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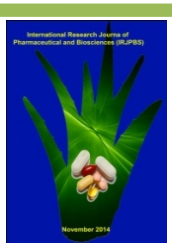

Formulation and In-Vitro Evaluation of Pulsatile Drug Delivery Tablets of Zaltoprofen

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Abstract

The current work gastro retentive floating matrix formulation of Zaltoprofen by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of Eudragit. 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. 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.

Keywords : Zaltoprofen, Pulsatile, Invitro drug release.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled [1] release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. But there are certain conditions which demand release of drug after a lag time.

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions.

INTRODUCTION FLOATING PULSATILE DRUG DELIVERY SYSTEM

FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems [2] are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.

ADVANTAGES OF FDDS

- *1. The Floating systems are advantageous for drugs meant for local action inthe stomach. E.g. antacids.*
- *2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.*
- *3. The Floating systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.*

DISADVANTAGES OF FDDS

- *1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.*
- *2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.*
- *3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, is only desirable candidate.*

Types of Floating Drug Delivery Systems

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS.

I) Non-Effervescent FDDS

The various types of this system are as:

- ***Single Layer Floating Tablets:***
- ***Bi-layer Floating Tablets:***

- ***Alginate Beads:***
- ***Hollow Microspheres:***

II) Effervescent FDDS

- ***Volatile liquid containing system:***
- ***Gas-generating Systems:***

Pulsatile drug delivery system

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. A pulsatile drug delivery system [3] is characterized by a lag time that is an interval of no drug release followed by rapid drug release.

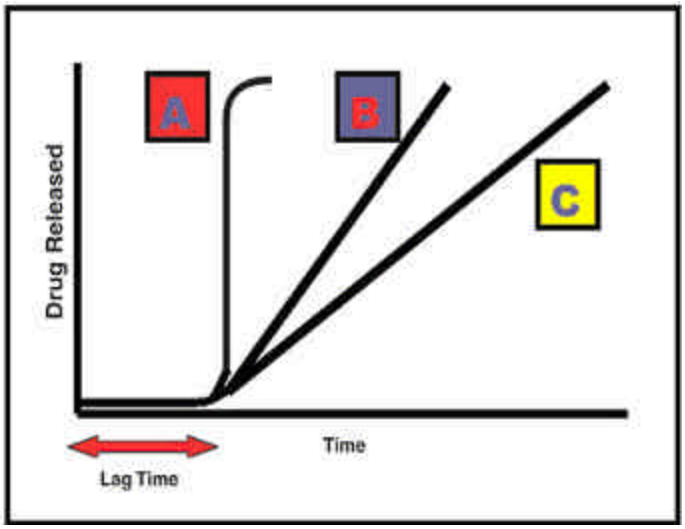

Fig 1: Drug release patterns

In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure 1).The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time [4] (patterns B & C in Figure).

Floating Pulsatile Drug Delivery System [5-9]

Site-and time-specific oral drug deliveries have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific or time-specific drug release in upper gastrointestinal tract. Over the last three decades, various approaches have been pursued to increase the retention of an oral dosage form in the stomach, including floating systems which decrease in density upon contact with gastric fluids based on swelling of polymer or carbon dioxide (CO_2) generation, muco adhesive systems which adhere to mucosal surfaces, modified-shape systems expandable (size-increasing), high-density systems, and other delayed gastric emptying devices.

A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in upper GI tract after a defined time period of no drug release. A pulsatile drug delivery that can be administered at bed time but releases drug in early morning would be a promising chronotherapeutic system. The potential benefits of floating pulsatile drug delivery system:

Advantages of floating pulsating drug delivery systems

- *Retention of drug delivery system in stomach prolongs overall.*
- *Acidic substance like aspirin cause irritation on the stomach wall when come into contact with it hence floating pulsatile formulation may be useful for administration of aspirin and other similar drugs.*
- *It has application also local drug delivery to the stomach and proximal small intestine e.g., ranitidine for nocturnal acid breakthrough.*
- *No risk of dose dumping.*

Floating pulsatile drug delivery increase drug bioavaibility; predictable, reproducible, and improved generally short gastric residence time; no risk of dose dumping; local drug action; and the flexibility to blend dosage form with different composition and release pattern.

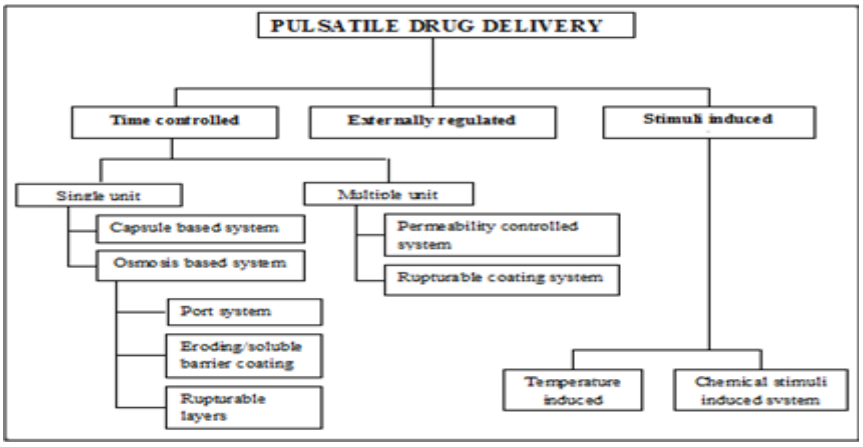

Fig 2: Pulsatile drug delivery system

MATERIALS AND METHODS

Zaltoprofen**,** Eudragit l100, Eudragit s 100, Sodium Bicarbonate, Microcrystalline Cellulose Magnesium Stearate, Talc.

METHODOLOGY

ANALYTICAL METHOD DEVELOPMENT

Preparation calibration curve

100mg of Zaltoprofen pure drug was dissolved in 100ml of water(stock solution)10ml of solution was taken and make up with100ml of water (100µg/ml).from this 10ml was taken and make up with 100 ml of water (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 2,4,6,8,10,20,30,40,50,60,70,80,90 and 100µg/ml of Zaltoprofen per ml of solution. The absorbance of the above dilutions was measured at 271 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 Linearityofstandardcurvewasassessedfromthesquareofcorrelationcoefficient (R^2)which determined by least-square linear regression analysis.

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 and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

PREFORMULATION PARAMETERS

The various characteristics of blends tested as per Pharmacopoeia areAngle of repose, Bulk density, Tapped density, Measures of powder compressibility.

FORMULATION DEVELOPMENT OF TABLETS

All the formulations were prepared by direct compression.

Procedure

1) Zaltoprofen and all other ingredients were individually passed through sieve no $\neq$ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table .1 : Formulation composition for floating tablets

Formulation No.	Zaltoprofen	Eudragit S100	Eudragit L 100	Eudragit RSPO	$NaHCO_3$	Mag. Stearate	Talc	MCC pH 102
F1	80	40	-----	-----	30	5	5	QS
F2	80	80	-----	-----	30	5	5	QS
F3	80	100	----	-----	30	5	5	QS
F4	80	-----	40	-----	30	5	5	QS
F5	80	-----	80	----	30	5	5	QS
F6	80	-----	100	-----	30	5	5	QS
F7	80	-----	-----	40	30	5	5	QS
F8	80	-----	-----	80	30	5	5	QS
F9	80	-----	-----	100	30	5	5	QS

All the quantities were in mg , total weight is 250 mg.

EVALUATION OF POST COMPRESSION PARAMETERS FOR PREPARED TABLETS

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

RESULTS AND DISCUSSION

All formulations were evaluated for physicochemical properties & in-vitro drug release studies.

ANALYTICAL METHOD

Graphs of Zaltoprofen were taken in Simulated Gastric fluid (pH 1.2) at 271 nm.

Table 2: Observations for graph of Zaltoprofen in 0.1N HCl (271 nm)

Conc [µg/l]	Abs
0	0
2	0.172
4	0.310
6	0.438
8	0.563
10	0.719

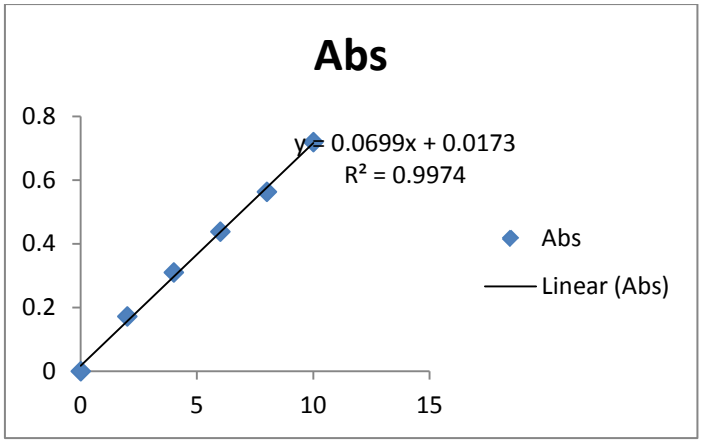

Figure 3: Standard graph of Zaltoprofenin0.1N HCl

PREFORMULATION PARAMETERS OF POWDER BLEND

Table 3: Pre-formulation parameters of blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped densit (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	26.01	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	24.8	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	22.74	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	25.33	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	26.24	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	26.12	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	27.08	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	25.12	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	25.45	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which show that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

OPTIMIZATION OF SODIUM BICARBONATE CONCENTRATION

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 75mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

Table 4: QUALITY CONTROL PARAMETERS FOR TABLETS:

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Flaoting lag time (min)
F1	202.5	3.5	0.52	4.8	99.76	4.0
F2	205.4	3.2	0.54	4.9	99.45	4.2
F3	198.6	3.4	0.51	4.9	99.34	4.5
F4	210.6	3.5	0.55	4.9	99.87	4.1
F5	209.4	3.4	0.56	4.7	99.14	4.0
F6	210.7	3.2	0.45	4.5	98.56	4.4
F7	202.3	3.1	0.51	4.4	98.42	4.5
F8	201.2	3.3	0.49	4.7	99.65	4.6
F9	198.3	3.5	0.55	4.6	99.12	4.7

IN-VITRO DRUG RELEASE STUDIES

Table 5.: Dissolution Data of Zaltoprofen Tablets

TIME(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	18.81	19.89	14.21	19.62	18.42	19.62	21.73	18.52	19.53
1	29.02	28.04	18.87	27.86	27.73	27.86	30.23	37.47	28.97
2	35.70	35.43	27.19	36.35	35.63	36.35	44.9	59.93	35.89
3	43.32	41.65	35.66	41.45	42.04	41.45	50.87	65.85	45.7
4	49.25	47.18	43.32	47.80	57.25	47.80	54.73	77.54	54.38
5	55.28	53.81	51.06	55.25	64.33	55.25	66.37	89.55	61.2
6	60.92	58.89	57.13	60.24	75.41	60.24	70.84	96.67	67.06
7	66.08	64.53	63.63	66.73	83.84	66.73	73.17	104.28	72.52
8	70.44	69.43	69.71	71.34	102.80	76.34	79.01		77.88
9	80.90	79.98	79.27	80.17		88.52	84.23		86.6
10	87.27	83.98	89.02	93.28		98.17	90.18		89.09

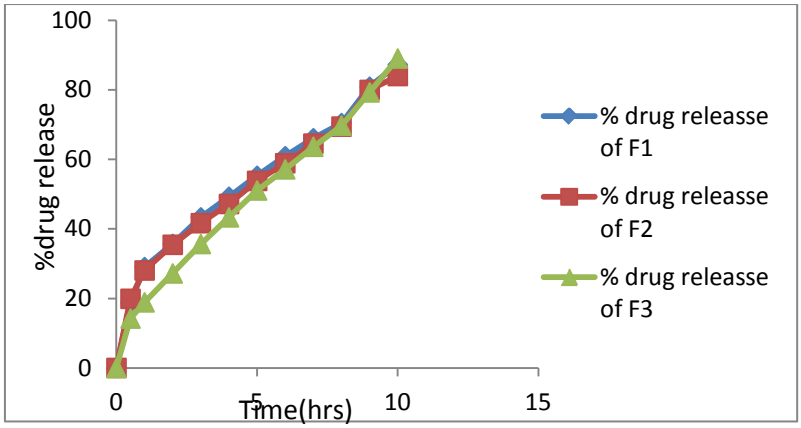

Fig 4.: Dissolution profile Zaltoprofen floating tablets (F1, F2, F3 formulations).

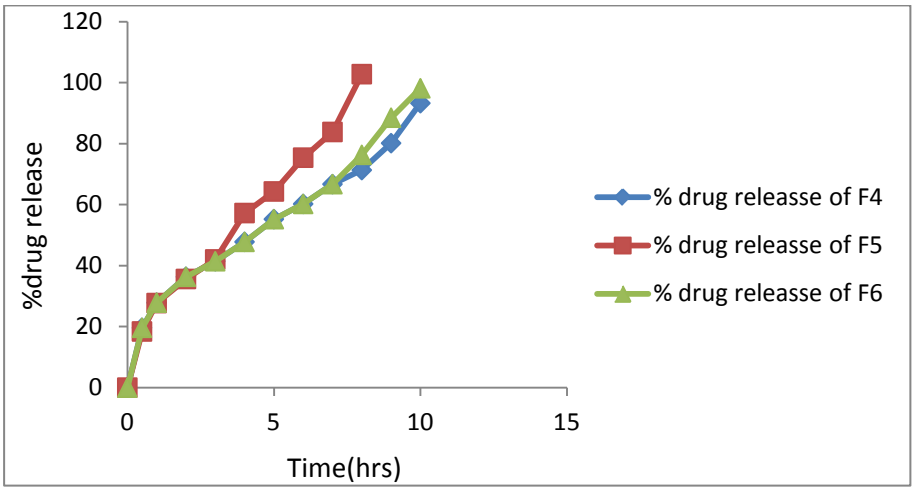

Fig 5.: Dissolution profile of Zaltoprofen HCl floating tablets (F4, F5, F6 formulations).

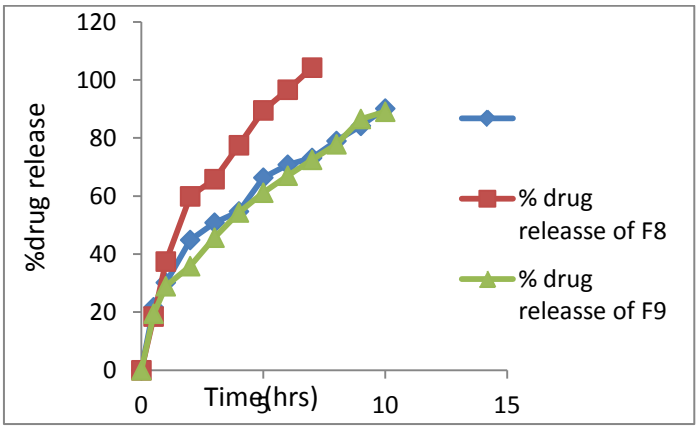

Fig 6: Dissolution profile of Zaltoprofen floating tablets (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Guar gum as polymer were unable to retard the drug release up to desired time period i.e., 10 hours. Whereas the formulations prepared with Eudragit L 100 retarded the drug release in the concentration of 60 mg (F6)showed required release pattern i.e., retarded the drug release

up to 12 hours and showed maximum of 98.17 % in 10 hours with good floating lag time and floating buoyancy time.

The formulations prepared with Eudragit L 100 showed more retardation even after 10 hours they were not shown total drug release. Hence they were not considered.

CONCLUSION

In the present research work gastro retentive floating matrix formulation of Zaltoprofen by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of Eudragit. 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 the formulations prepared by using Guar gum were unable to produce desired drug release, they were unable to retard drug release up to 10 hours. The formulations prepared with Eudragit L100 retarded the drug release up to 10 hours in the concentration of 100 mg (F6). Hence they were not considered.

REFERENCES

1.Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv 2006; 3(2): 217- 33.

2.Iannucelli V, Coppi G, Bernabei MT, Camerorni R. Air compertment multiple-unit system for prolonged gastric residence. Part-I. Formulation study. Int J Pharm 1998; 174: 47-54.

3.Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop. J Pharm Res 2008; 7(3): 1055-66.

4.Rouge N, Allemann E, Gex-Fabry M, Balant L, Cole ET, Buri P, Doelker E. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multipleunit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm ActaHelbetiae 1998; 73: 81-7.

5.Streubel A, Siepmann J, Bodmeier R. Multiple unit Gastroretentive drug delivery: a new preparation method for low density microparticles. J Microencapsul 2003; 20: 329-47.

6.Goole J, Vanderbist F, Aruighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int J Pharm 2007; 334: 35-41.

7.Shrma S, Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. Int J Pharm 2006; 313: 150-58.

8.Santus G, Lazzarini G, Bottoni G, Sandefer EP, Page RC, Doll WJ, Ryo UY, Digenis GA. An in vitro- in vivo investigation of oral bioadhesive controlled release furosemide formulations. Eur J Pharm Biopharm 1997; 44: 39-52.

Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Control Release 2003; 90: 143-62.