Heliyon 10 (2024) e25820

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Application of Tablet in Tablet technique to design and characterize immediate and modified release tablets of Timolol maleate

Sachin S. Gaikwad *, Sanjay J. Kshirsagar

Department of Pharmaceutics, MET's Institute of Pharmacy, Affiliated to Savitribai Phule Pune University, Bhujbal Knowledge City, Adgaon, Nashik 422003, India

ARTICLE INFO

Keywords:
Tablet-in-tablet
Modified release
PXRD
DSC
Core tablet
Outer shell

ABSTRACT

Hypertension is one of the major causes of mortality in the world. The non-selective -β-blocker which includes Timolol maleate (TM) is usually used in hypertension, at a given dose of 10–40 mg. The present research aims to design a tablet-in-tablet (TIT) formulation as a single-unit dosage form to achieve modified and rapid drug release. Wet granulation was used to create the inner core modified release tablet utilising the release modifying agent's Sodium alginate (SA) and Hydroxypropyl methylcellulose (HPMC K4M). The impact of independent factors, SA and HPMC K4M, in different percentages of w/w, which affect the in vitro drug release and swelling index, was investigated using a 3^2 complete factorial design. The TM outer instant-release shell, which was made using croscarmellose sodium and Microcrystalline cellulose (MCC) in three distinct sizes, was press-coated onto the optimised inner core tablet. The core and outer shell tablets are within acceptable ranges for several physicochemical properties. No indication of interactions between drugs, polymers, and excipients was found in the Fourier transform infrared (FTIR) and Differential scanning calorimetry (DSC) investigations. The inner core tablet's formulation F6 achieves a 96.38% in vitro drug release at 24 h and a swelling index of 52.7%. The TIT-2 was, however, considered as the final tablet-in-tablet formulation because contains fewer excipients and shorter disintegration time than TIT-3.

1. Introduction

Three-fourths of all medications are given as tablets, which are the most common dosage form [1]. Pharmaceutical tablets mostly include exterior coatings, which can be utilized for anything from controlling or enhancing API release to as basic as concealing the bitter taste of the API underneath [2]. Colour, texture, mouthfeel, and flavour masking are all aesthetic attributes that are improved by coating techniques. However, this coating technology has some drawbacks or restrictions that need to be addressed. The tablet-in-tablet formulation is one of the finest alternatives [3] for ordered release, where the medicine is present in both the core and shell sections. Biphasic fast/slow release has also been accomplished using this method. Time-controlled explosion system, created and used by Ueda and others, resulted in a burst of medication release. The lag time has been influenced by the thickness of the barrier, the presence of water-soluble excipients, and the molecular weight of any swelling excipients [4].

* Corresponding author.
E-mail address: sachingaikwad619@gmail.com (S.S. Gaikwad).

https://doi.org/10.1016/j.heliyon.2024.e25820
Received 18 May 2023; Received in revised form 1 February 2024; Accepted 2 February 2024
Available online 3 February 2024

Limited data is available in the context of tablet-in-tablet due to certain challenges while developing dosage form. Abdul Mannan and his colleagues undertook the development of a chewable tablet-in-tablet containing Orlistat and Venlafaxine hydrochloride to address obesity-related issues [1]. One of the primary challenges encountered during the development of tablet-in-tablet formulations was the precise placement of the core at the center of the entire tablet. This requirement necessitated maintaining a consistent thickness for the outer layer, a task often challenging with conventional dry-coated tablets. In 2004, Yuichi Ozeki and colleagues directed their efforts toward a novel technology known as One-Step Dry-Coated Tablets (OSDRC) to address this issue [2]. In 2013, Patrick Wray and his team conducted a study on the dissolution of tablet-in-tablet formulations using ATR-FTIR spectroscopic imaging [4].

In the present study, an effort has been undertaken to create a tablet-in-tablet of TM by developing a modified release core tablet of TM and its outer shell, which will act as an immediate release tablet of TM. The TM is a non-selective β-blocker, which inhibits β1 and β2 adrenergic receptors equally. It belongs to BCS class-I and has shown good permeability and solubility. When treating hypertension, TM is often administered in starting dosages of 10 mg per day. The usual maintenance dose ranges from 10 to 40 mg per day and in some cases, it will be 60 mg in a divided dose. The reported plasma half-life was 4 h. TM has a moderate first-pass metabolism and 50–75% bioavailability. So, the outer immediate release shell containing TM gives a burst effect and the modified release core tablet will release the drug in a controlled manner for a prolonged time.

The core tablet of TM was formulated by utilising different combinations of SA and HPMC K4M. When exposed to an acidic environment, HPMC K4M (a pH-independent polymer) hydrates to create a gel layer at the tablet's surface, while the SA precipitates in the hydrated gel layer as alginic acid and provides erosion resistance. As the pH rises during the passage of the tablets from the stomach to the intestinal tract, the SA in the matrix transforms into a soluble salt. As a result, the continuous drug release at varied pH levels is brought on by the increased gel layer permeability at high pH values [5].

The outer shell i.e. immediate release tablet consisting of the drug TM, croscarmellose sodium which acts as a disintegrant [6], and MCC has a significant impact on how tablets break down. It has great wicking and absorbing capabilities. It creates a channel for the fluid to enter the tablet and dissolve it, causing the disintegrant to quickly enlarge and the tablet to dissolve quickly [7]. Apart from this MCC also acts as a cushioning agent absorbing much of the compressive forces by deformation to prevent damage to the inner core tablet [8]. With this tablet-in-tablet approach, immediate release effect as well as delayed drug release were achieved, and along with that it helped in avoiding hepatic metabolism, and increasing its bioavailability while lowering the dosage frequency (due to the medication's limited half-life) [9].

2. Materials and methods

2.1. Materials

FDC Ltd., Mumbai, India has given the gift sample of TM; the following ingredients: HPMC K4M, SA, lactose, MCC (Avicel® PH 102), croscarmellose sodium, mannitol (Granular), and magnesium (Mg) stearate were bought from Modern Industries, Malegaon-Sinnar, India. Every other substance, including reagents, was of analytical grade.

2.2. Methods

2.2.1. Preformulation study

2.2.1.1. Melting point determination. By using the capillary method, the melting points of TM, HPMC K4M, SA, lactose, and Mg-stearate were determined [10]. A tiny dry capillary tube was taken, into which the substance whose melting point needed to be determined was filled inside after being dried, and the tube was then sealed at one end to form a compact column. The capillary was then inserted into Thiele's tube while still attached to a thermometer. Then, heating was initiated at a 3 °C/min temperature increase rate. The material was heated continuously until it melted. The thermometer reading was recorded at this point [11].

2.2.1.2. UV Spectroscopy study. A TM stock solution with a 100 μg/ml drug concentration in each medium was produced in 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4) respectively. From each stock solution, standard solutions ranging in concentration from 5 μg/ml to 30 μg/ml were created. Then, each standard solution's absorbance was calculated using UV spectrophotometry (Shimadzu 1800) at the acquired λmax [12,13]. It was discovered that every calibration curve was linear. For 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8) and phosphate buffer (pH 7.4), respectively, the coefficient of regression values was $R^2 = 0.999$, $R^2 = 0.9997$ and $R^2 = 0.9996$, and the slopes were found to be $y = 0.0218x + 0.0155$, $y = 0.0194x - 0.0011$, and $y = 0.0143x + 0.0215$. From this, it was determined that this method was suitable for further analysis.

2.2.1.3. Fourier transform infrared spectroscopy. FTIR (BRUKER OPTICS) was used to produce the FTIR spectra of TM, HPMC K4M, SA, lactose, and magnesium (Mg) stearate. The drug's spectra and that of all other excipients were scanned in the 4000-400 cm^{-1} frequency range [14]. The acquired spectra showed a variety of peaks. The important functional groups contained in the structure of the drug TM and excipients were subsequently discovered by comparing these spectra to the traditional spectra of the drug and excipients [15].

2.2.1.4. Differential scanning colorimetry. Shimadzu DSC-60 Plus was used to conduct the DSC analysis. The 6 mg of sample was taken in a pan, and a nitrogen flow at a pressure of 2 bar was applied while the container was sealed and heated with nitrogen at a rate of 10 °C/min. Analysis performed at temperatures between 30 and 350 °C [15].

2.2.1.5. Powder X-ray diffractometry. The powder X-ray diffraction technique (P-XRD) was used to research the drug's powder properties. The diffraction patterns of TM were examined using a Bruker AXS D8 Advance (Karlsruhe, Germany) instrument [16].

2.2.1.6. Drug excipient compatibility study by FTIR and DSC. The study involved assessing the stability of TM when combined with various excipients employed in the formulation while also investigating potential interactions between the medication and these excipients. This assessment was conducted through the application of FTIR and DSC techniques [17]. FTIR spectra were obtained for both individual TM and five physical mixtures, where each excipient and drug were present in a 1:1 proportion (meaning that one part of the drug corresponded to one part of the excipient, or each excipient was used separately as an individual 1 part). These spectra were recorded using FTIR (BRUKER OPTICS).

Physical Mixture 1: TM + SA.
Physical Mixture 2: TM + HPMC K4M.
Physical Mixture 3: TM + Lactose.
Physical Mixture 4: TM + Mg stearate.
Physical Mixture 5: TM + SA + HPMC K4M + Lactose + Mg stearate [18].

All the materials mentioned earlier were subjected to a 15-day storage period under controlled conditions of 75% ± 5% relative humidity and a temperature of 40 °C ± 2 °C prior to acquiring the FTIR spectra. During this storage period, regular visual inspections were conducted on all samples to detect any signs of clumping, liquefaction, or alterations in color, as well as any unusual odor or gas emissions [19].

The DSC analysis was carried out using the Shimadzu DSC-60 Plus instrument. To assess the stability of TM in the presence of the excipients used in its formulation (HPMC K4M, lactose, magnesium stearate, and sodium alginate), a mixture was prepared with a ratio of 1:1:1:1:1, respectively. To investigate possible interactions between the drug and excipients, the DSC spectra of the drug were compared with those of the physical mixture containing both the drug and the excipients [14].

2.2.2. Formulation development of inner core tablet of TM

2.2.2.1. Experimental design. To understand the impact of the concentration of polymers on the performance of the core modified release tablet, optimization was performed using a 3^2 factorial design. This design was implemented to quantify the impact of independent variables, viz., the % concentration of 'sodium alginate (X1)' and 'HPMC K4M (X2)' on the dependent variables, such as % drug release up to 20 h (Y1) and % swelling index (Y2). Independent variables were tested on three levels: lower (−1), middle (0), and higher (+1), and accordingly, nine batches were prepared as shown in Table 1. The obtained data was further statistically analysed by analysis of variance (ANOVA) after fitting information in DOE-v13 software (Design of Expert). The statistical significance of the obtained data was assessed using a regression coefficient [20].

2.2.2.2. Formulation of inner core tablet of TM tablets. Each ingredient was separately put through a mesh # 60 sieve after being correctly weighed. With the aid of a spatula, all ingredients, including TM, sodium alginate [21], and HPMC K4M, were well mixed on butter paper for 30 min. The aforementioned combination was then combined with lactose for 10 min in the mortar and pestle. For the manufacture of the dump mass, water was employed as a granulating liquid [22]. This damp material was then processed by passing it through a mesh # 18 sieve [23], and the resulting granules were then dried at 60 °C [24]. Finally, the Mg stearate was added and thoroughly mixed for 1–2 min. After that, the dried granules were once again passed through the mesh # 12 sieves. To analyses the flow characteristics of the produced granules, such as Carr's index and angle of repose, measurements were made. The granules were then compressed using 6 mm round concave punches on a rotary tablet compression [KAMBERT] machine to create a finished tablet of

Table 1
Percentage composition of the inner core tablet of TM formulation batches.

Name of Ingredients	Formulation Batches								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Timolol maleate (%)	20	20	20	20	20	20	20	20	20
Sodium alginate (%)	21	25	23	23	21	21	23	25	25
HPMC K4M (%)	20	20	20	35	35	50	50	50	35
Lactose (%)	37	33	35	20	22	7	5	3	18
Water	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s	q. s
Magnesium stearate (%)	2	2	2	2	2	2	2	2	2
Total Weight of Tablet (%)	100	100	100	100	100	100	100	100	100

Each Formulation Batch Size were prepared for 120 Tablets.
Each Single Tablet weight was 100 mg.
q.s- Quantity Sufficient.

100 mg [13]. Likewise, nine batches of the formulation (Table 1) were made.

2.2.3. Evaluation

2.2.3.1. Granules. The developed granules' compressibility, Carr's index, and angle of repose were measured to examine the granules' flow characteristics [25,26].

2.2.3.2. Evaluation of inner core tablet of TM

2.2.3.2.1. Thickness. Vernier calliper (AEROSPACE), which enables precise measurements and also offers details on the difference between tablet thicknesses, was used. Three randomly chosen tablets were measured for thickness from each batch of formulation, and the average and standard deviation values were computed [27].

2.2.3.2.2. Hardness. The hardness test was performed using a Monsanto hardness tester. From each batch of formulation, three tablets were randomly chosen, and a tablet was positioned diagonally between the tester's two plungers, and pressure was measured on a scale in Kg/cm2 [28], revealing that the tablet entirely fractured into two fragments. The mean and standard deviation values were computed [29].

2.2.3.2.3. Weight variation. By arbitrarily choosing 20 tablets from each batch, a weight variation test was conducted [30]. Then, each tablet was independently weighed using an electronic digital balance (SHIMADZU AY 20 JAPAN). From there, the average weight of the tablets was calculated and compared with their individual weights [24].

2.2.3.2.4. Friability. Using Roche's Friabilator [25] (ELECTROLABEF2W ver.1.45), the friability of the tablet was calculated. In accordance with USP, 6.5 gm of tablets were weighed as a sample (W1) which was taken from each formulation batch. After placing the tablets in the drum, it revolved for 4 min at a speed of 25 rpm (100 revolutions). Once the test was finished the tablets were taken out of the drum, dusted off, and weighed again (W2) [31,32]. One percent (1%) maximum mean weight loss is permitted [25,28]. The test was run three times, and the mean outcome was calculated. Equation (1) was used to calculate the friability.

$$f = \frac{W_1 - W_2}{W_1} \times 100 \ldots\ldots \quad (1)$$

2.2.3.2.5. Drug content uniformity. Five extended-release tablets from each batch were randomly chosen, and these five tablets were crushed and homogenised in a glass mortar to evaluate drug content homogeneity. Using phosphate buffer (pH 6.8) as the solvent, powder equivalent to 10 mg of TM from the above crushed tablets was dissolved in 100 mL of a volumetric flask to create a stock solution. Using the spectroscopic procedure mentioned above, 1 mL of this solution was taken out and diluted up to 10 mL in a volumetric flask to determine the drug concentration at 295 nm [33]. The aforementioned process was three times repeated for each batch, and the average value and its standard deviations were calculated.

2.2.3.2.6. Swelling index. A Petri dish filled with the study medium and a double-folded piece of plastic paper were used to examine the swelling behaviour of tablets. Three tablets were chosen randomly, and each one was weighed separately (W1). These tablets were then placed in a Petri dish on paper and submerged one at a time in 45 mL of 0.1 N HCl for 2 h, phosphate buffer (pH 6.8) for the following 5 h, and phosphate buffer (pH 7.4) for up to 24 h [34]. After a predetermined time, the tablets were taken out of the Petri dishes, and any extra surface water was carefully wiped off with tissue paper. The final weight (W2) of these enlarged tablets was then determined after a second weighing. The investigation was done in triplicate, and the swelling index was calculated using the subsequent Equation (2) [35].

$$SI = \frac{W_2 - W_1}{W_2} \times 100 \ldots\ldots \quad (2)$$

2.2.3.2.7. In vitro drug release. The United States Pharmacopoeia (USP) - type II dissolution equipment (ELECTROLAB TDT - 08-L) was used to conduct the in vitro drug release investigation. To simulate the GIT conditions, 900 ml of 0.1 N HCl (pH 1.2) dissolving media, phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4) were utilized. The experiment was conducted with a paddle rotating at a speed of 50 rpm at 37 °C ± 0.5 °C. The tablets were initially submerged for 2 h in 900 ml of 0.1 N HCl (pH 1.2), as the usual time for the stomach to empty is one to 2 h. As the average small intestine transit time is 3–6 h [36], the dissolving medium was then replaced with 900 ml of phosphate buffer (pH 6.8) for the following 5 h. Finally, 900 ml of phosphate buffer (pH 7.4) was used in place of the dissolving media, and a 24-h drug release study was conducted. After every hour, the 10 ml sample was taken out and filtered through the whatman filter paper. To preserve the sink conditions, at the same time, an equal volume of new dissolution medium was added.

Table 2
Formulations of TM Tablet in Tablet.

Ingradients (mg)	TIT-1	TIT-2	TIT-3
Optimised inner core tablets	100	100	100
Composition of TM Outer immediate release shell (mg)			
TM	10	10	10
Croscarmellose sodium	7.5	7.5	7.5
Micro Crystalline Cellulose	125	125	125
Magnesium Stearate	5	5	5
Mannitol	102.5	152.5	202.5
Total	250	300	350

After that, the samples were examined using a UV double-beam spectrophotometer (Shimadzu 1800) at 295 nm, 294.5 nm, and 294.5 nm at 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4), respectively.

2.2.4. Manufacturing of TM tablet-in-tablet

In tablet dosage form, the tablet consists of two parts: an inner core and an outer coating. Small tooling (6 mm concave) was used to create the internal core, which is a tiny tablet, as opposed to the larger tooling used to produce the exterior layer [3].

To prepare the outer tablet shell, each component listed in Table 2 was precisely weighed and subsequently passed through a #60 sieve. To ensure uniformity in the powder blend, TM, croscarmellose sodium, and MCC were meticulously mixed on butter paper for 30 min. Following this, mannitol was introduced into the mixture and geometrically blended for 10 min using a mortar and pestle. The Mg-stearate was then added and blended for 1–2 min. Subsequently, 50% of the powder weight was placed as the lower layer within the 8 mm round concave punch die cavity. Then the optimised F6 core modified release tablet of TM weighing 100 mg was placed at the centre of the die cavity. Then the remaining 50% powder of the outer TM tablet was weighed and manually added to the core modified release tablet of TM in the die cavity. Final compression was done at an optimum pressure on a rotary tablet compression [KAMBERT] machine to obtain a final tablet of 250 mg by using 8 mm concave punches. A similar process was repeated for 300 mg and 350 mg of outer TM tablets by using 9 mm and 10 mm round concave punches, respectively (Table 2) [1].

2.2.5. Characterization of tablet-in-tablet

According to the process shown above in the material method section, the characterizations, including thickness, weight variation, hardness, and friability, were carried out.

2.2.5.1. Disintegration test of outer shell. The disintegration instrument (Electrolab, EDI-2SA) was used to calculate how long it would take a tablet to disintegrate. Six randomly chosen tablets (n = 6) from every preparation were placed one by one in every tube of the disintegration test instrument, and discs were added to prevent the tablets from floating. The 0.1 N HCl (pH 1.2) was used as the medium for disintegration, which was maintained at a temperature of 37 ± 2 °C, and the amount of time it took for the outer tablet to completely break down was recorded.

2.2.5.2. Drug content uniformity of outer shell. It was quite challenging to determine the drug content of the outer shell of the tablet-in-tablet dosage form, especially when both the core and outer shell tablets contain similar drug. Five tablet-in-tablets were selected from each batch randomly, and individually placed in the type II dissolution equipment (ELECTROLAB TDT-08-L) which contains 900 ml of 0.1 N HCl (pH 1.2) dissolving media. The experiment was conducted with a paddle rotating at a speed of 50 rpm at 37 °C ± 0.5 °C. The inner core of the tablet was of modified release; the outer shell was released immediately. Only the outer tablet had broken down in the first 10 min, and the medium was immediately withdrawn from the dissolution flask to prevent drug release from the core tablet. Then the medium was sonicated for 10 min for the complete solubilization of the drug in the medium. After that removed the 10 ml sample from the medium, and filtered it through the Whatman filter paper, and determined the drug concentration at 295 nm. The aforementioned process was three times repeated for each batch, and the average value and its standard deviations were calculated.

2.2.5.3. In vitro drug release of outer shell. Similar to the assessment of drug content, determining the in vitro drug release from the

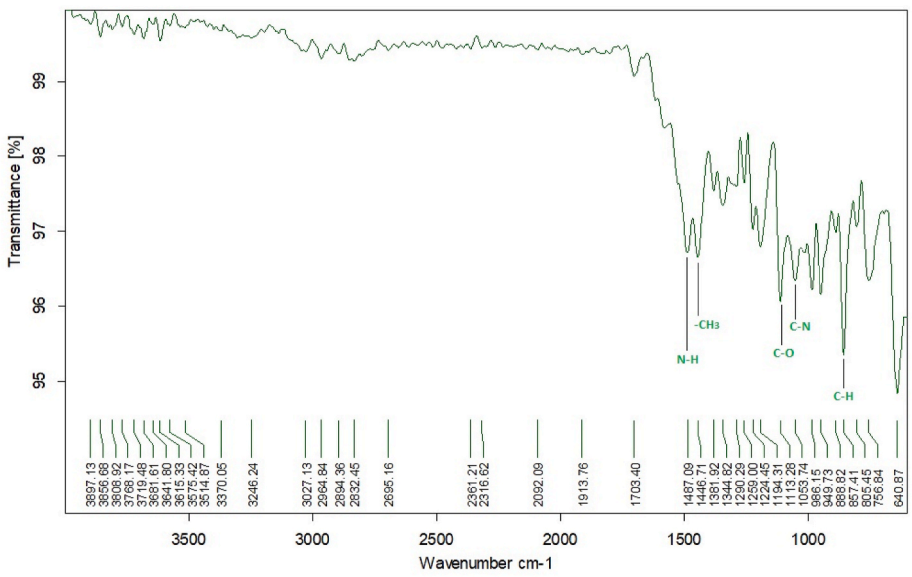


Fig. 1. FTIR spectra of TM.

tablet's outer shell was a challenging task. There is need for some modifications to the existing procedure. The United States Pharmacopoeia (USP) - type II dissolution equipment (ELECTROLAB TDT - 08-L) was used to conduct the in vitro drug release investigation of the outer shell of the tablet-in-tablet. To simulate the GIT conditions, 900 ml of 0.1 N HCl (pH 1.2) dissolving media were utilized. The experiment was conducted with a paddle rotating at a speed of 50 rpm at 37 °C ± 0.5 °C. After the disintegration of the outer shell, the inner core tablet was immediately removed from the dissolution liquid to stop drug release from the core tablet. Then the 10 ml sample from the dissolution flask was removed at 10 min intervals for 60 min and filtered through Whatman filter paper. To preserve the sink conditions, at the same time, an equal volume of new dissolution medium was added. After that, the samples were examined using a UV double-beam spectrophotometer (Shimadzu 1800) at 295 nm.

3. Results and discussions

3.1. Preformulation study

3.1.1. Characterization of pure drug and compatibility studies

The TM was seen to be a powder that was white, crystalline, and odourless. The melting point of the medication was its primary distinguishing feature. The melting point of TM was discovered to be between 199° and 200 °C. The pure TM's FTIR spectra (Fig. 1) showed a variety of peaks at frequency 857.41 cm^{-1}, 1053.74 cm^{-1}, 1113.28 cm^{-1}, 1446.71 cm^{-1}, 1487.09 cm^{-1} which may be due the C–H (Stretch), C–N, C–O, $–CH_3$ (Bend), and N–H functional group respectively [37] which are comparable to the functional groups found in the structure of TM [15]. The FTIR spectrum of TM revealed a several distinguishing features. The occurrence of absorption bands conforming to the functional groups found in a TM's structure and the non-appearance of any other uncountable peaks served as proof that the TM was pure [15,37].

Pure TM had a prominent endothermic peak on the DSC thermogram (Fig. 2) at 204.97 °C, which corresponds to its melting point. The diffraction pattern of pure TM was examined using an X-ray diffractometer. With peak intensities of 3997, 17754, and 7172, respectively, the main diffraction characteristics peaks of TM at a diffraction angle of 2h are at 7.360°, 14.52°, and 21.71° (Fig. 3). Peaks in the PXRD pattern of TM are extremely sharp and intense. Consequently, the results of DSC and PXRD, which also supported the compound's crystallinity [37].

The interactions between the drug and excipients as well as the stability of TM in the presence of different excipients utilized in the formulation were investigated using FTIR and DSC. For pure TM, TM and polymer mixtures, TM and excipient mixtures, as well as granules formed utilising TM and all of these polymers and excipients with the addition of water as granulating liquid, FTIR analyses were conducted. The major peaks of TM can be seen in all the recorded FTIR overlay spectra (Fig. 4), which suggests that there was no interaction between TM, polymers, and excipients [38]. The additional intensity peaks at frequencies 1462.09 cm^{-1}, 1548.89 cm^{-1}, 2854.74 cm^{-1}, and 2916.47 cm^{-1} which may be due to-CH_3 (Bend), $–CH_2$- (Bend), O–H, and C═O functional groups of Mg stearate that were labelled by blue colour on the spectra, Thus, it was established that TM, polymers, and excipients were not incompatible.

Both pure TM (Fig. 2) and TM with a physical mixture of excipients and polymers (Fig. 5) were used in the DSC experiment. The DSC thermogram of the TM (Fig. 2) shows a clear endothermic peak, which was also evident in the physical mixture of the drug,

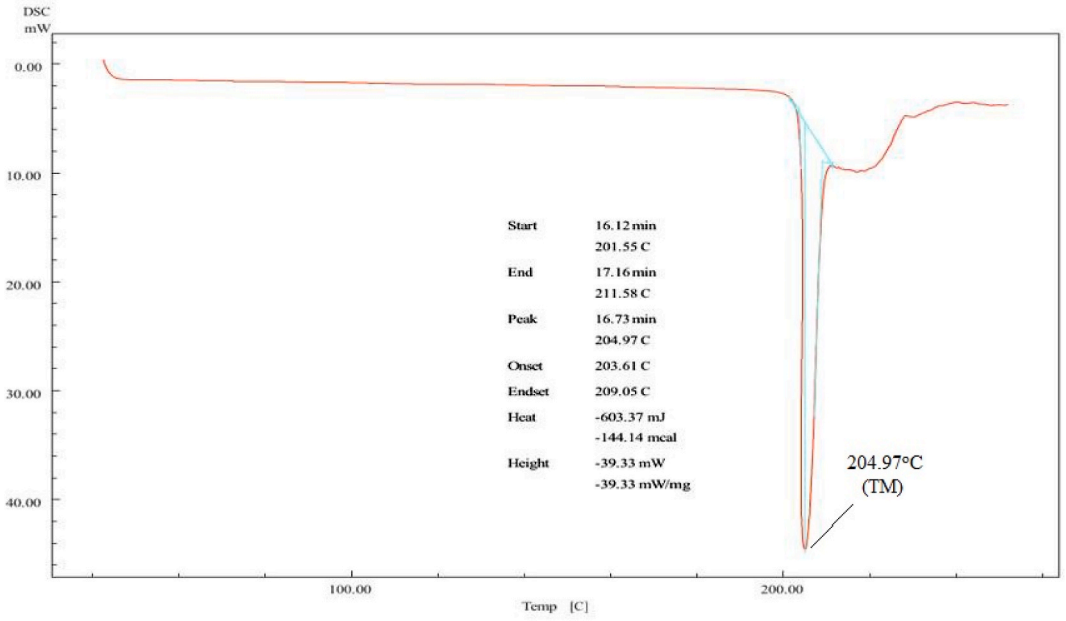


Fig. 2. Dsc peak of TM

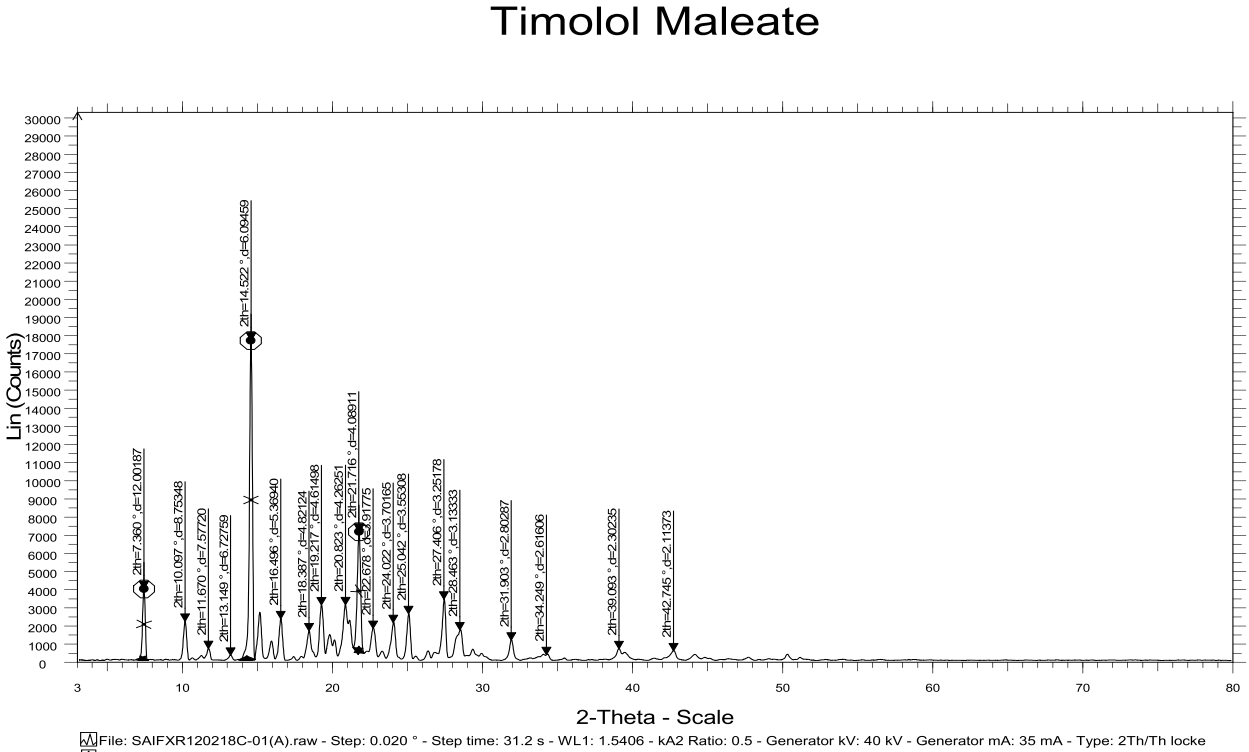


Fig. 3. Xrd of TM

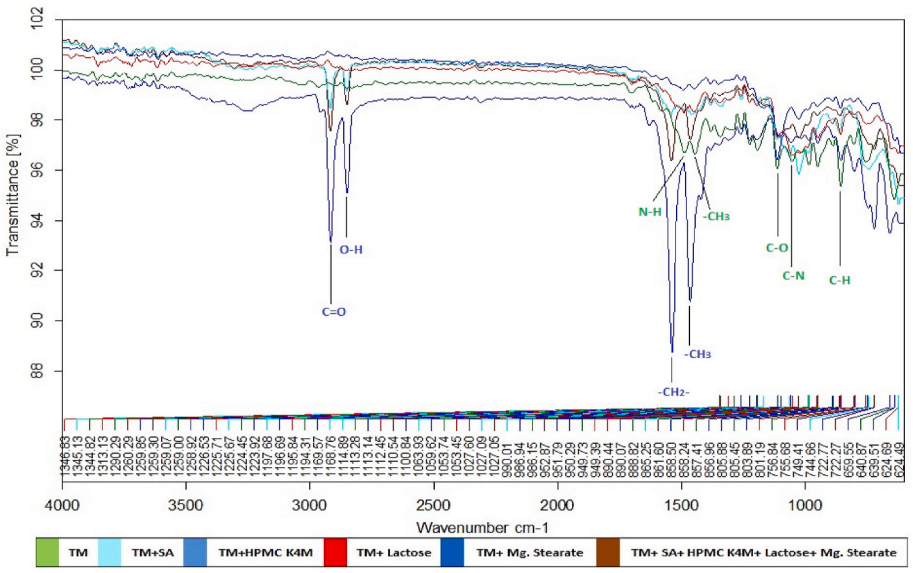


Fig. 4. Drug polymer/excipient compatibility studies by FTIR.

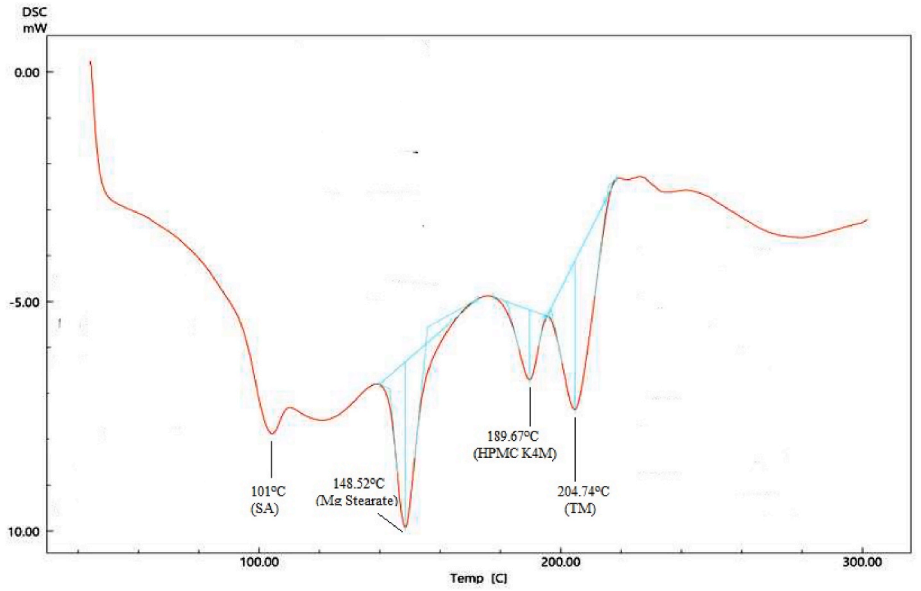


Fig. 5. Drug, polymer, and excipients physical compatibility determined by DSC.

polymer, and excipients at 204.74 °C (Fig. 5). These peak values are identical, demonstrating the compatibility of the TM, polymers, and excipients [39].

3.2. Evaluations

3.2.1. Granules

The bulk density, tapped density, Hausner ratio, angle of repose, and Carr's index of the granules were assessed before the modified release core tablet of TM was compressed. According to these researcher's observations, the bulk density ranged between 0.38 and 0.40 for each of the nine formulation batches. The tap density ranged from 0.42 to 0.47. The range of the Hausner ratio was 1.1–1.18. The angle of repose was determined to be between 24.78° and 29.30°, and Carr's index was found to be between 9.3 and 15.49. These findings led to the conclusion that every formulation possessed the good flow characteristics needed for tablet compression.

3.3. Data analysis, statistical optimization and validation

The nine batches were prepared by using two independent variables, as % concentration of sodium alginate and HPMC K4M, with three levels of upper, middle and lower design points as shown in Table 3 with their actual and coded forms.

The dependent variable, % cumulative drug release (Y1), was found to be in the range of 65.61–100 % as shown in Table 3. Software suggested a liner model for Y1 with a probability value of 0.0005. The percent swelling index (Y2) was found to be in the range of 33.33–62.59, for which software suggested a quadratic model (probability value 0.04). As the value of probability for each model was below to 0.05, the results of the ANOVA along with the regression analysis further confirmed that the suggested models and terms were significant (Table 4).

Table 3
Design parameters and characterization of core modified release tablets.

RUN	Formulation code	Independent variables (coded levels)		Response variable	
		Sodium-alginate (X1)	HPMC K4M (X2)	%DR (Y1)[a] Up to 20Hrs	%SI (Y2)*
1	F1	21	20	100 ± 0.581	33.33 ± 0.897
2	F2	25	20	95.49 ± 1.452	38.14 ± 0.602
3	F3	23	20	90.45 ± 1.469	34.84 ± 0.144
4	F4	23	35	85 ± 2.291	45 ± 0.984
5	F5	21	35	87.61 ± 1.822	39.94 ± 0.898
6	F6	21	50	80.3 ± 2.439	52.67 ± 0.585
7	F7	23	50	71.03 ± 2.493	58.33 ± 1.190
8	F8	25	50	65.61 ± 2.362	62.59 ± 1.342
9	F9	25	35	74.38 ± 1.444	47.59 ± 0.968

[a] Average (±SD) n = 3.

Table 4
Summary of results of regression analysis and ANOVA for measured responses.

Response	Model	R^2	SS	DF	MS	F value	P value	Model Significance
% CDR (Y1)	Liner	0.9208	968.78	2	484.39	34.87	0.0005	Significant
% Swelling Index (Y2)	Quadratic	0.9981	12.48	2	6.24	11.24	0.04	Significant

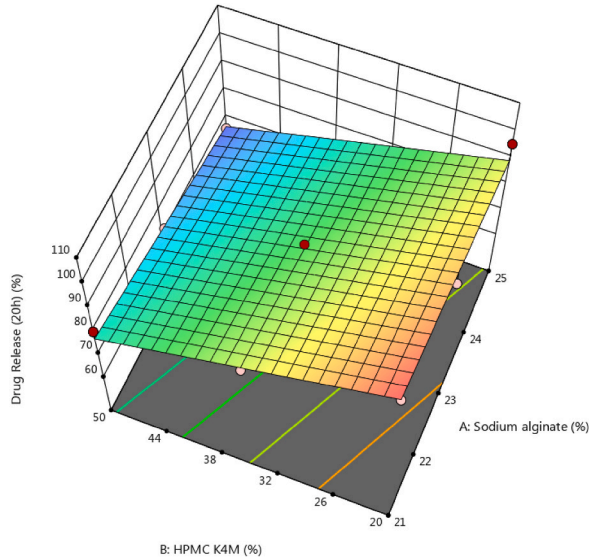
SS: Sum of Square; DF: Degree of freedom; MS: mean square.

Software suggested following polynomial Equations (3) and (4) for dependent variable

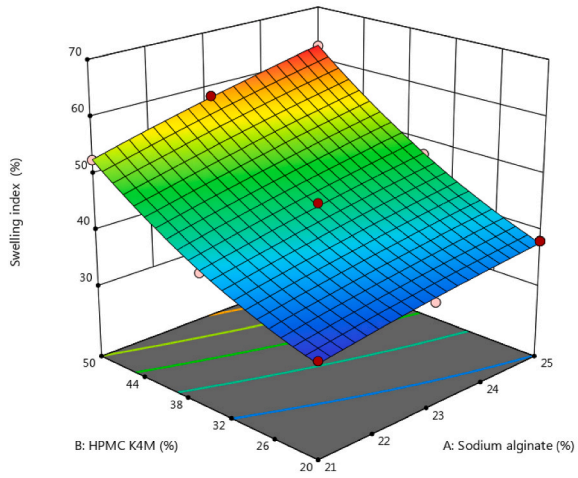
$$\mathbf{Y1} = +83.32 - 5.41\ X1 - 11.50\ X2 \quad (3)$$

$$\mathbf{Y2} = 44.41 + 3.73\ X1 + 11.21\ X2 + 1.28 \times 1 \times 2 - 0.34 \times 1^2 + 2.47 \times 2^2 \quad (4)$$

Through the optimization study, it was observed that both independent variables, i.e., the percent concentration of sodium alginate and HPMC K4M, have a negative impact on the drug release (Equation (3)). Henceforth, as the concentration of polymers increases, the drug release decreases. It might be due to the formation of a gel matrix by polymers when they come into contact with the dissolution medium. However, HPMC showed almost two folds more control over drug release in comparison to alginate.



A)



B)

Fig. 6. Three dimensional (3 D) response surface plot for response A) Y1: % cumulative drug release and B) % swelling index.

Equation (4) indicates the positive impact of the concentration of polymers on the swelling index. An increase in the concentration of polymers forms a gel of greater thickness which ultimately increases the swelling property of tablets. In this case, the impact of HPMC K4M was found to be more significant than that of alginate. The X1 and X2 showed a positive effect on the swelling index in the presence of a combination.

The impact of the independent variables on the drug release (Fig. 6A) and the swelling index (Fig. 6B) can be further explained by using a 3D response surface plot.

To select the optimised batch, the modified drug release up to 24h was the major criteria, which was directly related to the swelling index of the tablet. During the dissolution study, found that the F1 batch showed 100% drug release within 20h, and henceforth, for optimization purpose, the % drug release up to 20 h was considered. However, the rest of the batches were even tested for drug release until 24 h or it resulted in 100% drug release, whichever came earlier. Batch F2–F5 showed its maximum drug release before 24 h henceforth rejecting it from the selection criteria. Batch F6, F7, F8, and F9 showed good sustained drug release ability with 96.38, 83.52, 79.24, and 84.78% drug release till 24h. The results clearly indicate that batch F7–F9, due to the high concentration of polymers failed to release 100% of the drug, which makes them unsuitable for further use (as they may cause dose overload). Only batch F6 showed a satisfactory drug release pattern, and henceforth, it was selected as the optimised batch for further evaluation.

3.4. Characterization of core tablets of TM

3.4.1. In process quality control test

Two release retardants, sodium alginate and HPMC K4M, were used to manufacture the modified release core tablets of TM utilising the aqueous weight granulation method. A 3^2 factorial designs were used to develop the nine formulation batches. The physical characteristics of the developed tablets, such as their thickness, hardness, friability, average weight, and homogeneity of drug content, were assessed (Table 5). The thickness for all of the formulations was discovered to be between 2.17 and 2.77 mm, with an average of 2.37 mm. The average tablet hardness was 5.19 kg/cm^2, which is in accordance with the recommended values listed in the literature [28]. The weight of a tablet varies from 99.27 mg to 100.55 mg on average across all formulations. Consequently, all nine formulations passed the USP weight variation test [31]. The percent drug content was observed to range from 99.3% to 101.2% for all nine formulations. Consequently, all tablets met IP 2010 specifications [15].

3.4.2. Swelling index

When use polymers in development of formulation, swelling index was most important parameter. The swelling index was measured as % weight increased by tablet. The sodium alginate and HPMC K4M are both hydrophilic polymers [40]. Consequently, it was discovered in the current investigation that the concentration as well as the ratio of polymers have a significant impact on the swelling behaviour of TM's modified release tablet (Fig. 7.). From batch no. F8, the most swelling was measured. It swells by 38.79% at 0.1 N HCl (pH 1.2), 48.21% in phosphate buffer (pH6.8), and 62.59% in phosphate buffer (pH 7.4) (which is made up of 25% sodium alginate and 50% HPMC K4M) after 2h, 5h, and 24h respectively. The lowest degree of swelling was obtained by batch F1. It shows 9.09% swelling in 0.1 N HCl (pH 1.2) after 2 h, 20% in phosphate buffer (pH 6.8) after 5 h, and 33.33% in phosphate buffer (pH 7.4) after 24 h, which was composed of sodium alginate 21 % and HPMC K4M 20%. These findings showed that the swelling index increased when HPMC K4M and SA concentrations were increased, forming a more compact structure of the hydrated gel layer that prevented the penetration of fluids [41].

3.4.3. In vitro drug release study

Hydrophilic polymeric matrix systems are the basis of the modified release core tablets of TM. The drug was released from these systems by dissolving, diffusing through the gel layer, and eroding the hydrophilic polymeric matrix from which the drug particles are disseminated (Allen et al., 2013). Percent drug release in 0.1 N HCl (pH 1.2) after 2 h, F1 – 29.65%, F2 – 21.06%, F3 – 18.04%, F4 – 20.61%, F5 – 19.39%, F6 – 8.14%, F7 – 5.67%, F8 – 3.78%, and F9 – 8.14%. Less than 10% of the drug was released from formulations F6, F7, F8, and F9 after 2 h in 0.1 N HCl (pH 1.2) [42]. When tablets were delivered to the intestines after 2 h, the release rate increased

Table 5
Results of quality control tests of formulated modified release core tablets of TM.

Formulation	Thickness (MM)[a]	Hardness (Kg/cm^2)[a]	Weight (mg)[b]	Friability (%)	Drug Content (%)[c]
F1	2.77 ± 0.058	5 ± 0.200	99.71 ± 0.93	0.31	96.6 ± 0.608
F2	2.23 ± 0.058	4.93 ± 0.404	99.50 ± 1.154	0.77	99.3 ± 1.3
F3	2.30 ± 00	5.10 ± 0.200	99.83 ± 1.482	0.15	96.9 ± 1.410
F4	2.53 ± 0.058	5.47 ± 0.306	100.14 ± 1.309	0.46	98.8 ± 1.001
F5	2.50 ± 00	4.90 ± 0.361	99.72 ± 0.605	0.77	101.2 ± 0.721
F6	2.20 ± 00	5.70 ± 0.436	100.41 ± 1.074	0.15	99.1 ± 1.059
F7	2.37 ± 0.058	4.87 ± 0.208	100.46 ± 0.859	0.92	97.4 ± 1.331
F8	2.17 ± 0.0115	5. 37 ± 0.153	100.55 ± 0.817	0.46	98.4 ± 0.503
F9	2.30 ± 00	5.37 ± 0.115	99.27 ± 0.611	0.46	98.3 ± 1.571

[a] Average (±SD) of three independent determinations.
[b] Average Weight (±SD) n = 20.
[c] Average (±SD) n = 3.

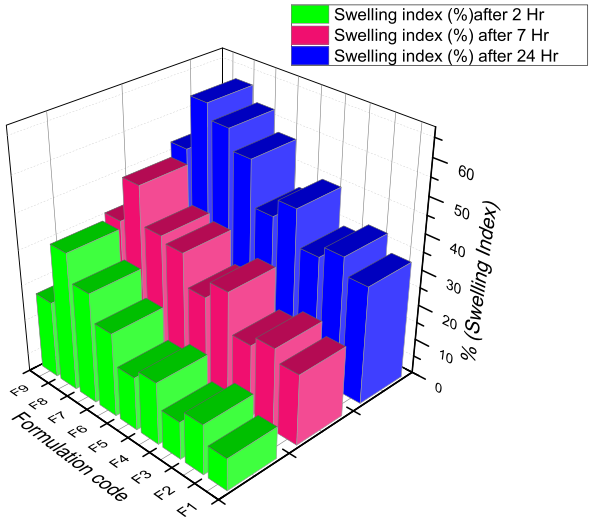


Fig. 7. Swelling index of tablet.

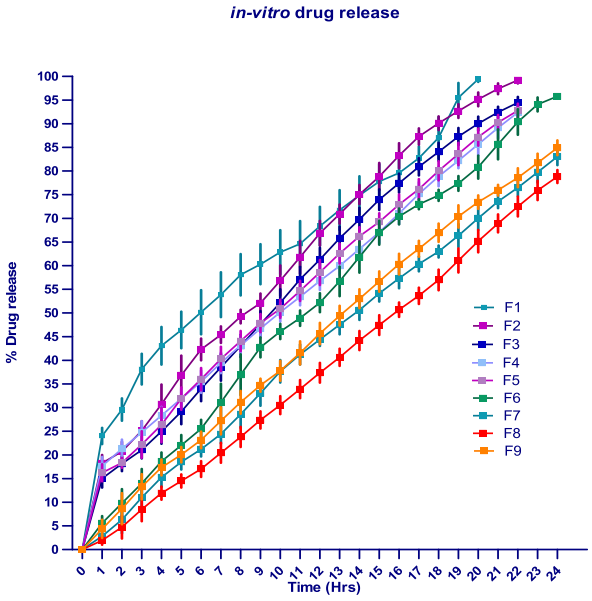


Fig. 8. Time Vs % Drug release.

slowly but steadily until 24 h had passed (Fig. 8). So, during the 24 h dissolution testing, a sustained-release pattern was seen [5]. This was caused by the alginate's mild gelling capabilities, which were pH dependant and allowed the medication to entrap itself in the polymer matrix. Alginate will shrink at stomach pH, preventing the release of the medication that was contained within the polymer matrix [29]. The above result was caused by the fact that the HPMC (pH-independent polymer) hydrates to form a gel layer at the tablet's surface when it is exposed to an acidic environment, while the SA precipitates in the hydrated gel layer as alginic acid and offers erosion resistance. The SA in the matrix turns into a soluble salt as the pH rises throughout the passage of the tablets from the stomach to the intestinal tract. As a result, the increased gel layer permeability at high pH values causes continuous drug release at various pH levels [5].

The percent drug release in phosphate buffer (pH 6.8) and phosphate buffer (pH 7.4) for formulations, F1-100%, in 20 h, F2-99.81%, F3-94.5%, F4-92.5%; and F5 – 93.1% in the 22 h period, respectively. These formulations were unable to sustain the drug release for up to 24 h because of the lowest concentration of polymers. Remaining formulations F6 – F9 sustained the drug release for up to 24 h. The drug release was found in F6-96.38%, F7-83.52%, F8-79.24%, and F9-84.78%, respectively. From all of these drug release study findings, it was determined that formulation F6 exhibits the highest percent drug release, 96.38%, up to 24 h and the lowest percent drug release, 8.14%, in 0.1 N HCl (pH 1.2), at 2 h, which is in accordance with standards described in the literature [42].

In relation to the other formulas, the greater drug release characteristics and swelling features of formulation F6 led to its selection as the best formulation.

The best model to represent drug release from tablets was selected using the coefficient of determination (R^2) value as a criterion. Formulation F6 showed zero-order release kinetics ($R^2 = 0.9819$). The Peppas model's ''n'' values were determined to be 0.7840, indicating that the medication was released following anomalous transport. The anomalous transport denotes non-Fickian diffusion, which denotes drug release that is controlled by both diffusion and erosion.

3.5. Characterization of Tablet-in-tablet of TM

The material method section's approach was followed in order to characterize the thickness, hardness, weight variation, friability, drug content, and in vitro dissolution (Table 6).

According to Table 2, three distinct batches of TM tablet-in-tablet (TIT-1, TIT-2, and TIT-3) were created with outer layer weights of 250 mg, 300 mg, and 350 mg, respectively, utilising 8 mm, 9 mm, and 10 mm round concaved punches and characterized them physically (Table 6). The major concern was the strength and time required to disintegrate the outer tablet. All three batches disintegrated within 10 min, so they passed the disintegration test. The initial TIT-1 batch's hardness was 2.30 ± 0.265 kg/cm^2, which was unsatisfactory because 4 kg/cm^2 is the minimum hardness needed for satisfactory tablet manufacture [28]. The outer shell's mass (250 mg) of powder was not enough to completely encase the tablet's inner core, which weighed 100 mg. As a result, during compression, there was weak bonding between the lower outer shell and the top outer shell. The friability test failed in the case of this tablet because of its poor bonding, which was greater than 3% [19]. In contrast, TIT-2 and TIT-3 were discovered to have hardness and friability of 5.03 ± 0.231 kg/cm^2 and 5.50 ± 0.361 kg/cm^2 and 0.92% and 0.62%, respectively. As a result, TIT-3 comprises 350 mg of the tablet's outer shell, while TIT-2 uses a minimum of excipients. In the present study, croscarmellose sodium was primarily employed as a disintegrant. The disintegration of tablets is caused by a number of factors, including swelling, erosion, the creation of pores, etc. [18]. According to Rowe et al. (2009), CCS was used in tablet formulations at a concentration of 0.5%–5.0% w/w. If its level is raised further, a viscous gel layer was formed which serves as a barrier for disintegration. A larger particle size of croscarmellose sodium leads to enhanced swelling and faster disintegration because croscarmellose sodium forms a viscous layer upon contact with water [6]. Along with this, MCC is also used to enhance the disintegration of the tablet. MCC has a significant impact on how to break down tablets. It has great wicking and absorbing capabilities. It creates a channel for the fluid to enter the tablet and dissolve it, causing the disintegrant to quickly enlarge and help the tablet dissolve quickly [7]. In the current investigation, the disintegration times (MM:SS) for TIT-1, TIT-2, and TIT-3, which include croscarmellose sodium in varying concentrations of 3%, 2.5%, and 2.14% of the total weight of the outer tablet or shell of TM, respectively, were determined to be 1.30 ± 0.200, 6.12 ± 0.586, and 9.59 ± 0.986. Out of these three separate batches, the TIT-1 batch exhibited the least amount of disintegration time because of its weaker strength, leading to more brittleness than the other two batches. Due to the TIT-2 batch's shorter disintegration time and usage of fewer excipients than the TIT-3 batch, it was decided that TIT-2 was the final tablet-in-tablet formulation.

4. Conclusion

In the present study, we have effectively created a tablet-in-tablet dosage form that achieves the dual release of drug within a single dosage unit. In essence, our research has resulted in the successful development of modified release core tablets with an immediate release outer shell, designed as a tablet-in-tablet formulation for TM. These novel formulations demonstrate both controlled and immediate drug release properties while meeting the necessary physical characteristics. As a result, they show great promise for potential therapeutic applications. This accomplishment aligns with the goals of our study and introduces new possibilities for practical medical applications of these formulations.

Data availability statement

The data that support the findings of this study are available from the corresponding authors, upon reasonable request.

Table 6
Results of quality control tests of Tablet in Tablet of TM.

FORMULATION	Thickness (MM) (Tablet in Tablet)[a]	Hardness (Kg/cm2) (Outer Shell)[a]	Weight (mg) (Tablet in Tablet)[b]	Friability (%) (Outer Shell)	Disintegration Time (MM:SS) (Outer Shell)[c]	% Drug Content (Outer Shell)[a]	% Drug Release (Outer Shell)[a]
TIT-1	4.17 ± 0.058	2.30 ± 0.265	349 ± 2.00	3.08	1.30 ± 0.200	98.34 ± 0.798	99.51 ± 1.304
TIT-2	3.67 ± 0.153	5.03 ± 0.231	399.5 ± 1.509	0.92	6.12 ± 0.586	99.81 ± 1.086	99.49 ± 1.095
TIT-3	3.23 ± 0.252	5.50 ± 0.361	449.8 ± 3.615	0.62	9.59 ± 0.986	101.21 ± 1.061	98.90 ± 1.512

TIT- Formulation Code for Tablet in Tablet.
[a] Average (±SD) n = 3.
[b] Average Weight (±SD) n = 20.
[c] Average (±SD) n = 6.

CRediT authorship contribution statement

Sachin S. Gaikwad: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Sanjay J. Kshirsagar:** Writing – review & editing, Supervision, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are grateful to the management of MET's Institute of Pharmacy, affiliated to Savitribai Phule Pune University, Bhujbal Knowledge City, Adgaon, Nashik-422003, India, for providing necessary facilities to carry out this work.

Abbreviations

TM	Timolol maleate
SA	Sodium alginate
HPMC	Hydroxypropyl methylcellulose
MCC	Micro crystalline cellulose
Mg-Stearate	Magnesium (Mg) stearate
FTIR	Fourier transform infrared spectroscopy
DSC	Differential scanning colorimetry
PXRD	Powder X-ray diffractometry
UV	Ultraviolet Spectrophotometer
DOE	Design of expert
TIT	Tablet-in-tablet formulation code

References

[1] A. Mannan, K.P. Rao, Novel chewable tablet-in-tablet dosage form of Orlistat and Venlafaxine hydrochloride development and evaluation, J. Appl. Pharmaceut. Sci. 5 (3) (2015) 91–97, https://doi.org/10.7324/JAPS.2015.50315.
[2] Y. Ozeki, M. Ando, Y. Watanabe, K. Danjo, Evaluation of novel one-step drycoated tablets as a platform for delayed-release tablets, J. Contr. Release 95 (2004) 51–60, https://doi.org/10.1016/j.jconrel.2003.10.028.
[3] S.S. Gaikwad, S.J. Kshirsagar, Review on tablet- in-tablet techniques, Beni-Suef Univ. J. Basic Appl. Sci. 9 (1) (2020) 1–7, https://doi.org/10.1186/s43088-019-0027-7.
[4] P.S. Wray, G.S. Clarke, S.G. Kazarian, Dissolution of tablet-in-tablet formulations studied with ATR-FTIR spectroscopic imaging, Eur J Pharm Sci 48 (2013) 748–757, https://doi.org/10.1016/j.ejps.2012.12.022.
[5] A. Mujtaba, K. Kohli, In vitro/in vivo evaluation of HPMC/alginate based extended-release matrix tablets of cefpodoxime proxetil, Int. J. Biol. Macromol. 89 (2016) 434–441, https://doi.org/10.1016/j.ijbiomac.2016.05.010.
[6] P. Zarmpi, T. Flanagan, E. Meehan, J. Mann, N. Fotaki, Biopharmaceutical aspects and implications of excipient variability in drug product performance, Eur. J. Pharm. Biopharm. 111 (2017) 1–15, https://doi.org/10.1016/j.ejpb.2016.11.004.
[7] Z. Bayrak, C. Tas, U. Tasdemir, H. Erol, C.K. Ozkan, A. Savaser, Y. Ozkan, Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: in vitro and in vivo evaluation, Eur. J. Pharm. Biopharm. 78 (3) (2011) 499–505, https://doi.org/10.1016/j.ejpb.2011.02.014.
[8] X. Li, D.S. Xu, M. Li, L. Lu, P. Heng, Preparation of co-spray dried cushioning agent containing stearic acid for protecting pellet coatings when compressed, Drug Dev. Ind. Pharm. 42 (5) (2016) 788–795, https://doi.org/10.3109/03639045.2015.1075034.
[9] S.C. Sweetman, Martin Dale the Complete Drug Reference, 34th ed., Pharmaceutical Press, London, 2005, pp. 1012–1013.
[10] H. Mohammedi, S. Shyale, S. Kumar, Physico-chemical characterization, UV spectrophotometric method development and validation studies of TM, Int. J. Pharm. 6 (2011) 163–166.
[11] K.S. Jain, P.B. Miniyar, T.S. Chitre, Experimental Pharmaceutical Organic Chemistry, second ed., Nashik, 2009.
[12] A.S. John, B.P. Sathesh, G. Divakar, M. Jangid, Development and evaluation of buccoadhesive drug delivery system for Atorvastatin calcium, Int. J. Curr. Pharm. 1 (2010) 131–138.
[13] S.S. Gaikwad, S.K. Thombre, Y.K. Kale, S.B. Gondkar, A.B. Darekar, Design and in vitro characterization of buccoadhesive tablets of timolol maleate, Drug Dev. Ind. Pharm. 40 (5) (2014) 680–690, https://doi.org/10.3109/03639045.2014.892955.
[14] Y. Shao, L. Li, X. Gu, L. Wang, S. Mao, Evaluation of chitosan-anionic polymers based tablets for extended release of highly water soluble drugs, Asian J. Pharm. Sci. 10 (1) (2015) 24–30, https://doi.org/10.1016/J.AJPS.2014.08.002.
[15] Indian Pharmacopoeia, Controller of Publication. Govt. of India, Ministry of Health and Family Welfare, New Delhi, 2010, pp. 281–973.
[16] H.G. Brittain, Analytical Profiles of Drug Substances and Excipients, vol. 25, Academic Press Inc, New Jersey, 1993.
[17] J.T. Carstensen, C.T. Rhodes, Drug Stability Principles and Practices, third ed., Marcel Dekker, Inc., New York (NY), 2000, pp. 252–255, 107.
[18] S.Y. Singh, Salwa, R.K. Shirodkar, Enhancement in dissolution rate of Atorvastatin Trihydrate calcium by formulating its porous tablet using Sublimation technique, J Pharm Innov 15 (2020) 498–520, https://doi.org/10.1007/s12247-019-09397-1.
[19] A.A. Liebermann, L. Lachman, J.B. Schwartz, Pharmaceutical Dosage Form Tablets, second ed., Marcel Dekker, Inc., New York, 2008, pp. 47–48.
[20] U.D. Laddha, S.J. Kshirsagar, Formulation of nanoparticles loaded in situ gel for treatment of dry eye disease in vitro, ex vivo and in vivo evidences, J. Drug Deliv. Sci. Technol. 61 (2021) 102–112, https://doi.org/10.1016/j.jddst.2020.102112.
[21] P. Sriamornsak, N. Thirawong, K. Korkerd, Swelling, erosion and release behaviour of alginate-based matrix tablets, Eur. J. Pharm. Biopharm. 66 (30) (2007) 435–450, https://doi.org/10.1016/j.ejpb.2006.12.003.

[22] N.C. Joshi, Z. Ahmad, S.K. Mishra, R. Singh, Formulation and evaluation of matrix tablet of tramadol hydrochloride, Indian J. Pharm. Educ. Res. 45 (4) (2011) 360–363.
[23] M.P. Sonawane, S.S. Gaikwad, D.V. Derle, Formulation, optimization and evaluation of pH dependent colon targeted drug delivery system of tizanidine hydrochloride, Invent Rapid Pharm Tech 1 (2013) 1–7.
[24] J. Jagtap, M. Patil, V. Patil, Development and in-vitro evaluation of colon specific satranidazole tablet for the treatment of amoebiasis, Asian J. Pharm. 7 (2013) 55–60, https://doi.org/10.22377/AJP.V7I2.26.
[25] R.K. Khar, S.P. Vyas, F.J. Ahmad, G.K. Jain, Lachman/Lieberman's the Theory and Practice of Industrial Pharmacy, fourth ed., CBS Publishers and Distributors, New Delhi, 2013, 186, 204, 483, 963.
[26] M.E. Aulton, Aulton's Pharmaceutics: the Science of Dosage Form Design, second ed., Churchill living stone, Spain, 2002, pp. 133–134.
[27] P.A. Borgaonkar, T.G. Virsen, R.C. Hariprasanna, M. Najmuddin, Formulation and in vitro evaluation of buccal tablets of loratadine for effective treatment of allergy, Int. J. Pharm. Chem. 1 (3) (2011) 551–559.
[28] L.V. Allen, L.A. Lawson, A. Adejare, Remington the Science and Practice of Pharmacy, twenty-second ed., Pharmaceutical Press, London, 2013, pp. 966–969, 989, 993.
[29] L. Li, J. Li, S. Si, L. Wang, C. Shi, Y. Sun, Z. Liang, S. Mao, Effect of formulation variables on in vitro release of a water-soluble drug from chitosan-sodium alginate matrix tablets, Asian J. Pharm. Sci. 10 (2015) 314–321, https://doi.org/10.1016/j.ajps.2014.09.002.
[30] V.T. Ishwariya, G.L. Soujanya, S. Santhoshi, S. Rani, Sabitha Haseeba, Formulation development and optimization of extended release matrix tablets of azilsartan using natural and synthetic polymers, Eur J Pharm Med Res 3 (4) (2016) 294–304.
[31] United States Pharmacopoeia NF, The official compendia of standards, in: Asian (Ed.), United States Pharmacopoeial Convention, 2009, pp. 725–726, 29 0, 386.
[32] H. Mobarak, B. Das, J. Chakraborty, Formulation, optimization and evaluation of capecitabine tablet for colon specific drug delivery system, Int. J. Pharm. Clin. Res. 9 (2017) 539–549, https://doi.org/10.25258/ijpcr.v9i7.8788.
[33] U.H. Shah, B. Patel, M. Patel, Formulation and evaluation of controlled release matrix tablet of diltiazem hydrochloride by using HPMC and guar gum as polymeric matrix material, Ars. Pharm 53 (2012) 16–20.
[34] K. Nayak, S. Sharma, M. Mishra, Formulation and evaluation of sustained release matrix tablets of glibenclamide, World J. Pharm. 5 (2016) 974–988, https://doi.org/10.20959/wjpr201611-7237.
[35] T. Agrawal, S.N. Narayana, K. Pal, K. Pramanik, S. Giri, I. Banerjee, Calcium alginate-carboxymethyl cellulose beads for colon-targeted drug delivery, Int. J. Biol. Macromol. 75 (2015) 409–417, https://doi.org/10.1016/j.ijbiomac.2014.12.052.
[36] Y.Y. Lee, A. Erdogan, S.S.C. Rao, How to assess regional and whole gut transit time with wireless motility capsule, J Neurogastroenterol Motil 20 (2) (2014) 265–270, https://doi.org/10.5056/jnm.2014.20.2.265.
[37] A.C. Moffat, M.D. Osselton, B. Widdop, Clarke's Analysis of Drugs and Poisons, third ed., Pharmaceutical Press, London, 2004, pp. 1637–1638, 2.
[38] B.W. Tekade, U.T. Jadhao, P. Jadhao, Formulation and in-vitro evaluation of capecitabine floating tablet, Pharma Innov J 6 (8) (2017) 171–175.
[39] S.W. Baertschi, K.M. Alsante, R.A. Reed, Pharmaceutical Stress Testing Predicting Drug Degradation, second ed., Informa Healthcare, London UK, 2011, p. 305.
[40] N.G. Raghavendra Rao, K.R. Raj, B.S. Nayak, Review on matrix tablet as sustained release, Int. J. Pharm. Res. Allied Sci. 2 (2013) 1–17.
[41] L. Segale, P. Mannina, L. Giovannelli, S. Muschert, F. Pattarino, Formulation and coating of alginate and alginate-hydroxypropylcellulose pellets containing ranolazine, J. Pharm. Sci. 105 (11) (2016) 3351–3358, https://doi.org/10.1016/j.xphs.2016.08.001.
[42] European Medicines Agency, Guideline on Quality of Oral Modified Release Products, An agency of the European Union, London (UK), 2014.