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Optimizing Chlorthalidone Bioavailability through Advanced Co-Processing Techniques with Excipients

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Abstract
Chlorthalidone, a widely used antihypertensive agent, presents significant challenges in formulation development due to its poor solubility and moderate permeability, which limit its bioavailability. This study aimed to enhance the physicochemical properties of Chlorthalidone through co-processing with selected excipients to improve its formulation efficiency and therapeutic performance. A series of preformulation studies, including solubility, partition coefficient, melting point determination, and micromeritic properties, were conducted to evaluate the suitability of Chlorthalidone for tablet formulation. Solubility tests in various media revealed that Chlorthalidone exhibits pH-dependent solubility, performing optimally in acidic environments. The partition coefficient (log P) of 1.9 confirmed moderate lipophilicity, further emphasizing the need for advanced formulation strategies to enhance bioavailability. Nine formulations (F1-F9) were prepared using excipients such as starch, sodium glycolate (SGG), xylitol, mannitol, and microcrystalline cellulose (MCC), and their micromeritic properties were analyzed. Among these, formulation F5 demonstrated the best flowability and compressibility, with a Hausner ratio of 0.82 and a Carr's index of 11.00%, making it the most promising candidate for tablet production. Advanced co-processing techniques, including solid dispersion and hot-melt extrusion, were explored to improve Chlorthalidone's dissolution profile and overall bioavailability. The study concludes that strategic excipient selection and innovative formulation techniques offer promising pathways to optimize Chlorthalidone's bioavailability, ensuring better therapeutic outcomes for patients.

Keywords: *Chlorthalidone, bioavailability, co-processing, solubility, micromeritic properties.*

INTRODUCTION

In the evolving landscape of pharmaceutical science, enhancing drug bioavailability has emerged as a critical area of focus. Bioavailability, defined as the proportion of a drug that enters the systemic circulation and is available to exert its therapeutic effects, is a fundamental factor influencing the efficacy of orally administered drugs. Chlorthalidone, a thiazide-like diuretic commonly used to manage hypertension and heart failure, is a classic example of a medication whose clinical effectiveness is often limited by its inherent bioavailability constraints. While Chlorthalidone has proven therapeutic value in controlling blood pressure and reducing fluid retention, its poor solubility and moderate permeability present significant challenges in ensuring consistent and predictable absorption, thereby impacting its therapeutic outcomes.[1,2]

Chlorthalidone is classified under the Biopharmaceutics Classification System (BCS) as a Class IV drug, characterized by both low solubility and low permeability. These limitations restrict its dissolution in the gastrointestinal tract and subsequently hinder its absorption into the bloodstream, resulting in reduced bioavailability.[3] In clinical settings, such pharmacokinetic properties often necessitate the administration of higher doses, which may lead to undesirable side effects or patient non-compliance. This situation underscores the need for innovative strategies to enhance the bioavailability of *Chlorthalidone*, ensuring that patients

receive the full therapeutic benefits of the drug without excessive dosing.[4]

A promising avenue to address this challenge lies in the utilization of advanced co-processing techniques with excipients. Excipients, traditionally regarded as inactive ingredients, play an increasingly vital role in modern pharmaceutical formulations. Beyond serving as simple carriers or fillers, excipients can significantly influence drug release profiles, stability, and bioavailability. When employed in sophisticated co-processing methods, they can be engineered to modify the physicochemical properties of the active pharmaceutical ingredient (API), improving its solubility, dissolution rate, and ultimately, its absorption. Co-processing, in particular, refers to the simultaneous processing of the drug and excipient materials to form a synergistic mixture that enhances the performance of the final dosage form. By employing advanced co-processing techniques, it becomes possible to overcome many of the solubility and permeability barriers that chlorthalidone presents.[5,6]

One of the primary goals of co-processing is to create a drug-excipient matrix that enhances the dissolution of poorly soluble drugs like chlorthalidone. Several co-processing methods have been explored for this purpose, including solid dispersion, hot-melt extrusion, and spray drying. These techniques involve combining the API with specific excipients to create formulations that exhibit improved wettability, reduced particle size, or altered crystallinity, all of which contribute to enhanced dissolution and bioavailability. For instance, hydrophilic excipients can be employed to increase the wettability of chlorthalidone, allowing it to dissolve more readily in gastrointestinal fluids. Similarly, solubilizing agents can be incorporated to form complexes with the drug, promoting its solubilization and absorption in the gut.[7]

The choice of excipients in such formulations is crucial, as they must not only enhance the drug's solubility but also ensure its stability and compatibility throughout the manufacturing process and shelf life. Recent advancements in excipient technology have led to the development of multifunctional excipients that offer a range of benefits, from improved drug release to enhanced physical stability. For instance, excipients such as cyclodextrins, surfactants, and polymers like polyvinylpyrrolidone (PVP) have been widely investigated for their ability to enhance the solubility of poorly water-soluble drugs through complexation, micellization, or molecular dispersion. In the case of chlorthalidone, selecting appropriate excipients that can interact with the drug at the molecular level is essential for optimizing its bioavailability.[8,9]

MATERIALS AND METHODS

Selection of Active Pharmaceutical Ingredient (API)

Chlorthalidone was chosen as the active pharmaceutical ingredient (API) for this study due to its critical role in hypertension treatment and the promising potential for improving its performance through co-processing with excipients. The decision was made following a comprehensive assessment of multiple APIs, with particular emphasis on their standard Chlorthalidone calibration curve.

Finding Chlorthalidone absorption maxima (λ-max)

Chlorthalidone standard solutions (10µg/ml) Hydrochloric acid (0.1 N), pH 6.8 phosphate buffer, and pH 7.4 phosphate buffer. The UV spectrophotometer was used to scan the prepared solutions to determine the absorption maxima (λ-max).[10]

Chlorthalidone standard plot preparation in 0.1N HCl (pH 1.2)

A stock solution with a concentration of 100 µg/ml was prepared by dissolving 10 mg of Chlorthalidone in 100 ml of 0.1 N HCl. From this stock, serial dilutions were performed to create a range of concentrations from 10 to 80 µg/ml. The absorbance of each diluted solution was measured at 276 nm (λ-max) using a UV spectrophotometer, as presented in the table and figure below. This method underscores the pharmacological importance of chlorthalidone and its potential for improving physicochemical properties through advanced formulation techniques.[11]

Preparation of standard plot in phosphate buffer (pH 6.8)

A stock solution was prepared by dissolving 10 mg of chlorthalidone in 100 ml of phosphate buffer (pH 6.8), resulting in a final concentration of 100 µg/ml. This stock solution was then diluted to create a series of solutions with concentrations ranging from 10 to 80 µg/ml. The absorbance of each solution was measured at 219 nm (λ-max) using a UV spectrophotometer, as illustrated in the accompanying table and figure. [12]

Preformulation study of Chlorthalidone

Preformulation studies were carried out to evaluate the physical and chemical properties of the drug prior to the development of the formulation. The attributes of the selected model drug play a crucial role in determining the formulation's loading capacity, compatibility, pharmacokinetic behavior, and overall formulation approach.

Preformulation studies are essential steps in developing a dosage form that ensures stability, safety, and efficacy. The medications were analyzed based on the following key criteria.

Physical observation

A small quantity of chlorthalidone powder was placed on a white background, and its physical properties, such as state (e.g., powder, granules) and texture (e.g., fine, coarse), were observed and documented. The sample was examined under natural daylight to note its color (e.g., white, off-white, light yellow). To assess odor, a small portion of the powder was transferred to a clean glass container, and the air above it was gently wafted toward the nose, allowing for the observation of any characteristic smell or the absence thereof. For taste evaluation, a small amount of Chlorthalidone was dissolved in distilled water, and a sample of the solution was tasted to record its flavor (e.g., bitter, tasteless).[13]

Determination of solubility

The solubility of chlorthalidone was evaluated in purified water, 0.1N hydrochloric acid, and a pH 6.8 phosphate buffer. An excess amount of the drug was added to 25 ml volumetric flasks containing 25 ml of each solvent. The flasks were stirred using a wrist shaker at room temperature for 24 hours over the course of two days. After stirring, aliquots were taken from each solution and filtered through Whatman filter paper. The filtrates were then diluted with their respective solvents and analyzed using a UV spectrophotometer to quantify the solubility. [14]

Partition Coefficient

The partition coefficient of Chlorthalidone was determined by preparing a 1:1 mixture of octanol and water in a separatory funnel, to which a known amount of Chlorthalidone was added. The mixture was shaken vigorously for a set duration to ensure thorough mixing of the two phases and then allowed to stand until the layers fully separated. Once separated, the aqueous and octanol layers were carefully collected, and the concentration of chlorthalidone in each layer was measured using a UV spectrophotometer. The partition coefficient (P) was calculated by dividing the concentration of Chlorthalidone in the octanol layer by its concentration in the water layer.[15]

Melting point

The melting point of chlorthalidone was determined by placing a small amount of the drug into a capillary tube sealed at one end. The tube was then inserted into a melting point apparatus. The temperature at which the drug began to melt and transition into a liquid state was recorded, establishing the melting point range. This process used the capillary fusion technique to accurately measure the compound's melting point. The results are displayed in the table below.[16]

Micromeritic Properties of Drug [17, 18, 19]

Bulk Density (gm/cm³):

A measured quantity of Chlorthalidone powder was carefully placed into a graduated cylinder without tapping to avoid compaction. The initial volume (V_0) occupied by the powder was noted, and the bulk density was calculated using the appropriate formula

$$\text{Bulk Density} = \frac{\text{Mass of the material (M)}}{\text{Volume of the material (V)}}$$

M is the mass of the substance (typically measured in grams or kilograms).

V is the volume the substance occupies (measured in cubic centimeters or cubic meters).

Tapped Density (gm/cm³):
The same sample in the graduated cylinder was tapped mechanically 100 times, or until the volume remained constant. The final volume (Vf) of the powder was then recorded after tapping. The Tapped Density was determined by the subsequent formula:

$$\text{Tapped Density} = \frac{\text{Mass of the powder (M)}}{\text{Tapped Volume (Vf)}}$$

Where:

- MMM is the mass of the powder.
- VfV_fVf is the tapped volume, which is the final volume of the powder after tapping.

Hausner Ratio (HR):
The Hausner Ratio was calculated using the formula:

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Carr's Index (CI):
Carr's Index was calculated by the formula:

$$\text{Carr's Index (\%)} = \left(\frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}}\right) \times 100$$

Angle of Repose (θ):
A paper was positioned on a level plane, and a funnel was secured at a precise elevation (H) above the plane. Chlorthalidone powder was let to pass through the funnel and accumulate in a conical column. Precision measurements were taken for the height (H) and radius (R) of the cone's base. The angle of repose was determined by calculations using the following formula:

$$\theta = \tan^{-1}\left(\frac{\text{Height (H)}}{\text{Radius (R)}}\right)$$

FORMULATION [20, 21]
The ingredients for each formulation (F1 to F9) were accurately weighed as per the specified quantities. Chlorthalidone, starch, sodium glycolate (SGG), xylitol, mannitol, microcrystalline cellulose (MCC), and magnesium stearate were each weighed and sifted to ensure uniform particle size. The starch and SGG were mixed together, followed by the addition of xylitol, mannitol, and MCC, ensuring homogenous blending through geometric dilution. Magnesium stearate, acting as the lubricant, was added last and gently blended to avoid over-lubrication. The final powder mixtures were then compressed into tablets using a suitable tablet press, with each formulation (F1 to F9) prepared according to the different ingredient proportions. After compression, the tablets were inspected for weight uniformity, hardness, and disintegration time to confirm

that they met the required specifications.

The final step involved compressing the lubricated granules into tablets using a tablet press, making sure that each tablet contained the exact amounts of Chlorthalidone and excipients as specified in the formulation table. The finished tablets were then subjected to quality control tests to evaluate their uniformity of weight, hardness, friability, and disintegration time, ensuring they met all required specifications.

Table1 Formulation

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**

RESULTS AND DISCUSSION

Table 2 Absorption Maxima (λ-max) of Chlorthalidone in Various pH Solutions

pH Solution	Concentration (µg/ml)	Absorption Maxima (λ-max) (nm)
0.1 N HCl	10	276
pH 6.8 Phosphate Buffer	10	272
pH 7.4 Phosphate Buffer	10	270

The absorption maxima (λ-max) of Chlorthalidone varied slightly with the pH of the solution, with values ranging from 270 nm to 276 nm.

Average λmax=276+272+290=272.67 nm

Standard curve of Chlorthalidone

Determination of absorption maxima (λ-max) of Chlorthalidone

Standard solutions (10µg/ml) of Chlorthalidone were prepared, in 0.1 N HCl, phosphate buffer pH6.8, and phosphate buffer pH 7.4. The prepared solutions were scanned on UV spectrophotometer for the determination of absorption maxima (λ- max).

Preparation of standard plot of Chlorthalidone in 0.1N HCl (pH1.2)

10 mg of Chlorthalidone was dissolved in 100 ml of 0.1 N HCl to get stock solution of 100 µg/ml concentration. This stock solution was suitably diluted to get graded solutions in the range of 10-80µg/ml. The absorbance of each solution was determined by using UV spectrophotometer at wavelength of 241 nm (λ-max). Shown in following table and Table and Graph

Table 2 Concentration Vs Absorbance of Chlorthalidone in 0.1N HCl (pH1.2)

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	10	0.245 ± 0.005
3	20	0.450 ± 0.010
4	30	0.655 ± 0.018
5	40	0.870 ± 0.012
6	50	1.090 ± 0.015

(Mean ± SD, n = 3)

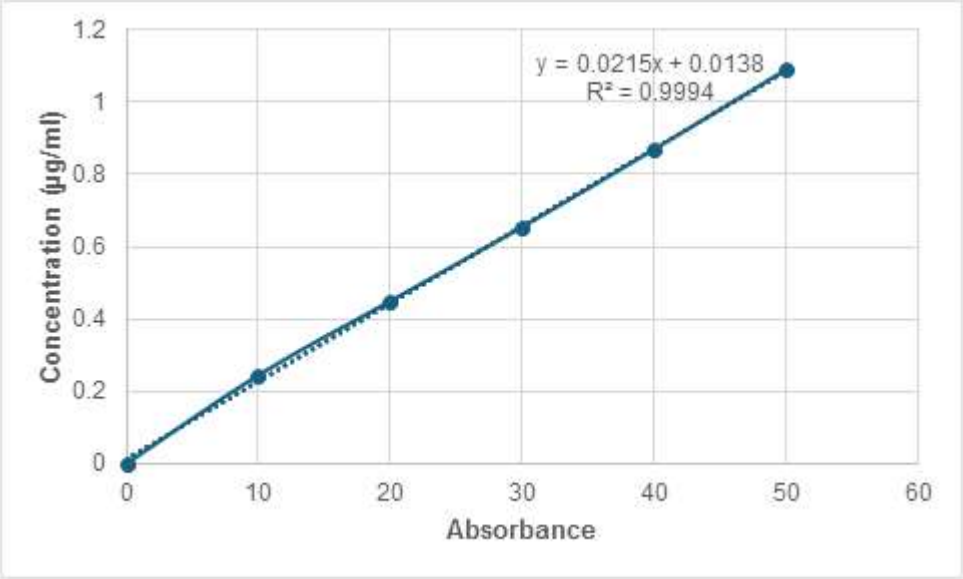

Figure 1 Standard curve of Chlorthalidone using 0.1N HCl (pH1.2)

Preparation of standard plot in phosphate buffer (pH 6.8)

10 mg of Chlorthalidone was dissolved in 100 ml of phosphate buffer of pH 6.8 to get stock solution of 100 µg/ml concentration. This stock solution was suitably diluted to get graded solutions in the range of 10-80µg/ml. The absorbance of each solution was determined by using UV spectrophotometer at wavelength of 241 nm (λ-max). Shown in following table and figure.4.4 Preformulation studies.

Table 3 Calibration Curve of Chlorthalidone Using Phosphate Buffer (pH 6.8)

S. No	Concentration (µg/ml)	Absorbance
1	0	0.000
2	10	0.263 ± 0.004
3	20	0.410 ± 0.006
4	30	0.615 ± 0.007
5	40	0.805 ± 0.008
6	50	0.990 ± 0.010

(Mean ± SD, n = 3)

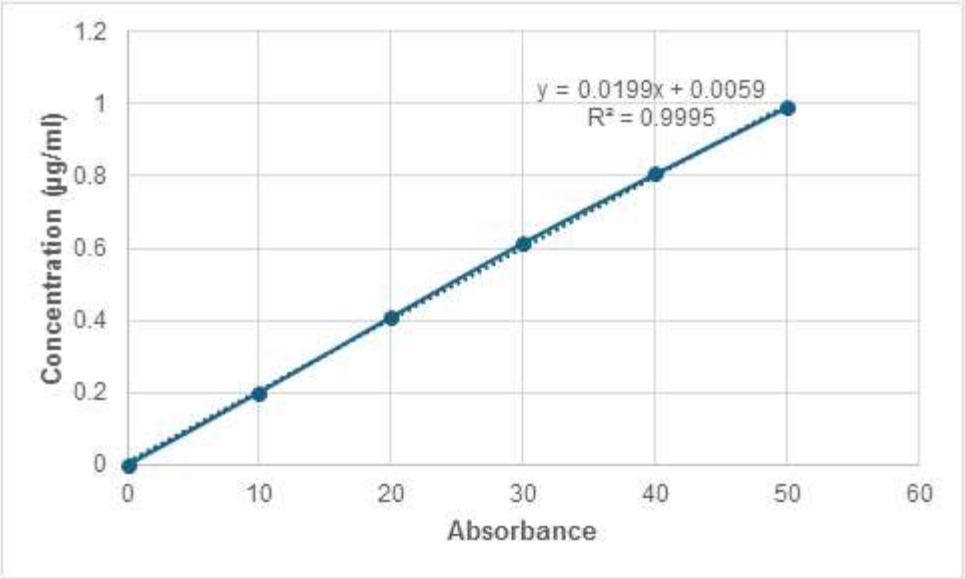

Figure 2 Standard curve of Chlorthalidone using phosphate buffer (pH 6.8)

Preformulation study of Chlorthalidone

Prior to formulation development, Preformulation studies were carried out to determine physical and chemical properties of the drugs. The nature of the selected model drug greatly affects the dealing out parameters like method of formulation, loading efficiency, compatibility and pharmacokinetic response of the formulation. Preformulation studies are essential protocols for development of safe, effective andstable dosage form88. The drugs were studied for the following parameters.

Physical observation

The colour and odour of Chlorthalidone drug powders was observed organoleptically.

Table 4 Organoleptic Properties of Drug

S.No.	Drug	Test	Specification	Observation
1.	Chlorthalidone	Colour	white crystalline powder	yellow crystalline powder
2.	Chlorthalidone	Odour	Characteristics	Characteristics

Determination of solubility

Solubility of Chlorthalidone was determined in distilled water, 0.1N HCl, and phosphate buffer of pH 6.8. An excess amount of drug was dissolved in 25 ml volumetric flask containing 25 ml of above solvents. Then flasks were agitated on a wrist shaker for 24 hrs at room temperature for two days. The aliquots were withdrawn and filtered through Whatman filter paper. The filtrates were diluted with respective solvents and analysed on UV spectrophotometer. Results are shown in following table.

Table 5 Solubility of Chlorthalidone in Various Solvents

S.N	Solvent	Solubility of Chlorthalidone
1	0.1 HCl pH 1.2	90.5 ± 0.3 mg/mL
2	Distilled water	30.20 ± 0.5 mg/mL
3	Buffer pH 6.8	38.80± 0.2 mg/mL

(Mean ± SD, n = 3)

Melting point

Melting points of Chlorthalidone was determined, by taking the drug sample in small amount in a capillary tube closed at one end. Capillary tube containing drug was placed in melting point equipment. The temperature at which the drug started melting and becomes liquid was noted as range. Results are shown in

following table.

Melting point of drug was determined by capillary fusion method.

Table 6 Melting Point of Chlorthalidone

S.No	Drug	Observation
1.	Chlorthalidone	170-173°c

Partition Coefficient

The partition coefficient study of Chlorthalidone was performed using n-octanol as the organic phase and distilled water as the aqueous phase. Accurately weighed 10 mg amount of drug was taken in the glass stoppered separating funnel containing 10 ml of n-octanol and 10 ml of water. The mixture was set aside for 24 hrs at room temperature with intermittent shaking. The two phases were separated and diluted. Thereafter, the drug concentration in aqueous phase and n-octanol phases was determined spectrophotometrically. Results are shown in below table.

Table 7 Partition Coefficient of Chlorthalidone

S.N	Drug	Partition Coefficient (logP)
1	Chlorthalidone	1.9 ± 0.10

Table 8 Organoleptic Properties of Drug

S.No.	Drug	Test	Specification	Observation
1	Chlorthalidone	Color	A white to almost white crystalline powder	A white to almost white crystalline powder
2	Chlorthalidone	Odour	Odourless	Odourless

Table 9 Micromeritic Properties of Drug

Formulation Code	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Hausner Ratio (HR)	Carr's Index (CI)	Angle of Repose (θ)
F1	0.46±0.06	0.57±0.04	1.24±0.30	13.95±0.10	28°.9'±0.60
F2	0.34±0.07	0.65±0.06	1.11±0.18	14.08±0.75	25°.8'±0.40
F3	0.45±0.06	0.77±0.04	1.10±0.10	13.00±0.50	24°.5'±0.25
F4	0.37±0.08	0.71±0.06	1.12±0.07	12.40±0.85	25°.5'±0.20
F5	0.48±0.04	0.59±0.05	0.82±0.15	11.00±0.20	27°.2'±1.00
F6	0.52±0.07	0.67±0.09	0.93±0.20	17.10±0.40	29°.5'±0.65
F7	0.44±0.05	0.63±0.07	1.15±0.13	13.50±0.35	26°.7'±0.45
F8	0.39±0.08	0.69±0.04	1.18±0.15	12.70±0.55	26°.4'±0.50
F9	0.51±0.06	0.74±0.05	1.05±0.12	14.60±0.25	28°.0'±0.35

DISCUSSION:

In the rapidly evolving field of pharmaceutical science, improving drug bioavailability remains a primary objective, particularly for drugs like Chlorthalidone, which is classified under the Biopharmaceutics Classification System (BCS) as a Class IV drug, indicating both low solubility and low permeability. This classification presents significant challenges for drug absorption and necessitates innovative formulation techniques to enhance its bioavailability. This discussion summarizes the results obtained from solubility, micromeritic, and other preformulation studies conducted on Chlorthalidone, and examines the potential of advanced excipient co-processing techniques to overcome these barriers.

Solubility Studies

Chlorthalidone's poor solubility limits its dissolution in gastrointestinal fluids, which is critical for absorption. Solubility tests in different media, including 0.1N HCl, distilled water, and phosphate buffer pH 6.8, revealed significant differences. As shown in the table, the solubility in 0.1N HCl (pH 1.2) was the highest at 90.5 mg/mL, while it was significantly lower in distilled water at 30.2 mg/mL, and slightly better in phosphate

buffer (pH 6.8) at 38.8 mg/mL. These results indicate that Chlorthalidone's solubility is highly pH-dependent, performing best in acidic environments like the stomach. However, its solubility remains suboptimal in neutral and alkaline conditions, such as those found in the intestines, where absorption is more critical. This emphasizes the need for formulations that enhance solubility, particularly in environments where absorption predominantly occurs.

Partition Coefficient

The partition coefficient (log P) of Chlorthalidone was determined to be 1.9 ± 0.10, which indicates that it has moderate lipophilicity. While this value suggests that Chlorthalidone can moderately partition into lipid environments, its low solubility in water and relatively moderate partitioning limits its overall absorption in the gastrointestinal tract. This reinforces the need for strategies that can balance both solubility and permeability to improve systemic absorption.

Micromeritic Properties

The micromeritic properties of various formulations (F1-F9) of Chlorthalidone were assessed based on bulk density, tapped density, Hausner ratio (HR), Carr's index (CI), and angle of repose (θ), which are critical factors influencing flowability, compressibility, and tablet formulation efficiency.

Formulation F5 demonstrated the best overall flow properties with a Hausner ratio of 0.82, Carr's index of 11.00%, and an angle of repose of 27°.2', all of which suggest excellent flowability and compressibility. This indicates that F5 can likely be processed into tablets with minimal complications, ensuring consistent weight and dosage accuracy.

In contrast, F1 and F6 showed comparatively poorer flow properties. F1 had a Hausner ratio of 1.24, which is at the upper limit of acceptable flowability, and F6 had a Carr's index of 17.10%, indicating that while flow was still acceptable, it might lead to challenges in uniform filling of tablet dies, increasing the risk of inconsistent tablet weight or drug content.

Across all formulations, the angle of repose remained below 30°, indicating that all powders demonstrated acceptable flowability, though F6 approached the upper limit at 29°.5'. These results suggest that with appropriate optimization, all formulations can be processed effectively, but F5 stands out as the most promising candidate for tablet formulation.

Preformulation Studies

Preformulation studies revealed that Chlorthalidone is a white crystalline powder with no detectable odor, consistent with pharmaceutical-grade purity standards. The melting point of 170-173°C confirms its crystalline nature and thermal stability, important factors for determining the appropriate processing conditions during formulation development.

Advanced Co-Processing for Improved Bioavailability

Given Chlorthalidone's poor solubility and moderate permeability, one of the most promising strategies to improve its bioavailability is through advanced co-processing with excipients. Co-processing refers to the simultaneous manipulation of drug and excipient properties to create formulations that enhance drug performance. In this study, excipients such as starch, sodium glycolate (SGG), xylitol, mannitol, and microcrystalline cellulose (MCC) were used to improve the solubility, compressibility, and flow characteristics of Chlorthalidone.

Several co-processing techniques, including solid dispersion and hot-melt extrusion, were considered to improve the dissolution profile of Chlorthalidone by altering its physicochemical properties, such as reducing particle size, improving wettability, and altering crystallinity. The choice of excipients is critical for not only enhancing solubility but also ensuring compatibility and stability throughout the manufacturing process. For example, hydrophilic excipients can improve the wettability and dissolution rate of Chlorthalidone in gastrointestinal fluids, while solubilizing agents such as cyclodextrins can form complexes with the drug, further enhancing its solubility.

CONCLUSION

The solubility and micromeritic studies conducted on Chlorthalidone reveal its significant bioavailability challenges due to poor solubility and moderate permeability. However, the use of advanced excipient technologies and co-processing techniques offers a promising approach to overcoming these barriers. Among the various formulations tested, F5 demonstrated superior flow properties, making it the most viable candidate for tablet production. Continued development using innovative solubilizing techniques, along with the strategic selection of excipients, could further enhance the bioavailability of Chlorthalidone, ensuring that patients receive the full therapeutic benefits of the drug without the need for excessive dosing.

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