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Comparative Forced Degradation Study of Marketed and In-House Paracetamol Tablet

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Abstract

The present study focuses on forced degradation studies and analytical method development of branded and in-house paracetamol tablet formulations. Forced degradation studies were performed to evaluate the stability and degradation behavior of paracetamol under different stress conditions. The drug samples were subjected to acidic, basic, hydrolytic and photolytic degradation conditions and were subsequently analyzed using UV-visible spectrophotometry at 248 nm. An in-house paracetamol tablet formulation was prepared and evaluated for weight variation, thickness, hardness, friability and disintegration. Solubility studies were performed using water and methanol, and methanol was selected as the solvent for further studies based on the observed absorbance. Analytical method validation was performed for linearity and repeatability. The study demonstrated different degradation behavior for the marketed and in-house formulations under the applied stress conditions. The findings provide useful information regarding the stability characteristics of paracetamol formulations and may assist in formulation, packaging, storage-condition and shelf-life considerations.

Keywords: Paracetamol, Forced Degradation, Analytical Method Development, UV-Visible Spectrophotometry, Method Validation, Stability, In-House Formulation, Marketed Formulation.

Introduction

- The process where natural degradation rate of product or material is increased by the application of additional stress.
- This can help to identify the components of the substance, its stability, and its potential reaction pathways. The project takes forced degradation analysis of brand product and in-house formulation of paracetamol.
- For In-house formulation we had done evaluation parameters like hardness thickness weight variation disintegration friability.
- Force degradation carried out by subjecting drug sample to various methods of degradation like acidic, basic, hydrolytic, photolytic degradation using solvents like methanol,0.1M HCL,0.1N NaOH, distilled water. Further analyzed by UV at the wavelength of 248 nm.

Aim & objectives

Aim: To analyses the forced degradation studies of paracetamol tablet of branded and in-house formulation.

Objectives: The objective of this study were carried out to achieve the following purposes-

- To analyze forced degradation studies for paracetamol branded drug.
- To provide the approach to analyses the stability of drug samples in pharmaceutical lab
- To provide the data for selecting proper formulation, package, proper storage conditions and shelf life.

- To reveal the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substance and drug product.

Literature Review

Behera and Ghanty (2012) reported a UV-visible spectrophotometric procedure for determining the amount of paracetamol present in tablet formulations. The method was validated for pharmaceutical analysis and showed that UV-visible spectrophotometry can be effectively applied for routine estimation of paracetamol. The study also indicated that the technique offers a straightforward and cost-effective alternative for quantitative drug analysis.

Murtaza and Khan (2011) developed a UV spectrophotometric method for the simultaneous analysis of aspirin and paracetamol in combined tablet formulations. Their investigation demonstrated that UV spectrophotometry could be successfully employed for the estimation of paracetamol even in the presence of another active pharmaceutical ingredient. The findings support the usefulness of UV-based methods for the analysis of combination dosage forms.

Kokilambigai and Lakshmi (2020) explored the application of green analytical chemistry concepts in the simultaneous determination of paracetamol, aceclofenac, and thiocolchicoside using UV spectrophotometry. The study focused on developing an analytical procedure that was relatively simple while also taking environmental considerations into account. Their work demonstrated that UV spectrophotometric analysis can be incorporated into pharmaceutical analysis using approaches consistent with the principles of green analytical chemistry.

Sharma and Reddy (2015) investigated a dual-wavelength UV spectrophotometric approach for the simultaneous estimation of paracetamol and caffeine in combined pharmaceutical formulations. The method was developed and validated for quantitative analysis, demonstrating that measurements at selected wavelengths can be used to determine paracetamol in the presence of caffeine. This study further established the usefulness of UV spectrophotometry for the analysis of multi-component pharmaceutical products.

From the available literature, it can be observed that UV-visible spectrophotometry has been widely investigated for the quantitative determination of paracetamol in individual as well as combination formulations. Previous researchers have mainly concentrated on assay methods, simultaneous drug estimation, and validation of spectrophotometric procedures. Comparatively, less attention has been given to examining the degradation behavior of paracetamol formulations under different stress conditions using a simple UV spectrophotometric approach.

In view of this, the present study focuses on the forced degradation behavior of paracetamol in both marketed and in-house prepared formulations. The formulations are subjected to different stress conditions, including acidic, alkaline, hydrolytic, and photolytic environments, and the resulting changes are evaluated using UV spectrophotometric analysis. A comparison between the marketed and in-house formulations may provide useful information regarding their susceptibility to degradation and overall stability under the selected stress conditions.

Research gap

Despite the extensive use of paracetamol and the availability of several analytical methods for its estimation, relatively limited research has focused on the comparative evaluation of degradation behavior in branded and in-house paracetamol formulations using a single validated stability-indicating method.

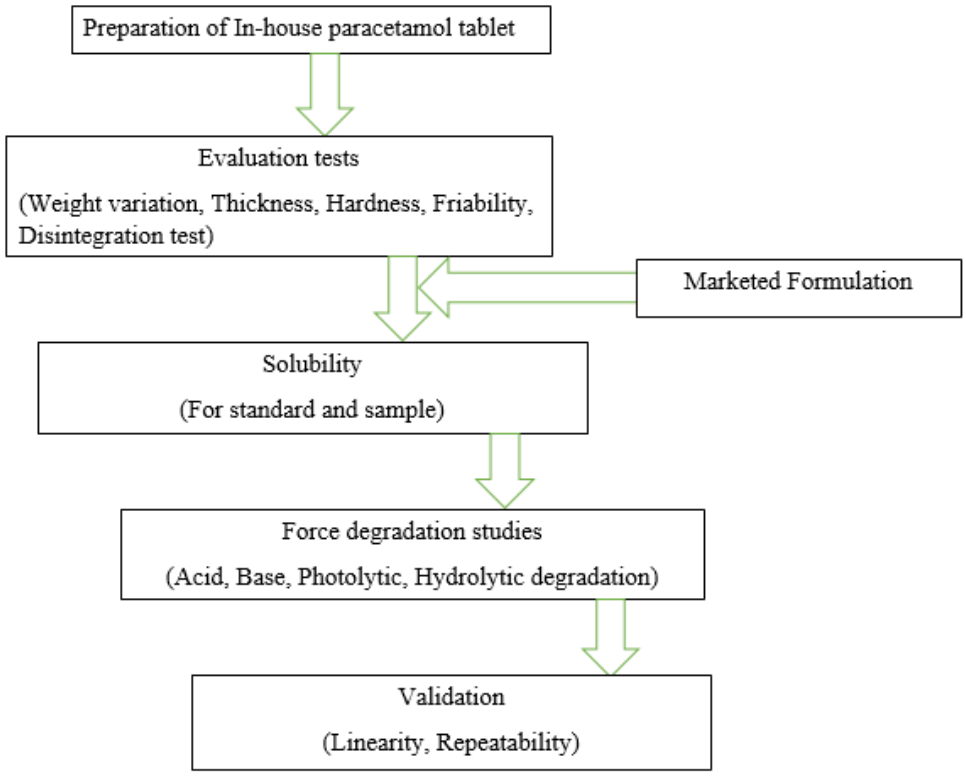
Existing studies often emphasize assay determination and provide limited assessment of degradation products generated under multiple stress conditions. Moreover, the influence of formulation composition and excipients on the stability of paracetamol
has not been sufficiently explored through direct comparison. Hence, there is a need to develop and validate a simple, reliable, precise, and stability-indicating analytical method capable of effectively distinguishing paracetamol from its degradation products and to comparatively investigate the stability of branded and in-house formulations under acid, alkali, oxidative, thermal, and photolytic stress conditions. The present study is designed to address this gap and provide comparative information on the stability and degradation profile of the two formulations.

Methodology / Materials & Methods

Method development:

- The purpose of analytical method development is to establish the identity, purity, physical characteristics, and potency of drugs, including the drug's bioavailability and stability.
- Analytical method development and validation can be understood as the process of showing that analytical procedures are adequate for the purpose of assessing drugs, and particularly the active pharmaceutical ingredient (API).
- Analytical procedures are developed to test specific characteristics of the substances against the predefined acceptance criteria for such characteristics.
- Thus, analytical method development involves the evaluation and selection of the most precise assay procedures to determine the composition of a drug.

Research methodology and experimental work:



Preparation of In-house paracetamol tablet:

- All ingredients were sieved by 80# sieve. In mortar paracetamol, lactose, starch was taken and mixed well with the help of pestle.
- Starch paste was prepared by mixing starch powder with boiled distil water. It is added to the mortar in small amounts which gave right consistent dough for granulation.
- When dough was sieved through sieve no.14# over a butter paper and then dried at 120 degrees Celsius for less than 20 min. These dried granules were sieved through 20# and through 40# sieve.
- Granules which had passed through sieve 40# are fines and from sieve 20# are granules. Further 15% fines, disintegrating agent, lubricating agents were added to granules and mixed well.
- Now these granules were sent to compressed into tablets.

Evaluation tests:

- Evaluation tests done for in-house formulation**:**
- **Weight Variation:**
  Average weight of tablets should not exceed than 0.3212-0.4092 according to IP
- **Thickness Test:**
  According to IP average thickness of tablet should not be exceeded than 5.605-6.195mm
- **Hardness Test:**
  Average weight or load should not exceed than 5 N according to IP
- **Friability Test:**

$$\text{Friability (\%)} = \frac{\text{Initial Weight (W1)} - \text{Final Weight (W2)}}{\text{Initial Weight (W1)}} \times 100$$

  According to Ip if loss is more than 1% then repeat the procedure, if not more than 1% then it is acceptable
- **Tablet Disintegration:**
  According to IP disintegration time for uncoated tab is 15 min.

Solubility:

- Solubility was done to find a suitable solvent experimental work
- It is performed for both Marketed and in house formulation
- Solvents used for solubility are water and methanol
- 10ppm solution was made for both formulation in water and as well methanol.
- spectra were taken with the help of UV.

SOLVENT	WATER	METHANOL
SPECTRA	244nm	248nm
ABSORBANCE	0.8954	0.9023

solubility studies of paracetamol with water and methanol, were in water it showed spectra at 244 nm and in methanol at 248 nm. Paracetamol exhibited maximum absorbance in methanol at wavelength of 248 nm. Also, paracetamol is freely soluble in methanol, so methanol is selected as solvent for further studies.

Force degradation studies:

- To carry out forced degradation studies Standard and sample are prepared.
- **Preparation of standard solution:**
  Tablets of marketed preparation was weighed and triturated. 10mg was weighed from triturated powder of marketed formulation dissolve in 100ml methanol. further dilution was done and 10 ppm solution was obtained.
  Absorbance for these solutions were recorded by using spectrophotometer at the range of 248nm.
- **Preparation of sample solution:**
  Tablets of In-house was weighed and triturated. 10mg was weighed from triturated powder of marketed formulation dissolve in 100ml methanol. further dilution was done and 10 ppm solution was obtained.
  Absorbance for these solutions were recorded by using spectrophotometer at the range of 248nm.

Acid degradation:

- Acid degradation of paracetamol was carried out with acidic medium.
- 10mg of powdered drug was measured accurately and transferred into 100ml volumetric flask.0.1M HCL in small quantity were added to same flask and dissolved powder completely by shaking flask. Volume was made up with o.1 M HCL
- Solution was kept at room temperature for at least 2 hours.
- 1ml solution was pipette out and transferred to 10ml volumetric flask and volume was made up to 10ml with 0.1M HCL.
- Absorbance was recorded at 248nm by using UV spectrophotometer.
- **Preparation of 0.1M HCl**: Accurately measured 8.5ml of HCL was transferred into 1000ml volumetric flask, dissolved and volume was made up to 1000ml by distilled water.

Base degradation:

- Base degradation of paracetamol was carried out with Basic medium.
- 10mg of powdered drug was measured accurately and transferred into 100ml volumetric flask.0.1N NaOH in small quantity were added to same flask and dissolved powder completely by shaking flask. Volume was made up to 100ml with 0.1N NaOH.
- Solution was kept at room temperature for at least 2 hours. After that 1ml solution was pipette out and transferred to 10ml volumetric flask and volume was made up to 10ml with 0.1N NaOH.
- Absorbance was recorded at 248nm by using UV spectrophotometer.
- **Preparation of 0.1N NaOH**: Accurately weighed 0.4g of NaOH was transferred into 1000ml volumetric flask, dissolved and volume was made up to 1000ml by distilled water.

Photolytic degradation:

- Photolytic degradation of paracetamol was carried out with sunlight.

- 10mg of powdered drug was measured accurately and transferred into 100ml volumetric flask.
- 100ml methanol in small quantity were added to same flask and dissolved powder completely by shaking flask. Volume was made up to 100ml with methanol.
- Solution was kept in sunlight for at least 2 hours. After that 1ml solution was pipette out and transferred to 10ml volumetric flask and volume was made up to 10ml with methanol.
- Absorbance was recorded at 248nm by using UV spectrophotometer.

Hydrolytic degradation:

- Hydrolytic degradation of paracetamol was carried out with distil water.
- 10mg of powdered drug was measured accurately and transferred into 100ml volumetric flask.100ml distil water in small quantity were added to same flask and dissolved powder completely by shaking flask.
- Volume was made up to 100ml with distil water.
- Solution was kept at room temperature for at least 2 hours. After that 1ml solution was pipette out and transferred to 10ml volumetric flask and volume was made up to 10ml with water.
- Absorbance was recorded at 248nm by using UV spectrophotometer.

Observations obtained after degradation:

For marketed preparation

TEST	ABSORBANCE
ACID	0.4869
BASE	0.6199
PHOTOLYTIC	0.9704
HYDROLYTIC	0.7132

For in-house formulation

TEST	ABSORBANCE
ACID	0.6358
BASE	0.8953
PHOTOLYTIC	0.8732
HYDROLYTIC	0.5479

Validation:

In validation linearity and repeatability was done.

- **Linearity:**
- Preparation of standard solution:

10 mg marketed paracetamol was dissolved in 100 ml methanol in a volumetric flask which has 100ppm. From this solution 1ml was pipette out and make up volume to 10ml with methanol to give 10ppm of paracetamol. This solution was used to prepare various concentrations of paracetamol.

- Sample solution:

100ppm solution was prepared by dissolving 10 mg in house formulation of paracetamol in 100ml methanol in a volumetric flask. From this solution 1ml was pipette out and make up volume to 10ml with methanol to give 10ppm of paracetamol. This solution was used to prepare various concentrations of paracetamol (0.5,1,2,5,10 ppm).

- After the standard and sample solution are prepared following steps were followed:

1. Calibration curve for paracetamol was prepared in concentration range of 0.5 to 10 ppm.
2. Absorbance of each solution was measured at 248 nm by UV spectrophotometer.
3. Graph was plotted as absorbance of solution versus concentration of paracetamol.
4. Linearity plot was constructed and best fit line was drawn through it.

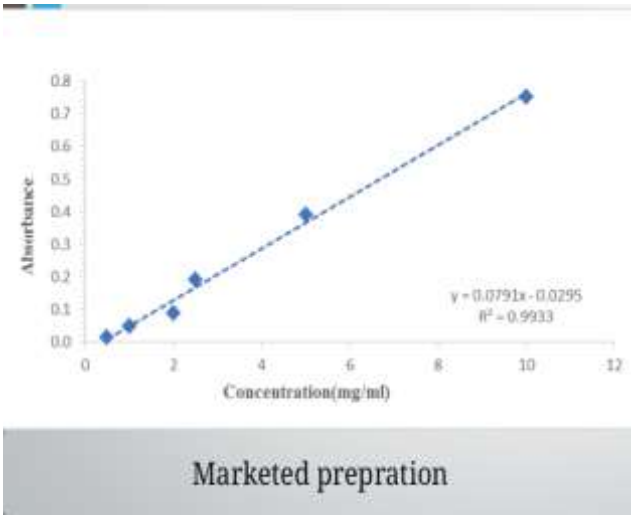
Observation obtained:

For marketed preparation

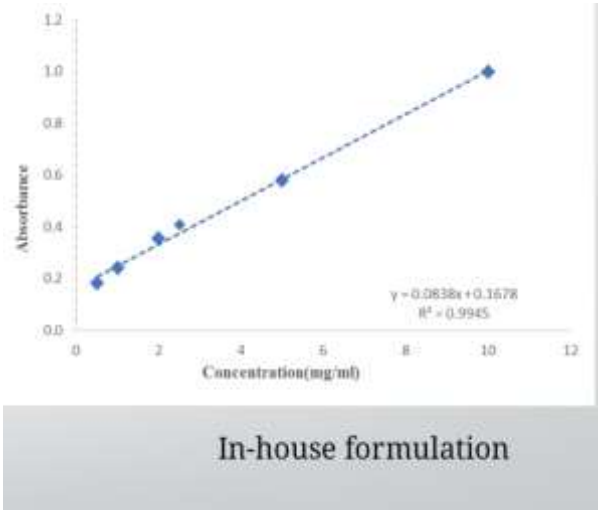
CONCENTRATION	ABSORBANCE
0.5	0.0140
1	0.0272
2	0.0547
5	0.5702
10	0.7579

For In-house formulation

CONCENTRATION	ABSORBANCE
0.5	0.2618
1	0.3442
2	0.4762
5	0.4258
10	0.6275



Marketed prepration



In-house formulation

Repeatability:

- The same concentrations were taken and repeatability was performed.
- For each concentration 3 times absorbance were recorded at same time, same day.
- Results of the same concentration should overlap.

Observations obtained were:

Marketed Preparation

Concentration	Absorbance
0.5 ppm	0.0140
	0.0130
	0.0159
1 ppm	0.0272
	0.0233
	0.0222
2 ppm	0.0547
	0.0508
	0.0530

In House Formulation

Concentration	Absorbance
0.5	0.2618
	0.2646
	0.2641
1	0.3442
	0.3432
	0.3435
2	0.4762
	0.4724
	0.4737

Result

Percent degradation was calculated by following formula using the absorbance of Forced degradation solution

FD = 100-% Assay

- **Marketed preparation:**

Standard: 0.9023

Name of degradation	Absorbance	% Assay	% Degradation
Acid	0.4869	53.96	46.04
Base	0.6199	68.70	31.3
Hydrolytic	0.7132	79.04	20.96
Photolytic	0.9704	107.5	-7.5

Analysis of marketed preparation for percentage of acid, base, hydrolytic and photolytic degradation. It showed maximum degradation in acidic medium and the minimum degradation at photolytic condition.

- **In-house preparation:**

Standard: 0.9998

Name of degradation	Absorbance	% Assay	% Degradation
Acid	0.6358	63.59	36.41
Base	0.8953	89.54	10.46
Hydrolytic	0.5479	54.80	45.2
Photolytic	0.8732	87.33	12.67

Analysis of inhouse preparation for percentage of acid, base, hydrolytic and photolytic degradation. It showed maximum degradation in hydrolytic medium and the minimum degradation at basic condition.

Discussion

The present study was carried out to develop and evaluate an analytical method for the assessment of paracetamol in marketed and in-house tablet formulations using UV-visible spectrophotometry. The study also focused on comparing the degradation behavior of both formulations under different stress conditions, including acidic, basic, hydrolytic and photolytic conditions.

Methanol and water were initially evaluated as solvents for the preparation of paracetamol solutions. The maximum absorbance was observed at 248 nm in methanol, whereas the spectrum in water was observed at 244 nm. Since paracetamol showed better suitability and maximum absorbance in methanol at 248 nm, methanol was selected as the solvent for further analytical studies.

The in-house paracetamol tablets were prepared using paracetamol along with lactose, starch and other formulation ingredients. The prepared tablets were subjected to various evaluation tests, including weight variation, thickness, hardness, friability and disintegration testing. These tests were performed to assess the physical quality and uniformity of the prepared tablets.

Forced degradation studies were performed to investigate the stability behavior of paracetamol under different stress conditions. The marketed and in-house formulations were separately exposed to acidic, basic, hydrolytic and photolytic conditions, followed by analysis using UV spectrophotometry at 248 nm. The use of different stress conditions helped in comparing the degradation behavior of the two formulations.

For the marketed formulation, the highest percentage degradation was observed under acidic conditions, with 46.04% degradation, followed by basic degradation (31.30%) and hydrolytic degradation (20.96%). The photolytic condition showed the lowest degradation according to the calculated results. Thus, the marketed formulation showed comparatively greater susceptibility to acidic conditions.

In contrast, the in-house formulation showed the highest degradation under hydrolytic conditions, with 45.20% degradation. Acidic degradation was 36.41%, while photolytic and basic degradation were 12.67% and 10.46%, respectively. Therefore, the in-house formulation showed comparatively greater degradation in hydrolytic conditions and the lowest degradation under basic conditions.

The difference in degradation behavior between the marketed and in-house formulations indicates that formulation composition and processing conditions may influence the stability behavior of the drug product. The in-house formulation contained excipients such as lactose and starch, and differences in formulation composition may contribute to differences in the response observed under various stress conditions. However, the present study data alone do not establish the specific contribution of individual excipients.

Method validation was performed by evaluating linearity and repeatability. The calibration curve was prepared over a concentration range of 0.5–10 ppm, and absorbance was measured at 248 nm. Repeatability was assessed by measuring the same concentrations three times on the same day under the same conditions. These studies were included to evaluate the consistency and suitability of the analytical procedure.

Overall, the forced degradation study demonstrated that the marketed and in-house paracetamol formulations exhibited different degradation patterns under the selected stress conditions. The marketed formulation showed maximum degradation in acidic conditions, whereas the in-house formulation showed maximum degradation under hydrolytic conditions. These findings demonstrate the usefulness of forced degradation studies for evaluating the stability behavior of pharmaceutical formulations and for obtaining information that can assist in the selection of appropriate formulation, packaging and storage conditions.

Conclusion

- The purpose of analytical method development is to establish the identity, purity, physical characteristics, and potency of drugs, including the drug's bioavailability and stability.
- Analytical method development and validation can be understood as the process of showing that analytical procedures are adequate for the purpose of assessing drugs, and particularly the active pharmaceutical ingredient (API).
- Analytical procedures are developed to test specific characteristics of the substances against the predefined acceptance criteria for such characteristics.
- Thus, analytical method development involves the evaluation and selection of the most precise assay procedures to determine the composition of a drug.
- The analysis of forced degradation of paracetamol marketed and in house formulation study was carried out by subjecting drug sample to FD parameters of acidic, basic, Hydrolytic, Photolytic and

further analysis by UV.

- The marketed preparation (reference standard) was degraded by Acid 46.04%, Base 31.3%, Hydrolytic 20.96% and Photolytic -7.5%. Then likely in-house preparation was degraded by the Acid36.41%, Base 10.46%, Hydrolytic 45.2% And Photolytic 12.67% of forced degradation method.
- The International Conference on Harmonization (ICH) guidance provides very little information about strategies and principles for conducting forced degradation studies, including problems of poorly soluble drugs and exceptionally stable compounds and International Conference on Harmonization guideline Q1A (R2). Because Economical maintenance and less equipment cost are generally over other method. Also, validation of development was done as per guideline of ICH.

Limitations

1. The study was limited to paracetamol tablets and may not be directly applicable to other drug formulations.
2. Only one marketed formulation and one in-house formulation were evaluated.
3. The forced degradation study was performed under selected stress conditions such as acid, base, oxidation, thermal and photolytic conditions.
4. The study was conducted on a laboratory scale, which may not completely represent large-scale manufacturing or storage conditions.
5. The number of samples and batches evaluated was limited due to time and resource constraints.
6. Only the selected analytical parameters were evaluated; advanced techniques such as LC-MS/MS or NMR were not included for detailed identification of degradation products.
7. The study primarily focused on comparing the stability/degradation behavior of the two formulations rather than evaluating long-term stability.

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