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Original Article

FORMULATION DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE GASTRORETENTIVE TABLET OF EMTRICITABINE

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ABSTRACT

Objective: The study aims for the design and evaluation of floating tablets of emtricitabine (EMT), post oral administration to sustain the release and enhance gastric residence time (GRT).

Methods: EMT is a nucleoside reverse-transcriptase inhibitor for the prevention and treatment of human immunodeficiency virus (HIV) infection. The investigation was considered to formulate a floating tablet of EMT with various agents. The formulation included with various concentrations of hydroxypropyl methylcellulose (HPMC) k4m, ethylcellulose, microcrystalline cellulose, polyvinylpyrrolidone (PVP) by wet granulation method. Various parameters for the prepared formulations were evaluated for weight variation, thickness, hardness, friability, floating lag time (FLT), total floating time (TFT), swelling index, *in vitro* drug release, and fourier-transform infrared spectroscopy (FTIR) studies.

Results: The best formulation F1 exhibited 88.28% release in 24 h duration, with a floating lag time of 7 min and swelling index of 52.1% and drug content was determined to be 98.27%. The release mechanism was determined to be first order with higuchi release kinetics displaying diffusion along with the dissolution of the EMT from the tablet by non fickian mechanism.

Conclusion: EMT tablets showed an increased GRT with a sustained release for 24 h thereby allowing a better window for absorption consequently improve the therapeutic effect of the drug.

Keywords: Emtricitabine, Sustained release, Gastro retention, HPMC k4m, Ethyl cellulose

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INTRODUCTION

Sustained drug delivery system yields a perpetual oral delivery of drugs at conceivable and reproducible kinetics for a preordained period throughout the course of gastrointestinal (GI) transit [1]. Conventional oral dosage forms agonize from mainly two predicaments the short GRT and unpredictable gastric emptying time. A relatively short GI transit time of most drug products hinder the formulation of single daily dosage forms. Altering the gastric emptying can overwhelm these problems. Therefore, it is desirable, to formulate a sustained release dosage form that gives an extended GI residence time. One of the most workable approaches for achieving a sustained and predictable drug delivery profiles in the GI tract is to control the GRT using gastro retentive dosage forms that offer a novel and better option for drug delivery [2].

Dosage forms that can be perpetuated in the stomach are called gastro retentive drug delivery systems. Gastro retentive systems can remain in the gastric region for several hours and hence significantly sustain the GRT of drugs. Sustained gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. Gastro retentive floating tablets have emerged as an efficient means of ameliorating the bioavailability of many drugs [3, 4]. Rapid GI transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of administered dose.

Hence, it was chosen in the present examination as a satisfactory applicant for the design of gastric floating drug delivery system for better retention time and bioavailability [5-7].

The present study was to develop a floatable drug delivery system of EMT using HPMC k4m, ethylcellulose, microcrystalline cellulose, sodium hydrogen carbonate, isopropyl alcohol for sustained drug delivery and gastric retentive property. Thus, the study aims to improve the oral bioavailability of the drug and to achieve extended retention in the stomach which may result in sustained absorption.

MATERIALS AND METHODS

Materials

EMT and HPMC k4m were procured from yarrow chem products (Mumbai, India), ethylcellulose and magnesium stearate were procured from loba chemie pvt. ltd. (Mumbai, India), microcrystalline cellulose, PVP and talc, were purchased from molychem (Mumbai, India), sodium hydrogen carbonate was procured from finar chemicals pvt. Ltd (Ahmedabad, India), and isopropyl alcohol was purchased from SRL pvt. Ltd (Mumbai, India).

Methods

Preparation of floating tablets of emtricitabine

EMT floating tablets were prepared by wet granulation method employing sodium hydrogen carbonate as gas-generating agent [8]. Microcrystalline cellulose and ethyl cellulose were used as release rate-controlling agents. The concentrations of the excipients were optimized as showed in (table 1). The drug was mixed with the release rate retarding polymers and other excipients. HPMC k4m was added in ascending order of its weight. The weighed powders were triturated well in a mortar pestle. 10 mg of PVP was dissolved in a sufficient quantity of isopropyl alcohol. This mixture was added drop by drop to the powder to obtain wet blend sufficient to form granules. This mass was allowed to pass through a sieve. The obtained granules were kept in an oven at 50℃ for eliminating moisture from the granules. Finally, magnesium stearate and talc were added. About 300 mg of granules were weighed accurately and fed into the die and compressed using 12 mm round surface punches.

Evaluation of EMT floating tablets

EMT floating tablets were scrutinized for post-compression parameters like weight variation, thickness, hardness, friability, floating lag time, total floating time, swelling index, *in vitro* drug release, and drug excipient compatibility study–FTIR [9].

Table 1: Composition of gastroretentive tablet formulation of emtricitabine

Ingredients (mg)	F1	F2	F3	F4	F5	F6
EMT	50	50	50	50	50	50
HPMC k4m	144	154	162	184	195	206
Ethyl cellulose	18	12	8	32	21	10
Microcrystalline cellulose	54	50	46	-	-	-
Sodium hydrogen carbonate	20	20	20	20	20	20
PVP	10	10	10	10	10	10
Isopropyl Alcohol	0.3	0.3	0.3	0.3	0.3	0.3
Talc	2	2	2	2	2	2
Magnesium state	2	2	2	2	2	2

Weight variation

Weight uniformity was established for the formulated tablets. Randomly 20 tablets were selected. They were weighed collectively and individually. Average weight was calculated from the collective weight. The weight of each tablet was compared with the average weight to ascertain whether it is within permissible limits or not [10].

Hardness

Hardness of a tablet indicates its ability to withstand mechanical shocks while handling. The crushing strength of a tablet was determined using Monsanto type hardness tester and expressed in kg/cm^2 [11, 12].

Friability

The friability of a tablet was determined using Roche friabilator. Randomly 20 tablets were taken and their weights were weighed. They were then transferred into friabilator which was operated at 25rpm/min for 4 min (100 revolutions). The tablets were weighed again for their final weights [13]. And the % friability was then calculated by

$$F = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

Determination of swelling index

The swelling index measured by studying weight gain. A tablet from each formulation was randomly selected and its weight was recorded. The weighed tablet from each formulation was transferred into a basket of dissolution apparatus using dissolution medium pH 1.2 buffers at 37±0.5°C. pre-determined intervals up to 12h, the tablet from the apparatus was withdrawn and blotted with a tissue paper to remove the excess water and recorded its weight on an analytical balance [14, 15].

Drug content determination

Powder equivalent to an average weight was dissolved in 10 ml of methanol, followed by sonication for 10 min. Then, 1 ml was withdrawn and was diluted to 10 ml with 0.1N HCl and was measured spectrophotometrically at 291 nm [16].

***In vitro* buoyancy studies**

In vitro buoyancy studies were performed for all the formulations. Randomly selected tablets from each formulation were kept in a 100 ml beaker containing buffer of pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as FLT. The duration of time the dosage form constantly remained on the surface of the medium was determined as the TFT [17].

***In vitro* dissolution studies**

In vitro drug release of the formulations was carried out using USP–type II dissolution apparatus at 37±0.5°C using 900 ml of 0.1N HCl (pH 1.2) as the dissolution medium at 50 rpm. One EMT tablet from each formulation was placed in each basket and was allowed to run for 24 h. Aliquot of 5 ml was withdrawn at predetermined interval subsequently replaced with an equivalent amount of fresh buffer to sustain a constant volume. Collected samples were suitably diluted as required and analysed at 291 nm spectrophotometrically [18].

Drug excipient compatibility studies

It is vital that formulations stress on physiochemical and biological characteristics of active and excipient employed for product development. Hence it suggests that compatibility of active and excipients to is essential for a stable and safe product. FTIR is an effective analytical technique utilized to study chemical interactions within active and excipients in the formulations. Active and excipient were mixed extensively with potassium bromide. The samples were introduced into diffuse reflectance sampler, and subsequent spectrums were recorded in wavelength region 4000-400 cm^{-1} in FTIR [19].

Drug release kinetics

In order to comprehend the underlying mechanisms involved in the release pattern, the dissolution data were fitted into zero-order, first order, and Higuchi's and Korsmeyer models. These kinetic equations were applied to interpret the release rate of the drug from the matrix system [20-22].

RESULTS AND DISCUSSION

EMT floating tablets were formulated to increase the GRT; thereby drug can sustain in the stomach for a longer period and benefit in sustained release for a minimum of 24 h. The tablets were formulated employing various polymers like HPMC k4m, ethylcellulose, microcrystalline cellulose, sodium hydrogen carbonate, PVP, isopropyl alcohol by wet granulation. When an amalgamation of gas entrapping along with release controlling system, the use of disintegrating agent is very significant which does not quickly break the matrix and also permit slow disintegration of the swollen matrix. Talc and magnesium stearate were used for their glidant and lubricant property. The prepared formulations were evaluated for weight variation, thickness, hardness, friability, floating lag time, total floating time, swelling index, *in vitro* drug release, and drug excipient compatibility study–FTIR and release kinetics.

Post–compression evaluation tests for formulated tablets

Post-compression parameters such as weight variation, thickness, hardness and friability were assessed for formulated tablets. All prepared formulations retained their off-white appearance with no visible crevices, in a flat-faced circular shape. The results for weight variation, thickness exhibited were within the limits. Minor variation in the tablet hardness was observed mostly due to trivial variation in compressional force. The polymers blend of HPMC k4m, ethylcellulose, microcrystalline cellulose yielded harder tablets when compared with tablets containing only a blend of HPMC k4m, ethyl cellulose. Friability results were determined to be within limits, it was observed that as the concentration of the HPMC k4m the friability of the tablets decreased. The results are given in (table 2), the results revealed the tablets are mechanically strong.

Weight variation

The EMT tablets were evaluated for weight variation and were in the range of 300.72±2.75 to 302.10±3.43. The results agreed with official limits, no significant deviation from average tablet weight courier suggesting consistency of dosage units.

Table 2: Results for post–compressional evaluation of EMT tablets

Formulation code	Weight variation* (mg)	Thickness# (mm)	Hardness* (kg/cm²)	Friability# (%)
F1	301.37±3.56	4.14±0.03	5.82±0.01	0.22±0.05
F2	300.35±2.26	4.13±0.05	5.78±0.03	0.23±0.11
F3	301.00±1.55	4.13±0.02	5.87±0.07	0.11±0.08
F4	302.10±3.43	4.12±0.04	5.55±0.10	0.23±0.03
F5	301.03±3.69	4.18±0.04	5.64±0.09	0.11±0.05
F6	300.72±2.75	4.15±0.06	5.62±0.06	0.11±0.06

*mean±SD (n=20), #mean±SD (n=10)

Thickness

Vernier callipers was used to measure the tablet thickness. The thickness of the tablets ranged between 4.12±0.04 to 4.18±0.04 mm.

Hardness

Hardness was measured by Monsanto tester. The variances in tablet density and porosity resonances with tablet hardness, which subsequently govern different release patterns of the drug by influencing the rate of penetration of the dissolution media at tablet surface. Hardness of the tablets was determined to be in the range of 5.55±0.10 to 5.87±0.07 kg/cm². The tablets were recommended good tensile strength.

Friability

Friability of the prepared tablets was measured by Roche Friabilator and determined to be in the range of 0.11±0.06 to 0.23±0.11, the friability of all prepared tablets was to be less than 1% which suggests acceptable mechanical resistance of the tablets.

Swelling index

The extent of swelling was determined by measuring the thickness of the tablet prior and after the tablet placed in pH 1.2 buffer. Formulation F1 exhibited the highest index of 52.1%, whereas F6 with minimum of 31.7%. The results are given in (table 3).

Drug content

A consistent drug content in the batch is very essential for delivering the accurate dose from the dosage form, the drug content for the prepared tablets was in the range of 97.12±0.32% to 98.27±0.22% suggesting uniform drug content in prepared formulations. The results are given in (table 3).

***In vitro* buoyancy studies**

FLT is the time taken by the tablet to rise to the surface after introducing in the medium, and float. The gas generated by the gas generating agents remain entrapped in the swollen polymer, formed post hydration, thereby lowering the tablet density. Once the density achieved remain less than the medium, the tablet remains buoyant. Results revealing that the formulations with blend of polymers of HPMC k4m, ethylcellulose, microcrystalline cellulose exhibited less FLT and high TFT (24h) in comparison with other formulations where microcrystalline cellulose was absent and higher ratios of polymers. The formulation with best combination of polymers F1 gave best FLT and TFT.

From the results it was observed that as the concentrations of HPMC k4m the FLT increased and TFT decreased; thus, an optimum blend of hydrophilic polymers lead to an efficient floating system. The results are given in (table 3).

***In vitro* dissolution studies**

The *in vitro* dissolution study was carried out for all prepared formulations for 24 h shown in (fig. 1). All formulations were exhibited good buoyancy. The formulation F1 with a low concentration of HPMC k4m showed the maximum release of drug when compared to other formulations. High concentration of polymer influences the formation of swollen mass that restricted the rate of diffusion into the matrix, which may result in retardation the drug release. Formulation F3 showed the least release of drug in 24h all the formulations released above 60% of the drug in 24h.

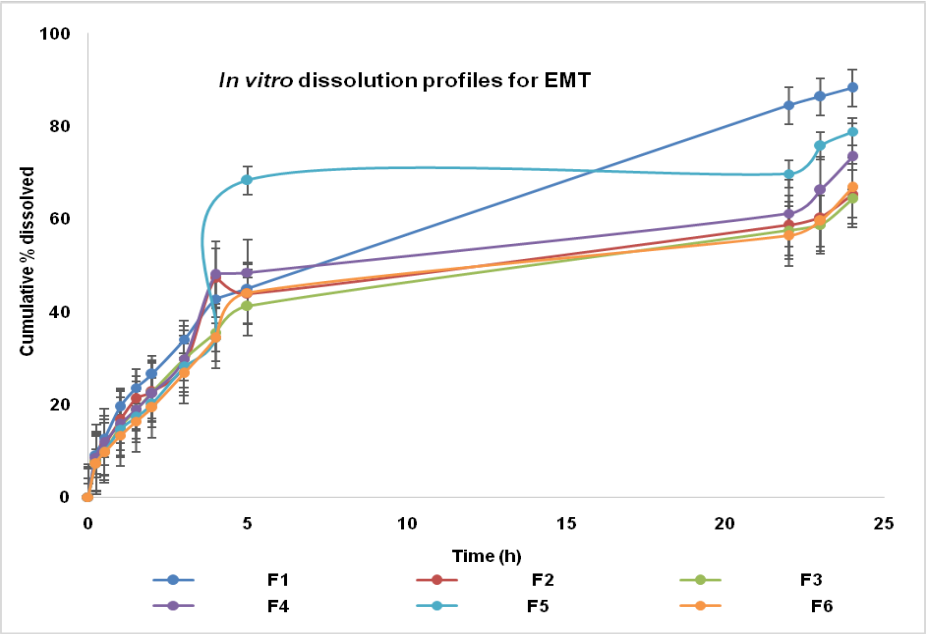

Fig. 1: *In vitro* dissolution profiles for EMT floating tablets data expressed in mean±SD (n=3)

Table 3: Results for evaluation tests–drug content, swelling index, FLT and TFT of EMT tablets

Formulation code	Drug content* (%)	Swelling index (%)	FLT (min)	TFT (h)
F1	98.27±0.22	52.1	7 min	24
F2	98.16±0.12	49.8	7 min 8 sec	24
F3	99.40±0.39	48.0	11 min	23
F4	97.58±0.28	45.3	13 min 12 sec	21
F5	98.62±0.41	31.7	14 min 3 sec	20
F6	97.12±0.32	32.6	15 min	20

*mean±SD (n=6)

Drug excipient compatibility studies

For understanding the compatibility between the pure EMT and the formulation components, FTIR was recorded for both pure EMT and the formulation components along with EMT individually, characteristic functional group peaks appeared in both samples at 3400 cm^{-1} signifying the N-H stretching, C=O stretching at 1600 cm^{-1}, –OH bending at 1420 cm^{-1} and C–N stretching at 1250 cm^{-1} all the results of FTIR indicating the there was no predominant interactions between the drug and the formulation components. FTIR peaks for both pure EMT and the formulation showed in (fig. 2a and 2b).

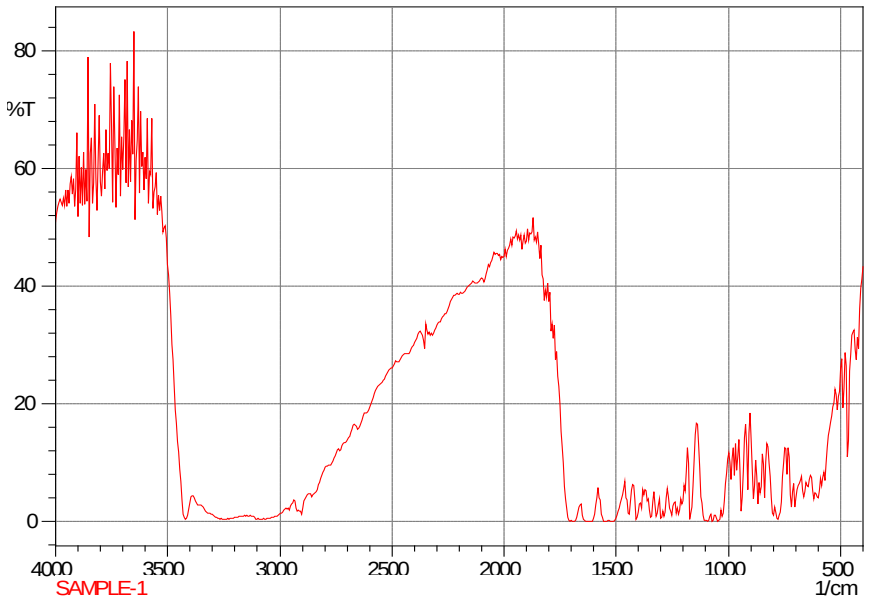

Fig. 2a: FTIR of EMT pure drug

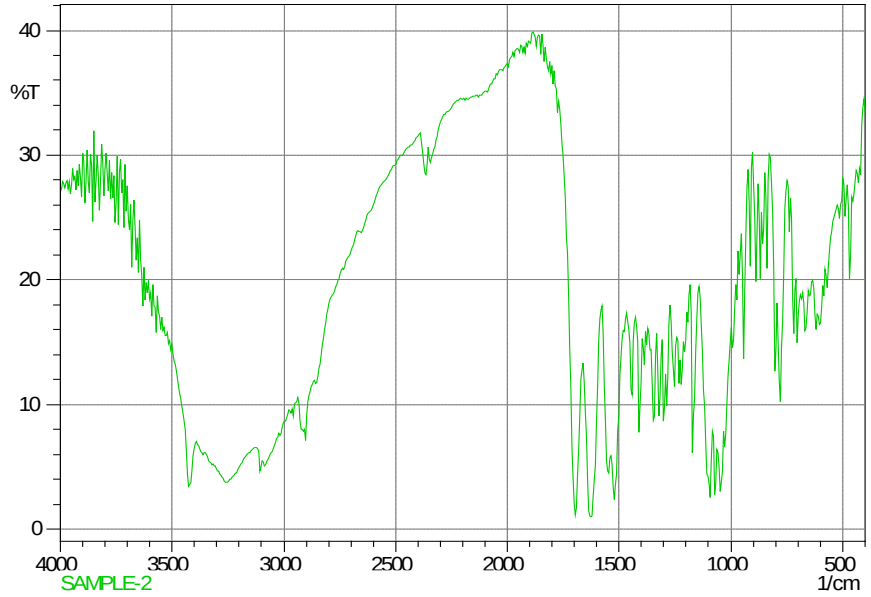

Fig. 2b: FTIR of formulation

Drug release kinetics

From the obtained data of *in vitro* dissolution studies of EMT tablets, the best and optimized formulation F1 were fitted into various models, zero order, first order, and Higuchi's and Korsmeyer models. Release kinetics are discussed in (table 4). From the models, it was determined that all formulations followed diffusion, dissolution mechanism throughout the release. The best formulation F1 formulations observed diffusion besides dissolution by non fickian mechanism. The release mechanism was determined to be first order with higuchi release kinetics showing diffusion besides dissolution by non fickian mechanism.

Table 4: Release kinetics of F1 formulation

Formulation code	Zero-order	First-order	Higuchi model	Peppas model
F1	0.92	0.99	0.995	0.64

CONCLUSION

The study was undertaken to develop and formulate a gastro-retentive drug delivery system of EMT to enhance the therapeutic effect and by achieving a sustained drug release over a period of 24h. The EMT is used along with other medications to treat human immunodeficiency virus (HIV) infection. EMT floating tablets were prepared using HPMCk4m, ethylcellulose, microcrystalline cellulose in various ratios by wet granulation method, employing sodium hydrogen carbonate as gas generating agent. From the obtained results, it could be concluded that formulation F1 offered best sustain release along with FLT of 7 min and TFT of 24 h and *in vitro* drug release of 88.28% by the end of 24h.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTRESTS

All authors have none to declare

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