RESEARCH PAPER

Formulation Development and Stability Evaluation of Phenazopyridine Film-Coated Tablets

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Abstract
The present study was aimed at developing and evaluating Phenazopyridine Hydrochloride direct compressible granules film-coated tablets and their stability under long term and accelerated storage conditions. Phenazopyridine Hydrochloride tablets were prepared by direct compression, followed by aqueous film coating using HPMC E5 as the film-forming polymer, polyethylene glycol 6000 as the plasticizer, purified water as the coating solvent and carnauba wax as the polishing agent. The optimized 200mg formulation was 303.03 mg in weight (core tablet) and 309.09 mg (coated tablet). The tablets were evaluated for description, average weight, thickness, diameter, hardness, friability, disintegration, dissolution, assay, organic impurities and microbial quality. Three batches were used for stability studies with long term conditions at 30°C ± 2°C and 75% RH ± 5% RH for up to 24 months and accelerated conditions at 40°C ± 2°C and 75% RH ± 5% RH for up to 6 months. The optimized tablets had acceptable physical properties and met the dissolution, assay, impurity and microbial specifications. Dissolution was around 93–94% in long term conditions and 93–95% in accelerated conditions. The assay values were within the range of ±90.0–110.0% of the label claim and the impurities were below the specified level. In the study, stable Phenazopyridine Hydrochloride film-coated tablets have been successfully developed.

Keywords: Phenazopyridine Hydrochloride; Film-coated tablets; Direct compression; Dissolution; Stability study
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1. Introduction

Phenazopyridine Hydrochloride is a urinary tract analgesic that is indicated for the symptomatic relief of discomfort related to irritation of the lower urinary tract. It is frequently used to alleviate symptoms associated with pain, burning, urgency, frequency and other unpleasant sensations associated with the irritation of the urinary tract. It does not cure the infection but only helps reduce symptoms and can be taken with antibiotic treatment when necessary for the treatment of a clinical infection. Stability and reproducibility of an oral solid dosage form are of importance in such therapy to ensure accurate dosing, patient acceptability and release of the drug.

Most used oral dosage forms are tablets, which are convenient, dosable, easy to take and can be mass produced. Tablet coating is often used to enhance the tablet's appearance as well as its handling characteristics, patient acceptability and protection from the tablet core. For immediate release tablets, however, the film coat should not adversely impact water penetration, disintegration or drug dissolution. Coating selection and process control become important during development of the tablet formulation, since immediate-release film coating has been demonstrated to affect the disintegration properties of tablets in recent studies [1].

Pharmaceutical coating is also well known as one of the important unit operations to enhance the product performance, appearance and stability of solid dosage forms [2], [3].

Phenazopyridine Hydrochloride has formulation problem due to dissolution being an important quality attribute of its tablet dosage form. Drug formulation in the current development project was carried out by using the direct compressible granules. Direct compression is an easy and simple tablet manufacturing process as it does not involve a wet granulation and drying step. But, for the successful direct compression, the flow, compressibility, compatibility and uniformity of powder filling the dies are important. Factors such as formulation composition, properties of raw material and manufacturing conditions affect tablet disintegration and dissolution performance of direct compression formulations significantly [4]. Also, the use of particle engineering technology, e.g. spray drying, is crucial for direct compression performance as it emphasizes the importance of granule properties in tablet technology [5].

Tablet formulation development process variables include the flow properties of the powder, the speed of the tablet press, the level of powder in the hopper, compression force exerted on the tablet and the tablet

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breaking force, among others, which can affect tablet weight, hardness, friability, disintegration, and dissolution. Inadequate compression can result in manufacturing related problems like sticking, picking, lamination and capping. So, optimization of the process is required to achieve a reproducible physical and chemical quality of the tablets. It has been demonstrated that material behaviour and tablet manufacturing conditions are well correlated with weight variability and compaction behaviour in studies of direct compression processes [6] and [7]. These are particularly critical for the formulation of good quality film coated tablets where the tablet core should have good mechanical strength such that it can resist the pressure of coating and yet be disintegrated and dissolved adequately.

The excipients used are also important in the formulation of Immediate Release Tablets. Excipients may affect hardness, disintegration, dissolution, physical stability and storage properties of tablets. The composition of directly compressed tablets and the behaviour during storage can be critical in terms of the effect it has on the dissolution [8]. Tablet disintegratability is also influenced by disintegrants and compression pressure and is directly related to the drug release from the dosage form [9]. The same applies to coated tablets, where the choice of polymer, plasticizer and solvent system influences on the coating's performance and the flexibility of the coating film, drug release, and drug stability [10].

Stability evaluation is an integral step of dosage form development that ensures that the product retains quality in storage. The important stability parameters for film coated tablets are physical description, assay, dissolution, organic impurities and microbial quality. A suitable formulation should ensure the drug content is maintained within the range of specifications, release of the drug is consistent, no significant increase in impurities and storage is microbiologically acceptable. Hence, long-term and accelerated stability testing give the valuable information about the strength of the formulation and the packaging system's suitability.

The aim of the present work was to develop formulation of Phenazopyridine Hydrochloride film coated tablets by using direct compressible granules and to study the optimized formulation for physicochemical properties, dissolution profile, assay, organic impurities, microbial and stability studies under accelerated and long-term storage condition.

2. Materials and Methods

2.1 Materials

Phenazopyridine Hydrochloride direct-compressible granules were selected to use as an active drug source in preparing film-coated tablets. The granules included microcrystalline cellulose, pregelatinized starch, Povidone K30, Croscarmellose sodium and magnesium stearate (E 574) and Phenazopyridine Hydrochloride. The film former used was Hypromellose/HPMC E5, the plasticizer polyethylene glycol 6000, the coating solvent was purified water and the polishing agent used was carnauba wax. The core tablet weight for the 200 mg tablet was 303.03 mg with a coated tablet weight of 309.09 mg. Assay and impurity analysis was performed using analytical reagent grade: acetonitrile, ammonium acetate, formic acid and HPLC grade water.

2.2 Characterization of Phenazopyridine Hydrochloride

Phenazopyridine Hydrochloride was characterized prior to the formulation development to establish identification, structure, thermal properties and solid-state properties. UV-spectroscopy, FTIR-spectroscopy, ^{1}H NMR-spectroscopy, mass-spectroscopy, elemental-analysis, differential scanning calorimetry and XRD/polymorphism-study were used for characterization. Absorption maxima 390 ± 2 nm and 238 ± 2 nm were obtained from the UV analysis. FTIR confirmed characteristic functional groups, ^{1}H NMR supported proton assignments, mass spectroscopy had a prominent peak at m/z = 214, DSC had a decomposition peak at ~239°C and XRD/polymorphism study indicated no polymorphic variation.

2.3 Drug–Excipient Compatibility Study

To determine the effects of Phenazopyridine Hydrochloride on the selected excipients, drug–excipient compatibility studies were carried out. The drug/direct-compressible granules were stored in binary mixtures with Hypromellose, polyethylene glycol and carnauba wax for 1 month at 40°C ± 2°C / 75% RH ± 5% RH. Samples were analysed for physical changes, chemical changes, by monitoring organic impurities. Physical and chemical compatibility was not observed, thereby verifying the selection of excipients for the formulation.

2.4 Formulation Development and Optimization

The formulation developed by direct compression of Phenazopyridine Hydrochloride direct-compressible granules. Direct compression was chosen as it eliminated extra granulation steps and made the manufacturing of the tablets simpler. Trial batches were developed to address and alleviate manufacturing issues, including sticking, capping, hardness, variation, friability, disintegration and dissolution. Trial A had sticking and capping, Trial B resolved capping and Trial C resolved both sticking and capping. To validate the robustness of the optimized formulation, reproducibility batches Trial D, Trial E and Trial F were then prepared.

2.5 Preparation of Core Tablets

A suitable sieve was used to sift the required quantity of Phenazopyridine Hydrochloride direct-compressible granules using a vibro-sifter to remove agglomerates and to increase flow. The sifted granules were compressed with tablet compression machine. 9.00 mm round, plain punches were used to prepare the target Core tablet weight of 303.03 mg for the 200 mg strength. The in-process controls were tablet weight, tablet hardness, tablet thickness, tablet diameter, friability and appearance. The 200 mg compressed tablets were targeted to be maroon/dark brown, round and plain on both sides.

2.6 Film Coating and Polishing

The coating solution was made by dissolving Hypromellose/HPMC E5 and PEG 6000 in purified water with continuous stirring until the product became a clear solution (about 45 minutes). The solution was filtered prior to use. Coated compressed tablets were produced from the compressed tablets in an auto-coater in controlled conditions. The main coating parameters: pan speed 2-6 rpm, spray rate 80-120 g/min, inlet temperature of about 40°C, atomizing air pressure 2-4 kg/cm², nozzle diameter 1.0 mm, target gain ratio 1.5-2.0%. The coated tablets were then carved with carnauba wax to give a smooth and shiny surface.

2.7 Evaluation of Film-Coated Tablets

The physical quality attributes of the optimized film-coated tablets were studied. Colour, shape, uniformity of coating and surface defects were checked visually by description. 20 tablets were used to find the mean weight. Individual tablet weight and the assay value were used to check uniformity of dosing units, the value of which was accepted NMT 15.0. A Vernier calliper was used to measure the thickness and diameter. The hardness was determined with an appropriate hardness testing machine. The friability was tested by using a friability tester with acceptance limit NMT 1.0% w/w. The disintegration test was carried out in purified water at 37 ± 2°C with an acceptance criterion of NMT 30 minutes.

2.8 Dissolution, Assay and Organic Impurity Testing

The dissolution test was carried out in purified water (USP apparatus 2, paddle, at 37 ± 0.5 °C and 50 r.p.m.). Samples were taken after 45 minutes and filtered through Nylon/PVDF membrane with a pore size of 0.45 µm followed by UV spectrophotometry at 422 nm. The acceptance criterion was 45 minutes, NLT 75% Q. The HPLC conditions were Acetonitrile: water 10:90 was used as a diluent, C18 column, flow rate 1.0 mL/min, injection volume 20 µL, UV detection at 280 nm, and run time 40 minutes. Organic impurities were determined by HPLC with UV detection at 240 nm with limits of NMT 0.2% for the individual impurities not specified and NMT 2.0% for the total of impurities.

2.9 Microbial Evaluation

The tablets thus developed were subjected to microbial evaluation for confirmation of the microbiological quality of the developed tablets. Tests conducted were total aerobic microbial count, total combined yeast and mold count and presence of specific microorganisms. Acceptance criteria were TAMC of NMT 1000cfu/g, TYMC of NMT 100cfu/g, *Escherichia coli* absent/g, *Salmonella sp.* absent/10g, *Staphylococcus aureus* absent/g *and Pseudomonas aeruginosa* absent/g.

2.10 Stability Study

Three batches of Phenazopyridine Hydrochloride Tablets USP 200 mg (22007, 22008 and 22009) were used for the stability studies. The tablets were formulated in PVDC coated PVC – Aluminium blister pack. The long-term stability was performed at 30 °C ± 2 ° C/ 75%RH ± 5%RH for 24 months and accelerated stability was performed at 40 ° C/ 75%RH ± 5%RH for 6 months. Stability samples were checked for description, dissolution, assay and organic impurities and microbial quality at each stability time point to ensure that the tablets remained physically and chemically stable and in terms of dissolution and microbiological quality during storage.

3. Results

3.1 Characterization of Phenazopyridine Hydrochloride

The drug substance phenazopyridine Hydrochloride was characterized prior to the formulation development to verify the identity, molecular structure, thermal behavior and solid-state characteristics of the drug substance. The characterization studies involved the following: UV spectroscopy, FTIR spectroscopy, ^{1}H NMR spectroscopy, Mass spectroscopy, Elemental analysis, Differential scanning calorimetry and the XRD/polymorphism evaluation. The results showed that the drug substance met the expected structural and physicochemical properties of Phenazopyridine Hydrochloride.

The characteristic absorption behaviour of Phenazopyridine Hydrochloride was confirmed by UV spectroscopic analysis which revealed characteristic absorption maxima at about 390 ± 2 nm and at about 238 ± 2 nm. The UV spectrum exhibited the characteristic absorption maxima of Phenazopyridine Hydrochloride, which confirmed its identity as can be seen in figure 1.

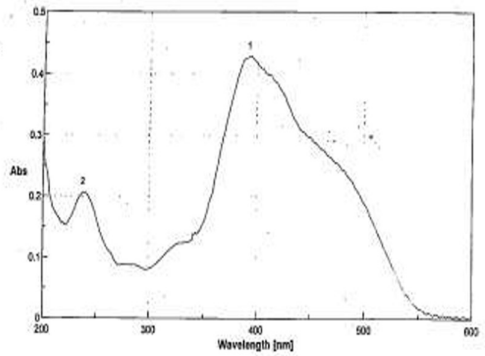

Figure 1. UV absorption spectrum of Phenazopyridine Hydrochloride showing characteristic absorption maxima

The UV spectrum of the working standard was comparable with the reference standard, indicating identity confirmation by UV spectroscopy.

FTIR spectroscopy showed characteristic absorption bands corresponding to major functional groups of Phenazopyridine Hydrochloride. The important peaks included N–H stretching, aromatic C–H stretching, aromatic ring vibrations, NH_2 deformation, pyridine ring deformation and benzene ring deformation. The FTIR spectrum of the working standard was consistent with the reference standard, confirming the presence of characteristic functional groups. The FTIR spectrum

showed characteristic absorption bands corresponding to functional groups of Phenazopyridine Hydrochloride, as shown in Figure 2.

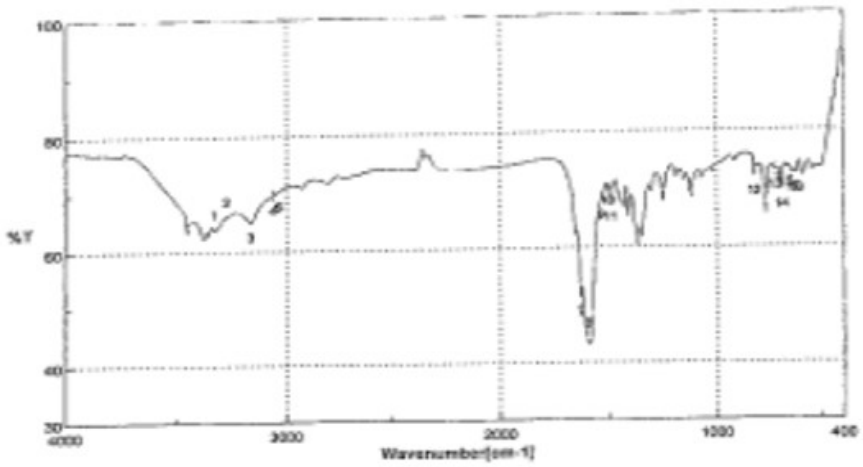

Figure 2. FTIR spectrum of Phenazopyridine Hydrochloride showing characteristic functional group absorption bands

^{1}H NMR spectroscopy was used to confirm the structure of Phenazopyridine Hydrochloride. The chemical shifts corresponded well with the proton assignments that were expected for the drug. This was confirmed by the NMR spectrum of the working standard, which was like that of the reference standard. As shown in Figure 3, the ^{1}H NMR spectrum corresponded to the structure of the compound.

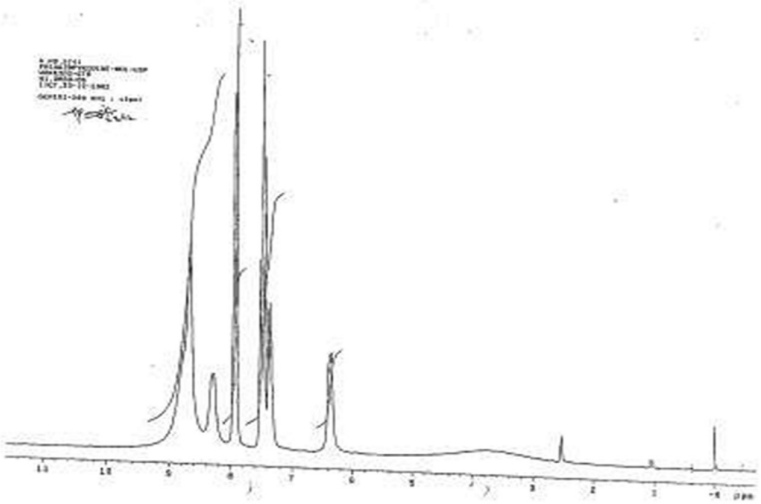

Figure 3. ^{1}H NMR spectrum of Phenazopyridine Hydrochloride confirming proton assignments

Mass spectroscopic analysis showed a prominent ion peak at m/z = 214, which was consistent with the reported value and supported the molecular structure of Phenazopyridine Hydrochloride. Elemental analysis showed that the observed values of carbon, hydrogen and nitrogen agreed with theoretical values, supporting the molecular formula $C_{11}H_{11}N_5 \cdot HCl$.
Differential scanning calorimetry showed exothermic decomposition at approximately 239°C, confirming the thermal behavior of the drug substance. The DSC thermogram showed thermal decomposition of Phenazopyridine Hydrochloride, as shown in Figure 4.

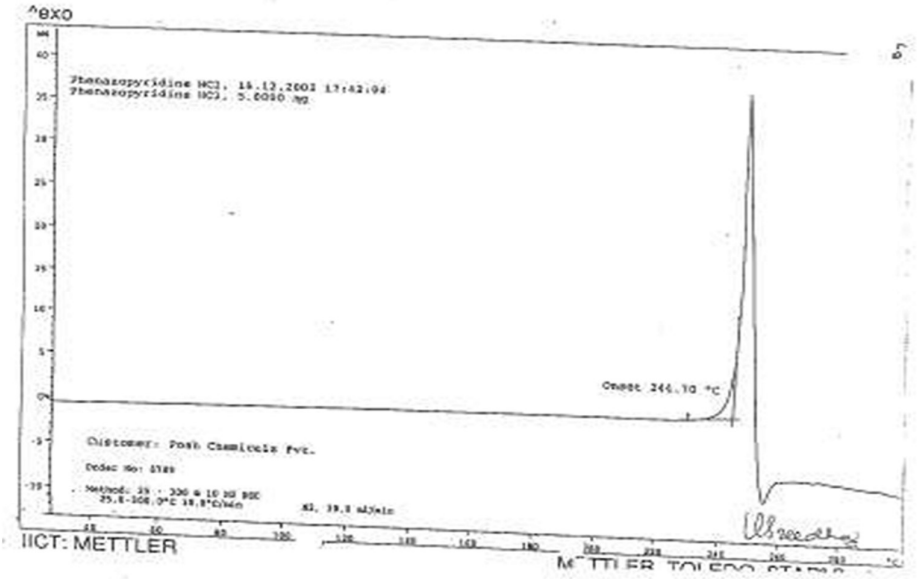

Figure 4. DSC thermogram of Phenazopyridine Hydrochloride showing exothermic decomposition behavior

Polymorphism evaluation was performed using samples recrystallized from methanol, ethanol and isopropyl alcohol. The recrystallized samples showed melting points around 234.4–234.8°C, close to the expected value of about 235°C. Based on melting point, IR and XRD data, no polymorphic variation was observed in Phenazopyridine Hydrochloride. The XRD pattern supported the crystalline nature of Phenazopyridine Hydrochloride and showed no evidence of polymorphic variation, as presented in Figure 5.

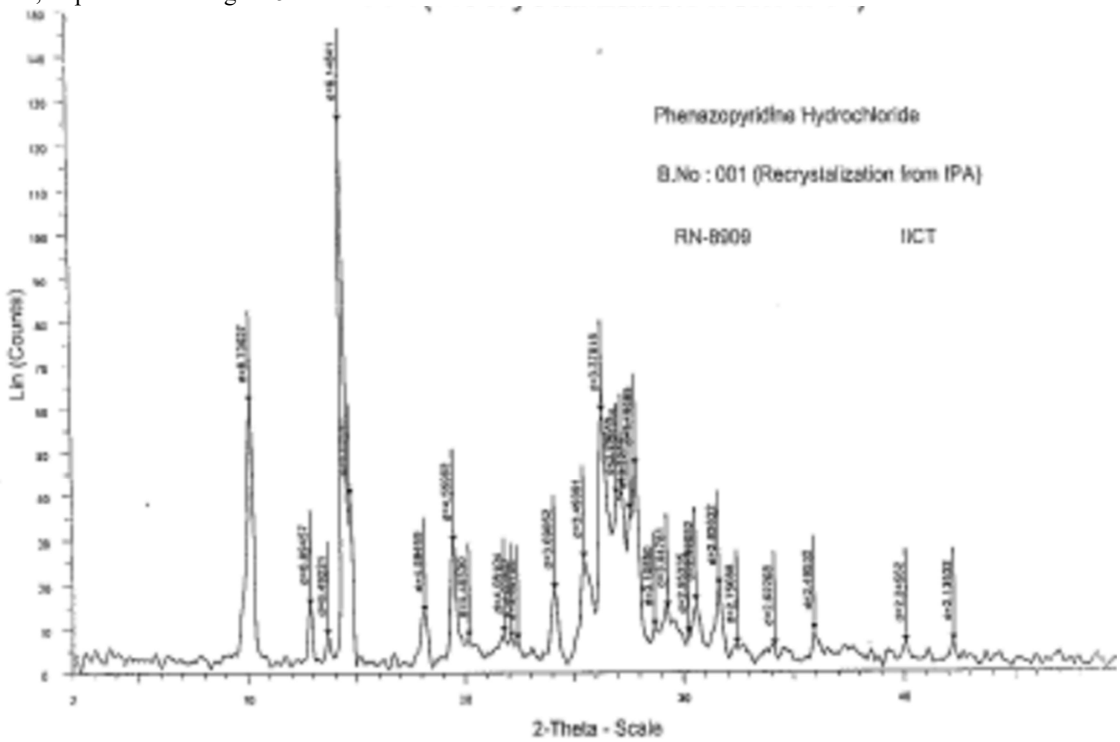

Figure 5. XRD pattern of Phenazopyridine Hydrochloride recrystallized from isopropyl alcohol

The characterization results of Phenazopyridine Hydrochloride are summarized in Table 1.

Table 1. Characterization Data of Phenazopyridine Hydrochloride

Test	Result	Interpretation
UV spectroscopy	λmax observed at approximately 390 ± 2 nm and 238 ± 2 nm	Characteristic absorption of Phenazopyridine Hydrochloride confirmed

FTIR spectroscopy	N–H stretching, aromatic C–H stretching, aromatic ring vibrations and NH_2 deformation peaks observed	Characteristic functional groups confirmed
^1H NMR spectroscopy	Proton assignments matched expected chemical shift values	Proposed molecular structure supported
Mass spectroscopy	Prominent peak observed at m/z 214	Molecular structure supported
Elemental analysis	Carbon, hydrogen and nitrogen values matched theoretical values	Molecular formula $C_{11}H_{11}N_5 \cdot HCl$ confirmed
DSC	Exothermic decomposition observed at approximately 239°C	Thermal behavior confirmed
XRD / polymorphism study	No polymorphic variation observed, melting points around 234.4–234.8°C	Solid-state consistency confirmed

Overall, the characterization results confirmed that Phenazopyridine Hydrochloride was suitable for further formulation development of film-coated tablets.

3.2 Drug–Excipient Compatibility Results

Drug–excipient compatibility was evaluated to confirm that Phenazopyridine Hydrochloride direct-compressible granules did not show any undesirable interaction with the selected excipients used in the film-coated tablet formulation. The compatibility study was important because any incompatibility between the drug and excipients could affect the assay, impurity profile, dissolution behavior, appearance or long-term stability of the final product.

Binary mixtures of Phenazopyridine Hydrochloride direct-compressible granules with selected excipients, including Hypromellose/HPMC, polyethylene glycol 6000 and carnauba wax, were stored under accelerated stress conditions at 40°C ± 2°C / 75% RH ± 5% RH for one month. After storage, the samples were examined for physical changes such as change in colour, lump formation, odour, moisture uptake or visible incompatibility. Chemical compatibility was assessed by monitoring the organic impurity profile.

There was no observable change in physical properties after storing the drug-excipient combinations. There was no significant difference between the physical appearance of the mixtures before and after testing. Moreover, chemical analysis revealed no observable increase in organic impurities, which implied that the chosen excipients did not cause any chemical reaction leading to the degradation of the Phenazopyridine Hydrochloride.

Based on this, Hypromellose/HPMC, polyethylene glycol 6000, and carnauba wax were found compatible with Phenazopyridine Hydrochloride direct-compressible granules. Hence, the chosen excipients were deemed acceptable for the final optimized film-coated tablets. Drug-excipient compatibility is summarized in Table 2 below.

Table 2. Drug–Excipient Compatibility Results

Sample	Storage condition	Physical observation	Chemical observation
Phenazopyridine HCl DC granules	40°C ± 2°C / 75% RH ± 5% RH, 1 month	No significant physical change	No significant impurity increase
Drug + Hypromellose/HPMC	40°C ± 2°C / 75% RH ± 5% RH, 1 month	No colour change, lumping or visible incompatibility	Organic impurities within limit
Drug + PEG 6000	40°C ± 2°C / 75% RH ± 5% RH, 1 month	No significant physical change observed	Organic impurities within limit
Drug + Carnauba wax	40°C ± 2°C / 75% RH ± 5% RH, 1 month	No significant physical change observed	Organic impurities within limit

Overall, the compatibility study demonstrated that the selected coating and polishing excipients were physically and chemically compatible with Phenazopyridine Hydrochloride and could be safely used for further formulation development.

3.3 Formulation Development and Optimization Results

Phenazopyridine Hydrochloride film-coated tablets were developed by means of direct-compressible granules and through direct compression methodology.

In general, the main objective of formulation development is to develop an optimized formulation that can be compressed into tablets possessing desired properties, i.e., good compressibility, proper mechanical strength, desirable disintegration and dissolution properties and absence of any manufacturing defects. Common compression problems, such as sticking and capping should be considered while designing tablets, since they have negative influence on tablet appearance, weight uniformity, friability and coating properties.

In Trial A, sticking and capping problems were encountered during compression of the formulated blend. Sticking was caused by the tendency of the granules to stick to the punch surface, whereas capping implied splitting of the top and bottom layers of the tablet. In view of these defects, Trial A could not serve as the optimized base trial.

While performing Trial B, the process/formulation adjustment resulted in the elimination of capping problem. Nevertheless, the problem of sticking during compression was still present. Considering the negative impact of sticking on tablet surface appearance and film coating problems, Trial B could not be chosen for further experiments.

Trial C involved further modification in order to solve the compression defects. In this trial, problems related to sticking and capping were overcome. Tablets possessed good physical properties in terms of hardness, friability and disintegration. Trial C was chosen as the optimal base trial.

To verify the reproducibility of the optimized formulation, three other reproducibility batches, Trial D, Trial E and Trial F were also prepared following the optimized process/formulation procedure. As the results showed, all trials exhibited good physical parameters and dissolution profile. Absence of compression/finishing defects in trials confirmed the suitability of the optimized formulation and process for the manufacture of Phenazopyridine Hydrochloride film-coated tablets. Details of the trials are presented in Table 3 below.

Table 3. Summary of Formulation Development and Optimization Trials

Trial	Purpose / Development Stage	Key Observation
Trial A	Initial compression trial	Sticking and capping observed during compression
Trial B	Trial to improve compression behavior	Capping resolved, but sticking remained
Trial C	Further optimization of compression behavior	No sticking or capping; physical parameters satisfactory
Trial D	First reproducibility batch	Physical parameters and dissolution result satisfactory
Trial E	Second reproducibility batch	Physical parameters and dissolution result satisfactory
Trial F	Third reproducibility batch	Physical and chemical parameters satisfactory

In general, all formulation development trials revealed that the compression problem that we had faced in the beginning had been effectively overcome by optimizing the process. Trial C appeared to be more appropriate regarding compression, while reproducibility trials showed good reproducibility of our formulation.

3.4 Optimized Formulation Composition

Phenazopyridine Hydrochloride film-coated tablet optimized formulation was obtained based on the results of formulation development and reproducibility batch testing. Finally, Phenazopyridine Hydrochloride direct-compressible granules were chosen as the active substance for the formulation of 200 mg dose strength of tablets due to its direct compressibility.

The optimized core tablet weight is 303.03 mg. Core tablets consist of Phenazopyridine Hydrochloride direct-compressible granules – they contain active substance along with compression, binding, disintegration and lubrication aids.

Finally, optimized core tablets exhibited desirable characteristics during compression process and were ready for the film-coating process.

Film-coated tablets have been formulated via an aqueous solution of Hypromellose (HPMC E5) and polyethylene glycol 6000 (PEG). Film-forming polymer for this film-coated system is Hypromellose (HPMC E5), because it produces a thin, uniform and even coating layer on the surface of tablet cores. PEG 6000 serves as a plasticizer and reduces a chance of cracking and film layer tearing during the further handling of tablets. The film-coating solution is made of purified water, which evaporates during the drying process.

Finally, after film-coating process, Carnauba wax was applied as a polishing agent. It improves surface properties of the tablets provides them better surface quality and appearance. Weight gain of the film-coated tablets reached 309.09 mg, that means that the weight gain was properly controlled. This coating system was a non-functional coating since it did not influence on drug release kinetics. Its main purpose is to improve product appearance, physical stability, protect tablet from environment influences. The optimized formulation composition is presented in Table 4.

Table 4. Optimized Composition of Phenazopyridine Hydrochloride Film-Coated Tablet 200 mg

Ingredient	Function	Quantity per tablet
Phenazopyridine Hydrochloride DC granules	Active drug source / compression blend	303.03 mg
Hypromellose / HPMC E5	Film former	4.94 mg
Polyethylene glycol 6000	Plasticizer	1.03 mg

Purified water	Solvent for coating solution	Removed during drying
Carnauba wax	Polishing agent	0.09 mg
Final coated tablet weight		309.09 mg

Overall, the optimized composition provided a suitable balance between tablet strength, coating uniformity, surface finish and drug release performance. Therefore, this formulation was selected for further physicochemical evaluation, dissolution testing and stability studies.

3.5 Core Tablet and Coating Process Results

The optimum formulation and process optimization resulted in the development of compressible granules with satisfactory compression behaviour. Problems of sticking and capping were seen during preliminary trials; but were effectively resolved during optimization. Granules had satisfactory flow and compression characteristics, hence uniform core tablets could be prepared using direct compression.

Preliminary trials indicated that 9.00 mm round, plain punches be used in the compression of core tablets for the 200 mg tablet strength. For the 200 mg dose, core tablets of 303.03 mg were successfully made. Core tablets were maroon to dark brown in colour, circular and plain on both sides. Compression resulted in the formation of tablets without any observable defects, including lamination, sticking, picking and capping. Uniform film coated tablets were successfully achieved through this compression process.

Aqueous system was used for coating of tablets. HPMC E5 was employed as the film former while PEG 6000 was used as plasticizer. Purified water was used as the solvent. Coating was done under proper conditions to yield film coated tablets with no observable defects, including roughness, peeling, cracking and colour variation.

Proper process conditions were maintained during coating operation. These included pan speed, spray rate, inlet temperature and atomization air pressure. The weight gain was kept between 1.5 % and 2.0%. This level of weight gain ensured achievement of uniform non-functional film coating without any interference with immediate release characteristic of tablets. Finally, polishing of tablets with carnauba wax was done after film coating. Polishing improved smoothness of the tablet surface.

The optimum compression and coating process resulted in the production of maroon round film-coated tablets with satisfactory appearance and uniform coating. The process is appropriate for further assessment of various physical parameters, dissolution, assay, impurities and stability. Summary of the results of optimized process conditions for core tablet and coating processes is provided in Table 5 below.

Table 5. Core Tablet and Coating Process Results

Parameter	Result
Tablet strength	Phenazopyridine Hydrochloride Tablets USP 200 mg
Manufacturing method	Direct compression followed by aqueous film coating
Tablet tooling	9.00 mm round, plain punches
Target core tablet weight	303.03 mg
Core tablet appearance	Maroon/dark brown, round, plain on both sides
Film former	HPMC E5
Plasticizer	PEG 6000
Coating solvent	Purified water
Pan speed	2–6 rpm
Spray rate	80–120 g/min
Inlet temperature	Around 40°C
Atomizing air pressure	2–4 kg/cm²
Nozzle diameter	1.0 mm
Number of spray guns	3
Target coating weight gain	1.5–2.0%
Polishing agent	Carnauba wax
Final appearance	Maroon, round, smooth film-coated tablets

The optimized core tablet and coating process confirmed that the formulation could be manufactured reproducibly and that the coating system was suitable for producing acceptable Phenazopyridine Hydrochloride film-coated tablets.

3.6 Physical Evaluation Results

Phenazopyridine Hydrochloride film-coated tablets after optimization were tested for the physical characteristics to ensure that the tablets meet all criteria for handling, coating, packing and administration. Based on visual inspection, the tablets were found to be coloured maroon, round-shaped, film-coated and plain on both faces. There were no signs of any physical

abnormalities such as chipping, cracking, delamination, mottling, etc.

The average tablet weight was found to be within the specified limits, indicating uniform filling of the tablet die by compressed mass. Also, the drug content in individual tablets met the acceptance criteria as the uniformity of dosages showed the average value (AV) less than 15.0%. Furthermore, the dimensions of the tablets were also found to be within the specified limits. Hardness of the tablets was appropriate, i.e., not too low, as it would affect tablet handling during coating process, nor too high as it may lead to delayed disintegration. In addition, friability tests showed that the percentage of mass loss of the tablets was within the accepted range of less than 1.0% w/w, thus the tablets possess enough mechanical strength to withstand stress.

As a result, disintegration time of the tablets was within the specified limit of NMT 30 minutes, which proves that film coating does not affect the process of tablet disintegration in an aqueous environment, i.e., the tablets show rapid dissolution and release of the drug from the formulation. Results obtained through physical evaluation are presented in Table 6.

Table 6: Physical Evaluation of Optimized Film-Coated Tablets

Parameter	Specification
Description	Maroon, round, film-coated, plain on both sides
Average weight	Within specified limit
Diameter	9.00 ± 0.15 mm
Thickness	Within specified limit
Hardness	Suitable for handling and coating
Friability	NMT 1.0% w/w
Disintegration time	NMT 30 minutes
Uniformity of dosage units	AV NMT 15.0

Overall, the physical evaluation results confirmed that the optimized formulation produced tablets with acceptable appearance, mechanical strength, dimensional uniformity and disintegration behavior. These results indicated that the tablets were suitable for further dissolution, assay, impurity and stability evaluation.

3.7 Dissolution Results

The dissolution profile of the optimal Phenazopyridine Hydrochloride film-coated tablets was studied. The experiment was conducted in 900 mL purified water by USP Apparatus II Paddle method at 50 rpm and 37 ± 0.5°C. The criteria for the successful dissolution process is that no less than 75% (Q) of the label claim quantity must be released in 45 minutes.

In this case, the optimized Phenazopyridine Hydrochloride film-coated tablets showed proper dissolution activity. During all the tests performed, all batches passed the criterion and released an amount greater than required. It proves that the optimization process made the drug formulation behave as an immediate-release tablet and the film coating did not have an adverse effect on the drug release process. It can be said that the chosen coating system consisting of HPMC E5 and PEG 6000 was the optimal one.

As for the stability studies, the same trend was observed; dissolution values under both long-term and accelerated conditions did not fall below the acceptance limit. When stored long-term (30°C ± 2°C/ 75% RH ± 5% RH) at 24 months, the dissolution values were approximately 93-94%. When stored at accelerated (40°C ± 2°C/ 75% RH ± 5% RH) conditions, the values were maintained approximately at the level of 93-95%. Thus, there was no adverse effect of storage on the dissolution of the drug.

Moreover, this proves that the core, the disintegrant system, as well as the film coating remained stable throughout the process of the study. The results of dissolution under stability conditions (long-term and accelerated) are represented in Table 7.

Table 7. Dissolution Results During Stability Study

Condition	Batch	Dissolution result
Long-term 30°C/75% RH	22007	Average 93–94% up to 24 months
Long-term 30°C/75% RH	22008	Average 94% up to 24 months
Long-term 30°C/75% RH	22009	Average 93–94% up to 24 months
Accelerated 40°C/75% RH	22007	Average 94–95% up to 6 months
Accelerated 40°C/75% RH	22008	Average 94% up to 6 months
Accelerated 40°C/75% RH	22009	Average 93–94% up to 6 months

Overall, the dissolution results confirmed that the developed Phenazopyridine Hydrochloride film-coated tablets met the dissolution requirement and maintained consistent drug release throughout the stability study.

3.8 Assay and Organic Impurity Results

Assay and organic impurities tests were conducted to assess the quality and stability of optimized

Phenazopyridine Hydrochloride film coated tablets. Assay test was carried out using HPLC technique to assess the quantity of drug present in the tablets whereas organic impurities analysis was done to ensure that there is no formation of degradation products and/or other impurities in the tablets.

All the stability batches were observed to fall within the range of 90.0–110.0% of label claim in terms of assay. For long term stability study conducted at 30°C ± 2°C / 75% RH ± 5% RH, the assay range was 97.4% to 100.8% for the three batches till 24 months. Whereas in case of accelerated stability study conducted at 40°C ± 2°C / 75% RH ± 5% RH, the assay results were in the range of 97.4% to 100.0% after six months. This clearly suggests that the formulation is stable in terms of drug loss.

In terms of organic impurities, the selected formulations also satisfied the specified limits. In this regard, an upper limit of 0.2% for individual unknown impurity and 2.0% for total impurities was set. In case of long-term stability, the maximum impurity observed was 0.12% for batch number 22009 whereas in case of accelerated stability study, the maximum impurity level was observed to be 0.08% for batch 22008. Thus, in both cases, the maximum impurity levels were significantly lower than the specified limits.

The results demonstrate that the formulation process and packaging have been selected in such a way that ensures the chemical stability of the product. In addition to this, absence of significant impurity increase indicates that the presence of film coating or other excipients does not affect the stability of active ingredient. Stability results of assay and organic impurities are shown in Table 8.

Table 8. Assay and Organic Impurity Results During Stability Study

Condition	Batch	Assay range	Highest observed impurity
Long-term 30°C/75% RH	22007	98.3–100.8%	0.08%
Long-term 30°C/75% RH	22008	97.4–100.4%	0.08%
Long-term 30°C/75% RH	22009	98.1–100.7%	0.12%
Accelerated 40°C/75% RH	22007	98.3–100.0%	0.07%
Accelerated 40°C/75% RH	22008	97.4–99.2%	0.08%
Accelerated 40°C/75% RH	22009	98.1–99.4%	0.07%

Overall, the assay and impurity results confirmed that the optimized Phenazopyridine Hydrochloride film-coated tablets maintained acceptable drug content and chemical purity throughout the stability study.

3.9 Microbial Evaluation Results

Tests for microbial assessment have been carried out to determine whether the optimized Phenazopyridine Hydrochloride film-coated tablets are free from microbial contaminants. Tests such as total aerobic microbial count, total combined yeast and mold count, and presence of specified microorganisms were conducted since microbial contamination is an issue that must be assessed due to its potential effects on product quality, patient safety, and stability.

It was determined that total aerobic microbial count was NLT 100 cfu/g (less than 100 colony-forming units per gram). This result fell well within the required limit of not more than 1000 cfu/g. Total combined yeast and mold count was also NLT 100 cfu/g (less than 100 colony-forming units per gram) in compliance with the specified limit of not more than 100 cfu/g. Hence, microbial count in the finished tablets is rather low.

Specified microorganisms such as Escherichia coli, Salmonella sp., Staphylococcus aureus, and Pseudomonas aeruginosa were absent. Absence of these microorganisms indicates that there is no problem with the microbiological quality of the products. This test result also indicates that the manufacturing process, handling, and packaging of the product meet the necessary standards for microbial quality. Microbial tests for the optimized tablets are presented in Table 9.

Table 9. Microbial Evaluation Results

Test	Specification	Result
Total aerobic microbial count	NMT 1000 cfu/g	Less than 10 cfu/g
Total combined yeast and mold count	NMT 100 cfu/g	Less than 10 cfu/g
Escherichia coli	Absent/g	Absent
Salmonella sp.	Absent/10 g	Absent
Staphylococcus aureus	Absent/g	Absent
Pseudomonas aeruginosa	Absent/g	Absent

Overall, the microbial evaluation confirmed that the developed Phenazopyridine Hydrochloride film-coated tablets complied with the required microbiological specifications. The low microbial counts and absence of specified pathogens demonstrated that the product was microbiologically acceptable for further stability evaluation and intended use.

3.10 Stability Study Results

Stability studies were conducted to determine the shelf-life of optimized Phenazopyridine Hydrochloride film-

coated tablets by evaluating its quality characteristics in storage conditions. Batches 22007, 22008, and 22009 were packaged in PVDC coated PVC–Al blister packaging and exposed to long term and accelerated storage conditions. Long term stability study was conducted at 30°C ± 2°C / 75% RH ± 5% RH for 24 months while accelerated stability study was conducted at 40°C ± 2°C / 75% RH ± 5% RH for 6 months.

During each time point of stability testing, the following parameters were determined: description, dissolution, assay, organic impurities, and microbial quality. During the entire stability study period, all three batches maintained their appearance as maroon, round, film-coated tablets without any visible change in their colour, film coating, and surface appearance. No evidence of cracking, peeling, mottling, or other film coating defects was noted during the study period.

Dissolution profiles did not change and stayed above the specification limit of not less than 75% Q in 45 minutes. During long term storage condition, dissolution profiles stayed around 93-94% up to 24 months, while during accelerated storage conditions, dissolution profiles stayed around 93-95% up to 6 months. It indicated good stability of tablet cores and film coatings during the storage period, and no effect on drug release was observed.

Similarly, assay values did not fluctuate much and stayed within the specification limit of 90.0-110.0% label claim. Assay values during long term stability study varied between 97.4 and 100.8 percent while during the accelerated study varied between 97.4 and 100.0 percent. It indicated that no loss in drug content was observed during the entire stability period; thus, Phenazopyridine Hydrochloride was stable chemically in the optimized formulation.

Impurities levels were low as per the specification of not more than 0.2% for individual unspecified impurity and not more than 2.0% for total impurities. During the long-term stability study, the highest impurity found was 0.12% while during the accelerated study, the highest impurity found was 0.08%. These impurity levels were much below the specification limit, indicating no degradation of the drug. Microbial test data were also within the limits specified. Long term stability results at 30°C ± 2°C / 75% RH ± 5% RH are given in Table 10.

Table 10. Long-Term Stability Results at 30°C ± 2°C / 75% RH ± 5% RH

Batch	Time points studied	Description	Dissolution	Assay range	Highest impurity
22007	Initial to 24M	No change	93–94%	98.3–100.8%	0.08%
22008	Initial to 24M	No change	94%	97.4–100.4%	0.08%
22009	Initial to 24M	No change	93–94%	98.1–100.7%	0.12%

The accelerated stability results at 40°C ± 2°C / 75% RH ± 5% RH are summarized in Table 11.

Table 11. Accelerated Stability Results at 40°C ± 2°C / 75% RH ± 5% RH

Batch	Time points studied	Description	Dissolution	Assay range	Highest impurity
22007	Initial to 6M	No change	94–95%	98.3–100.0%	0.07%
22008	Initial to 6M	No change	94%	97.4–99.2%	0.08%
22009	Initial to 6M	No change	93–94%	98.1–99.4%	0.07%

Overall, the stability study confirmed that the optimized Phenazopyridine Hydrochloride film-coated tablets maintained acceptable physical appearance, drug release, assay, impurity profile and microbial quality under both long-term and accelerated storage conditions. The assay trend of all three stability batches remained within the specification range throughout the long-term stability period, as shown in Figure 6.

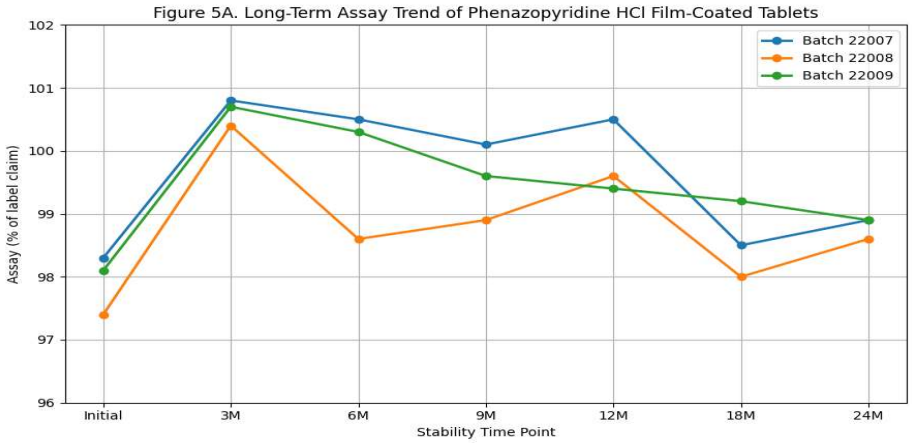

Figure 6. Long-term assay trend of Phenazopyridine Hydrochloride film-coated tablets stored at 30°C ± 2°C / 75% RH ± 5% RH

The results demonstrated that the formulation and packaging system were suitable for maintaining product quality throughout the evaluated stability period.

4. Discussion

The present study was conducted to obtain the stable film coated tablet formulation of Phenazopyridine Hydrochloride by direct compressible granules. The development strategy was the confirmation of the suitability of the drug substance, selection of excipients that were compatible, optimization of compression and coating process, and evaluation of the final product for physical and chemical attributes, dissolution properties, microbiological and stability properties. Characterization studies were performed and results showed that Phenazopyridine Hydrochloride had the expected identity and structure. The identity and molecular structure of the drug substance was supported by spectroscopy, such as UV, FTIR, ^{1}H NMR and mass spectroscopy and elemental analysis, while the thermal and solid-state behaviour was verified by DSC and XRD/polymorphism studies. This was relevant as properties of the drug substance can directly affect the disintegration, dissolution and overall performance of a direct compression tablet formulation [11].

Drug-excipient compatibility studies showed that the drug Phenazopyridine Hydrochloride was compatible with all selected excipients that were incorporated in the final formulation of the Phenazopyridine Hydrochloride direct-compressible granules. No physical change or gains in the amount of impurities were observed in mixtures with the presence of hypromellose, polyethylene glycol and carnauba wax when stored under accelerated conditions. This showed that the chosen excipients will not cause degradation of the active ingredient and will be appropriate for formulation. In directly compressed tablets, where excipients are in direct contact with the drug, compatibility is of particular importance, as excipients may affect the physical stability, tablet structure, moisture sensitivity and storage behaviour of the tablets [12].

Since the drug was available as direct compressible granules, the formulation formulation was developed using a direct compression process, without further wet granulation work during formulation. Problems occurred in the early formulation trials, principally sticking and capping during compression. Trial A was found to have both sticking and capping and was not chosen. Sticking was eliminated in Trial B. Both problems were overcome by further optimization in Trial C and tablets with satisfactory physical properties were obtained. The optimized formulation and process were validated by reproducibility batches for Trials D, E and F. This step-wise development approach was found necessary due to the formulation dependent effect on the tablet performance such as dissolution behavior and stability of directly compressed tablets [13].

Compression and optimization of the process were important in achieving acceptable tablets. The initial sticking and capping problems suggested the necessity of changing the granule parameters and compression conditions. Following optimisation, direct-compressible granules with suitable flow and compression properties were obtained, and the tablets were manufactured without any obvious manufacturing faults. Suitable compression conditions were used to control tablet hardness, friability, disintegration and dissolution. The performance of direct compression is highly dependent on the properties of powder flow, compressibility and compatibility, therefore optimization of these properties is very important to make tablets of consistent quality [14]. The studies on co-processed and direct-compression excipients also indicate that by selecting appropriate excipients and granules suitable excipient and granule performance can enhance the strength of the tablets produced, disintegration and drug release behaviour [15].

Optimized core tablets were coated successfully using the aqueous coating system with HPMC E5 as film forming polymer and PEG 6000 as plasticizer. HPMC E5 was used to provide uniform coating on the surface of the tablet, and PEG 6000 was used to make the coating film more flexible, so as to reduce the occurrence of cracking and peeling. The use of Carnauba wax enhanced the smoothness of the surface and the final appearance of the tablets. Drug release was not affected by the coating, with a coating weight gain of 1.5% to 2.0%, enough to yield a smooth and non-functional film coat. Direct compression and controlled coating conditions enabled efficient manufacturing of tablets and ensured the quality of the product [16].

Results of the physical evaluation indicated that the optimised tablets met the quality requirements. The tablets were maroon coloured, round, film-coated and plain on both sides. Average weight, diameter and thickness were within the set range, which means the compression and dimension were uniform. Friability was in the limit of NMT 1.0% w/w which indicated that the tablets were strong enough to handle, coat, package and transport. The disintegration time was within the specified limit (NMT 30 minutes), thus tablets in this formulation were immediate release. Drug content uniformity with respect to the acceptance criterion also met the requirement, showing consistency of content among each tablet. Powder flow and performance of the direct compression process [17] have significant impact on tablet uniformity and content uniformity.

Optimized formulation was proved to give satisfactory release of the drug during dissolution testing. The tablets fulfilled acceptance criterion and dissolution was always above the limit throughout the stability testing period of 45 minutes. Long-term dissolution values were found to be around 93–94% till 24 months and accelerated dissolution values were found to be around 93–95% till 6 months. These results indicate that there is no delay in drug release and the immediate release performance was preserved during storage of the formulation using the selected coating system. The dissolution performance of DCTs may be affected by a number of factors including compression pressure, porosity and disintegration behavior [18]. Additionally,

dissolution behavior is strongly correlated with formulation composition, changes in the tablet structure and storage-related changes, thus dissolution is an important factor of the product performance [19].

Optimized formulation chemical quality was confirmed by the assay and organic impurity results. When tested under long-term or accelerated conditions, the assay values were within the range of 90.0-110.0% of label claim. The assay values obtained in long term storage ranged from 97.4% to 100.8% and accelerated storage ranged from 97.4% to 100.0%. There were also relatively low levels of organic impurities which are included in the standard. Long-term stability found the highest impurity of 0.12% which was below the limit of NMT 0.2% for individual unspecified impurity; highest impurity observed during accelerated stability was 0.08% which was below the limit of NMT 2.0% for total impurities. The results indicated that no major degradation of this drug occurred during manufacture or storage. Appropriate control of tablet disintegration, compression pressure and excipient performance is crucial for ensuring tablet quality and performance [20].

The optimized formulation was very well supported by the stability study, which indicated long-term and accelerated storage stability. The three batches 22007, 22008 and 22009 were packed in PVDC coated PVC–aluminium blister packaging and tested for description, dissolution test, assay, organic impurities and microbial quality. The tablets were stable for up to 24 months in long-term stability test at 30°C ± 2°C / 75% RH ± 5% RH and did not exhibit any defect that would compromise the appearance of the table. Dissolution was satisfactory, assay was within limits, impurities were low and microbial test was satisfactory. No significant change was observed for the physical appearance, drug release, assay or impurity profile during accelerated stability study at 40°C ± 2°C / 75% RH ± 5% RH for 6 months. The results showed that the formulation could withstand high temperature and humidity. The results for the stability of coated tablets were found to support the suitability of the coating system used of HPMC E5 and PEG 6000 because coated tablet composition and selection of plasticizer may have an impact on stability and release behavior of coated tablets.

In conclusion, the developed stable immediate release Phenazopyridine Hydrochloride film coated tablets with the direct compressible granules was a success. The first production issues of sticking and capping were overcome by formulation and process optimisation. The optimized tablets exhibited good physical properties, dissolution profile, assay within specification, low levels of impurities and microbiological quality. The formulation stability studies showed that the formulation showed stability in long-term and accelerated trials with respect to physical, chemical, dissolution and microbiological quality. Hence, the formulated and fabricated packaging system was found to be appropriate for the film-coated tablets containing Phenazopyridine Hydrochloride.

5. Conclusion

The direct-compressible granules and the direct compression method were used to successfully develop Phenazopyridine Hydrochloride film-coated tablets. Compression related issues of sticking and capping were encountered in initial formulation trials but were overcome by formulation and process modifications. The optimized 200 mg tablets exhibited good physical properties namely uniform appearance, tablet size suitable, mechanical strength, friability within acceptable limit and disintegration within the specified time. Aqueous film-coating system with HPMC E5 and polyethylene glycol 6000 was able to coat the tablets to a smooth, uniform surface without altering the immediate release properties of the formulation. Optimized tablets met dissolution, assay requirements and organic impurity and microbial requirements. Three batches were used in stability studies, which indicated that the tablets were physically, chemically and microbiologically stable under long and accelerated storage conditions. The dissolution values were above the acceptance criterion, and the assay values were within the range and the impurities were below the prescribed limits during the stability period. In conclusion, the developed formulation and packaging system were adequate for ensuring the quality and stability of the film-coated tablets of Phenazopyridine Hydrochloride. Thus, the optimized formulation is stable and can be used as an immediate-release film-coated tablet dosage form.

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