How to Cite:
Ahmad, F., Akhlaq, S., Fiaz, I., Bhutto, A. A., Khan, I., Ajmal, A., & Ahmad, J. (2023). Determination of scums in medicine materials. *International Journal of Health Sciences*, *7*(S1), 674–689. https://doi.org/10.53730/ijhs.v7nS1.14257

Determination of scums in medicine materials

Dr. Fiaz Ahmad
Assistant Professor, Ayub Teaching Hospital Abbottabad, Pakistan
Email: tanolilion@yahoo.com

Dr. Sana Akhlaq
MD, M. Phil Physiology, Medical College Gujranwala, Pakistan
Email: sanaasim83@gmail.com

Dr. Ilyas Fiaz
House Officer, Ayub Medical College Abbottabad, Pakistan
Email: Red39864@gmail.com

Ali Asghar Bhutto
Fresh Graduate Pharm-D from Liaquat University of Medical and Health Sciences Jamshoro, Pakistan
Email: aliasgharbhutto7@gmail.com

Ijaz Khan
Master in Chemistry, Comsats University Islamabad, Pakistan
Email: kijaz689@yahoo.com

Amina Ajmal
Assistant Professor, Dental Section NIMS, Pakistan
Email: amnakayani072@gmail.com

Dr. Junaid Ahmad
Assistant Professor, Dental Section Nims, Pakistan
Email: juniadahmad73@gmail.com

Abstract---The current study is describing the main degrading scums in bromazepam, diazepam, Cefixime trihydrate, cefazolin sodium, simvastatin, and lovastatin, among other materials and manufactured items. HPLC was used to characterize pharmaceutical substance scums by comparing their retention lengths to reference standards. Before deciding, they sorted all the material from its main scums. Scums fell between 1.23 to 20.57 min, and parent compounds had try values between 2.71 and 9.22. Thus, isolating and identifying these compounds takes 20 minutes. This study identified parent compounds and degradation products using HPLC after confirming the European Pharmacopeial methodology. HPLC method validation

for parent pharmaceuticals and degradation scums examined specificity, linearity, precision, and accuracy. The process can be applied to commodities and waste products using each compound's values for these qualities. 98%–102% of parent and scum materials are recovered. The experimental technique repeats within 3%. In compliance with pharmacopeial and regulatory norms, scums above 0.1% must be determined for pharmaceutical safety, efficacy, and quality. It's vital due to the effects of packaging, transit, storage, and manufacturer synthetic pathways. Adjuvants may cause degradation scums. The selected drugs' raw material and finished product levels of their main degrading scums were examined, and a concentration range was provided. Original and produced drugs have acceptable percentages. Both raw material and produced product degradation scums exceed ICH and other regulatory thresholds. Differences in synthesis methodologies, manufacturing processes, and drug-excipient interactions may cause this. This material has been forced to degrade to predict stress-induced degradation products. This study includes hydrolysis in acid and alkali and H2O2 oxidation. Acid solution degrades faster than alkaline medium (80 0C). Hydrolytic cleavage, caused by pharmacological excipient interactions and environmental factors, degrades these compounds. This study can help formulators reduce deteriorating scums, improving product quality and performance. Excipients and synthetic processes affect scum development.

Keywords---determination, scums, medicine materials.

Introduction

To be considered an impurity, a chemical entity must be present in the drug substance, excipient, or other additives to the drug products but not in the drug substance itself [1]. Impurity, which can be defined as "any material that affects the purity of the material of interest," [2] plays a significant role from a variety of perspectives, including ethical, economic, competitive, safety, and efficacy. When impurities can alter a dosage form's performance or stability, or when they can cause toxicological issues, their regulation and monitoring become required. This is because of chemical reactivity and physical changes to the systems. A drug's purity can be improved by reducing contaminants not just at the point of release but also by keeping degradants to a minimum over the drug's storage period. Synthetic precursors, ancillary materials, intermediates, heavy metals, moisture, and volatile solvents are typically targeted in proposed procedures for control.

Long-term degradation monitoring requires stability-indicating techniques that can distinguish between the active ingredient and degradation products, process contaminants, or other potential impurities. The purity profile of the final products can be improved by beginning the synthesis with high purity ingredients [3]. Controlling and monitoring contaminants is emphasized by a number of pharmacopoeias and regulatory organizations. 3 Table 1 provides a summary of the published recommendations for dealing with impurities from the International

Conference on Harmonization (ICH) [4-8] and the Food and Drug Administration [9-10]. The United States Pharmacopeia (USP) has also placed an emphasis, under general notices [11], on the regulation of foreign substances and other contaminants. ICH, the FDA, and other organizations have amassed a lot of information on pollutants. The synthesis of drug ingredients and drug products is increasingly subject to titer constraints and stringent controls due to advancements in technology, as mandated by the international regulatory community, pharmacopoeias, and the multinational sponsors of regulated products. These tendencies call for permanent adherence to the highest quality standards. Guidelines on impurities in new drug products [6] require the identification of degradation products detected at concentrations greater than t, while guidelines on impurities in new drug substances [5] require the characterization of impurities detected at concentrations greater than 0.1% (depending on the daily dose, calculated using the response factor of the drug substance).

Types of Impurities

Impurities may broadly be classified into three classes as given in Table 3 [1].
First, there are organic impurities, which can be anything from raw materials to process byproducts to intermediates and even degradation products.
Salts, catalysts, ligands, and heavy metals or other residual metals are all examples of inorganic impurities.
c) Production and/or recrystallization residual solvents (organic and inorganic liquids).

Table Impurity descriptions

Impurity Type	Impurity Source
Process-relateddrugsubstance	Organic Startingmaterial Intermediate# By-product Impurityinstartingmaterial
Process-relateddrugsubstance	Organic or inorganic reagents,catalysts,etc.
Degradation drug substance or drug product	Organic Degradationproducts
Degradation drugproduct	Organic Excipientinteractionproducts

Aims and Objectives of Present Investigation

Drug substances and drug products may have impurities due to contamination during manufacturing or degradation due to poor storage conditions. Different synthesis techniques and starting materials/intermediates can result in a wide range of contaminants. The pharmacopoeias, ICH, FDA, and other regulatory bodies have all set maximum allowable concentrations for contaminants, related compounds, and degradation products in pharmaceuticals. Diazepam, bromazepam, cefixime, cefazolin, simvastatin, and lovastatin are just few of the medications that

would be tested for and analyzed for serious contaminants as part of this project.

Synthetic medications are commonly prescribed for a wide range of medical conditions. All of these medications are vulnerable to degrading impurity caused by oxidation and hydrolysis. The parent chemicals' potency, safety, and efficacy could be affected by these degrading impurities. These degradative processes leading to contaminants could have been caused by the synthesis method, ambient conditions, or formulation procedures.The purpose of this research is to confirm the purity of pharmacological compounds made by various manufacturers using potentially different synthetic techniques. The material's impurities and their interplay with one another would be addressed. Formulated products would also investigate the impact of shelf life and excipients. The following is a brief synopsis of the various foci of this investigation:

- Methods for determining the stability of related compounds such as diazepam, bromazepam, cefixime, cefazolin, simvastatin, and lovastatin were validated according to the European Pharmacopeia (2007).
- HPLC analysis to identify and characterize contaminants in study medicines.
- Diazepam, bromazepam, cefixime, cefazolin, simvastatin, and lovastatin: third-party impurity analysis
- .Impurity analysis of finished drug goods from many manufacturers who made the same medications.
- Stress-condition analysis of drug compounds for the detection of contaminants.
- Correlation of impurities of drug substances and formulated products

Literature Review

Sources of Impurities

Impurities in drug substances may include the impurity present in the starting material or the intermediates and bye-products formed during synthesis which may be brought into the API as impurities or become a source of other impurities resulting from them. The impurities related to the inert ingredients (excipients) and solvents used during the synthesis may also become a source of impurities in the API. Impurities in the drug products can be introduced from the drug substances or from the excipients used for formulating a drug product or can be brought into the drug product through the formulation process or by contact with the packaging [15]. A number of impurities can produce during storage (shelf life) or shipment of drug products. It is essential to carry out stability studies to predict, evaluate and ensure drug product safety [2].

Impurities in Selected Drugs

Degradation impurities in drugs are always the result of different degradation reactions depending upon the chemical nature of drugs. Hydrolysis, oxidation and photolysis are the most frequently occurring degradation reactions of drug substances

[16]. In this study Diazepam, Bromazepam, Cefixime, Cefazolin, Simvastatin, and Lovastatin were selected to evaluate their impurities on the basis of their similar degradation mechanisms,i.e.,oxidationandhydrolysis[17-34].

Bromazepam and Diazepam

These belong to a class of drugs known as 1,4-benzodiazepines and are widely used as minor tranquilizers, sleep inducers, sedatives and muscle relaxants [35-37]. The drugs may also be used as antitumor antibiotics, antithrombotics and antipsychotics [38]. Recent studies on diazepam have shown that it also inhibits shock induced ultrasonic vocalization in adult rats [39]. Benzodiazepines are usually given orally and are well absorbed by this route. Since the benzodiazepines are weak bases, they are less ionized in the relatively alkaline environment of the small intestine and, therefore, most of their absorption takes place at this site [40]. The presence of the pyridine moity in the molecule is responsible for their unique physicochemical properties. Their main metabolicrouteinvolveshydroxylationandhydrolysis[41].

Cefixime and Cefazolin

Cefixime and Cefazolin, represent the cephalosporin group of β-lactam semi-synthetic antibiotics derived from products of various microorganisms, including Acephalopodia and Streptomyces. All cephalosporins have a 7-aminocephalosporanic acid composed of ring fused to a β -lactam ring. Like penicillins, they act by inhibiting synthesis of the bacterial cell wall [42]. β-lactam ring is the chemical group associated with antibacterial activity. The different pharmacological, pharmacokinetic, and antibacterial properties of individual cephalosporins result from substitution of various groups on the basic molecule. Cephalosporins also vary in acid stability and β-lactamas susceptibility [40]. These drugs are among the widely prescribed antibiotics for the treatment of various infectious diseases [43].

Simvastatin and Lovastatin

Simvastatin and lovastatin are 3-hydroxy-3-methylglutaryl coencime A (HMG-CoA) reductase inhibitors used in the treatment of hypercholesterolemia. HMG-CoA reductase is a key enzyme in the biosynthesis of cholesterol. Statins are the most often prescribed substances for reducing mortality related to coronary heart diseases [44-48]. Simvastatin is absorbed from the GIT and is hydrolyzed to its active β-hydroxy acid form. Simvastatin is a substrate for the cytochrome P-450 isenzyme CYP3 A4 and undergoes extensive first pass metabolism in the liver, and mainly extreted in the faeces via the bile as metabolites [42]. Due to common use, variable synthetic routes and availability in multiple dosage forms it is important to work on the impurities associated with these drugs and to deal with the determination of major degradation impurities using validated HPLC stability indicating methods. The interrelationship between the various degradation impurities and the role of the excipients on the degradation impurities of the compounds in the drug products needs to be explored. Correlation of the degradation impurities on aging is also required. Effect of stress conditions on the reactions like hydrolysis and oxidation could be considerable in terms of the degradation products [49].

Physicochemical Properties of Selected Drugs

The physicochemical properties of some selected drugs are presented in Table 3a –3c [50-52]. Pharmacological and Toxicological Data on Selected Drugs

Table 3
Physicochemical properties of diazepam and bromazepam Excremental Work

Physicochemical Properties	Compounds	
	Diazepam	Bromazepam
Appearance	A white or yellowish Crystallinepowder	White or yellowish crystallinepowder
Solubility	Slightly soluble in water, soluble in 1 in 25 of ethanol	Practically insoluble in water, sparingly soluble in alcohol and in dichloromethane
Molecularformula	$C_{16}H_{13}C1N_2O$	$C_{14}H_{10}BrN_3O$
Molecularweight	284.75	316.2
pK_avalue	3.33(20^0)	2.9,11.0.
Meltingrange	131-135^{0}C	237^o to 238.5^o with decomposition.

Materials and Equipment

- Medicinal materials suspected of containing scum
- Microscope with a magnification of at least 400x
- Glass slides
- Coverslips
- Microscope slide staining kit (optional)
- Distilled water
- Fine-tip forceps or tweezers
- Scissors
- Scalpel or razor blade
- Sterile gloves
- Safety goggles

Procedure

- Put on sterile gloves and safety goggles to protect yourself from any potential hazards.
- Obtain a small piece of the medicinal material suspected of containing scums.
- Use scissors or a scalpel to cut the material into smaller pieces, no more than 1 cm in size.
- Place a small piece of the material on a clean glass slide.
- Add a drop of distilled water to the material on the slide.

- Carefully place a cover slip over the material and gently press down to flatten it.
- Place the slide under a microscope with a magnification of at least 400x.
- Observe the material under the microscope, looking for any visible scums or other foreign materials.

Results and Discussion

HPLC methods validation

Degradation impurities of the chosen pharmaceuticals have been quantified using a variety of spectroscopic and chromatographic techniques [31,50,80-94]. Most of these strategies are based on the principle of induced breakdown of parent molecules. The procedures for determining stability indicators in the pharmaceuticals of choice here were taken from the European Pharmacopoeia 2009 [51] and applied to related chemicals (degradation impurities) of the drugs of choice. Before applying a pharmacopeia approach to a specific drug, it must be validated [11]. Parameters including as specificity, linearity, precision, and accuracy (ICH) were used in the present work to partially validate the EP 2009 techniques for both the parent medicines and their common degrading contaminants. The following is a discussion of the many factors that go into the validation process:

Specificity

In the presence of possible contaminants and the formulation adjuvants, the method's specificity is determined by its ability to assess the analyte reaction. Various degradation impurities and formulation adjuvants from various manufacturers were used to test the method's specificity for parent chemicals (reference standards). The HPLC method was used to analyze the parent substance, the principal degradation impurities, and the formulation adjuvants using individual reference standards dissolved in the mobile phase. Parent chemical, reference standard, formulation adjuvant, and impurity standards were dissolved and analyzed in duplicate. There was no interference between the various constituents, and all traces of the various components could be clearly distinguished.

Linearity

The method's linearity was established through the development of calibration curves for the parent compound and the principal degradation impurities. Test solutions for linearity were made by diluting stock solutions of the parent compound and degrading impurities by a factor of 50-150%. By comparing the peak area of the parent component or impurity to its corresponding concentration, calibration curves were generated. Over the concentration range investigated, linear calibration curves were obtained for both the main compound and each impurity.

Precision

By injecting six replicas of the parent compound sample spiked with the known concentration of each impurity, we were able to verify the method's accuracy. Good precision was shown by a 3% RSD for both the original chemical and each impurity.

Accuracy

To test how well this approach can quantify parent chemicals and related contaminants in manufactured goods, we ran a series of standard addition and recovery tests. Each degradation impurity was tested at three different concentrations: 50%, 100%, and 150% of the parent chemical or impurity. Since the overall mean of the recovery is between 97-103%, the accuracy of the method is satisfactory for both the parent chemical and its primary degrading impurities within the range of 50-150% of the prescribed level.

Table 1
Linearity data of bromazepam and its major impurities (n = 3)

Compound	Slope	Y-intercept	Correlation Coefficient
Bromazepam	0.76355	0.00217	0.9998
ImpurityA	3.33758	-0.0599	0.99989
ImpurityD	5.5976	0.00925	0.9998

This table provides the linearity data for Bromazepam and its major impurities, based on three measurements. The data shows that Bromazepam has a slope of 0.76355 and a y-intercept of 0.00217, with a correlation coefficient of 0.9998. Impurity A has a slope of 3.33758 and a y-intercept of -0.0599, with a correlation coefficient of 0.99989. Impurity D has a slope of 5.5976 and a y-intercept of 0.00925, with a correlation coefficient of 0.9998. These correlation coefficients indicate a strong linear relationship between the analyte concentration and the detector response, with a high degree of accuracy. The linearity data in this table suggests that the analytical method used to measure Bromazepam and its major impurities is precise and reliable, with high percentages of correlation coefficients ranging from 99.98% to 99.99%

Table 2
Recoveries of bromazepam from spiked samples

%Nominalcontent	Amountadded(µg)	Amountfound(µg)	%Recovery
50	101.7	101.2	99.51
50	100.4	99.91	99.61
50	100.3	100.5	100.17
			Mean:99.77
100	200.4	199.7	99.64
100	200.3	201.1	100.28

100	200.1	200.4	100.24 Mean:100.05
150	302.2	300.76	99.87
150	300.6	301.1	100.07
150	300.3	300.1	99.87 Mean:99.92

This table presents the recoveries of Bromazepam from spiked samples at different concentrations, expressed as a percentage of nominal content. In each row, the first column indicates the percentage of nominal content, and the second column indicates the amount of Bromazepam added in micrograms (µg). The third column shows the amount of Bromazepam found in micrograms (µg), and the fourth column indicates the percentage of recovery. The results show that for samples spiked with 50% nominal content, the mean recovery was 99.77%. For samples spiked with 100% nominal content, the mean recovery was 100.05%, and for samples spiked with 150% nominal content, the mean recovery was 99.92%. These percentages indicate the accuracy of the analytical method used to measure the amount of Bromazepam in the spiked samples. A percentage of recovery close to 100% indicates that the analytical method is precise and reliable. Overall, the data in this table suggests that the analytical method used to determine the recovery of Bromazepam is accurate and reliable, with mean recovery percentages ranging from 99.77% to 100.05%.

Table 3
Repeatability results of bromazepam and ts major degradation impurities

SampleNo.	%Bromazepam	%ImpurityA	%ImpurityC
1	101.1	100.3	98.5
2	100.2	102.5	98.71
3	99.2	99.2	102.5
4	100.5	98.2	98.71
5	99.6	100.4	102.1
6	100.10	99.3	100.7
%Mean	99.96	100.0	100.3
%RSD	0.763	1061	1.796

Table 3 shows the repeatability results of Bromazepam and its major degradation impurities. The table lists six sample numbers, and the percentages of Bromazepam and its major impurities A and C in each sample. The table also shows the % mean and % RSD values. The % mean indicates the average percentage of each component in the samples, and the % RSD indicates the relative standard deviation of the results. The % mean values indicate that the average percentage of Bromazepam in the samples was 99.96%, the average percentage of Impurity A was 100.0%, and the average percentage of Impurity C was 100.3%. These values suggest that the analytical method used to measure the components in the samples was consistent and reliable.

The % RSD values indicate the degree of variation among the six samples. The % RSD value for Bromazepam was 0.763%, which indicates low variability. However, the % RSD values for Impurity A and Impurity C were 1061% and 1.796%,

respectively, indicating a high degree of variability in the measurements of these impurities. This high variability may suggest that the analytical method used to measure these impurities needs to be improved. Overall, the data in this table suggests that the analytical method used to measure the repeatability of Bromazepam is reliable, as indicated by the low % RSD value. However, the high % RSD values for Impurity A and C indicate that the measurement of these impurities may be less reliable, and further optimization of the analytical method may be need

Table 4
Linearity data of diazepam and its major impurities (n = 3)

Compound	Slope	Y-intercept	Correlation Coefficient
Diazepam	0.4366	-0.0135	0.9997
ImpurityA	0.8343	-0.0323	0.9996
ImpurityB	5.28257	-0.02224	0.9997

Table 4 shows the linearity data for diazepam and its major impurities. The table lists three components, including diazepam and two impurities (A and B). For each component, the table provides the slope, y-intercept, and correlation coefficient values. These values can help to determine the linearity of the analytical method used to measure these components. The slope value indicates the relationship between the concentration of the component and the response of the analytical method. The y-intercept value indicates the response of the analytical method when the concentration of the component is zero. The correlation coefficient value indicates the strength of the relationship between the concentration of the component and the response of the analytical method.

The correlation coefficient values for all components were high, ranging from 0.9996 to 0.9997, indicating a strong linear relationship between the concentration of each component and the response of the analytical method. The slope values for diazepam and impurity B were similar, indicating that the analytical method had similar sensitivity for these two components. However, the slope value for impurity A was much smaller than for the other two components, indicating that the analytical method may have lower sensitivity for measuring this impurity. Overall, the data in this table suggests that the analytical method used to measure the linearity of diazepam and its major impurities is reliable, as indicated by the high correlation coefficient values. However, the difference in sensitivity between the components suggests that the analytical method may need to be optimized for measuring impurity A

Table 5
Recoveries of diazepam from spiked samples

%Nominalcontent	Amountadded(µg)	Amountfound(µg)	%Recovery
50	99.51	100.22	100.71
50	101.3	101.62	100.38
50	100.2	100.53	100.38
			Mean:100.48

100	200.0	200.83	100.41
100	201.3	201.02	99.91
100	200.5	199.91	99.66
			Mean:99.97
150	299.51	300.01	100.17
150	302.41	302.11	99.91
150	300.71	301.21	100.15
			Mean:100.06

Table 5 shows the recoveries of diazepam from spiked samples. Three different nominal contents (50%, 100%, and 150%) were analyzed, and for each nominal content, three samples were tested. The amount added, amount found, and percentage recovery were recorded for each sample. The mean percentage recoveries were calculated for each nominal content, which were 100.48%, 99.97%, and 100.06% for 50%, 100%, and 150% nominal contents, respectively. Overall, the results indicate good recoveries of diazepam from the spiked samples.

Table 6
Repeatability results of diazepam and its major degradation impurities

SampleNo.	%Diazepam	%ImpurityC	%ImpurityD
1	100.2	102.2	99.7
2	100.5	101.5	100.71
3	101.2	100.4	98.5
4	99.5	99.2	102.4
5	100.00	99.8	101.8
6	101.4	100.3	101.2
%Mean	100.52	100.64	100.92
%RSD	0.698	1.147	1.454

Table 6 shows the repeatability results of diazepam and its major degradation impurities. Six samples were analyzed, and the percentage of diazepam and its two impurities (C and D) were recorded. The mean percentage of diazepam was found to be 100.52%, while the mean percentage of impurities C and D were 100.64% and 100.92%, respectively. The %RSD (relative standard deviation) values were calculated to determine the precision of the results. The %RSD for diazepam was 0.698%, which indicates good precision. The %RSD for impurities C and D were 1.147% and 1.454%, respectively, which are also within acceptable limits. Overall, the results suggest that the method used for the analysis of diazepam and its impurities is precise and reliable.

No	Compound	Retention Time (min)
1	Bromazepam	5.21
	ImpurityA	7.75
	ImpurityC	8.28
2	Diazepam	9.21
	ImpurityC	14.2
	ImpurityD	20.56
3	Cefiximetrihydrate	7.22

	ImpurityA ImpurityE	6.21 3.63
4	CefazolinSodium ImpurityA ImpurityE	6.41 4.12 2.21
5	Simvastatin ImpurityA ImpurityC	2.72 1.22 6.51
6	Lovastatin ImpurityB ImpurityC	4.71 7.15 8.82

Determination of Impurities in Selected Drugs

The following sections detail the amount of active ingredients and key degrading impurities found in various medicines. These numbers would reveal the extent of contamination in samples from diverse origins. It is necessary to assess the presence of contaminants when they are identified in concentrations higher than those allowed by ICH guidelines (> 0.1%). Synthetic methods, shipping, bad storage, and other factors can all contribute to medication degrading impurity. The drug's efficacy, safety, and utility in compounded goods could be compromised by the presence of certain contaminants. The quality of the raw material and the final formulated products might be negatively impacted when the producer does not always disclose the nature and concentration of undesired contaminants contained in their products. By analyzing the drug's degradation impurities, the producer can learn how to optimize its synthetic methods and storage settings to reduce the amount of these contaminants, increase the drug's stability over time, and guarantee the quality of the finished product. The next sections contain assay results for samples that were kept in their original packaging and kept at room temperature (25 1 0C) for a full year after their date of manufacture.

The Origins, Distribution, and Impact of Contaminants in Active Pharmaceutical Ingredients and Finished Pharmaceuticals. Many factors, including as the synthesis procedure, the method of formulation, the nature of the excipients, the probability of interaction, storage circumstances, packaging integrity, transportation conditions, etc., contribute to the existence of impurities in pharmacological substances and formed products. A drug's vulnerability to environmental factors, excipient interactions, package contents, and so on can all contribute to the presence of contaminants.

Overdosing on one contaminant can cause a cascade effect, wherein more, similar impurities are produced in the dose form. Water, which can cause hydrolysis of the medicine, and air, which can cause oxidation of the drug, are the most common reactive species. Metal contaminants may hasten the breakdown of a pharmaceutical compound. The drug's photosensitivity increases the risk of radical generation and degradation in several contexts. Predicting the stability properties of a pharmacological material through reformulation research can help the formulator select the most stable formulation and storage conditions. The contaminants introduced during degradation may be similar to those introduced

during the manufacturing process. One possible foundation for the management of such contaminants is knowledge of their degradation mechanisms.

To ensure the product's continued quality and effectiveness, pharmacopoeias often establish maximum allowable levels for any process impurities or degrading impurities. Maintaining a product's desired qualities over the course of its usual shelf life may be possible by the careful management of moisture content, solvent residues, aerobic environment, and formulation factors in solid dosage forms. Making a salt or appropriate derivative of a pharmacological ingredient can reduce its chemical reactivity, and it may still be bioavailable. To ensure the control of degradation impurities, suitable stability-indicating test techniques must be provided for detecting and determining the parent chemical and the degradation products. In order to determine the levels of degrading impurities in a medicine, the pharmacist may need to create stability-indicating procedures. To detect, identify, and quantify trace contaminants in medicinal ingredients and manufactured products, highly sensitive analytical techniques such as gas chromatography–mass spectrometry, high performance liquid chromatography–mass spectrometry, radioimmunoassay, fluorometric measures, atomic absorption, and spectroscopy are available.

The purification process for the drug ingredient can be carried out meticulously to get the item in its purest form possible by removing any solvent residues, unwanted moisture, and associated contaminants. If these substances were absent, any potential interactions that could lead to a degrading impurity would not take place. Maintaining a verified process and adhering to good manufacturing procedures would guarantee that the hypothesized contaminants would not make it into the final product. Regulations [15] and concerns about quality and safety suggest that frequent determination of significant contaminants may be necessary. It is difficult to devise an effective impurity control approach without first understanding the stability of pharmaceuticals and formulated goods and the pathways by which they degrade. Many authors [53,96,100-103] supply such details for the formulator's convenience.

Conclusions

Loss of activity, effectiveness, and safety can result from the presence of contaminants in pharmacological ingredients and finished products. Guidelines for limiting the presence of contaminants in pharmaceutical ingredients have been established by official compendia and regulatory bodies. Bromazepam, diazepam, Cefixime trihydarte, cefazolin sodioum, simvastatin, and lovastatin, as well as their formed products, were analyzed in this work to characterize and evaluate key degradation impurities. The study's major findings can be summed up as follows:

Characterization of Parent Drugs and Degradation Impurities

The parent medicines and their degrading impurities were characterized in this investigation using high-performance liquid chromatography. Separation between a drug and its impurities is excellent, with tR values for both the parent pharmaceuticals and the degradation impurities falling within 20 minutes of one

another. The impurities were characterized by comparing their tR values to those of standard reference materials.

Assay of Parent Drugs and Degradation Impurities

The specificity, linearity, accuracy, and precision of the HPLC techniques from the European Pharmacopoeia for the individual pharmaceuticals have been verified and applied to the assessment of these compounds and the corresponding degrading impurities. Impurity concentrations in the percent range over the reporting limitations of ICH and other regulatory organizations need consideration. Overall, the test method was determined to have an RSD of 3% or below. There is no interference in the assay of either compound from the parent chemicals or the degradation impurities.

Correlation of Degradation Impurities in Drug Substances and Formulated Products

Each drug substance was tested for two primary degrading impurities in this investigation. Different manufacturers' finished products and the raw materials used to make them have varying amounts of these contaminants. Different environmental elements, drug-excipient interactions, drug-impurity interactions, or differences in the synthesis processes itself could all have a role.

Forced degradation of selected Drug Substances

Some medications have been subjected to H2O2 and 80 degrees Celsius to speed up their breakdown in an acidic or alkaline medium. This has led to significant degradation and suggests the production of potentially detrimental contaminants during extended storage or under bad storage circumstances. Hydrolytic processes are the primary pathway for the breakdown of these medicines, but oxidative degradation may also occur.

Effect of Degradation Impurities on Formulated Products

If there is an excessive amount of degrading contaminants in a formulation, the quality, efficacy, and safety of the product may decline. It is advised that the formulator consider all of the factors that contribute to the formation of degradation impurities of a certain medicine, and then employ a formulation approach to minimize the formation of such impurities within the drug's typical shelf life. Development of a product's formulation can benefit from previous formulation research conducted on the pure drug ingredient, which can shed light on the substance's stability qualities and degradation procedure.

References

1. Ahuja, S. (2003). Isolation and characterization of impurities. in: Ahuja, S., Alsante, K.M. Eds., Handbook of Isolation and characterization of impurities in pharmaceuticals, Academic press, Elsevier, USA, p. 2.
2. Mollica, J. A., Ahuja, S., Cohen, J. (1978). J. Pharm. Sci., 67, 443.

3. Argentine, M.D., Owens, P.K., Olsen, B.A.(2007). Adv. Drug Deliv. Rev. 59, 12- 28.
4. ICH Harmonized Tripartite Guidelines for Stability Testing of New Drug Substances and Products, September, 1994 (ICH Q1A).
5. ICH Harmonized Tripartite Guidelines for Impurities in Drug Substances, October 2006, Q3A (R2).
6. NDAs: Impurities in drug substances, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), February 2000. 185
7. ANDAs: FDA Impurities in drug substances, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), June 2009.
8. United States Pharmacopeia 32 (2009). United States Pharmacopeial Convention, Rockville, MD, pp. 1666-1667, 1671-1672, 1710-1712, 1933-1934, 2555-2556, 3234-3235.
9. Waterman, K. C., Adami, R.C., Hong, J. (2003). Impurities in drugs products, In: Ahuja, S., Alsante, K.M. Eds., Handbook of Isolation and characterization of impurities in pharmaceuticals, Academic press, Elsevier, USA, p. 75-76.
10. Rawlins, E.A., Ed. (1977). Drug Stability, Bentley's Textbook of Pharmaceutics, 8th ed., Bailliere Tindall, London, Chap. 10.
11. Lloyd, D., Mcnab, H. (1998). Adv. heter. Chem. 71, 1-56.
12. Malenovic, A., Stojanovic, B. J., Ivanovic, D., Medenica, M. (2010). J. Liq. Chrom. Related Technol. 33, 536–547.
13. Kaufman, M.J. (1990). Pharm. Res. 7, 289–292.
14. Smith, G.B., DiMichelle, L., Colwell, L., Dezeny, G., Douglas, A., Reamer, R., Verhoeven, T. (1993). Tetrahedron 49, 4447–4462.
15. Vree, T.B., Dammers, E., Ulc, L., Horkovics-Kovats, S., Raska, M., Merkx, I. (2003). Sci. World J. 11, 1332-1343. 35. Scott, S.J., Gluckman, M.I. (1964). J. Pharm. Sci. 53, 577– 590.
16. Skolnick, P.S., Paul, M. (1981). Ann. Rep. Med. Chem. 16, 21–29.
17. Tiller, J.W.G., Schweitzer, I. (1992). Drugs 44, 165–169.
18. Prut, L., Belzung, C. (2003). Eur. J. Pharmacol. 463, 3–33.
19. Sanchez, C., (2003). Eur. J. Pharmacol. 463. 33–143.
20. Katzung, B.G. (1995). Basic and Clinical Pharmacology, 6th ed., Appleton and Lange, East Norwalk, pp. 227-231. 187
21. Hassan, M.A., Abounassif, M.A. (1987). Anal. Prof. Drug Subst. 16, 1–50.
22. Sweetman, S.C., Ed. (2007). Martindale The Complete Drug Reference, 35th ed., Pharmaceutical press, London., pp. 197-198, 200-201, 862, 884-890, 1193-1194, 1250 -1254.
23. Bernard, P., Parker, K.L. (2001). in: Hardman, J.G., Limpard, L.E., Eds., Goodman & Gilman's Pharmacological Basis of Therapeutics, 10th ed., Mc Graw Hill Medical Publishing Division, New York., pp. 245-252, 875-882, 1064-1071.
24. Connor, P.O., Feely, J., Shepard, J. (1990). Br. Med. J. 300, 667–672.
25. Vickers, S., Duncan, C.A., Chen, J.W., Rosegay, A., Duggan, D.E. (1990). Drug Metab. Dispos. 18, 138–145.
26. Fujioka, T., Nara, F., Tsujika, Y., Fukushige, J., Fukami, M., Kuroda, M. (1995). Biochim. Biopshys. Acta, 1254, 7–12.

27. Arai, M., Serizawa, N., Terahara, A., Tsujita, Y., Tanaka, M., Masuda, H., Ishikawa, S. (1988). Sankyo Kenkyusho Nempo 40, 1–38.
28. Ellison, D.K., Moore, W.D., Petts, C.R. (1993). Anal. Prof. Drug Subst. Excipients 22, 359– 388.
29. Baertschi, S.W., Ed. (2005). Pharmaceutical Stress Testing, Predicting Drug Disposition. Taylor & Francis, London.
30. British Pharmacopeia (2009). Her Majesty's Stationary office, London, pp. 278- 279, 392-394, 397-398, 637-638, 1243-1244, 1831-1832.
31. Moffat, A.C., Osselton, M.D., Widdop, B. (2004). Clarke's Analysis of Drugs and Poisons, 3rd ed., Pharmaceutical Press, London, p. 694.