Research Article

Development And Evaluation of A Telmisartan Immediate-Release and Metformin Hydrochloride Sustained-Release Multiparticulate Tablet Using Fluidized-Bed Pelletization

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Abstract

Background: Hypertension and type 2 diabetes mellitus frequently coexist, creating a need for dosage forms capable of delivering antihypertensive and antihyperglycemic therapy in a coordinated manner. Multiparticulate systems prepared by fluidized-bed processing provide an approach for combining immediate-release and modified-release components in a single oral dosage form.
Objective: To develop and preliminarily evaluate a tablet containing immediate-release Telmisartan and sustained-release Metformin hydrochloride using fluidized-bed drug layering and polymer coating.
Methods: Metformin hydrochloride was layered onto sugar spheres and subsequently coated with HPMC K4M/PVP K30-based release-retarding systems to obtain sustained-release pellets. Telmisartan was incorporated into an immediate-release granule fraction. Five formulations (F1–F5) were prepared and compressed with the sustained-release pellets, Telmisartan, lactose, talc, magnesium stearate and parabens. Powder-flow properties, tablet physical characteristics, disintegration and in-vitro dissolution were evaluated.
Results: Pre-compression batches showed bulk density of 0.421–0.476 g/mL, tapped density of 0.442–0.521 g/mL, Carr's index of 3.61–9.26%, Hausner's ratio of 1.03–1.19 and angle of repose of 22.37–28.78°. Tablet hardness was 5.41–5.88 kg/cm² and friability was 0.24–0.61%. Telmisartan immediate-release disintegration times ranged from 5.31 to 7.01 min. Metformin release at 12 h was 95.76%, 97.06%, 99.70%, 99.04% and 96.44% for F1–F5, respectively.
Conclusion: Fluidized-bed palletization successfully generated a multiparticulate tablet exhibiting rapid disintegration of the immediate-release component and extended release of Metformin hydrochloride for up to 12h under the reported in-vitro conditions.

Keywords: Telmisartan; Metformin hydrochloride; multiparticulate tablet; sustained release; immediate release; fluidized-bed coating; pellets; HPMC K4M.

Introduction

Oral solid dosage forms remain widely used because they offer convenient administration, accurate dosing and relatively efficient manufacturing. Modified-release systems are particularly useful when prolonged drug exposure is desired and when reduction in dosing frequency is an objective. Multiparticulate dosage forms are attractive because drug-containing particles can be coated individually and subsequently incorporated into a final dosage form, allowing release characteristics to be engineered at the particle level[1,2].
Fluidized-bed processing is an established pharmaceutical technology for granulation, drying, drug layering and film coating. In a

Wurster-type system, particles are repeatedly transported through a coating zone and a drying zone, enabling relatively uniform deposition of functional coatings. Published studies describe fluidized-bed coating as an industrially scalable route for producing sustained-release multi-particulates, while process variables such as particle size, air flow, spray rate, atomization and coating thickness can influence the final release profile. Recent work has also emphasized the importance of controlling coating thickness and process parameters when targeting prolonged release[3,4].

Telmisartan is an angiotensin II receptor blocker used in hypertension, whereas metformin hydrochloride is an oral antihyperglycemic agent used in type 2 diabetes mellitus. Because hypertension and type 2 diabetes commonly require concurrent long-term pharmacotherapy, a single dosage form containing an immediate-release antihypertensive component and a sustained-release metformin component may provide a formulation strategy for reducing dosage-form burden. However, the formulation must demonstrate appropriate release characteristics for each drug rather than simply combining the two active ingredients[5, 6].

A previous study reported bilayer tablets containing immediate-release Telmisartan and sustained-release Metformin hydrochloride using wet granulation, with HPMC-based matrices for the sustained-release layer7. The present project differs in its use of drug-loaded Metformin pellets prepared by fluidized-bed layering/coating and subsequent compression with the immediate-release Telmisartan component. Thus, the work explores a pellet-containing single-unit tablet as an alternative manufacturing strategy[8].

The aim of the present study was therefore to develop and evaluate Telmisartan immediate-release/Metformin hydrochloride sustained-release multiparticulate tablets prepared using fluidized-bed palletization and to investigate the influence of the tested polymer compositions on powder properties, tablet characteristics, disintegration and in-vitro Metformin release

2. Materials and Methods

2.1 Materials

Telmisartan and Metformin hydrochloride were used as active pharmaceutical ingredients. Sugar spheres were used as starter cores for Metformin drug layering. HPMC, HPMC K4M, polyvinylpyrrolidone K30 (PVP K30), microcrystalline cellulose, talc, lactose, magnesium stearate, methyl paraben, propyl paraben, isopropyl alcohol and water were used during pellet preparation and tablet manufacture.

2.2 Preformulation studies

Organoleptic properties, melting point, solubility and UV-visible spectrophotometric characteristics were examined. The melting points were compared with reported pharmacopoeial values. Drug-excipient compatibility was planned using Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) [9-11].

Calibration curves were reported for Metformin hydrochloride in 0.1 N HCl and Telmisartan in ethanol. The reported regression equations were $y = 0.0344x - 0.00234$ ($R^2 = 0.99941$) for Metformin hydrochloride and $y = 0.04964x - 0.0510$ ($R^2 = 0.99423$) for Telmisartan[12-14].

2.3 Preparation of Metformin hydrochloride sustained-release pellets

Metformin hydrochloride was incorporated onto sugar spheres by solution layering. The drug-layering composition per batch was reported as 500 mg Metformin hydrochloride, 300 mg sugar spheres, 15 mg HPMC, 5 mg microcrystalline cellulose and 2 mg talc, using isopropyl alcohol and water as processing liquids. The resulting drug-loaded pellets were subjected to functional polymer coating using HPMC K4M and PVP K30. Five experimental formulations (F1–F5) were prepared[15,16].

The work contains HPMC K4M at 1–3% and PVP K30 at 1–2%, and the exact F1–F5 mapping of polymer concentrations is important because polymer concentration is a critical determinant of release rate.

2.4 Preparation of immediate-release Telmisartan fraction and pellet-containing tablets

The drug-loaded sustained-release pellets were combined with the immediate-release Telmisartan component and excipients and compressed using direct compression. The reported formulation composition consisted of 830 mg sustained-release drug-containing pellets, 40 mg Telmisartan, 1 mg methyl paraben, 1 mg propyl paraben, 12 mg magnesium stearate, 7 mg talc and lactose q.s. to 1000 mg. Tablets were manufactured at a reported batch size of 10 tablets using 12-mm D tooling [17].

The formulation was conceptually designed as a multiparticulate tablet rather than a conventional bilayer tablet:

the immediate-release Telmisartan fraction was intended to provide rapid drug availability, while coated Metformin pellets were intended to provide prolonged release[18].

2.5 Evaluation of powder blend

Bulk density and tapped density were determined from the measured powder mass and corresponding volumes. Carr's compressibility index and Hausner's ratio were calculated from bulk and tapped density. Angle of repose was determined by the fixed-funnel method. These parameters were used to assess flow and packing behavior prior to compression.

2.6 Evaluation of tablets

Weight variation, diameter, thickness, hardness and friability were evaluated. Friability was determined after 4 min of rotation at 25 rpm. Disintegration of the immediate-release tablet fraction was measured using an Electrolab disintegration tester in phosphate-buffered saline at pH 7.4 and 37 ± 0.5°C. Dissolution was performed using USP Apparatus II.

Hausner's ratio is an indirect index of ease of power flow

$$Hausner's\ ratio = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Low Hausner's ratio (<1.25) indicates better flow properties than higher ones.
(>1.25) indicates poor flow.

Table 1. Relation between Hausner's ratio and Flow Properties.

Sr. No.	Hausner's ratio	Flow properties
1	<4.25	Good flow
2	>1.5	Poor flow
3	1.25-1.5	Addition of glidant normally improve the flow

Carr's index: Data from bulk density and tapped density testing were used to calculate compressibility index follow:

Compressibility index = [(Taped density – Bulk density)/ Tapped density] ×100

Table 2. Relation between Carr's index and Flow Properties.

Sr. No.	Carr's index	Flow properties
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to possible
4	23-35	Poor
5	33-38	Very poor
6	>40	Very very poor

3. Results and Discussion

3.1 Identification and Preformulation characteristics

Metformin hydrochloride was described as a white to off-white crystalline powder with a slightly sulphurous odour, while Telmisartan was described as a white crystalline material. The observed melting point of Metformin hydrochloride was 222–224°C compared with a reported range of 222–226°C. Telmisartan showed an observed melting point of 261–263°C; the project reported comparison with its cited pharmacopoeial standard. The solubility observations recorded in the project indicated that Metformin hydrochloride was freely soluble in water and soluble in alcohol, whereas Telmisartan was described as freely soluble in water and slightly soluble in alcohol and methanol.

3.2 UV-visible analytical characteristics

The reported calibration data showed strong linearity over the investigated ranges, with R^2 values of 0.99941 for Metformin hydrochloride and 0.99423 for Telmisartan. These values indicate a linear response within the tested

ranges, but linearity alone does not constitute full analytical-method validation.

UV – Visible Spectrophotometry

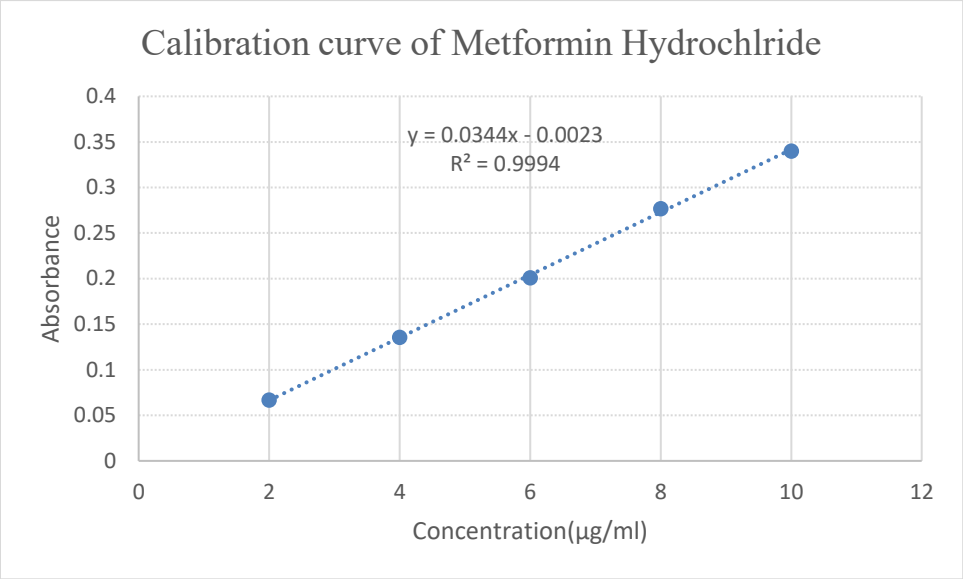


Figure 1. UV-Spectrum of Metformin Hydrochloride in 0.1N HCL

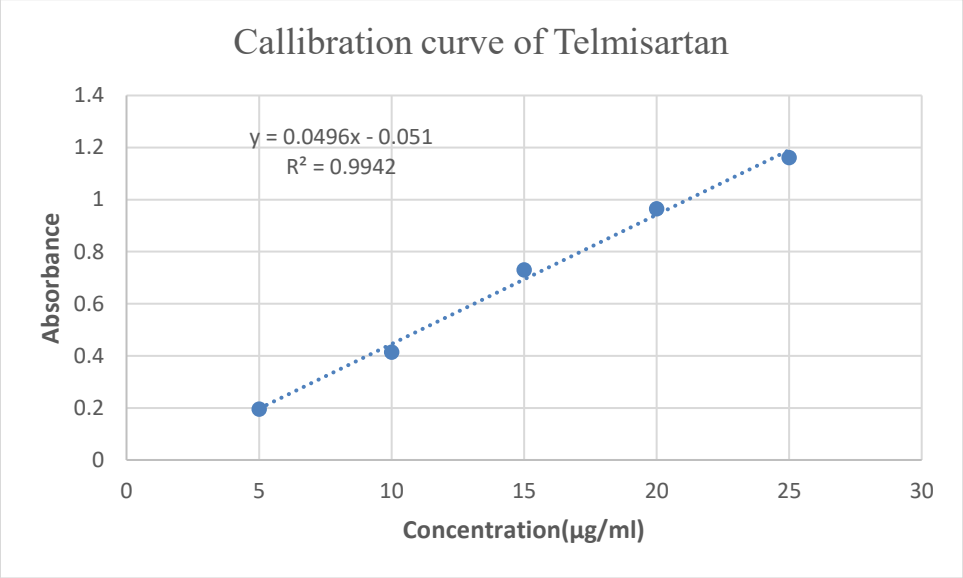


Figure 2. UV-Spectrum of Telmisartan in Ethanol

3.3 Powder-flow properties

Table 3. Pre-compression Studies

Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F1	0.426	0.442	3.61	1.03	28.51
F2	0.476	0.516	7.75	1.08	22.37
F3	0.421	0.442	4.75	1.04	24.84
F4	0.436	0.521	6.71	1.19	25.40
F5	0.421	0.464	9.26	1.10	28.78

All five batches exhibited relatively low Carr's index values (3.61–9.26%) and Hausner's ratios of 1.03–1.19. The measured angles of repose were 22.37–28.78°. Collectively, these values suggest acceptable flow and packing behavior for compression of the tested blends. F2 showed the lowest angle of repose, whereas F5 showed the highest Carr's index and angle of repose among the five batches.

3.4 Physical characteristics of tablets

Table 4. Post-compression Studies

Batch	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)
F1	998 ± 49.76	12	5.5	5.41	0.61
F2	1008 ± 52.14	12	5.6	5.55	0.36
F3	1002 ± 50.12	12	5.0	5.88	0.24
F4	996 ± 47.80	12	5.1	5.51	0.31
F5	997 ± 48.90	12	5.2	5.62	0.34

The tablets showed comparable dimensions and hardness across F1–F5. Friability ranged from 0.24 to 0.61%, remaining below the commonly applied 1% criterion stated in the project. F3 exhibited the highest reported hardness and the lowest friability. The reported weight values should be checked against the individual-tablet raw observations because the large ± values are unusually high for a nominal 1000-mg tablet and may represent a reporting or transcription issue.

3.5 Disintegration of the immediate-release component

Table 5. Disintegration Study

Batch	Disintegration time (min)
F1	7.01
F2	6.21
F3	5.31
F4	5.46
F5	6.14

Disintegration times ranged from 5.31 to 7.01 min. F3 showed the shortest disintegration time, followed by F4. The results support the intended rapid-disintegration behavior of the Telmisartan fraction, although an immediate-release claim should ultimately be supported by drug-specific dissolution data rather than disintegration alone.

3.6 In-vitro dissolution of Metformin hydrochloride

Table 6. In-vitro Dissolution Study

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)
0	0	0	0	0	0
60	18.58	22.51	23.61	20.00	20.50
120	30.87	32.83	45.74	38.62	34.75
240	43.84	47.08	61.99	54.85	53.54
360	56.82	60.71	78.21	71.72	65.26
480	71.73	74.98	90.56	84.72	78.23
600	84.72	87.96	98.37	95.76	91.20
720	95.76	97.06	99.70	99.04	96.44

All formulations demonstrated progressive drug release throughout the 12-h test. F1 consistently showed the slowest release, with 18.58% released at 60 min and 95.76% at 720 min. F3 released the greatest proportion at each

reported time point after 60 min and reached 99.70% at 720 min. F4 and F5 showed intermediate release patterns.

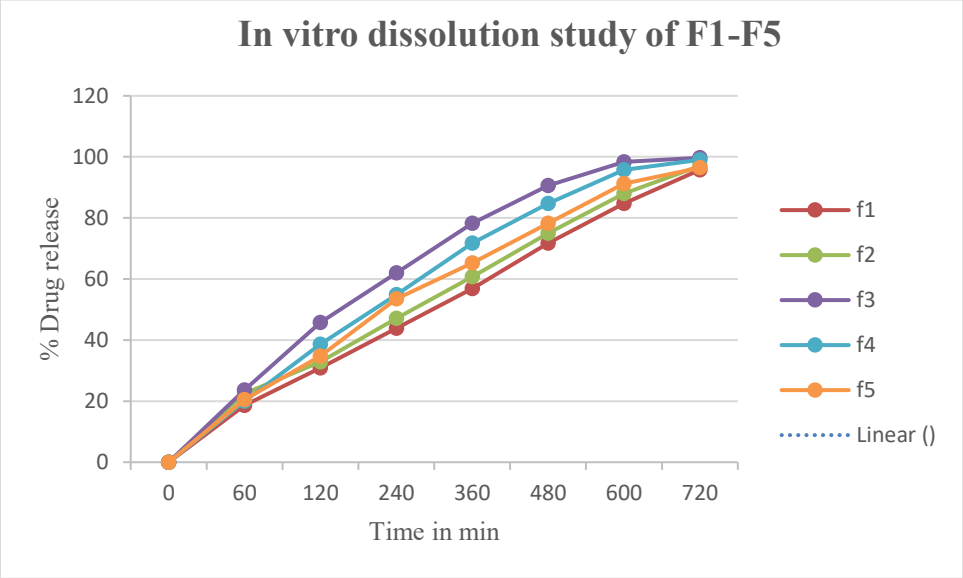


Figure 3. In-vitro Dissolution Study

The differences are consistent with the expected influence of polymer composition and coating characteristics on diffusion and/or erosion pathways; however, the exact polymer composition assigned to each formulation must be confirmed before attributing the differences to a specific polymer concentration.

The release profile demonstrates that the fluidized-bed coated pellets can retard Metformin release compared with an immediate-release presentation. Published work has similarly shown that fluidized-bed coating can be used to produce sustained-release Metformin multiparticulates and that coating variables materially influence release. More recent studies have emphasized the relationship between coating thickness and prolonged drug release, supporting the need to document coating weight gain and process conditions in future work.

Notably, the supplied data do not include replicate values, standard deviations, similarity/difference statistics, release-kinetic fitting, or comparison with a marketed/reference sustained-release product.

3.7. Analytical study

DSC analysis

DSC analysis was considered as a Preformulation tool to evaluate the thermal characteristics of Telmisartan, Metformin hydrochloride and the developed formulation. Metformin hydrochloride exhibited a characteristic endothermic thermal transition at approximately 222–224°C, which was consistent with the observed melting point reported in the present study. Telmisartan showed a characteristic thermal transition at approximately 261–263°C. These thermal events were considered characteristic of the respective drug substances.

In the physical-mixture thermogram, the characteristic thermal transitions of both drugs were retained, with the Metformin hydrochloride-related event appearing around 222–223°C and the Telmisartan-related event around 260–262°C. In the final formulation thermogram, the corresponding transitions appeared broader and slightly shifted toward lower temperatures. Such broadening or minor displacement may occur because of dilution of the drug with formulation excipients and the presence of the polymeric matrix containing HPMC K4M and PVP K30.

Importantly, the retention of recognizable drug-related thermal transitions in the formulation suggests that the characteristic thermal behavior of both active pharmaceutical ingredients may be preserved during formulation processing. No additional prominent thermal event was introduced in the thermogram that would, by itself, indicate formation of a new major crystalline phase.

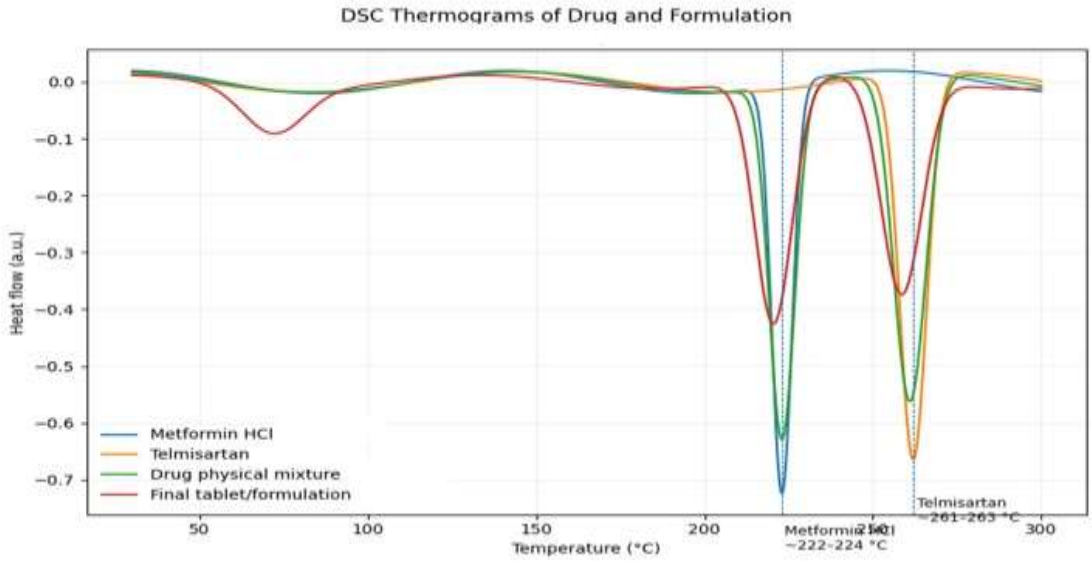


Figure 4. DSC thermogram of Drug and Formulation

FTIR study

FTIR spectroscopy was considered for evaluation of the compatibility of Telmisartan and Metformin hydrochloride with the selected formulation excipients. The spectrum of Metformin hydrochloride exhibited characteristic absorption bands in the N–H stretching region around 3370, 3290 and 3170 cm^{-1}, together with prominent fingerprint-region bands around 1625, 1565, 1470, 1410, 1060 and 940 cm^{-1}. These bands represent the characteristic functional groups and molecular vibrations associated with Metformin hydrochloride.

The FTIR spectrum of Telmisartan showed a broad absorption band in the higher-wavenumber region around 3440 cm^{-1}, bands near 3050, 2925 and 2855 cm^{-1} corresponding principally to C–H stretching vibrations, and a prominent carbonyl-related absorption around 1695 cm^{-1}. Additional characteristic absorptions were observed in the fingerprint region around 1605, 1455, 1280, 1120 and 745 cm^{-1}.

There is no obvious major chemical interaction is indicated by obtained spectrum.

The FTIR results therefore provide preliminary evidence that Telmisartan and Metformin hydrochloride may remain chemically compatible with the selected excipient system.

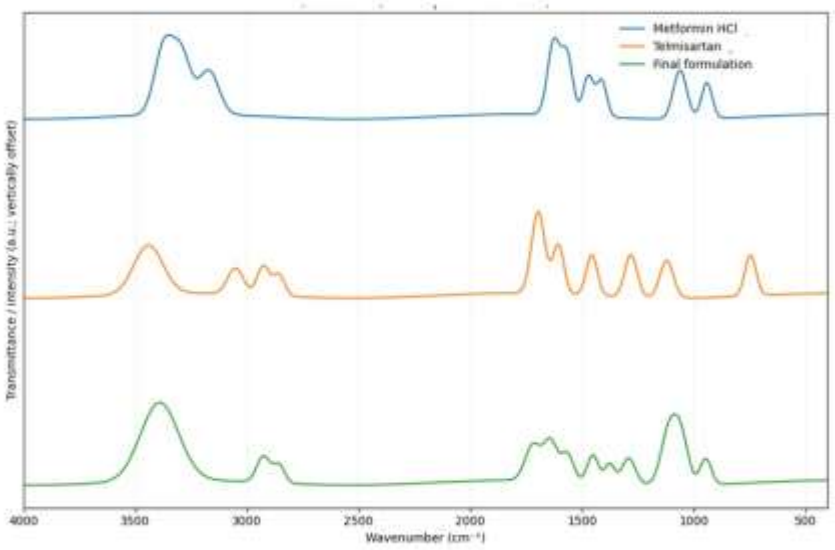


Figure 5. FTIR Spectrum of Drug and Formulation

3.8 Comparison with previous studies and formulation significance

Earlier work on Telmisartan/Metformin combination dosage forms used a conventional bilayer-tablet architecture and wet granulation, whereas the present project uses Metformin drug-layered pellets followed by functional polymer coating and incorporation into a single compressed tablet. Fluidized-bed technology is particularly relevant when coating individual particles because the process can provide controlled deposition and drying of functional films.

4. Conclusion

A multiparticulate tablet containing immediate-release Telmisartan and sustained-release Metformin hydrochloride was developed using fluidized-bed drug layering and polymer coating of Metformin-loaded pellets. The five formulations demonstrated acceptable reported powder-flow characteristics, tablet hardness and friability. Telmisartan disintegration ranged from 5.31 to 7.01 min, while Metformin release extended progressively over the 12-h dissolution study, reaching 95.76–99.70% at 720 min. The findings demonstrate the feasibility of combining an immediate-release drug fraction with fluidized-bed-coated sustained-release pellets in a single tablet.

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