ISSN: 2395-0536

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FORMULATION AND EVALUATION OF FLOATING TABLETS WITH NON EFFERVESCENCE NATURAL / SYNTHETIC POLYMERS OF OSELTAMIVIR

M. Anvitha*, Shaik. Harun Rasheed, P. Shanmukhi

***Department of Pharmaceutics DCRM College of Pharmacy, Inkollu, Prakasam District -523167, Andhra Pradesh, India.**

ABSTRACT

The present developed floating tablets with non effervescence natural/synthetic polymers of osaltamivir which were designed to prolong the gastric residence time after oral administration. Osaltamivir floating tablets were prepared by Direct Compression method incorporating natural polymer/synthetic like guar gum, HPMC, Xanthum gum, guar gum, ethyl cellulose, pvp, MCC, Magnesium sterate with sodium bicarbonate as gas generating agent and were evaluated for physico-chemical parameters i.e; drug content, swelling index, dissolution studies. All the formulations showed compliance with pharmacopeia standards. Based on the evaluation results,F5 formulations were selected as the best formulations and were checked for stability as per ICH guidelines. These results indicated that the selected formulations were stable. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas equation.

Key words: Osaltamivir, oral controlled release formulation, gas generating agent, direct compression method.

Author for correspondence:
M.Anvitha,
Department of Pharmaceutics,
DCRM College of Pharmacy, Inkollu, Prakasam District -523167, Andhra Pradesh, India**.**

Email: anvitha01@gmail.com.

INTRODUCTION

Oral Controlled Release Drug Delivery Systems (1, 2)

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action. All the pharmaceutical products formulated for systemic delivery via the oral

route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are (3, 4): -

1) Development of a drug delivery system
2) Modulation of gastrointestinal transit time
3) Minimization of hepatic first pass elimination

SCOPE OF THE STUDY

Conventional oral controlled dosage forms suffer from mainly two adversities. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms. Altering the gastric emptying can overcome these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time.

Extended release dosage form with prolonged residence time in stomach are highly desirable for drugs.

i. That are locally active in stomach,
ii. That have an absorption window in the stomach or in the upper small intestine,
iii. That are unstable in the intestinal or colonic environment,
iv. Have low solubility at high pH values.

Gastro retentive Dosage Form (GRDF) (5, 6)

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS).

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as –

This application is especially effective in sparingly soluble and insoluble drugs, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.

GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the sub mucosal tissue of stomach)

GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents are taken up only from very specific sites of the GI mucosa.

Factors Controlling Gastric Retention Time of Dosage Form (6, 7) The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system.

- Density of dosage form
- Size of the dosage from
- Shape of dosage
- Single or multiple unit
- Fed or unfed state
- Nature of meal
- Caloric content
- Frequency of Gender
- Age
- Posture

BIOLOGICAL ASPECTS OF GRDFS

Role of GI tract

Stomach

The stomach is 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 hydrochondriac 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 barrier to the delivery of drugs to small intestine.

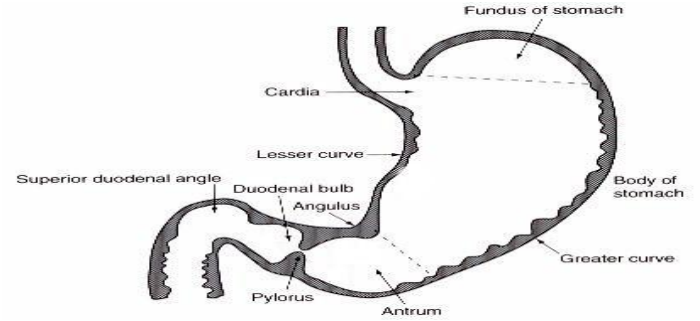

Fig-1 Anatomy of Stomach

The stomach is divided into three anatomical regions. I) Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted 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 interdigestive mode. In case of fasted state an interdigestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as interdigestive my electric cycle.

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

Buoyant/ Floating Systems

Floating Drug Delivery System (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.

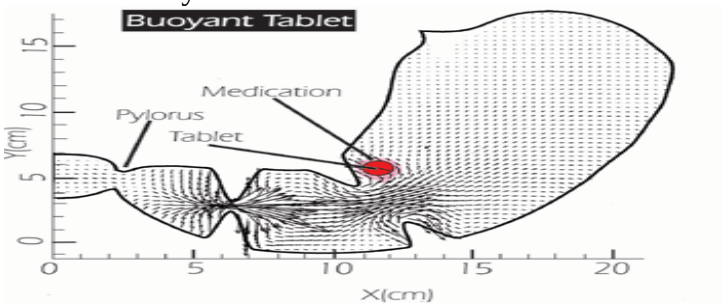

Fig-2 Graphic of Buoyant tablet, which is less dense than the stomach fluid and therefore remains in the fundus

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 system in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

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

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 logged at the pyloric sphincter if

that exceed a diameter of approximately 12-18 mm in their expanded state.

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 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach.

Osmotic Regulated Systems

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio erodible capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Advantages of FDDS

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.Delivery of drugs for local action in the stomach.
3. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.

Disadvantages of FDDS

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametric size. Therefore patients should not be dosed with floating forms just before going to bed.

Floatable Drug Delivery Systems (8)

Table- 1 Lists of Drugs

S.	DOSAGE FORM	DRUGS
1	Microspheres	Aspirin, Griseofulvin, p-nitroanilline, Ibuprofen,
2	Granules	Diclofenac sodium,
3	Films	Cinnarizine
4	Powders	Several basic drugs

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

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

A. Effervescent System, and
B. Non- Effervescent System.

EFFERVESCENT SYSTEM

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

- Gas Generating systems
- Volatile Liquid/Vacuum Containing Systems

NON-EFFERVESCENT SYSTEMS:

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as Polycarbonate,

Polyacrylate, Polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol

MATERIALS

Osaltamivir, HPMC, Xanthum gum, Guar gum, Ethyl Cellulose, PVP, Sodium bicarbonate, MCC, Magnesium Stearate.

METHODS

STANDARD GRAPH OF OSELTAMVIR

A.Standard Stock solution

100 mg of oseltamvir was dissolved in 100 ml of 0.1N HCL (1000 µg/ml)

Calibration curve of oseltamivir in 0.1N HCL

From the above stock solution, 1 ml was transferred into a 10 ml volumetric flask and volume was adjusted to 10 ml that corresponded to 100 µg/ml oseltamvir in solution. From that solution different aliquots of 1.6, 1.8, 2, 2.2 and 2.4 ml were transferred to 10ml volumetric flask, volume was adjusted with 0.1N HCL, which gave a concentration of 16,18,20,22 and 24 µg/ml of final standard. Standard curve was plotted by taking absorbance of secondary stock solutions in UV double beam spectrophotometer at 216 nm.

B.Drug-Excipients Compatiblity study

Oseltamvir was mixed with all excipients, used in the formulation in different ratios and subjected to Physical observation/FTIR.

Drug-Excipient Compatiblity study (FTIR)

The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-400 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide .These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press.

EXPERMENTAL METHODS

FORMULATION AND PREPARATION OF OSELTAMVIR FLOATING TABLETS

All the formulations were prepared by direct compression method using different Polymers.

PROCEDURE:

1. Oseltamvir and all other ingredients were individually passed through sieve ≠ 60.
2. All the ingredients were mixed thoroughly by triturating up to 15 min.
3. The powder mixture was lubricated with Magnesium stearate the tablets were prepared by using direct compression method according to the formulation table-2.

Table-2 Composition of different formulations

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Oseltamivir	75	75	75	75	75	75
HPMC	105	122.5	140	--	--	--
Xanthum gum	--	--		105	--	--
Guar gum	--	--		--	105	--
Ethyl cellulose	--	--		--	--	105
PVP	17.5	17.5	17.5	17.5	17.5	17.5
Sodium bicarbonate	52.5	52.5	52.5	52.5	52.5	52.5
MCC	96.5	79	61.5	96.5	96.5	96.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5
Total weight	**350 mg**	**350 mg**	**350 mg**	**350 mg**	**350 mg**	**350 mg**

PVP – Poly vinyl pyrrolidine , HPMC- Hydroxy Propyl methyl cellulose, MCC- Micro crystalline cellulose

EVALUATION OF FORMULATION (TABLETS)

Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage (Table-4).

Dissolution Study

900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 ±

0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 10 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 216 nm (Table-5).

RESULTS AND DISCUSSION

STANDARD GRAPH OF OSELTAMIVIR (Table-3 and Fig-3)

Table-3 Standard graph of Oseltamivir

Conc (µg/ml)	Absorbance
16	0.421
18	0.472
20	0.520
22	0.562
24	0.612

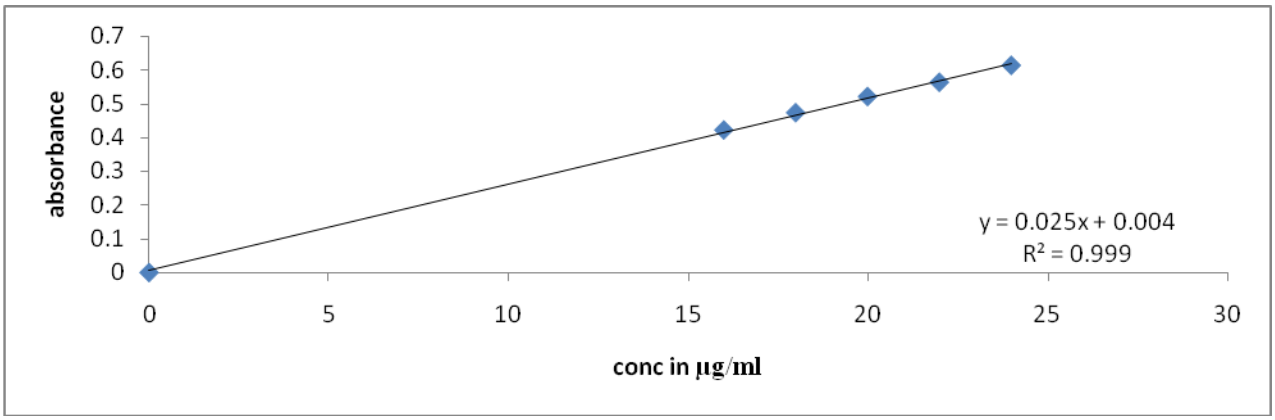

Fig-3 Standard calibration curve of Oseltamivir

FT-IR STUDIES

The FTIR spectra of the drug (alone), polymer (alone) and the drug-polymer (mixture) were recorded by the potassium bromide pellet method. From the infrared spectra it is clearly evident that there were no drug-polymer interactions of the drug (Fig-4 and 5).

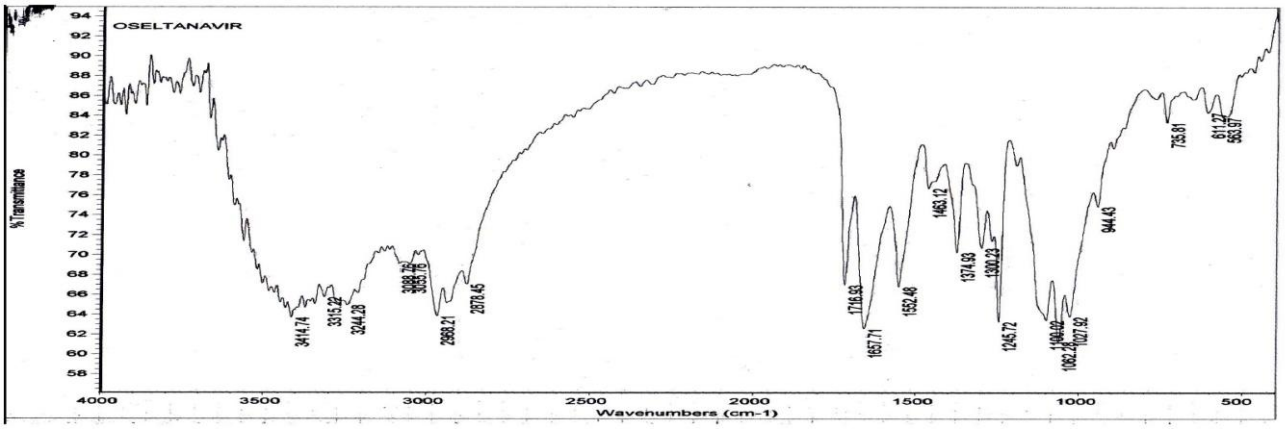

Fig- 4 FT-IR spectra of Oseltamivir

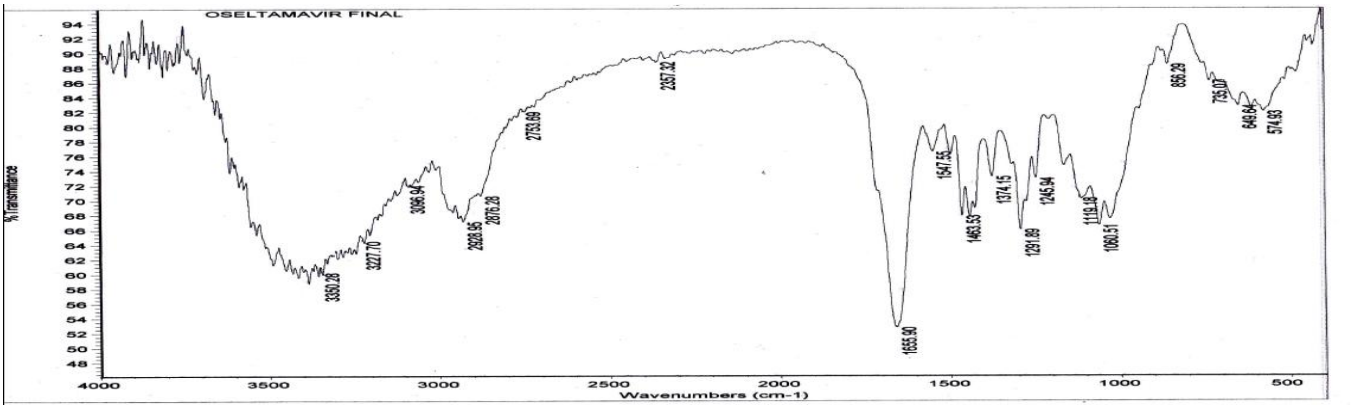

Fig-5 FT-IR spectra of Oseltamivir final formulation

Table-4 Average Fill Weight

Formulation No.	Avg. Weight (Mean± S.D) (n=20)
F1	353±0.6
F2	350±0.9
F3	347±0.3
F4	351±0.4
F5	346±0.8
F6	354±0.8

Table- 5 Dissolution Data of Oseltamivir Floating Tablets

TIME (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	18.8	14.3	11.3	16.5	12.4	9.2
2	39.9	22.2	21.4	29.8	30.8	19.3
3	52.3	37.6	32.8	41.9	42.3	26.9
4	76.9	46.8	46.1	50.2	49.4	38.2
5	92.8	76.8	58.4	61.1	60.3	46.8
6	--	96.3	69.5	72.7	76.4	58.3
8	--	--	79.9	96.3	90.2	71.4
10	--	--	90.4	--	97.4	84.9

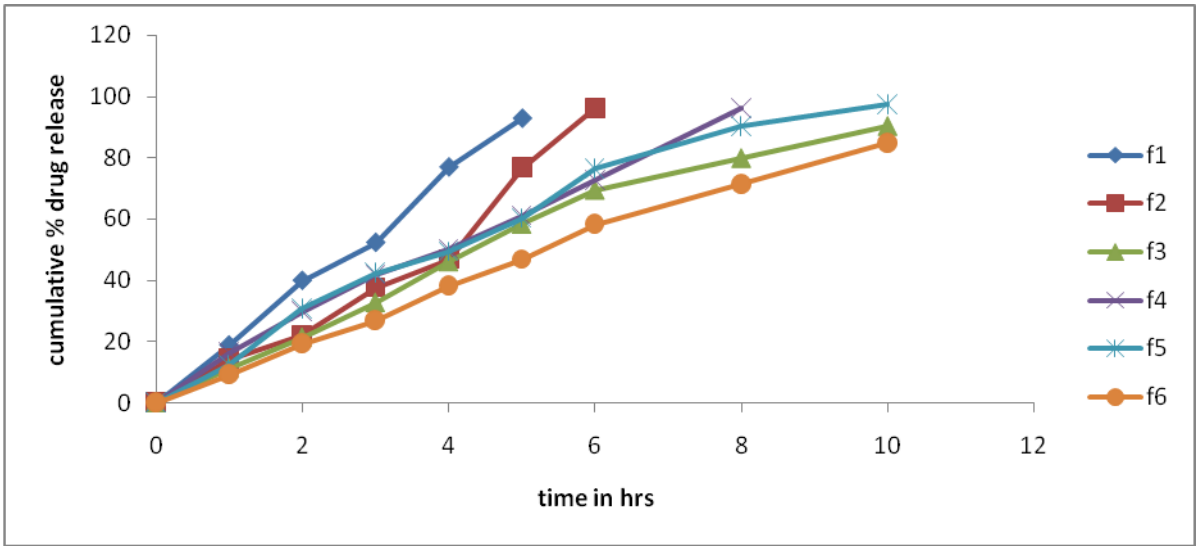

Fig-6 Dissolution profile of Oseltamivir Floating Tablets

The % Cumulative drug release of all the formulations F1, F2, F4 was not able to sustain the drug release for 10 hrs. F3 and F6 formulations showed good integrity for 10 hrs. F4 formulation was optimised based on the floating behaviour. The optimized formulation F5 showed a %drug release of 97.4% for 10 hrs which shows greater release compare to all other formulation (Fig-6).

CONCLUSION

- Gastro retentive dosage form using Guar gum was prepared to develop a floating tablet of Oseltamvir that could retain in the stomach for longer periods of time delivering the drug to the site of action, i.e., stomach.
- The pre-compression parameters of all formulations showed good flow properties and these can be used for tablet manufacture.
- The post-compression parameters of all formulations were determined and the values were found to be satisfactory.
- From the drug content and *in-vitro* dissolution studies of the formulations, it was concluded that the formulation F5 i.e. the formulation containing Guargum, PVP, Sodium bicarbonate, micro crystalline cellulose and Magnesium stearate is the best formulation.
- The % Cumulative drug release of all the formulations F1, F2, F4 was not able to sustain the drug release for 10 hrs. F3 and F6 formulations showed good integrity for 10 hrs. F4 formulation was optimised based on the floating behaviour. The optimized formulation F5 showed a %drug release of 97.4% for 10 hrs which shows greater release compare to all other formulation.
- As a result of this study it may be concluded that the floating tablets using a guar gum in optimized concentration can be used to increase the GRT of the dissolution fluid in the stomach to deliver the drug in a controlled manner. The concept of formulating floating tablets of Oseltamvir offers a suitable and practical approach in serving desired objectives of gastro retentive floating tablets.

REFERENCES

1. Robinson JR, Lee VHL. Controlled drug delivery: Fundamentals and Applications, 2nd ed. Marcel Dekker, New York, 1978, 24-36.
2. Chein YW. Novel Drug Delivery Systems, 2nd ed.: Marcel Dekker; New York, 1992, 4-56.
3. Banker GS, Rhodes CT. Modern Pharmaceutics. 3rd ed., Marcel Dekker, New York, 1996, 678-721.
4. Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances, 1st ed., Vallabh prakashan, New Delhi, 2002, 345-376.

5. Yeole PG. Floating Drug Delivery System: Need and Development. *Ind J Pharm Sci*, 2005; 67: 265-272.
6. Shweta A. Floating Drug Delivery: A Review, *AAPS Pharmscitech* 2005; 47: 268-272.
7. Desai S, Bolton S. A Floating Controlled Release System: *In-vitro* and *In-vivo* evaluation, *J Pharm Re*., 1993; 10: 1321-1325.
8. Garg S, Sharma S. Gastro retentive Drug Delivery Systems, *Pharma Tech*, 2003; 160-164.
9. Narendra C, Srinath MS, Babu G. Optimization of Bilayer Floating Tablet Containing Nevirapine as a Model Drug for Gastric Retention. *AAPS Pharm Sci Tech* 2006; 1-7.
10. Srivastava AK, Wadhwa S, Ridhurkar D, Mishra B. Oral sustained delivery of atenolol from floating matrix tablets-formulation and in vitro evaluation. *Drug Dev Ind Pharm* 2005; 31: 367-374.
11. Dave BS, Amin AF, Patel MM. Gastro retentive Drug Delivery System of Ranitidine Hydrochloride: Formulation and In Vitro Evaluation. *AAPS Pharm Sci Tech* 2004; 1-5.
12. Dalavi VV, Patel JS. Gastro retentive drug delivery system of an antiretroviral agent. *Int J Pharm Tech Res* 2009; 1: 1678-1684.