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FORMULATION AND IN VITRO EVALUATION OF FLOATING TABLET OF HYDROXY PROPYL METHYL CELLULOSE, XANTHAN GUM AND CARBOPOL 934P USING ZIDOVUDINE AS A MODEL DRUG

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ABSTRACT

The present study demonstrated successful development of effervescent based floating tablets by employing gel forming polymers and effervescent couple as a promising approach to increase the gastric residence time and drug release up to 24 hrs there by reducing the dosing frequency. Floating tablets are prepared by direct compression method by using different polymers like hydroxyl propyl methyl cellulose, Xanthan gum, and Carbopol 934 P. The sodium bi carbonate and citric acid were used as the gas generating agents. The powder blend was subjected to precompressional parameters. The prepared tablets are evaluated for post compressional parameters such as hardness, friability, weight variation, thickness, drug content, lag time, buoyancy time, in vitro dissolution studies, and swelling index and stability studies as per ICH guidelines at 40±20c/75±5% RH for 3 months. All the pre and post compressional parameters were within the acceptable limits. The values of invitro buoyancy time ranges from 3 hrs. to 24 hrs. whereas floating lag time ranges from 10-40 seconds. The in vitro drug release study reveals that formulation F1-F4 containing different grades of HPMC in which HPMC K100M was able to sustain up to 24 hours without effervescent couple. Formulation F5 containing HPMC K100 M and effervescent couple shows initially burst release indicate insufficient amount of polymer. Formulations F6-F9 contains Carbopol 934P and F10-F13 contains Xanthan gum gives sustained release. The formulation F9 shows maximum drug release at the end of 24 hrs and the release kinetics of F9 follows Korsemeyer peppas model.

KEYWORDS: Floating tablets, controlled release, HPMC K 100M, Carbopol 934 P, Xanthan gum, effervescent couple

INTRODUCTION

Delivery of the drugs in continuous and controlled manner have a lower level of side effects and provide their effects without the need for repeated dosing or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolong the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited. Appropriate candidates for controlled release gastro retentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT. Selection of excipients is an important strategic decision for designing a dosage form with consistence and controlled residence in the stomach. Water soluble cellulose derivatives represent a typical class of polymers best suited for such purposes. It has been suggested that higher molecular weight polymers and slower rates of polymer hydration are usually associated with better floating behaviour. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the non floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the non floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.[1] Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. FDDS have a bulk density less than gastric fluids and so 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. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The device must have sufficient structure to form a cohesive gel barrier, it must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010) and it should dissolve slowly enough to serve as a drug reservoir.[2] Effervescent systems pepared with swellable polymers such as methylcellulose, chitosan and various effervescent compounds, e.g.

sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.[3] Model drug belongs to anti-HIV widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life of0.8-1.5 hrs. and poor bioavailability 65%. AIDS is not a disease but a collection of conditions which resulting from the damage done to the immune system and other parts of the body as a result of infection by HIV. The success of AIDS therapy is to maintain the systemic drug concentration consistently above its target anti retro viral concentration throughout the course of the treatment. Present research work is an attempt to develop the floating tablets for controlled release to improve patient compliance in such a way that it reduces dosing frequency, reduces side effects, prolong the gastric residence time, improves the bioavailability and reduces the drug waste.[4]

MATERIALS AND METHODS

Model drug including chemicals used for the formulation and evaluation purchased from yarrow chem products.

Preformulation studies

The following pre-formulation studies were performed for the obtained sample of drug.

1. Organoleptic properties
2. Solubility analysis
3. Determination of λ_{max}
4. Standard calibration Curve
5. Drug-excipients compatibility study
6. Differential Scanning Calorimetry
7. Particle size determination

Solubility studies

Saturation solubility studies were performed by adding known excess quantity of drug (5 times the dose of drug) in 250ml respective media i.e., 0.1N Hydrochloric acid, pH 4.5 Acetate buffer pH 6.8 phosphate buffer and distilled water and subjected to incubated shaking at 100 rpm for 24hrs at 37 ^{0}C. The resultant super saturated solutions were collected and filtered through 0.45µ membrane filters and the concentration of drug was determined spectrophotometrically at their respective λ_{max} values.[6]

Drug- excipients compatibility study

Drug- excipients compatibility study by physical evaluation

To select the suitable excipients for the formulation of GRDDS, the powder mixture of drug with various excipients in different ratios was prepared and stored at 40^{o}C / 75% RH in glass vials covered with aluminum foils. The sample was visually inspected for any changes in characteristics of blend after 1 month.[7]

Table 1: Drug-Excipients Compatibility ratios.

S.No	Ingredients	Ratio
1	Drug	-
2	Drug + HPMC K100M	1:1
3	Drug +Xanthan gum	1:1
4	Drug +carbopol 934p	1:1
4	Drug +Microcrystalline cellulose(Avicel 200)	1:1
5.	Drug + Sodium bicarbonate	1:1
6	Drug +Citric acid monohydrate	1:1
7	Drug + Colloidal silicon dioxide(Aerosil 200)	1:1
8.	Drug + Magnesium stearate	1:1

Drug-excipients compatibility study by DSC

A differential scanning calorimeter was used for thermal analysis of drug and mixture of drug and excipients. The drug and excipients were passed through the #60 sieve and mixed. Accurately transferred 5 mg of drug alone and mixture of drug and excipients were taken separately in a pierced aluminum crucible with a capacity of 40µL and evaluated in METTLER TOLEDO 822e equipment using eSTAR software in temperature range of 25-350º C at a heating rate of 10 º C/min with a stream of nitrogen. The thermogram was recorded and the obtained thermogram was compared for any interaction between the drug and excipients with that of thermogram of pure drug. After every week of study, physical appearance of these compositions were made and compared with the initial observations.[6]

Drug-excipients compatibility study by FT-IR

IR spectra of pure drug and mixtures were recorded in a FT-IR spectrophotometer with KBr pellets.[6]

Preparation of gastro retentive floating matrix tablets of Zidovudine

- All the tablets, each containing 300 mg of Zidovudine, were prepared by direct compression method.
- The respective powders drug, polymers, fillers and other additives accurately weighed and passed individually through #30 mesh.

- Above powder mixture is lubricated with lubricant after passing through #60 meshes.
- Finally, the lubricated blend was compressed into tablets using 10 station rotary compression machine with punch size 16.6 x 8.2 mm concave oval shaped punches.

Table 2: Composition for extended release tablets (F1-F4).

Ingredients	Mg/tablet			
	F_1	F_2	F_3	F_4
Zidovudine	300	300	300	300
HPMC K4M premium	90	_	_	_
HPMC K15M premium	_	90	_	_
HPMC K100M premium	_	_	90	_
HPMC E50 premium	_	_	_	90
Microcrystalline cellulose (Avicel 200)	190	190	190	190
Colloidal silicon dioxide (Aerosil 200)	10	10	10	10
Magnesium Stearate	10	10	10	10
Total	**600**	**600**	**600**	**600**

Table 3: Composition for extended release floating tablets without carbopol 934P (F5) and carbopol 934P (F6-F9).

Ingredients	Mg/tablet				
	F_5	F_6	F_7	F_8	F_9
Zidovudine	300	300	300	300	300
Sodium bi carbonate	50	50	60	70	80
Microcrystalline cellulose (Avicel 200)	130	120	90	70	60
HPMC K100M	90	90	90	90	90
Carbopol 934P	_	10	20	30	40
Citric acid monohydrate	10	10	20	20	10
Colloidal silicon dioxide (Aerosil 200)	10	10	10	10	10
Magnesium stearate	10	10	10	10	10
Total	**600**	**600**	**600**	**600**	**600**

Table 4: Composition for Extended release floating tablets with xanthan gum (F10-F13).

Ingredients	Mg /tablet			
	F_{10}	F_{11}	F_{12}	F_{13}
Zidovudine	300	300	300	300
Sodium bi carbonate	50	60	70	80
Microcrystalline cellulose(Avicel 200)	120	90	70	60
HPMC K100M	90	90	90	90
Xanthan gum	10	20	30	40
Citric acid monohydrate	10	20	20	10
Colloidal silicon dioxide (Aerosil 200)	10	10	10	10
Magnesium stearate	10	10	10	10
Total	**600**	**600**	**600**	**600**

Evaluation of powder blend

Powder blends were evaluated for bulk density, tapped density, compressibility index and Hausner's ratio.[7,8]

Evaluation of Extended Release Floating Tablets

In process samples were tested for weight variation, hardness (Monsanto hardness tester), friability (Roche Friabilator, Thickness (Verneir Calliper) and drug content.[7,8]

Content uniformity test

Ten tablets from each formulation were powdered. The powdered sample equivalent to 100 mg of drug was transferred to a volumetric flask and dissolved in methanol, mixed and filtered. Required amount of 0.1 N Hydrochloric acid buffer was added to the filtrate suitably diluted with media and drug content was analyzed against blank by UV spectrophotometer at 266nm. The percentage of drug present in the tablets was calculated.[7,8]

Floating lag time and Total floating time determination

The time between the introduction of the tablet into the medium and its rise to top of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats constantly is termed as the Total floating time. These tests are usually performed in a

dissolution vessel filled with 900 ml of 0.1 N HCI (P^H 1.2) with rpm of 50. [7] [8]

Floating lag time and Total floating time determination

The time between the introduction of the tablet into the medium and its rise to top of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats constantly is termed as the Total floating time. These tests are usually performed in a dissolution vessel filled with 900 ml of 0.1 N HCI (P^H1.2) with rpm of 50.[7,8]

In vitro dissolution studies

The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus, type II (paddle). One tablet was placed in each of the six dissolution flasks containing 900 ml of dissolution medium, maintained at 37 ± 0.5°C.

After completion of each specified time interval, a 5 ml was replaced by dissolution media from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1 cm from vessel wall and filtered through 0.45 µm membrane filter. The samples were collected at specified time intervals and diluted to required volume with dissolution medium. Finally, the percentage drug dissolved was calculated.

Dissolution conditions

Medium: 0.1 N Hydrochloric acid
Volume: 900 ml
Temperature: 37°C ± 0.5°C
Apparatus: USP Type-II (Paddle)
RPM: 50
Time interval: 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24hours

Drug release kinetic studies

The dissolution data was fitted to kinetic models such as zero-order, first-order, Higuchi and Peppas-Korsmeyer equation models. The order of drug release from floating systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppas-Korsmeyer equation.[9]

Stability studies

The prepared gas generated floating tablets were subjected for stability study. To assess the stability of the optimized formulation stability study were conducted as per the ICH guide lines. Formulations were packed in HDPE bottles and were kept in the humidity chamber (Thermo lab) maintained at 40^0c/75%RH for 3 months. At the end of studies, samples were analyzed for the physicochemical parameters appearance, hardness, friability, floating behavior, drug content and *in-vitro* dissolution. [15]

RESULTS AND DISCUSSION

Organoleptic Properties

Table 5: Organoleptic properties of Zidovudine.

Properties	Observation
Description	Off White to beige powder

Flow Properties

Table 6: Flow properties of Zidovudine.

Test	Observations
Bulk density	0.523 gm/ml
Tapped density	0.634gm/ml
Carr's index	17.50 %
Hausner's ratio	1.21

Discussion: Based on the above data, the drug exhibit fair flow property

Particle Size Distribution

The particle size distribution of Zidovudine is tabulated as follows

Table 7: Particle size determination of Zidovudine

Sieve Mesh No. ASTM	Sieve Size Opening (µm)	Mass of Sample Retained On Each Sieve(g)	Cumulative amount of Sample Retained on Each Sieve	% cumulative 0f sample on each sieve
20	850	0.044	0.044	0.146
30	600	0.096	0.14	0.46
40	425	3.86	4.0	13.33
50	300	5.04	9.04	30.13
60	250	6.56	15.6	52.0
80	180	3.26	18.86	62.86
100	150	1.84	20.7	69.0
120	125	2.5	23.2	77.33
Pan	-	6.8	30	100

Discussion: From percentage cumulative size distribution it was found that around 99.54% of particles were passed through ASTM Sieve no: 30 (600 microns) and not less than 75% retained on ASTM Sieve No: 120 (125 microns).

Drug-Excipients Compatibility Study
Physical observation
Table 8: Physical observation of drug-excipients compatibility study.

Composition Code	Initial	40°C/75% RH, 1 week	40°C/75% RH, 2 weeks	40°C/75% RH, 3weeks	40°C/75% RH, 4 weeks
Drug	off-white in colour	NC	NC	NC	NC
Drug + microcrystalline Cellulose (Avicel 200)	off-white in colour	NC	NC	NC	NC
Drug + Carbopol 934p	off-white in colour	NC	NC	NC	NC
Drug + HPMC K100M	off-white in colour	NC	NC	NC	NC
Drug+ Xanthan gum	off-white in colour	NC	NC	NC	NC
Drug+ Sodium bicarbonate	off-white in colour	NC	NC	NC	NC
Drug + Citric acid monohydrate	off-white in colour	NC	NC	NC	NC
Drug+ Colloidal silicon dioxide	off-white in colour	NC	NC	NC	NC
Drug+ Magnesium stearate	off-white in colour	NC	NC	NC	NC

NC- No Change; HPMC- Hydroxypropyl Methylcellulose

Discussion: The compatibility of selected excipients with drug was evaluated by physical observation. There was no change in the physical characteristics of drug-excipient binary mixture as compared to the initial. Hence it can be concluded that the drug is compatible with selected excipients.

DSC Thermograms

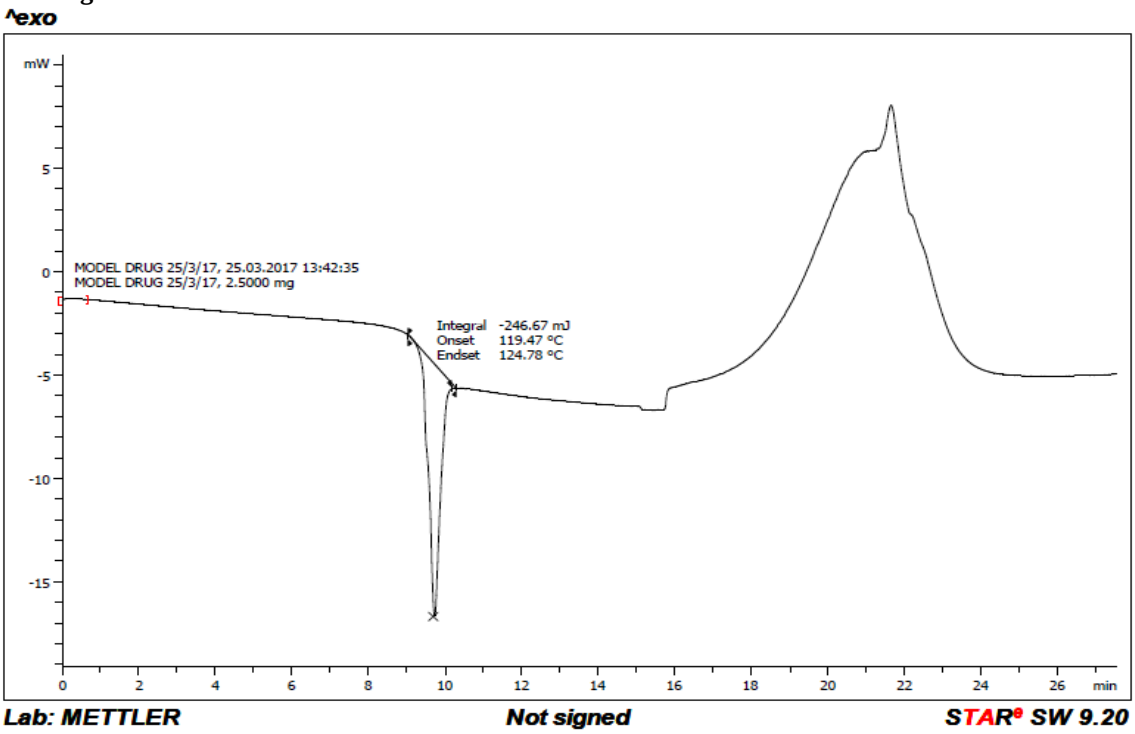


Figure 1: DSC Thermogram of Zidovudine.

Discussion: DSC thermo gram of API shows an endothermic peak in the range of 119– 125^{0}c.

DSC Thermogram of Zidovudine containing physical mixture with xanthan gum

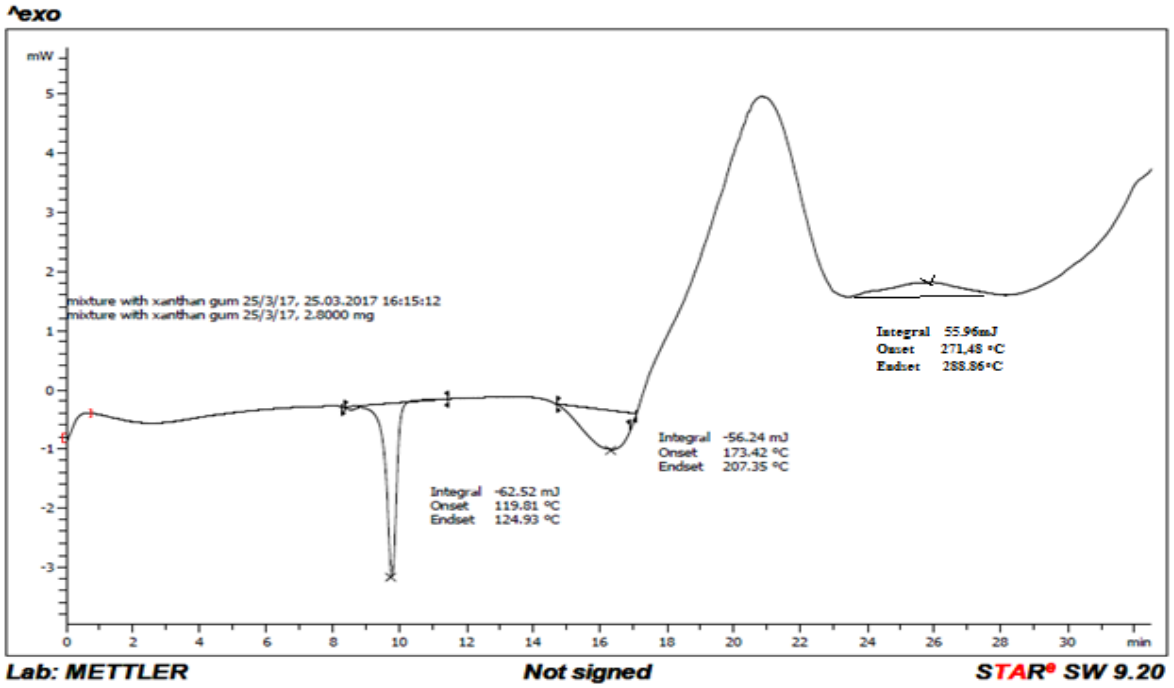


Figure 2: DSC Thermogram of Zidovudine containing physical mixture with xanthan gum.

Discussion: The above figure shows a sharp endothermic peak in the range of 119-125ºC, indicating the compatibility of all the excipients in the formulation with the Zidovudine.

DSC Thermogram of final formulation containing Carbopol 934P

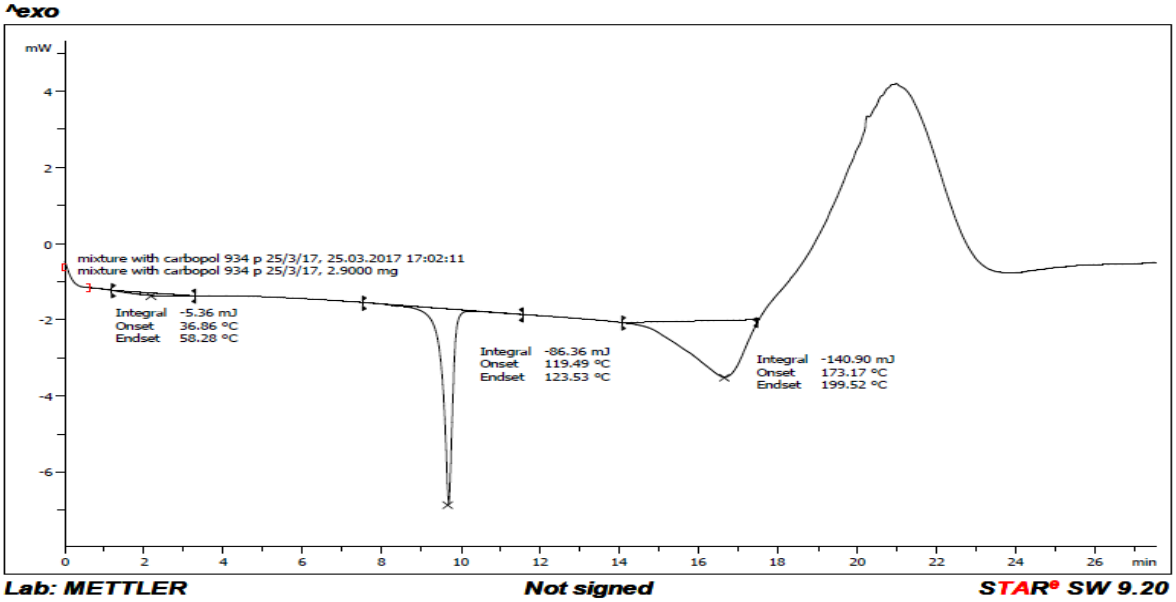


Fig 4: DSC Thermogram of final formulation containing Carbopol 934P.

Discussion: The above figure shows a sharp endothermic peak in the range of 119-125ºC, indicating the compatibility of all excipients with the Zidovudine.

FT-IR STUDIES

FT-IR spectrum of Zidovudine

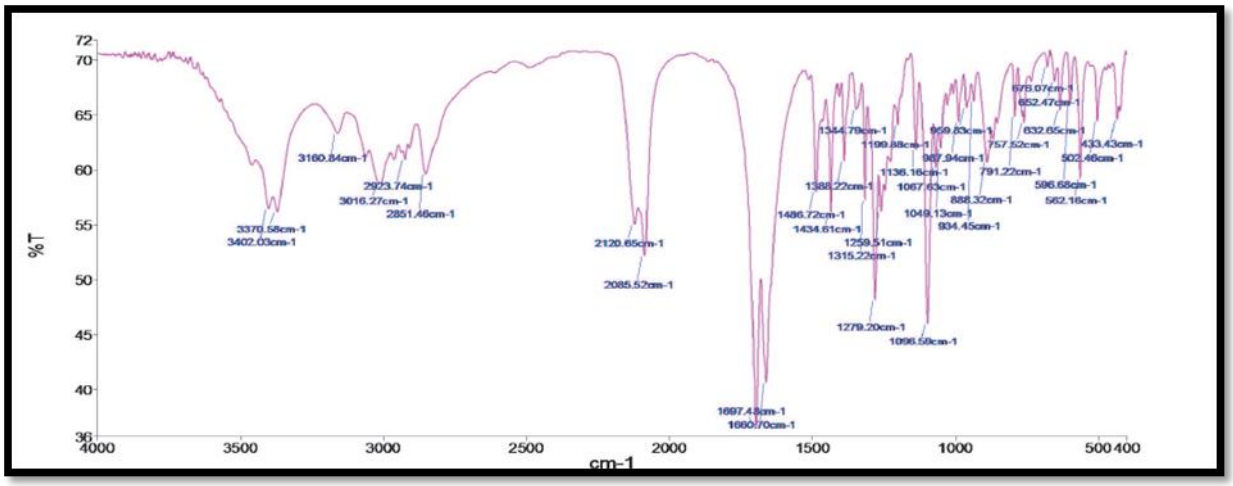


Figure 5: FT-IR spectrum of Zidovudine.

FT-IR Spectrum of physical mixture of Zidovudine containing xanthan gum [F13]

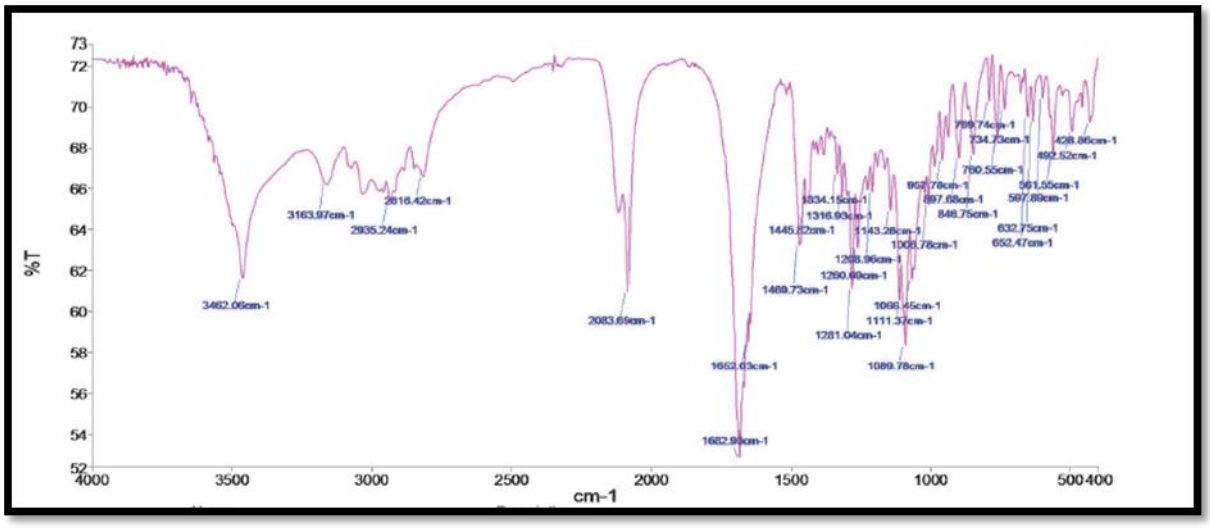


Figure 6: FT-IR Spectrum of physical mixture of Zidovudine containing xanthan gum

FT-IR Spectrum of final formulation containing Zidovudine and carbopol 934P [F9]

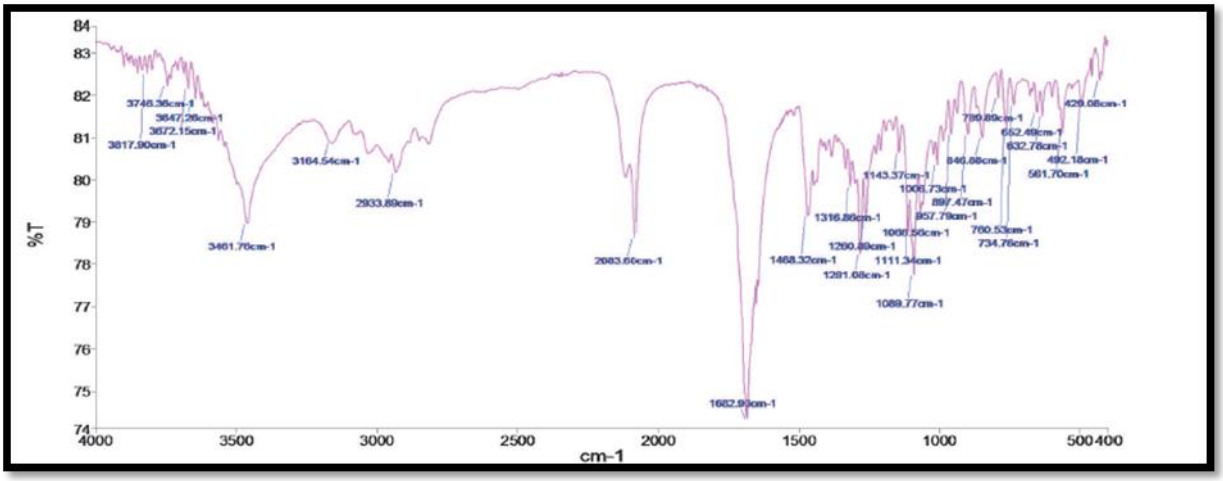


Fig: 7 FT-IR spectrum of final formulation containing Zidovudine and carbopol934P [F9]

DISCUSSION

The IR Spectra of model drug was recorded and it has showed short absorption peak due to -OH group present in the drug molecules. In this case -NH absorption peak present in the form of amine because of its weak characters exhibits a weak absorption at3313 cm-1. The aliphatic -CH absorption peak are seen from 3212-2800 cm-1. The amide C=O present in the molecules gave a short absorption peak at 1683 cm-1.

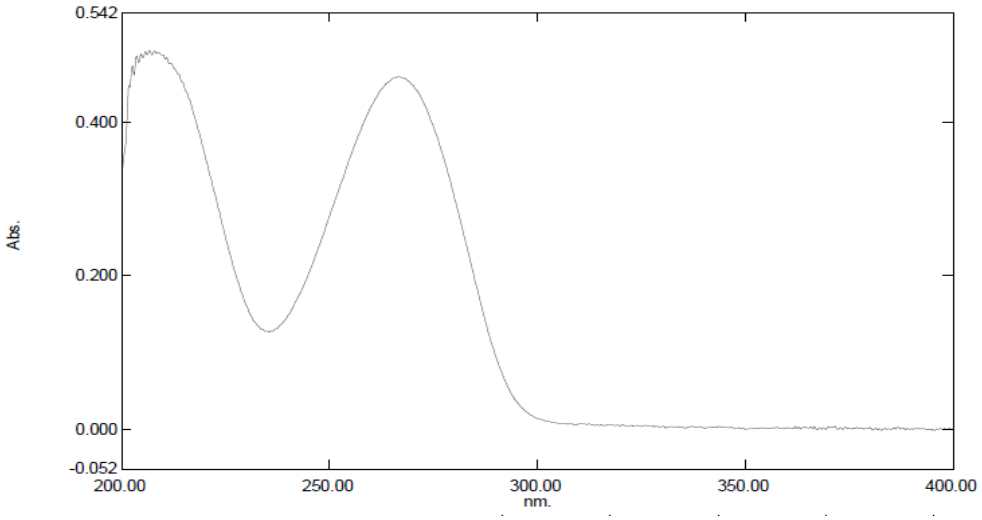
It is observed that in the IR spectrum all the characteristics absorption peaks of functionality of drug as well as excipients have remained unaffected. It suggests that the formulation obtained is a mixture of all these constituents, but not the reaction mixture. Finally, it was concluded that the drug as well as excipients are in the unreacted form.

Analytical method development results

Determination of λ_{max} for Zidovudine

10 mg of pure drug was taken and dissolved in 100 ml of buffer solutions and after suitable dilution; it was scanned from 200-400 nm against the blank solution to determine the absorption maxima for the Zidovudine.

λ_{max} for Zidovudine in 0.1 N Hydrochloric acid



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Sampling Interval: 0.2
Auto Sampling Interval: Enabled
Scan Mode: Single

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Measuring Mode: Absorbance
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Light Source Change Wavelength: 360.0 nm
S/R Exchange: Normal

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InterPolate: Disabled
Average: Disabled

[Sample Preparation Properties]
Weight:
Volume:
Dilution:
Path Length: 1.0 cm
Additional Information:

No.	P/V	Wavelength	Abs.	Description
1	↑	266.60	0.458	

Figure 8: UV spectrum of Zidovudine in 0.1N Hydrochloric acid.

Discussion: From the above spectrum, it was found that maximum wavelength was obtained at 266.60 nm.

Calibration curve of Zidovudine in 0.1N Hydrochloric acid

Table 9: Calibration curve of Zidovudine in 0.1N Hydrochloric acid.

SL. No	Concentration(µg/ml)	Absorbance
1	0	0
2	2.5	0.161
3	5	0.272
4	7.5	0.375
5	10	0.457
6	12.5	0.598
7	15	0.709
8	17.5	0.859
9	20	0.935

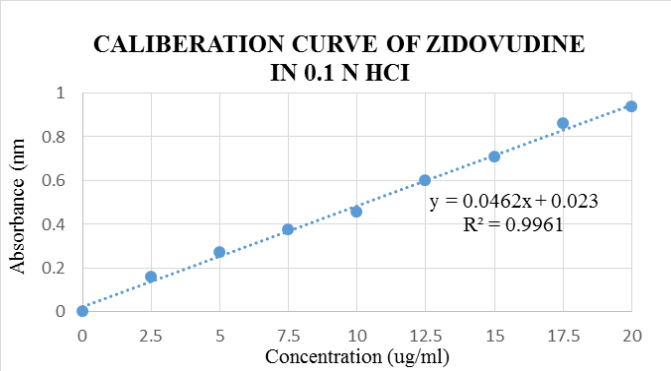


Figure 9: Calibration curve of Zidovudine in 0.1 N HCI.

Discussion: Considering the λ_{max}, calibration curve of Zidovudine was plotted (table and figure). The standard graph constructed conferred that the concentration of drug ranging from 2.5-20 ug/ml obeyed the Beer lamberts law principle. Moreover, the calibration curve of Zidovudine exhibits a good correlation between the concentration and absorbance in this range (R^2=0.9961).

λ_{max} of Zidovudine in pH 4.5 acetate buffer

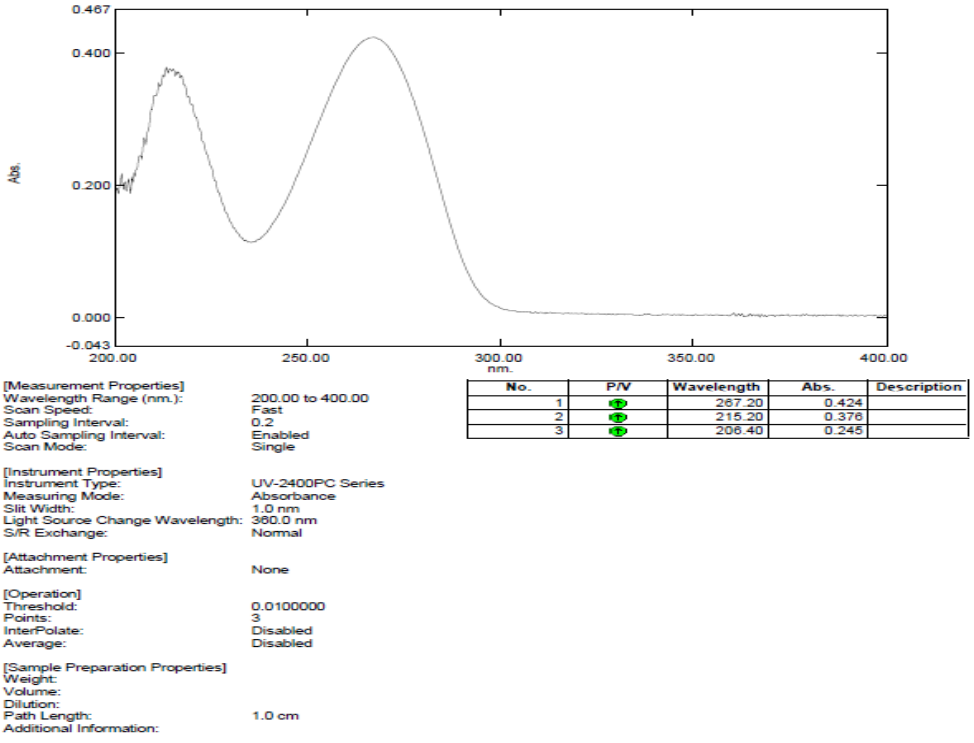


Figure 10: UV spectrum of Zidovudine in pH 4.5 acetate buffer.

Discussion: From the above spectrum, it was found that maximum wavelength was obtained at 267.20 nm.

Calibration curve of Zidovudinein pH 4.5 acetate buffer.

Table 10: Calibration curve of Zidovudine in 4.5 acetate buffer.

S. No	Concentration(µg/ml)	Absorbance (nm)
1	0	0
2	2.5	0.142
3	5	0.242
4	7.5	0.32
5	10	0.434
6	12.5	0.538
7	15	0.667
8	17.5	0.765
9	20	0.890

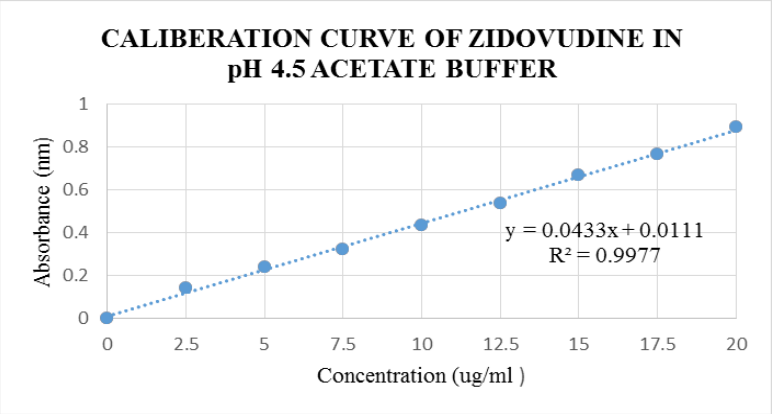
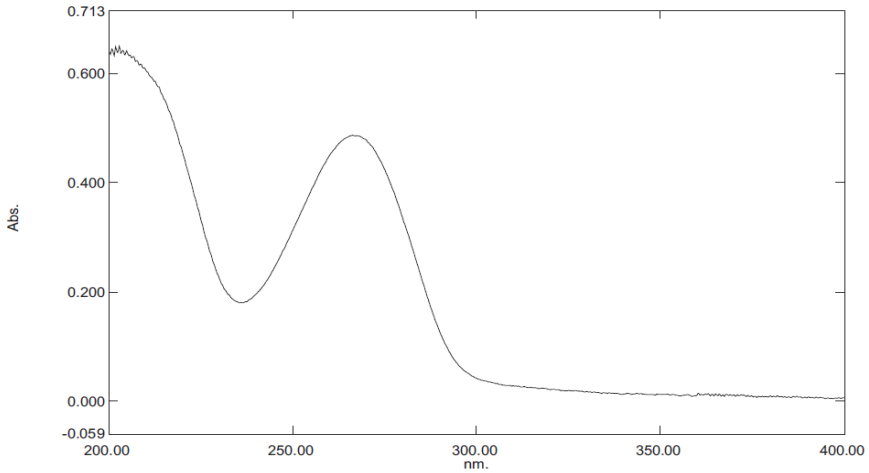
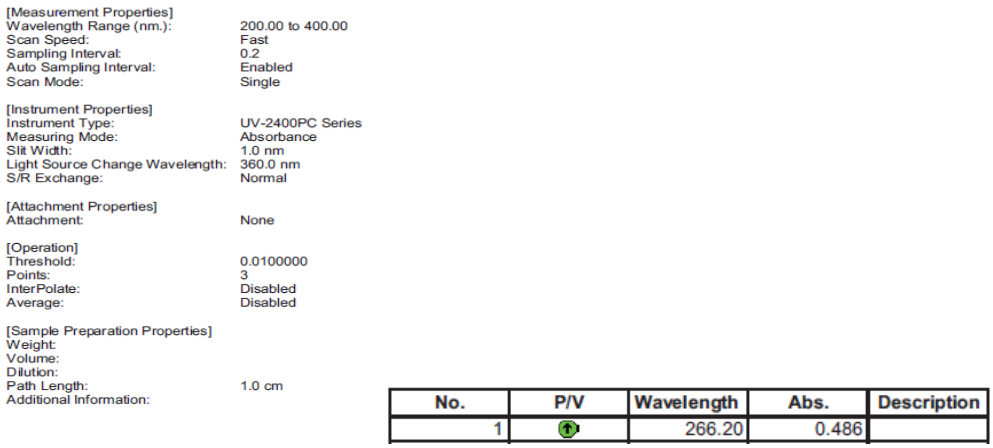


Figure 11: Calibration curve of model drug in pH4.5 acetate buffer.

Discussion: Considering the λ_{max} the calibration curve of Zidovudine was plotted (table and figure). The standard graph constructed conferred that the concentration of Zidovudine ranging from 10-50ug/ml obeyed the Beer lamberts law principle. Moreover, the calibration curve of Zidovudine exhibits a good correlation between the concentration and absorbance in this range (R^2=0.9977).

λ_{max} of Zidovudine in pH 6.8 phosphate buffer





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Scan Speed: Fast
Sampling Interval: 0.2
Auto Sampling Interval: Enabled
Scan Mode: Single

[Instrument Properties]
Instrument Type: UV-2400PC Series
Measuring Mode: Absorbance
Slit Width: 1.0 nm
Light Source Change Wavelength: 360.0 nm
S/R Exchange: Normal

[Attachment Properties]
Attachment: None

[Operation]
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Average: Disabled

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Volume:
Dilution:
Path Length: 1.0 cm
Additional Information:

No.	P/V	Wavelength	Abs.	Description
1	1	266.20	0.486	

Figure 11: UV spectrum of Zidovudine in pH 6.8 phosphate buffer.

Discussion: From the above spectrum, it was found that maximum wavelength was obtained at 266.20 nm.

Calibration curve of Zidovudine in pH 6.8 phosphate buffer

Table 12: Calibration curve of Zidovudine in pH 6.8 phosphate buffer.

S. No	Concentration(µg/ml)	Absorbance
1	0	0
2	2.5	0.175
3	5	0.244
4	7.5	0.342
5	10	0.432
6	12.5	0.568
7	15	0.689
8	17.5	0.791
9	20	0.907

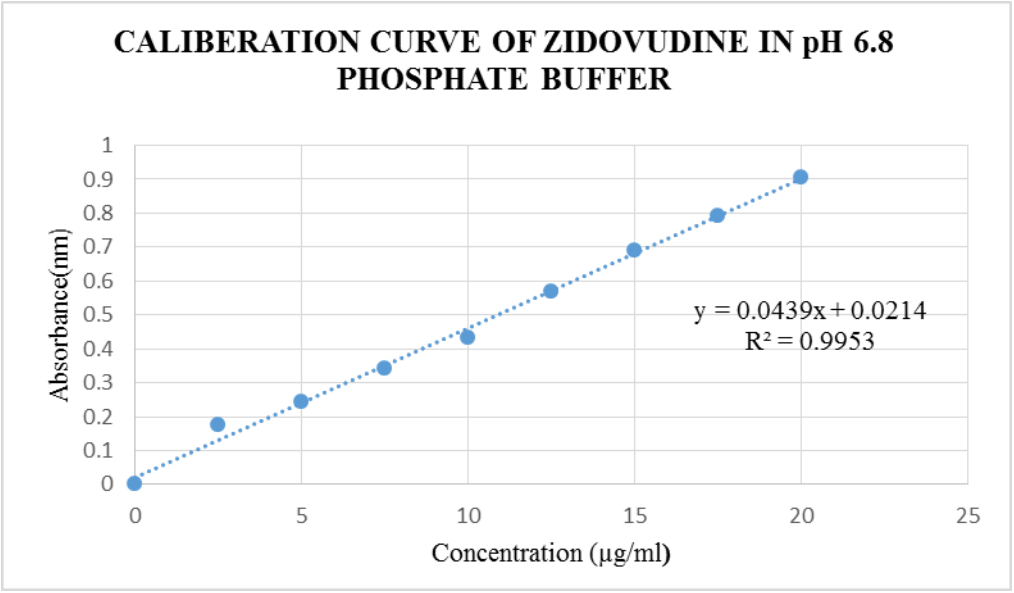

Figure 12: Calibration curve of Zidovudine in 6.8 phosphate buffer.

Discussion: Considering the λ_{max} the calibration curve of Zidovudine was plotted (table and figure). The standard graph constructed conferred that the concentration of drug ranging from 2.5-20µg/ml obeyed the Beer lamberts law principle. Moreover, the calibration curve of Zidovudine exhibits a good correlation between the concentration and absorbance in this range (R^2=0.9953).

API solubility study

Table 13: Solubility of drug in various pH conditions.

S. No	Solubility media	Solubility(mg/ml)
1	0.1N Hydrochloric acid	28.90
2	pH4.5 Acetate buffer	21.36
3	pH6.8 Phosphate buffer	20.10
4	Purified Water	27.36

The solubility data indicates that Zidovudine is having highest solubility in 0.1N Hydrochloric acid.

Evaluation of floating tablets

Evaluation properties of Powder blend of different batches:

The flow properties of all the proposed formulations (F1 to F13) were summarized in the table.

Discussion

Table 14: Blend characterization of formulations of trial batches.

S. No	Formulation Code	Bulk density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index (CI) (%)	Hausner's ratio (HR)	Angle of repose
1	F1	0.502	0.594	15.48	1.18	30.43
2	F2	0.474	0.561	15.50	1.18	30.66
3	F3	0.486	0.568	14.43	1.16	30.23
4	F4	0.468	0.549	14.75	1.17	31.23
5	F5	0.512	0.607	15.65	1.18	29.81
6	F6	0.515	0.589	12.56	1.14	29.09
7	F7	0.494	0.598	17.39	1.2	29.67
8	F8	0.486	0.568	14.43	1.13	29.09
9	F9	0.468	0.549	14.75	1.17	30.25
10	F10	0.486	0.568	14.43	1.16	28.68
11	F11	0.494	0.598	17.39	1.2	29.56
12	F12	0.468	0.549	14.75	1.17	30.45
13	F13	0.512	0.607	15.65	1.18	31.27

Discussion: The values of the bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio of the 13 trial batches indicate that all blends possess good flow properties.

Post Compression Parameters

Table 15: Physical characterization of tablets.

Formulation code	Average weight of Tablet(mg) (N=20)	Average thickness (mm) (N=5)	Average hardness (Kp) (N=5)	Friability (%)	Swelling index (%) (N=5)
F1	600.12±0.42	5.35±0.02	8.9±0.02	0.38	89.40±0.02
F2	602.72±0.57	5.34±0.08	8.9±0.08	0.39	105.59±0.12
F3	598.20±0.76	5.35±0.03	9.9±0.06	0.36	112.82±0.09
F4	597.70±0.72	5.32±0.04	10.0±0.03	0.46	-
F5	601.70±0.51	5.34±0.02	8.5±0.08	0.39	-
F6	603.50±0.79	5.35±0.07	9.5±0.02	0.39	158.72±0.09
F7	599.90±0.54	5.30±0.02	9.3±0.09	0.37	169.28±0.08
F8	600.10±0.74	5.38±0.01	9.1±0.02	0.39	169.20±0.07
F9	601.40±0.42	5.35±0.04	8.7±0.04	0.36	133.27±0.12
F10	600.50±0.38	5.30±0.06	8.1±0.05	0.39	155.05±0.09
F11	602.70±0.62	5.35±0.02	8.9±0.06	0.38	160.30±0.11
F12	603.10±0.65	5.33±0.04	8.5±0.06	0.38	177.80±0.10
F13	600.12±0.72	5.30±0.08	9.4±0.06	0.37	171.16±0.09

Discussion

The observed weight was found to be within 598-604mg. The thickness of tablets was found to be between 5.3-5.4 mm.The hardness for different formulations was found to be between 8 to 10 Kp, indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet.

Drug content estimation

Table 16: Drug content of the prepared formulations.

Formulation Code	%Drug content
F1	99.92%
F2	91.95%
F3	99.96%
F4	95.99%
F5	99.89%
F6	99.80%
F7	96.90%
F8	99.96%
F9	99.92%
F10	99.89%
F11	98.99%
F12	97.90%
F13	99.96%

Discussion: As per above data prepared floating tablets were shown percentage drug content within range of 95-100%.

***Invitro* drug release studies**

Optimization of HPMC

Table 17: *In vitro* dissolution studies of formulations (F1- F5).

Time (in hours)	% Drug Release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	13.77	10.67	6.20	19.58	36.19
2	21.80	16.05	11.20	30.28	50.66
4	29.65	23.52	18.23	39.90	62.30
6	35.68	32.98	27.67	51.22	68.30
8	47.88	41.92	34.01	63.66	76.35
10	55.22	50.28	42.73	75.25	86.98
12	64.24	58.24	51.64	88.90	99.92
14	72.20	67.29	59.62	99.98	-
16	81.20	75.52	68.21	-	-
18	92.21	82.21	75.34	-	-
20	99.88	90.11	83.98	-	-
22	-	99.80	91.54	-	-
24	-	-	99.98	-	-

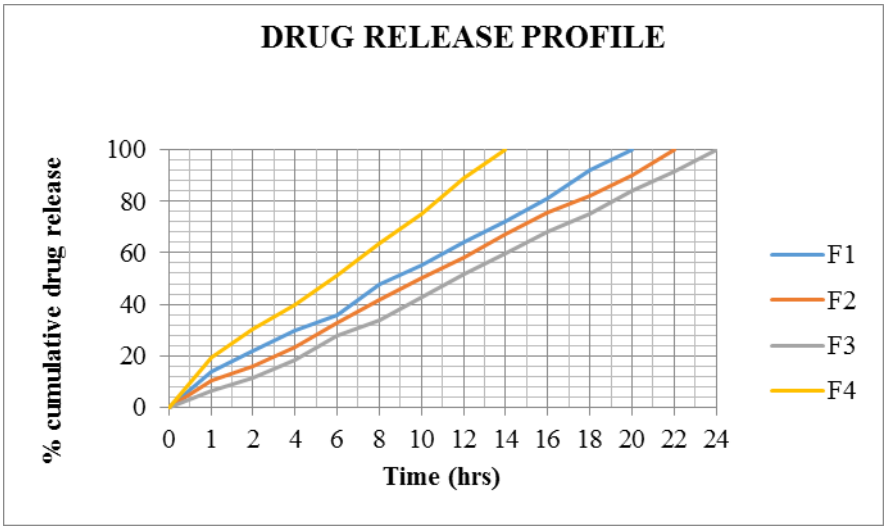

Figure 13: *In vitro* dissolution profile of F1-F4 tablets in 0.1 N Hydrochloric acid

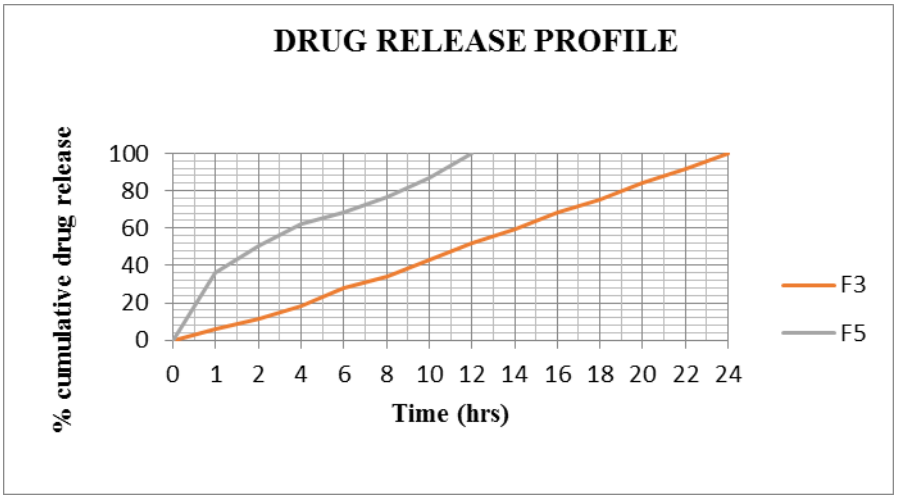

Figure 14: *In vitro* dissolution comparison profile of F3 and F5 tablets in 0.1N HCI.

DISCUSSION

The drug release profiles of formulations F1, F2, F3 with 90 mg of HPMC K4M, HPMC K15M, HPMCK100M and HPMC E50M respectively were compared. The percentage of drug release decreased in the rank order of HPMC E50> HPMC K4M >HPMC K15M >HPMC K100M due to the increasing viscosity grade of polymer.Polymer molecular chains of HPMC hydrate quickly and entangle to form a gel matrix. Rapid formation of this gelatinous layer is critical to prevent the wetting of the interior and disintegration of tablet core. At lower HPMC grade, rapid swelling of matrices with less tight hydrogel structure resulted in higher initial drug release followed by complete release within short time period. Conversely at the higher HPMC grade, the initial drug release was diminished and drug diffuses slowly continuously for 24 hours. Formulation F3 containing HPMCK100M being a high viscosity grade polymer showed controlled drug release pattern and maintains the tablet integrity compared to F1, F2, F4. F5 shows burst release initially due to the formation of carbon di oxide and insufficient amount of polymer.

Optimization of Carbopol 934P concentration

Table 18: In vitro dissolution studies of formulations (F6- F9)

Time (in hours)	% Drug Release			
	F6	F7	F8	F9
0	0	0	0	0
1	19.99	16.70	10.69	5.96
2	23.09	20.90	15.80	10.20
4	34.50	30.54	24.98	17.26
6	46.80	42.95	33.89	25.32
8	57.10	53.76	42.57	33.01
10	66.09	62.87	51.98	41.73
12	78.99	73.65	62.99	49.84
14	89.99	82.89	70.91	57.36
16	99.86	90.09	81.09	65.87
18	-	99.98	89.90	73.29
20	-	-	99.87	81.98
22	-	-	-	89.98
24	-	-	-	99.29

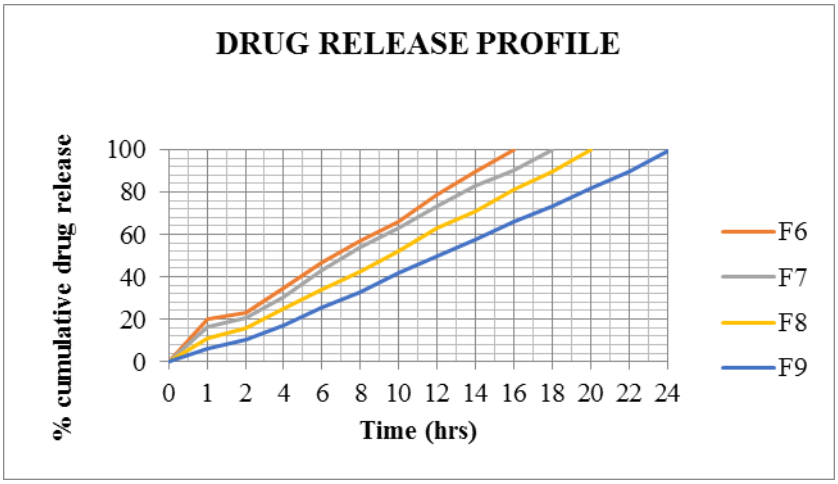

Figure 15: *In vitro* dissolution profile of F6-F9 tablets in 0.1 N Hydrochloric acid.

DISCUSSION

Carbopol 934P have very fine particle size and also bearing static charge thus it is not free flowing so Inclusion level of Carbopol 934p is 3-7% for direct compression. The drug release profiles of formulations and F5, F6, F7 and F8 with 90 mg of HPMCK100 and varying concentration of carbopol934P performed. If the polymer concentration is too low, as in case of F6, a complete gel layer formation may be hindered thereby resulting in a significant amount of drug being released initially. There is an existence of inverse proportionality between the drug release rate and thickness of this hydrogel layer, because it takes time for drug molecules to travel across the gel layer and reach the dissolution medium. The higher proportion of polymer in the tablet enables the formation of a thicker hydrogel layer and subsequently delays the time required for drug release. Synergistic interaction is observed between Carbopol 934P and HPMC in controlled drug release. This combination minimizes the release of drug in the initial phase of the release profile, leads to flatten the shape of the release profile i.e. it produces more zero order release. It has been observed that drug release from the tablet matrix has been decreased with an increase in the concentration of the polymers in the formulation.The results were revealed that as the concentration of sodium bi carbonate increases from 30-60 mg per tablet, there is an increase in the floating time and an increase in citric acid concentration increased the release rate but reduced the floating time, probably due to the excess carbon dioxide disturbing the monolithic tablet. From these results the ratio between sodium bicarbonate and citric acid 8:1 gives the optimum results. Hence on comparing F6, F7, F8 and F9, it can be inferred that F9 is best suited for depicting extended release profile showing 99.29% drug release at the end of 24 hours.

Optimization of xanthan gum concentration

Table 19: *In vitro* dissolution studies of formulations of F10– F13.

Time (in hours)	% Drug Release			
	F10	F11	F12	F13
0	0	0	0	0
1	26.40	19.91	10.75	8.76
2	32.65	22.69	18.97	15.00
4	41.76	37.83	31.72	27.47
6	53.75	50.15	48.45	34.77
8	64.98	62.46	61.78	44.66
10	73.54	75.98	69.98	58.97
12	87.88	88.15	80.74	69.98
14	98.99	99.21	89.10	78.99
16	-	-	99.82	85.99
18	-	-	-	92.96
20	-	-	-	99.96
22	-	-	-	-
24	-	-	-	-

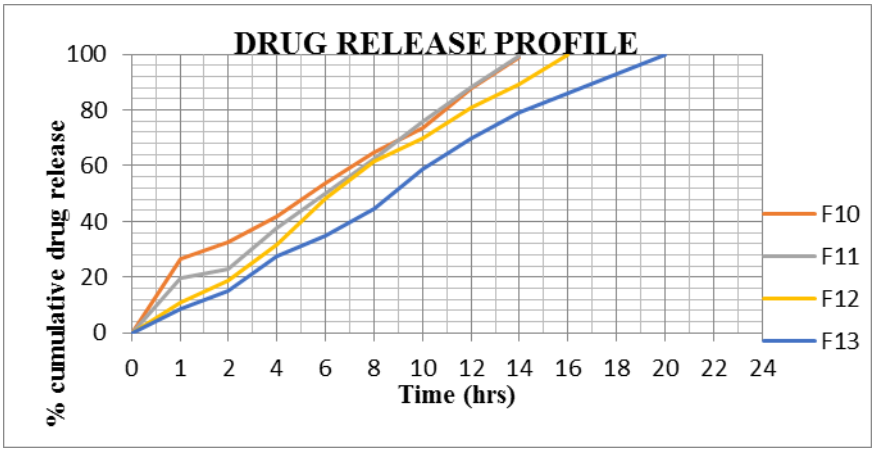

Figure 16: *In vitro* dissolution profile of F10-F13 tablets in 0.1 N Hydrochloric acid

Discussion: Results showing that compared to formulation containing carbopol 934P it show faster drug release due to its larger water uptake.On comparing F10, F11 and F12 and F13, it can be inferred thatF13 is best suited for depicting extended release profile.

***In vitro* buoyancy studies**

Buoyancy lag time and duration of floating

Table 20: *In vitro* floating lag time studies for formulation trials (F1to F4)

Formulation code	Buoyancy lag time	Duration of floating (in hours)
F1	Sinked	-/-
F2	Sinked	-/-
F3	Sinked	-/-
F4	Sinked	-/-

DISCUSSION

Insignificant buoyancy lag time and floating duration was observed with formulations F1, F2, F3, and F4which was due to the incapacity of the polymers. From the in vitro buoyancy studies it was being inferred that addition of sodium bicarbonate and citric acid was a requisite for the tablet to depict gastro retentive property.

Table 21: *In vitro* Floating lag time studies for formulation trials (F6-F9).

Formulation code	Buoyancy lag time (in sec) (N=5)	Duration of floating (in hours) (N=5)
F6	40±0.01	6±0.11
F7	17±0.03	9±0.07
F8	15±0.02	13±0.09
F9	12±0.01	24±0.10

Discussion

From the above table, it was observed that formulations F6-F8 showed buoyancy lag time in the range of 15 to 60 seconds. Duration of floating 24 hours for F9 in which $NaHCO_3$ and citric acid concentrations were 80mg/tablet and 10mg/tablet respectively. When floating characteristics of the four formulations were compared, shorter floating lag time and longer duration of floating was observed in formulation F9. Formulation F9 floated within 12 seconds upon immersion in to the media and floated for 24hours, hence F9was considered to be the optimized formulation for exhibiting gastro retentive floating properties.

Table 22: *In vitro* Floating lag time studies for formulation trials (F10-F13)

Formulation code	Buoyancy lag time (in sec) (N=5)	Duration of floating (in hours) (N=5)
F10	30±0.01	3±0.19
F11	15±0.02	8±0.11
F12	13±0.02	10±0.09
F13	10±0.01	18±0.11

Formulation F13 floated within 12 seconds upon immersion in to the media and floated for 18hrs, due to larger water uptake and high swelling capacity. So floating hours is limited to 18 hours.

Effect of Sodium bicarbonate and Citric acid concentration on buoyancy lag time and duration of floating time.

Tablets were prepared by effervescent technique using sodium bicarbonate and citric acid as a gas generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of citric acid and dissolution medium (0.1 N Hydrochloric acid). The gas generated is trapped and protected within the gel formed by hydration of polymer, leading to decreasing the density of the tablet below 1 and the tablet becomes buoyant. The P^H of the stomach is elevated under fed condition, therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate. The results of *in vitro* buoyancy studies revealed that the concentration of sodium bi carbonate increases there is increase in total buoyancy time and decrease lag time. It is evident from the *in vitro* dissolution data that increase in citric acid concentration increased the release rate but reducing the floating time probably due to the excess of carbon di oxide disturbing the monolithic tablet.

Drug release kinetics

The dissolution data of all the formulations were fitted to zero order, first order, Higuchi model, and Korsmeyer-Peppas model to study the drug release kinetics.

Table 23: *In-vitro* release kinetics for proposed formulation of extended release floating tablets of drug

Formulation Code	Zero order	First order	Higuchi	Korsemeyerpeppas	
				(R^2)	n
F1	0.983	0.96	0.975	0.987	0.580
F2	0.993	0.970	0.975	0.991	0.669
F3	0.998	0.973	0.969	0.997	0.828
F4	0.979	0.228	0.173	0.990	0.563
F5	0.86	0.035	0.026	0.985	0.354
F6	0.985	0.626	0.969	0.965	0.542
F7	0.986	0.943	0.978	0.973	0.591
F8	0.995	0.950	0.969	0.994	0.684
F9	**0.999**	**0.977**	**0.988**	**0.997**	**0.807**
F10	0.962	0.238	0.133	0.974	0.449
F11	0.987	0.261	0.196	0.963	0.604
F12	0.986	0.661	0.992	0.997	0.828
F13	0.994	0.954	0.974	0.996	0.806

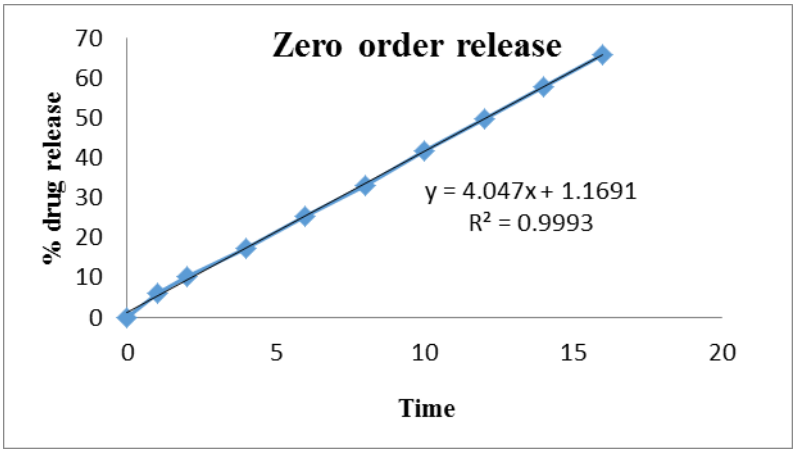

Figure 17: Zero order plot of F9.

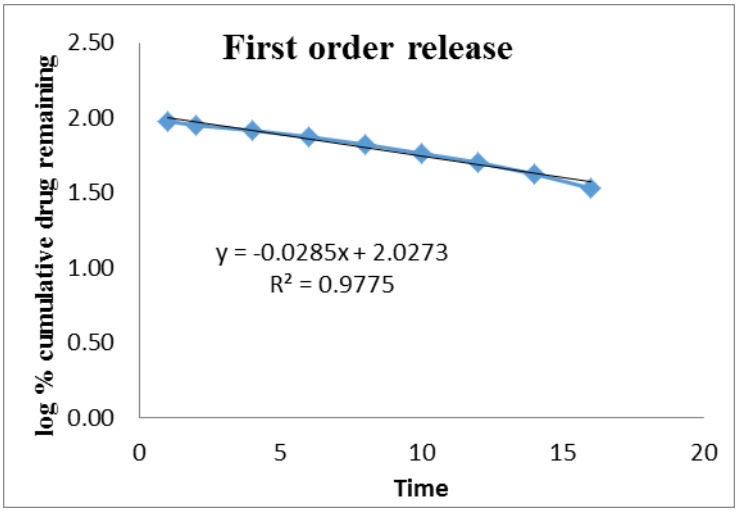

Figure 18: First order plot of F9.

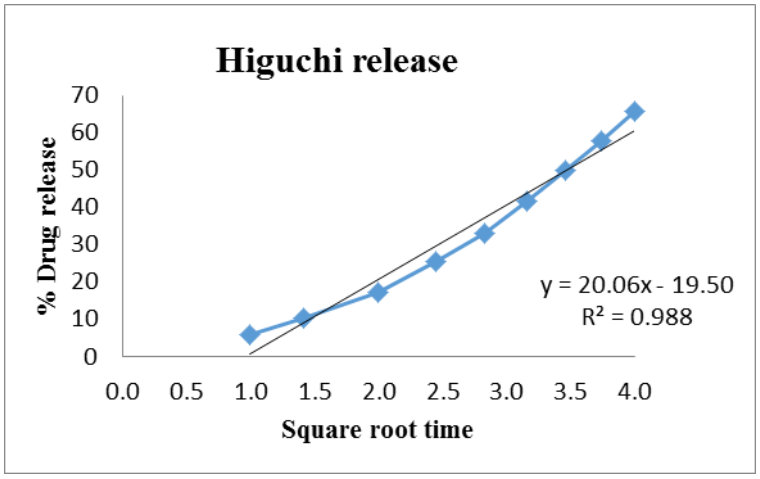

Figure 19: Higuchi plot of F9.

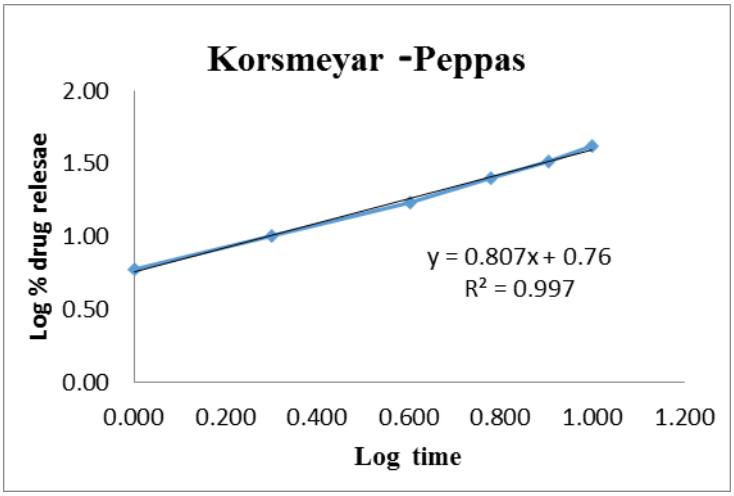

Figure 20: Korsmeyer- peppas plot of F9.

Discussion: Different kinetic equations (zero-order, first-order and Higuchi equation) were applied to interpret the release mechanism of drug from the floating tablets.

The zero order plots were found to be fairly linear as indicated by the high regression values (R^2 =0.979-0.999). To ascertain, the drug release mechanism the in vitro release data were also subjected to Higuchi's diffusion equation, it should be > 0.95 suggests that the drug released by diffusion mechanism. To confirm the exact mechanism of drug release from the tablets, the data were fitted according to Korsemeyer's equation. Regression analysis was performed and regression values were (R^2=0.973- 0.997) for different formulations. Slope

values 0.45-0.89 suggests that the release from gas powdered tablets follows anomalous or non-fickian type of diffusion. The anomalous behavior corresponds to sum contribution from diffusion, erosion and swelling-controlled mechanisms. It is observed that in the case of HPMC and carbopol 934P polymers, Fickian diffusion predominates in the initial period of the dissolution, gradually decreasing until polymer erosion becomes predominant. In the later stage, the thickness of the viscous gel layer around the matrix will increase with time creating a longer path length for the drug to diffuse into the dissolution medium. Thereafter, the polymer chains increasingly relax, disentangle, and erode. It is noted that drug release due to erosion takes over the declining diffusional release mechanism about the half way through the dissolution time period. Overall, the release mechanisms from these polymers can be explained as a result of rapid hydration of the polymers on the surface of the tablets, which results in a gel or a highly viscous solution surrounding the matrix that restrict water penetration in to the center. The net result is a reduction of the rate of drug release as a function of time. From this study, it can be concluded that the drug release predominantly follows non-Fickian diffusion. In the case of F9 the zero order plots were found to be fairly linear as indicated by their high regression value of 0. 999. To ascertain, the drug release mechanism the data were also subjected to Higuchi's diffusion equation the R^2 value found to be 0.988suggest that drug released by diffusion mechanism. To confirm the exact mechanism of drug, release the data were fitted to Korsmeyer-Peppas model gives R^2value of 0.997. As the n value for the Korsmeyer-Peppas model was found to be less than 0.89 (0.807), it follows anomalous or non-Fickian type of diffusion.

Stability studies

Floating tablets of formulation F9 was subjected to stability study at 40°C/75% RH for 3 months. The tablets were evaluated for Appearance, Weight variation, Thickness, Diameter, Hardness, Friability, Assay and Dissolution.

Physico chemical properties of final formulation F9 after 3 months

Table 24: Physicochemical properties of F9 after stability study.

Parameters	After 3 months
Physical appearance	No change
Tablet weight (mg) (N=5)	600.02±0.02
Thickness (mm) (N=5)	0.54±0.09
Hardness (Kp) (N=5)	9.2±0.12
Friability (%)	0.36±0.11
Drug content (%)	98.99%
Buoyancy lag time (sec) (N=5)	12±0.02
Total floating time (hours) (N=5)	24±0.19

Dissolution profile after 3 months

Table 25: In vitro dissolution profile after stability study.

Time (in hours)	% drug release
0	0
1	5.99
2	11.23
4	17.13
6	25.10
8	33.01
10	41.23
12	49.13
14	57.36
16	65.43
18	72.99
20	81.10
22	89.98
24	99.19

DISCUSSION

The results do not show any significant change in physical appearance, hardness, friability, content uniformity, buoyancy and dissolution behavior of floating tablets in comparison with initial values. No visible changes in the appearance of the tablets were observed at the end of the storage period and there was no change in the drug content.

CONCLUSION

- The basic goal of formulation is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design

of proper dosage form is an important element to accomplish this goal. One such area of research is design of gastro retentive floating drug delivery system

- Floating drug delivery system is one of the most attractive and promising approach for increasing oral bioavailability by means of increasing gastric retention time
- Zidovudine is one of the most important anti- retro viral agents used in the treatment for HIV/AIDS with a half-life of 0.5 to 3 hours and requires multiple daily doses to maintain adequate plasma concentrations. Hence Zidovudine can be regarded as a suitable candidate for controlled release dosage forms
- The objective of this present work is to develop an extended release formulation of Zidovudine for 24 hrs. and thereby reducing the frequency of administration.
- Preformulation study was performed by formulating binary mixtures of drug with selected excipients. Binary mixtures were screened for physical appearance at initial and 40°C ± 2°C / 75% ± 5% RH, 4 weeks in close condition. Physical observations of binary mixtures and DSC study revealed that there is no incompatibility between selected excipients and Zidovudine.
- UV spectrophotometric analytical method was developed for the Zidovudine in 0.1 N HCl. Absorption maxima was found to be at 266.60 nm and the linearity was fixed between the ranges of 2 to 20 µg/ml.
- Saturation solubility studies of Zidovudine were performed in different medias 0.1N HCl, pH 4.5 Acetate buffer, & pH 6.8 Phosphate buffer
- Preformulation study was done initially. DSC data revealed that the drug and polymers used were compatible. Various physical properties of blend like specific surface area, shape, hardness, surface characteristics, and practical size can significantly affect the rate of dissolution of drugs contained in a formulation. Various formulation trials of extended release tablets of Zidovudine were developed using polymers like HPMC, carbopol 934P and xanthan gum in different proportions by using direct compression technique.

Physicochemical evaluation of floating extended release tablets:

The results of the thickness, hardness, and weight variation, friability, floating duration and floating lag time were evaluated. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references.

- Gastro retentive tablets were formulated with effervescent couple citric acid and sodium bicarbonate and binding polymers like HPMC, carbopol 934P, and xanthan Gum.
- The formulation was optimized for polymer and effervescent couple concentration by formulating and evaluating different trials (F1-F13). Formulation F9 had showed better release profile of 99.29 % with extended release period of 24 hours and also provides 24 hours floating time.
- Based on the *in-vitro* drug release studies, the data were fitted into different kinetic models shows zero order release pattern followed by non-Fickian transport mechanism.

SUMMARY

The present study demonstrated the successful development of an effervescent based floating drug delivery system by employing gel forming polymers (combination of HPMC K100M and carbopol 934 p) and an effervescent couple (sodium bicarbonate and citric acid) as a promising approach to increase the gastric residence time and drug release of model drug up to 24 hours, thereby reducing the dosing frequency.

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Last but not the least, we would like to thank my family, my mother and to my brothers and sisters for supporting me spiritually throughout writing the thesis and my life in general.

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