

## RESEARCH ARTICLE

**EFFET OF COMBINATION OF HPMC AND CARBOPOL 934P ON THE PROPERTIES OF THE GASTRIC FOATING TABETS TIMOLOL MALATE****Charyulu Narayana R\*, Girish S K, Amit B Patil.**

Department of Pharmaceutics, Nitte Gulabi Shetty Memorial Institute of Pharmaceutical Sciences, Deralakatte, Mangalore, INDIA-575 018

\*corresponding Author's Email: [charyulun@yahoo.co.in](mailto:charyulun@yahoo.co.in)

**ABSTRACT:**

The purpose of the present research was to evaluate the effect of carbopol 934P on gastroretentive drug delivery system. Floating tablet containing timolol maleate were prepared by direct compression method, using three grades of polymer HPMC [K15M, K4M, K100M] and carbopol 934P. Sodium bicarbonate and citric acid was incorporated as a gas-generating agent. The floating tablets were evaluated on the basis of pre-compression and post-compression characteristics. The pre-compression characteristics such as angle of repose, bulk density, tapered density and compressibility index showed satisfactory results for all the nine formulations. The results of post-compression such as weight variation, hardness, friability and drug content estimation showed that all the nine formulations complied with the official requirement of IP. The buoyancy lag time indicated that the formulation F1, F4 and F7 without carbopol 934P were less than 8 sec, whereas formulation containing carbopol 934P had greater lag time. Formulation containing only HPMC grade polymers floated less than 8 h as compared to the formulation containing HPMC with carbopol 934P floated more than 12 h. The *in vitro* dissolution studies indicated 94.2% drug release in 12 h by the formulations F2, F3, F5, F6, F8 and F9 containing different concentration of carbopol 934P with different grades of HPMC, when compared to 100% drug release within 9 h by the formulation F1, F4 and F7 containing only different grades of HPMC polymers. All formulation followed the Higuchi release model. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed. Hence it can be inferred that the inclusion of carbopol 934P can result in sustained drug delivery over 12 h, enhances the gastric floating time and also increases buoyancy lag time.

**Keywords:** Timolol maleate, HPMC, carbopol 934P, Floating tablets, direct compression

**INTRODUCTION:**

Timolol maleate is a non-selective beta-adrenergic receptor blocker, prescribed in antihypertensive, antiarrhythmic and migraine. Timolol maleate is rapidly absorbed on oral administration with peak plasma concentration within 1-2 h. Plasma half-life of Timolol maleate is 2.5-4 h. The oral bioavailability is 50% - 60% due to extensive metabolism in liver<sup>1</sup>. Hence an attempt is been made to formulate a gastro retentive delivery system for timolol maleate that can not only avoid its metabolism in liver but also enhance the bioavailability. The advantage of floating drug delivery system is that it retains the drug in gastric environment and improvises sustain delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. Hence the aim is to formulate a timolol maleate gastric floating delivery system that will release the drug continuously at predetermined rate before it reaches the absorption window thus ensuring optimal bioavailability, improved patient compliance and reduced dose frequency<sup>2</sup>.

The gastric floating drug delivery systems have a bulk density less than gastric fluid and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. This also results in an increased gastric retention time and better control of fluctuations of plasma drug concentration.

**MATERIALS AND METHODS:****MATERIALS:**

Timolol maleate was obtained as a gift sample from Ajanta Pharma, Mumbai. HPMC grade K4M, K15M, K100M and carbopol 934P was a gift sample from Merck Chemicals,

Germany. Sodium bicarbonate, citric acid, PVPK30, talc and magnesium stearate purchased from Reachem chemicals, Mumbai. All the chemicals used were of analytical grade.

**METHODS:****1. Formulation of timolol maleate floating tablet:**

The formulation was prepared according to the principle of effervescent technique, in which all the ingredients were weighed accurately as per the formulation Table 1. Initially a powder mixture of timolol maleate, HPMC grade K4M, K15M, K100M, carbopol 934P, Micro crystalline cellulose (MCC), sodium bicarbonate, citric acid and PVP K30 was prepared in a clear and dry mortar and pestle, then passed through sieve No #80. Later magnesium stearate and talc were added as lubricant and glidant respectively. An appropriate amount of the mixture was weighed and fed manually into the die of rotary single punch tablet machine using 8.5 mm punch to get tablets of average weight 330 mg. The punched tablets were wrapped in aluminium foil and stored in an air tight pouch in a controlled environment of temperature and humidity until further studies<sup>3</sup>.

**2. EVALUATION OF TIMOLOL MALEATE FLOATING TABLETS:**

Evaluation was performed to assess the pre-compression properties of the powder blend and post-compression properties of developed gastric floating tablet formulations.

## 2.1. Pre-compression evaluation parameters of powder blends:

### Angle of repose:

The angle of repose of powder blend was determined by the funnel method. Accurately weighed powder blends were filled in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the

surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation<sup>4</sup>.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where,

$\theta$  = angle of repose;  $h$  = height of the pile;  $r$  = radius of the cone made by powder blend

**Table 1: Formulation of timolol maleate gastric floating tablet**

Ingredients	Formulation code								
	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
HPMC K15M	150	120	120	-	-	-	-	-	-
HPMC K4M	-	-	-	150	120	120	-	-	-
HPMC K100M	-	-	-	-	-	-	150	120	120
Carbopol 934P	-	20	30	-	20	30	-	20	30
Timolol maleate	25	25	25	25	25	25	25	25	25
Sodium bicarbonate	60	60	60	60	60	60	60	60	60
Citric acid	20	20	20	20	20	20	20	20	20
MCC	60	70	60	60	70	60	60	70	60
PVP K30	10	10	10	10	10	10	10	10	10
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3	3	3
Total	330	330	330	330	330	330	330	330	330

### Bulk density:

Both loose bulk density and tapped bulk density were determined. A quantity accurately equal to 10 g of powder from each formulation was introduced into a 10 ml measuring cylinder. Initial volume was observed, the cylinder was allowed to tap. The tapping was continued until no further change in volume was noted. Bulk density was calculated by using formula<sup>4</sup>.

$$\text{Bulk density} = M / V_0$$

Where,

$M$  = mass of powder.  $V_0$  = bulk volume of the powder.

$$\text{Tapped density} = M / V_t$$

Where,

$M$  = mass of powder,  $V_t$  = tapped volume of the powder.

### Compressibility Index (Carr's consolidation Index):

Another indirect method of measuring flow from bulk densities was developed by Carr. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability. It is calculated according to the following equation<sup>4</sup>.

$$\text{Carr's index (\%)} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

## 2.2. Post-compression evaluation parameters of timolol maleate gastric floating tablet

### Thickness test:

Thickness test was performed by measuring the thickness of the tablet at different positions using a standard calibrated screw gauge meter. The thickness was expressed in mm. Three tablets from each formulation were selected randomly<sup>5</sup>.

### Hardness test:

The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm<sup>2</sup>. Three tablets from each formulation were selected randomly<sup>5</sup>.

### Friability:

Roche friabilator was used for testing the friability of the tablets. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min the tablets were weighed and the percentage loss in tablet weight was determined<sup>5</sup>.

### Weight variation test:

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated<sup>5</sup>.

### Drug content estimation:

Randomly selected ten tablets were weighed and powdered in a mortar and pestle. Powder weighing equivalent to 330 mg of timolol maleate was accurately weighed and transferred into a 100 ml volumetric flask and dissolved in 0.1N HCl, pH 1.2. Subsequently the solution from volumetric flask was filtered and suitable dilutions were made. These aliquots were analyzed at 275 nm using UV-Visible spectrophotometer. The drug content of each sample was estimated from standard curve of clarithromycin using 0.1N HCl, pH 1.2<sup>7</sup>.

**Swelling index:**

Swelling property of tablet was determined by placing it in the dissolution test apparatus, in 900 ml of 0.1 N HCl at  $37 \pm 2$  °C. The weight and volume reached by the matrix tablets over time was determined by withdrawing the tablets periodically from dissolution medium. The tablets were weighed on an analytical balance after slight blotting with tissue paper to remove the excess liquid. The volume of the tablets was obtained by measuring the thickness and diameter, considering a right circular cylinder form. The determined weight and volume were used to calculate the tablet density over the dissolution study. Swelling characteristics were expressed in terms of percentage water uptake (WU %) or swelling index according to the equation<sup>8</sup>.

$$\text{Swelling index (WU\%)} = \frac{W_f - W_i}{W_i} \times 100$$

Where,

Wi = initial weight of tablet, Wf = final weight of tablet

**The buoyancy lag time and the total floating time:**

Buoyancy or floating behavior studies was carried out in a USP Dissolution Testing Apparatus II (Paddle type) at paddle speed 50 rpm in 900ml 0.1 N HCl at  $37 \pm 0.2$  °C for 24 h to mimic *in vivo* conditions. For determining the optimized buoyancy lag time and total floating time of the delivery system, various formulations prepared according to table 1 were studied. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as

floating lag time, the duration of system floatation and also the relative matrix integrity was observed visually<sup>7</sup>.

***In vitro* drug release**

The *in vitro* release rate of timolol maleate from floating tablets was determined using USP dissolution testing apparatus II (paddle type). The test was performed using 900 ml of 0.1 N HCl at  $37 \pm 0.5$  °C and 50 rpm for study. The amount of drug released over time was determined by withdrawing samples at various determined time intervals for 24 hrs and were replaced with fresh dissolution medium. The aliquots were filtered through Whatman filter paper Grade-1 and concentration of drug was obtained by measuring the absorbance at 275 nm using UV-Visible spectrophotometer<sup>8</sup>.

**RESULTS:****Pre-compression evaluation parameters of powder blends:**

The pre-compression parameters such as angle of repose, bulk density, tapped density and compressibility index were evaluated. The results of all the pre compression parameters were found to comply with the specification of IP. The results are displayed in Table 2.

**Post-compression evaluation parameters of timolol maleate gastric floating tablet:**

All the formulations subjected for post-compression characterization of morphological properties such as thickness, hardness, weight variation and friability test showed satisfactory results which were within the limits for all the formulation. The results of these tests are reported in Table 3.

**Table 2: Pre-compression evaluation parameters of gastric floating tablets**

Formulation code	Angle of repose* ± SD (°)	Bulk density* ± SD (g/ml)	Tapped density* ± SD (g/ml)	Compressibility index* ± SD (%)
F1	18.24±0.11	0.464±0.08	0.542±0.09	15.12±0.09
F2	19.71±0.09	0.479±0.06	0.512±0.08	18.94±0.09
F3	20.14±0.09	0.462±0.05	0.571±0.07	18.91±0.10
F4	18.96±0.14	0.483±0.10	0.563±0.09	14.20±0.12
F5	20.04±0.21	0.492±0.11	0.593±0.01	17.03±0.12
F6	20.62±0.11	0.487±0.05	0.581±0.01	16.17±0.11
F7	19.13±0.13	0.493±0.09	0.577±0.09	14.55±0.05
F8	20.45±0.09	0.461±0.08	0.542±0.09	15.12±0.04
F9	22.50±0.09	0.487±0.07	0.581±0.10	16.17±0.05

\*Each reading is an average of 6 determinants

**Table 3: Post-compression parameters of gastric floating tablets**

Formulation code	Average thickness* ± SD (mm)	Hardness* ± SD (kg/cm <sup>2</sup> )	Weight variation* ± SD (mg)	Percentage friability
F1	4.4±0.001	5.1±0.2	328±2.43	0.48%
F2	4.5±0.004	5.4±0.8	327±2.40	0.39%
F3	4.6±0.003	5.2±0.9	330±2.71	0.21%
F4	4.8±0.001	5.3±0.8	332±2.41	0.28%
F5	4.5±0.002	5.1±0.5	328±2.74	0.34%
F6	4.6±0.003	5.2±0.6	329±2.49	0.42%
F7	4.4±0.002	5.4±0.7	329±2.33	0.19%
F8	4.3±0.005	5.3±0.9	328±2.98	0.35%
F9	4.4±0.006	5.1±1.1	327±2.64	0.36 %

\*Each reading is an average of 6 determinants

**Buoyancy studies:**

From the results it can be noted that the formulations containing different grades of HPMC polymer only such as

F1, F4 and F7 showed good buoyancy lag time less than 10 sec, but it did not float for more than 9 h. The batch containing HPMC polymer with Carbopol 934P in concentration of 20 mg and 30 mg such as F2, F3, F5, F6, F8 and F9 showed poor lag time less than 2 mins but exhibited good total floating time of more than 12 h. The results are reported in Table 4.

**Table 4: Buoyancy lag time and total floating time of gastric floating tablets**

Formulation code	Buoyancy Lag time* $\pm$ SD (sec)	Total floating time (h)	Percentage Drug content* $\pm$ SD
F1	8 $\pm$ 1.2	$\leq$ 9	97.14 $\pm$ 0.15
F2	48 $\pm$ 2.8	>12	96.53 $\pm$ 0.23
F3	67 $\pm$ 3.3	>12	93.72 $\pm$ 0.12
F4	6 $\pm$ 2.3	$\leq$ 9	97.95 $\pm$ 0.22
F5	51 $\pm$ 4.5	>12	95.88 $\pm$ 0.34
F6	72 $\pm$ 6.6	>12	100.01 $\pm$ 0.4
F7	7 $\pm$ 3.1	$\leq$ 9	97.91 $\pm$ 0.23
F8	40 $\pm$ 2.7	>12	92.40 $\pm$ 0.17
F9	54 $\pm$ 1.8	>12	91.2 $\pm$ 0.44

\*Each reading is an average of 6 determinants.

#### **Swelling index studies:**

The swelling index studies performed on all the formulations showed that the swelling index of HPMC K15M, K4M and K100M was found to be 184.3, 164.3 and

278.8 at the end of 8 h respectively. Whereas formulation F2, F3, F5, F6, F8 and F9 containing HPMC K15M, K4M and K100M with 20 and 30 mg of Carbopol 934P was 245.6, 261.7, 228.7, 258.3, 296.3 and 311.8 respectively at the end of 9 h. The results are shown in Table 5.

**Table 5: Swelling index studies**

Time (h)	F1*	F2*	F3*	F4*	F5*	F6*	F7*	F8*	F9*
0.5	32.81 $\pm$ 0.08	51.23 $\pm$ 0.19	63.71 $\pm$ 0.09	31.85 $\pm$ 0.06	45.22 $\pm$ 0.02	56.35 $\pm$ 0.05	64.13 $\pm$ 0.15	78.38 $\pm$ 0.11	80.19 $\pm$ 0.19
1	48.43 $\pm$ 0.20	75.32 $\pm$ 0.03	81.42 $\pm$ 0.03	40.64 $\pm$ 0.17	60.34 $\pm$ 0.14	78.65 $\pm$ 0.13	89.3 $\pm$ 0.01	110.4 $\pm$ 0.05	116.3 $\pm$ 0.29
2	64.52 $\pm$ 0.01	108.8 $\pm$ 0.12	117.1 $\pm$ 0.19	60.71 $\pm$ 0.09	89.65 $\pm$ 0.12	110.8 $\pm$ 0.09	119.4 $\pm$ 0.06	134.5 $\pm$ 0.08	143.2 $\pm$ 0.06
3	101.5 $\pm$ 0.15	158.3 $\pm$ 0.17	176.1 $\pm$ 0.14	94.31 $\pm$ 0.07	108.9 $\pm$ 0.13	154.9 $\pm$ 0.04	169.1 $\pm$ 0.16	166.6 $\pm$ 0.14	176.8 $\pm$ 0.07
4	143.7 $\pm$ 0.22	175.3 $\pm$ 0.10	201.3 $\pm$ 0.15	132.1 $\pm$ 0.05	148.1 $\pm$ 0.14	188.1 $\pm$ 0.03	184.2 $\pm$ 0.11	189.7 $\pm$ 0.15	199.1 $\pm$ 0.14
5	158.6 $\pm$ 0.19	195.1 $\pm$ 0.11	223.6 $\pm$ 0.15	141.7 $\pm$ 0.01	174.4 $\pm$ 0.12	213.3 $\pm$ 0.08	213.4 $\pm$ 0.19	217.9 $\pm$ 0.13	227.3 $\pm$ 0.13
6	169.2 $\pm$ 0.16	220.3 $\pm$ 0.09	246.7 $\pm$ 0.11	154.8 $\pm$ 0.07	193.3 $\pm$ 0.17	236.4 $\pm$ 0.11	246.3 $\pm$ 0.13	234.1 $\pm$ 0.19	249.2 $\pm$ 0.15
7	175.5 $\pm$ 0.17	236.4 $\pm$ 0.05	254.7 $\pm$ 0.14	158.1 $\pm$ 0.14	210.1 $\pm$ 0.05	247.2 $\pm$ 0.14	269.7 $\pm$ 0.12	256 $\pm$ 0.11	267.5 $\pm$ 0.19
8	184.3 $\pm$ 0.16	241.7 $\pm$ 0.06	258.9 $\pm$ 0.01	164.3 $\pm$ 0.11	221.6 $\pm$ 0.08	253.1 $\pm$ 0.18	278.8 $\pm$ 0.09	279.1 $\pm$ 0.19	284.5 $\pm$ 0.12
9			245.6 $\pm$ 0.09	261.7 $\pm$ 0.02		228.7 $\pm$ 0.02	258.3 $\pm$ 0.16	296.3 $\pm$ 0.09	311.8 $\pm$ 0.07

\*Each reading is an average of 6 determinants.

#### **In vitro drug release:**

The *in vitro* drug release data for Formulation F1, F4 and F7 was found to be above 95% drug release in 8 h containing only different grades of HPMC and 90 – 95% in 12 h for formulation F2, F3, F5, F6, F8 and F9 containing different grades of HPMC with carbopol 934P. The results are given in fig. 1.

#### **Drug Release Kinetics:**

The various drug release kinetic models were studied for the value of correlation coefficient. The best linearity was found in Higuchi's plot as its linear regression is nearer to '1' indicating the release of drug from matrix as a square root of time. The 'n' values which characterizes diffusion release mechanism by Krospeyer peppas model was found to be in the range of 0.45 to 0.63. (Table 6).

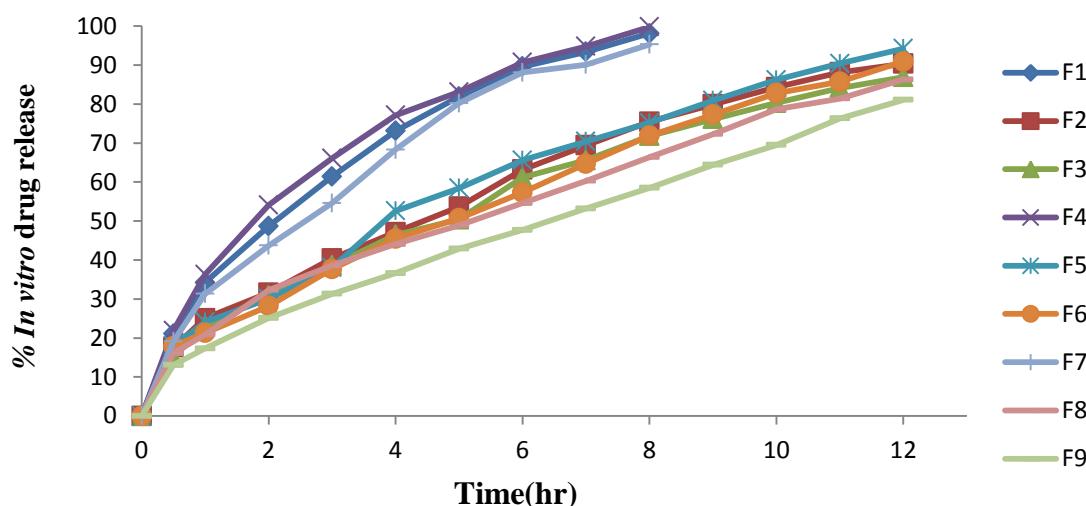
Figure 1: *In vitro* drug release profile of timolol maleate gastric floating tablet.

Table 6: Drug Release kinetics profile of dissolution studies

Formulation code	Kinetic models			
	Zero order	First order	Higuchi order	Korsmeyer-peppas order
F1	$y = 11.393x + 18.559$ $R^2 = 0.9212$	$y = -0.0859x + 1.4951$ $R^2 = 0.138$	$y = 36.326x - 1.6586$ $R^2 = 0.9962$	$y = 0.9776x + 1.1816$ $R^2 = 0.4513$
F2	$y = 8.4222x + 11.599$ $R^2 = 0.9613$	$y = -0.0272x + 1.5656$ $R^2 = 0.0467$	$y = 26.179x - 2.1993$ $R^2 = 0.988$	$y = 0.9056x + 1.0774$ $R^2 = 0.4586$
F3	$y = 6.6968x + 14.636$ $R^2 = 0.9557$	$y = -0.0163x + 1.5511$ $R^2 = 0.0178$	$y = 26.084x - 3.6259$ $R^2 = 0.9939$	$y = 0.9264x + 1.0459$ $R^2 = 0.4851$
F4	$y = 11.286x + 21.074$ $R^2 = 0.8956$	$y = -0.1114x + 1.5182$ $R^2 = 0.1968$	$y = 36.432x + 0.2845$ $R^2 = 0.9928$	$y = 0.9662x + 1.203$ $R^2 = 0.4362$
F5	$y = 7.2149x + 15.559$ $R^2 = 0.9552$	$y = -0.0377x + 1.5894$ $R^2 = 0.0827$	$y = 28.07x - 4.0487$ $R^2 = 0.9912$	$y = 0.874x + 1.0839$ $R^2 = 0.5636$
F6	$y = 6.9517x + 13.299$ $R^2 = 0.9719$	$y = -0.024x + 1.5793$ $R^2 = 0.0361$	$y = 26.746x - 4.9501$ $R^2 = 0.9863$	$y = 0.866x + 1.0599$ $R^2 = 0.5695$
F7	$y = 11.241x + 15.559$ $R^2 = 0.9425$	$y = -0.0514x + 1.4665$ $R^2 = 0.0577$	$y = 35.383x - 3.6081$ $R^2 = 0.9933$	$y = 0.9914x + 1.1477$ $R^2 = 0.4727$
F8	$y = 6.4249x + 14.039$ $R^2 = 0.964$	$y = -0.011x + 1.5513$ $R^2 = 0.0081$	$y = 24.886x - 3.1854$ $R^2 = 0.9915$	$y = 0.8518x + 1.0543$ $R^2 = 0.5656$
F9	$y = 6.1067x + 9.8305$ $R^2 = 0.9827$	$y = -0.0535x + 2.0016$ $R^2 = 0.965$	$y = 23.276x - 5.7325$ $R^2 = 0.9787$	$y = 0.8761x + 0.9799$ $R^2 = 0.6137$

### Stability studies

Accelerated stability studies were conducted to observe any change in colour, appearance and drug content test at room temperature and oven temperature ( $40 \pm 2$  °C) buoyancy lag time for a period of eight weeks. There was no significant colour and drug content change observed at the end of eight weeks in all the formulations.

### DISCUSSION:

The aim of the present research was to formulate gastric floating tablets of timolol maleate by using three different grades of HPMC polymer (K15M, K4M and K100M) alone and then by combining these HPMC polymers individually with two different concentration (6% and 9%) carbopol 934P and study the effect of carbopol 934P on the different properties of the gastric floating tablet. Hence three formulations of each grade of HPMC polymer with and without carbopol 934P were prepared yielding a total of nine formulations.

The characterization was carried out in two stages i.e. pre-compression and post-compression evaluation parameters. The pre-compression evaluation parameters comprised of powder properties like angle of repose, bulk density, tapered density and compressibility index which was done to ensure that the mixture of powder possessed the necessary characteristics to undergo compression. The results of the pre-compression parameters showed that the powder mixture of all the nine formulations were well within the limits as prescribed in IP, indicating its suitability to undergo compression. The post-compression parameters were carried out in two stages, namely morphological and physico-chemical evaluation. The post-compression morphological characteristics included thickness, hardness, weight variation and friability test which were carried out under standard controlled environment. According to the results of Table 3, it can be interpreted that all the nine formulations showed satisfactory results which were within the limits prescribed

by IP. The post-compression physico-chemical characteristics included buoyancy studies, swelling time, *in vitro* drug release, drug release kinetics and stability studies. The buoyancy studies reviled that formulation F1, F4 and F7 which contained HPMC K15M, K4M and K100M showed buoyancy lag time less than 10 sec and total floating time of  $\leq 9$  h when compared to formulations F2, F3, F5, F6, F8 and F9 with buoyancy lag time less than 2 min and total floating time more than 12 h. Increased buoyancy lag time and satisfactory total floating can be attributed to the presence of carbopol 934P in different concentration.

Optimum swelling index was seen for tablets of batch F8 containing 120 mg of HPMC K100M and 20 mg of Carbopol 934P as compared to other formulations. The nominal viscosity of F8 was found to be more than 1,04,120 cps. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the results of Table 5 it can be concluded that linear relationship exists between swelling process and viscosity of polymer. Thus swelling index showed the following order HPMC K100M > HPMC K15M > HPMC K4M i.e. F7 > F1 > F4; with addition of carbopol 934P there was further increase in the swelling property but the order remained same i.e. F9 > F8 > F3 > F6 > F2 > F5.

The formulation F1, F4 F7 containing polymer HPMC K15M, K4M and K100M in 30% concentration floated for  $\leq 9$  h but later it get disintegrated. The formulation containing Carbopol 934P with concentration of 6% and 9% are F2, F3, F5, F6, F8, F9 shown total floating time more than 14 h without any disintegration or erosion. A perusal to figure 1, it can be concluded that combination of anionic carbopol 934P and non ionic HPMC polymer produce synergistic inclusion in viscosity which could be due to H-bonding between carboxyl group of carbopol and OH group of HPMC that lead to stronger cross linking between two polymer and retarding the drug release.

The *in vitro* drug release data for Formulation F1, F4 and F7 was found to be above 95% in 8 h. Improvement in the drug release was seen by including 6% carbopol 934P in Formulation F2, F5 and F8 showing *in vitro* drug release between 90 – 95% in 12 h. Carbopol acted as drug release retarding agent, by swelling and forming colloidal mucilage that may help resist disintegration of gastric floating tablet in gastric fluid. By increasing the concentration of carbopol 934P to 9% as in case of F3, F6

and F9 formulations, the drug release was less than 90% in 12 h which proved to be optimum concentration of polymer and gas generating agent. Among all the formulations prepared, formulation F5 exhibit optimum drug release 94.2 % in 12 h with buoyancy lag time of 51 sec.

The drug release kinetic data showed best linearity in Higuchi's plot as its linear regression was nearer to '1' indicating the release of drug from matrix as a square root of time. This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon was involved. The 'n' values can be used to characterize diffusion release mechanism by Krospeyer peppas model. The 'n' value for all formulations was found to be in the range of 0.45 to 0.63 which indicates that the release approximates non-fickian diffusion mechanism. Hence combination of diffusion and erosion can be considered as mechanism of drug release from the formulations.

Accelerated stability studies showed that there was no significant change in colour, appearance and/or drug content at room temperature and oven temperature. And also no changes in buoyancy lag time after a period of eight weeks in all the 9 formulations. This indicated good stability of the prepared formulations.

## CONCLUSION

The effervescent-based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer HPMC (K100, K15M, K4M) with carbopol 934P and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve *in vitro* buoyancy. Carbopol 934P has given extra adhesion property and helped to maintain the integrity of the floating tablet. The drug release from the timolol maleate floating tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.

## ACKNOWLEDGEMENT:

The authors express their sincere gratitude to the NITTE University and the Principle, NGSM Institute of Pharmaceutical Sciences, Mangalore, for providing necessary facility to carry out the research work.

## CONFLICTS OF INTEREST:

The authors do not have any conflicts of interest.

## REFERENCES:

1. Sweetman SC (Eds), Martindale: The complete drug reference, 33rd ed. Great Britain, Pharmaceutical press. 2002. P. 1269.
2. Jain SK, Jain NK, Agarwal GP. Gastro retentive floating drug delivery: Drug delivery technology 3<sup>rd</sup> ed. 2005; 5:7:1-9.
3. Jaimini M, Rana AC, Tanwar YS, Formulation and evaluation of Famotidine floating tablets, Curr Drug Deliv, 2007; 4, 51-55.
4. Liebermann HA, Lachman L, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Mumbai: Varghese Publishing house; 1990. P. 253-96.
5. Rowe RC, Shekey PJ, Owen SC. Handbook of Pharmaceutical Excipients, 5th ed. London: The pharmaceutical press; 2006. P. 295-98.
6. Liebermann HA, Lachman L, Schwartz JB. Pharmaceutical dosage forms: Tablets. Vol 1. New York: Marcel Dekker Inc; 1989. P. 48-9.
7. The United States Pharmacopoeia and The National Formulary, United States Pharmacopoeia Convention INC Rockville; 2003. P. 89-99.
8. Gohel MC, Mehta PR, Dave PK, Bariya NH. More relevant dissolution method for evaluation of FDDS, Dissolution Technologies. 2005, 22-5.
- 9.