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Design, Formulation and Evaluation of Fixed-Dose Combination of Telmisartan and Metformin Hydrochloride Filled in Hard Gelatin Capsules

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Abstract:

Background: Hypertension and type 2 diabetes mellitus are chronic diseases that frequently coexist, sharing overlapping pathophysiological mechanisms and risk factors. Their simultaneous presence significantly increases cardiovascular complications, necessitating effective combination therapy.

Methods: The present study was undertaken to design, formulate, and evaluate a fixed-dose combination capsule containing immediate-release Telmisartan granules and sustained-release Metformin hydrochloride pellets. Metformin pellets were prepared using suitable release-retarding polymers to achieve controlled drug release, while Telmisartan granules were formulated with appropriate disintegrants and excipients to ensure rapid onset of action. The prepared pellets and granules were evaluated for pre-formulation and post-formulation parameters, including particle size distribution, flow properties, friability, drug content, disintegration, and dissolution. Optimized formulations were filled into hard gelatin capsules using a manual capsule filling method and further assessed for capsule quality parameters such as weight variation, content uniformity, disintegration time, and drug release characteristics.

Results: Both pellets and granules exhibited satisfactory physicochemical properties and complied with pharmacopeial standards. Dissolution studies confirmed sustained drug release of Metformin over an extended period, while Telmisartan demonstrated rapid release consistent with immediate-release requirements. Capsule evaluation parameters, including weight variation and physical integrity, were within acceptable limits, confirming the suitability of the formulation for oral administration.

Conclusion: The developed pellet-granule filled capsule system successfully achieved the intended release characteristics of both drugs. This novel dosage form offers improved patient convenience, reduced pill burden, and enhanced therapeutic efficacy in the simultaneous management of hypertension and type 2 diabetes mellitus.

Keywords: Telmisartan, Metformin hydrochloride, fixed-dose combination, sustained release, immediate release, capsule formulation, hypertension, type 2 diabetes mellitus

1. INTRODUCTION

Hypertension is a chronic medical condition characterized by persistently elevated arterial pressure, clinically defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in adults [1]. It is a major risk factor for cardiovascular diseases such as myocardial infarction, stroke, and renal failure. According to the World Health Organization (WHO), more than 1.28 billion adults worldwide are affected, yet nearly half remain undiagnosed [2]. The asymptomatic nature of hypertension makes regular monitoring essential.

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from insulin resistance and impaired insulin secretion [4]. It is the most common form of diabetes, typically developing in adults but increasingly prevalent among younger populations due to obesity, sedentary lifestyle, and poor dietary habits. Long-term uncontrolled diabetes can lead to complications such as nephropathy, retinopathy, neuropathy, and cardiovascular disease.

Coexistence of hypertension and diabetes is common, with studies indicating that 50-80% of patients with T2DM also suffer from hypertension [7]. This dual burden significantly increases cardiovascular and renal risks. Shared mechanisms include impaired insulin action, vascular stiffness, chronic inflammation, overactivity of the renin-angiotensin-aldosterone system (RAAS), and lifestyle factors such as obesity and physical inactivity. Effective management therefore requires simultaneous control of blood pressure and blood glucose levels.

Telmisartan is an angiotensin II receptor blocker (ARB) widely prescribed for hypertension. It selectively blocks the AT_1 receptor, producing vasodilation and reducing aldosterone secretion. With a long half-life, once-daily dosing, and favorable tolerability, Telmisartan not only lowers blood pressure but also provides cardiometabolic benefits, making it suitable for patients with metabolic disorders [3].

Metformin hydrochloride is a biguanide oral antidiabetic agent and the most widely prescribed drug for T2DM. It reduces hepatic glucose production and enhances peripheral insulin sensitivity without causing significant hypoglycemia. Its advantages include weight neutrality, cardiovascular risk reduction, and long-term safety. Metformin is particularly valuable in combination therapy with Telmisartan, as it complements the cardiovascular protective effects of the ARB while maintaining glycemic control [6].

Capsule dosage form is considered appropriate for combining immediate-release Telmisartan and sustained-release Metformin. Capsules allow incorporation of drugs with distinct release profiles, improve patient compliance, and mask unpleasant taste. Immediate-release Telmisartan granules ensure rapid antihypertensive action, while sustained-release Metformin pellets maintain prolonged glycemic control. Compared to bilayer or conventional tablets, capsules offer greater formulation flexibility, reduced risk of dose dumping, and improved patient acceptability [8-10].

2. MATERIALS AND EQUIPMENT

2.1 Materials

All materials used in the present study were of analytical or pharmaceutical grade and were used without further purification. The active pharmaceutical ingredients and excipients were selected based on their compatibility, functional role in pellet formulation, and suitability for capsule filling. The materials used in the formulation of the fixed-dose combination capsule containing Telmisartan and Metformin Hydrochloride are listed in Table 4.1.

Table 3: Materials

Sr. No.	Material	Category/Function
1	Metformin Hydrochloride	Active pharmaceutical ingredient (Antidiabetic drug)
2	Telmisartan	Active pharmaceutical ingredient (Antihypertensive drug)
3	Sugar Spheres	Pellet core material
4	Hydroxypropyl Methylcellulose (HPMC E5)	Film-forming polymer
5	Polyvinylpyrrolidone (PVP	Binder

	K30)	
6	Crospovidone	Super disintegrant
7	Carbopol	Release-controlling polymer
8	Polyethylene Glycol (PEG 4000)	Plasticizer
9	Ethanol	Solvent
10	Acetone	Solvent
11	Magnesium stearate	Lubricant
12	Sodium carbonate	Solubility enhancer
13	MCC	Disintegrant
14	Lactose	Dissolution enhancer
15	Hard Gelatin Capsule Shell	Capsule filling material

Sugar spheres were used as inert pellet cores for drug layering. HPMC E5 served as a film-forming polymer during coating, while PVP K30 acted as a binder to ensure proper adhesion of drug particles. Crospovidone was incorporated as a super disintegrant to facilitate rapid drug release, whereas Carbopol functioned as a release-modifying polymer to control drug release from the pellets. PEG 4000 was used as a plasticizer to enhance the flexibility of the polymer coating. Ethanol served as a solvent during coating and drug layering processes, and hard gelatin capsules were used for encapsulation of the prepared pellets

Fig 1: Telmisartan, Carbopol, HPMC E5

Fig 2: Metformin hydrochloride, Ethanol, PEG 4000

Fig 3: PVP, Sugar sphere, Lactose

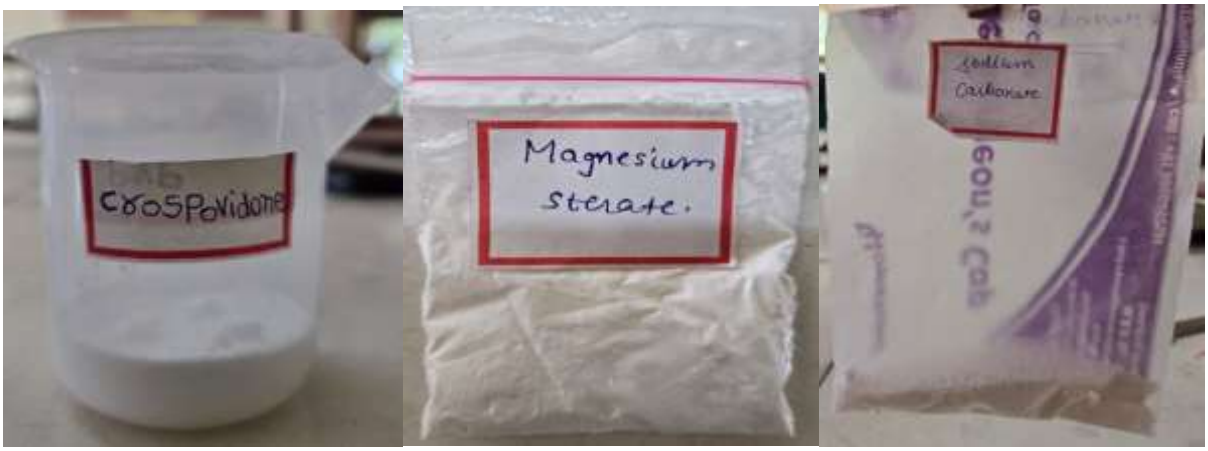


Fig 4: Crospovidone, Magnesium stearate, Sodium carbonate

Fig 5: MCC, Empty capsule shell, Acetone

2.2 Instruments

Various analytical instruments were used for drug analysis and evaluation of the formulated pellets, granules and capsules.

Table 4: Instruments Used in the Study

Sr. No.	Instrument	Application
1	UV-Visible Spectrophotometer	Drug estimation and dissolution analysis
2	Analytical Balance	Accurate weighing of materials
3	Dissolution Test Apparatus (USP Type II)	In-vitro drug release study
4	Vernier Calliper	Measurement of pellet size and capsule dimensions

The **UV-Visible spectrophotometer** was used to determine the absorbance of drug solutions during drug content analysis and dissolution studies. The **analytical balance** ensured precise weighing of drugs and excipients. The **dissolution apparatus** was used to evaluate the in-vitro release profile of the drugs, and the **vernier calliper** was employed to measure capsule dimensions.

2.3 Equipments

Several pieces of laboratory equipment were utilized during the preparation, drying, coating, and filling of pellets and granules.

Table 5: Equipment Used

Sr. No.	Equipment	Function
1	Hot Air Oven	Drying of coated pellets
2	Magnetic Stirrer	Preparation of polymer and drug solutions
3	Pellet Coating Pan	Coating of pellets
4	Capsule Filling Device	Filling pellets into capsule shells
5	Sieve #40, #20, #30	Prepare granules
6	Spatula	For mixing
7	Butter paper	For weighing

2.4 Glasswares

Standard laboratory glassware was used throughout the experimental work for preparation of solutions and analytical procedures.

Beaker, Conical flask, Measuring cylinder, Volumetric flask, Glass funnel, Glass rod, Mortal pestle, Test tube, Dropper

2.5 Role of materials

Table 8: Role of material

Material	Role	Reference
Metformin Hydrochloride	Active Pharmaceutical Ingredient (API) Widely reported as a first-line antihyperglycemic agent with high aqueous solubility, suitable for immediate and modified release systems	Wen et al., 2019
Telmisartan	Active Pharmaceutical Ingredient (API) Poorly water-soluble angiotensin II receptor blocker; requires formulation strategies to enhance dissolution and bioavailability	Wen et al., 2019
Sugar Spheres	Inert core for pellets Reported to provide spherical shape, smooth surface, and uniform size distribution, facilitating efficient drug layering	Ghebre-Sellassie, 1989
Hydroxypropyl Methylcellulose (HPMC E5)	Film-forming polymer Hydrophilic polymer forming a gel layer upon hydration, enabling uniform coating and controlled drug release	Colombo et al., 2000
Polyvinylpyrrolidone (PVP K30)	Binder Enhances adhesion of drug particles and improves mechanical strength of pellets during layering	Rowe et al., Handbook of Pharmaceutical Excipients
Crospovidone	Super disintegrant Exhibits high capillary activity and rapid water uptake, promoting fast disintegration and drug release	Desai et al., 2016
Carbopol	Release-controlling polymer High swelling capacity and gel-forming ability help in sustaining drug release from dosage forms	Patil et al., 2014
Polyethylene Glycol (PEG 4000)	Plasticizer Improves flexibility of polymer coatings and prevents film cracking during processing	Aulton & Taylor, Pharmaceutics
Ethanol	Solvent Volatile solvent widely used for drug layering due to rapid evaporation and uniform distribution	Remington, Pharmaceutical Sciences
Magnesium stearate	Lubricant Volatile solvent widely used for drug layering due to rapid evaporation and uniform distribution	Aulton's pharmaceutics
Sodium carbonate	Alkalizing agent Enhances solubility of poorly soluble drugs(like telmisartan) by increasing pH and improving dissolution rate	Remington, Pharmaceutical Sciences
MCC	Diluent Provides bulk to formulation and improves compressibility and flow properties of granules/pellets	Aulton's and Taylor
Lactose	Diluent Widely used filler that enhances powder flow and content uniformity	Remington, Pharmaceutical Sciences
Acetone	Solvent Organic solvent used for granulation or coating dur to its rapid evaporation and compatibility with polymer	Aulton's pharmaceutics
Hard Gelatin	Dosage form	Aulton & Taylor

Capsule Shell	Used for encapsulation of pellets, ensuring dose uniformity and improved patient compliance	

3. Methodology

3.1 Pre-formulation studies:

Pre-formulation studies are an important part of the development of any pharmaceutical dosage form. They involve the evaluation of it is characterized by examination of physicochemical charecteristics of the drug material in relation to excipients. In the present work, pre-formulation studies of both metformin and telmisartan were used for the development of a capsule formulation containing sustained release pellets of metformin and immediate release granules of telmisartan.

3.1.1 Organoleptic properties

The physical characteristics of metformin HCL and telmisartan including its appearance, colour and odour, were assessed though visual inspection

3.1.2 Melting point

Aim: to determine the melting point of the drug

Procedure: a small quantity of drug was placed in a capillary tube and heated in a melting point apparatus. The temperature at which the drug melted was recorded

3.1.3 Particle size analysis

Aim: to determine the particle size of metformin hydrochloride and telmisartan method: sieve analysis method

Procedure: the sample was taken and placed on a set of standard sieves (#16, #20, #30, #40)arranged in descending order of mesh size. The sieves were shaken manually for 10 minutes. After shaking, the amount of sample retained on each sieve was collected separately and evaluated.
Significance: uniform particle size distribution improves flow properties, ensures uniform drug distribution, and contributes to consistent drug release.it is especially important.

3.1.4 LOD (loss on drying)

Aim: to determine the moisture content
Procedure: 2 gm of sample weighed and dried in hot air oven weight loss was recorded.

$$\text{Calculation: \%LOD} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

3.1.5 Solubility study

Aim: to determine the solubility and telmisartan in different solvents

Procedure: an excess amount of drug was added to different solvents such as water, 0.1N HCL, 6.8 PH phosphate buffer solution, and organic solvent(acetone). The solutions were shaken and allowed to equilibrate. The solubility was observed visually.

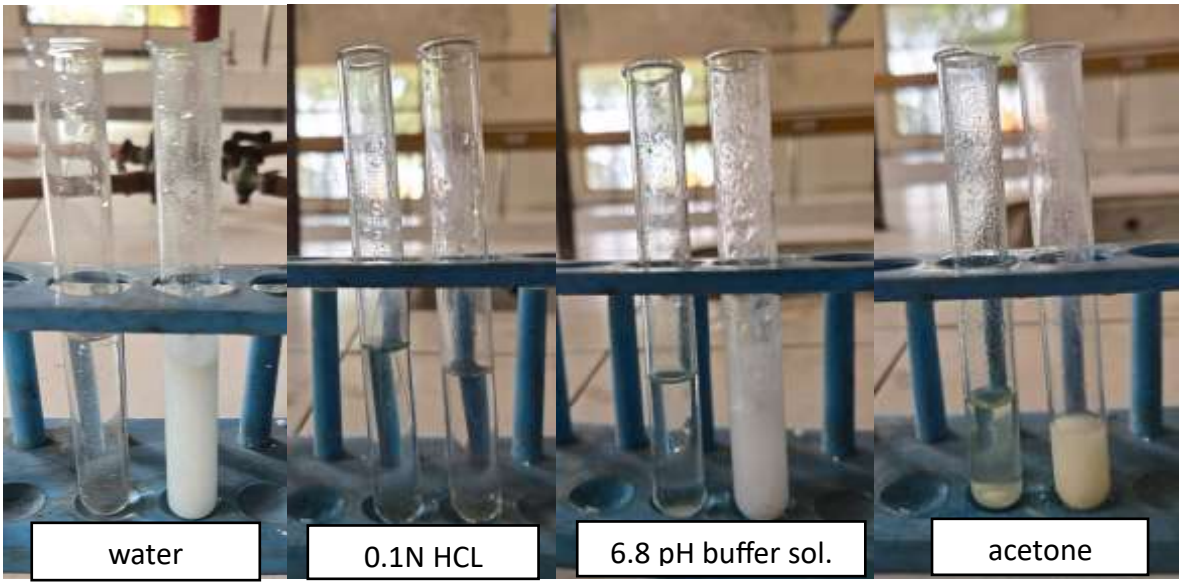


Fig 6: Test tube I: Metformin, Test tube II: Telmisartan

4. Flow properties

4.1 Bulk density

Bulk density was determined by placing a known quantity of pellets into a graduated cylinder and measuring the bulk volume.

$$\text{Formula: Db} = \frac{W}{Vb}$$

Where:

W = Weight of pellets

Vb = Bulk volume

4.2 Tapped Density

Tapped density was determined by USP method II. Pellets were filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum

Formula: $Dt = \frac{\mathrm{W}}{\mathrm{Vt}}$

W= weight of pellets taken

Vt= tapped volume

4.3 Compressibility Index (Carr's Index)

Calculated by following equation

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

4.4 Hausner's Ratio

Calculated by following equation

$$\text{Hausnerr's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

4.5 Angle of repose

It was determined by using funnel method. Pellets were poured funnel, that can be raised vertically until a maximum cone height(H) was obtained diameter heap D was measured. The angle of repose ϕ was calculated by formula

$$\phi = \tan - 1\frac{h}{r}$$

Where, h=height of tip of funnel from horizontal ground surface and r = the radius of base of conical pile.

4.6 Drug assay (purity determination)

Method: UV Spectrophotometric method

Fig 7: UV-Visible spectrophotometer

Procedure:

1. Preparation of stock solution: accurately weighed 100 mg of metformin hydrochloride was transferred into a 100 ml volumetric flask.it was dissolved and the volume was made up to 100 ml using distilled water to obtain a stock solution of 1000 µg/ml.

2. Preparation of working standard solution: from the stock solution, 10 ml was pipetted out and transferred into a 100 ml volumetric flask. The volume was made up to 100 ml with distilled water to obtain a solution of 100 µg/ml.

3. Preparation of calibration solutions: from the working standard solutions different dilutions were prepared (1ml, 2 ml, 3 ml, 4 ml, 5 ml) diluted up to 10 ml to obtain concentrations of 10, 20, 30, 40, 50 µg/ml respectively.

4. Determination of ʎmax: the prepared solution was scanned in the UV range of 200-400 nm, and the maximum absorbance was obtained at 233 nm.

5. Measurement of absorbance: the absorbance of prepared solutions was measured at 233 nm using distilled water as blank.

Calculation:

Drug concentration ∝ absorbance

$$\text{Percentage purity} = \frac{actual\ concentration}{\text{theortical concentration}} \times 100\ \%$$

5. Formulation design/ composition table

5.1.1 Flow chart for preparation of metformin SR pellets

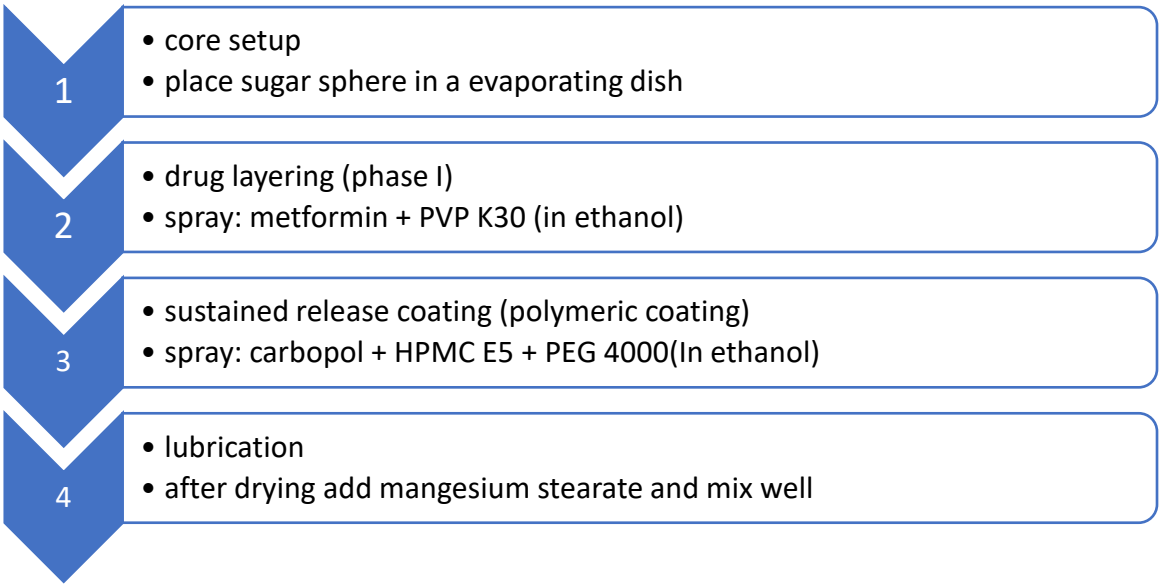


Fig 8: Flow chart for preparation of metformin SR pellets

Table 9: Formulation Table of Metformin hydrochloride sustained release pellets

Material	F1	F2	F3	F4	F5
Metformin	500	500	500	500	500
Sugar sphere	30	30	30	30	30
Carbopol	40	36	30	24	18
PVP K30	32	26	20	14	10
HPMC E5	18	18	18	18	18
PEG	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	2	2	2	2	2
Ethanol	q.s	q.s	q.s	q.s	q.s
Total	600 mg				

5.2.2 Preparation of metformin sustained release pellets

The sustained release pellets containing metformin hydrochloride were prepared by manual spray-layering technique. First, 30 mg of sugar spheres were introduced into an evaporating dish. A coating solution was prepared by dissolving 500 mg of metformin hydrochloride powder with binder PVP K30, in an ethanolic medium. Ethanol was selected for its high volatility, which facilitates rapid drying during the layering process

Step: 1 Drug-binder layering

Using a manual micro-sprayer, the drug-binder solution was incrementally applied to the sugar spheres. During this process, the evaporating dish was subjected to continuous manual rotation and ensure that the drug was uniformly layered around each core and to prevent the formation of aggregates. Once the entire drug-binder solution applied, the drug-loaded pellets were dried in a hot air oven(50-60 ˚C) until a constant weight was achieved.

Fig 9: Drug-polymer binding of pellets

Step: 2 Polymer coating

A polymeric solution of Carbopol and HPMC E5, PEG 4000 was prepared using ethanol as a solvent. This polymeric solution was manually sprayed onto the drug-layered pellets, this step create the sustained-release barrier. The pellets were dried in a hot air oven (50-60 ˚C) until a constant weight was achieved.

Step: 3 Finishing and lubrication

Once both coating layers were completed, the double-coated pellets were transferred to the hot air oven for a final, extended drying period.

Fig 10: Metformin hydrochloride pellets formulation

5.2.3 Flow chart for preparation of telmisartan IR granules

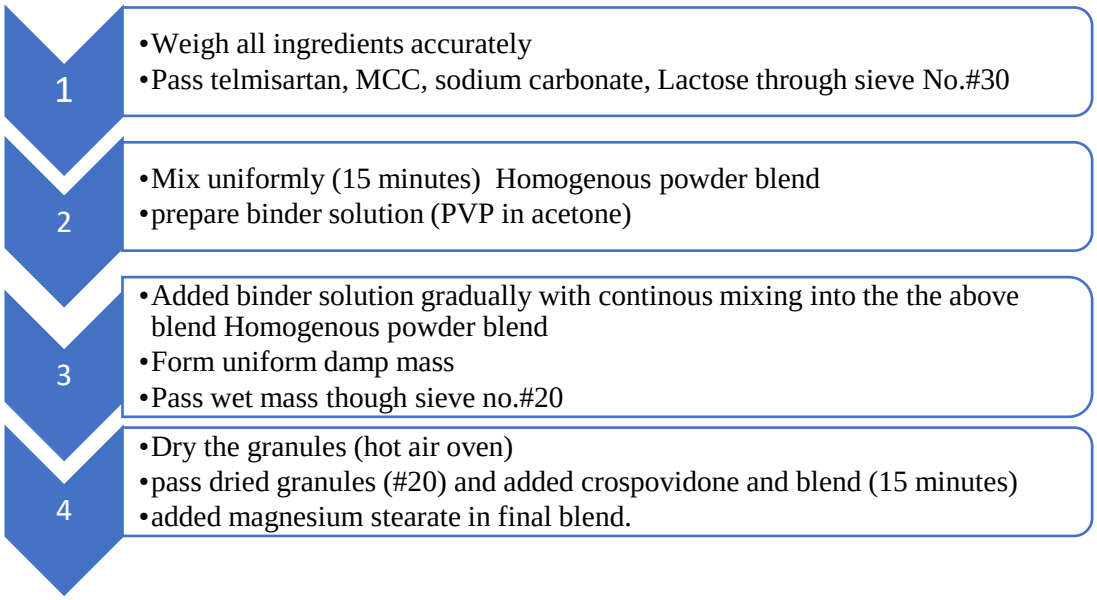


Fig 11: Flow chart for preparation of telmisartan IR granules

Table 10: formulation table of telmisartan immediate release granules

Material	T1	T2	T3	T4	T5
Telmisartan	40	40	40	40	40
Sodium carbonate	10	15	20	25	30
Crospovidone	10	10	10	10	10
MCC	35	30	25	20	15
lactose	20	20	20	20	20
Magnesium stearate	5	5	5	5	5
Acetone	q.s	q.s	q.s	q.s	q.s
Total	120 mg				

5.2.3 Preparation of Telmisartan Immediate Release Granules

1. All ingredients were accurately weighed according to the formulation table. Telmisartan, sodium carbonate, microcrystalline cellulose (MCC), and lactose were passed through sieve No. 30 and blended uniformly in a polyethylene bag for about 15 minutes to obtain a homogeneous powder mixture.
2. A binder solution of polyvinylpyrrolidone (PVP) was prepared using acetone as solvent and added gradually to the powder mixture with continuous mixing until a uniform damp mass was formed. The wet mass was then allowed to air dry, and the dried material was passed through sieve No. 20 to obtain uniform granules.
3. Crospovidone was passed through sieve No. 30 and mixed with the prepared granules for 15 minutes, followed by the addition of magnesium stearate passed through sieve No. 40 and blended for 2 minutes to complete the formulation. The same procedure was followed for formulations T2 to T5, with variation only in the quantities of sodium carbonate and MCC as specified in the formulation table.

Fig 12: Telmisartan immediate release granules

5.2.4 Capsule filling method

Hard gelatin capsules of size 00 were selected based on the total fill weight and flow properties of the prepared Metformin pellets and Telmisartan granules. Prior to filling, the capsules were visually inspected to ensure absence of any physical defects. The capsule shells were manually separated into cap and body portions.

An accurately weighed quantity of 600 mg of Metformin pellets and 120 mg of Telmisartan granules was filled into the capsule body manually using a spatula. The filling process was carried out carefully to ensure uniform distribution of both the sustained-release pellets and immediate-release granules within the capsule. Gentle tapping of the capsule body was performed to facilitate proper settling of the fill material and to achieve uniform packing.

After filling, the capsule caps were placed over the bodies and pressed firmly to ensure proper locking. A total of 10 capsules were prepared using this manual filling method. The filled capsules were then evaluated for weight variation to ensure uniformity of fill.

5.3 factorial design

5.3.1 Telmisartan

A 2^2 full factorial design was employed with two independent variables: sodium carbonate and crospovidone. The dependent variables were % drug release at 8 or 12 hours (Y1) and dissolution efficiency (Y2). Nine experimental batches were prepared, representing all possible combinations of factor levels.

Table 11: Layout of factorial Design of Telmisartan IR granules

Batch	X1(Sodium carbonate)	X2 (crospovidone)	Coded Level
F1	-1	-1	Low-Low
F2	-1	+1	Low-High
F3	+1	-1	High-Low
F4	+1	+1	High-High
F5	0	0	Centre

Formulation composition of 2^2 full factorial batches:

Table 12: Independent Variable (Telmisartan IR granules)

Factor	Variable	Level
X1	Sodium carbonate	-1,0,+1
X2	Crospovidone	-1,0,+1

Dependent Variable:

Table 13: Dependent Variable (Telmisartan IR granules)

Response	Variable
Y1	% drug release
Y2	Disintegration time

Table 14: Formulation composition of 2^2 full factorial batches (Telmisartan IR granules)

Material	F1	F2	F3	F4	F5
TELMISARTAN	40	40	40	40	40
SODIUM CARBONATE	10	10	20	20	15
CROSPOVIDONE	5	10	5	10	7.5
MCC	40	35	30	25	32.5
LACTOSE	20	20	20	20	20
MAGNESIUM STEARATE	5	5	5	5	5

5.3.2 Metformin

A 2^2 full factorial design was employed with two independent variables: Carbopol (15, 20, 25%) and PVP K30 (10, 15, 20%). The dependent variables were % drug release at 8 or 12 hours (Y1) and dissolution efficiency (Y2). Nine experimental batches were prepared, representing all possible combinations of factor levels.

Table 15: Layout of Factorial Design of Metformin hydrochloride SR pellets

Batch	X1(Carbopol)	X2(PVP K30)	Coded Level
F1	-1	-1	Low-Low
F2	-1	+1	Low-High
F3	+1	-1	High-Low
F4	+1	+1	High-High
F5	0	0	Centre

Formulation composition of 2^2 full factorial batches:

Table 16: Independent Variable (Metformin hydrochloride SR pellets)

Factor	Variable	Levels
X1	Carbopol	-1,0,+1

X2	PVP K30	-1,0,+1

Dependent Variable:

Table 17: Dependent Variable (Metformin hydrochloride SR pellets)

Response	Variable
Y1	% drug release at 8 or 12 hours
Y2	Dissolution efficiency

Table 18: Formulation composition of 2^2 full factorial batches (Metformin hydrochloride SR pellets)

Material	F1	F2	F3	F4	F5
Metformin	500	500	500	500	500
Sugar sphere	30	30	30	30	30
Carbopol	15	15	25	25	20
PVP K30	10	20	10	20	15
HPMC E5	25	25	25	25	25
Magnesium stearate	5	5	5	5	5
PEG 4000	15	5	5	0	5

6.1 Evaluation of Metformin pellets and Telmisartan granules

6.1.1 Particle size and size distribution

The particle size distribution of prepared metformin pellets was determined by sieve analysis using a mechanical sieve shaker. The pellets were passed through a series of standard sieves arranged in descending order.

The pellets were found to predominantly pass through #40 sieve, indicating uniform pellet size suitable for capsule filling and ensuring consistent drug release.

6.1.2 Bulk Density

Bulk density was determined by placing a known quantity of pellets into a graduated cylinder and measuring the bulk volume.

Formula: $Db=\frac{W}{Vb}$

Where:

W = Weight of pellets

Vo = Bulk volume

6.1.3 Tapped Density

Tapped density was determined by USP method II. Pellets were filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum

Formula: $Dt = \frac{\mathrm{W}}{\mathrm{Vt}}$

W= weight of pellets taken
Vt= tapped volume

6.1.4 Compressibility Index (Carr's Index)

Calculated by following equation

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

6.1.5 Hausner's Ratio

Calculated by following equation

$$\text{Hausnerr's ratio} = \frac{\text{bulk density}}{\text{tapped density}}$$

6.1.6 Angle of repose

It was determined by using funnel method. Pellets were poured funnel, that can be raised vertically until a maximum cone height(H) was obtained diameter heap D was measured. The angle of repose ϕ was calculated by formula

$$\phi = \tan - 1\frac{h}{r}$$

Where, h=height of tip of funnel from horizontal ground surface and r = the radius of base of conical pile.

6.1.7 Friability

Metformin Pellets were subjected to Friabilator and percentage weight loss was calculated

6.1.8 Drug content

A. Drug Content Analysis of metformin hydrochloride sustained release pellets by UV Spectrophotometry

An accurately weighed quantity of metformin hydrochloride sustained release pellets equivalent to 100 mg of metformin hydrochloride from each batch (F1-F5) was transferred into separate 100 mL volumetric flasks. About 70 mL of phosphate buffer (pH 6.8) was added and the mixtures were shaken thoroughly to dissolve the drug.

The solutions were sonicated for 10-15 minutes to ensure complete extraction of the drug from the polymer matrix containing Carbopol, PVP K30, and HPMC E5. The volume was then made up to 100 mL with the same buffer and filtered through Whatman filter paper No. 41.

From each filtrate, 1 mL of solution was pipetted into a 10 mL volumetric flask and diluted to volume with phosphate buffer (pH 6.8). The absorbance of each solution was measured using a UV spectrophotometer at 233 nm, and drug content was calculated using the calibration curve of metformin hydrochloride.

B. Drug Content Analysis of Telmisartan Immediate Release Granules by UV Spectrophotometry

An accurately weighed quantity of telmisartan immediate release granules from each batch (T1-T5), equivalent to 100 mg of telmisartan, was transferred into separate 100 mL volumetric flasks. About 70 mL of phosphate buffer (pH 7.5) was added, and the mixtures were shaken thoroughly to dissolve the drug.

The solutions were sonicated for 10-15 minutes to ensure complete dissolution of telmisartan from the granules. The volume was then made up to 100 mL with the same buffer and filtered through Whatman filter paper No. 41.

From each filtrate, 1 mL of solution was diluted to 10 mL with phosphate buffer (pH 7.5). The absorbance was measured using a UV spectrophotometer at 296 nm against phosphate buffer as blank. The drug content was calculated using the calibration curve of telmisartan.

6.1.9 disintegration test

Fig 13: Disintegration test apparatus

The disintegration test for telmisartan immediate release granules of batches T1 to T5 was performed using a disintegration test apparatus. Distilled water was used as the disintegration medium and maintained at a temperature of 37 ± 0.5 °C throughout the test.

An accurately weighed quantity of granules equivalent to one dose (120 mg) from each batch was placed in the disintegration test apparatus basket. The apparatus was operated, and the time required for the complete disintegration of granules, with no visible residue remaining on the mesh screen except fragments of insoluble excipients, was recorded.

The test was carried out for all batches under identical conditions, and the average disintegration time was calculated and reported in minutes.

Table 19: Disintegration test parameters

Parameter	Specification
Apparatus	Disintegration test apparatus
Medium	Distilled water
Temperature	37 ± 0.5 °C
Sample quantity	Granules equivalent to 120 mg
Endpoint	Complete disintegration of granules
Units	Minutes

6.1.10 dissolution study

Fig 14: dissolution test apparatus

Dissolution testing was carried out using USP apparatus II (paddle method) at 50 RPM and 37 ± 0.5 ˚C.
The dissolution medium used was:

- 0.1N HCL For first 2 hours
- pH 6.8 phosphate buffer for further study

samples were withdrawn at predetermined time intervals, filtered, an analysed using UV spectrophotometer.

6.1.11 content uniformity

Individual samples were analysed separately for drug content. The percentage of drug present in each sample was calculated and compared with the label claim.

6.1.12 loss on drying (LOD)

A known quantity of granules was weighted and dried in a hot air oven at 105 ˚C until constant weight was obtained. The percentage loss in weight was calculated

$$\text{LOD } \% = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

6.2 Evaluation of capsules

6.2.1 Appearance

Capsules were visually inspected for colour, size, shape, and physical defects such as cracks and improper locking

6.2.2 Weight variation test

10 capsules were selected randomly and weighted individually. The average weight was calculated, and individual weights were compared with the average.

Calculation

$$\% \text{ deviation} = \frac{\text{individual weight} - \text{average weight}}{\text{average weight}} \times 100$$

6.2.3 Content uniformity

Each capsule was opened and contents were transferred into a 100 ml volumetric flask dissolved in a mixture of methanol and phosphate buffer pH 6.8. the solution was sonicated to ensure complete dissolution, filtered through Whatman filter paper to remove any undissolved particles. From this stock solution 1 ml was pipetted into a 10 ml volumetric flask, and the volume was made up to the mark with methanol to obtain a diluted solution. The absorbance of the resulting solution was measured using a UV spectrophotometer at 233 nm for metformin and 296 nm for telmisartan. the amount of drug present n each capsule was calculated using the calibration curve.

6.2.4 Disintegration test

The disintegration test was carried out using a USP disintegration test apparatus. Six capsules were placed individually in each tube of the apparatus. A disc was placed over each capsule to prevent floating. The apparatus was operated using distilled water as the medium, maintained at a temperature of 37 ± 0.5 ˚C. the basket was allowed to move up and down at a constant frequency as pharmacopeial specifications. The time required for complete disintegration of the capsule shell was observed and recorded.
The behaviour of the contents was also noted:

- disintegration of telmisartan immediate release granules
- integrity of metformin sustained release pellets

6.2.5 Dissolution study

The dissolution study was carried out using USP Apparatus II (paddle method)

The dissolution medium consists of:

0.1 N HCL (900 ml) for the first 2 hours to stimulate gastric conditions followed by pH 6.8 phosphate buffer(900 ml) to stimulate intestinal conditions of the temperature of the medium was maintained at 37 ± 0.5 ˚C , and the paddle rotation speed was set at 50 rpm. One capsule was placed in each dissolution vessel. At predetermined time interval(0.5, 1,2,4,6,8 and 12 hours). 5 ml of sample was withdrawn using the pipette. After each withdrawal, and equal volume(5ml) of fresh dissolution medium was added to maintain sink conditions and constant volume. The withdrawn sample were filtered through Whatman filter paper. From the filter solution, 1ml was diluted to 10ml with the respective dissolution medium. The absorbance of the sample was measured using a UV spectrophotometer at: 233 nm for metformin, 296 nm for telmisartan. The percentage drug release at each time was calculated using the calibration curve.

Table 20: Dissolution test parameter

Parameter	Metformin	Telmisartan
Apparatus	USP II (Paddle)	USP II (Paddle)
Dissolution medium	0.1 N HCl (0-2 h), pH 6.8 buffer (2-12 h)	0.1 N HCl (0-2 h), pH 6.8 buffer (2-12 h)
Volume	900 mL	900 mL
Temperature	37 ± 0.5 °C	37 ± 0.5 °C
Rotation speed	50 rpm	50 rpm
Sampling intervals	0.5, 1, 2, 4, 6, 8, 10, 12 h	0.5, 1, 2, 4, 6, 8, 10, 12 h
Sample volume withdrawn	5 mL	5 mL
Replacement volume	5 mL fresh medium	5 mL fresh medium
Detection wavelength	233 nm	296 nm
Dosage equivalent	500 mg Metformin	40 mg Telmisartan

6.2.6 Drug content

An accurately weighted quantity of capsule content equivalent to the labelled dose was transferred into a 100 ml volumetric flask. About 60 ml of methanol was added, and the solution was sonicated for 15 minutes to ensure complete dissolution of both metformin and telmisartan. The volume was then made up

to 100 ml with methanol. The solution was filtered through Whatman filter paper to remove any undissolved particles. From the stock solution, 1ml was pipetted into a 10ml volumetric flask, and the volume was made up to the mark with methanol. The absorbance of the resulting solution was measured using a UV spectrophotometer at 233nm for metformin and 296 nm for telmisartan. The concentration of each drug was determined using the respective calibration curves, and the percentage drug content was calculated.

7 Result and Discussion

7.1 Pre-formulation studies

7.1.1 Organoleptic properties

A. Metformin

Table 21: Result of organoleptic properties of Metformin HCL

Colour	White
State	Crystalline
Odor	Odourless
Taste	Intense bitter

B. Telmisartan

Table 22: Result of organoleptic properties of Telmisartan

Colour	White to slightly yellowish,
State	Crystalline
Odor	Odourless
Taste	bitter

Discussion

The observed organoleptic properties confirmed the identity and purity of the drugs and indicated their suitability for formulation development.

7.1.2 Melting point

Table 23: Result of melting point determination of metformin HCL and telmisartan

Drug	Melting point
Metformin hydrochloride	223-226 ˚C
Telmisartan	261-263 ˚C

Discussion

The melting points were within the reported pharmacopoeial range and indicated the purity of both drugs.

7.1.3 Solubility studies

Table 24: result of solubility study of Active Pharmaceutical ingredient

Solvent	Metformin	Telmisartan
Distilled 0.Water	Freely soluble	Insoluble
0.1N HCL	Freely soluble	Slightly soluble
6.8 pH phosphate buffer	Soluble	Poorly soluble
Acetone	Insoluble	Soluble(clear/yellowish solution)

Discussion

The solubility results indicated that metformin hydrochloride was hydrophilic, whereas telmisartan was poorly water-soluble.

7.1.4 Flow properties

Table 25: flow properties of Active Pharmaceutical ingredient

Drug	Weight	Bulk	Bulk	Tapped	Tapped	Carr's	Hausner

	(g)	volume	density	volume	density	index	ratio
Metformin	5	8.9	0.561	7.7	0.649	13.55	1.15
Telmisartan	5	10.3	0.485	9.1	0.549	11.65	1.13

Discussion

These values indicated good flow properties and acceptable compressibility of the powders.

7.1.5. Angle of repose

Table 26: angle of repose Active Pharmaceutical ingredient

Drug	Height	Radius	Angle of repose	Flow property
Metformin	2	4.24	25.3	Excellent
Telmisartan	2	4.27	25.1	Excellent

Discussion

The values indicated excellent flow properties of both drug powders.

7.1.6 particle size analysis

Total weight = 10 gm

Table 27: particle size distribution of Active Pharmaceutical ingredient

Metformin				Telmisartan		
Sieve No.	Weight retained (g)	% retained	Cumulative % retained	Weight retained (g)	% retained	Cumulative % retained
#10	0.58	5.8%	5.8%	0.39	3.9%	3.9%
#22	1.21	12.1%	17.9%	0.91	9.1%	13%
#44	2.74	27.4%	45.3%	2.61	26.1%	39.1%
#60	2.19	21.9%	67.2%	2.43	24.3%	63.4%
#85	1.46	14.6%	81.8%	1.89	18.9%	82.3%
Pan	1.11	11.1%	92.9%	1.24	12.4%	94.7%

Discussion

The low moisture content indicated adequate drying and stability of the drugs.

7.1.7 LOD (loss on drying)

Table 28: loss on drying of Active Pharmaceutical ingredient

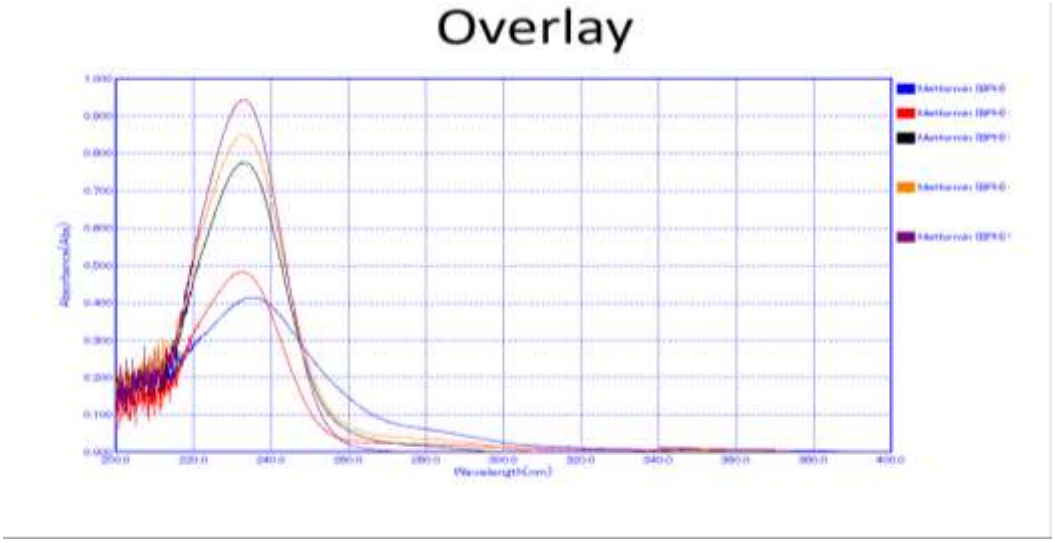
Drug	W1	W2	W3	Initial weight (g)	Loss in weight (g)	LOD (%)
Telmisartan	42.750	43.745	43.732	0.995	0.013	1.31%
Metformin	41.250	43.275	43.263	2.025	0.012	0.59%

Discussion

The low moisture content indicated adequate drying and stability of the drugs.

7.1.8 Drug assay

A. Metformin



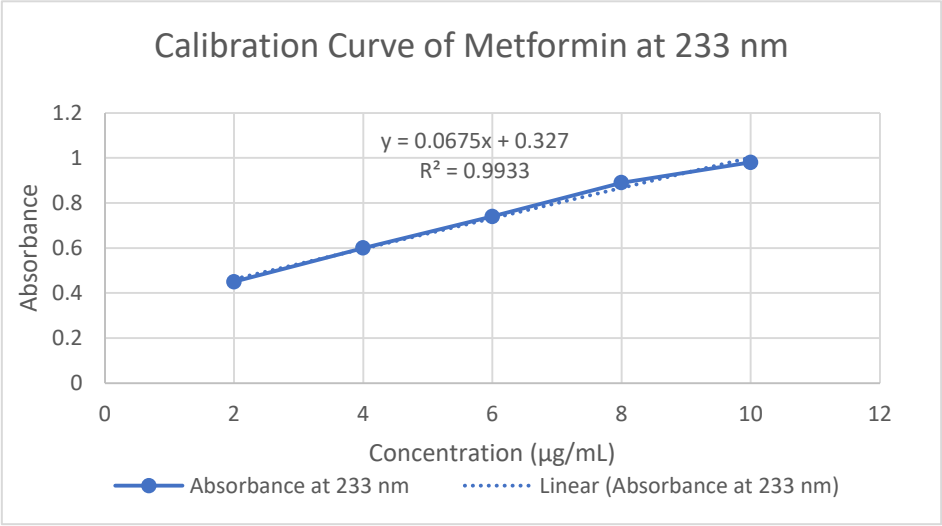


Table 29: assay result of metformin HCL by UV spectrophotopmeter

Parameter	Observation
Wavelength (λmax)	233 nm
Absorbance of sample	0.748
Concentration obtained from calibration curve	9.99 µg/mL
Standard concentration	10 µg/mL
% Purity of drug	99.2 %

Calculation

Standard concentration = 10 µg/mL

Sample concentration = 9.92 µg/mL

% Drug Purity = (Sample concentration / Standard concentration) × 100

= (9.92 / 10) × 100

= 99.2 %

Result

The purity of metformin was determined by UV spectrophotometric method at 233 nm using phosphate buffer as solvent. The absorbance of the prepared sample solution was measured and compared with the standard calibration curve. The obtained results indicated that the metformin sample complied with acceptable purity limits.

Discussion

The purity of metformin was found to be 99.2 %, which is within the acceptable pharmacopeial limit of 98-102 % for active pharmaceutical ingredients. The result confirms that the metformin sample used in the study possessed adequate purity and was suitable for further formulation development. Minor variation from the theoretical value may be due to instrumental sensitivity, weighing accuracy, and sample preparation during analysis.

7.2 Evaluation of metformin pellets and telmisartan granules

7.2.1. Particle Size and Size Distribution

7.2.1.1 Particle Size and Size Distribution of Telmisartan Immediate Release

Granules

Sample weight: 10 g

Table 30: particle size distribution of telmisartan IR granules

Sieve No.	Aperture Size (µm)	Weight Retained (g)	% Retained	Cumulative % Retained
20	850	0.35	3.5	3.5
30	600	2.05	20.5	24.0
40	425	3.90	39.0	63.0
60	250	2.45	24.5	87.5
Pan	<250	1.10	11.0	98.5

Total weight recovered: 9.85 g

Loss during handling: 0.15 g (1.5%)

Discussion

The results indicated that the prepared telmisartan granules possessed uniform particle size distribution suitable for immediate release formulation. The small amount of fines observed in the pan was expected in manual granulation processes. Uniform granule size is important for ensuring consistent drug release and good flow properties during capsule filling.

7.2.1.2 Particle Size and Size Distribution of Metformin Sustained Release Pellets

Sample weight: 10 g

Table 31: particle size distribution of metformin SR pellets

Sieve No.	Aperture Size (µm)	Weight Retained (g)	% Retained	Cumulative % Retained
16	1180	0.28	2.8	2.8
20	850	1.75	17.5	20.3
25	710	4.35	43.5	63.8
30	600	2.30	23.0	86.8
Pan	<600	1.05	10.5	97.3

Total weight recovered: 9.73 g

Loss during handling: 0.27 g (2.7%)

Discussion

The results suggested that the prepared metformin pellets had uniform size distribution suitable for sustained release formulation. Minor loss of material during sieving was considered acceptable and commonly occurs during manual processing. Uniform pellet size is essential for maintaining controlled drug release and consistent product quality.

7.2.2 Flow properties

Table 32: Flow Properties of Metformin hydrochloride sustained release pellets (F1-F5)

Batch	Weight (g)	Bulk Volume (mL)	Bulk Density (g/mL)	Tapped Volume (mL)	Tapped Density (g/mL)	Carr's index	Hausner's ratio
F1	10.02	18.6	0.54	15.7	0.64	15.6	1.19
F2	9.98	18.3	0.55	15.5	0.64	14.8	1.17
F3	10.05	18.9	0.53	15.8	0.64	17.2	1.21
F4	9.96	18.4	0.54	15.6	0.64	16.0	1.19
F5	10.01	18.7	0.54	15.9	0.63	14.3	1.17

Table 33: Flow Properties of telmisartan immediate release granules (F1-F5)

Batch	Weight Taken (g)	Bulk Volume (mL)	Tapped Volume (mL)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio
T1	10.02	17.3	14.5	0.58	0.69	15.94	1.19
T2	9.97	17.0	14.2	0.59	0.70	15.71	1.19
T3	10.04	17.8	15.0	0.56	0.67	16.42	1.20
T4	9.99	17.5	14.7	0.57	0.68	16.18	1.19
T5	10.01	18.1	15.3	0.55	0.65	15.38	1.18

Discussion

The obtained values indicated good flow properties of both pellets and granules as per pharmacopoiel standards. Good flowability is essential for uniform mixing and accurate capsule filling. Therefore, the prepared formulations were considered suitable for further processing and packaging.

7.2.3 Angle of repose

A. Telmisartan granules

Table 34: angle of repose of telmisartan IR granules

Batch	Height	Radius	Angle of repose	Flow property
T1	2	3.71	28.3	Good
T2	2	3.77	27.9	Good
T3	2	3.55	29.4	Good
T4	2	4.06	26.3	Good
T5	2	3.80	27.7	Good

B. Metformin hydrochloride pellets

Table 35: angle of repose of metformin SR pellets

Batch	Height	Radius	Angle of repose	Flow property
F1	2	3.58	29.2˚	Good
F2	2	3.84	27.5 ˚	Excellent
F3	2	3.10	32.8 ˚	Good
F4	2	3.81	27.7 ˚	Good
F5	2	3.41	30.3 ˚	Poor

Discussion

The results indicated acceptable flow properties of both granules and pellets. Slight variation in angle of repose among batches may have been due to differences in particle size and surface characteristics. Overall, the prepared formulations showed satisfactory flow behaviour suitable for capsule filling.

7.2.4 Friability

Metformin pellets

Table 36: friability of metformin SR pellets

Batch	Initial weight	Final weight	Friability (%)	Result
F1	5	4.93	1.4	Acceptable
F2	5	4.96	0.8	Excellent

F3	5	4.90	2.0	Fair
F4	5	4.94	1.2	Acceptable
F5	5	4.96	0.8	Excellent

Discussion

The results indicated that the prepared pellets possessed adequate mechanical strength to withstand handling and transportation. Friability values below 1% were considered excellent, while values up to 2% were acceptable for pellets prepared by manual methods. Therefore, the pellets were considered physically stable.

7.2.5 Drug content

A. Drug content of metformin hydrochloride sustained release pellets

Table 37: drug content of metformin SR pellets

Batch	Label Claim (mg)	Absorbance at 233 nm	Amount of Drug Found (mg)	Drug Content (%)
F1	500	0.701	468.5	93.70
F2	**500**	**0.742**	**495.2**	**99.04**
F3	500	0.736	491.6	98.32
F4	500	0.724	483.8	96.76
F5	500	0.716	478.4	95.68

B. Drug content of telmisartan IR granules

Table 38: drug content of telmisartan IR granules

Batch	Label Claim (mg)	Absorbance at 296 nm	Amount of Drug Found (mg)	Drug Content (%)
T1	40	0.594	38.52	96.30
T2	40	0.607	39.34	98.35
T3	40	0.618	39.96	99.90
T4	40	0.611	39.58	98.95
T5	40	0.586	38.06	95.15

Discussion

The results showed that the drug content of all batches was within acceptable pharmacopoeial limits, indicating uniform distribution of drug in the formulations. Uniform drug content is essential for consistent therapeutic effect and patient safety. Therefore, the formulation process was considered reliable and reproducible.

7.2.6 Disintegration

Table 39: Telmisartan IR granules disintegration time

Batch	Disintegration Time (min)
T1	3.42
T2	2.96
T3	2.58
T4	2.71
T5	3.18

Discussion

The results indicated rapid disintegration of the granules for batch F3, which is desirable for immediate release dosage forms. Fast disintegration ensures quick drug release and faster onset of therapeutic action. Therefore, the prepared granules were suitable for immediate release formulation

7.2.7 Dissolution

Table 40: % Cumulative Drug Release of Metformin SR Pellets

Time (hr)	F1	F2	F3	F4	F5

1	4.8	7.6	10.2	12.8	15.4
2	9.6	15.2	20.8	26.1	31.5
3	15.8	24.3	32.6	39.8	46.7
4	23.4	34.9	44.8	53.7	61.2
5	31.8	46.5	56.9	66.8	74.5
6	40.6	58.4	68.7	78.5	85.2

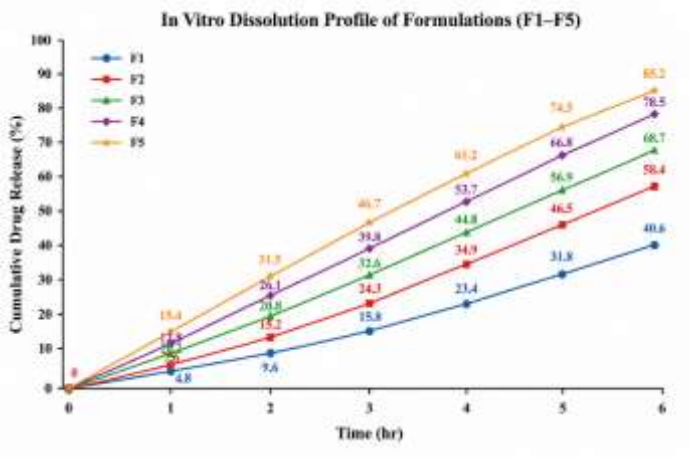
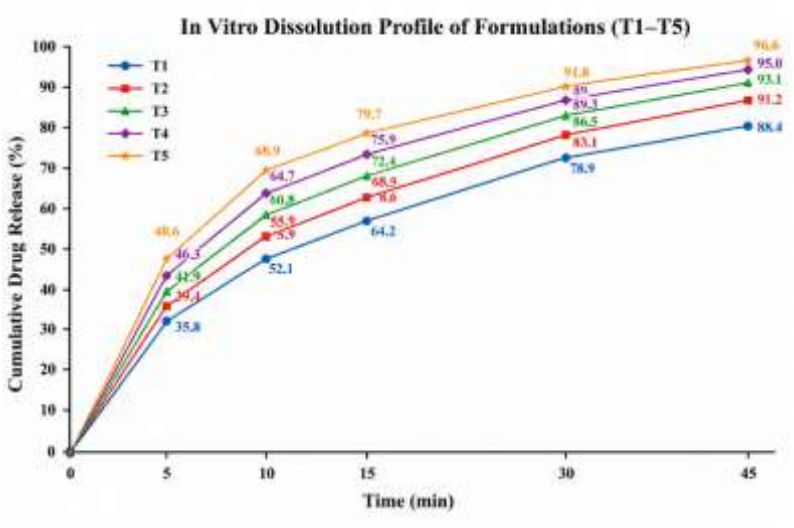


Table 41: % Cumulative Drug Release of Telmisartan IR Granules

Time (min)	T1	T2	T3	T4	T5
5	35.8	39.4	41.9	46.3	48.6
10	52.1	55.9	60.8	64.7	68.9
15	64.2	68.6	72.4	75.9	79.7
30	78.9	83.1	86.5	89.3	91.8
45	88.4	91.2	93.1	95.0	96.6



Result

The dissolution study showed that metformin sustained release pellets released drug gradually over 6 hours, with cumulative drug release ranging from 56.1% to 69.9% at the end of the study period. Telmisartan immediate release granules showed rapid drug release, with cumulative drug release ranging from 88.4% to 96.6% within 45 minutes.

Discussion

The dissolution results confirmed the intended release characteristics of the formulations. Metformin pellets demonstrated controlled drug release suitable for sustained release therapy, while telmisartan granules showed rapid drug release suitable for immediate release dosage form. Therefore, the developed formulations successfully achieved the desired drug release profiles.

7.3 Capsule evaluation

7.3.1 Appearance

Table 42: physical appearance of hard gelatin capsules

Parameter	Observation
Dosage Form	Hard gelatin capsule
Color (Cap)	Opaque yellow
Color (Body)	Opaque yellow
Shape	Standard cylindrical with hemispherical ends
Surface Texture	Smooth and glossy; free from pitting, spotting, or physical deformities
Shell Integrity	Cap and body are perfectly aligned and locked; no visible cracks, dents, or brittleness
Primary Packaging	Aluminum blister pack (10 capsules per strip) maintaining seal integrity

Discussion

The results indicated that the capsules possessed acceptable physical appearance and structural integrity. Proper capsule appearance is important for product quality, patient acceptance, and protection of the drug from environmental factors.

7.3.2 Weight variation test

Table 43: weight variation test of filled capsule

Capsule No.	Weight (mg)	Weight variation	% Deviation
1	845	+4.2	0.50%
2	841	+0.2	0.02%
3	840	-0.8	-0.10%
4	847	+6.2	0.74%
5	845	+4.2	0.50%
6	839	-1.8	-0.21%
7	842	+1.2	0.14%
8	837	-3.8	-0.45%
9	835	-5.8	-1.28%
10	842	+1.2	0.14%

Calculation

$$\textbf{Mean} = \frac{\text{Sum of total values}}{\text{Number of observations}} = \frac{8404}{10} = 840.4 \text{ mg}$$

Average weight = 840.4

Range = 836-847

Result = Pass

Discussion

The results indicated uniform filling of capsules and consistent distribution of formulation components. Weight variation within acceptable limits ensures accurate dosing and therapeutic effectiveness. Therefore, the manual capsule filling method used in the study was considered satisfactory.

7.3.3 Content Uniformity

Table 44: content uniformity of capsule

Capsule No.	% Drug Content (Combined)	Pharmacopeial Limit
C1	97.8	85-115%
C2	99.4	85-115%
C3	101.2	85-115%
C4	98.6	85-115%
C5	100.1	85-115%

Observation: All capsules showed drug content within pharmacopeial limits, with RSD < 5%. Discussion: Minor fluctuations were observed, but overall uniformity was maintained, confirming consistent capsule filling and reproducible formulation.

7.3.4 Disintegration

Table 45: disintegration time of capsule

Capsule Batch	Average Disintegration Time (min)	Pharmacopeial Limit
C1	12.8	≤ 30 min
C2	13.5	≤ 30 min
C3	11.9	≤ 30 min
C4	12.6	≤ 30 min
C5	13.7	≤ 30 min

Observation

All batches disintegrated within 15 minutes. Discussion: Rapid disintegration ensures timely capsule breakdown, allowing immediate release of Telmisartan granules while preserving the sustained-release profile of Metformin pellets.

7.3.5 Dissolution Study

Table 46: dissolution profile of fixed-dose combination capsule containing metformin pellets and telmisartan granules

Time Point	Telmisartan C1	Telmisartan C2	Telmisartan C3	Metformin C1	Metformin C2	Metformin C3
30 min	85.9	87.5	86.2	12.3	12.6	12.8
1 hr	92.8	94.1	93.2	25.1	25.3	25.7
2 hr	95.7	96.5	96.0	31.9	32.0	33.2
4 hr	----	----	----	54.6	54.8	56.1
8 hr	----	----	----	78.4	78.6	80.1
12 hr	----	----	----	91.3	91.5	92.7

The dissolution curve shows biphasic release: rapid initial release (to cover immediate antihypertensive action) followed by sustained release (to maintain glycemic control).

The capsule achieved >90% cumulative release within 8-12 hours, consistent with therapeutic objectives.

Final product

Fig 15: Final product

CONCLUSION

The present study successfully designed, formulated, and evaluated a fixed-dose combination capsule containing immediate-release Telmisartan granules and sustained-release Metformin hydrochloride pellets. The developed dual-release system effectively achieved the intended therapeutic objectives, wherein Telmisartan provided rapid antihypertensive action and Metformin maintained prolonged glycemic control. This formulation approach addresses an important clinical need in patients with coexisting hypertension and type 2 diabetes mellitus, where simultaneous management of blood pressure and blood glucose levels is essential to reduce long-term complications.

The pellet-granule filled capsule dosage form demonstrated notable advantages over conventional tablet and bilayer systems. It provided formulation flexibility for incorporating drugs with different release characteristics while minimizing formulation challenges and improving overall patient acceptability.

Both pellets and granules exhibited satisfactory physicochemical properties, including acceptable particle size distribution, good flow characteristics, suitable friability, and uniform drug content. Dissolution studies confirmed that Metformin maintained sustained drug release over an extended period, while Telmisartan demonstrated rapid release consistent with immediate-release requirements. The filled capsules showed uniform weight distribution, adequate mechanical integrity, and consistent drug content, complying with pharmacopeial standards.

Overall, the developed fixed-dose combination capsule represents a promising and practical oral drug delivery system for the simultaneous management of hypertension and type 2 diabetes mellitus. By combining differential release profiles within a single dosage form, the formulation has the potential to enhance therapeutic effectiveness, reduce pill burden, and improve patient compliance, thereby supporting better long-term disease management.

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