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Formulation and Evaluation of Metoprolol Controlled Release Formulations

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Authors' contributions

This work was carried out in collaboration between both authors. Author RV the guarantor of this study has designed and carried out the experimental process and prepared the manuscript. Author CSKB has analyzed the results and contributed in preparation and review of manuscript. Both authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Aim: The main perspective of the present research work was to prepare Metoprolol floating controlled release formulations.
Methodology: After performing the characterization studies, Metoprolol tablets were prepared using various concentrations of poly ethylene oxide (PEO) WSR 303 (5% to 30%) by direct compression method. Formulations MP1 and MP6 were formulated using PEO WSR 303. Various pre and post compression parameters were evaluated. Dissolution studies were performed for the prepared tablets using dissolution medium of 0.1N hydrochloric acid.
Results: Characterization studies like Fourier Transform Infra Red (FTIR) and Scanning Electron Microscopy (SEM) for Metoprolol, Polyethylene oxide WSR 303 and their combination were carried out, which revealed that there is no interaction between drug and polymer. The dissolution studies showed the controlled release pattern of Metoprolol up to 24h. The formulation MP5 prepared using 25% w/w of PEO WSR 303 showed maximum drug release of 98.22% at 24h. Similar drug release profile was observed for MP6 which was formulated using 30%w/w PEO WSR 303. These two formulations were further added with various concentrations of sodium bicarbonate (5% to 15%) and citric acid (2.5% to 10%) which enhanced floating of drug. Formulation MP8 containing 10% of

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sodium bicarbonate with 25% PEO WSR 303 showed less buoyancy lag time and prolonged drug release. Formulation MP15 showed very less buoyancy lag time of 4sec.
Conclusion: Thus the prepared Metoprolol floating tablets showed prolonged drug release which could be a promising formulation for anti-hypertensive patients.

Keywords: Controlled release; hypertension; poly ethylene oxide; sodium bicarbonate.

1. INTRODUCTION

Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range which is needed for the treatment, only when taken multiple times in a day. Dosage forms which could retain in the stomach for prolonged and predictable period of time are considered as gastro retentive drug delivery systems (GRDDS) [1]. Prolonged gastric retention enhances bioavailability, reduces drug wastage and improves solubility for drugs that are less soluble in a high pH environment [2]. Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate [3]. In these systems, the drug is released slowly at a desired rate from the system, which causes an increase in the gastric residence time and a better control of fluctuations in the plasma drug concentrations. This could be achieved by employing certain polymers [4]. Effervescent systems include use of gas generating agents, carbonates like sodium bicarbonate and other organic acids like citric acid and tartaric acid [5]. When they are present in the formulation, they produce carbon dioxide gas, thus reducing the density of the system and making it float on the gastric fluid [6].

In present research work, the drug Metoprolol is selected for the preparation of floating tablets. Metoprolol is an antihypertensive agent which acts by competitively binding with adrenergic neurotransmitters like catecholamines and binds to β1 adrenergic receptors in heart. As a result, these β1 adrenergic receptors gets blocked that leads to decrease in heart rate, cardiac output and blood pressure. Metoprolol gets rapidly and almost completely absorbed after oral administration with mean elimination half-life of 3 to 7 hours [7]. Polymers like poly ethylene oxides are hydrophilic in nature and are available in various grades. Recent works suggested the usage of PEO WSR as polymer in the formulation of controlled release formulations. They help in prolonged drug release [8].

The aim of the present research work is to formulate and evaluate Metoprolol floating tablets with poly ethylene oxide WSR 303 as polymer, sodium bicarbonate and citric acid as effervescence agents, which causes the floating of tablets on gastric fluid and helps in extended drug delivery.

2. MATERIALS AND METHODS

Materials: Metoprolol (Gift sample from Apotex Pharma Ltd., Bangalore); Poly ethylene oxide WSR 303 (Gift sample from M/s Colorcon Asia Pvt Ltd., Goa); Sodium Bicarbonate (Loba Chemie Pvt. Ltd, Mumbai); Citric acid (Thermo Electron LLS India Pvt. Ltd., Mumbai) and Methanol (Loba Chemie Pvt. Ltd, Mumbai).

2.1 Characterization Studies

The drug and polymer along with its combination were subjected to FTIR and SEM analysis. The results of FT-IR were showed in Fig. 1 and SEM images were represented in Fig. 2.

2.2 Preparation of Metoprolol Tablets using PEO WSR 303

Metoprolol tablets were prepared by direct compression method using poly ethylene oxide WSR 303 (PEO WSR 303) as polymer. The concentration of polymer was increased in the range of 5% to 30% w/w of total tablet weight. The raw materials required for the tablet preparation were weighed separately and placed in a mortar. The components were mixed well and the granules thus formed were passed through sieve no 40. The granules were placed in a plastic bag and talc and magnesium stearate were added to provide lubrication. Then they were compressed using CLIT 10 station mini press [9]. The compositions of Metoprolol tablet formulations were given in Table 1.

2.3 Evaluation of Pre-Compression Parameters

The prepared granules were evaluated for various pre-compression parameters such as

angle of repose, Carr's index and Hausner's ratio [10]. The results were given in table 2.

2.4 Evaluation of Post Compression Parameters

The compressed tablets were further evaluated for post compression parameters such as weight uniformity, hardness, friability, wetting time, dispersion test and drug content [11]. The results were given in Table 3.

2.5 *In vitro* Dissolution Studies of Metoprolol Tablets

Dissolution studies for Metoprolol tablets were performed in a calibrated dissolution test apparatus (USP apparatus II method) using 900 ml of 0.1N hydrochloric acid as dissolution medium. The paddles were operated at 50rpm and temperature was maintained at 37±1ºC throughout the experiment [12]. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 10 and 12, 16, 20 and 24h and replaced with equal volume of the same dissolution medium to maintain the constant condition. The drug release was compared with the marketed formulation of Metoprolol. The amount of drug dissolved was estimated using U.V (Ultra Violet) spectrophotometer at 224 nm. The dissolution profiles were given in Fig. 3.

2.6 *In Vitro* Buoyancy Studies

Metoprolol tablets thus prepared were subjected to *in vitro* buoyancy studies. Here, the floating lag time was measured, which is considered as the time taken by the tablet to rise to the surface. Along with this, the total floating time, i.e., the time which the tablet constantly remained on the surface of the medium was also measured [13]. *In vitro* buoyancy results were given in Table 4.

2.7 Preparation of Metoprolol Tablets using Sodium Bicarbonate and Citric Acid

The formulation which exhibited best dissolution profile with PEO WSR 303 was selected and to it, different concentrations of sodium bicarbonate (5% to 15%) and citric acid (2.5% to 10%) were added as effervescent agents and tablets were prepared by direct compression technique. The other raw materials were weighed individually and transferred to mortar. The components were mixed well and the granules thus formed were passed through sieve no 40. The granules were placed in a plastic bag and mixed with talc and magnesium stearate which acts as lubricants. Then they were compressed as tablets under identical conditions. The composition of various tablet formulations was given in table 5.

The prepared tablets were evaluated for pre and post compression parameters along with dissolution studies which were given in Tables 6 and 7 and shown in Figs. 4 and 5. The buoyancy test was performed for the tablets and the results were shown in Table 8.

3. RESULTS AND DISCUSSION

3.1 Characterization Studies

3.1.1 FT-IR Spectral studies

Metoprolol exhibited principle FT-IR spectral peaks at wave numbers of 2975.71 cm^{-1} (N-H Stretching), 1512.93 cm^{-1} (CO_2 asymmetric Stretching), 1385.95 cm^{-1} (C-H Stretching), and 1242.24 cm^{-1} (C-O symmetric Stretching). N-H stretching, CO_2 asymmetric stretching, C-H stretching and C-O symmetric stretching of Metoprolol and its combination with PEO WSR 303 were almost in the same region of wave number. It revealed that IR spectrum of Metoprolol and its combination with polymer were having similar fundamental peaks and pattern. This showed that there were no drug excipient interactions in the formulation. The FT-IR spectral peaks were shown in Fig. 1.

SEM analysis was performed for Metoprolol pure drug, PEO WSR 303 and their combination. The SEM photographs showed that the Metoprolol was well mixed and equally distributed with polymer. SEM photographs were shown in Fig. 2.

3.2 Preparation of Metoprolol Tablets using PEO WSR 303

Metoprolol tablets were prepared using various concentrations of PEO WSR 303 by direct compression technique. Formulations MP1 to MP6 were prepared using 5% to 30% of PEO WSR 303. The formulation MP doesn't contain any polymer. The composition of various Metoprolol tablets was given in Table 1.

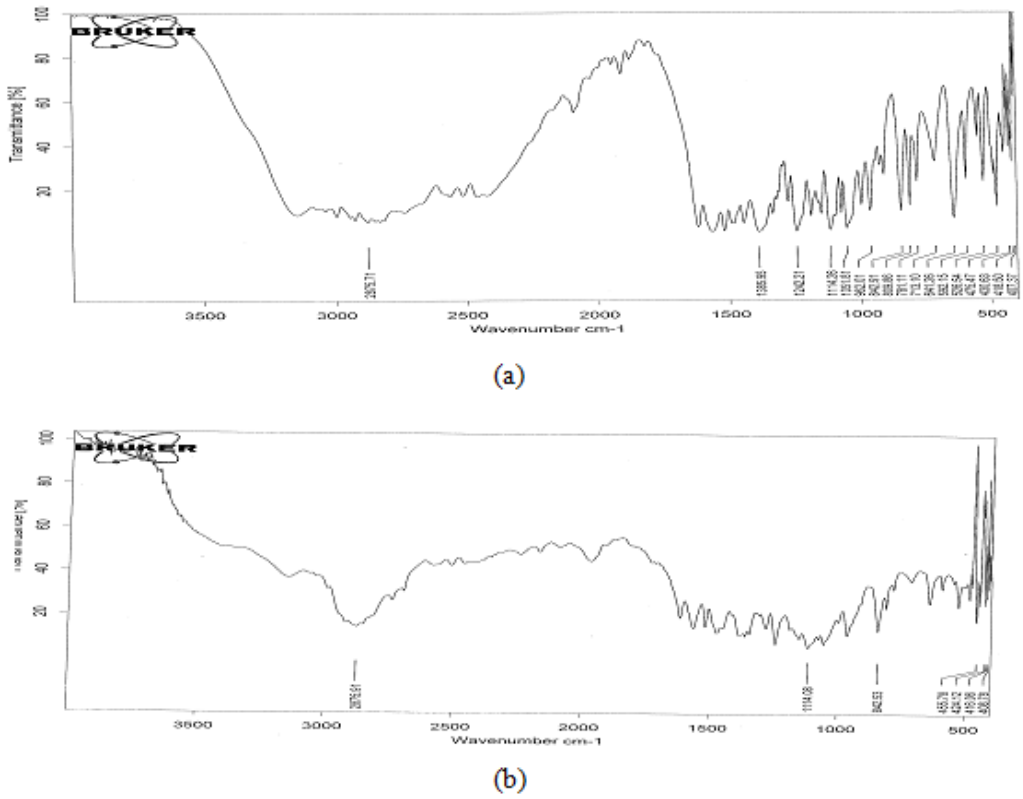

Fig. 1. FTIR Spectra of (a) Metoprolol Pure Drug (b) Metoprolol with PEO WSR 303

SEM Analysis

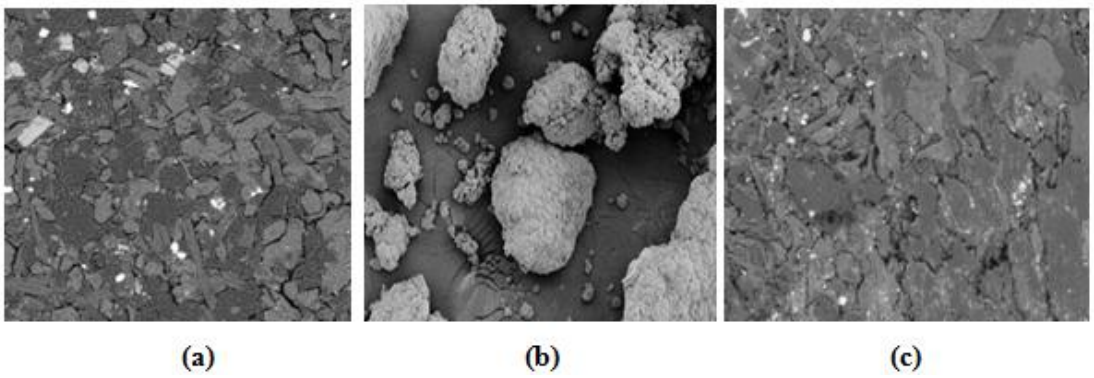

Fig. 2. SEM Photographs of (a) Metoprolol Pure Drug (b) PEO WSR 303 (c) Metoprolol with PEO WSR 303

Table 1. Composition of metoprolol tablets with different polymer concentrations

Ingredient (mg/tablet)	Formulations						
	MP	**MP1**	**MP2**	**MP3**	**MP4**	**MP5**	**MP6**
Metoprolol	100	100	100	100	100	100	100
PEO WSR 303	-----	12.50	25.0	37.50	50.0	62.50	75
MCC (PH 102)	145.0	132.50	120.0	107.50	95.0	82.50	70.0
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**

3.3 Evaluation of Pre-compression Parameters

The pre-compression parameter values obtained for Metoprolol granules were given in the Table 2. The angle of repose, Carr's index and Hausner's ratio values for granules were within the range specified. Thus all the prepared granules were found to be stable and suitable for compression of tablets.

3.4 Evaluation of Post Compression Characteristics of Metoprolol Tablets

The direct compression method was found to be suitable for preparation of tablets. Metoprolol tablets were prepared and evaluated for post compression parameters. The results were given in Table 3. Weight uniformity, hardness and friability loss of tablet formulations were within the specified limits and were found to be suitable for further studies.

3.5 *In vitro* Dissolution Studies of Metoprolol Tablets

Dissolution studies were carried on Metoprolol tablets using U.S.P paddle method (apparatus II) with 0.1N hydrochloric acid as dissolution medium. The bath temperature was maintained at 37±1°C throughout the experiment and the paddles were operated at 50rpm. The study clearly showed with increase in the concentration of PEO WSR 303, the delay in drug release was also increased. Formulation MP5 having 25% w/w of PEO WSR 303 exhibited controlled and prolonged drug release without any sodium bicarbonate. Similar drug profile was observed with MP6 formulation which was made using 30% w/w of PEO WSR 303. Thus this current research data highly recommend the incorporation of PEO in controlled release formulations which was in par with several recent findings [14,15]. The results were shown in Fig. 3.

Table 2. Pre-compression parameters of metoprolol granules

Formulation	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio
MP	32	22	1.24
MP1	27	18	1.20
MP2	25	17	1.17
MP3	24	15	1.14
MP4	23	14	1.13
MP5	22	13	1.12
MP6	22	13	1.12

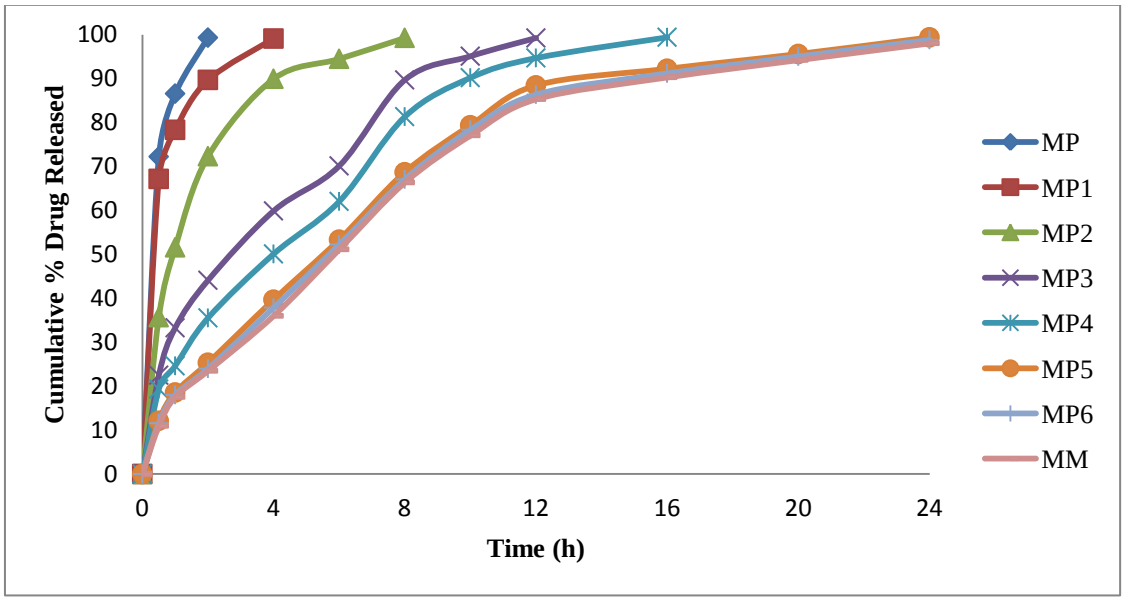

Fig. 3. Dissolution profiles of metoprolol tablets

Mean ± S.D = Mean values ± Standard Deviation of three experiments

Table 3. Post compression parameters of metoprolol formulations

Formulation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (% loss)	Swelling Index (%)	Drug content (mg/tablet) (Mean ± S.D)
MP	250±1.07	3.6±0.26	0.4	---	100.01±1.01
MP1	249±0.75	3.3±0.32	0.3	86	99.92±0.61
MP2	250±0.38	3.3±0.28	0.3	131	100.11±0.77
MP3	249±0.94	3.2±0.34	0.2	164	100.09±0.58
MP4	250±1.11	3.3±0.19	0.2	205	99.98±0.83
MP5	250±0.59	3.3±0.15	0.3	234	101.04±0.40
MP6	250±0.71	3.3±0.22	0.3	261	100.13±0.56

n=6; S.D is standard deviation

3.6 *In Vitro* Buoyancy Studies

In vitro buoyancy studies were performed on prepared Metoprolol formulations. The buoyancy lag time along with total floating time were indicated in Table 4.

3.7 Preparation of Metoprolol Tablets using Sodium Bicarbonate and Citric Acid

Formulations MP7 to MP9 were prepared using 25% w/w PEO WSR 303 and sodium bicarbonate in 5%, 10% and 15% w/w concentrations. Whereas MP10 to MP12 were prepared using 30% w/w of PEO WSR 303 along with various concentrations of sodium bicarbonate (5%, 10% and 15%). MP13 to MP15 were prepared using 25% w/w of PEO WSR 303 along with 5% and 10%w/w of sodium bicarbonate and 2.5%, 5% and 10%w/w of citric acid. The composition of Metoprolol formulations was indicated in Table 5.

3.8 Evaluation of Pre-compression Parameters

The pre compression parameter values obtained for various prepared granules were given in the table 6. The angle of repose, Carr's index and Hausner's ratio values for granules were within the range specified. All the prepared granules were found to be stable and suitable for compression of tablets.

3.9 Evaluation of Post Compression Characteristics of Metoprolol Tablets

The direct compression method was found to be suitable for preparation of tablets. Metoprolol tablets were prepared and evaluated for post compression parameters. The results were given in Table 7. Weight uniformity, hardness and friability loss of tablet formulations were within the specified limits and were found to be suitable for further studies.

3.10 *In vitro* Dissolution Studies of Metoprolol Tablets Prepared using Sodium Bicarbonate and Citric Acid

Dissolution studies were carried on Metoprolol tablets using U.S.P paddle method (apparatus II) with 0.1N hydrochloric acid as dissolution medium by maintaining the bath temperature at $37\pm1^{o}C$ and the paddles were operated at 50rpm. The current work showed that as the concentration of sodium bicarbonate increased,

Table 4. Buoyancy test for metoprolol formulations

Formulation Code	Buoyancy Lag Time (sec)	Total Floating Time (h)
MP	945	2
MP1	521	4
MP2	334	8
MP3	288	12
MP4	165	16
MP5	147	24
MP6	135	24

Table 5. Composition of metoprolol tablets with different polymer concentrations

Ingredient (mg/tablet)	Formulations									
	MP	**MP7**	**MP8**	**MP9**	**MP10**	**MP11**	**MP12**	**MP13**	**MP14**	**MP15**
Metoprolol	100	100	100	100	100	100	100	100	100	100
PEO WSR 303	-----	62.50	62.50	62.50	75.0	75.0	75.0	62.50	62.50	62.50
MCC (PH 102)	145.0	70.0	57.5	45.0	57.5	45.0	32.50	63.75	45.0	32.5
Sodium Bicarbonate	-----	12.5	25.0	37.50	12.5	25.0	37.50	12.5	25.0	25.0
Citric Acid	-----	-----	-----	-----	-----	-----	-----	6.25	12.50	25.0
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Table 6. Pre-compression parameters of metoprolol granules

Formulation	Angle of Repose (^{0})	Carr's Index (%)	Hausner's Ratio
MP	32	22	1.24
MP7	23	14	1.14
MP8	22	13	1.13
MP9	22	13	1.12
MP10	22	13	1.13
MP11	21	12	1.12
MP12	22	13	1.11
MP13	21	11	1.11
MP14	22	13	1.12
MP15	21	11	1.12

the buoyancy lag time has reduced. This might be due to the effervescence property of sodium bicarbonate. Formulation MP8 containing 25% w/w of PEO WSR 303 with 10% w/w of sodium bicarbonate exhibited controlled and prolonged release of drug with less buoyancy lag time. Formulation MP15 with 10% w/w citric acid exhibited very less buoyancy lag time. The initial drug release was faster, when citric acid and sodium bicarbonate were added to the formulation. This is due to their effervescence nature. However, due to the presence of PEO WSR 303 in the formulation, the drug release was delayed in later hours. Thus, the current research strongly showed the result that employing effervescence agents in the formulations achieved better floating. Similar suggestions have also been mentioned in some recent research [16-18]. The results were shown in Figs. 4 and 5.

3.11 *In Vitro* Buoyancy Studies

In vitro buoyancy studies were performed on prepared Metoprolol formulations prepared using sodium bicarbonate and citric acid. Incorporation of sodium bicarbonate and citric acid has greatly reduced the buoyancy lag time which was also supported by the recent studies [19,20]. The buoyancy lag time and total floating time measured were indicated in Table 8.

Table 7. Post compression parameters of metoprolol formulations

Formulation	Weight Uniformity (mg)	Hardness (kg/cm^2)	Friability (% loss)	Swelling Index (%)	Drug Content (mg/tablet) (Mean ± S.D)
MP	250±1.07	3.6±0.26	0.4	---	100.01±1.01
MP7	251±1.12	3.3±0.15	0.3	215	100.18±0.63
MP8	249±0.88	3.3±0.23	0.4	192	101.09±0.30
MP9	250±1.28	3.2±0.11	0.2	175	100.15±0.57
MP10	251±0.41	3.2±0.26	0.2	244	99.98±0.84
MP11	250±1.04	3.3±0.31	0.3	221	101.05±0.61
MP12	249±1.13	3.3±0.19	0.3	188	99.94±1.08
MP13	251±0.79	3.2±0.14	0.3	180	100.09±0.76
MP14	250±0.94	3.2±0.17	0.2	167	100.33±1.04
MP15	251±1.10	3.2±0.23	0.2	149	99.81±1.20

n=6; Mean ± S.D = Mean values ± Standard Deviation of three experiments

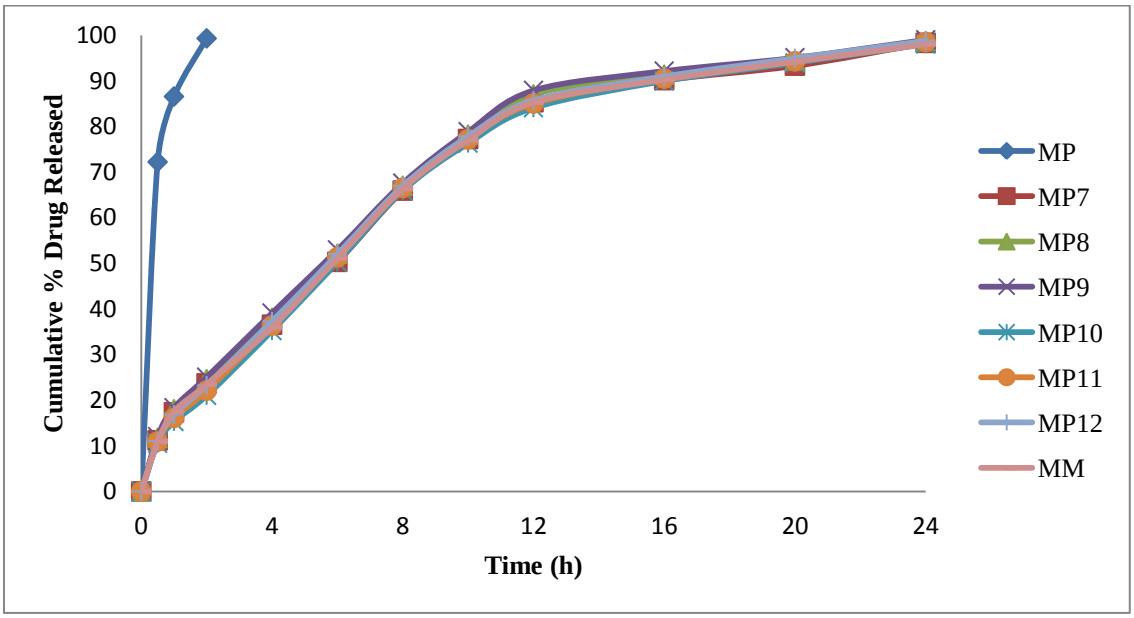

Fig. 4. Dissolution profiles of metoprolol tablets prepared using sodium bicarbonate
Mean ± S.D = Mean values ± Standard Deviation of three experiments

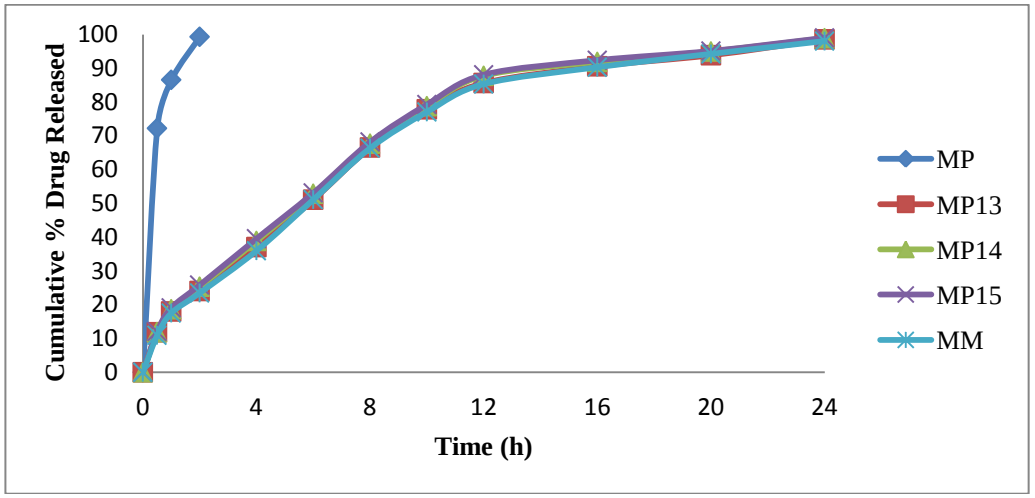

Fig. 5. Dissolution profiles of metoprolol tablets prepared using sodium bicarbonate and Citric Acid

Mean ± S.D = Mean values ± Standard Deviation of three experiments

Table 8. Buoyancy test for various metoprolol formulations

Formulation Code	Buoyancy Lag Time (sec)	Total Floating Time (h)
MP	945	2
MP7	40	24
MP8	32	24
MP9	20	24
MP10	36	24
MP11	26	24
MP12	15	24
MP13	10	24
MP14	8	24
MP15	4	24

4. CONCLUSION

The present work was focused on preparation of controlled release floating tablets of Metoprolol. From the present work, it was concluded that incorporation of PEO WSR 303 in the formulation showed delay in drug release. Incorporation of sodium bicarbonate and citric acid has increased the buoyancy of the formulation and led to floating with in short period. Thus the formulations made using PEO WSR 303 as polymer and sodium bicarbonate and citric acid as effervescent agents brought a promising novel controlled release floating formulation which could be beneficial for hypertensive patients.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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