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"Preparation And Characterization Of Co-Processed Excipient For Enhancement Of Physicochemical Properties"

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Over the last three decades, advancements in pharmaceutical technology have led to the development of Sustained Release Tablets (SRTs), which release drugs slowly over time, maintaining consistent therapeutic levels and reducing the need for frequent dosing. This study focuses on Telmisartan, an antihypertensive agent, to develop a co-processed excipient suitable for SRT formulations. A pregelatinized starch-polyvinyl pyrrolidone (PGS-PVP) co-processed excipient was prepared by gelatinizing potato starch (49 parts) with PVP (1 part). The excipient was characterized for its physical and micromeritic properties, including solubility, compressibility index, particle size, angle of repose, bulk density, tapped density, and pH. Preformulation studies of Telmisartan with various excipients were conducted using FTIR, XRD, and DSC methods to assess compatibility and stability. The FTIR spectra of Telmisartan and excipients showed no significant shifts in characteristic peaks, indicating no chemical interactions. XRD patterns revealed that the crystalline nature of Telmisartan remained unchanged, suggesting no significant interactions with excipients. DSC analysis confirmed that the melting point of Telmisartan was unaffected by the presence of excipients, indicating good thermal stability and compatibility. The PGS-PVP co-processed excipient demonstrated excellent physical and micromeritic properties, including good flowability and compressibility. Post-formulation studies of Telmisartan tablets showed that formulation F8, with high drug content, appropriate hardness, low friability, and an excellent dissolution profile, performed best. Compared to the marketed formulation (Telma 40), F8 exhibited comparable drug release, indicating its potential as an effective alternative. The PGS-PVP co-processed excipient offers significant advantages for the formulation of Telmisartan tablets, providing a high-quality, directly compressible vehicle with superior flow properties and stability. This study demonstrates the potential of PGS-PVP co-processed excipient for the pharmaceutical industry, paving the way for the development of effective and stable Telmisartan SRT formulations, thereby enhancing patient adherence and therapeutic outcomes.

Keywords: Telmisartan, Sustained Release Tablets, co-processed excipient, PGS-PVP, preformulation studies.

INTRODUCTION

Over the last three decades, advancements in pharmaceutical technology have transformed the development of patient-centred dosage forms. Among these, Sustained Release Tablets (SRTs) have emerged as a key area of research and innovation. Unlike conventional tablets, SRTs are designed to release the drug slowly over a prolonged period, maintaining consistent therapeutic levels and reducing the need for frequent dosing. This is particularly beneficial for managing chronic conditions like hypertension.[1]

Telmisartan, an angiotensin II receptor antagonist used to manage hypertension, is an ideal candidate for SRT formulations. SRTs offer a way to maintain steady blood pressure control with just one dose per day, significantly improving patient compliance, especially among paediatric and geriatric patients who often struggle with frequent dosing schedules.[2]

Various methods are employed in the production of SRTs, including sublimation, molding, lyophilization (freeze-drying), mass extrusion, melt granulation, and direct compression. A critical innovation in this field is the co-processing of excipients, which combines different materials to create a single excipient with enhanced properties. This technique improves flow properties, compressibility, dilution potential, and reduces sensitivity to lubricants, among other benefits. Co-processed excipients can thus provide the necessary characteristics for an effective SRT.[3]

In recent years, formulation scientists have recognized that no single excipient can meet all the requirements for SRTs. As a result, co-processing of existing excipients has been introduced to develop multifunctional excipients. These excipients help achieve rapid disintegration, good mouthfeel, and prolonged drug release.[4]

For this study, we focused on developing a co-processed excipient using the wet granulation method. We selected excipients based on their physicochemical properties, safety for oral medication, and their functional role in SRTs. We also considered the critical quality attributes of each ingredient. The quantities of each ingredient were determined through a design of experiments approach. Initial batches were manufactured and evaluated for their physicochemical parameters to select the most suitable formulation for SRTs with Telmisartan, accommodating both low and high drug content.[5]

This approach aims to deliver effective antihypertensive therapy with Telmisartan, enhancing patient adherence by reducing the dosing frequency. By leveraging the benefits of co-processed excipients, we aim to provide a sustained release formulation that ensures consistent therapeutic effects and improved quality of life for patients managing hypertension.

MATERIALS AND METHODS

Materials

Telmisartan, Microcrystalline cellulose (MCC), Starch, Magnesium stearate, PGS, PVP.

Telmisartan was obtained as a free gift sample from Unique Pharmaceutical Laboratories,

9	20	37.5	85.39

Daman (Gujrat) and other ingredients were obtained from Research lab Mumbai. The entire ingredients obtained were analytical grade.

Experimental Design

A 3^2 factorial design was used to evaluate the impact of two factors (starch and co-processed excipients) on drug release. Each factor was tested at three levels: low (-1), medium (0), and high (+1). The design matrix included nine runs, with each run representing a unique combination of the factors (Table 1).

Trial Design- 3^2 Factorial Design

ANOVA for Quadratic model

Response 1: Drug Release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	513.18	5	102.64	10.57	0.0402	significant
A-Starch	426.22	1	426.22	43.90	0.0070	
B-Co-processed Excipient	49.13	1	49.13	5.06	0.1100	
AB	0.6724	1	0.6724	0.0693	0.8095	
A^2	0.0249	1	0.0249	0.0026	0.9628	
B^2	37.12	1	37.12	3.82	0.1455	
Residual	29.13	3	9.71			
Cor Total	542.30	8				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 10.57 implies the model is significant. There is only a 4.02% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Fit Statistics

Std. Dev.	3.12	**R^2**	0.9463
Mean	80.55	**Adjusted R^2**	0.8568
C.V. %	3.87	**Predicted R^2**	0.3645
		Adeq Precision	9.2829

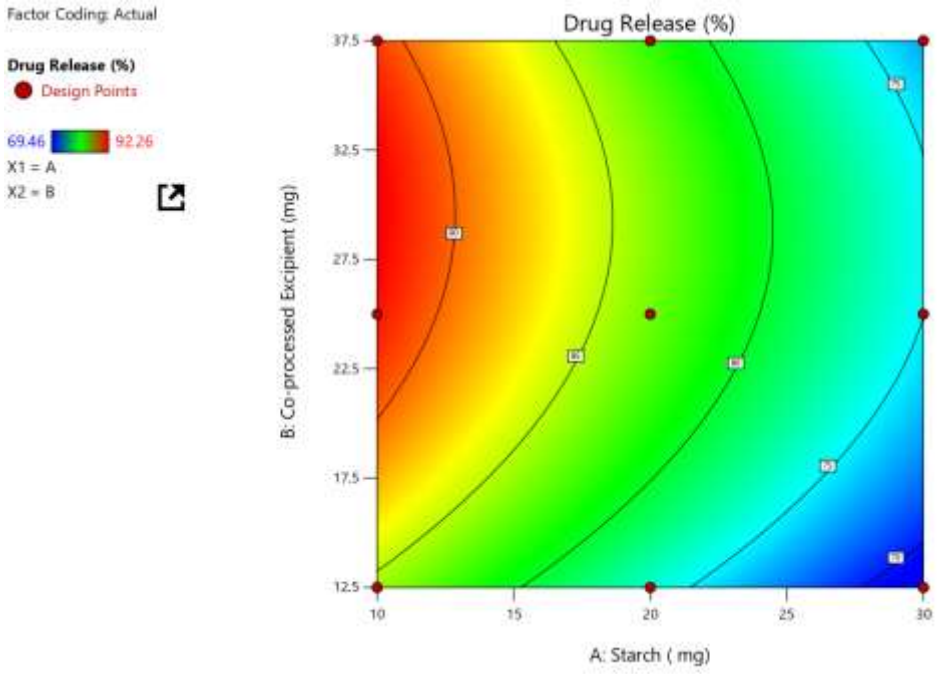
The **Predicted R^2** of 0.3645 is not as close to the **Adjusted R^2** of 0.8568 as one might normally expect; i.e. the difference is more than 0.2. This may indicate a large block effect or a possible problem with your model and/or data. Things to consider are model reduction, response transformation, outliers, etc. All empirical models should be tested by doing confirmation runs.

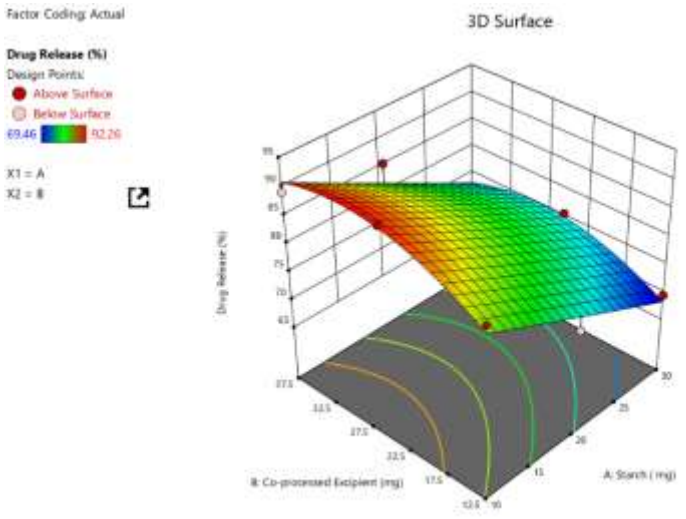
Adeq Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 9.283 indicates an adequate signal. This model can be used to navigate the design space.

Final Equation in Terms of Coded Factors

Drug Release	=
+83.35	
-8.43	A
+2.86	B
-0.4100	AB
+0.1117	A^2
-4.31	B^2

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.





Preparation of PGS-PVP Co-Processed Excipient [6, 7]

To prepare the PGS-PVP co-processed excipient, the following steps were carried out:

Created the Slurry: 49 parts of potato starch and 1 part of polyvinyl pyrrolidone (PVP) were dispersed in 20 parts of water and mixed thoroughly to form a smooth slurry.

Boiled the Water: In a separate beaker, 40 parts of purified water were heated until it reached a rolling boil.

Combined Ingredients: The starch-PVP slurry was gradually added to the boiling water while continuously stirring. Stirring and heating were maintained for 15 to 20 minutes until a thick mass formed.

Dried the Mixture: The thickened product was transferred onto a stainless-steel tray and dried at 80°C for 12 hours to ensure complete dehydration.

Ground and Sized: Once dried, the product was ground into a fine powder and sized appropriately to ensure uniform particle size distribution.

Characterization of PGS-PVP Co-Processed Excipient [8,9]

The PGS-PVP co-processed excipient was thoroughly characterized through various tests and measurements. The following properties were determined:

Melting Point: The melting point of the co-processed excipient was measured to understand its thermal stability.

Solubility: Solubility tests were conducted to assess how well the excipient dissolves in different solvents.

Swelling Index in Water: The swelling index was determined by measuring how much the excipient expands when immersed in water.

pH: The pH of the excipient was tested to ensure it falls within an acceptable range for pharmaceutical applications.

Micromeritic Properties: Various micromeritic properties were analyzed, including:

Particle Size: The size distribution of the particles was measured to ensure consistency.

Bulk Density: The bulk density was determined to understand the packing properties of the excipient.

Tapped Density: Tapped density measurements were taken to assess the excipient's compressibility.

Angle of Repose: The angle of repose was measured to evaluate the flowability of the excipient.

Solubility

The solubility of the PGS-PVP co-processed excipient was tested in various solvents. This included water, aqueous buffers with pH levels of 1.2, 4.5, and 7.4, and organic solvents such as alcohol, dichloromethane, chloroform, acetone, and petroleum ether.

pH

The pH was measured by preparing a 1% w/v slurry of the excipient in water and then using a pH meter to determine the value.

Melting Point

The melting point of the PGS-PVP excipient was determined using a standard melting point apparatus.

Bulk Density

Bulk density, expressed in grams per cubic centimeter (g/cc), was determined using the three-tap method in a graduated cylinder. This involved tapping the cylinder three times to settle the powder and then measuring the volume.

Compressibility Index

The compressibility index (CI) was determined by measuring the initial volume (V0) and the final volume (V) of a sample after tapping it 100 times in a measuring cylinder. The CI was calculated using the following equation:

$$\mathrm{CI} = \frac{(V0 - V)}{V0} \times 100$$

Particle Size

Particle size analysis was performed using standard sieves to ensure uniformity in the size distribution of the particles.

Angle of Repose

The angle of repose, which indicates the flowability of the powder, was measured using the fixed funnel method. This involved allowing the powder to flow through a funnel and form a cone, then measuring the angle of the cone.

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy (FTIR) [10,11]

Sample Preparation: Telmisartan, polymers, and excipients were individually mixed with potassium bromide (KBr) in a 1:100 ratio and compressed into thin discs using a hydraulic press.

Analysis: FTIR spectra were recorded using an FTIR spectrometer in the range of 4000-400 cm^{-1}. The spectra were analyzed to identify characteristic peaks and any potential interactions between the API and excipients.

X-ray Diffraction (XRD) [12,13]

Sample Preparation: Pure Telmisartan, polymers, excipients, and their physical mixtures were finely ground and placed on a sample holder.

Analysis: XRD patterns were obtained using an X-ray diffractometer with Cu-Kα radiation (λ = 1.5406 Å). The diffraction angle (2θ) was scanned from 5° to 60°. The diffraction patterns were examined for changes in crystallinity and possible interactions between the components.

Differential Scanning Calorimetry (DSC) [14,15]

Sample Preparation: Approximately 2-5 mg of Telmisartan, polymers, excipients, and their physical mixtures were accurately weighed and sealed in aluminum pans.

Analysis: Thermal analysis was performed using a DSC instrument. Samples were heated from 25°C to 300°C at a rate of 10°C/min under a nitrogen atmosphere. The thermograms were analyzed for shifts in melting points, enthalpy changes, and any signs of interaction between the API and excipients.

Formulation Process [16.17,18,19]

The formulations were prepared by blending the ingredients in specified proportions, followed by direct compression to form tablets. The formulations were coded as F1 to F9, representing different combinations of starch and co-processed excipients.

Table formulation

S.N.	Ingredients	Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Telmisartan	40	40	40	40	40	40	40	40	40
2	MCC	70	65	60	75	80	85	55	50	70
3	Starch	45	55	70	45	50	45	60	65	60
4	Magnesium Stearate	70	65	55	65	55	55	70	70	55
5	PGS	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
6	PVP	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Total		250	250	250	250	250	250	250	250	250

Preparation of Telmisartan Tablets by Direct Compression Method

Tablets containing Telmisartan (40 mg) were prepared by the direct compression method as per the formula provided in Table 2. All materials required according to the formula were accurately weighed and blended thoroughly in a closed polyethylene bag to ensure uniform mixing.

Blending: The Telmisartan and excipients were mixed in a closed polyethylene bag to achieve a homogenous blend.

Compression: The blended mixture was then compressed into tablets using a tablet punching machine. Tablet Hardness: The compression process was adjusted to achieve tablets with a hardness of 6 kg/cm^2.

Evaluation of Telmisartan Tablets [20,21,22]

The prepared Telmisartan tablets underwent a series of evaluations to ensure they met the necessary quality standards. The tests conducted included:

Content of Active Ingredient: The amount of Telmisartan in each tablet was determined to ensure uniformity and proper dosage.

Hardness: The hardness of the tablets was measured using a Monsanto hardness tester to ensure they could withstand handling without breaking.

Friability: The friability of the tablets, which indicates how easily they might crumble, was tested using a Roche Friabilator.

Dissolution Rate: The rate at which Telmisartan was released from the tablets into a solution was assessed to confirm that the drug would be available for absorption in the body within the expected timeframe.

Estimation of Drug Content in Telmisartan Tablets

For each batch of Telmisartan tablets, we accurately weighed 20 tablets and then powdered them. We took a portion of this powder equivalent to 50 mg of Telmisartan and placed it in a 100 ml conical flask. The powder was extracted using three 20 ml portions of methanol. These methanolic extracts were then filtered and collected into a 100 ml volumetric flask. We made up the volume to 100 ml with methanol.

Next, we diluted this solution with water containing 2% sodium lauryl sulfate (SLS). Using a UV-Vis spectrophotometer, we measured the absorbance of the solution at 296 nm. The drug content in the tablets was determined using a standard calibration curve for Telmisartan.

Dissolution Rate Study

To study the dissolution rate of the Telmisartan tablets, we used a USP 8-station Dissolution Rate Test Apparatus equipped with a paddle stirrer set to 50 rpm. We used 900 ml of 0.1 N hydrochloric acid as the dissolution medium, maintaining it at a temperature of 37±1°C.

One tablet was placed in each test station. At various time intervals, we withdrew 5 ml samples of the dissolution medium through a 0.45 µm filter. The Telmisartan content in these samples was then measured at 296 nm using a UV-Vis spectrophotometer. To ensure the reliability of our results, all dissolution experiments were conducted in triplicate (n=3).

RESULT & DISCUSSION

Directly compressible vehicles can be created using various methods, with co-processing being one of the most widely explored and commercially utilized techniques. Co-processing excipients can result in materials with superior properties compared to simple physical mixtures of their components. The objective of this study was to prepare and characterize a pregelatinized starch-polyvinyl pyrrolidone (PGS-PVP) co-processed excipient and evaluate its effectiveness as a directly compressible vehicle in tablet formulations.

To prepare the PGS-PVP co-processed excipient, we gelatinized potato starch (49 parts) in the presence of PVP (1 part). The resulting PGS-PVP co-processed excipient was characterized by determining its various physical and micromeritic properties. The prepared excipient was found to be a crystalline, discrete, and free-flowing powder. We ground it to various particle sizes using a dry mortar, and particles sized -80+120 mesh (182.3 µm) were collected for further studies.

The physical and micromeritic properties of the PGS-PVP co-processed excipient are summarized in Table 1. The findings indicate that the co-processed excipient has excellent flow properties and is suitable for use as a directly compressible vehicle in tablet formulations. This study demonstrates the potential of PGS-PVP as a high-quality excipient for the pharmaceutical industry.

Table 1: Physical and Micromeritic Properties of PGS-PVP Co-processed Excipient

S.No	Property/Test	Result
1	Solubility	Insoluble in water, methanol, ethanol, acetone, chloroform, dichloromethane, and petroleum ether
2	Compressibility index (%)	8.2
3	Particle size (µm)	80/120 mesh (182.3 µm)
4	Angle of repose (°)	25.10
5	Bulk density (g/cc)	0.442
6	Melting point	Charred at 255°C
7	Tapped density (g/cc)	0.472
8	pH (1% aqueous dispersion)	6.9

Pre-formulation Studies

Preformulation studies are crucial in understanding the compatibility and stability of an Active Pharmaceutical Ingredient (API) with excipients. For this study, we focused on

evaluating the compatibility of Telmisartan with various polymers and excipients using FTIR, XRD, and DSC methods.

Fourier Transform Infrared Spectroscopy (FTIR)

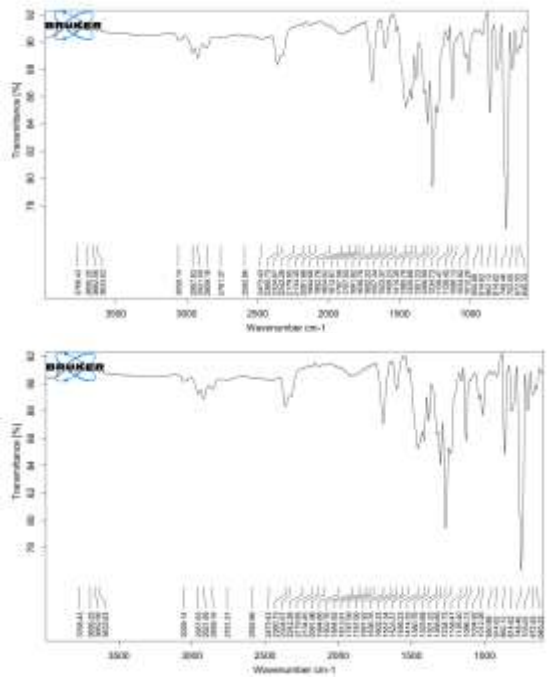


Figure 1 FTIR Spectra of Pure Telmisartan and Telmisartan with Excipient and Polymers

FTIR spectra were obtained to identify any potential interactions between Telmisartan and the selected excipients. The characteristic peaks of Telmisartan were compared with those of the physical mixtures. No significant shifts or changes in the characteristic peaks were observed, indicating that there are no chemical interactions between Telmisartan and the excipients.

X-ray Diffraction (XRD)

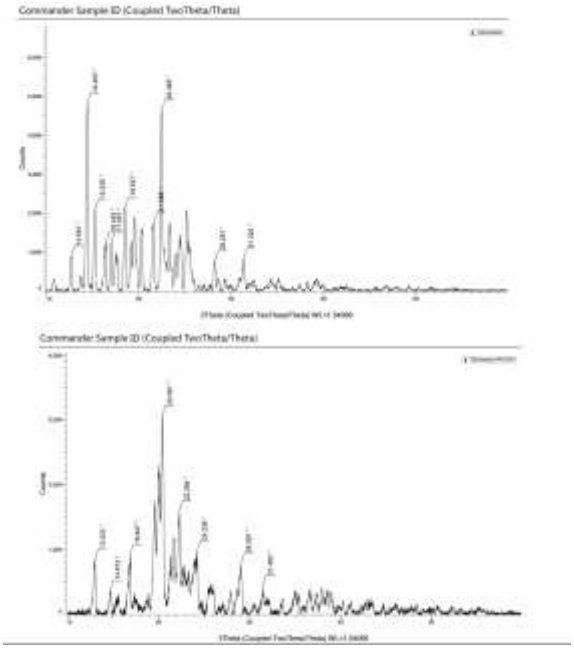


Figure 2 XRD of Pure Telmisartan and Telmisartan plus Excipients and Polymers

XRD patterns of Telmisartan, the excipients, and their physical mixtures were recorded to assess the crystalline nature and any possible interactions. The diffractograms showed that the characteristic peaks of Telmisartan were retained in the physical mixtures, suggesting that the crystalline structure of Telmisartan remained unchanged. This implies that there are no significant interactions between Telmisartan and the excipients that could affect its crystalline nature.

Differential Scanning Calorimetry (DSC)

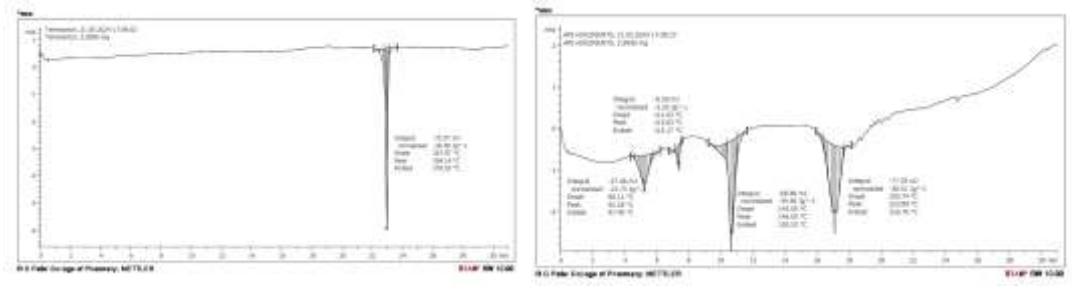


Figure 3 DSC of Pure Telmisartan and Telmisartan plus Excipients and Polymers

DSC analysis was conducted to investigate the thermal behaviour and compatibility of Telmisartan with the excipients. The DSC thermograms of pure Telmisartan exhibited a sharp endothermic peak corresponding to its melting point. When Telmisartan was combined with the excipients, the DSC thermograms showed that the melting point of Telmisartan

remained unchanged, indicating no significant interaction. The absence of additional peaks suggests that there are no incompatibilities between Telmisartan and the excipients.

Post formulation studies

Table 2 Physical properties of Telmisartan co-processed tablets

Formulation Code	Average Weight of Tablet (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	249 ± 3.20	6.1 ± 0.3	4.68 ± 1.32	0.15	80
F2	251 ± 1.41	6.8 ± 1.3	4.13 ± 1.11	0.08	79
F3	247 ± 3.49	6.1 ±1.7	4.23 ± 0.99	0.30	89
F4	248 ± 3.26	5.9 ± 0.8	3.11 ± 1.85	0.10	88
F5	254 ± 1.02	5.4 ± 0.6	4.98 ± 1.21	0.12	87
F6	246 ± 2.11	6.5 ± 1.7	4.14 ± 0.88	0.19	81
F7	252 ± 3.41	6.4 ± 1.1	3.99 ± 1.21	0.17	90
F8	250± 2.09	6.8 ± 0.6	4.88 ± 1.23	0.21	90
F9	253 ± 3.12	6.2 ± 1.2	4.90 ± 1.45	0.24	88

Dissolution Studies

Table 3 Dissolution Profiles of formulations F1-F9

Time (hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	16.53	5.26	19.53	4.26	15.24	20.53	4.01	3.10	4.0
1	24.37	11.58	28.45	11.04	23.27	30.89	10.47	9.27	10.14
2	30.37	18.47	39.51	17.87	29.78	39.51	19.65	17.87	18.28
4	46.31	28.25	60.89	26.90	48.12	64.22	26.0	25.33	25.12
6	67.82	40.24	75.14	39.57	70.47	77.54	40.12	39.98	38.87
8	-	55.12	-	54.14	-	-	56.47	58.74	53.22
10	-	62.14	-	64.15	-	-	61.44	72.12	61.84
12	-	75.52	-	76.12	-	-	75.98	83.90	72.15
14	-	84.26	-	88.23	-	---	85.63	94.52	84.22

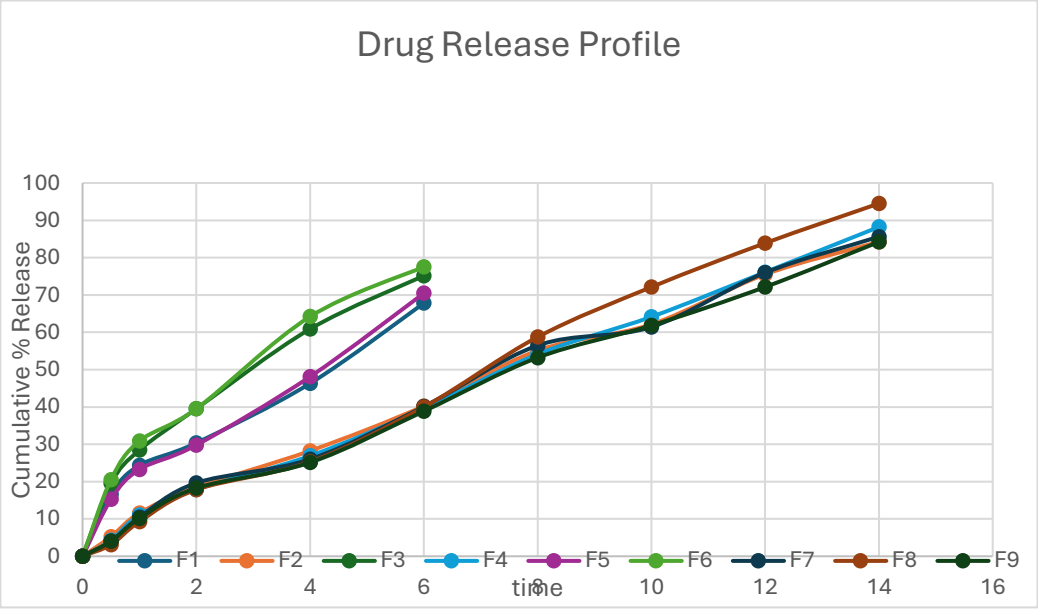


Figure 4 Drug Release Profile of Various formulations

Table 4 Comparative Dissolution Profile

Time (hours)	F10{Pure API Without Polymer	F8 (Best Formulation with Polymer)	F11 (Marketed Formulation (Telma 40)
0	0	0	0
0.5	10.22	3.10	55
1	28.87	9.27	70
2	38.24	17.87	88
4	55.71	25.33	-
6	-	39.98	-
8	-	58.74	=
10	-	72.12	-
12	-	83.90	-

14	-	94.52	-

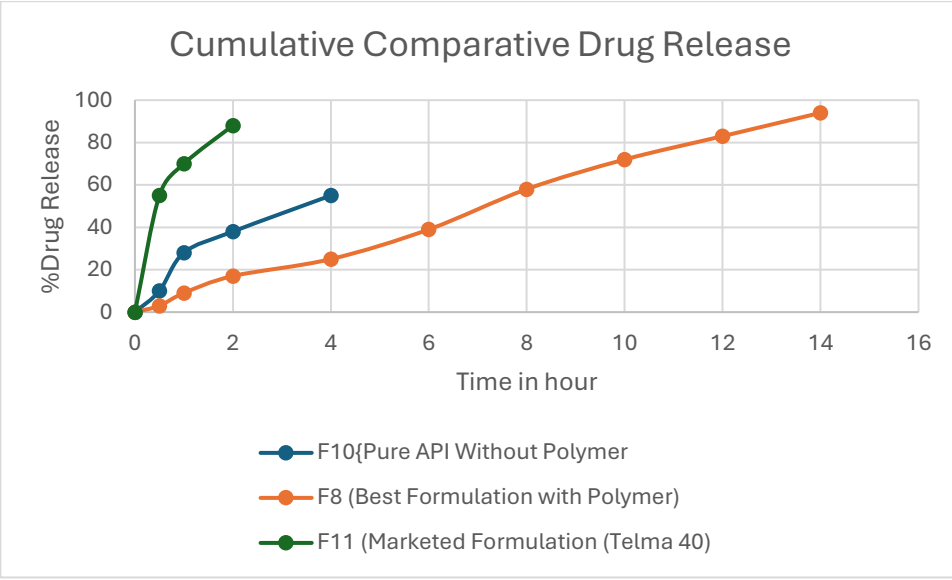


Figure 5 % Cumulative Drug Release of Pure drug (F10) Drug with Polymer

(F8) Best formulation and F11 Marketed formulation Telma 40)

CONCLUSION

The preformulation studies of Telmisartan with various excipients using FTIR, XRD, and DSC methods confirmed the compatibility and stability of the API with the selected excipients. The FTIR spectra showed no significant shifts in the characteristic peaks of Telmisartan when mixed with excipients, indicating the absence of chemical interactions. The XRD patterns demonstrated that the crystalline nature of Telmisartan remained unchanged in the physical mixtures, suggesting no significant interactions that could affect its crystalline structure. DSC analysis further supported these findings, showing no significant changes in the melting point of Telmisartan in the presence of excipients, indicating good thermal stability and compatibility.

The PGS-PVP co-processed excipient was successfully prepared and characterized, showing excellent physical and micromeritic properties such as good flowability, compressibility, and appropriate particle size distribution. These properties make it suitable as a directly compressible vehicle in tablet formulations.

Post-formulation studies of the Telmisartan tablets, including evaluations of physical properties and dissolution profiles, revealed that the tablets exhibited desirable characteristics. Among the formulations, F8 demonstrated the best performance with high drug content, appropriate hardness, low friability, and an excellent dissolution profile.

Compared to the marketed formulation (Telma 40), the best formulation (F8) showed comparable drug release, indicating its potential as an effective alternative.

In conclusion, the PGS-PVP co-processed excipient offers significant advantages in the formulation of Telmisartan tablets, providing a high-quality, directly compressible vehicle with superior flow properties and stability. This study demonstrates the potential of the PGS-PVP co-processed excipient for use in the pharmaceutical industry, paving the way for the development of effective and stable Telmisartan tablet formulations.

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