Design Development *In Vitro* and *In Vivo* Characterization of Gastro Retentive Floating Drug Delivery System for Piretanide

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Abstract: The aim of the present study was to develop floating matrix formulation of Piretanide to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of natural polymers and celluloses were employed as polymers. Piretanide dose was fixed as 20 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 25, 50 and 75 mg. All the formulations passed various physicochemical evaluation parameters and they were found to be within limits. From the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern 96.33 % in 12 hours. It followed zero order release kinetics mechanism.

***Keywords*:** Piretanide, Eudragit RL 100, Eudragit RS 100, Ethyl cellulose, Sustained release tablets.

I. INTRODUCTION

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems[1]. Controlled release drug delivery systems provide drug release at a pre determined, predictable, and controlled rate. Controlled release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half life drugs, elimination of side effects; reducing frequency of dosing and wastage of drugs[2].
The successful development of oral controlled drug delivery systems requires an understanding of the three aspects of the system, namely[3],

- The physiochemical characteristics of the drug
- Anatomy and physiology of GIT and
- Characteristics of Dosage forms.

1.1 Gastro Intestinal Retention:

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. To successfully modulate the gastro intestinal transit time of a drug delivery system through floating drug delivery system (FDDS) for maximal gastro intestinal absorption of drugs and site specific delivery in the human GIT.

List of Materials Used: Piretanide, Guar Gum, Chitosan, Sodium CMC, Sodium bicarbonate, Magnesium stearate, Micro crystalline cellulose, Talc, HPMC K4M, HPMC K100M.

2. METHODOLOGY

2.1 Analytical Method Development:

a) Determination of Absorption Maxima: A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400nm.
b) Preparation Calibration Curve: 100mg of Piretanide pure drug was dissolved in 100ml of 0.1N HCl (stock solution)10ml of solution was taken and make up with100ml of 0.1N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 1,2,3,4 and 5µg/ml of Piretanide per ml of solution. The absorbance of the above dilutions was measured at 266 nm by using UV- Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve.

2.2 Drug – Excipient Compatibility Studies:

Fourier Transform Infrared (FTIR) Spectroscopy: The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation Parameters: The quality of tablet is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced.

Angle of Repose: The frictional force in a loose powder can be measured by the angle of repose if more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. 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 blend was 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 was calculated using the following formula.

$\theta = Tan^{-1} h / r$ Tan θ = Angle of repose, h = Height of the cone, r = Radius of the cone base

Bulk Density: Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read. The bulk density was calculated using the formula.

Bulk Density = M / Vo Where, M = weight of sample, Vo = apparent volume of powder

Tapped Density: After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V Where, Tap= Tapped Density, V= Tapped volume of powder.

Measures of Powder Compressibility: The Compressibility Index (Carr's Index) is a measure of the bulk and tapped densities. It is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. a greater difference between the bulk and tapped densities will be observed. The Compressibility Index was calculated using the following formulas.

Carr's Index = [(tap - b) / tap] × 100 Where, b = Bulk Density, Tap = Tapped Density

Formulation Development of Tablets: All the formulations were prepared by direct compression. The tablets were prepared as per the procedure given below and aim is to prolong the release of Piretanide. Total weight of the tablet was considered as 300 mg.

Procedure:

- Piretanide and all other ingredients were individually passed through sieve no 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using direct compression method.

Table 1: Formulation Composition for Floating Tablets

Formulation No.	Piretanide	Sodium CMC	Chitosan	Guargum	NaHCO3	Mag. Stearate	Talc	MCC pH 102
F1	20	25	-----	-----	50	5	5	QS
F2	20	50	-----	-----	50	5	5	QS
F3	20	75	-----	-----	50	5	5	QS
F4	20	-----	25	-----	50	5	5	QS
F5	20	-----	50	-----	50	5	5	QS
F6	20	-----	75	-----	50	5	5	QS
F7	20	-----	-----	25	50	5	5	QS
F8	20	-----	-----	50	50	5	5	QS
F9	20	-----	-----	75	50	5	5	QS

All the quantities were in mg, Total weight is 300 mg.

Table 2: Formulation Composition for Floating Tablets

Formulation No.	PIRETANIDE	HPMC K4M	HPMC K15M	HPMC K100M	NaHCO3 +Citric acid	Mag. Stearate	Talc	MCC pH 102
F10	20	50	----	-----	50	5	5	QS
F11	20	75	----	-----	50	5	5	QS
F12	20	100	----	-----	50	5	5	QS
F13	20	----	50	-----	50	5	5	QS
F14	20	----	75	----	50	5	5	QS
F15	20	----	100	-----	50	5	5	QS
F16	20	----	----	50	50	5	5	QS
F17	20	----	----	75	50	5	5	QS
F18	20	----	----	100	50	5	5	QS

All the quantities were in mg, total weight is 300 mg

Evaluation of Post Compression Parameters for Prepared Tablets:

The designed compression tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight Variation test: 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 percent deviation was calculated using the following formula:

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

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness: Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed 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 re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as,

% Friability = [(W1-W2) / W] × 100 Where, W1 = Initial weight of three tablets W2 = Weight of the three tablets after testing.

Determination of Drug Content:

Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Piretanide were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* Buoyancy studies:** The *invitro* buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

3. RESULTS AND DISCUSSION

The present study was aimed to developing gastro retentive floating tablets of Piretanide using various polymers. All the formulations were evaluated for physicochemical properties and *invitro* drug release studies.

Table 3. Invitro Quality Control Parameters for Tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Floating lag Time (min)
F1	300.5 ±0.7	4.5±0.8	0.52±0.8	4.8±0.8	99.76 ±0.7	4.0±0.4
F2	300.4 ±0.4	4.2±0.7	0.54±0.8	4.9±0.5	99.45 ±0.4	4.2±0.7
F3	300.6 ±0.5	4.4±0.4	0.51±0.7	4.9±0.4	99.34 ±0.7	4.5±0.8
F4	300.6 ±0.8	4.5±0.5	0.55±0.4	4.9±0.7	99.87 ±0.8	4.1±0.8
F5	300.4 ±0.5	4.4±0.4	0.56±0.7	4.7±0.4	99.14 ±0.7	4.0±0.7
F6	300.7 ±0.4	4.2±0.7	0.45±0.8	4.5±0.5	98.56 ±0.4	4.4±0.7
F7	300.3 ±0.7	4.1±0.4	0.51±0.5	4.4±0.8	98.42 ±0.7	4.5±0.4
F8	300.2 ±0.3	4.3±0.7	0.49±0.4	4.7±0.7	99.65 ±0.4	4.6±0.5
F9	300.3 ±0.8	4.5±0.8	0.55±0.7	4.6±0.4	99.12 ±0.5	4.7±0.8
F10	301.4 ±0.4	4.2±0.8	0.56±0.5	4.9±0.8	99.56 ±0.4	4.1±0.3
F11	302.4 ±0.5	4.3±0.4	0.52±0.8	4.9±0.4	99.55 ±0.8	4.2±0.4
F12	301.5 ±0.3	4.5±0.8	0.50±0.4	4.9±0.8	99.54 ±0.3	4.1±0.8
F13	302.3 ±0.8	4.2±0.4	0.50±0.3	4.9±0.4	99.85 ±0.8	4.1±0.3
F14	301.4 ±0.4	4.3±0.3	0.51±0.4	4.8±0.8	99.54 ±0.4	4.2±0.8
F15	303.8 ±0.3	4.3±0.4	0.54±0.8	4.8±0.3	98.55 ±0.8	4.1±0.4
F16	301.2 ±0.4	4.2±0.8	0.53±0.3	4.9±0.8	98.45 ±0.4	4.2±0.5
F17	300.2 ±0.8	4.2±0.4	0.57±0.8	4.8±0.4	99.55 ±0.3	4.1±0.5
F18	300.5 ±0.3	4.3±0.8	0.59±0.4	4.9±0.3	99.15 ±0.5	4.2±0.3

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies:** From the dissolution data it was evident that the formulations prepared with Sodium CMC as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with Chitosan retarded the drug release in the concentration of 75 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.33 % in 12 hours (Formulation F6) with good floating lag time and floating buoyancy time. The formulations prepared with Guar gum showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

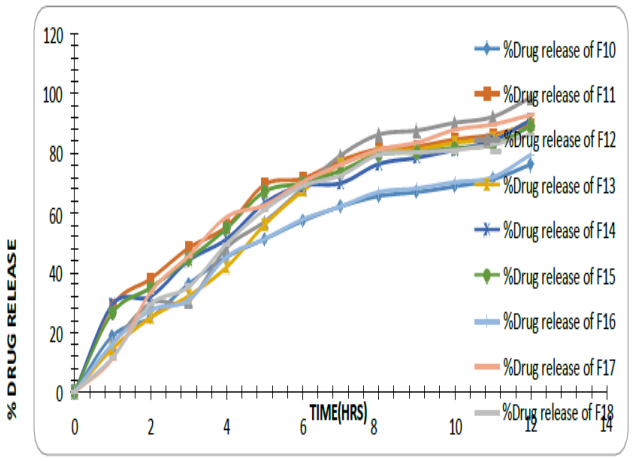

Fig 1: *In-vitro* Drug Release Profile

From the dissolution values it was evident that the formulations F13 & F18 retarded the drug release up to 12 hours, they shown drug release of 98.69 and 86.45 % respectively. Formulations F11 –F13 contains HPMC K4M alone.

4. CONCLUSION

In the present research work gastro retentive floating matrix formulation of Piretanide using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Then the formulation was developed by using different concentrations of various natural polymers. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations prepared by using Sodium CMC were unable to produce desired drug release, they were unable to retard drug release up to 12 hours. The formulations prepared with Chitosan retarded the drug release up to 12 hours in the concentration of 75 mg (F6).The formulations prepared with Guar gum were also retarded the drug release for more than 12 hours. The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

REFERENCES

1. Abeda Aqther, B. Pragati kumar, Peer Basha indian Journal of Research in Pharmacy and Biotechnology ISSN: 2321-5674(Print) ISSN: 2320 – 3471.

2. Swalin Parija International Journal of Research in Pharmaceutical and Biomedical Sciences ISSN: 2229-3701 Vol. 4 (1) Jan– Mar 2013.

3.Abbaraju Prasanna Lakshmi, Giddam Ashwini Kumar, T. Karnaker Reddy, M. Anand Kumar International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491 Vol 4, Issue 1, 2012 360-363.