IJMPR 2024, 8(12), 45-52

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 6.669

FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF TIMOLOL BY SOLVENT EVAPORATION METHOD USING DIFFERENT POLYMERS

Jyoti Shukla[1]*, Anamika Jain[2], Ravish Kumar Sahu[3], Sonu Ahirwar[1] and Kashiram Prajapati[4]

[1]Vedic Pharmacy College Sagar, MP.
[2]Dr. Harisingh Gour Vishwavidyalaya, Sagar, MP.
[3]SVN Institute of Pharmacy and Research, Swami Vivekanand University, Sagar, MP.
[4]Dr. Anar Singh College of Pharmacy, Farrukhabad, UP.

Article Received on: 12/10/2024
Article Revised on: 03/11/2024
Article Accepted on: 23/11/2024

***Corresponding Author**
Jyoti Shukla
Vedic Pharmacy College Sagar, MP.

ABSTRACT

Timolol is a non-selective beta1 and beta2 adrenergic receptor blocker that lacks considerable intrinsic sympathomimetic, direct myocardial depressive, or membrane-stabilizing local anaesthetic effect. Timolol has a half-life of three to four hours, and after an hour, its plasma concentration peaks. This study's primary goal was to create and assess floating timolol microspheres utilising various polymers in order to extend their stomach residence period. Ethyl cellulose and hydroxy propyl methyl cellulose were among the many ratios of polymers used in the solvent evaporation process to create the microspheres. K4M. Additional evaluations of the floating microspheres included fourier transform infrared spectroscopy (FTIR) (compatibility studies), in vitro drug release study, release kinetics, drug content, swelling index, percentage yield, particle size, entrapment efficiency, floating capacity, and micromeritic properties such as bulk density, tapped density, angle of repose, etc. Timolol was discovered to be a white, crystalline powder with no smell. Timolol was discovered to have a melting point of 202–203ºC. The n-octanol:water partition coefficient value was 0. 980, indicating that the medication is hydrophilic and somewhat lipophilic. The reference spectra of I.P. 2010 were consistent with the peaks in the timolol infrared spectrum. Timolol's standard curves were created by employing the UV absorption technique at λmax 294 nm in pure water. It was discovered that the correlation coefficients were 0.99465. All of the formulations had an average particle size between 122.02±1.2 µm and 147.70±1.23 µm. The produced floating microsphere of timolol had a yield percentage that ranged from 66.75±0.92% to 97.75±0.84%. According to this evaluation measure, F6 has a satisfactory production yield of 97.75±0.84. Formulations from F1–F6 had entrapment efficiencies ranging from 85.60± 0.69% to 92.80± 0.97%. SEM was used to examine the internal and external morphology of the floating microsphere. The prepared microsphere had a hollow interior and was spherical with a smooth surface. It was discovered that the formulation F6 had the higher entrapment efficiency value. According to an in vitro release research, as the percentage of NaHCO3 rose, the drug release rate increased non-significantly ($p>0.05$). The generated floating microspheres of timolol were found to be an appropriate and useful method for prolonged drug release over an extended period of time, improving oral bioavailability, efficacy, and patient compliance.

KEYWORDS: Solvent diffusion evaporation method, Timolol, Ethyl cellulose, Hydroxyl propyl methyl cellulose.

INTRODUCTION

Because the pH varies in different parts of the gastrointestinal tract, the gastric emptying time varies, and it can be difficult to locate an oral delivery system in a specific area of the gastrointestinal tract, developing stomach-specific oral controlled-release drug delivery systems is a difficult task. Oral route of administration is the most practical and popular method of drug administration. Since most medications are absorbed in the stomach or upper portion of the small intestine, rapid gastrointestinal transit might hinder the absorption of the entire drug in the absorption zone and decrease the effectiveness of the prescribed dose.[1,2] Many forms of oral controlled drug delivery systems with extended gastric residence times have been reported to address the aforementioned problems. These include other delayed gastric emptying devices, floating drug dosage systems (FDDS)[3,7] swelling or expanding systems[8],

mucoadhesive system[9,10], modified-shape systems[11], and high-density systems. Since FDDS have a lower density than gastric fluids, they float in the stomach fluid for an extended amount of time without interfering with gastric emptying.[11-,13] The medicine is gradually released from the system at the desired rate while the system is floating in the stomach juice.[14,15] Light mineral oils, highly swellable hydrocolloids, and carbon dioxide gas-forming agents (carbonate or bicarbonate compounds)[8.13] are among the materials employed for FDDS. There have also been other unit systems and floating systems created using solvent evaporation techniques[12.16-20] Products based on a multiple unit system, which consists of numerous small units, have been demonstrated to have advantages over single-unit preparations, as matrix tablets.[21] There is less individual variance and a more constant, progressive stomach emptying of multiple unit dosage forms.[2,22] By reducing the impact of numerous factors in the gastrointestinal environment, multiple unit dosage forms can also disperse extensively over a sizable area in the stomach and small intestine, resulting in a more consistent drug release. There should be reduced chance of dosage dumping because multiple unit dosage forms are made up of numerous small units.[23]

Timolol is a non-selective beta1 and beta2 adrenergic receptor blocker that lacks considerable intrinsic sympathomimetic, direct myocardial depressive, or membrane-stabilizing local anaesthetic effect. Timolol has a half-life of three to four hours, and after an hour, its plasma concentration peaks. to create timolol floating microspheres with polymers such as hydroxypropyl methyl cellulose and ethyl cellulose. Timolol, an antihypertensive medication, is delivered under control via K4M. Floating microspheres are a type of multiarticulate delivery system that can be used to target drugs to specific areas and improve bioavailability through controlled or prolonged drug administration.[24] Additionally, microspheres can provide benefits such as minimising site effects, lowering dosage frequency, enhancing patient compliance, and limiting variation within the therapeutic range.[25]

MATERIAL AND METHODS

Material

A gift sample of Timolol was sent by Hyderabad-based Vasavaa Pharmaceuticals Pvt Ltd. We bought isopropyl alcohol, ethanol, and dichloromethane from E. Merck (India) Ltd. in Mumbai. We bought hydroxyl propyl methyl cellulose, ethyl cellulose, and K4M from Loba Chem. Pvt. Ltd. in Mumbai. Fresh double-distilled water was made and used as needed. Every chemical employed in this project was of analytical quality.

Preformulation Studies

Physical appearance

Timolol was discovered to be an odourless, white, crystalline powder.

Melting point

Using a melting point device, the melting point of timolol was discovered to be between 202 and 203°C.Timolol was discovered to be an odourless, white, crystalline powder.

Solubility

The maximum amount of a solute that may dissolve in a given volume of solvent at a given temperature is known as its solubility. A wrist action shaker (Yarco, New Delhi) was used to shake the excess solute for 24 hours after it had been suspended in 5 mL of each of the several solvents at room temperature in firmly sealed test tubes. Table 1 displays the solubility profiles of timolol in different solvents.

Table 1: Solubility profile of Timolol

Solvent	Solubility
Distilled water	Freely soluble
PBS (7.4)	Soluble
Chloroform	freely soluble
Ethanol	Freely soluble
n-Butanol	Soluble

Partition coefficient

Ten milligrams of the medication were dissolved in ten millilitres of each of n-octanol and water/PBS (pH 7.4) in order to determine the drug's partition coefficient. For twenty-four hours, the medication in the combination of stages was shaken on a wrist action shaker. A separating funnel was used to separate the two phases, and a UV visible spectrophotometer was used to measure the amount of medication in the aqueous phase following an appropriate dilution. The difference between the starting concentration and the concentration in the aqueous phase was used to calculate the concentration in the organic phase. This was utilised to apply the formula to determine the drug's partition coefficient in two chosen phases. Timolol's partition coefficient was supposed to be 0.980.

Po/w = Coctanol /Cwater/PBS (pH 7.4)

FT-IR spectroscopy

FT-IR spectrum of timolol was obtained using FTIR spectrophotometer (Shimadzu, Japan) and the obtained peaks were interpreted and compared with standard spectrum of drug. FT-IR of the sample was matched with the FT-IR spectrum as reported in IP 2010.[26]

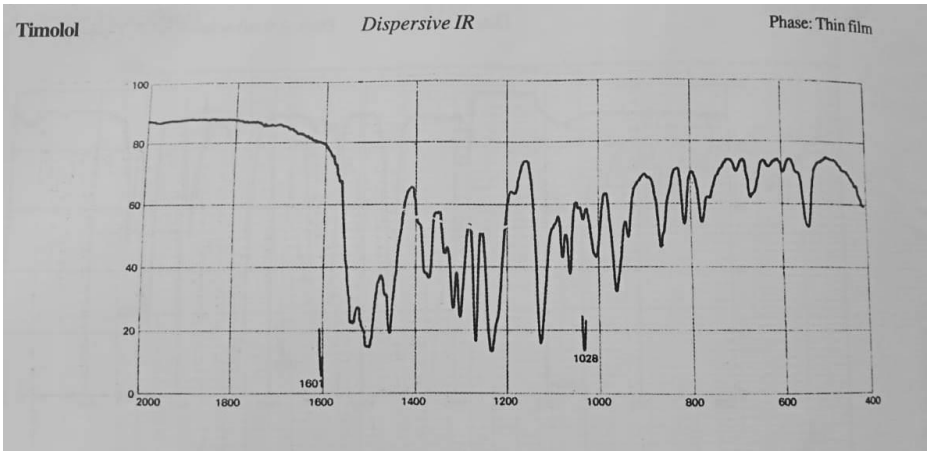

Figure 1: FT-IR Spectroscopy of Timolol in IP.

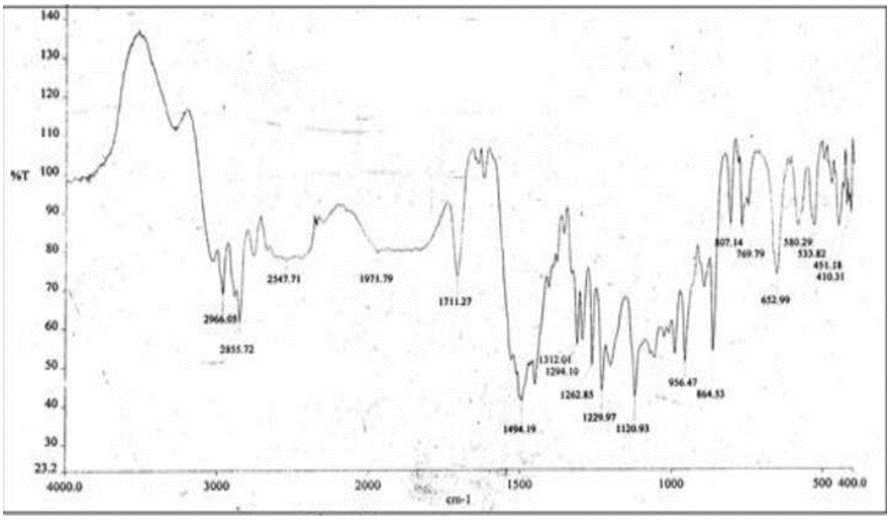

Figure 2: FT-IR Spectroscopy of Timolol.

Preparation of standard curve

In a volumetric flask, 10 mg of precisely weighed medication was dissolved in 100 ml of solvent to create a stock solution of 100 µg/ml. The Cintra 10 UV Visible Spectrophotometer was used to analyse the stock solution at λmax 294 nm after aliquots of 0.5 ml, 1.0 ml, and so on up to 5 ml were placed into a series of 10 ml volumetric flasks and the volume was increased to 10 ml with solvent (5-50µg/m). Plotting the standard curve between absorbance and concentration was done. Timolol in water standard curve (Figure 3, 4) was created.

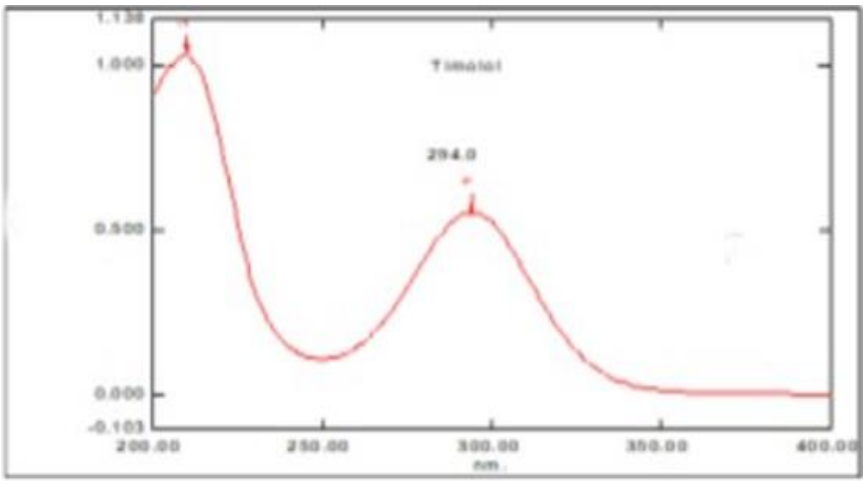

Figure 3: UV Spectrum of Timolol.

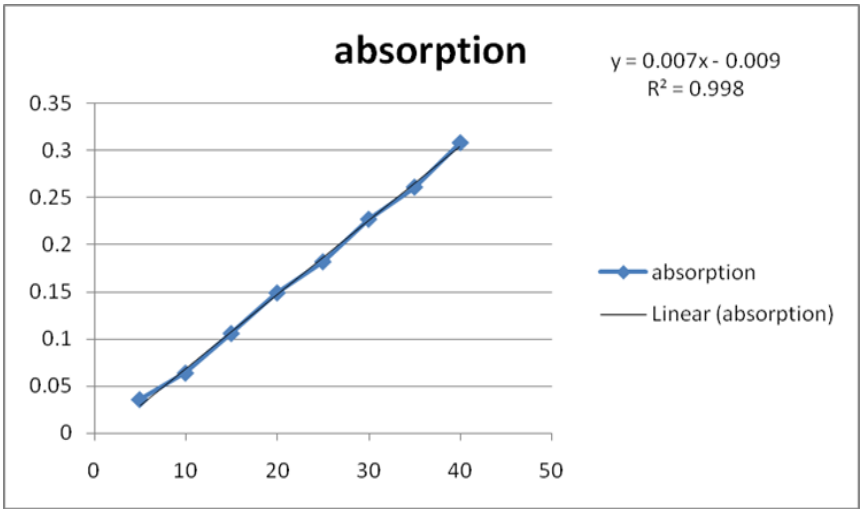

Figure 4: Standard curve of timolol in distilled water.

Preparation of floating microspheres

Emulsion solvent diffusion was used to create floating microspheres. A total of six floating microsphere formulations were created. A 1:1 mixture of ethanol and dichloromethane (DCM) was combined with varying quantities of HPMC K4M and ethyl cellulose. The resultant suspension was gradually added while stirring to 250 millilitres of room temperature water that included 0.01 millilitres of Tween 80. A mechanical stirrer set to 300 rpm was used to constantly stir the resulting emulsion for two hours. A constant temperature of 40°C was maintained. Through solvent diffusion, the drug's polymer solution's finely distributed droplets solidified in an aqueous phase, filling the microspheres' cavity with water. The resulting microspheres were filtered and repeatedly cleaned with purified water. Desiccators were used to retain the obtained floating microspheres after they had been dried at room temperature.[27] Table 2 displayed the formulations' components.

Table 2: Formulations of the Floating Microspheres of Timolol.

Formulation code	Drug: polymer	IPV (ml)(DCM)	PVA	EVS (ml)
F1	1:0.5	10	0.5	100
F2	1:0.1	10	0.5	100
F3	1:1.5	10	0.5	100
F4	1:2.0	10	0.5	100
F5	1:2.5	10	0.5	100
F6	1:3.0	10	0.5	100

IPV- Internal phase volume (ml), EPV- External phase volume, DCM- Di-chloro methane, PVA- Polyvinyl alcohol. S.D.±n=3

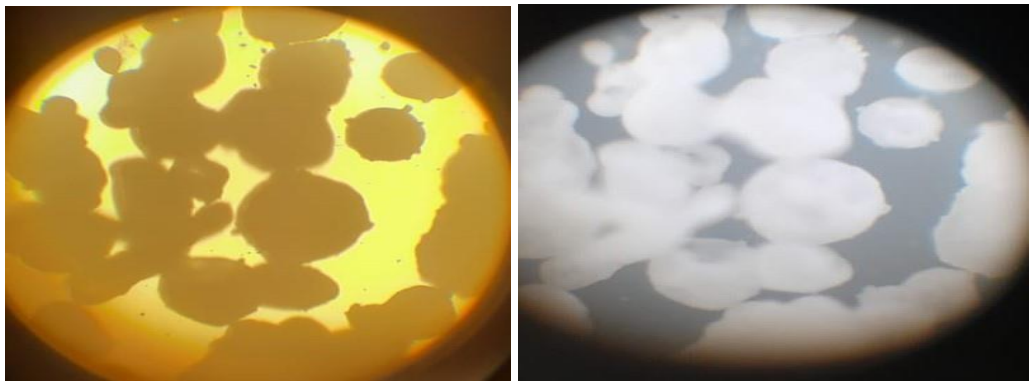

Figure 5 Images of Floating Microsphere.

Characterization of Floating Microsphere[26-29]

Particle size analysis

The optical microscope approach was used to analyse the floating microsphere particle size in each sample. All of the formulations had an average particle size between 122.02±0.23µm and 149.65±0.62µm. Because of the increased viscosity brought on by the ethyl cellulose, the particle size increases and larger droplets form, creating a larger floating microsphere.

Table 3: Particle Size Analysis of Floating Microsphere.

S. No.	Formulation Code	Particle Size(um)
1	F1	122.02 ±0.23
2	F2	125.48 ±0.42
3	F3	130.20±0.32
4	F4	139.41±0.40
5	F5	142.60± 0.56
6	F6	149.65 ±0.62

S.D.±n=3

Percentage Yield

Weighing the floating microsphere formulation after drying allowed us to calculate its percentage yield. The produced floating microsphere of timolol had a yield percentage that ranged from 66.75±0.92% to 97.75±0.84%. According to this evaluation measure, F6 has a satisfactory production yield of 97.75±0.84. The yield of F1 is the lowest at 66.75±0.92%. When compared to microspheres that included more HPMC, the microsphere containing ethyl cellulose showed a high percentage yield.

Table 4: Percentage Yield of Floating Microsphere.

S. No.	Formulation Code	Percentage yield %(SD)
1	F1	66.75 ±0.92
2	F2	71.11 ±0.97
3	F3	70.30 ±0.82
4	F4	82.88±0.48
5	F5	90.70 ±0.50
6	F6	97.75 ±0.48

S.D.±n=3

Bulk density

A 10 ml measuring cylinder was filled with a precisely weighed 2 g quantity of powder. Without moving the cylinder, the volume occupied by the powder was measured, and the bulk density was computed using the formula (values expressed in gm/$cm3$).

Bulk density = Weight of sample/ Bulk volume of the sample

Table 5: Bulk density of floating microsphere.

S. No.	Formulation Code	Bulk Density
1	F1	0.433±0.12
2	F2	0.472±0.04
3	F3	0.908±0.23
4	F4	0.802±0.02
5	F5	0.775±0.14
6	F6	0.777±0.08

S.D.±n=3

Tapped density

A 10 ml measuring cylinder was filled with a precisely weighed 2 g quantity of powder. One inch of height was used to drop the cylinder 100 times at 2-second intervals onto a hard hardwood platform. The following formula was used to determine the tapped density once the final volume was measured (values reported in gm/cm3).

Tapped density = Weight of sample/ Tapped

Table 6: Tapped density of floating microsphere.

S.NO.	Formulation code	Tapped density
1	F1	0.493±0.09
2	F2	0.527±0.11
3	F3	0.95 ±0.17
4	F4	0.830±0.07
5	F5	0.837±00.01
6	F6	0.891±0.32

S.D.±n=3

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to examine the microspheres' interior and exterior morphologies. The microsphere powder was softly sprinkled onto a double-sided adhesive tape that adhered to a stub to create the samples for the SEM. After that, a gold putter module in a high vacuum evaporator was used to coat the stubs with platinum in an argon atmosphere. After that, the samples were scanned at random, and higher magnification photomicrographs were taken to examine the surface morphology.

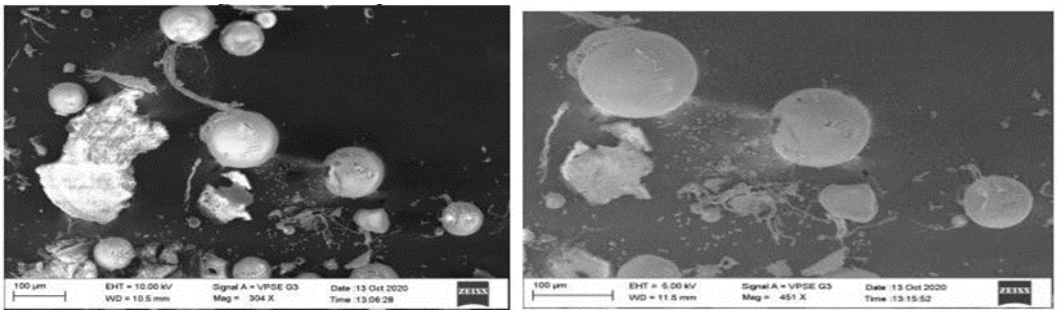

Figure 6: SEM image of floating microsphere

Drug entrapment efficiency

Table 7 lists the timolol floating microsphere formulations' entrapment efficiency. Formulations F1–F6 had entrapment efficiencies ranging from 67.30 ±0.67% to 91.80 ±0.97%. It was discovered that the formulation F6 had the higher entrapment efficiency value. The assessment of the prepared microsphere's entrapment efficiency indicates that the values of entrapment efficiency rise as the ethyl cellulose concentration does.

Table 7: Entrapment efficiency of floating microsphere.

S.NO.	Formulation code	Entrapment efficiency%
1	F1	85.60 ±0.69
2	F2	72.82 ±0.37
3	F3	67.30 ±0.67
4	F4	87.61 ±0.76
5	F5	85.40 ±0.82
6	F6	91.80 ±0.97

S.D.±n=3

In Vitro drug release of floating microsphere

Using a paddle-style six-station dissolving test device (Copley, UK), the in vitro drug release rate from the floating microspheres was confirmed. A precise quantity of floating microspheres corresponding to 5, 10, and 20 mg of medication was maintained in 0.1 N HCl (1.2 pH), and the dissolving fluid was kept at 37±0.5°C while rotating at 50 rpm. During the in vitro drug release investigation, sink condition predominated. A 0.45-µm membrane filter was used to filter a 2-ml sample at 5, 10, 15, 20, 30, 60, 120, 180, 240, 300, 360, 480, 600, 720, and 1440 minutes. After every withdrawal, 2 mL of new dissolving fluid was added to maintain the initial volume of the fluid. To find out how much timolol was in the medium, the samples were examined using a UV Spectrophotometer set to 219 nm. Every experiment was carried out three times.

Table 8: Cumulative percentage drug release for different batches of microsphereformulation.

S. N0.	Time(h)	Cumulative percentage drug release					
		F1	F2	F3	F4	F5	F6
1	1	2.62±1.72	2.64±2.23	2.75±2.23	2.8±1.78	3.85±1.47	4.45±0.5
2	2	11.07±2.23	14.70±3.45	15.81±2.47	20.92±1.56	13.79±2.47	16.81±2.56
3	3	14.15±0.42	27.76±4.23	26.80±1.56	24.31±2.52	20.15±1.45	21.50±1.85
4	4	27.39±1.75	31.85±2.55	27.52±2.56	27.74±2.44	27.85±1.76	23.49±1.74
5	5	30.05±2.45	35.05±1.72	29.72±2.89	30.10±2.46	27.76±0.45	30.42±1.96
6	8	30.83±3.45	40.86±1.75	30.58±1.84	35.47±1.47	39.50±0.75	46.02±2.78
7	24	38.30±2.27	40.01±1.65	42.12±0.56	45.18±1.62	45.40±1.69	52.70±2.63
8	48	41.62±1.74	52.56±2.29	49.02±1.74	49.42±2.47	50.32±2.86	58.75±1.45

S.D.±n=3

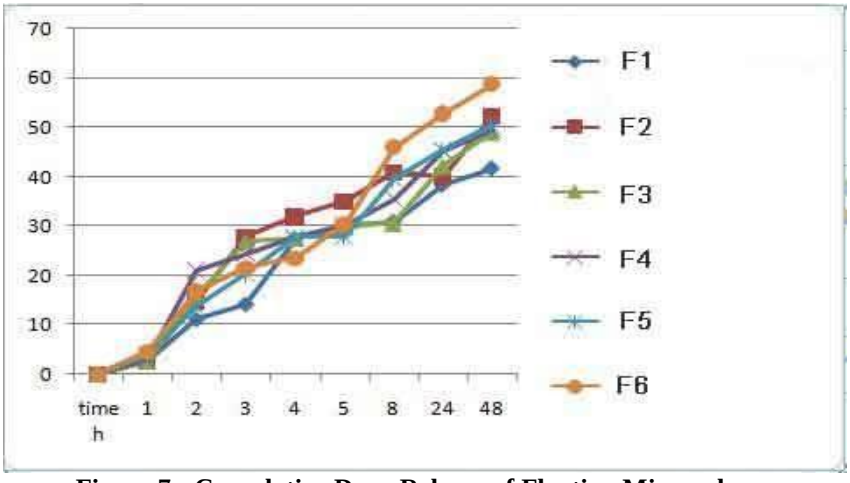

Figure 7: Cumulative Drug Release of Floating Microsphere.

In vitro floating time

To investigate the flotation behaviour of microspheres in the produced formulations, an in vitro floating microsphere was established. First, 50g of microspheres were dispersed in 100 ml of 0.1 N HCl (pH 1.2). A magnetic stirrer was then used to agitate the mixture at 100 rpm. The layer of buoyant microparticles was collected using a pipette and separated by filtering after eight hours. Filtration was used to separate the particulate sinking layer particles. Both kinds of particles were dried in a desiccator until their weight remained constant. The following formula was used to get the buoyancy percentage.

Floating time = Weight of floating microsphere/ Total weight of floating and settled microsphere x 100

All formulations were able to float over the dissolution medium (0.1 N HCl, pH 1.2) for 24 hours, according to the floating time % that was computed for each formulation. As indicated in Table 3, it was discovered that the buoyancy percentage of the microspheres decreased as the concentration of sodium alginate, denoted by F1–F3, increased. This results from the higher viscosity of the polymer solution, which also causes more dense microspheres and less pore and cavity formation during preparation.

Table 9: Floating time

S. No.	Formulation Code	Floating Time
1	F1	75.20±0.21
2	F2	70.10±0.53
3	F3	68.89±0.44
4	F4	92.41±0.21
5	F5	70.17±0.37
6	F6	76.12±0.27

S.D.±n=3

CONCLUSION

Timolol can be effectively made into floating microspheres from HPMC and EC for the delivery of gastroprotective medications. F6 may be regarded as a promising formulation based on drug release, percentage yield, drug entrapment, percentage buoyancy, and floating lag time. The produced floating microspheres could therefore be viable options for multiple-unit delivery systems that can be tailored to any intragastric situation.

REFERENCES

1. Kaushik K, C Haurasia D, Chaurasia H, Mishra SK, Bhardwaj P. Development and characterization of floating alginate beads for gastroretentive drug delivery system. Acta Pharma Sci., 2011; 53(4): 551-562.
2. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro-in vivo evaluation in healthy human volunteers. Eur J Pharm Biopharm., 2010; 74(2): 332-339.
3. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm, 2000; 195(1-2): 125-135.
4. Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein-gelatin beads floating properties. Int J Pharm., 2000; 198(2): 157-165.
5. Davoudi ET, Noordin MI, Kadivar A, Kamalidehghan B, Farjam AS, Javar HA. Preparation and characterization of a gastric floating dosage form of capecitabine. Biomed Res Int 2013; doi: 10.1155/2013/495319.
6. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release, 2000; 63(3): 235-259.
7. Garg R, Gupta G. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res., 2008; 7(3): 1055-1066.
8. Chen J, Park K. Synthesis of fast-swelling, superporous sucrose hydrogels. Carbohyd Polym., 2000; 41(3): 259-268.
9. Shaikh R, Singh TRR, Garland MJ, W oolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci., 2011; 3(1): 89-100.
10. Boddupalli BM, Mohammed ZNK, Nath RA, Banji D. Mucoadhesive drug delivery system: an overview. J Adv Pharm Technol Res., 2010; 1(4): 381-387.
11. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, H offman M, Maincent P. Evaluation of peroral silicone dosage forms in hymans by gamma-scintigraphy. J Control Release, 1999; 58(2): 195-205.
12. Rouge N, Allémann E, Gex-Fabry M, Balant L, Cole ET, Buri P, et al. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. Pharm Acta Helv, 1998; 73(2): 81-87.
13. Prajapati PH, Nakum VV, Patel CN. Formulation and evaluation of floating matrix tablet of stavudine. Int J Pharm Investig, 2012; 2(2): 83-89.
14. Chaturvedi K, Umadevi S, Vaghani S. Floating matrix dosage form for propranolol hydrochloride based on gas formation technique: development and in vitro evaluation. Sci Pharm, 2010; 78(4): 927-939.
15. Murata Y, Sasaki N, Miyamoto E, Kawashima S. U se of floating alginate gel beads for stomach-specific drug delivery. Eur J Pharm Biopharm, 2000; 50(2): 221-226.
16. Jagtap YM, Bhujbal RK, Ranade AN, Ranpise NS. Effect of various polymers concentrations on physicochemical properties of floating microspheres. Indian J Pharm Sci., 2012; 74(6): 512-520.
17. Jain AK, Jain CP, Tanwar YS, Naruka PS. Formulation, characterization and in vitro evaluation of floating microspheres of famotidine as a gastro retentive dosage form. Asian J Pharm., 2009; 3(3): 222-226.
18. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. Int J Pharm, 2001; 220(1-2): 13-21.
19. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Development of floating microspheres to improve oral bioavailability of cefpodoxime proxetil. Int J Pharma, 2001; 220: 13-21.
20. Wakde PH, K asliwal RH, Mane SB. Design and fabrication of gastroretentive bilayer floating tablet of propronolol HCl using natural polymer. Int J Pharm Sci Res., 2013; 4(12): 4715-4728.
21. Pandya N, P andya M, Bhaskar VH. Preparation and in vitro characterization of porous carrier-based

glipizide floating microspheres for gastric delivery. J Young Pharm, 2011; 3(2): 97-104.
22. Jagdale SC, Agavekar AJ, Pandya SV, Kuchekar BS, Chabukswar AR. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. AAPS PharmSciTech., 2009; 10(3): 1071-1079.
23. Hussain MN, M asum MAA, Akhter S, Sharmin F, Reza MS. Formulation and evaluation of gastro retentive floating tablets of simvastatin using hydrophilic rate retardant. Bangladesh Pharm J, 2012; 15(2): 119-126.
24. Ramarao T, Yugandhar T. Design formulation and evaluation of floating microspheres of timolol. World Journal of Pharmaceutical Research, 2017; 6(16): 430-43.
25. Haznedar S, Dortunc B. Preparation and in vitro evaluation of eudragit microspheres containing acetazolamide. Int J Pharm., 2004; 269(1): 131-140.
26. Indian pharmacopoeia 2010, government of India ministry of health & family welfare published by the Indian pharmacopoeia' commission Ghaziabad. 445.
27. Tanwar YS, Naruka PS, Ojha GR. Development and evaluation of floating microspheres of verapamil hydrochloride. Brazilian Journal of Pharmaceutical Sciences, 2007; (4)3; 529-534.
28. Tanwar YS, Naruka PS, Ojha GR. Development and evaluation of floating microspheres of verapamil hydrochloride. Revista Brasileira de Ciências Farmacêuticas., 2007; 43: 529-34.
29. Deepa MK, Karthikeyan M. Cefpodoxime Proxetil Floating Microsphere: Formulation and In vitro Evaluation. Iran J Pharm Sci., 2009; 5(2): 69-72.