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FORMULATION AND EVALUATION OF MARAVIROC EFFERVESCENT FLOATING TABLETS

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ABSTRACT

The oral route is considered the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as the gastric emptying process, the gastrointestinal transit time of dosage form, drug release from the dosage, form, and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release, and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having an absorption window, especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The main objective of this study is to prepare an effervescent floating tablet formulation for Maraviroc and evaluate the gastric retention time. This formulation is expected to have an increased bioavailability of Maraviroc. The tablets are prepared by direct compression method using low-density polymers such as HPMC K100M, Carbopol 940, and Xanthum Gum. Sodium bicarbonate and citric acid are used as effervescence agents.

INTRODUCTION

The idea of gastric retention comes from the need to localize drugs to a specific region of the gastrointestinal tract such as the stomach in the body. Many drugs get absorbed only in the upper intestinal tract. Designing such molecules as once-daily formulations is exclusive to these molecules. Thus, GI retention platforms had emerged. One of the major challenges in developing gastric retention devices is overcoming the housekeeping waves, particularly in the fasted state. Often, the extent of drug absorption is limited by the residence time of the drug at the absorption site. The transit time in the gastrointestinal tract i.e., tract from the mouth to anus, varies from one person to other. It also depends upon the physical properties of the object ingested and the physiological condition of the alimentary canal. To successfully modulate the gastrointestinal tract transittime of a drug through a gastro retentive drug delivery system for maximal GI absorption of drugs and site-specific delivery, one needs to have an understanding of the human GI tract.

MATERIALS AND METHODS

Chemicals used in the study

Maraviroc, HPMC K100M, Carbopol 940, Xanthum Gum, Microcrystalline Cellulose, Sodium bicarbonate, Citric acid, Talc, and Magnesium stearate.

Preformulation Studies

Colour: A small quantity of powders is taken in butter paper and observed in awell-illuminated place.

Solubility: The Solubility is determined by dissolving drug substances in water, Methanol, Ethanol, and 0.1 N HCl. The solubility study was conducted by taking excess amounts of the drug in 10 ml in respective solvents. Then the samples were kept in the water bath shaker and agitated for 24 h at 37±0.5°C. The samples were filtered and diluted suitably with respective solvents.The samples were analysed spectrophotometrically at absorption maxima. The concentration of the drug was determined using a standard graph.

Construction of Standard Calibration Curve: Accurately weighed amount of 100mg of Maraviroc was transferred into a 100ml volumetric flask. 0.1N HCl was added to dissolve the drug & volume was made up to 100 ml with 0.1 N HCl. This gives solution of strength 1 mg/ml (1000 µg/ml) (stock I) stock solution. From this stock solution 10 ml of solution was taken and transferred in to 100 ml volumetric flask and volume was made up to 100 ml with 0.1 N HCl. This gives solution of strength 100 µg/ml (stock II). From this stock II solution 0.5,1.0,1.5,2.0,2.5,3.0,3.5 and 4.0 quantities were transferred to 10mL volumetric flasks and the volume was made up to 10 ml with 0.1 N HCl to give drug concentrations of 5,10,15,20,25,30,35 and 40 µg/mL solutions respectively. The absorbance of volumetric solutions was recorded at lambda max of the drug using UV Visible spectrophotometer and plotted graphically to give the standard graph Maraviroc (210 nm).

FT-IR studies

The FT-IR spectrum of pure drug and formulation was determined. An FT-IR (Thermonicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 - 400cm-1 and 4cm-1 resolutions. The reagents were the means of 6 determinations. A quality equivalent to 2mg of pure drug was used for the study.

DSC Studies: The thermal properties of the pure drug and the formulation were evaluated by Differential scanning calorimetry (DSC) using a diamond. The analysis was performed at a range of 50c min-1 to 2000C temperature range under nitrogen flow of 25ml min-1.

Evaluation studies

Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it is packed down.

RESULTS AND DISCUSSION

Organoleptic properties

Color: White to pale coloured powder

Melting Point: The melting point of Maraviroc was found to be 197-198 °C.

Standard curve for Maraviroc: The study started with the construction of the standard calibration curve of Maraviroc. The scanning of the volumetric solution of Maraviroc in the ultraviolet range against 0.1 N HCl determined the λ_{max} of absorbance is 210 nm. The standard graph of Maraviroc in 0.1N HCl was plotted by taking concentrations ranging from 5 to 40 µg/ml and showed good linearity with an R^2 value of 0.999. **Carr's Index**

The calculated Carr's index was found to be 11. This indicates a good flow of the sample.

Hausner's ratio: The calculated Hausners's ratio was found to be 1.13, this indicates good flow properties of the sample.

Angle of repose: The calculated angle of repose is found to be 21, which indicates good flow of sample.

Effect of sodium bicarbonate concentration on floating lag time: The tablets were prepared by using different concentrations of sodium bicarbonate along with the same concentrations of remaining other comp onents (PF1-PF3 batches) From the results shown in the above table it can be concluded that as concentration of sodium bicarbonate increased the floating lag time decreased. Both were inversely proportion. As sodium bicarbonate concentration increase the ability to produce CO_2 in the formulation was also increased, this made tablets buoyant. When 5% sodium bicarbonate is used the tablets were not floated, as the percentage of floating aid is not enough for the tablet to float. 10% sodium bicarbonate is used as an optimized percentage of the floating aid which made the tablets to float for 12 hrs.

Table 1: Standard values of Maraviroc

Concentration(µg/ml)	Absorbance(nm)
0	0
5	0.148
10	0.287
15	0.410
20	0.524
25	0.653
30	0.781
35	0.893
40	1.029

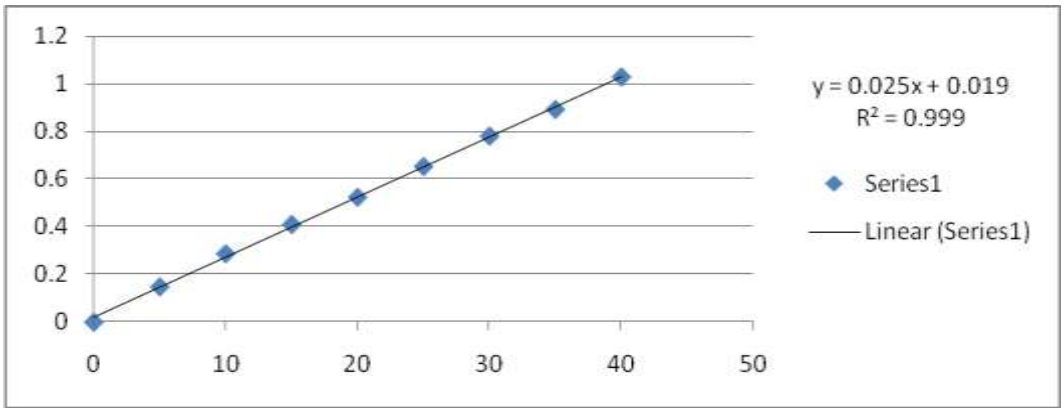


Fig. 1: Standard curve of Maraviroc

Table 2: Effect of sodium bicarbonate concentration on floating lag time

S.No	$NaHCO_3$ (mg)	Concentration (%)	Floating lag time (sec)
1	25	5	Not floated
2	50	10	40-45sec
3	75	15	30-40sec

The 10% concentration of sodium bicarbonate was selected because it showed less lag time i.e., less than 1 min and the tablets remained rigid throughout the study whereas the tablets with15% Sodium bicarbonate concentration also showed less lag time but the total floating time was less when compared to 10% concentration.

Formulation development of Maraviroc floating matrix with HPMC K100

All of the Maraviroc floating tablets were evaluated for various physicochemical parameters such as weight variation, hardness, thickness, friability and drug content. All the formulated tablets passed the weight variation test as the % weight variation was within pharmacopeial limits. The hardness of the tablets was in the range of 5.2 – 5.4 kg/cm^2 this ensures good handling characteristics of all the batches. The thickness of the tablets was in the range of 4.49-4.59 mm, all the batches showed uniform thickness. The Friability of the prepared matrix tablets was found to be 0.3%-0.57% which was below 1% indicating sufficient mechanical integrity of the tablets. The drug content estimation showed values in the range of 99.78- 100.44 % which reflects good uniformity in the drug content among different formulations. *In vitro* buoyancy study in 100 ml of the 0.1 N HCl shows that the prepared matrix tablets were rapidly floated to the surface of the medium within 1min.

In vitro dissolution studies were conducted in 900ml of 0.1 N HCl using USP-II apparatus. The results of dissolution studies of formulations F1-F4 composed of different concentration of HPMC K100M polymer (15%, 20%, 25%, 30%). Formulations F1, F2, F3 and F4 release about 100.8%, 100%, 101% and 101.2% of drug 9hrs, 10hrs, 11hrs and 12hrs respectively of testing period.

The dissolution data of all formulations were fitted to various kinetic models such as Zero-

order, First-order, Higuchi and Peppas models. Drug release kinetic data for Maraviroc floating tablets formulation (F1 to F4). All the formulations follow zero order release kinetics with regression values ranging from 0.950-0.977. Korsmeyer-Peppas plots, 'n' value ranges from 0.665 – 0.870 indicating that the Maraviroc release mechanism followed anomalous mechanism.

Table 3: Formulation development and physicochemical parameters of the Formulation with various concentrations of HPMC K100 M

INGREDIENTS	F1	F2	F3	F4
Maraviroc	100	100	100	100
HPMC K100 M	75	100	125	150
MCC	250	235	220	205
$NAHCO_3$	37	27	17	7
Citric acid	12	18	18	18
Talc	8	12	12	12
Magnesium stearate	5	8	8	8
Total weight	**500**	**500**	**500**	**500**
Evaluation parameters				
Thickness (mm)	4.59±0.08	4.58±0.07	4.49±0.16	4.39±0.08
Weight variation (mg)	500.1±1.37	499.9±1.29	500.0±1.49	500.2±1.32
Tablet Hardness kg/cm^2	5.2±0.45	5.2±0.27	5.4±0.22	5.4±0.42
Friability (%)	0.57	0.43	0.37	0.30
Drug Content (%)	100.22±0.77	100.44±1.02	100.0±0.67	99.78±1.39
Floating lag time	30sec	40sec	45sec	50sec
Floating time	10 hrs	10 hrs	11 hrs	12 hrs

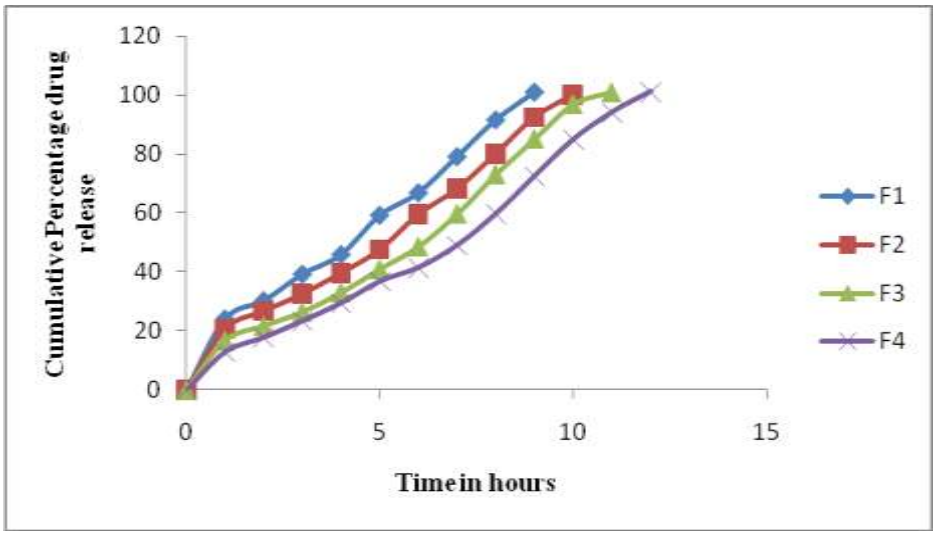


Fig. 2: Cumulative percentage drug release profiles of Formulation F1-F4

Formulation development of Maraviroc floating matrix tablets with Carbopol 940

The floating matrix tablets of Maraviroc were prepared to observe the release rate. Tablets were prepared with 4 different concentrations of Carbopol 940 polymer (15%, 20%, 25%, 30%) to the target weight. Accurately weighed drug, polymer, $NaHCO_3$ and MCC were mixed thoroughly and then the above blend was lubricated with talc and magnesium stearate. Sodium bicarbonate (10%) is used as a floating aid. The lubricated blend was compressed using 11 mm punch.

All of the Maraviroc floating matrix tablets with different concentrations of Carbopol was evaluated for various physicochemical parameters such as weight variation, hardness, thickness, friability and drug content. The Hardness of the tablets was found in the range of 5.5-6.1 kg/cm^2. Thickness of the tablets was in the range of 4.38-4.59 mm, all the batches showed uniform thickness. Friability of below

0.27%-0.47% clearly indicates the good mechanical strength of the prepared tablets. Assay of the prepared matrix tablets was found in the range of 99.11- 100.22% clearly indicating the good content uniformity. *In vitro* buoyancy study in 100 ml of the 0.1 N HCl shows that the prepared floating matrix tablets were rapidly floated to the surface of the medium with in 1min. All the formulations floated and drug release got retarded for 10-12hours. *In vitro* dissolution studies were conducted in 900ml of 0.1 N HCl using USP-II apparatus. The results of dissolution studies of formulations F5-F8 composed of different concentration of Carbopol 940 polymer (15%, 20%, 25%, 30%) are shown in table 6.7 and Fig 6.3. Formulations F5, F6, F7 and F8 release about 101.2%, 100.8%, 101% and 101% of drug 10hrs, 11hrs, 11hrs and 12hrs respectively of testing period. This is indicating that as the polymer concentration of Carbopol 940 increases the drug release rate was retarded.

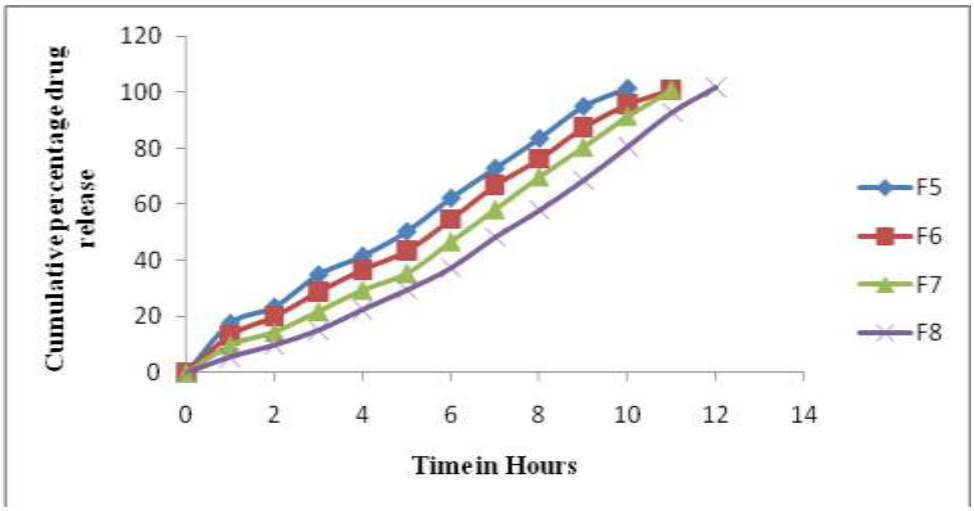
Table 4: Formulation development and physicochemical parameters of the formulation with various concentrations of Xanthan Gum

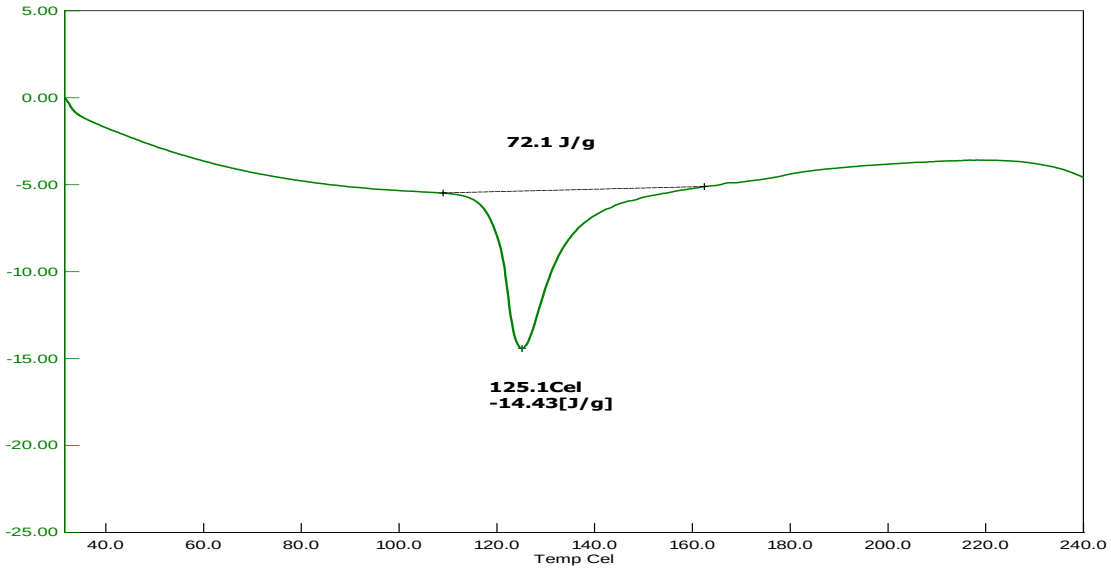
INGREDIENTS	**F9**	**F10**	**F11**	**F12**
Maraviroc	100	100	100	100
Xanthan Gum	75	100	125	150
MCC	250	235	220	205
$NAHCO_3$	37	27	17	7
Citric acid	18	18	18	18
Talc	12	12	12	12
Magnesium stearate	8	8	8	8
Total weight	**500**	**500**	**500**	**500**
Evaluation parameters				
Thickness (mm)	4.85±0.05	4.81±0.04	4.79±0.02	4.78±0.08
Weight variation (mg)	500.1±1.20	499.9±1.52	500.2±0.92	500.3±1.34
Tablet Hardness kg/cm^2	5.3±0.45	5.3±0.45	5.5±0.5	5.6±0.42
Friability (%)	0.60	0.47	0.40	0.33
Drug Content (%)	100.67±0.67	100.89±1.39	99.78±0.38	100.22±0.77
Floating lag time	<1min	<1min	<1min	<1min
Floating time	11 hrs	12 hrs	12 hrs	12 hrs

Table 5: Cumulative percentage drug release and release kinetics of the prepared Maraviroc floating matrix tablets with various concentrations of Xanthan Gum

Time (hr)	**Formulation code**			
	F9	**F10**	**F11**	**F12**
0	0	0	0	0
1	17.52±0.39	8.16±0.43	5.28±0.83	04.40±1.51
2	26.62±0.50	13.40±0.49	8.64±0.28	05.70±0.52
3	35.12±0.45	19.60±0.46	12.84±0.21	09.30±0.51
4	42.36±0.48	29.02±0.54	17.18±1.14	12.92±0.57
5	51.92±0.54	37.36±0.46	25.34±0.31	18.36±0.43
6	63.60±0.60	46.94±0.49	34.46±0.24	24.16±0.46
7	72.80±0.35	55.52±0.41	45.94±1.17	32.68±0.39
8	85.00±0.69	67.20±0.0.60	56.60±1.33	41.48±0.35
9	93.40±0.92	79.40±0.92	67.40±0.35	59.82±1.21
10	101.6±0.35	86.92±0.49	79.60±0.69	70.20±0.60
11	-	94.40±0.35	90.60±0.60	79.60±0.92
12	-	100.4±0.92	101.0±0.35	89.00±0.35
Release kinetics				
Zero order (r^2)	0.974	0994	0.975	0.945
First order (r^2)	0.868	0.782	0.686	0.822

Higuchi (r^2)	0.973	0.958	0.906	0.860
Peppas (r^2)	0.988	0.990	0.972	0.946
Peppas (n)	0.770	1.078	1.274	1.334





The floating matrix tablets of Maraviroc were prepared to observe the release rate. Tablets were prepared at four different concentrations of Xanthan Gum such as (15%, 20%, 25%, 30%) to the target weight. The drug, polymer, $NaHCO_3$ and MCC were directly mixed uniformly and then the above blend was pre lubricated with talc and finally lubricated with magnesium stearate. Sodium bicarbonate (10%) is used as a floating aid. The lubricated blend was compressed using 11 mm punch.

All of the Maraviroc floating matrix tablets with different concentrations of Xanthan Gum (F9 to F12) was evaluated for various physicochemical parameters such as weight variation, hardness, thickness, friability and drug content. The Hardness of the tablets was found in the range of 5.3-5.6kg/cm^2. of 0.1 N HCl using USP-II apparatus. The results of dissolution studies of formulations F9-F12 composed of different concentration of Xanthan Gum polymer (15%, 20%, 25%, 30%) are shown in the table 6.9 and Fig 6.4. Formulation F9, F10, F11 and F12 release about 101.6%, 100%, 100% and 89% of drug 11hrs, 12hrs, 12hrs and 12hrs respectively of testing period. This is indicating that as the polymer concentration of Xanthan Gum increases the drug release rate was retarded. .

Differential scanning calorimetric study (DSC) DSC study was conducted on the selected formulations. DSC Thermogram of pure Maraviroc shows sharp endothermic peak at 125.1°C. Similar endothermic peaks were obtained at 124.0°C for the formulations prepared with HPMC K100 M ,

at 124.0°C for the formulation prepared with Carbopol and 124.0 ^{0}C for the formulation prepared with Xanthan gum. The DSC Thermograms were given in the following section.

FTIR studies on the selected formulations

FTIR study on the selected formulation prepared with different polymers such as Xanthan Gum, HPMCK100, and Carbopol 940. The spectrum peak points of the formulation were similar with that of the pure Maraviroc, clearly indicating that there is no drug-polymer interaction.

SUMMARY AND CONCLUSION

It can be concluded that a single unit matrix floating drug delivery system containing, HPMC K100M, Xanthan gum, and Carbopol was developed. Sodium bicarbonate was added as a gas-generating agent to improve the floating capacity of the tablet. Formulated tablets gave satisfactory results for various physical properties for tablets like tablet thickness, hardness, weight variation, friability, floating time, floating lag time, content uniformity, and *in vitro* drug release. Altering concentrations of polymer and the gas-evolving agent have a significant influence on the release rate of the drug. Formulated floating tablets best fitted to the Korsmeyer-Peppas model and zero-order kinetics. Formulation F11 gave better-controlled drug release (100% in 12hrs) in comparison to other prepared formulations. *In vitro floating* studies revealed that F11 tablets remained floated for 12hrs, which indicated that GRT was increased by the floating principle and was considered desirable for improving the bioavailability of the absorption window drugs. Thus, the results of the current study clearly indicate, a promising potential of the Maraviroc floating system as an alternative to the conventional dosage form. However, further clinical studies are needed to assess the utility of this system for patients suffering from HIV/AIDS.

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