

"Design And Development Of Co Process Excipients For Enhancement Of Physico-Chemical Properties"

S. V. Deore^{1*}, M. S. Gambhire²

^{1.} *Research Scholar, School of Pharmaceutical Sciences, Sandip University, Nashik.*

^{2.} *School of Pharmaceutical Sciences, Sandip University, Nashik.*

Correspondence author: mahadeore@gmail.com

The development and optimization of chlorthalidone tablets employing a co-processed excipient combination of mannitol (10%), microcrystalline cellulose (MCC, 80%), and xylitol (10%) was the main goal of this work. A 3² factorial design was used in the experiment to assess how different parameters affected drug release and other important characteristics. With an overall F-value of 22.03 and a p-value of 0.0143, the ANOVA analysis revealed sodium starch glycolate as a significant factor influencing drug release, with a p-value of 0.0020. With a compressibility index of 8.2%, particle size uniformity of 182.3 μm , and an angle of repose of 25.10°, the improved formulation showed outstanding micromeritic properties. It also had acceptable flowability and compressibility. Wet granulation, spray drying, milling, and final blending using magnesium stearate as a lubricant were the steps used to make the co-processed mix. With a pH of 6.9 in a 1% aqueous dispersion and thermal stability up to 255°C, the final formulation retained stability. By compressing the tablets with the optimal blend, robustness during handling was ensured by reduced friability and a hardness of 6 kg/cm². Studies on drug dissolution demonstrated effective drug release, resulting in the active medicinal ingredient being easily absorbed.

Key words: Chlorthalidone, Co-Processed Excipients, Drug Release, Tablet Formulation, Factorial Design.

INTRODUCTION

In the pharmaceutical industry, developing therapeutic candidates with poor solubility is still a major difficulty. Improving these medications' physicochemical characteristics—such as their rate of dissolution and solubility—is essential to raising their oral bioavailability and therapeutic effectiveness. The creation of co-processed excipients, which can successfully increase optimizing the rate of solubility, dissolution, and bioavailability of drugs that are barely soluble is a potential option to address this challenge.^{1, 2}

The literature has a wealth of information on the basic ideas that underpin the use of co-processed excipients to improve drug solubility and dissolution. Increased surface area, amorphization, and reduced particle size can all result in higher wettability and dissolving

rates. Formulation scientists have experimented with a number of methods, utilizing hot-melt extrusion, milling and spray drying techniques to produce co-processed additives that transcend the shortcomings of each excipient and jointly enhance the drug's physicochemical characteristics.³

The performance of the finished dosage form can be significantly impacted by the choice of suitable excipients, in addition to altering the physical characteristics of the medication. Drug-excipient interactions can have a major positive or negative impact on the drug's absorption and disintegration. For example, it has been demonstrated that adding hydrophilic carriers to solid dispersions improves their wettability and solubility, which in turn improves their bioavailability.⁴

Research is currently being conducted on the creation of co-processed excipients to improve the physicochemical characteristics of medications that are poorly soluble. To overcome the difficulties involved in the formulation of these medicines, formulation experts are still investigating cutting-edge strategies such the application of synergistic excipient combinations. The limitations of poorly soluble drug candidates can be solved by designing robust and efficient drug delivery systems that take advantage of the complementing features of co-processed excipients.^{5, 6}

Recent developments in co-processing technology have increased the possibility of creating better medicinal formulations even more. Novel approaches to produce co-processed excipients with improved functional qualities include co-precipitation, solvent evaporation, and supercritical fluid processing. The precise control of particle size, shape, and dispersion made possible by these techniques results in a more homogeneous and reliable drug-excipient blend. Additionally, new paths for enhancing medication solubility and bioavailability have been made possible by the use of nanotechnology into the production of co-processed excipients. Using nanoparticles and nanocrystals can greatly expand the surface area that is accessible for dissolution, improving the solubility of medications that are not very soluble. The application of sophisticated co-processing methods is anticipated to be crucial in resolving solubility issues and developing drug delivery systems as this field of study develops.^{7,8}

MATERIALS AND METHODS

Materials

Chlorthalidone, Starch, Xylitol, Mannitol, MCC, Magnesium stearate,

The free gift sample of chlorthalidone was received from Unique Pharmaceutical Laboratories in Daman (Gujrat), while the remaining substances were procured from Research Lab Mumbai. Every substance that was acquired was of an analytical grade.

Experimental Design

3² Factorial Design

Run	Starch in %	SSG in %
1	5	5
2	15	5
3	10	8
4	5	8
5	10	2
6	15	8
7	5	2
8	10	5
9	15	2

ANOVA for Quadratic model

Response 1: Drug Release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	110.30	5	22.06	22.03	0.0143	significant
A-STARCH	3.07	1	3.07	3.06	0.1784	
B-SODIUM STARCH GLYCOLATE	106.01	1	106.01	105.86	0.0020	
AB	0.0090	1	0.0090	0.0090	0.9304	
A ²	1.07	1	1.07	1.07	0.3772	
B ²	0.1494	1	0.1494	0.1492	0.7251	
Residual	3.00	3	1.00			
Cor Total	113.31	8				

Factor coding is **Coded**.

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

A **Model F-value** of 22.03 indicates that the model is statistically significant. About a 1.43% probability exists for an F-value of this magnitude to arise from random variation..

Significance of model terms is indicated by p-values below 0.0500. The model term **B** is of considerable importance in this one. Values beyond 0.1000 suggest that the model terms lack statistical significance. If your model contains numerous inconsequential terms (except those necessary for supporting hierarchy), reduction in model may enhance its quality.

Fit Statistics

Std. Dev.	1.00		R ²	0.9735
Mean	87.03		Adjusted R ²	0.9293
C.V. %	1.15		Predicted R ²	0.7223
			Adeq Precision	12.1176

The **Predicted R²** of 0.7223 deviates significantly from the **Adjusted R²** of 0.9293, with a discrepancy over 0.2. This finding suggests the presence of a significant block effect or a potential issue using your model as well as data. Areas of consideration include modeling elimination, response modification, outliers, and other related factors. The validation of all empirical frameworks should be conducted by confirmatory runs.

Adeq Precision quantifies the ratio of transmitted signal to noise. An optimal ratio is one that exceeds 4. The ratio of 12.118 you have provided suggests a satisfactory signal. This conceptual framework can be employed to traverse the design domain.

Factor Coding: Actual

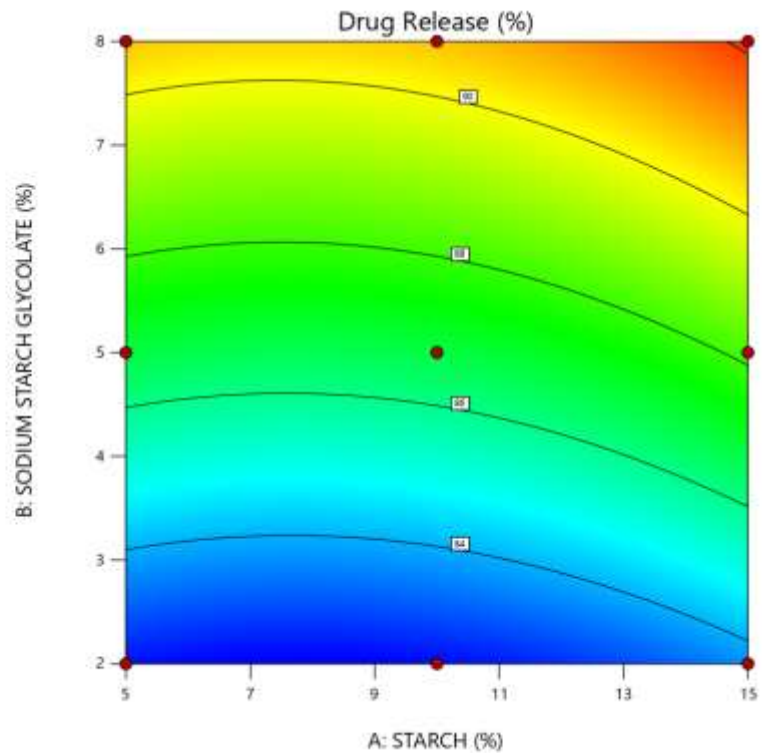
Drug Release (%)

● Design Points

82.16 92.65

X1 = A

X2 = B



Factor Coding: Actual

Drug Release (%)

Design Points:

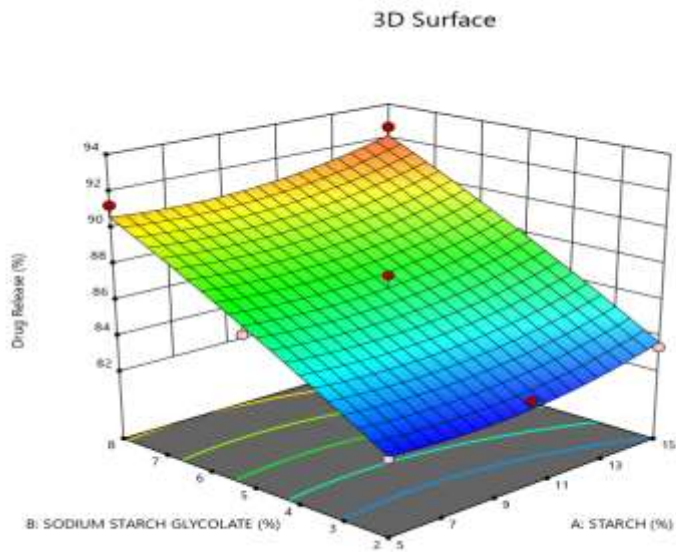
● Above Surface

○ Below Surface

82.16 92.65

X1 = A

X2 = B



Preparation of Co-Processed Excipient

Following precise weighing, a mixture of 10% xylitol, 10% mannitol, and 80% microcrystalline cellulose was pre-mixed in a high-shear mixer to achieve even distribution. Following that, the mixture underwent wet granulation by progressively adding a granulating fluid while mixing continued, resulting in the formation of a wet mass. In order to eliminate moisture, the mass was thereafter dried using a spray dryer set at regulated temperatures. To obtain the appropriate particle size, the dry granules were pulverized. Finally, the granules were blended with a small amount of magnesium stearate as a lubricant to ensure homogeneity and improve flow properties, resulting in a co-processed excipient suitable for tablet formulations.⁹

A range of tests and measurements were used to fully characterize the co-processed excipient. It was established that the following qualities existed:

Melting Point: To determine the co-processed excipient's thermal stability, its melting point was determined.

Solubility: To find out how effectively the excipient dissolves in various solvents, soluble tests were carried out.

Water Swelling Index: Measuring the excipient's expansion in water immersion yielded the swelling index.

pH: The excipient's pH was measured to make sure it is within a range that is suitable for use in pharmaceutical applications.

Micromeritic Properties: A number of micromeritic characteristics were examined, such as:

Particle Size: To guarantee uniformity, the size distribution of the particles was measured.

Bulk Density: To comprehend the excipient's packing characteristics, the bulk density was ascertained.

Tapped Density: The capacity for compression of the excipient was assessed by conducting tapping density measurements.

Angle of Repose: In order to assess the excipient's flowability, the angle of repose was measured.

The ability to dissolve

The co-processed excipient's solubility was examined in a range of solvents. Water, aqueous buffers with pH values of 1.2, 4.5, and 7.4, and organic solvents including acetone, dichloromethane, alcohol, and petroleum ether were among them.

pH

A 1% weight/volume dispersion of the additive within the water was made and its pH was subsequently determined using a pH metre.

Melting Point

A typical melting point device was used to ascertain the excipient's melting point.

Mass Density

The bulk density was calculated using the three-tap technique in a graduated cylinder., which is measured in grams per cubic centimetre (g/cc). To settle the powder, tap the cylinder three times, and then measure the volume.

Compressibility Index

In order to establish the compressibility index (CI), the starting volume (V₀) and final volume (V) of a sample were measured after subjecting it to 100 taps in a cylinder for measurement. The CI was calculated using the following equation:

$$CI = \frac{(V_0 - V)}{V_0} \times 100$$

Particle Size

Quantitative analysis of particle size was conducted using conventional sieves to guarantee consistency in the overall distribution of particle sizes.

Angle of Repose

Using the predefined funnel technique, we determine the angle of repose, that corresponds to powder's flowability. This was letting the powder run down a funnel to create a cone, then calculating the cone's angle.^{10, 11, 12}

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy (FTIR)

Sample Preparation: Chlorthalidone, 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: The spectrum of FTIR were obtained by utilization of an FTIR spectrometer within the wavelength region of 4000-400 cm⁻¹. The spectra were analysed to identify characteristic peaks and any potential interactions between the API and excipients.^{14,15}

X-ray Diffraction (XRD)

Sample Preparation: Pure Chlorthalidone, polymers, excipients, and their physical mixtures were finely ground and positioned on a specimen support.

Analysis: The X-ray diffraction (XRD) patterns were acquired utilizing an X-ray diffractometer equipped with Cu-K α radiation ($\mu = 1.5406 \text{ \AA}$). The resultant diffraction angle (2θ) has been measured across a range of 5° to 60° . The diffraction patterns were examined for changes in crystallinity and possible interactions between the components.^{16,17}

Differential Scanning Calorimetry (DSC)

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

Analysis: Thermal analysis was performed using a DSC instrument. Temperatures of the samples went up from 25°C to 300°C at a rate of 10°C per minute in an atmosphere of nitrogen. The thermograms were analysed for shifts in melting points, enthalpy changes, and any signs of interaction between the API and excipients.^{18,19}

Formulation Process

The formulations were made by directly compressing the coprocessed ingredients and excipients to create tablets after they had been blended in the designated amounts. The formulations, which represented various combinations of starch and co-processed excipients, were classified as F1 through F9.

S.N.	Ingredients	Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Chlorthalidone	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
2	Starch	50	53	46	52	48	51	49	51	47
3	SGG	30	32	34	33	35	28	36	34	32
4	Xylitol	35	30.5	31.5	32	33	34.5	32.2	34.5	36.5
5	Mannitol	35	34.5	38.35	33	34	36.5	33	30.5	34.5
6	MCC	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
7	Magnesium Stearate	50	50	50	50	50	50	50	50	50
	Total	250	250	250	250	250	250	250	250	250

Table 2 formulation

Preparation of Chlorthalidone Tablets by Direct Compression Method

Drug tablets comprising Chlorthalidone (12.5 mg) were manufactured using the direct compression technique according to the formula given in Table 2. The appropriate elements specified in the formula were precisely measured and meticulously mixed in a sealed polyethylene bag to guarantee consistent blending.

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

Compression: The blended mixture was subsequently squeezed into tablets by a tablet hammering machine.

Tablet Hardness: The compression process was adjusted to achieve tablets with a hardness of 6 kg/cm².

Evaluation of Chlorthalidone Tablets

The prepared Chlorthalidone 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 Chlorthalidone in each tablet was determined to ensure uniformity and proper dosage.

Hardness: The pills were quantitatively assessed for hardness utilizing a Monsanto roughness tester 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: To make sure the medication would be available for the body to absorb within the anticipated timeframe, the rate at which chlorthalidone was released from the tablets into a solution was measured.^{19, 20, 21}

Estimation of Drug Content in Chlorthalidone Tablets

Twenty tablets of chlorthalidone pills were precisely weighed before being powdered. We put 50 milligrams of Chlorthalidone (the amount of this powder) into a 100 ml conical flask. To get rid of the powder, three 20 ml portions of methanol were employed. These methanolic extracts were filtered and then collected into a 100 ml volumetric flask. We increased the capacity to 100 millilitres by adding methanol.

To dilute this solution, we then added 2% sodium lauryl sulphate (SLS) water. Find the absorbance of the solution at 229 nm using a UV-Vis spectrophotometer. Drug content within the Tablets was measured using a conventional calibration curve specifically designed for chlorthalidone.²³

Dissolution Rate Study

We used a USP 8-station dissolving Rate Experimental setup using a paddle stirrer set at 50 revolutions per minute. to investigate the dissolving rate of the Chlorthalidone tablets. As the dissolution medium, we utilized 900 ml of 0.1 N hydrochloric acid and kept it at 37±1°C.

Every test station has a single tablet. We removed 5 ml samples of the dissolving medium at different intervals by passing them through a 0.45 µm filter. At 296 nm, the amount of Chlorthalidone in these samples was then determined using a UV-Vis spectrophotometer. Three replications of each dissolving experiment these experiments were conducted to ensure the precision of our results. ²⁴

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

S.No	Property/Test	Result
1	Solubility	Water, methanol, ethanol, acetone, chloroform, dichloromethane, and petroleum ether are insoluble in it.
2	Compressibility Index (%)	8.2
3	Particle Size (µm)	80/120 mesh (152.9 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

Understanding the stability and compatibility of an Active Pharmaceutical Ingredient (API) with excipients is largely dependent on preformulation studies. In this work, we used FTIR, XRD, and DSC techniques to assess Chlorthalidone’s compatibility with different polymers and excipients.

Fourier Transform Infrared Spectroscopy (FTIR)

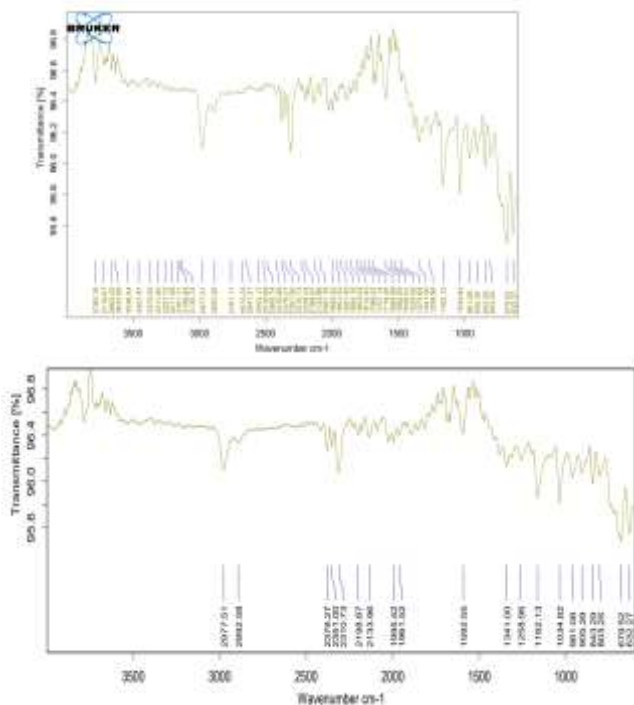


Figure 1 FTIR Spectra of Pure Chlorthalidone and Chlorthalidone with Excipient and Polymers

To find any possible interactions between Chlorthalidone and the chosen excipients, FTIR spectra were acquired. The physical mixes' peaks and chlorthalidone's distinctive peaks were contrasted. There were no discernible shifts or modifications to the distinctive peaks, suggesting that Chlorthalidone and the excipients do not interact chemically.

X-ray Diffraction (XRD)

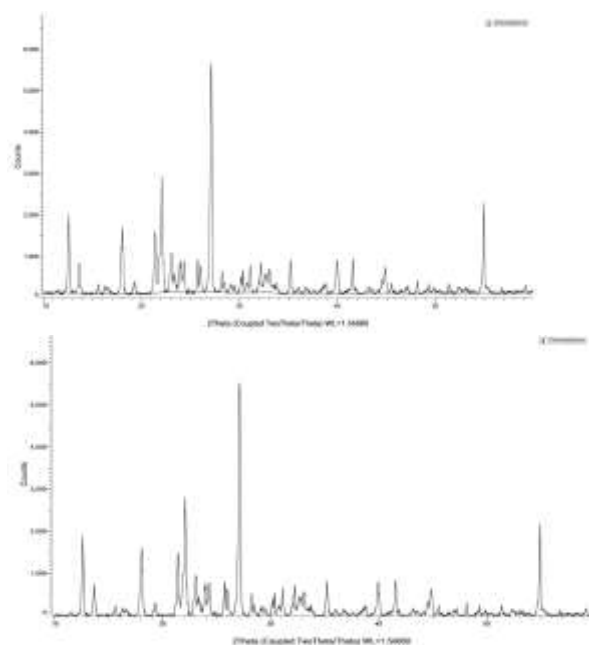


Figure 2 XRD of Pure Chlorthalidone and Chlorthalidone plus Excipients and Polymers

In order to evaluate the crystalline nature and potential interactions, XRD patterns of chlorthalidone, the excipients, and their physical mixes were recorded. The diffractograms revealed that the distinctive peaks of chlorthalidone were still present in the physical combinations, indicating that the compound's crystalline structure did not alter. This suggests that Chlorthalidone and the excipients do not interact significantly in a way that could change the drug's crystallinity.

Differential Scanning Calorimetry (DSC)

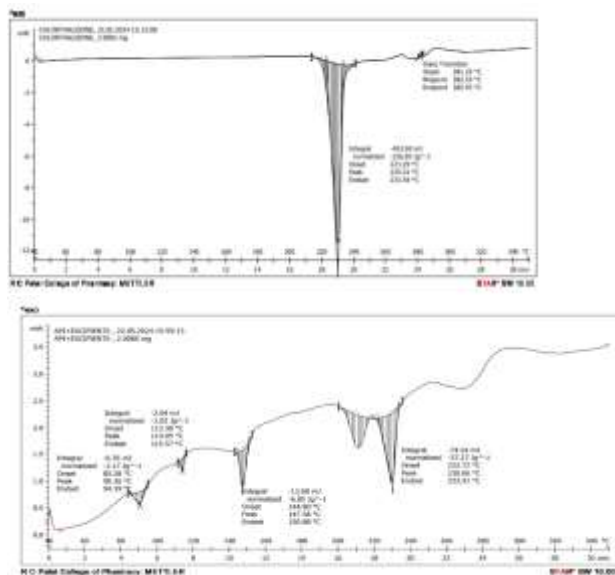


Figure 3 DSC of Pure Chlorthalidone and Chlorthalidone plus Excipients and Polymers

The thermal behaviour and compatibility of chlorthalidone with the excipients were investigated using DSC analysis. The melting point of pure chlorthalidone was represented by a prominent endothermic peak in the DSC thermograms. The DSC thermograms revealed that there was no discernible interaction when chlorthalidone and the excipients were mixed since the compound's melting point did not change. There may not be any incompatibilities between Chlorthalidone and the excipients if there are no extra peaks.

Post formulation studies

Table 2 Physical properties of Chlorthalidone co-processed tablets

Formulation Code	Average Weight of Tablet (mg)	Hardness (Kg/cm ²)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	253.96 ± 3.18	5.39 ± 0.34	3.43 ± 1.32	0.12	85
F2	259.90 ± 1.79	7.00 ± 0.81	5.73 ± 1.41	0.14	95
F3	242.67 ± 3.01	6.74 ± 1.70	3.84 ± 1.25	0.37	80
F4	248.76 ± 3.23	4.18 ± 0.95	3.52 ± 1.56	0.01	94
F5	253.48 ± 0.67	5.19 ± 0.41	5.94 ± 1.64	0.21	91
F6	245.16 ± 2.44	6.19 ±	3.47 ±	0.16	91

		1.38	0.62		
F7	246.25 ± 3.07	7.67 ± 1.57	4.57 ± 1.62	0.26	88
F8	256.55 ± 1.73	6.93 ± 0.43	6.29 ± 1.09	0.31	89
F9	255.74 ± 3.24	4.77 ± 1.33	4.13 ± 1.49	0.21	83

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	6.50±0.62	7.60±0.17	8.50±0.10	7.903±0.56	7.203±0.56	8.303±0.44	7.803±0.54	8.103±0.98	8.403±0.17
1	12.00±0.47	13.80±0.29	15.40±0.14	14.30±0.89	13.10±0.78	15.60±0.51	14.90±0.11	15.30±0.10	15.70±0.14
2	20.00±0.41	23.±0.33	26.10±0.78	23.90±0.57	22.00±0.74	25.90±0.41	24.80±0.64	26.10±0.23	27.00±0.65
4	30.00±0.25	33.40±0.47	37.20±0.21	34.70±0.55	32.00±0.88	37.20±0.70	36.20±0.14	38.20±0.14	38.80±0.47
6	40.00±0.75	43.20	47.30±0.29	44.50±0.18	42.00±0.47	47.50±0.41	46.80±0.17	48.90±0.17	50.50±0.54
8	50.00±0.11	53.10±0.44	57.40±0.38	54.30±0.78	52.00±0.24	57.80±0.78	57.40±0.47	59.70±0.47	62.20±0.45
10	60.00±0.05	63.00±0.21	67.50±0.47	64.10±0.78	62.00±0.87	68.10±0.23	68.00±0.87	70.50±0.78	73.90±0.57
12	85.19±0.10	89.16±0.27	90.74±0.19	92.10±0.45	83.54±0.50	94.23±0.44	81.11±0.59	88.42±0.51	82.47±0.13

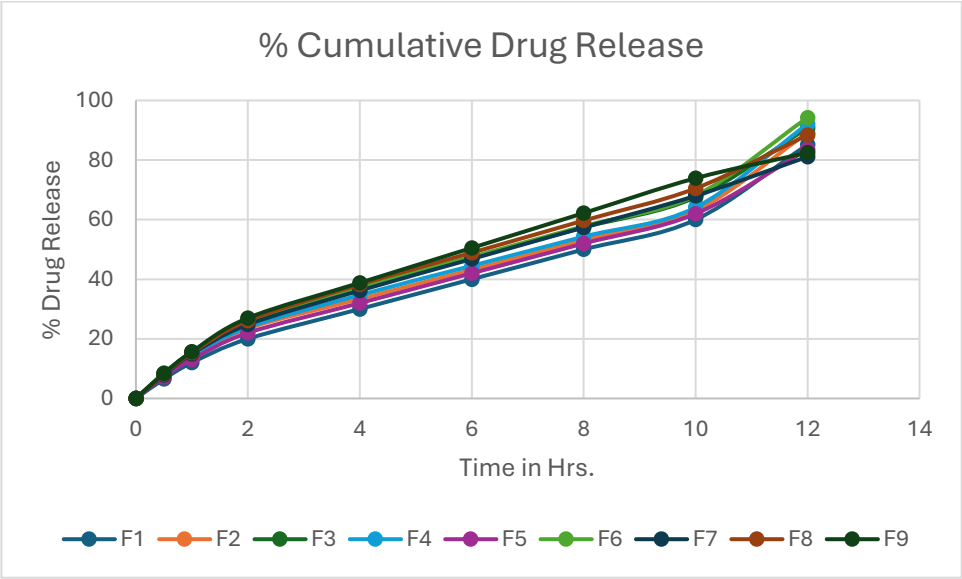


Figure 4 Drug Release Profile of Various formulations

Table 4 Comparative Dissolution Profile

Time (hours)	F10{Pure API Without Polymer	F6 (Best Formulation with Polymer)	F11 Marketed Formulation (CTD)
0	0	0	0
0.5	10.22± 1.18	8.30±0.44	50.50
1	25.87± 3.18	15.60±0.51	75.23
2	40.24± 2.23	25.90±0.41	83.47
4	50.45±1.17	37.20±0.70	-
6	56.78±2.07	47.50±0.41	-
8	-	57.80±0.78	-
10	-	68.10±0.23	-

12	-	94.23±0.44	-
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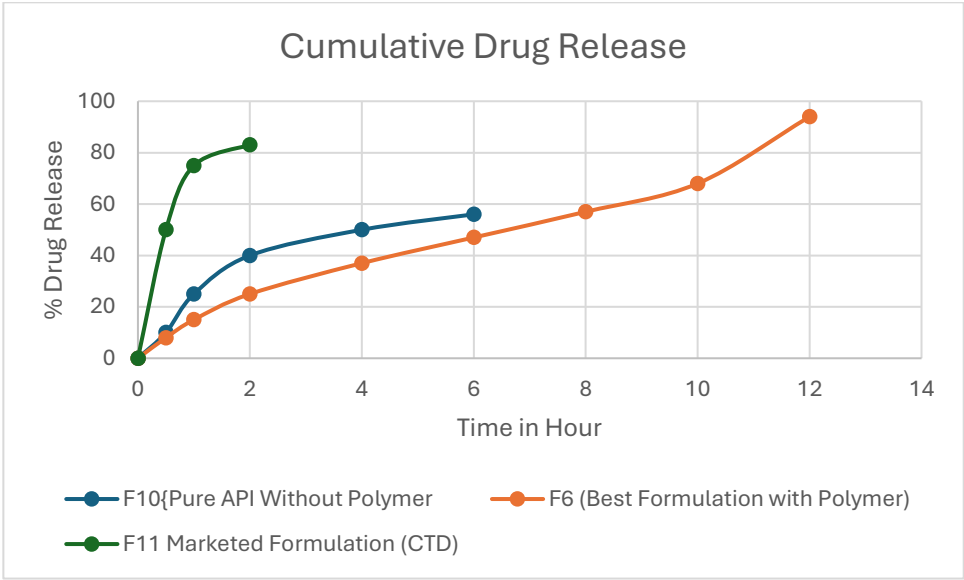


Figure 5 % Cumulative Drug Release of Pure drug (F10) Drug with Polymer (F6) Best formulation and F11 Marketed formulation Telma 40)

RESULT & DISCUSSION

The experimental design and statistical analysis of the co-processed formulation of chlorthalidone tablets using a 3² factorial design yielded significant insights into the optimization process. Among the various formulations (F1 to F9), the optimized formulation was identified based on several key parameters, including drug release, compressibility, and micromeritic properties. The ANOVA results indicated that sodium starch glycolate (B) was a significantly different model component as indicated by a p-value of 0.0020, implying its critical role in enhancing drug release. The model exhibited statistical significance, as indicated by an F-value of 22.03 and a p-value of 0.0143, and the optimized formulation showed a drug release profile that met the desired criteria, ensuring rapid and complete release of chlorthalidone.

The optimized formulation exhibited favourable micromeritic properties with a compressibility index of 8.2%, indicating good flow properties, and a particle size uniformity of 152.9 µm, ensuring consistent blending and tablet formation. The angle of repose measured at 25.10° suggested excellent flowability of the powder blend, The tapped densities and bulk were measured to be 0.472 g/cc and 0.442 g/cc and, respectively, providing a compressibility ratio suitable for direct compression. The optimized formulation remained insoluble in water and organic solvents, maintaining stability under various

conditions, with a pH of 6.9 in a 1% aqueous dispersion and a charring point at 255°C, confirming its thermal stability.

The prepared chlorthalidone tablets underwent a series of evaluations to ensure they met the required standards. The content uniformity was consistent across tablets, ensuring proper dosage, and the tablets had a hardness of 6 kg/cm², sufficient to withstand handling without breaking. The friability tests showed low friability, indicating that the tablets would not crumble easily. The dissolution study demonstrated that the optimized formulation released chlorthalidone efficiently, making the drug available for absorption within the expected timeframe.

CONCLUSION

In conclusion, the optimized formulation of chlorthalidone tablets, using a co-processed blend of xylitol, mannitol, and microcrystalline cellulose, exhibited excellent pharmaceutical properties. The factorial design and ANOVA analysis revealed that sodium starch glycolate played a crucial role in enhancing drug release, ensuring rapid and complete availability of chlorthalidone. The micromeritic properties, including a compressibility index of 8.2%, particle size uniformity of 152.9 µm, and an angle of repose of 25.10°, indicated good flowability and compressibility, making the blend suitable for direct compression. Furthermore, the formulation-maintained stability under various conditions with a pH of 6.9 and thermal stability up to 255°C.

The prepared chlorthalidone tablets met all the required quality standards, including consistent content uniformity, sufficient hardness, low friability, and efficient drug dissolution rates. Thus, these results emphasize the need of systematic formulation development and rigorous testing to achieve an optimized pharmaceutical product. The successful optimization of the chlorthalidone tablets demonstrates the capacity of co-processed additives to improve the performance and manufacturability of drug formulations, paving the way for their broader application in the pharmaceutical industry.

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REFERENCES:

1. Melia, C D., & Davis, S. (1989, December 1). Review article: mechanisms of drug release from tablets and capsules. 2. Dissolution. Wiley-Blackwell, 3(6), 513-525. <https://doi.org/10.1111/j.1365-2036.1989.tb00243.x>
2. Cao, Y., Shi, L., Cao, Q., Yang, M., & Cui, J. (2016, January 1). In-Vitro Characterization and Oral Bioavailability of Organic Solvent-free Solid Dispersions Containing Telmisartan. National Institutes of Health, 15(2), 385-94. <https://pubmed.ncbi.nlm.nih.gov/27642309>
3. Kanikkannan, N. (2018, February 1). Technologies to Improve the Solubility, Dissolution and Bioavailability of Poorly Soluble Drugs. MedCrave Group, 7(1). <https://doi.org/10.15406/japlr.2018.07.00198>
4. Williams, H D., Trevaskis, N L., Charman, S A., Shanker, R., Charman, W N., Pouton, C W., & Porter, C J H. (2013, January 1). Strategies to Address Low Drug Solubility in Discovery

- and Development. American Society for Pharmacology and Experimental Therapeutics, 65(1), 315-499. <https://doi.org/10.1124/pr.112.005660>
5. Jackson, K., Young, D., & Pant, S. (2000, October 1). Drug–excipient interactions and their affect on absorption. Elsevier BV, 3(10), 336-345. [https://doi.org/10.1016/s1461-5347\(00\)00301-1](https://doi.org/10.1016/s1461-5347(00)00301-1)
6. Ahuja, N., Katare, O. P., & Singh, B. (2007). Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. *European Journal of Pharmaceutics and Biopharmaceutics*, 65(1), 26-38. doi: 10.1016/j.ejpb.2006.07.007
7. Chaudhari, P., Uttekar, S., Somwanshi, S., & Kuchekar, B. S. (2012). Enhancement of solubility and dissolution rate of poorly water-soluble drug by preparing solid dispersion using fluid bed coating technique. *AAPS PharmSciTech*, 13(4), 1283-1295. doi:10.1208/s12249-012-9861-8
8. Kapoor, B., Kaur, R., Behl, G., & Jain, S. (2017). Oral bioavailability enhancement of poorly absorbed drugs: barriers, recent advancements and approaches. *Journal of Drug Delivery Science and Technology*, 41, 59-75. doi: 10.1016/j.jddst.2017.07.011
9. Rojas, J., Buckner, I S., & Kumar, V. (2012, September 12). Co-processed excipients with enhanced direct compression functionality for improved tableting performance. *Taylor & Francis*, 38(10), 1159-1170. <https://doi.org/10.3109/03639045.2011.645833>
10. 10. Kaur, I. P., Singh, M., & Kanwar, M. (2000). Formulation and evaluation of ophthalmic preparations of acetazolamide. *International journal of pharmaceutics*, 199(2), 119-127.
11. 11. Jaimini, M., Rana, A. C., & Tanwar, Y. S. (2007). Formulation and evaluation of famotidine floating tablets. *Current drug delivery*, 4(1), 51-55.
12. 12. Jaimini, M., Rana, A. C., & Tanwar, Y. S. (2007). Formulation and evaluation of famotidine floating tablets. *Current drug delivery*, 4(1), 51-55.
13. 13. Malke, S., Shidhayee, S., & Kadam, V. J. (2007). Formulation and Evaluation of Oxcarbazepine Fast Dissolve Tablets. *Indian journal of pharmaceutical sciences*, 69(2).
14. 14. Kala, S., & Juyal, D. (2016). Preformulation and characterization studies of aceclofenac active ingredient. *The Pharma Innovation*, 5(9, Part B), 110.
15. 15. Cristea, M., Baul, B., Ledeți, I., Ledeți, A., Vlase, G., Vlase, T., ... & Ștefănescu, M. (2019). Preformulation studies for atorvastatin calcium: An instrumental approach. *Journal of Thermal Analysis and Calorimetry*, 138, 2799-2806.
16. 16. Cristea, M., Baul, B., Ledeți, I., Ledeți, A., Vlase, G., Vlase, T., ... & Ștefănescu, M. (2019). Preformulation studies for atorvastatin calcium: An instrumental approach. *Journal of Thermal Analysis and Calorimetry*, 138, 2799-2806.
17. 17. Ledeți, I., Budiul, M., Matusz, P., Vlase, G., Circioban, D., Dehelean, C., ... & Bolintineanu, S. (2018). Preformulation studies for nortriptyline: Solid-state compatibility with pharmaceutical excipients. *Journal of Thermal Analysis and Calorimetry*, 131, 191-199.
18. 18. Brown, M., Antunes, E., Glass, B., Lebet, M., & Walker, R. (1999). DSC screening of potential prochlorperazine-excipient interactions in preformulation studies. *Journal of Thermal Analysis and Calorimetry*, 56(3), 1317-1322.
19. 19. Ghaderi, F., Nemati, M., Siahi-Shadbad, M. R., Valizadeh, H., & Monajjemzadeh, F. (2016). DSC kinetic study of the incompatibility of doxepin with dextrose: application to pharmaceutical preformulation studies. *Journal of Thermal Analysis and Calorimetry*, 123, 2081-2090.
20. 20 . Goldsmith, J. (2017). A comparative user evaluation of tablets and tools for consecutive interpreters. *Proceedings of Translating and the Computer*, 39, 40-50.

21. 21. Patel, S. G., & Siddaiah, M. (2018). Formulation and evaluation of effervescent tablets: a review. *Journal of drug delivery and therapeutics*, 8(6), 296-303.
22. 22. Jaimini, M., Rana, A. C., & Tanwar, Y. S. (2007). Formulation and evaluation of famotidine floating tablets. *Current drug delivery*, 4(1), 51-55.
23. 23 Kondawar, M. S., Shah, R. R., Waghmare, J. J., Shah, N. D., & Malusare, M. K. (2011). UV spectrophotometric estimation of paracetamol and lornoxicam in bulk drug and tablet dosage form using multiwavelength method. *International Journal of PharmTech Research*, 3(3), 1603-1608.
24. 24. Islam, S. A., Islam, S., Shahriar, M., & Dewan, I. (2011). Comparative in vitro dissolution study of aceclofenac marketed tablets in two different dissolution media by validated analytical method. *Journal of Applied Pharmaceutical Science*, (Issue), 87-92.