powder

Formulation code	Angle of repose(^{0})	Bulk density (gm/cm2)	Tapped density (gm/cm2)	Carr's index	Hausner ratio
F1	30.4	0.373	0.442	15.61	1.18
F2	30.8	0.375	0.445	15.73	1.16
F3	29.7	0.375	0.446	15.91	1.18
F4	32.0	0.3766	0.438	14.91	1.18
F5	31.5	0.378	0.444	14.86	1.18
F6	32.4	0.385	0.436	11.69	1.16
F7	34.3	0.380	0.438	13.24	1.13
F8	28.0	0.384	0.439	12.52	1.17
F9	30.8	0.375	0.446	15.72	1.15

STANDARD CALIBRATION:

The scanning of drug solution in UV range showed maximum absorbance at 219 nm and hence, the calibration curve was developed at this wavelength. The calibration curve was linear between 0, 4, 8, 12, 16, 20 µg/ml concentration ranges. The calibration readings are shown in table 5 and the calibration curve is shown in Figure 3

Table 5: Standard calibration of Pindolol

Concentration (µg/ml)	Absorbance
0	0
4	0.2
8	0.37
12	0.52
16	0.71
20	0.85

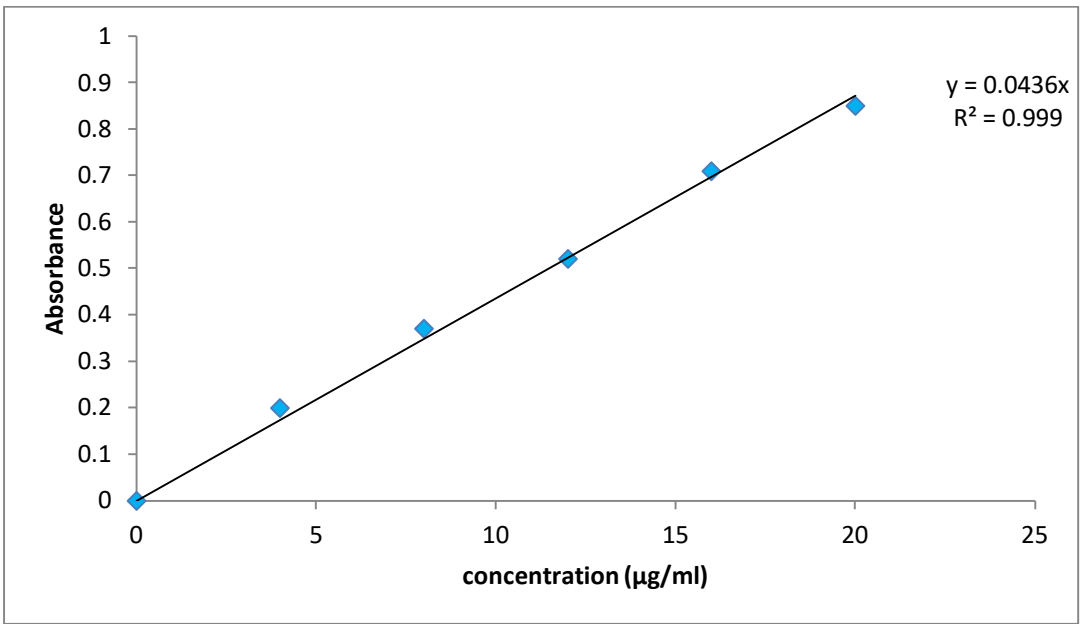

Figure 4: Graph for Standard Calibration Curve

EVALUATION OF FLOTTING TABLETS:

Physical Properties of Tablets:

The prepared tablets of each formulation showed acceptable uniformity of weight ,hardness, thickness and drug content, floating time, log time for the tablets of each formulation are showed in table.6

Table 6: Physical properties of pindolol

Formulation code	Weight variation	Hardness (Kg/cm2)	Friability (%)	Lag time(sec)	Floating time (Hr)	Content uniformity
F1	199.9	4.3	0.21	80	>8	97.8
F2	198.7	4.5	0.24	82	>9	99.2
F3	200.0	4.5	0.15	75	>10	98.3
F4	200.0	5.0	0.12	85	>10	98.5
F5	198.2	5.0	0.11	90	>10	99.8
F6	199.5	4.5	0.14	105	>10	93.5
F7	199.7	4.5	0.18	110	>10	97.8
F8	200.0	5.5	0.16	125	>10	98.5
F9	200.0	5.5	0.14	130.3	>10	97.5

Swelling index studies of pindolol floating tablets:

The swelling index for the tablets of F5 to F6 varied from. The result of swelling study are shown in table and the swelling profile of the tablets is shown in Figure 4.

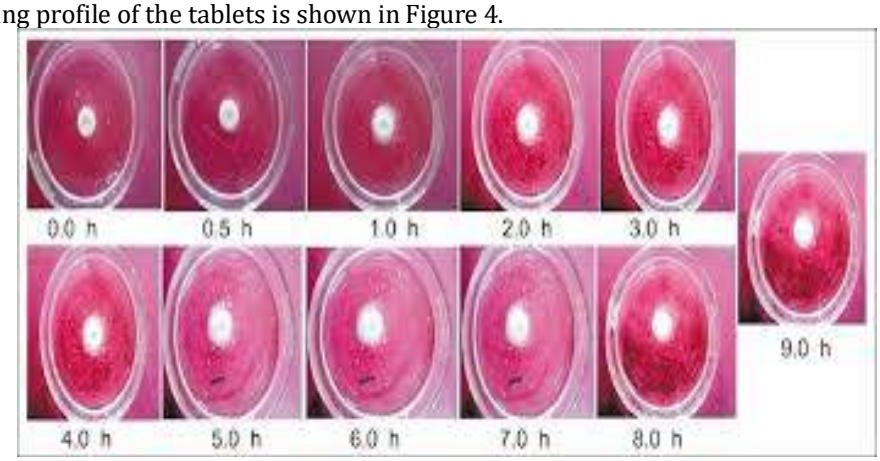

Figure 5: The Swelling Index of pindololfloting tablets

Table 7: Swelling index of Pindolol

Time (hr)	% swelling index	
	Formulation code	
	F5	F6
1	42	38
2	53	45
3	78	76
4	92	86

***In vitro* buoyancy studies:**

In-vitro buoyancy of Pindolol floating tablets were prepared by effervescent technique using sodium bicarbonate as a gas generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of dissolution medium (0.01 N HCl). The gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1 g/ ml, the tablet becomes buoyant. The effect of sodium bicarbonate on buoyancy of the tablets was evaluated by using 20 mg per tablet. The result shows that the total floating time for the formulations was more than 10 hours irrespective to the amount of sodium bicarbonate where as floating lag time increasing to give rapid buoyancy. Sodium bicarbonate at the level of 20 mg per tablet showed a floating lag time of 80 to 130.3 seconds.

Floating Time of Pindolol:

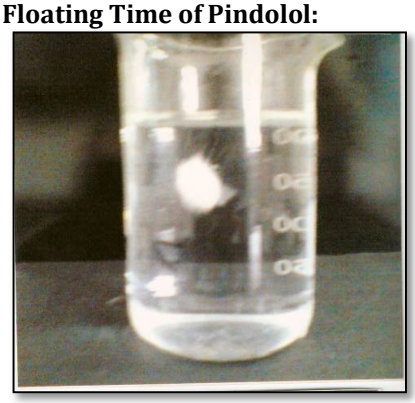

Figure 6: Floating of tablet after 45 sec

Figure 7: Floating of tablet after10 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: 37º ± 5ºC
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-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, HPMCK4M, in the different ratiosF1-1:2, F3-1:3, F5-1:4, F7-1:1, F8-1:1.5and F9-1:2.The formulation (F2, F4, F6, F7, F8 & F9) containing combination of polymers like NaHCO3, HPMC K100M in the ratio of F2-1:2, F4-1:3, F61:4, F7-1:1, F8-1:1.5 and F9-1:2 release the drug before residence time. The formulations F8 in 1:1ratio NaHCO3, HPMC K4M and NaHCO3, HPMCK100Mshows the release of drug in 69.3.The formulations F5 containing combination of polymers like $NaHCO_3$, 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 table 8.

Table.8 In-vitro drug release of Pindolol floating tablets

Time (hr)	% drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	25.6	22.3	10.8	12.8	15.2	13.2	10.2	8.4	9.5
2	37.2	36.4	14.5	22.3	20.3	25.6	18.5	15.2	14.3
4	60.8	58.2	33.6	30.5	29.7	31.2	29.5	24.8	22.4
6	79.4	75.4	69.2	42.8	56.4	45.8	38.5	39.8	36.2
8	95.3	92.8	92.5	67.9	78.5	70.3	62.8	57.6	54.5
10	-	-	-	79.2	99.3	88.5	75.3	69.3	60.2

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 10h(table 9).

The drug permeation data were analyze 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 8-11.

Release Kinetics:

Table 9: In-vitro Kinetic Release of Pindolol

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

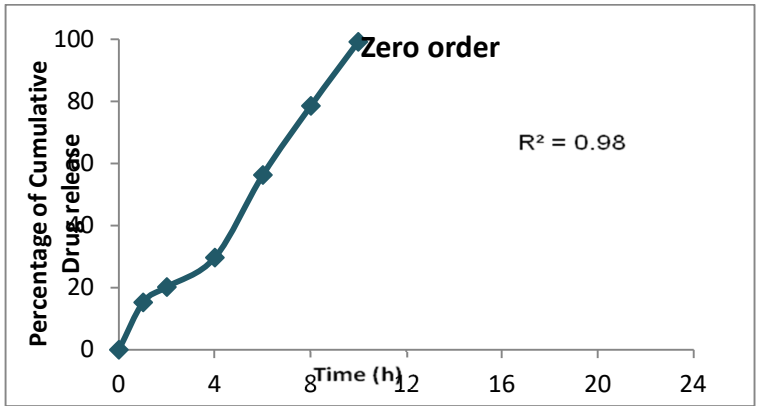

Figure 8: Graph for Zero-order Kinetics

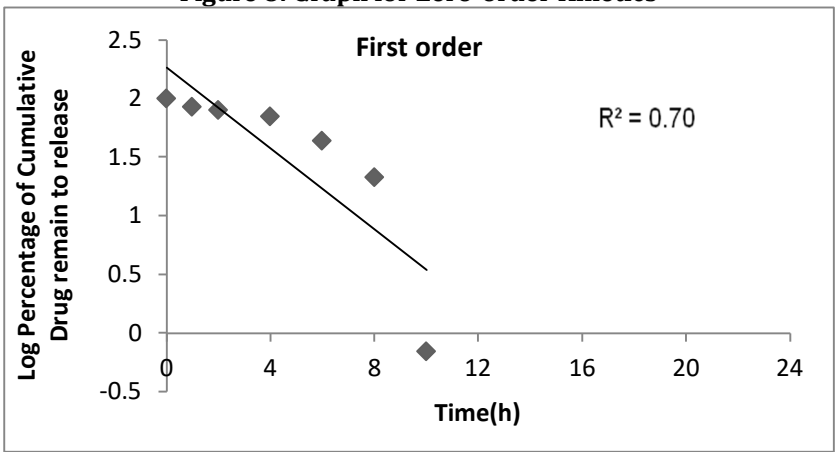

Figure 9: Graph for First order kinetics

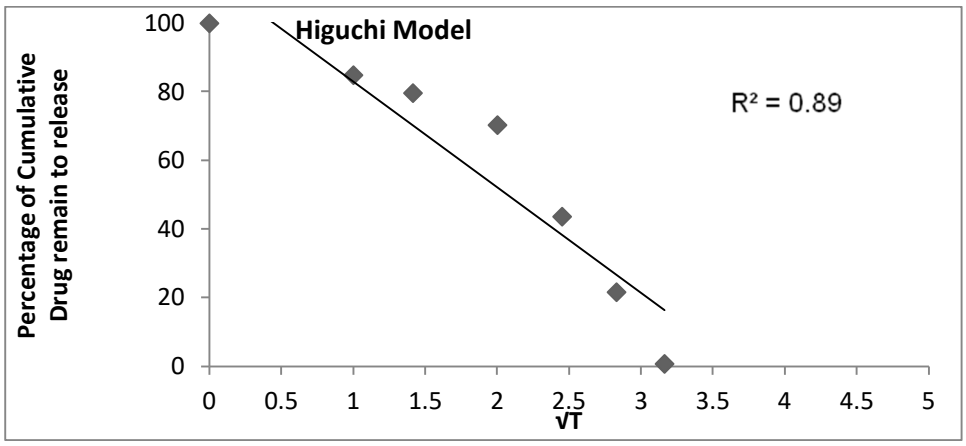

Figure 10: Graph for Higuchi model

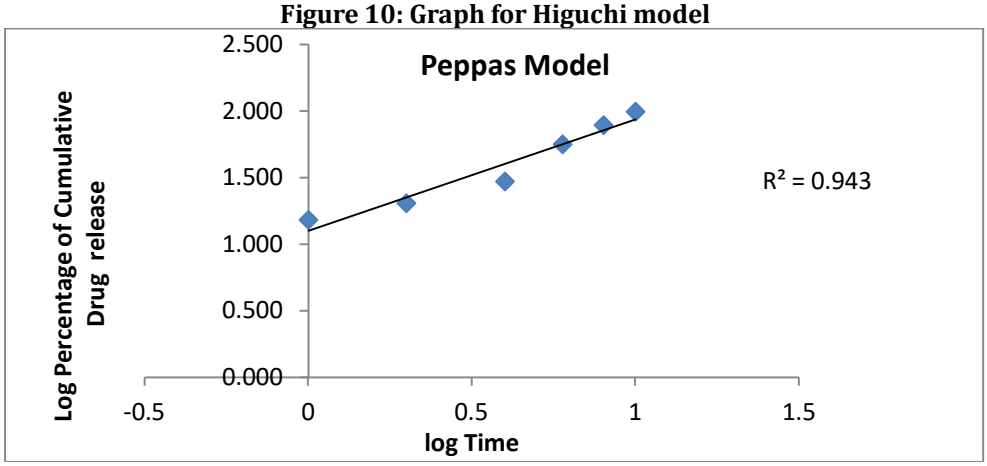

Figure 11: Graph for Peppas model

DICCUSION

QUALITATIVE STUDIES:

A.FT-IR spectroscopy:

Beta-adrenoceptor-blocking agents (beta-blockers) are on the list of the top selling drugs. Pindolol is a representative of this type of compound, either from the structural point of view, or as reference for comparison of the pharmacokinetic properties of the beta-blockers. A study of the pindolol structure based on infrared spectroscopy and natural bond orbital (NBO) theory is the main aim of the present research. FTIR spectra of the solid pindolol were recorded from 4000 to 400cm (-1), at temperatures between 25 and -170^0 C. For spectral interpretation, the theoretical vibrational spectra of the conformer present in the solid was obtained at the B3LYP/6-31G* level of theory.[99] NBO analysis of the reference conformer, before and after optimization, was carried out at the same level of theory referred above. Characteristic absorption vibrational bands of the spectra of solid pindolol and of the isolated conformer were identified. Intra- and intermolecular interactions in pindolol were confirmed by the frequency shift of the vibrational modes and by the NBO theory. A detailed molecular picture of pindolol and of its intermolecular interactions was obtained from spectroscopy and NBO theory. The combination of both methods gives a deeper insight into the structure [10-12].

B.DSC of pure pindolol:

Crystallization of pindolol from the melt was studied by differential scanning calorimetry (DSC) and polarized light thermomicroscopy (PLTM) in order to discriminate the polymorphic forms obtained by this method [13]. The crystallization process originates one exothermic signal localized in two different well-defined temperature ranges. Fusion gives rise to overlapped curves, which were analysed by peak-fitting. The polymorphs were identified as the clusters formed with the values obtained for T (peak) of the component curves. Three polymorphic forms were exhibited by pindolol crystallized from the melt. Commercial pindolol presents only two of these form [14].

C. Flow properties of pindolol powder:

The Flow properties of pindololpowde were showing acceptable Angle of repose, Bulk density, Tapped density, Carr's index, and Hausner ratio.

D. Calibration Curve for Pindolol:

The calibration curve of Pindolol was obtained in the range of 0, 4, 8, 12, 16, 20µg at the wavelength of 219nm it has shown the good linearity with a regression coefficient 0.98 (r^2value).

E. Physical Parameters:

The tablet of each formulation show acceptable uniformity of weight, drug content, hardness, friability, floating time, log time.

F. Swelling Index Study:

From the data the swelling index for two different formulations which named as F5 and F6, with the time of 4 hours period. F5 formulations using HPMC K4M,F6 on using HPMC K100M as a polymers. With time interval, F5 formulation found to satisfactory results in comparative study of two formulations, which is 92%.From the above data of swelling index F5 formulation having is peered to prepare dosage form.

G. In - Vitro Dissolution Studies:

The formulation containing $NaHCO_3$ and HPMCK4M as a polymers in the ratio of 1:4 shows best percentage release of drug i.e. 99.3% up to 10 hours comparing to other formulations. This might be due to Sodium bicarbonate as a Gas-generating agent, and also by HPMCK4M as a rate controlling polymer for sustained release.The optimized formulation F5 were subjected for In-vitro drug permeation study showed good drug permeation through Floating in 10 hours. The In-vitro drug permeation of F5 followed Zero order kinetics r^2=0.98.The In-vitro drug permeation profile of drug and the formulation shown same drug release pattern. The r^2=0.94 of Korsmeyer peppas equation, r^2=0.98 for zero order, n=0.80 the drug release was occurred via non-Fickian diffusion+6.

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 undergoes extensive first-pass metabolism. Pindolol is an anti-hypertensive agents. 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 survey on the HPMC, Sodium bicarbonate and DCP polymers have strongly suggested that they have total floating time and log time properties. The purity of 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 effervescent approach. HPMC and DCP were used as the polymers and sodium bicarbonate was used as a gas generating approach. It was seen that chaining 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 HPMCK4M and sodium bicarbonate increasing the floating lag time. But the amount of sodium bicarbonate did not have any effect on 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 sustained release floating tablets of Pindolol by incorporating appropriate concentration of sodium bicarbonate for gas generation. Such system 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 First 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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