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FORMULATION AND EVALUATION OF ORAL FLOATING TABLET OF ETHAMSYLATE

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ABSTRACT

The most important route of administering drug for systemic effects is the oral route of drug administration among all the route of drug delivery system. Floating tablet of ethamsylate formulated to increase gastric residence and thereby improve its therapeutic efficacy. The objective of this study was to formulate an oral floating tablet of ethamsylate using HPMC E15 LV, beeswax and ethyl cellulose. A fractional factorial design was applied systemically to assess the influence of 3 independent variables namely: amount of HPMC (X1), amount of beeswax(X2) and amount of ethyl cellulose(X3). EC and HPMC were used as floating and rate controlling polymers while beeswax used as hydrophobic meltable binders. From the present study it was observed that varying amount of the HPMC E15, beeswax and ethyl cellulose had significant influence on the lag time and % drug release of the prepared floating tablets. Tablets were prepared by melt granulation and evaluated by various parameters such as hardness, friability, weight variation test, In vitro buoyancy, drug content, in vitro drug release. Hardness was found to being the range from 4.3±0.13– 5.3±0.25kg/cm, The friability of prepared tablets was found in the range from 0.38%-0.72% which was satisfactory according to I.P.(0.5%-1%), The drug content varied from 93.75±0.87 to 104.62±0.38. All the prepared batches show it satisfactory floating time and in vitro drug release properties but F3can be considered to be the best optimised formulation because of least floating lag time and highest similarity factor.

KEYWORDS: Ethamsylate, HPMC, floating drug delivery, beeswax, ethyl cellulose.

INTRODUCTION

The oral route of drug administration is the most important route of administering drugs for systemic effects. To achieve and maintain the concentration of administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and this result in fluctuating levels in plasma. Controlled drug delivery systems have been introduced to overcome the drawbacks of fluctuating drug levels associated with conventional dosage forms.[1]

Controlled and targeted drug delivery to the stomach could be achieved via prolongation of the gastric residence time. Gastro retentive systems are important for drugs which exert local effect in the stomach; drugs which are poorly soluble in the intestine, such systems improve gastrointestinal absorption of drug with narrow absorption window as well as controlling release of drugs having site specific absorption limitations. Drugs that are slowly absorbed from G.I.T can be given as slow release gastric retention system to improve the absorption and bioavailability (Fig 1). To design such a system many factors are to be considered. Recently several approaches have been developed to increase gastric residence time of drug formulation.[4,5.6,7]

Recently, several technical advancements have led to the development of several novel drug delivery system (NDDS) that could revolutionise method of medication and provide number of therapeutic benefits by coupling the drug to carrier particles such-as microspheres, nanoparticles and liposomes, which modulate the release and absorption characteristics.[5]

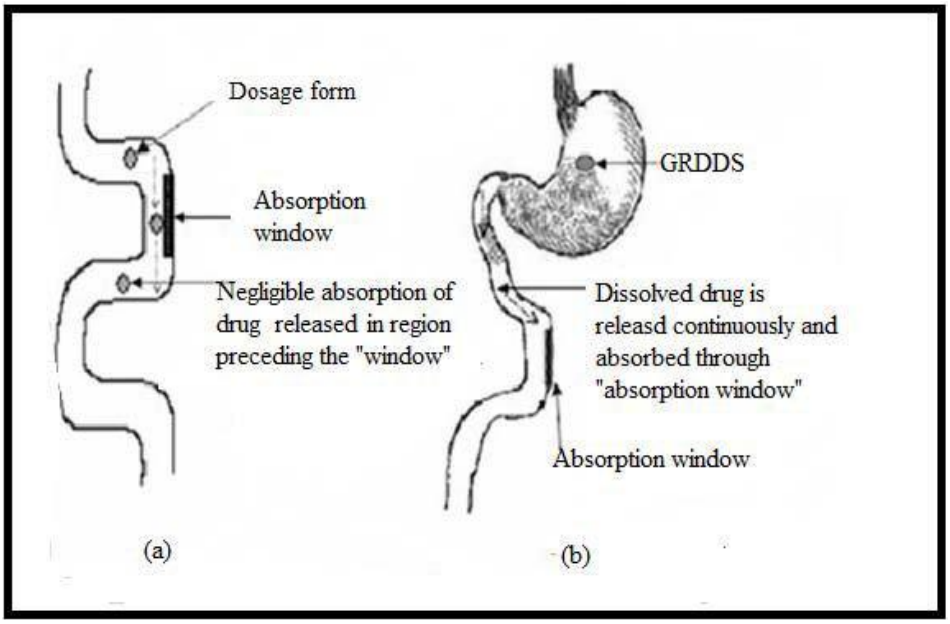

Figure 1: Drug absorption in case of (a) conventional dosage forms (b) gastroretentive drug delivery systems.[7]

Approaches to gastric retention

Approaches for gastric retention include:mucoadhesion, floatation, sedimentation, swelling and are represented in Fig.2.

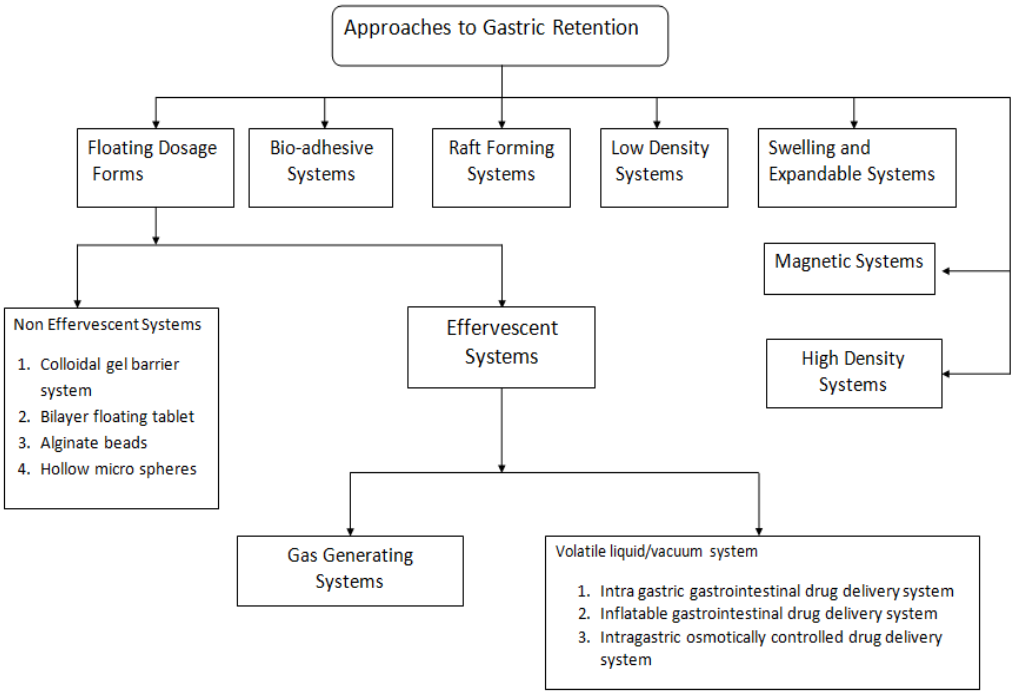

Figure 2: Approaches to gastric retention.

Among them the principle of floating drug delivery preparations offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.[8]

Floating drug delivery system

Floating drug delivery system is also called the hydrodynamically balanced system (HBS). Floating drug delivery systems (FDDS) have a bulk density less than gastric fluid and so remain buoyant in the stomach without being affected by gastric emptying rate for a prolonged period of time. This delivery system is further divided into non effervescent and effervescent (gas-generating system).[9]

A) Non-effervescent system

a) Colloidal gel barrier system

Hydrodynamically balanced systems (HBS) contain drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. On coming in contact with gastric fluid, the hydrocolloids in the system hydrate and form a colloidal gel barrier around its surface.[10]

b) Micro porous compartment systems

This technology is based on the encapsulation of adrug reservoir inside a micro porous compartmentwith apertures along its top and bottom walls. Theperipheral walls of the drug reservoir compartmentare completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolveddrug.[11]

c) Multiparticulate system: Floating Beads

In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00mm. To deliver the recommended total dose, these subunits are filled into a sachet.[12]

d) Microballoons

Hollow microspheres are known as the microballoons Microballoons are floatable in vitro for 12 hrs, when immersed in aqueous media. Microballoons (hollow microspheres) loaded with drugs in their polymer shelf were prepared by simple solvent evaporation or solvent diffusion/ evaporation method to create a hollow inner core (Figure 3), which prolongs the GRT of the dosage form.[13]

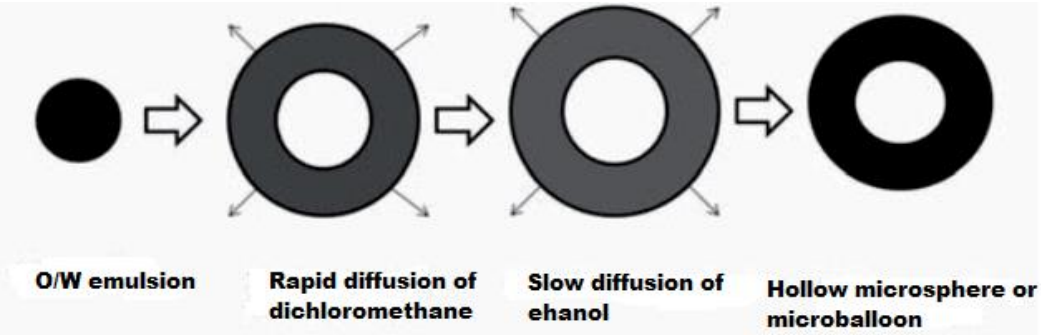

Figure 3: Formulation of floating hollow microsphere or microballoon.

(B) Effervescent systems

A drug delivery system can be made to float in thestomach by incorporating a floating chamber, which may be filled with vacuum, air or inert gas.

a) Volatile liquid containing systems

These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach.

b) Gas generating systems

These buoyant delivery systems utilizes effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the jellified hydrocolloid layer of the system, thus decreasing its specific gravity andmaking it float over chime.

Advantages of floating drug delivery system[15]

The advantages of floating drug delivery system are as follow:

- Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
- Controlled delivery of drugs.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosal irritation due to drugs, by releasing drug gradually at controlled rate.
- Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
- Simple and conventional equipment is required for manufacture.
- Ease of administration and better patient compliance.

Disadvantages of floating drug delivery system[16,17]

The disadvantages of floating drug delivery system as follow:

- Floating system is not feasible for those drugs that have solubility or stability problem in GIT.
- These systems require a sufficiently high level of fluids in the stomach for enabling to float and to work efficiently.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo extensive first pass metabolism, may not be suitable for FDDS as the slow gastric emptying limits the systemic bioavailability.
- Some drugs present in the floating systems cause irritation to gastric mucosa.

Melt granulation technique[18]

Hot-melt extrusion is one of the most widely applied processing technologies in the plastic, rubber and food industry. Currently, more than half of all plastic products, including plastic bags, sheets and pipes are manufactured by this process. Recently melt extrusion has found its place in the array of the pharmaceutical manufacturing operations. Several research groups have evaluated this technology to achieve enhancement

in remove liquid for poorly water soluble drugs, to modify drug release and transdermal passage of the drug. Extrusion is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under pressure. Melt granulation is one of the most widely applied processing technique in the array of pharmaceutical manufacturing operations. Melt granulation process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets.

Advantages[18]

- Neither solvent nor water is used in this process.
- Fewer processing steps are needed thus time consuming drying steps of melt granulation are eliminated.
- There are no requirements on the compressibility of active ingredients and the entire procedure is simple, continuous and efficient
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non-swellable and water insoluble nature.[1,3]

Disadvantages[18]

- Requires high energy input.
- The melt granulation technique cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.
- Lower-melting-point binder risks situations where melting or softening of the binder occurs during handling and storage of the agglomerates
- Higher-melting-point binders require high melting temperatures and can contribute to instability problems especially for heat-labile materials.

METHODS AND MATERIALS

Selection of drug: Ethamsylate

Rationale

Ethamsylate (Dicynene/Dicynone) is a haemostatic drug. It is believed to work by increasing capillary endothelial resistance and promoting platelet adhesion. It also inhibits biosynthesis and action of those prostaglandins which cause platelet disaggregation, vasodilation and increased capillary permeability. It also promotes angioprotective and proaggregant action. It stimulates thrombopoiesis and release thromboplastin from bone marrow. Haemostatic action is due to activation of thromboplastin formation on damaged sites of small blood vessels and decrease of PgI2 (Prostacyclin I2) synthesis; it also facilitates platelet aggregation and adhesion, leading assert of hemorrhage.

Drug profile

Table 1: Profile of ethamsylate.

Parameters	**Description**		
a. Analytical profile			
CAS number	2624-44-4		
Chemical structure			
Chemical name	2,5-dihydroxybenzenesulfonic acid; N-ethylethanamine		
Molecular formula	$C_{10}H_{17}NO_5S$		
Molecular weight(g/mol)	263.31068 g/mol		
Pharmaceutical profile			
Appearance	White solid		
Melting Point	125°C		
Solubility	Freely soluble in water, sparingly soluble in methanol		
c.Pharmacodynamic profile			
Therapeutic category	Hemostatic		
Mechanism of action	Haemostatic action is due to activation of thromboplastin formation on damaged sites of small blood vessels and decrease of PgI2 (Prostacyclin I2) synthesis; it also facilitates platelet aggregation and adhesion,		
Indication	a) Prophylaxis and control of haemorrhages from small blood vessels, neonatal intraventricular haemorrhage, capillary bleeding of different etiology, including: menorrhagia and metrorrhagia without organic pathology, after trans-urethral resection of the prostate, hematemesis, melena, hematuria, epistaxis; secondary bleeding.		
b) **d. Pharmacokinetic profile**			
Absorption	c) Absorption from the gestointestinal tract.		
Half life	d) 3.7 hrs		
Protein binding	e) 60%		
Bioavailability	35-40%		
e. Marketed formulation			
Brand name	Dosage form	Strength	Marketed by

ALSTAT	Tablet 500 Injection	250,500mg 250mg/2ml	Albert david
BLOC	Tablet	250mg	Finecure Pharma
CAPSTAT	Tablet	250,500mg	Hygeia Pharma
CLOWTAWIN	Tablet	250,500mg	Bestochem

Polymer Profile

Table 2: Profile of HPMC E15 LV.

Parameters	Description
CAS No.	9004-65-3
Chemical name	Hydroxypropyl methyl cellulose
Chemical formula	C12H20O10
Description	HPMC is a solid, slightly off-white powder
Functional category	Food additive, an emulsifier, thickening and suspending agent, and an alternative to animal gelatin
Solubility	Freely Water soluble
Molecular weight	324.2848

Table 3: Profile of bees wax.

Parameters	Description
Chemical structure	
CAS No.	8012-89-3
Chemical name	Bees wax
Chemical formula	$C_{15}H_{31}COOC_{30}H_{61}$
Description	Yellow (crude) white (bleached0 and beeswax absolute (treated with alcohol)
Functional category	A glazing agent, stiffening agents, thickeners, emulsifiersFragrance in soaps and perfumes, polish pills.
Solubility	Insoluble in water, soluble in alcohol
Molecular weight	415
Melting point	62 to 64 °C

Table 4: Profile of ethyl cellulose.

Parameters	Description
Chemical structure	
CAS No.	9004-57-3
Chemical name	Ethyl cellulose
Chemical formula	C20H38O11
Description	Free-flowing, white to light tan powder
Functional category	Coating agent, flavoring fixative, tablet binder and filler, film-former, and as a viscosity-increasing agent, emulsifier, floating enhancer
Solubility	Insoluble in water, readily soluble in many organic solvents
Melting point	160°–210°C

AIM AND OBJECTIVES

In the present dissertation work, attempt was made to prepare floating tablets of ethamsylate by melt granulation technique by using.

Different polymers and assess the influence of 3 independent variables namely as HPMC, bees wax and ethyl cellulose, on the quality attributes of tablets.

Plan of work

In order to achieve the aim, the dessertation work was carried out as follows:

Preformulation studies of Ethamsylate

a) Identification by IR spectroscopy.
b) Melting point determination by capillary method.
c) Solubility determination in different solvents.
d) Drug-excipient compatibility studies by IR spectroscopy.
e) Analytical studies by UV-spectrophotometry

Formulation of floating tablets of ethamsylate by melt granulation technique. (F1-F6)

a) Process flow chart
b) Formulation design
c) Preparation of floating tablets

Evaluation of the prepared floating tablets of ethamsylate

a) Precompressional characterization of prepared granules
b) Bulk density
c) Tapped density
d) Carr's index
e) Hausner's ratio
f) Angle of repose
g) Post compressional evaluation of floating tablets
h) Hardness
i) Weight variation
j) *In-vitro* buoyancy
k) Drug content
l) *In-vitro* drug release studies
m) Release kinetics

METHODS, MATERIALS USED

Equipments/ Instruments used

S. No.	Name of Equipment	Make and Model
1.	IR Spectrophotometer	Bruker, ALPHA-E
2.	UV Spectrophotometer	Elico-Elicost 160
3.	Dissolution apparatus	Electrolab
4.	Weighing balance	Adir Dutt-FX 200
5.	Rotory punching machine	Clit
6.	Oven	Swastika lab. Equipment
7.	Tablet hardness tester	Monsanto
8.	Vernier caliper	
9.	Friabiliator	Roche Friabiliator

API used

S. No.	Name of item	Manufacturer	Batch no.	Mfg. date
1.	Ethamsylate	Hiral Labs Pvt Ltd Roorkee (U.K.)	ET07	2013

Chemicals / Reagent Used (All the chemicals were of IP/AR or equivalent grade)

S. No.	Name of Item	Manufacturer/Supplier
1.	Ethyl cellulose	Loba Chemie, Mumbai
2.	Bees wax	S. D. Fine-chem Ltd., Mumbai
3.	HPMC	Ases Chemical Work, Jodhpur
4.	Sodium bicarbonate	Loba Chemie, Mumbai
5.	Talc	S. D. Fine-chem Ltd., Mumbai
6.	Magnesium stearate	S. D. Fine-chem Ltd., Mumbai
7.	Deionized Water	In laboratory

Glasswares used

S. No.	Name of Item	Specification (grade, pack size)	Quantity required	Cost per unit	Total Cost
1.	Beaker	Borosil, 250 ml	4	70	280
2.	Conical flask	JSGW borosilicate, 250 ml	2	70	140
3.	Volumetric flask	Borosil, 100 ml	2	135	270
4.	Measuring cylinder	Borosil, 10 ml, 50 ml, 100ml	3	175, 240, 260	675
5.	Pestle mortar	Borosil	1	135	135
6.	Burette	Borosil	1	150	150
7.	Pipette	Borosil	1	130	130
8.	Funnel	Borosil	1	20	20
9.	Spatula	Borosil	1	20	20
10.	Test tubes	-	-	-	-
11.	Water bath	-	1	80	80

Preformulation studies

1. **Identification by IR spectroscopy:** The IR analysis of the sample was carried out for qualitative compound identification. Ethamsylate was placed in the cell and scanned over the wavelength 4000 cm^{-1} - 500 cm^{-1} and spectrum was recorded using powder dispersive technique. The recorded spectra as per BP 2010 are presented in Figure 4.

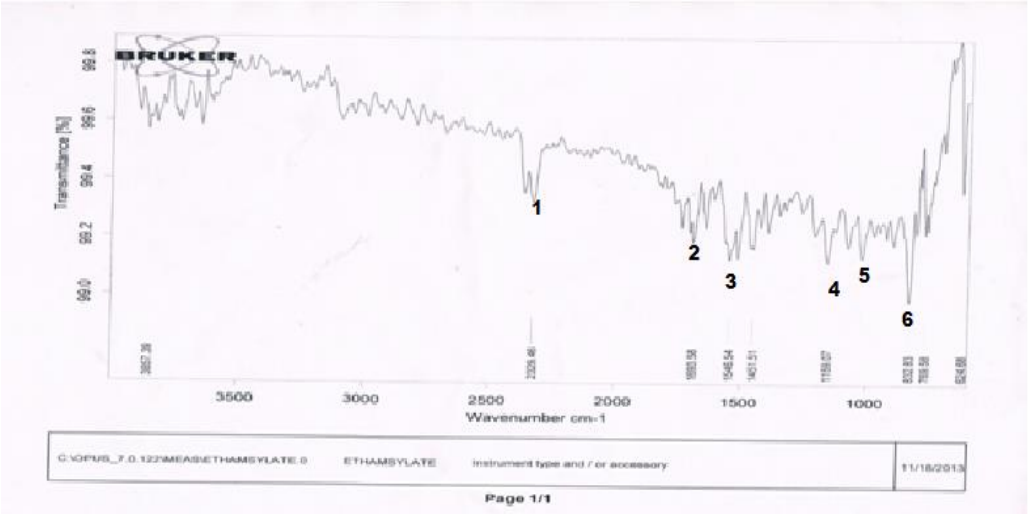

Figure 4: Recorded IR Spectrum of Ethamsylate.

Table 5: **Peak table for interpretation of IR spectra of ethamsylate.**

Peak No.	Wave no. (cm^{-1})	Bandwidth (cm^{-1})	Characteristics functional group/vibration
1.	2329.49	2400-2300	S=O
2	1580	1600-1400	C=C Aromatic
3	1365	1400-1300	C-H Bending
4	1245	1300-1000	C-O-C bending
5	1105	1360-1080	C-N bending
6.	715	800-600	C-S di substitution

RESULT AND DISCUSSION

The transmittance peaks exhibited in the spectrum of ethamsylate sample was found to be similar with functional group present in the structure.

2. Preparation of calibration curve

a) Preparation of stock solution

Accurately weighed 100 mg of ethamsylate was taken in 100 ml volumetric flask and dissolved in 100ml of 0.1 N HCl to get a stock solution of 1000 µg/ml. 10 ml of stock solution was taken in a volumetric flask and diluted to 100 ml with 0.1 N HCl to get a solution of 100 µg/ml.

b) Preparation of standard solution

From the above stock solution aliquots of 0.5, 1, 1.5, 2, 2,5, 3, 3.5, 4, 4.5, 5, 5.5, 6 and 6.5 ml were transferred separately into 10 ml volumetric flasks and volume was made up to 10 ml with 0.1 N HCl to get the standard solutions of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, and 65 µg/ml respectively.

c) Determination of □max.: The absorbance of the resulting solution was scanned in the range 400 to 200 nm against 0.1N HCl as blank. The spectrum is shown in Figure 5.

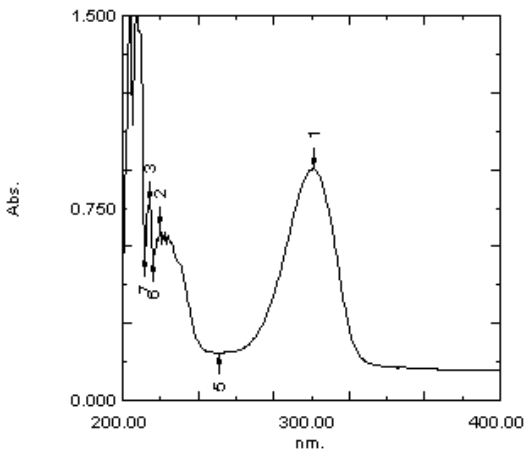

Figure 5: Scan for determination of □ max. of ethamsylate in 0.1N HCl.

Result and discussion
The absorption maximum was found to be 301.0 nm.

d) Preparation of calibration curve for ethamsylate
The absorbance of all the standard solutions wasmeasured at 301 nm against 0.1N HCl as blank. The results are shown in Table 6 and Figure 6.

Table 6: Calibration curve data of ethamsylate.

Concentration (µg/ml)	Absorbance			
	1	2	3	Average
5	1.1301	0.1314	0.1287	0.1302
10	0.940	0.1919	0.1928	0.1929
15	0.2897	0.2883	0.2893	0.2891
20	0.3108	0.3132	0.3121	0.3119
25	0.4039	0.4022	0.4030	0.4031
30	0.4744	0.4768	0.4755	0.456
35	0.5162	0.5773	0.5429	0.5454
40	0.6439	0.6128	0.6338	0.6319
45	0.7652	0.6856	0.7058	0.7188
50	0.7532	0.7861	0.7431	0.7608
55	0.8361	0.8992	0.8896	0.8749
60	0.9646	0.9132	0.9372	0.9388
65	1.009	1.0159	1.0235	1.0164

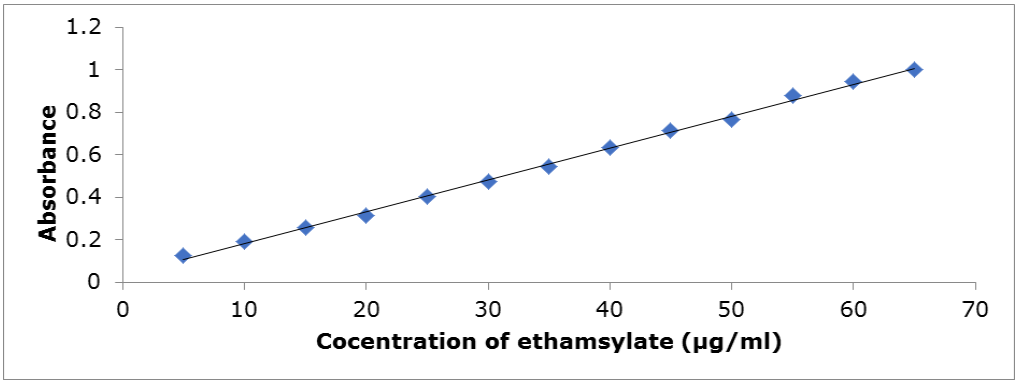

Figure 6: Calibration curve for ethamsylate in 0.1N HCl at 301 nm.

Results and discussion
The method was found to be linear and the Beer's law was obeyed in concentration range of 5-65 □g/ml at 301 nm. The slope and intercept were found to be 0.033 and 0.022 respectively with correlation coefficient of 0.998**.**

3. Melting point determination by capillary method: Melting point of ethamsylate was determined using melting point apparatus. Comparison of observed and reported melting points is presented in Table 7.

Table 7: Observed and reported melting point of ethamsylate.

Drug	Reported melting point (ºC)	Observed melting point (ºC)
Ethamsylate	131-134	132

Result and discussion
The melting point of ethamsylate was found to be 132^{o}C compared to the reported melting point. This signifies purity of the sample of ethamsylate.

4. Solubility of ethamsylate: The solubility of ethamsylate was determined using shake flask method. Saturated solution of ethamsylate was prepared by adding excess amount of ethamsylateinto 0.1N HCl and allowed to equilibrate for 24 hrs. The solution was filtered, suitably diluted and analyzed spectrophotometrically at 301 nm. The solubility of ethamsylate is shown in Table 8.

Table 8: Solubility of ethamsylate.

Solvent	Solubility (mg/ml)	Volume of solvent required to dissolve single dose (250 mg) of drug (ml)	Part of the solvent required to dissolve 1 part of the drug
0.1N HCl	9.760	25.61	102.45

Result and discussion

Ethamsylate was found to be freely soluble (Appendix Table A1) in 0.1 N hydrochloric acid as per B.P.III.Volume of solution required to dissolve ethamsylateequivalent to its single dose was found to be 25.61 in 0.1N HCl.

5. Drug-excipient compatibility studies

Physical mixture of ethamsylate and polymers (Ethyl cellulose, HPMC and bees wax) was prepared in the ratio of 1:1:1:1 and IR spectrum was recorded in the range from 4,000 to 500 cm^{-1}. This mixture was kept for 14 days at 37^0C and IR spectrum was again recorded. The spectra are shown in the Figure 7, 8respectively.

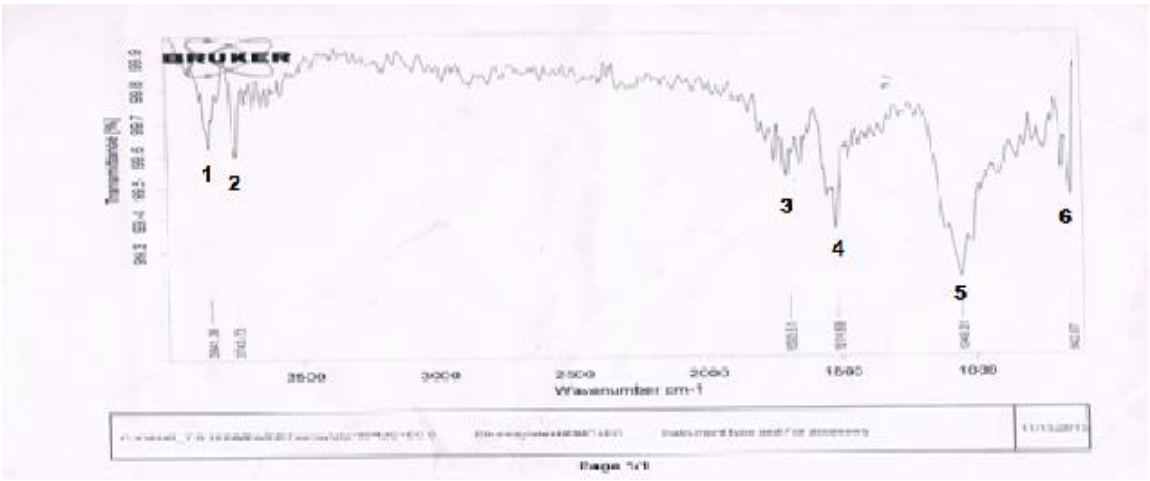

Figure 7: IR spectrum of ethamsylate+ ethyl cellulose+ HPMC + Bees wax (Day 0).

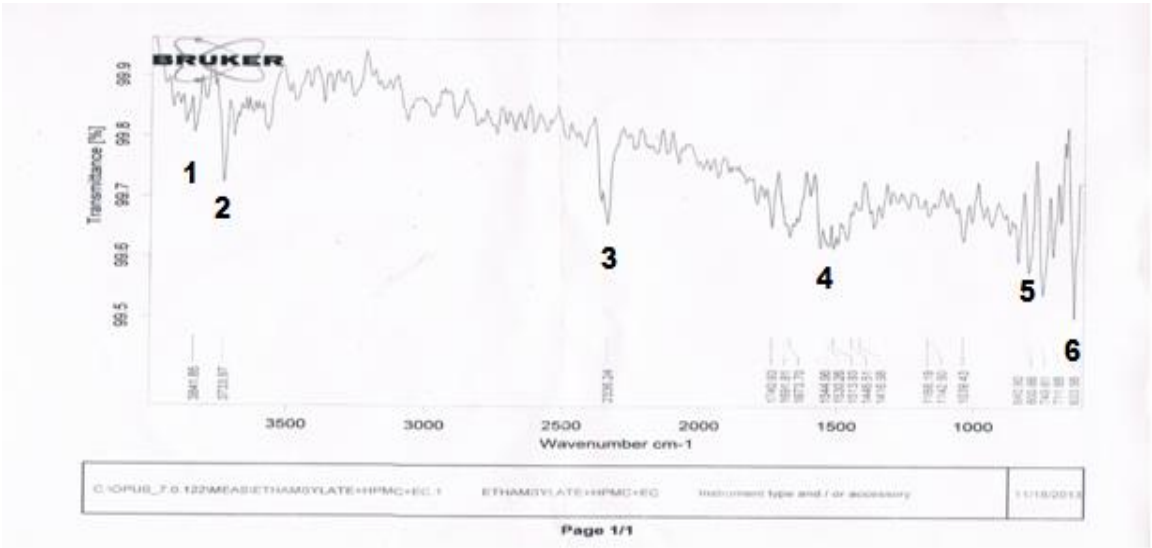

Figure 8: IR spectrum of ethamsylate + ethyl cellulose + HPMC + Bees wax (Day 14).

Result and discussion

The spectrum of physical mixture as on day 0 and day 14, were compared with the peaks of ethamsylate. It was found that there was neither any change/disappearance of peaks nor there was appearance of any new peaks. It indicates chemical compatibility of the ethamsylate with the polymers. Also no physical incompatibility was observed, since there was neither discolouration nor liquefaction.

- **Formulation of floating tablet of ethamsylate by melt granulation technique**

1. Process flow chart

The process flow chart for the preparation of ethamsylate floating tablet is presented in Figure 9.

Process	Unit operation	Variables
Beeswax was melted in a china dish ↓ Required quantity of Ethamsylate was added to the molten mass ↓ Previously prepared geometric mixture of HPMC E15 LV and /or Ethyl cellulose and sodium bicarbonate were added to the molten Ethamsylate-Beeswax mixture and stirred well to mix. ↓ The mass was removed from the hot plate and subjected to scraping until it attained room temperature. ↓ The coherent mass was passed through a 36- mesh sieve, and the resulting granules were resifted on a 100-mesh sieve to remove the fines. ↓ Then the granules were mixed with 10mg of talc and 5mg of magnesium stearate per tablet. ↓ The lubricated blend was compressed in to tablets.	Heating Mixing Size reduction Size separation Compression	Type of binder's ConcentrationConcentration Speed, Time of mixing Time Temprature Sieves no. ConcentrationCompression force, speed

The process flow chart for the preparation of ethamsylate floating tablet is presented in Figure 9

From amongst the various formulation and process variables, the influence of polymer concentration shall be investigated.

2. Formulation Design

Fractional factorial design was used to prepare batches of floating tablet of ethamsylate to assess the influence of 3 critical variables each at 3 levels as presented in Table 9 and the factorial design is presented in Table 10.

Table 9: Independent Variables and their levels

Level / Variables	Low	Medium	High
HPMC(gm)(X_1)	100	150	200
Bees wax(gm)(X_2)	25	50	75
Ethyl cellulose (gm)(X_3)	25	50	75

Table 10: Full 3^2 factorial design for formulation of ethamsylate floating tablet.

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethamsylate (mg)	250	250	250	250	250	250	250	250	250
HPMC (mg)	100	100	100	150	150	150	200	200	200
Sodium Bicarbonate (mg)	25	25	25	25	25	25	25	25	25
Bees Wax (mg)	25	50	25	50	25	50	25	50	75
Ethyl Cellulose (mg)	25	50	75	25	50	75	25	50	75
Talc (mg)	10	10	10	10	10	10	10	10	10
Magnesium Stearate (mg)	10	10	10	10	10	10	10	10	10

Here HPMC is selected for retarding the release rate of drug. Bees wax is selected as meltable material for melt granulation and due to it also sustained action itself. Ethyl cellulose is used as hydrophobic material to control the release of the drug as well as it shows floating enhancer property. Sodium bi carbonate is selected for generation of CO_2 for floating the tablet. Magnesium stearate and talc are selected for lubricating and improving the flow properties.

3. Preparation of floating tablets

Adequate quantities of ethamsylate and polymers (HPMC, ethyl cellulose and bees wax) were weighed. Bees wax was melted in china dish and the above

quantities were mixed in it to make the molten mass. Granules were prepared by sieving and air dried. The required quantity of magnesium stearate and talc were added and tablets were compressed using punching machine.

Characterization of prepared floating tablet of ethamsylate

- **Precompressional characterization of granules**

1. Bulk density

An accurately weighed sample of granules was transferred in 25 ml graduated cylinder and carefully leveled without compacting, and the unsettled apparent volume (V_0) was noted. The apparent bulk density in g/ml was calculated by the following formula.

Bulk density= (Weight of the powder)/Bulk volume

2. Tapped density

An accurately weighed sample of granules was transferred in 10 ml graduated cylinder. Power was carefully leveled without compacting, and the unsettled apparent volume (V_0) was noted. Then the cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight for 100 times and the tapped volume (V_1) measured. The tapped bulk density in gm/ml was calculated by the following formula.

Tapped density = (Weight of the powder)/ Tapped Volume

3. Carr's index (% Compressibility)

The Carr's Index of the granules was determined by using the formula:

Carr's index= [(Tapped Density-Bulk Density)/ Tapped Density] X 100

4. Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material and is calculated with formula:

Hausner's ratio = (Tapped Density)/Bulk Density

5. Angle of repose

The angle of repose of the prepared ethamsylate granules was determined by the funnel method. The accurately weighed granules were taken in the funnel. The height of the funnel (taken constant) was adjusted in such a way that the tip of the funnel just touched the apex of the granules. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

The flow properties of the prepared ethamsylate granules are shown in Table 11.

Table 11: Characterization of prepared ethamsylate granules.

Parameters	F1	F2	F3	F4
Bulk density(gm/ml)	0.39	0.43	0.38	0.42
Tapped density(gm/ml)	0.43	0.49	0.46	0.49
Carr's index (%)	9.30	12.24	17.39	14.28
Hausner's Ratio	1.10	1.13	1.21	1.16
Angle of repose(Θ)	24.45°	26.66°	25.53°	25.78°

Results and discussion

All formulations exhibit excellent/good flow properties. (Appendix Table A2, A3 and A4).

- **Postcompressional evaluation of floating tablet**

1. Hardness or crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10kg; however, hypodermic and chewable tablets are usually much harder (10-20 kg). The hardness of tablets is presented in table no. Table 12:

Table 12: Hardness of the floating tablet of ethamsylate.

Parameter	F1	F2	F3	F4
Hardness(kg/cm^2)	5.0±0.31	4.8±0.17	4.3±0.13	5.3±0.25

Data indicates mean ± S.D. n=5

Results and discussion: The hardness of tablets was found in the range from 4.3±0.13 – 5.3±0.25 and was found to be significantly different (one way ANOVA, $P \leq 0.01$) for the different batches The effect of amount of HPMC, Bees wax and Ethylcellulose on tablets hardness is show in figures 10,11 and 12 respectively.

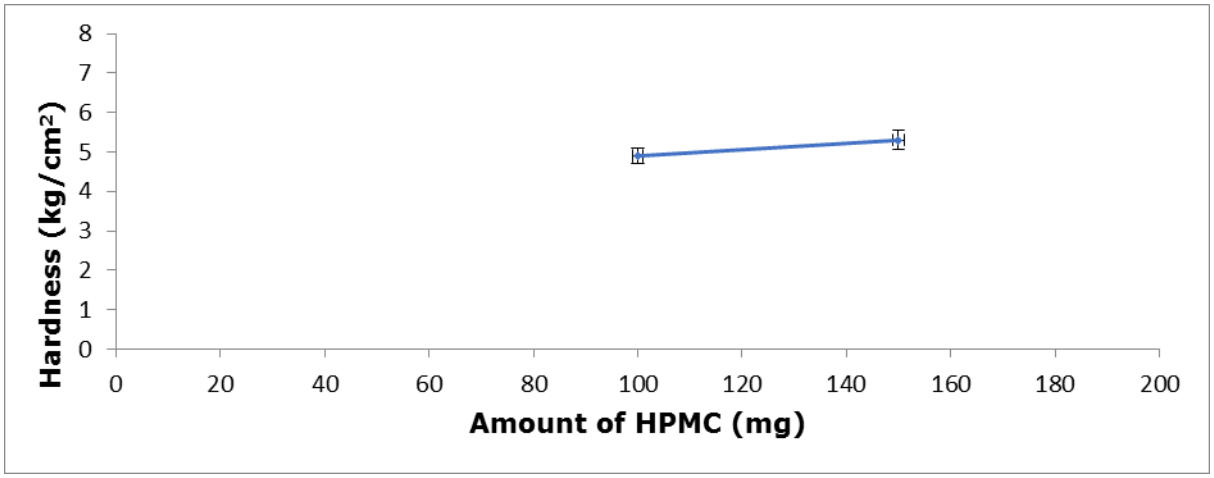

Figure 10: Effect of amount of HPMC on hardness.

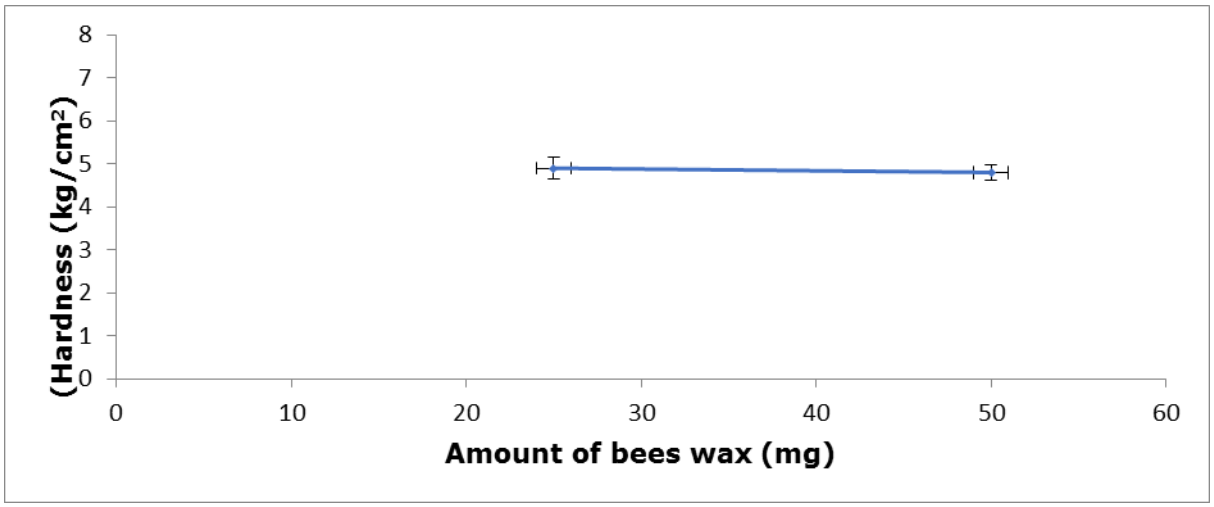

Figure 11: Effect of amount of Bees wax on hardness.

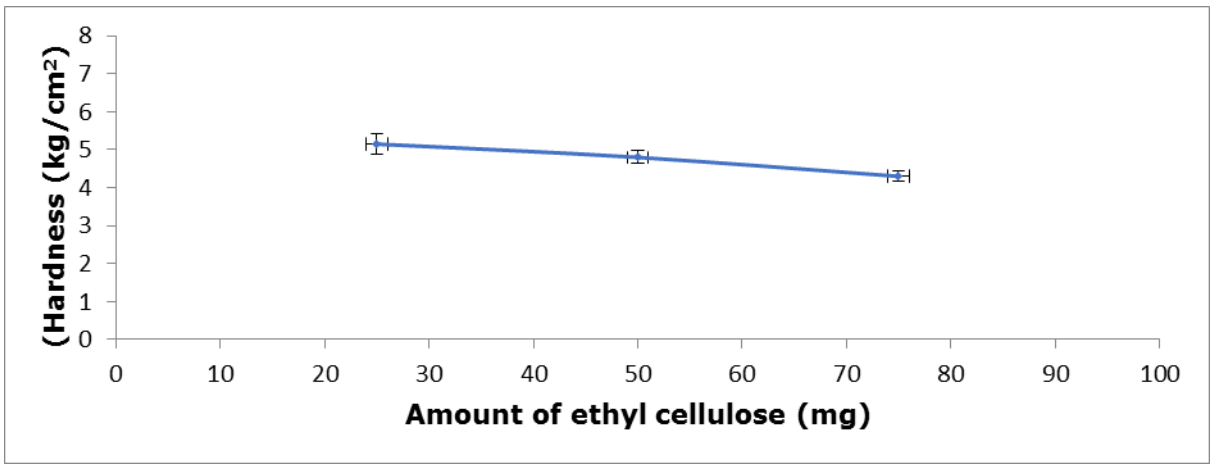

Figure 12: Effect of amount of Ethyl cellulose on hardness.

Hardness was found to increase with increase the amount of HPMC, Bees wax while decease with the increase the amount of ethylcellulose.

2. Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight

F - Final weight

The readings were recorded in % as presented in table no. 14.

Table 13: Friability of floating tablet of ethamsylate.

Parameter	F1	F2	F3	F4
Friability (%)	0.59	0.67	0.72	0.38

Results and discussion: The friability of prepared tablets was found in the range from 0.38%-0.72% which was satisfactory according to I.P. (0.5%-1%). The effect of HPMC, bees wax and ethyl cellulose shown in figures no. 13, 14, 15respectively.

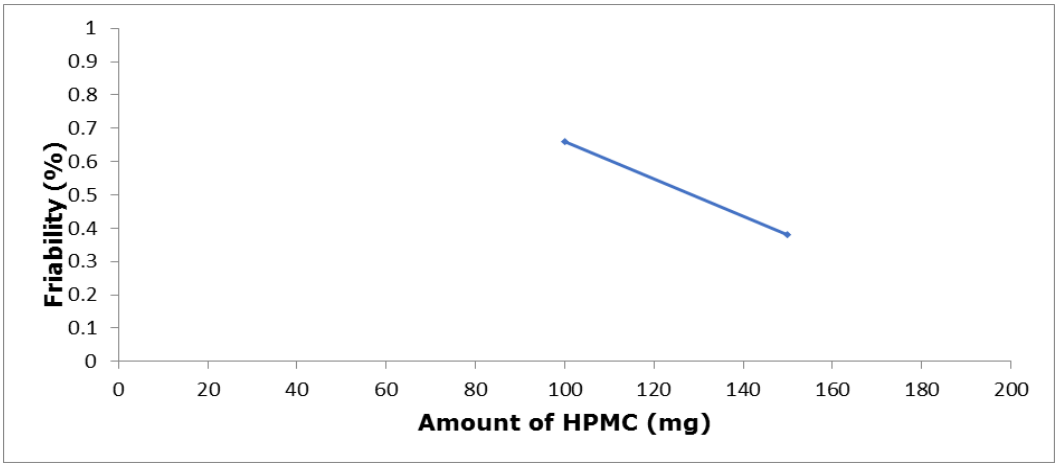

Figure 13: Effect of amount of HPMC on % friability of tablet.

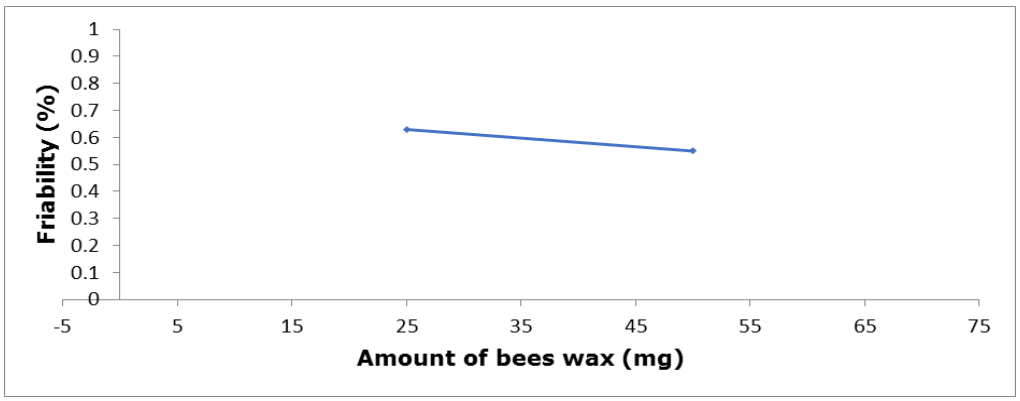

Figure 14: Effect of amount of bees wax on % friability of tablet.

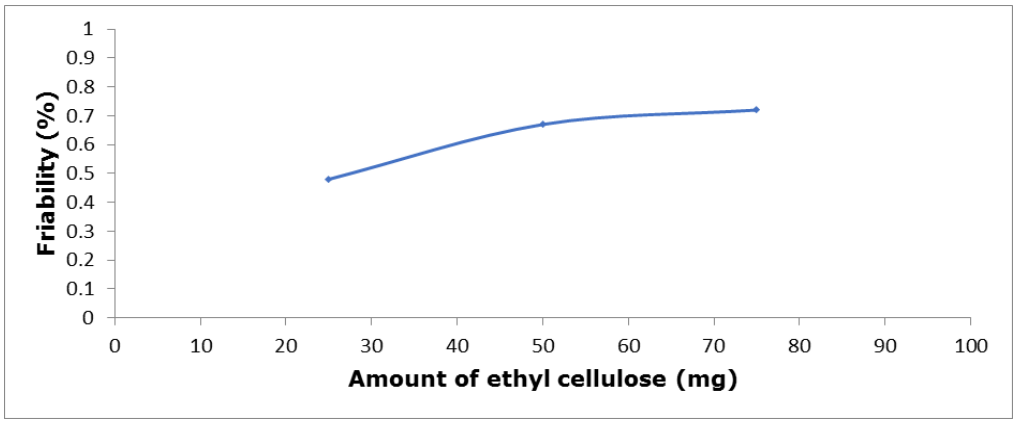

Figure 15: Effect of amount of ethyl cellulose on % friability of tablet.

Friability decreased with decrease the amount of HPMC, bees wax while increased with increase the amount of ethyl cellulose.

3. Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

Percentage deviation = [X/ X*] × 100

X - Actual weight of the tablet

X* - Average weight of the tablet

Table 14: Weight variation of prepared floating tablet of ethamsylate.

Parameter	F1	F2	F5	F9
Weight variation (%)	98.21	103.32	99.47	100.15

Results and discussion: All formulations were within the specification (Appendix Table A5).

4. In-vitro buoyancy

The time taken for tablet to emerge on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form constantly remains on the surface of the medium is called the total floating time (TFT). The buoyancy of the tablets was studied in USP type II dissolution apparatus at 37±0.5^{o}C in 900ml of simulated 0.1N HCL. The time of duration of floatation was observed visually.

Table 15: Buoyancy of prepared ethamsylate floating tablets.

Formulation	Floating lag time* (min)	Floating time
F1	5.25±0.06	>12 hrs
F2	4.20±0.14	>12 hrs
F3	3.35±0.18	>12 hrs
F4	6.50±0.24	>12 hrs

*Data indicates mean ± S.D., n=3

(a)

(b)

Figure 16: Photograph of buoyant tablet at time t=0 (a) and at time t=3 min (b)

Result and discussion

In-vitro buoyancy studies reveals that 100% tablets in formulation floated for more than 12 hrs. Indicating excellent buoyancies, an effect ascribed to the porous structural density of tablets. The effect of amount of ethyl cellulose, HPMC and Bees wax on lag time of prepared tablets is shown in Figure 17, 18, 19respectively.

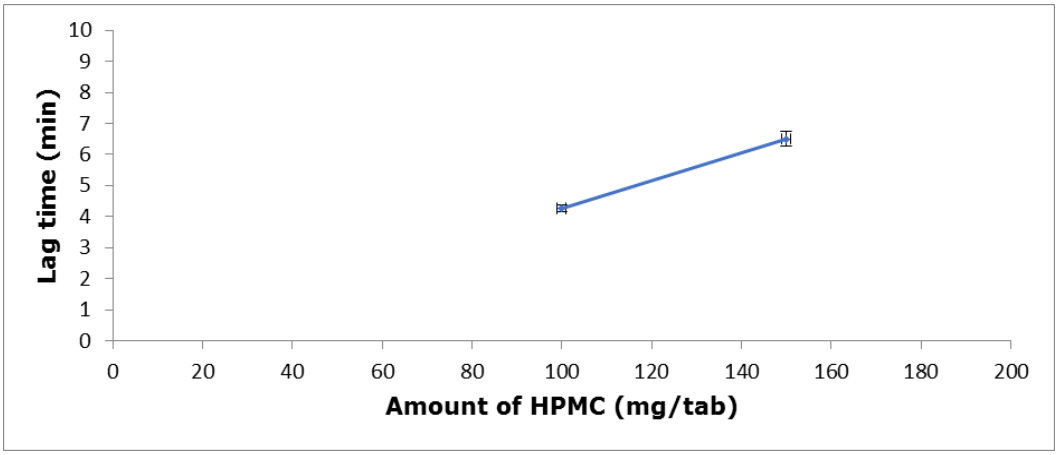

Figure 17: Effect of amount of HPMC on lag time of prepared tablet of ethamsylate.

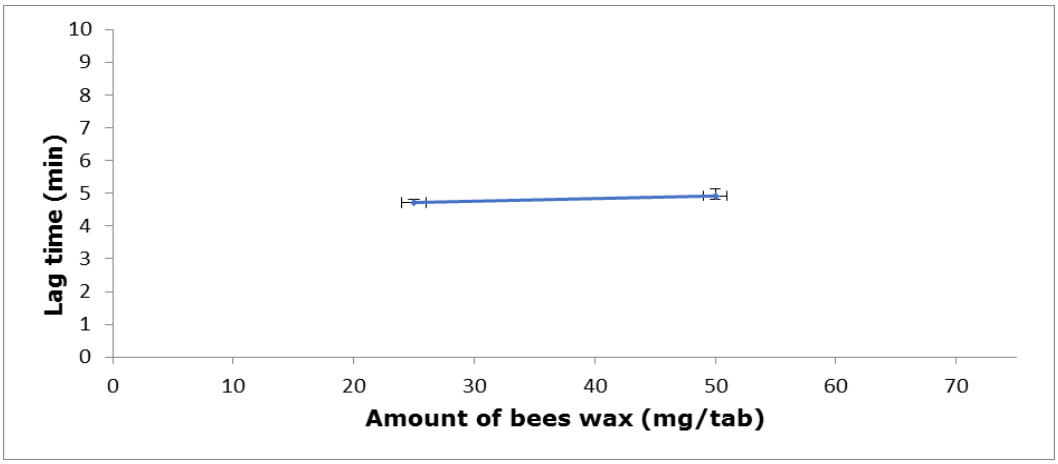

Figure 18: Effect of amount of bees wax on lag time of prepared tablet of ethamsylate.

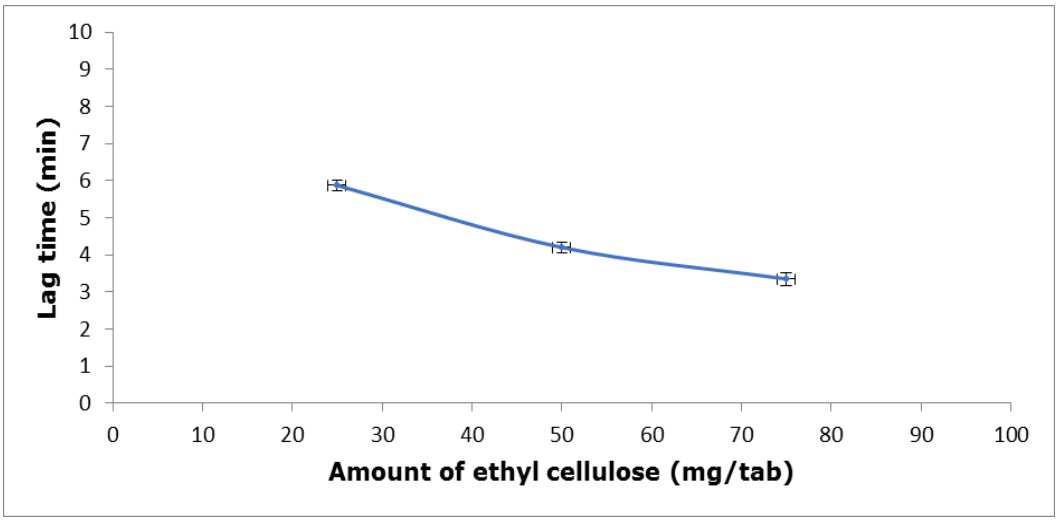

Figure 19: Effect of ethyl cellulose on lag time of prepared tablet of ethamsylate.

Here, it was observed that with increase in the amount of HPMC and Bees Wax there was significant (P≤0.01) increase in the lag time because they have tendency to stick and make compact mass. While with increase in the amount of ethyl cellulose there was significant (P≤0.01) decrease in the lag time because it has floating enhancer property.

5. Estimation of Drug Content

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was transferred into 250 ml volumetric flask, it was shaken with 150 of 0.1N HCL and volume was adjusted to 250ml 0.1N HCL. The solution was filtered, suitable dilutions were made and absorbance was recorded by using U.V. spectrophotometer at 301nm.

The experiment was repeated three times. The estimated drug content of prepared floating tablets of ethamsylate is shown in table no.16

Table 16: Drug content of prepared ethamsylate tablets.

Formulations	Drug content
F1	99.23±1.31
F2	104.62±0.38
F3	93.75±0.87
F4	100.51±0.29

Data indicate mean±SD of triplicate determinations

Result and discussion

The drug content varied from 93.75±0.87 to 104.62±0.38. Which is within the specified limit 0f 85-115%.

6. In-vitro drug release studies

Release of ethamsylate from the tablets was studied in 0.1 N HCl (900 ml) using a USP Type II dissolution apparatus i.e paddle type at 100 rpm and 37± 0.5°C. Two tablets of each formulation in which one equivalent to 250 mg of ethamsylate was taken for dissolution study. Samples (5 ml) were withdrawn at interval of 15, 30, 45, 60, 90, 120, 180, and 240 minutes and same volume (5 ml) of the dissolution medium was replenished after each sampling. The samples withdrawn were filtered and analysed for drug content released spectrophotometrically at 305nm. Considering zero order constant drug release fora period of 12 hrs., a theoretical drug release profile was computed. The *in-vitro* drug release from tablets along with theoretical release profile and dissolution profile of plain ethamsylate is presented in Table 17and shown in Figure 20.

Table 17: *In-vitro* drug release of various formulations, plain ethamsylate and theoretical profile

Time (min.)	% Release					
	Theoretical Profile	F1	F2	F3	F4	P
15	2.08	0.97±0.95	1.05±0.74	1.23±0.32	0.73±0.64	34.40□0.59
30	4.16	1.83±0.32	2.32±0.26	2.39±0.16	1.27±0.57	48.80□0.78
45	6.25	2.52±0.56	3.97±0.84	4.36±0.41	2.06±0.21	56.75±0.98
60	8.32	4.17±0.28	5.53±0.47	6.49±0.38	3.69±0.82	67.60□0.20
90	12.50	7.96±0.16	9.41±0.38	10.27±0.63	6.24±0.19	75.54±0.48
120	16.66	11.38±0.37	12.93±0.80	13.84±0.85	9.82±0.35	82.20□0.44
180	25.00	15.04±0.59	16.82±0.16	17.97±0.51	13.93±0.48	85.40□0.17
240	33.33	20.89±0.19	22.72±0.63	23.64±0.82	18.57±0.24	86.00□0.20
Similarity factor,f_2		59.04	63.66	66.53	55.49	

Data indicates mean ± S.D., n=2

P: Plain ethamsylate **TP:** Theoretical profile. Points represent the mean and error bars represent the standard deviation n=2

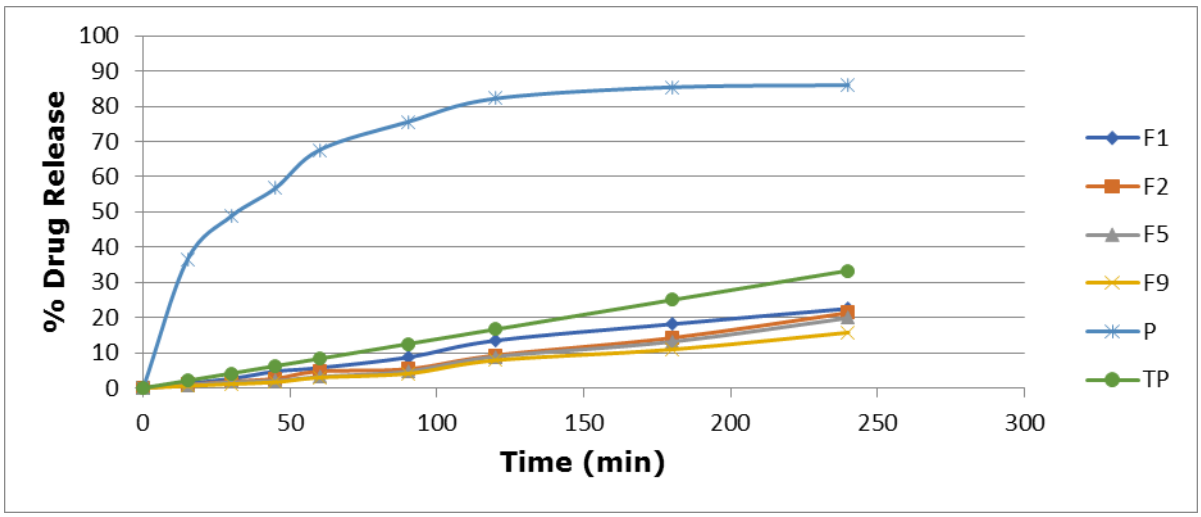

Figure 20: Dissolution profile of various formulations, plain ethamsylate and theoretical profile.

RESULT AND DISCUSSION

The dissolution of the different formulation was as follows in the decreasing order i.e. F3>F2>F1>F4. there was sustained release of drug in all formulations. The dissolution profile of formulation was compared against theoretical profile using similarity factor f_2 and all formulations were found to have similarity factor more then 50. (Appendix table no. A7)

In comparison to the dissolution of plain drug, dissolution from all the formulation were significantly lower (P≤0.05) as at 4 hrs. Which makes evident the function of ethyl cellulose, HPMC and Bees wax for retarding the rate of drug release attributed to the slower rate of diffusion of dissolution medium into the tablets. The effect of amount of ethyl cellulose, HPMC and bees wax is shown in Figure 21,22,23respectively.

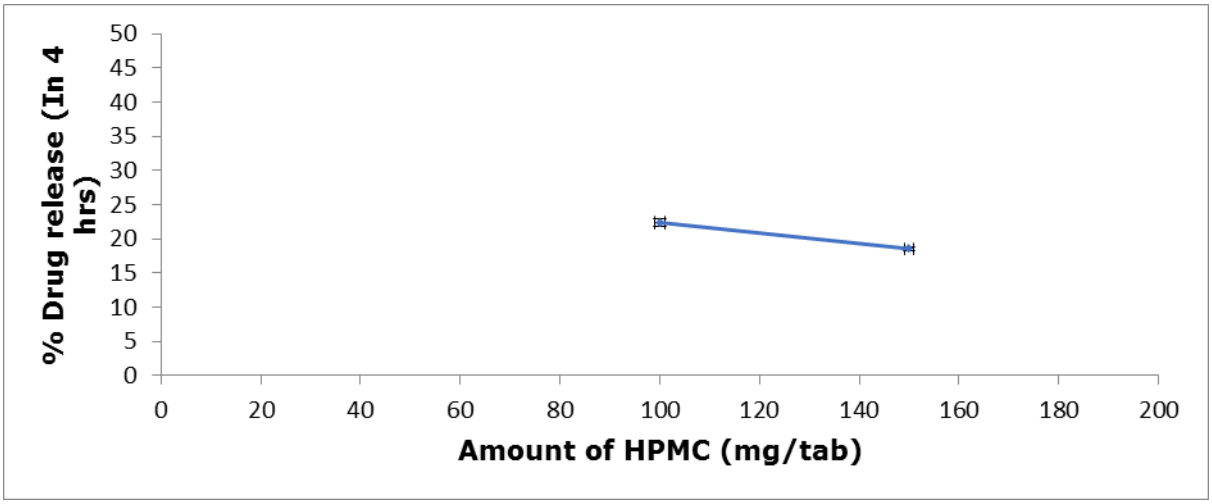

Figure 21: Effect of amount of HPMC on *in-vitro*release of ethamsylate from the prepared floating tablet.

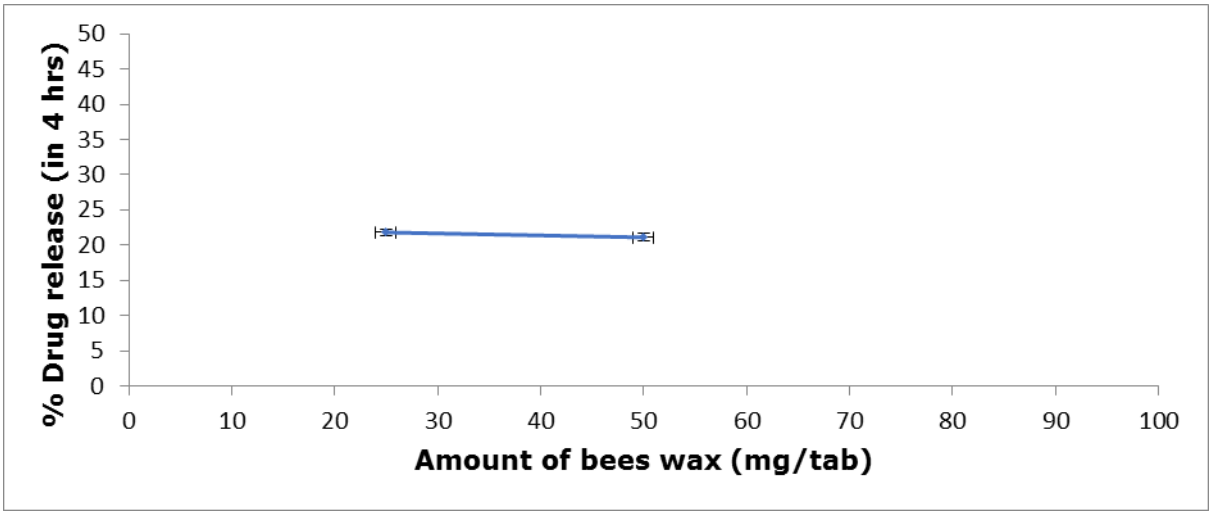

Figure 22: Effect of amount of bees wax on *in-vitro* release of ethamsylate from the prepared floating tablet.

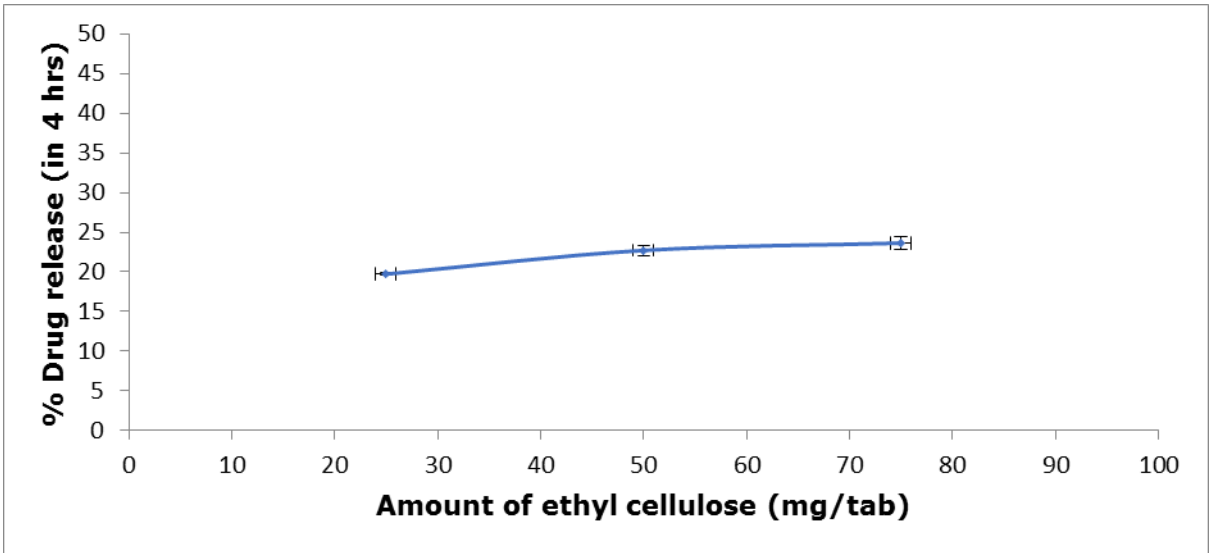

Figure 23: Effect of amount of ethyl cellulose on *in-vitro* release of ethamsylate from the prepared floating tablet.

It was observed that with increase in amount of ethyl cellulose release increases significantly (P≤0.01) while increase in the amount of HPMC and bees wax release decrease significantly (P≤0.01).

7. Release kinetics

Method

The raw dissolution data were fit into different release models like zero-order (Appendix table no. A7). First-order, Higuchi's, Hixson Crowell's and Korsmeyer's Peppas equations. Kinetic constant (k) and diffusional release exponent (n) were also computed based upon relationship proposed by Korsmeyer and Peppas.

The release kinetics of various formulations is shown in Table 18.

Table 18: Release kinetics of prepared ethamsylate tablets.

Formulation	Zero order	First order	Higuchi	Hixson Crowell	Korsmeyer Peppas			Best fit model
					K	n	r	
	r	r	r	r				
F1	**0.998**	0.958	0.975	0.990	0.068	1.023	0.991	**Zero order**
F4	**0.995**	0.937	0.954	0.973	0.025	1.127	0.974	**Zero order**
F9	**0.993**	0.948	0.978	0.989	0.051	1.143	0.985	**Zero order**
F5	**0.997**	0.969	0.984	0.948	0.074	1.193	0.990	**Zero order**

RESULT AND DISCUSSION

The best fit model for the prepared formulations F1, F2, F3, F4 was zero order with correlation coefficient of 0.998, 0.995, 0.993 and 0.997 respectively which indicating drug release independent of concentration.

CONCLUSION

In the present dissertation work, attempt was made to prepare floating tablets of ethamsylate by melt granulation technique. Tablets were prepared using fractional factorial design to assess the influence of 3 independent variables namely: X_1-amount of HPMC, X_2-amount of bees wax and X_3- amount of ethyl cellulose, on the quality attributes of tablets. EC and HPMC were used as floating and rate controlling polymers while bees wax as hydrophobic meltable binders.

Initially, drug excipient compatibility studies were performed using IR spectrophotometry and no incompatibility was detected. The prepared tablets were evaluated and results both Precompressional and postcompressional are presented in Table 19.

Table 19: Results of evaluation of prepared floating Tablet of ethamsylate.

Batch Parameter	F1	F2	F3	F4
Bulk density(gm/ml)	0.39	0.43	0.38	0.42
Tapped density(gm/ml)	0.43	0.49	0.46	0.49
Hausner's Ratio	1.10	1.13	1.21	1.16
Carr's index(%)	9.30	12.24	17.39	14.28
Angle of repose(Ɵ)	24.45°	26.66°	25.53°	25.78°
Hardness (kg/cm^2)	5.0±0.31	4.8±0.17	4.3±0.13	5.3±0.25
Friability (%)	0.59	0.67	0.72	0.38
Weight variation (%)	98.21	103.32	99.47	100.15
Floating Lag time (min)	5.25±0.06	4.20±0.14	**3.35±0.18**	6.50±0.24
Floating duration (hrs)	>12 hrs	>12 hrs	>12 hrs	>12 hrs
Drug content (%)	99.23±1.31	104.62±0.38	93.75±0.87	100.51±0.29
***In-vitro* drug release (at 4 hrs)**	20.89±0.19	22.72±0.63	**23.64±0.82**	18.57±0.24
Similarity factor	64.61	57.39	**54.03**	51.61
Best fit model	Zero order	Zero order	**Zero order**	Zero order

From the present study it was observed that varying amount of the HPMC E15, bees wax and ethyl cellulose had significant influence on the lag time and % drug release of the prepared floating tablets as summarized in table 20.

Table 20: Effect of variables on floating lag time and % drug release.

Variables	Floating lag time	% drug release
Amount of HPMC onincreasing from 100-200 mg/tab	Significantly increase	Significantly decrease
Amount of bees waxon increasing from 25-75 mg/tab	Significantly increase	Significantly decrease
Amount of ethyl cellulose on increasingfrom 25-75/tab	Significantly decrease	Significantly increase

Further, with increase in the hardness of tablets, it was observed that floating lag time increase (Figure no.), and in-vitro drug release decrease (figure no.)

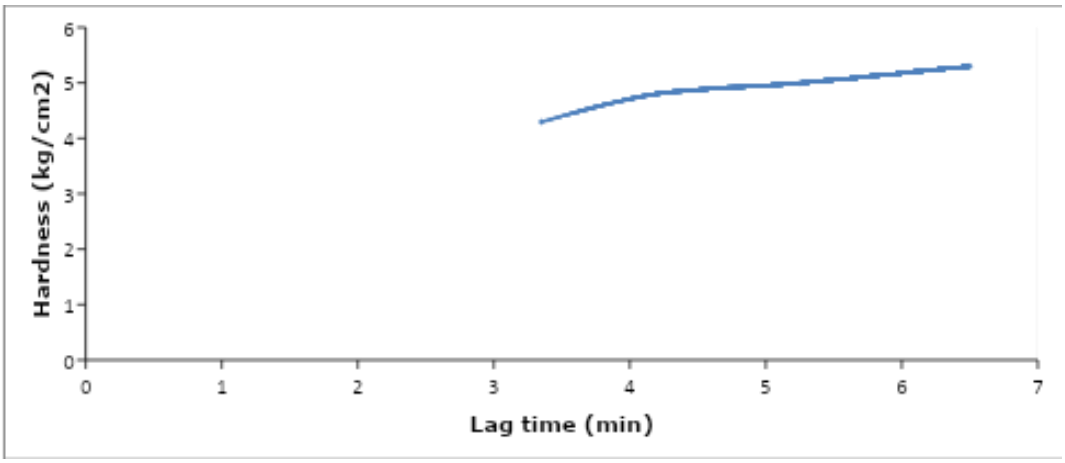

Figure 24: Effect of hardness on floating lag time.

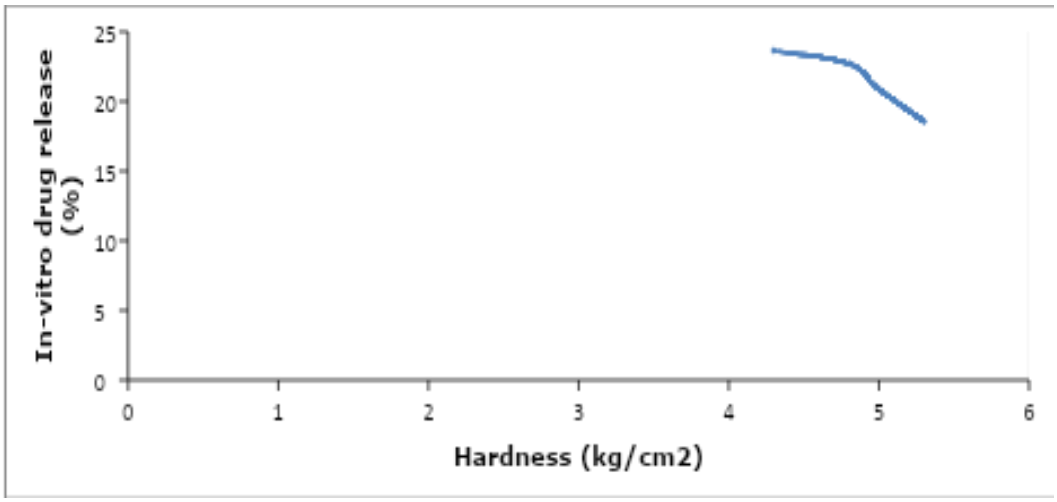

Figure 25: Effect of hardness on in-vitro drug release.

This can be ascribed to the alteration in the porosity and density of the prepared tablet making it to difficult for the dissolution medium to enter the tablet.All the prepared batches show it satisfactory floating time and in-vitro drug release properties, but F3 can be considered to be the best optimized formulation because of least floating lag time and highest similarity factor.

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