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Original Article

Formulation and evaluation of pH activated dosage form as minitablets in capsule for delivery of fesoterodine

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الملخص

أهداف البحث: في هذه الدراسة، جرت محاولة لتطوير أقراص صغيرة جديدة متعددة الوظائف ذات إطلاق مستدام في نظام الكبسولة عن طريق غلاف فلم من فيسوتيرودين لعلاج سلس البول (زيادة تكرار التبول).

طرق البحث: تم استخدام تقنية الضغط المباشر لتكوين الأقراص الصغيرة وضغط الغلاف باستخدام فثالات هيدروكسي بروبيل ميثايل السلولوز. تم إجراء دراسة ما قبل التركيبة باستخدام أدوات مثل قياس الكالوري التفرسي التفريقي، والتحليل الطيفي بالأشعة تحت الحمراء ، ومؤشرات ما بعد التركيبة مثل الصلابة ، والسمك ، وتغير الوزن ، والتوحيد ، وإطلاق الدواء. تمت دراسة حركية إطلاق الدواء للتركيبات ف1 إلى ف11.

النتائج: تم العثور على جميع مؤشرات ما قبل التركيبة وما بعد التركيبة ضمن الحدود. ينتج عن تركيبة ف1 و ف2 إطلاق سريع للدواء في غضون 30 دقيقة. تظهر التركيبات ف3 و ف4 و ف5 فثالات هيدروكسي بروبيل ميثايل السلولوز المغلفة إطلاقا بنسبة 100 ٪ تقريبا خلال 3 و 4 و 5 ساعات ؛ على التوالي. تظهر التركيبات ف6 و ف7 و ف8 (2.5٪ و 5٪ و 10٪ أقراص صغيرة مغلفة بالفورمالدهيد، على التوالي) إطلاقات دوائية في الأمعاء الدقيقة وتم إطالة الإطلاق لمدة 24 ساعة حيث كانت التركيبات ف9 و ف10 و ف11 (2.5٪ ، 5٪ ، 10٪ أقراص صغيرة مغلفة بالغلوتارالدهيد، على التوالي) تطلق في الأمعاء الدقيقة ولكن يستغرق الأمر أكثر من 20 ساعة لإطلاق الدواء.

الاستنتاجات: تم تطوير الأقراص الصغيرة المغلفة بالفلم إلى مستوى مرضي من حيث العديد من مؤشرات ما بعد الضغط مثل الصلابة ، والسماكة ، والتفتت ، وتغير الوزن ، وتوحيد المحتوى. كشفت دراسات الأشعة تحت الحمراء و قياس الكالوري التفرسي التفريقي أنه لا يوجد تفاعل كبير بين السواغات الدوائية. يتم إطلاق أقراص صغيرة مغلفة بفثالات هيدروكسي بروبيل ميثايل في دارئة وكان من المفترض أن يتحرر الدواء في الأمعاء مما يؤدي إلى امتصاص أفضل للدواء واتباع حركية إطلاق كورسماير-بيباس.

الكلمات المفتاحية: فيسوتيرودين؛ غلاف الفلم؛ الأقراص الصغيرة؛ فثالات هيدروكسي بروبيل ميثايل؛ هيدروكسي بروبيل ميثايل

Abstract

Objectives: In the present study, an attempt is made to develop novel multifunctional sustained-release minitablets in a capsule system by film coating Fesoterodine for the treatment of urinary incontinence (increased urinating frequency).

Methodology: The direct compression technique was used to formulate the minitablets, and coating was applied using hydroxypropyl methylcellulose (HPMC) phthalate. The pre-formulation study was performed using tools like differential scanning calorimetry (DSC), infrared spectroscopy (IR) and post-formulation parameters such as hardness, thickness, weight variation, uniformity, and drug release. Drug release kinetics were studied for the formulations F1–F11.

Results: All the pre- and post-formulation parameters were found to be within the limits. F1 and F2 result in burst release of the drug within 30 minutes. For the F3, F4, and F5 formulations, HPMC phthalate-coated minitablets show almost 100% drug release in 3, 4, and 5 hours, respectively. F6, F7, and F8 (2.5%, 5%, and 10% formaldehyde-coated minitablets, respectively) show drug releases in the small intestine, and the release was prolonged for 24 hours, whereas F9, F10, and F11 (2.5%, 5%, and 10% glutaraldehyde-coated minitablets, respectively) release in the small intestine, but drug release takes more than 20 hours.

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Conclusion: Film-coated minitablets were satisfactorily developed in terms of various post-compression parameters like hardness, thickness, friability, weight variation, and content uniformity. IR and DSC studies revealed no significant drug excipient interactions. HPMC phthalate-coated minitablets released in the buffer, and it was supposed that the drug releases in the intestine, which leads to better absorption and follows Korsmeyer-Peppas release kinetics.

Keywords: Fesoterodine fumarate; Film coating; HPMC phthalate; Hydroxypropyl methylcellulose phthalate; Minitablet

Introduction

The main purpose of drug delivery is to deliver the drug to the action site to produce the desired therapeutic effect. Different drug administration routes are available. Among those commonly used are parenteral, transdermal, inhalation, oral, and topical. Oral drug delivery is preferred. Tablets and capsules are more commonly used than liquid dosages. Some drugs are susceptible to the gastric environment, and some show better absorption in the intestinal tract. The conventional form does not meet these requirements; hence, the formulation is modified to a sustained or controlled release system.[1–3] These systems are further classified as single and multiple unit dosage forms. The single unit dosage form was most widely used for sustained release, but it was observed that these systems encounter problems like dose dumping, which led to the development of multi-component drug delivery systems such as pellet, granules, minitablets, etc. Pellets and granules may increase cost and production complications; hence, minitablets manufactured using the conventional tableting method become the formulation of choice.[3,4]

Minitablets are a compact dosage unit that can be produced using the routine tableting method. The size of a minitablet may vary, ranging from 2 to 5 mm. Minitablets have advantages like ease of manufacturing, dosage uniformity, multiple units, high drug loading, and minimal risk of dose dumping. Minitablets can be formulated in the tablet-in-tablet or the tablet-in-capsule system.[3,4] In the tablet-in-tablet system, the tablet has two parts: the internal core and the external coat. The core is a small porous tablet prepared on one turret. After the tablet core is manufactured, it is transferred (centrally positioned) to another slightly larger die that is partially filled with coating powder. More coating powder is filled on top of the core and compressed again, resulting in a tablet within a tablet.[3,4] In the tablet-in-capsule system, the formulation process can be divided into two steps: The first step involves the formulation or production of minitablets, and the second step involves filling these mini-tablets into hard gelatin or HPMC capsules.[3,4] Low dose (less than 50 mg), oral bioavailability (50%–60%), and a short biological half-life (2–8 h) are the ideal drug properties for minitablet formulation.[3,4] pH-responsive drug release is required when drug absorption is better at a particular site. This can be achieved by coating with pH-responsive release polymers to formulate pH-responsive minitablets.[3] Hadi Mohd et al. developed a pH-responsive minitablet of naproxen for ileocolonic targeted delivery.[4]

Urinary incontinence

Urinary incontinence is a condition in which the bladder muscles contract uncontrollably, causing frequent urination, an urgent need to urinate, and the inability to control urination. Urinary incontinence is a widespread disorder affecting millions of individuals worldwide, but its prevalence is still underestimated due to stigmatisation. It affects females more than males.[5] Normal bladder contractions are mediated via muscarinic (cholinergic) receptors in the detrusor muscle. Antimuscarinic drugs competitively block acetylcholine and increase bladder storage capacity.[5] Currently, approved common drugs for the treatment of urinary incontinence include Oxybutynin, Solifenacin, Darifenacin, and Fesoterodine. Fesoterodine is superior to the others in terms of its effectiveness and cost.[5]

Fesoterodine fumarate is chemically designated as (*E*)-but-2-enedioic acid [2-[(1*R*)-3-[di(propan-2-yl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl] with a 2-methylpropanoate chemical structure, as depicted in Figure 1. It is an antimuscarinic agent used in the treatment of urinary incontinence. The drug is well absorbed through the intestinal region. Furthermore, its low dose and short biological half-life make it an ideal candidate to formulate a sustained release minitablet.[5,6] Mock et al. observed that Fesoterodine is an antimuscarinic agent with a unique pharmacokinetic profile. Fesoterodine acts as a prodrug. It is converted to its active form by plasma enzyme esterases, independent of the cytochrome p450 enzyme system. Fesoterodine is marketed under the trade name Toviaz™ as an extended-release formulation.[7] Reddy et al. developed a sustained release formulation of Fesoterodine to maintain constant therapeutic levels of the drug for 12 hours.[8] Lee et al. discussed a dual-release bilayer tablet containing Fesoterodine fumarate 5 mg and Mirabegron 50 mg. They prepared and investigated the release behaviour of each drug in the bilayer tablet.[9] A previous study found that either the formulation was not targeted to the desired region, or if it was targeted, there was a deficiency in prolonging release. Hence, the present study aimed to develop a suitable delivery system that would allow Fesoterodine to be absorbed well through the intestinal region and prolong its release with the help of a pH dependant minitablet in the capsule system.

Materials and Methods

Chemicals: (materials)

Fesoterodine fumarate was obtained as a gift sample from Wockhardt Research Centre in Aurangabad, India. Xylitol,

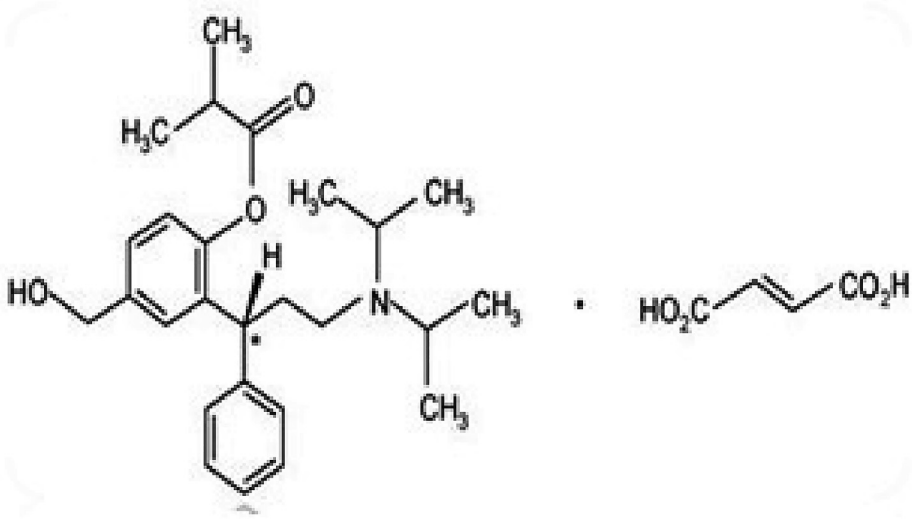

Figure 1: Structure of Fesoterodine fumarate.

PVP K-30, croscarmellose, magnesium stearate, and Aerosil were obtained from FDC Limited in Mumbai, India.

Pre-formulation study

Pre-formulation studies like melting point determination, Fourier transform infrared spectroscopy, and differential scanning calorimetry (DSC) were performed for Fesoterodine fumarate.[10,11]

Melting point

The melting point of Fesoterodine fumarate was determined by taking a small amount of the sample in a capillary tube that was closed at one end and placed in Thiele's melting point apparatus. The melting point was noted at room temperature.

Fourier transform infrared spectroscopy

The drug sample was mixed with potassium bromide powder. The baseline correction of FTIR (4100 Jasco) was carried out using dried KBr, and then the spectrum of a dried mixture of the drug and KBr was recorded by placing the powder in the light path and scanning the sample over the range of 4000−400 cm^{-1}.

Differential scanning calorimetry

Fesoterodine's thermal behaviour was studied using the Shimadzu DSC TA60 WS Thermal Analyser. Accurately weighed Fesoterodine samples were hermetically sealed in an aluminium pan and heated at a constant rate of 20 °C/min over a temperature range of 70 °C−300 °C.

Drug excipient compatibility study

The successful formulation of a suitable and effective solid dosage form depends upon the careful selection of excipients. Excipients are added to facilitate administration and promote consistent drug release and bioavailability. It is necessary to study excipients' compatibility with the drug. The melting point, thermal analysis, and FTIR spectroscopy were used to investigate and predict any physicochemical interaction between the components of the formulations and select suitably compatible excipients.

Formulation

In all the formulations, the dose of Fesoterodine fumarate was kept at 8 mg, as per Table 1. The excipients used were Xylitol (diluent), PVP K-30 (binder), cross carmellose sodium (super disintegrant), Aerosil (glidant), and magnesium stearate (lubricant). The minitablets were made using the direct compression technique. Compression was carried out on a Karnavati eight-station minitablet press using a 4.8 mm punch. Amongst the three batches, Batch III was selected because it shows the best result; that is, the result confirms all the parameters to a satisfactory level. In Batch I, the tablet was too large to fit in the capsule shell, so the weight was reduced. In Batch II, the formulated tablets were not as hard, and the tablets were breaking during the friability test due to the lower amount of binder. The quantity of binder was therefore increased in the Batch III formulation. Coating material was applied via techniques such as film coating (spray coating) and deep coating, using isopropyl alcohol and dichloromethane as solvents in the ratio of 40:60.

Preparation of coating solution

The coating solution was prepared as per the composition in Table 2. The polymers were dissolved in isopropyl alcohol. The mixture was stirred well until a clear solution was formed. This was followed by the addition of dichloromethane.

Coating core minitablets

The core tablets were film-coated in a conventional pharma R & D coater (manufactured by Ideal cures Pvt.

Ltd., Mumbai, India): 4 inches with three baffled stainless steel pans by spray coating. The coating parameters were optimised on placebo tablets made of lactose monohydrates and 0.5% magnesium stearate. Initially, the tablets were kept at 40 °C for 10 minutes while the pan rotated at 15 revolutions per minute (rpm). The rotating speed was then increased to 15–30 rpm, and the coating solution was sprayed at a rate of approximately 1–2 ml/min. The atomising pressure was adjusted to 1–2 kg/cm^2, and the inlet and outlet temperatures were varied from 35 °C to 55 °C. The process was continued until the whole solution was sprayed onto the tablets, causing a 2% weight gain. The coated tablets were rotated for a further 15 minutes under the blower to allow the coat to dry completely.[12–14]

Evaluation of the powder blend flow properties by formulation batch

Different parameters like bulk density, tapped density, Carr's index, angle of repose, and Haussner's ratio were evaluated.

Evaluation of the finished minitablet

Appearance

The minitablets' thickness was evaluated as a dimensional variable. Minitablet thickness was controlled within the average value. The colour, odour, and any other flaws like chips, cracks, surface texture, etc., and other important morphological characteristics were also observed.[15–19]

Hardness

Minitablet hardness is defined as the force required to crush the minitablet in the diametric compression test. The hardness was measured with a Monsanto hardness tester. The minitablets were placed diametrically between two plungers, and the lower plunger was kept in contact with the minitablet to read as zero. The upper plunger was forced against a spring by turning the screw until the minitablet fractured.[16–24]

Friability

Twenty minitablets were weighed and subjected to a friability test in the Roche friabilator. The pre-weighed sample was placed in a friabilator that revolves at 25 rpm for 4 minutes, dropping the minitablets a distance of 6 inches with each revolution. The formulations were evaluated for friability, and the percentage friability was calculated.[16–24]

Weight variation test

Given a minitablet weighing 40 mg or more, not more than two minitablets differed from the average weight by a 10% deviation. The fact that the weight variation was within the limits indicates uniformity in terms of minitablet compression and consequently the content of the drug in a unit. Twenty minitablets were taken to determine the average weight of the minitablet. The minitablets were weighed individually, and the weight variation was determined.[16–24]

Thickness and diameter

The minitablets' thickness and diameter were determined using a Vernier calliper. The minitablets' average diameter and thickness were calculated. The test was passed if none of the individual diameter and thickness values deviated from the average by ± 5%.[16–24]

Table 1: Formula for trial batches.

Sr.	Ingredients	Batch I	Batch II	Batch III
1	Fesoterodine Fumarate (Drug)	8 mg	8 mg	8 mg
2	Xylitol (Diluent)	62 mg	38 mg	37 mg
3	Cross carmellose Sodium (Super disintegrant)	4 mg	4 mg	4 mg
4	PVP K-30 (Binder)	3 mg	2 mg	3 mg
5	Aerosil (Glidant)	2.5 mg	2.5 mg	2.5 mg
7	Magnesium Stearate (Lubricant)	2.5 mg	2.5 mg	2.5 mg
	Total Weight	75 mg	50 mg	50 mg

Drug content

Five randomly selected minitablets from each batch were crushed using a mortar and pestle. Crushed powder equivalent to 8 mg of Fesoterodine fumarate was diluted with an appropriate amount of phosphate buffer at pH 6.8 and subjected to analysis using the UV spectrophotometer at 220 nm.[16–24]

In vitro dissolution study parameters

Dissolution medium: pH 6.8 phosphate buffer.
Apparatus: USP type I Basket.
Speed: 50 rpm.
Volume of dissolution medium: 900 ml.

Drug excipient compatibility study

Excipients' drug compatibility plays a major role in formulation development. Excipients are added to improve the drug's characteristics. Thermal analysis and FTIR spectroscopy were used to study the excipients' compatibility with the drug.[16–24]

Drug release kinetics

In vitro dissolution has been recognised as an important element in drug development. Under certain conditions, it can be used as a surrogate for the assessment of bioequivalence. Several theories or a kinetic model can describe drug

Table 2: Formulation and their codes.

Batches	Formulation composition
F1	Minitablets in soft gelatin capsule shell
F2	Uncoated minitablets in pre heated soft gelatin capsule shell
F3	5% Film-coated minitablets (5% w/w of HPMC)
F4	10% Film-coated minitablets (10% w/w of HPMC)
F5	15% Film-coated minitablets (15% w/w of HPMC)
F6	2.5% Formaldehyde coated gelatin capsule shell
F7	5% Formaldehyde coated gelatin capsule shell
F8	10% Formaldehyde coated gelatin capsule shell
F9	2.5% Glutaraldehyde coated gelatin capsule shell
F10	5% Glutaraldehyde coated gelatin capsule shell
F11	10% Glutaraldehyde coated gelatin capsule shell

The composition in percent stands for %w/w of particular polymer in the coating solution.

Table 3: Evaluation of pre compressional parameters.

Batches	Bulk density (gm/c m^3)	Tap-density (gm/cm^3)	Carr's index (%)	Angle of repose	Hausner ratio
1	0.3076 ± 0.005	0.3333 ± 0.012	7.7107 ± 0.55	28.95 ± 1.34	1.0835 ± 0.04
2	0.3571 ± 0.003	0.4166 ± 0.010	14.28 ± 0.76	32.38 ± 1.20	1.1666 ± 0.02
3	0.2272 ± 0.010	0.250 ± 0.032	9.12 ± 1.05	32.55 ± 1.08	1.1003 ± 0.07
4	0.2777 ± 0.006	0.2941 ± 0.005	5.57 ± 0.30	32.23 ± 1.44	1.0590 ± 0.09
5	0.3030 ± 0.021	0.40 ± 0.016	24.25 ± 0.90	34.90 ± 1.32	1.3201 ± 0.02
6	0.3030 ± 0.004	0.3571 ± 0.011	15.14 ± 0.78	29.16 ± 1.26	1.1785 ± 0.05
7	0.2777 ± 0.007	0.2127 ± 0.013	22.23 ± 0.44	34.65 ± 1.08	1.2859 ± 0.03
8	0.1785 ± 0.015	0.2127 ± 0.023	16.07 ± 1.03	36.32 ± 1.10	1.1915 ± 0.05
9	0.3125 ± 0.020	0.4166 ± 0.021	24.98 ± 1.42	36.19 ± 1.22	1.331 ± 0.07
9	0.2525 ± 0.021	0.3540 ± 0.010	21.15 ± 0.95	34.52 ± 1.11	1.2578 ± 0.09
10	0.2741 ± 0.015	0.2256 ± 0.015	22.23 ± 0.44	35.53 ± 1.15	1.2854 ± 0.06
11	0.2788 ± 0.021	0.2941 ± 0.005	15.14 ± 0.78	34.90 ± 1.32	1.1785 ± 0.05

Table 4: Evaluation of post compressional parameters.

Batches	Weight variation	Hardness (kg/cm^2)	Friability %	Thickness (mm) ±sd
1	49.95 ± 0.013	3.42 ± 0.07	0.56 ± 0.09	2.98 ± 0.02
2	50.37 ± 0.09	3.47 ± 0.09	0.64 ± 0.05	2.94 ± 0.08
3	50.51 ± 0.12	3.41 ± 0.06	0.58 ± 0.13	2.96 ± 0.09
4	50.32 ± 0.13	3.38 ± 0.10	0.62 ± 0.08	2.96 ± 0.06
5	50.28 ± 0.02	3.3 ± 0.09	0.74 ± 0.05	2.94 ± 0.09
6	50.44 ± 0.13	3.39 ± 0.08	0.68 ± 0.10	2.92 ± 0.09
7	50.47 ± 0.12	3.34 ± 0.07	0.6 ± 0.09	2.92 ± 0.08
8	50.550.09	3.33 ± 0.09	0.54 ± 0.05	2.98 ± 0.09
9	50.48 ± 0.08	3.37 ± 0.08	0.52 ± 0.08	2.94 ± 0.09
10	50.54 ± 0.10	3.42 ± 0.10	0.62 ± 0.05	2.920 ± 0.06
11	50.25 ± 0.13	3.4 ± 0.10	0.58 ± 0.05	2.96 ± 0.09

dissolution from immediate and modified release dosage forms. Several models represent drug dissolution profiles where f_t is a function of t (time) related to the amount of the drug dissolved from the pharmaceutical dosage system. These drug release kinetics were analysed using PCP Disso Version 2.08 software to study the kinetics of the drug release mechanism.[16–24]

Results

Pre-compressional parameters

All the pre-compressional parameters were found to be within the limits, as per Table 3 and the limits prescribed in Indian pharmacopoeia.

Evaluation of the finished minitablet

The minitablets were evaluated for various post-compressional parameters like weight variation, friability, hardness, etc., and the parameters were found to be within the desired specifications, as per Table 4 and the limits prescribed in Indian pharmacopoeia.

Drug–excipient compatibility study

The results of IR and DSC of the pure drug, as shown in Table 5 and Figure 2, were compared with the results of IR and DSC of the drug excipients mixture, as shown in Figure 3 and Table 5. No significant interactions were found between the drugs and the excipients (Figure 4).

Table 5: IR study.

Peak observation for pure drug	Standard range	Fesoterodine fumarate Functional group	Peak observation for drug and excipients mixture
3477	3500–3200	O–H Stretching	3482.81
2973	3000–2850 (m)	C–H Stretching	2950.55
2696	2830–2695	C–H–O Stretching	2695.43
1756.	1760–1665	C=O Stretching	1751.05
1493	1500–1400	C–C Stretching	1490.63
1127	1320–1000	C–O Stretching	1091.51

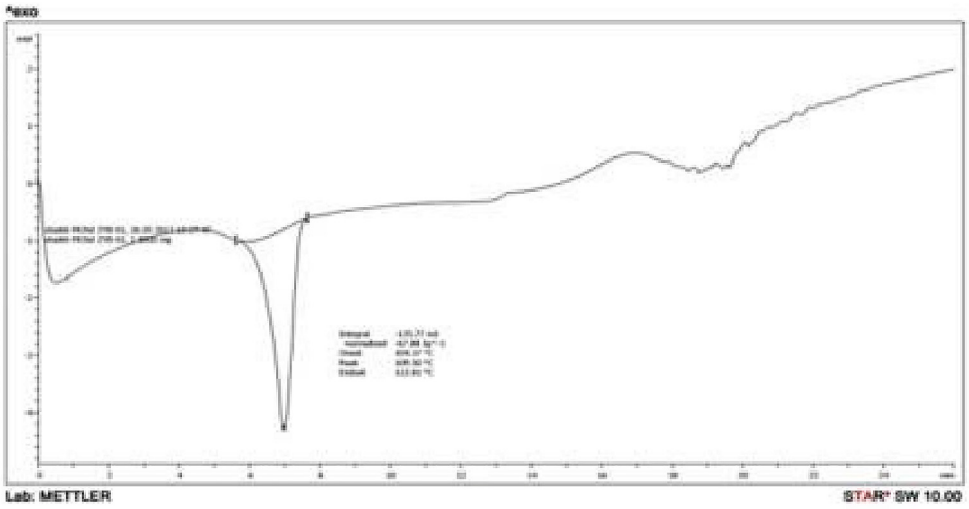

Figure 2: DSC thermogram of pure drug.

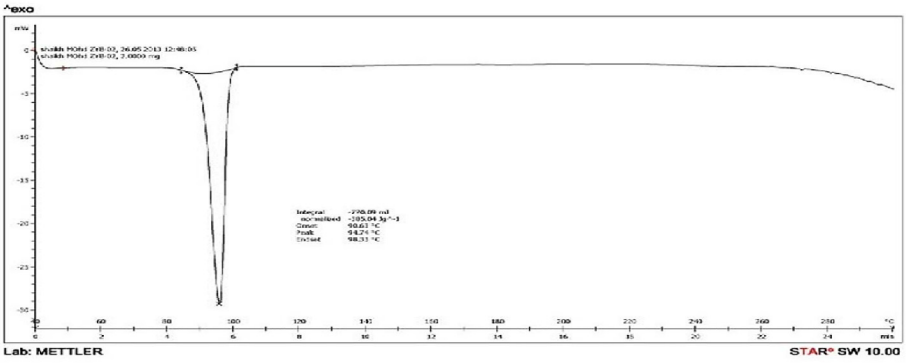

Figure 3: DSC thermogram of drug and excipients.

In vitro dissolution study

The present dosage form is enteric-coated minitablets in capsules (film-coated minitablets using HPMC phthalate). The purpose of film coating is to prevent drug dissolution in the stomach's gastric environment. This is done to facilitate drug release in the basic small intestine environment, as it gives a good absorption window. Moreover, the minitablets are filled into a soft gelatin capsule that holds the multi-particulate minitablets together. This makes it easy to take

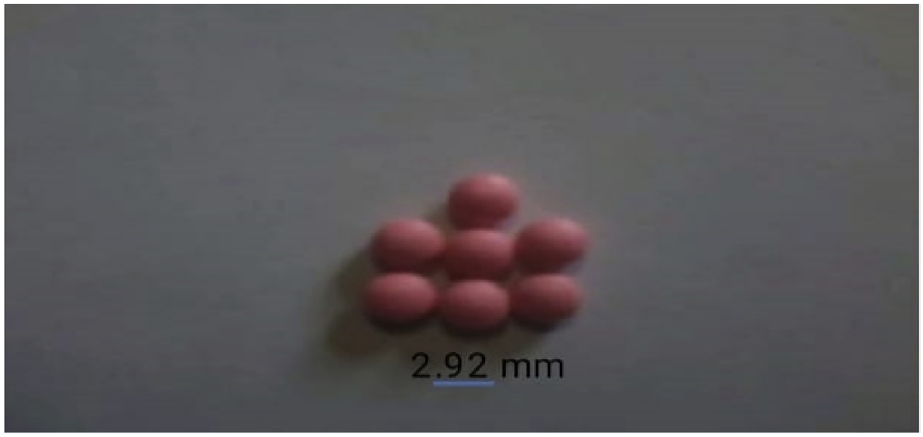

Figure 4: Minitablets.

Table 6: Drug release study.

Time Hrs	Percent drug release										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0	0	0	0	0	0
0.5	96.02 ± 0.16	97.00 ± 0.17	7.02 ± 0.28	7.02 ± 0.07	7.41 ± 0.05	13.242 ± 0.07	11.493 ± 0.24	10.521 ± 0.20	10.543 ± 0.23	9.549 ± 0.05	7.606 ± 0.05
1	97.48 ± 0.20	98.66 ± 0.25	6.71 ± 0.18	6.71 ± 0.23	6.91 ± 0.10	19.413 ± 0.05	13.564 ± 0.20	12.193 ± 0.24	12.581 ± 0.20	11.016 ± 0.05	10.605 ± 0.23
2	99.13 ± 0.24	99.74 ± 0.24	7.75 ± 0.15	7.17 ± 0.10	7.37 ± 0.08	30.316 ± 0.20	31.203 ± 0.24	13.687 ± 0.05	15.635 ± 0.05	11.720 ± 0.05	11.894 ± 0.24
3			96.45 ± 0.98	55.05 ± 0.80	30.06 ± 0.50	40.365 ± 0.24	38.348 ± 0.20	25.496 ± 0.23	16.389 ± 0.20	12.919 ± 0.20	12.699 ± 0.23
4				65.20 ± 0.54	45.92 ± 0.43	48.579 ± 0.24	44.209 ± 0.20	36.658 ± 0.20	16.955 ± 0.05	13.510 ± 0.05	13.518 ± 0.20
5				97.30 ± 0.60	98.17 ± 0.21	56.880 ± 0.78	51.296 ± 0.23	42.694 ± 0.51	17.525 ± 0.05	15.144 ± 0.06	14.244 ± 0.23
6						64.295 ± 0.43	58.068 ± 0.20	48.986 ± 0.50	18.920 ± 0.23	15.987 ± 0.08	15.265 ± 0.20
8						72.758 ± 0.30	66.463 ± 0.87	56.315 ± 0.45	19.950 ± 0.89	16.542 ± 0.93	15.908 ± 0.90
12						78.392 ± 0.12	73.391 ± 0.05	64.691 ± 0.75	20.684 ± 0.76	17.889 ± 0.67	16.852 ± 0.87
24						86.023 ± 0.27	79.610 ± 0.23	72.182 ± 0.90	91.771 ± 0.89	90.348 ± 0.94	89.514 ± 0.97

the whole minitablet at once, without loss (stated dose) or handling difficulty. The release profiles for all batches are described in Table 6 and Figures 5–6.

Release kinetics study

The release kinetics study, as per Table 7, showed that the different formulation batches follow different release kinetics for sustained and controlled release towards better absorption. Minitablets in a capsule shell (uncoated minitablets in a capsule) and microwave-assisted capsules (uncoated minitablets filled in a pre-heated capsule shell) dissolve immediately in the stomach. Minitablets coated with HPMC phthalate show release in intestinal pH, resulting in better drug absorption, following Korsmeyer-Peppas release kinetics. Gelatin cross-linked with formaldehyde shows slow, sustained release in intestinal pH. Gelatin cross-linked with glutaraldehyde follows zero-order release kinetics.

Discussion

A thermogram of Fesoterodine fumarate and other excipients showed one endothermic fusion peak, with a maximum peak of 98.330 °C, in line with the literature. The reported melting point is 105.0 °C. This was confirmed using the capillary tube method. Our observed melting point was 104.0 °C.

Based on the study of the interaction between the drug and other polymer IR spectra and the drug and other polymers, the combination was compared with single drug IR spectra. It was concluded that there was no interaction between the drug and other polymers. The F1 formulation, which was uncoated minitablets in a capsule shell, results in burst release of the drug. For the F2 formulation, the minitablets were placed in the cross-linked gelatin shell with the aid of microwave oven heating; unfortunately, the F2 formulation also resulted in burst release of the drug within 30 minutes. These results suggest that the microwave cross-linking technique is not effective for use with a gelatin shell. This finding correlates with other authors' results, which indicate that physically cross-linking the gelatin shell either by heating or irradiation is not an effective tool for prolonged or targeted release. To overcome this problem, the enteric coating polymer material HPMC phthalate was selected, as it is another physical approach for releasing the drug into the intestine.

The F3, F4, and F5 formulations contain minitablets coated with HPMC phthalate in a gelatin shell, showing almost 100% drug release in 3, 4, and 5 hours, respectively. These results suggest that an increase in coating thickness could delay drug release. Increased thickness can cause weight gain and large minitablets that might not allow for placement in the capsule shell. There has also been concern about the use of phthalate, possibly due to toxicity. In vitro drug release in F3, F4, and F5 show burst release within the basic environment pH. It can be concluded that HPMC phthalate is used to protect drugs from gastric acid degradation. Hence, a 5%–15% HPMC phthalate coating could provide burst intestine drug release, rather than slow, sustained release. Burst intestinal release may result in local accumulation as well as irritation and local toxicity.

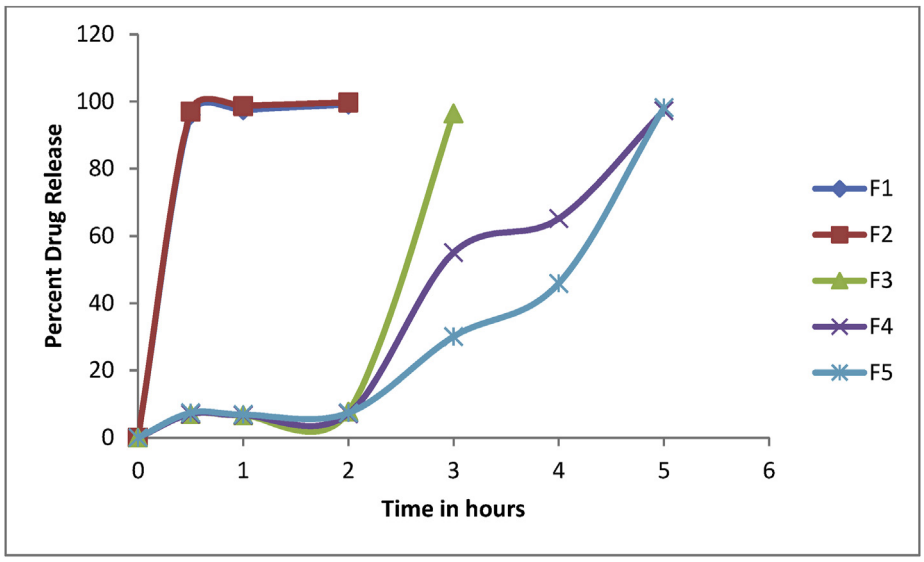

Figure 5: Drug release profiles batch F1-F5.

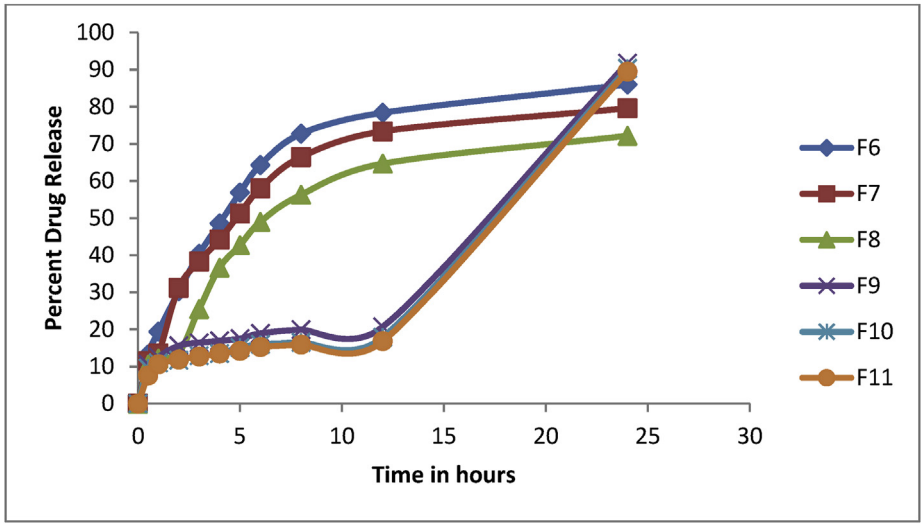

Figure 6: Drug release profiles batch F6-F11.

Table 7: Release kinetics.

Batch code	R^2					N	K
	Zero order	1st order	Matrix	Peppas	Hixson Crowell		
F1	0.9926	0.9816	0.9817	0.9998	0.9958	0.7141	164.03
F2	0.9926	0.9659	0.9795	0.9998	0.9940	0.7242	165.60
F3	0.9989	0.9785	0.985	0.9998	0.9233	0.8556	185.68
F4	0.9989	0.9052	0.9856	0.9998	0.9758	0.8555	185.58
F5	0.9998	0.9754	0.985	0.9998	0.9334	0.8571	185.89
F6	0.3769	0.8633	0.9494	0.9753	0.7604	0.5296	21.39
F7	0.41248	0.8264	0.9511	0.9635	0.7340	0.5651	18.34
F8	0.6619	0.8700	0.9604	0.9571	0.8151	0.608	13.80
F9	0.9187	0.8714	0.8016	0.7980	0.8950	0.4059	10.9969
F10	0.9202	0.8648	0.7733	0.7749	0.8872	0.4254	9.1074
F11	0.9210	0.8651	0.7705	0.8054	0.8870	0.4601	8.2882

N= Release exponent, K= Release rate constant.

This burst release problem can be solved with the aid of a chemical cross-linking agent. The gelatin shell was cross-linked with an aldehyde derivative. Various alternatives are available to overcome the burst release effect, but the gelatin cross-linking method is preferred because it offers advantages over the other methods. The major advantage is the ability to supply simple conventional minitablets for immediate release; sustained release is also an option that is achievable by incorporating the cross-linked gelatin shell.

The F6, F7, and F8 formulations (2.5%, 5%, and 10% formaldehyde) show drug releases in the small intestine (performed by maintaining the intestinal pH), and the release was prolonged for 24 hour, which follows matrix-type release kinetics. This is because formaldehyde is cross-linked with the gelatin capsule shell. Drug release tends to decrease with increased formaldehyde concentration. This could be due to the chemical reaction between the gelatin shell and the formaldehyde, which tends to contribute to the decreased performance of the formaldehyde stressed hard gelatin capsule shell in water. Gelatin reacts with formaldehyde through the initial formation of amine methylols on lysine and arginine. This drug release in the intestine due to the gelatin shell could be possible because of pancreatin, a proteolytic enzyme that can depolymerise the cross-linked gelatin material. The decreased drug release could be due to the formaldehyde concentration used or may be because of increasing the cross-linking duration, which also corresponds to increasing the cross-linking degree.

F9, F10, and F11 show drug releases in the small intestine, but it takes more than 20 hours to release the drug from the glutaraldehyde-coated capsule, which follows zero-order release kinetics. This is because glutaraldehyde is strongly cross-linked with the gelatin capsule and acts as a strong coating agent, which delays drug release from the dosage form. In the future, in vivo studies can be performed to gain a better understanding of the release profile, and in vitro–in vivo correlation (IVIVC) can be obtained to further understand the external factors that may affect performance. The advantage of the current research is the development of pH responsive Fesoterodine minitablets in the capsule system. The minitablets release the drug in the desired pH range (intestine), allowing for better drug absorption, following Korsmeyer-Peppas release kinetics. The observed study limitation was coating with different concentrations of polymers.

Conclusion

The minitablets were formulated using the direct compression technique. The drug powder blend and other excipients had flow properties as per the specifications, resulting in better minitablet compression. IR and DSC studies revealed that there was no interaction between the drug and the excipients. Film-coated minitablets were satisfactorily developed in terms of various post-compression parameters like hardness, thickness, friability, weight variation, and content uniformity. It can be concluded that the minitablets coated with HPMC phthalate showed release in the buffer, and it was supposed that the drug was released in the intestine, which gives better drug absorption and follows Korsmeyer-Peppas release kinetics.

Recommendations

Further in vivo studies should be carried out to obtain results for various IVIVC parameters and drug release studies.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

The authors confirm that this study was prepared in accordance with COPE rules and regulations. Given the nature of the letter, Institutional Review Board (IRB) review was not required.

Authors' contributions

SMS and PR designed and conducted the formulation study. KG and DH performed the pre-formulation study. SMS and KG drafted the manuscript, and DH and PR verified it. All authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

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