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Development of a Rapid Analytical Method on UV Spectrophotometer for Analysis of Trace Level APIs Telmisartan in Cleaning Validation Sample

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ABSTRACT:
Since the 1990's, cleaning validations have gained a lot of interest within pharmaceutical and bio-pharmaceutical companies. In 1988, the FDA experienced its first major incident with cross contamination traceable to inadequate cleaning and cleaning validation. The finished drug product, Cholestyramine Resin USP, was recalled due to contamination with low levels of intermediates and degradants from the production of agricultural pesticides. The cross-contamination was believed to have come from the use of drums in the production of the active pharmaceutical ingredient (API). These drums had previously been used to store solvents for the manufacture of agricultural pesticides at another plant. Extra pure methanol procured from Chempura Enterprises Indore of make Merck and Analytical Grade water procured from the SK Traders Indore M.P. Reference materials, Telmisartan from Axiom Analytical Services Indore M.P. HPLC grade methanol (MeOH), HPLC Grade Water were purchased from Chempura Enterprises Indore M.P.. All chemicals were used as received, without any further purification.
In recent years, increased emphasis has been placed in pharmaceutical companies for implementing robust validated cleaning procedures. The cleaning procedure is one of the most important tasks to avoid contamination and cross- contamination of APIs in pharmaceutical products manufactured on the same equipment trains. The cleaning procedures must be supported byappropriate analytical methods and related sampling methodologies.
KEYWORDS: Telmisartan, UV-spectroscopy, HPLC, ICH, λ max, APIs

1. Introduction

Since the 1990's, cleaning validations have gained a lot of interest within pharmaceutical and bio-pharmaceutical companies. In 1988, the FDA experienced its first major incident with cross contamination traceable to inadequate cleaning and cleaning validation. This incident raised the FDA's awareness to the potential impact of cross- contamination from un-validated cleaning processes.

The U.S Food and Drug Administration (FDA) issued its Guide to Inspections – Validation of Cleaning Process in 1993. Previously, validation was required only for the manufacturing process of drug products and not for the cleaning process of the manufacturing equipment.

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The objective of cleaning validation is to prove that the equipment is consistently cleaned from product, detergent and microbial residues to an acceptable level, to prevent possible contamination and cross-contamination. The driving force for cleaning validation is patient safety and product quality. Cross- contamination with residues of any kind presents a safety risk to patients consuming the drug product. It threatens to alter the strength, chemical identity, and integrity of the drug substance and formulation. For these reasons, it is essential to have a robust validated cleaning process that is suited to its intended purpose.

1.1. Establishing residue acceptance limits

An important aspect of a cleaning validation is to establish what level of API residue is allowed to remain on the manufacturing equipment surfaces after the cleaning process has been carried out post-production. This is a critical aspect as any residue remaining on the manufacturing equipment after cleaning will be transferred over into the first batch of the next pharmaceutical product as shown in Figure 1.1 [1-7]. In the past, detection and quantitation of trace level residues was more difficult due to the limited analytical technologies available. Today however, there are many analytical technologies available such as UV spectroscopy, HPLC and Mass Spectrometry (MS) that are capable of detecting and quantitating trace amounts of API residues that may remain on the manufacturing equipment after the cleaning process has been carried out.

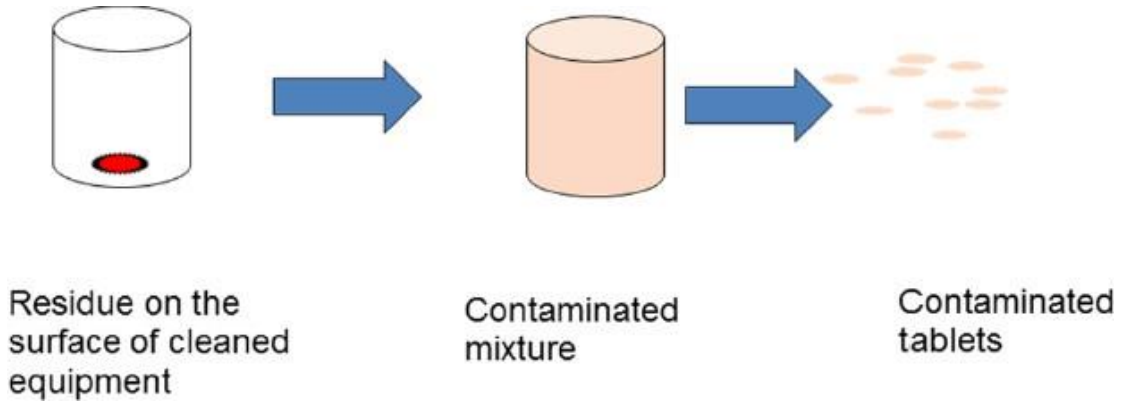

Figure 1.1: Residue contamination of pharmaceutical product

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2. Aim and Objective

The aim of the developed analytical method described in this Chapter was to quantitate the residues of a range of drug substances that included Telmisartan in support of cleaning validation.

In the pharmaceutical industry, there is an incredible need for cleaning equipment and handling regions. Inappropriate cleaning can prompt defilement and cross-contamination (Agrawal et al., 2020). A drug product can be tainted by different residue materials like residues of recently utilized dynamic drug fixings, a natural substance, cleaning specialists and residue particles (Baokar et al., 2013). The primary goal of GMP comprises the anticipation of contamination and cross-contamination of materials. The purpose of cleaning validation is to check the adequacy of the cleaning strategies for the evacuation of deposits of the past item, additives, cleaning specialists and microbial pollutants.

2. DRUG PROFILE

2.1 Drug Introduction

2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl] methyl] phenyl] benzoic acid, is a novel, potent, highly selective non peptide Angiotensin II type 1 (AT1) receptor blocker which is administered orally as Telmisartan, which is rapidly and completely hydrolyzed to Telmisartan, the active moiety, during absorption from the gastrointestinal tract (PS Blake.,2002) (Moffat C et al.,2004) (H Singh et al.,2001). Telmisartan has much greater affinity (> 10,000 folds) for the AT1 receptor than for the AT2 receptor blockade of the renin-angiotensin system with ACE inhibitors; it does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation (A Rall et al., 1990) (A Davidson et al., 2007). UV spectrophotometry method was developed and validated as per ICH guidelines. Spectrophotometry is generally preferred especially by small-scale industries as the cost of the equipment is less and the maintenance problems are minimal. The method of analysis is based on measuring the absorption of a monochromatic light by colorless compounds in the near ultraviolet path of spectrum (200-380nm).

(JK Singh., 2009) (Crouch., 2007) (D hong, 2008).The API is subjected to a number of force

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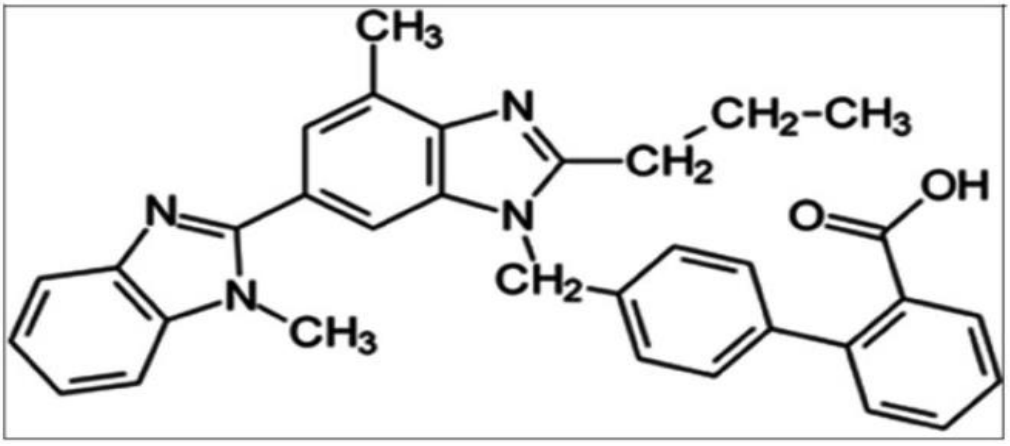
of degradation conditions to include acidic, basic, and oxidative conditions. Force of degradation should be one of the activities performed early in the development process to ensure that the method is discriminating before a lot of time, effort and money have been expended. Depending on the API, not every stress agent may effect de-gradation, but each agent has to be evaluated to determine whether degradation results (Matthews et al., 2008).

2.1.1 Drug Profile of the selected drug

CASNo.	144701-48-4
Officialin	USP,IP,BP,EP Pharmacopoeia
Description	Angiotensin II receptor (AT_1) antagonist (i.e., angiotensin II receptor blocker [ARB]).
Chemical Formula	$C_{33}H_{30}N_4O_2$
Mol.Weight	514.62g/mol

Telmisartan Structure



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Specific Drugs

Drug	Interaction	Comment
Acetaminophen	Interactions unlikely	
ACE inhibitors	Increased risk of renal impairment, hyperkalemia, and hypotension	Generally avoid concomitant use; monitor BP, renal function, and electrolytes if used concomitantly
Aliskiren	Increased risk of renal impairment, hyperkalemia, and hypotension	Generally avoid concomitant use; monitor BP, renal function, and electrolytes if used concomitantly Concomitant use contraindicated in patients with diabetes mellitus. Avoid concomitant use in patients with GFR <60 mL/minute
Amlodipine	Interactions unlikely	
Angiotensin II receptor antagonists	Increased risk of renal impairment, hyperkalemia, and hypotension	Generally avoid concomitant use; monitor BP, renal function, and electrolytes if used concomitantly
Digoxin	Increased plasma digoxin concentrations	Monitor serum digoxin concentrations when telmisartan therapy is initiated, adjusted, or discontinued in patients stabilized on digoxin
Glyburide	Interactions unlikely	

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Hydrochlorothiazide	Additive hypotensive effects	
Ibuprofen	Interactions unlikely	
Simvastatin	Interactions unlikely	
Warfarin	Possible decreased plasma warfarin concentrations; INR not affected	

3. Material and Method

3.1 Reagents and materials

Extra pure methanol procured from Chempura Enterprises Indore of make Merck and Analytical Grade water procured from the SK Traders Indore M.P.Reference materials, Telmisartan from Axiom Analytical Services Indore M.P. HPLC grade methanol (MeOH), HPLC Grade Water were purchased from Chempura Enterprises Indore M.P.. All chemicals were used as received, without any further purification.

3.2 Instrumentation

Analytical instruments and equipment, Digital balance, Ultra sonicator, a double-beam UV-Visible spectrophotometer, Perkin Elmer Model: Lamda 25 with spectral band width of 2nm, wavelength accuracy ± 0.5nm and a pair of 1-cm matched quartz cells and operated by UV Win Lab 21 CFR compliance Software was used to measure absorbance of the resulting solutions.

3.3 Standard preparation

Standard stock solution of Telmisartan was prepared by dissolving 10 mg of drug in 100ml of Methanol: Water (9:1). Shake it properly to dissolve the drug and then adjusted the volume with methanol: water (9:1) to get 100 µg/ml.

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3.3.1 Preparation of working Standard Solutions

The Prepared stock solution was further diluted with methanol: water (8:2) to get working standard solution of 5ppm, 10ppm, 15 ppm, 20ppm, 25ppm, 30ppm, 35ppm, 45ppm to construct Beer's law plot for, Telmisartan. The absorbance of each solution was measured at 298 nm against methanol: water (8:2) as blank. The standard graph for Telmisartan was plotted by taking concentration of drug on X-axis and absorbance on Y-axis.

3.4 Scanning and determination of maximum wavelength (λ max)

In order to ascertain the wavelength of maximum absorbance (λmax) of the pharmacodynamics agents solutions of particular concentrations of drugs 100 mg/ml and 10 mg/ml in methanol: water (8:2) were scanned within the wavelength range of 200-400nm against a corresponding reagent blank. The resulting spectra were presented in fig 1.The absorption curves showed characteristic absorption maxima at 298 nm for Telmisartan.

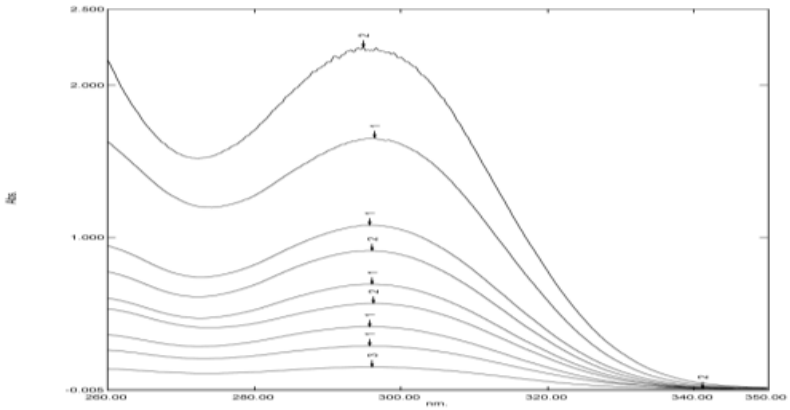

Figure 3.3.1: A typical UV Chromatogram Showing Telmisartan at 298 nm

3.4 Method

The spectroscopic analysis was performed on UV-Vis spectrophotometer with detection by UV at 298 nm for Telmisartan.

3.4.1 Swab standard solution preparation

Stock standard solutions Telmisartan in MeOH:water (80:20, v/v); at a concentration of 100

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µg/mL. The standards were stored in a refrigerator at 4 °C, for two weeks with no significant loss of API. Appropriate dilutions were made with MeOH:water (80:20, v/v) to obtain solutions containing 5 µg/mL, to 50 µg/mL respectively.

3.5 Swab sample preparation

3.5.1 Product contacting surface preparation

The selected surfaces (25 cm2) of stainless steel, glass, teflon and silicone were cleaned and dried. 100 µL of the swab standard solution was applied onto the coupons as shown in Figure 3.1 at the three concentration levels in triplicate to give theoretical concentrations of 0.2 µg/25 cm2, 1 µg/25 cm2 and 5 µg/25 cm2. The coupons were allowed to dry before swabbing. The swabbing procedure was carried out as shown in next Section.

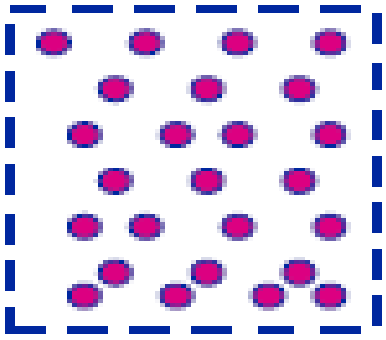

Figure 3.5: Application of the swab standard solution onto the coupons

3.6 Swabbing procedure

(i) The region to be swabbed was defined.

(ii) The swab head was dampened with the selected extraction solvent.

(iii) As shown from Figure 3.1, Step 1 and Step 2, the product contact surface was swabbed with an overlapping pattern. The swab was flipped over and the step was repeated, passing the swab in a perpendicular direction. The product contact surface was swabbed with the entire swab head flat against the surface.

(iv) The above swabbing process was repeated with a second swab at a 45° angle as shown in Step 3, Figure 3.2. The swab was flipped over and the step was repeated, passing the swab in a perpendicular direction (step 4).

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(v) The swab heads was cut, placed into a sample vial and sonicated for minutes to extract the residue.

(vi) The extracted sample was transferred to a HPLC vial for analysis.

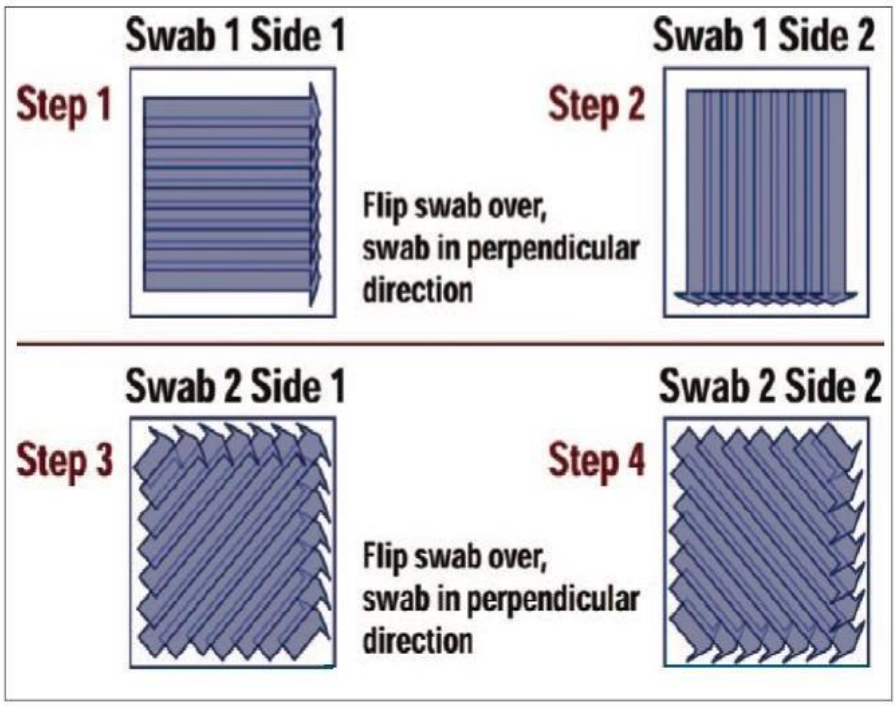

Figure 3.6: Swabbing procedure

4. Results and Discussion

Preparation Calibration Curve

The calibration curve was plotted by taking concentration of drug on x-axis and absorbance on y-axis and was shown in Fig:2 the drug has obeyed Beer's law in the concentration range of 5-50 µg/ml, and it was found to be linear with R = 0.999.

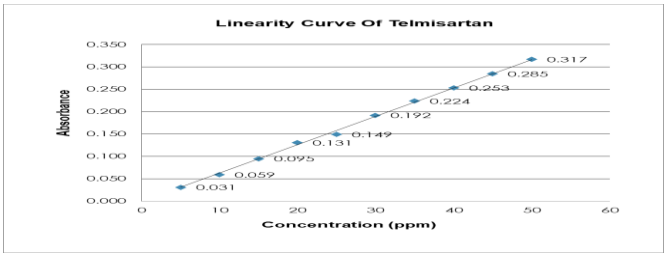

Fig:4.1: Linearity graph of Telmisartan

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Linearity

The linear fit of the system was illustrated graphically. Least square regression analysis was carried out for the slope, intercept and correlation coefficient. The linearity range was found to be in between 5-45 µg/ml. The linearity range and linearity graphs were shown in Table 6.1.

Sr.No	Concentration (ppm)	Absorbance
1	5	0.031
2	10	0.059
3	15	0.095
4	20	0.131
5	25	0.149
6	30	0.192
7	35	0.224
8	40	0.253
9	45	0.285
10	50	0.317
Correlation Coefficient		**0.999**

Precision

The precision of the proposed method was ascertained by actual determination of eight replicates of fixed concentration of the drug within the beer's range and finding out the absorbance's by the proposed method. From his absorbance's mean, Standard deviation, %R.S.D was calculated and presented in the table 4.2.

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Statistic Analysis		
Sr.No	**Concentration (ppm)**	**Absorbance**
1	10	0.031
2	10	0.032
3	10	0.032
4	10	0.031
5	10	0.032
6	10	0.031
Mean		0.032
Std Deviation		0.001
%RSD		1.733

Table : Precision Results Showing Repeatability of Telmisartan

Analysis of Swab sample

For analysis of swab sample weighed 10mg of Telmisartan were transferred into 100ml volumetric flasks and dissolved in methanol: water (8:2) to get 100 µg/ml solutions. Then the solution was sonicate for 15 min and filtered and further dilutions were made with methanol: water (8:2) to get the concentrations within the linearity range of respective drugs and measured the absorbance at 298 nm for solution against methanol: water (8:2). Here 3ml was taken and made up to 10ml.

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Calculation Formula

Absorbance of Sample	X	Wt. of Std.	X	Dilution	X Purity Of Standard			X 100
Absorbance of Standard	X	Dilution	X	Wt. of Spl.	X	100		
0.010	X	10	X	1	X	99.5		X 100
0.032	X	100	X	1	X	100		

Result = 3.10 ppm

% Recovery =3.10/3.0 = 96.77 %

5. CONCLUSION

A relatively rapid, robust UV-Vis Spectrophotometric method was developed for the determination and quantitation of drug substances. This work demonstrates for the first time a single UV-Vis Spectrophotometer method directly applicable for analysis of a range of API and provides the pharmaceutical industry with a robust analytical cleaning method with broad applicability. The proposed method is simple, sensitive and reliable with good linearity and precision and also method is specific while estimating the commercial formulation without interference of excipients and the other additives. Hence, this method can be used for routine determination of Telmisartan in different washing samples in bulk sample and pharmaceutical formulation industry. The proposed UV- Spectrophotometric method is evaluated over the linearity, precision, and proved to be convenient and effective for the quality control of Telmisartan.

Swab sample is analyzed on the developed method and found the recovery 96.77% which

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showed that this developed method can be used for the analysis of cleaning samples of Telmisartan to check the traces of drug to avoid cross contamination during manufacturing changeovers.

In recent years, increased emphasis has been placed in pharmaceutical companies for implementing robust validated cleaning procedures. The cleaning procedure is one of the most important tasks to avoid contamination and cross- contamination of APIs in pharmaceutical products manufactured on the same equipment trains. The cleaning procedures must be supported by appropriate analytical methods and related sampling methodologies. The cleaning analytical methods and related sampling methodologies are critical in establishing quality validated cleaning programs, as they quantitatively determine the amount of residual API, if present, on the manufacturing equipment post-cleaning. Therefore, the aim of this project was to develop and validate a robust cleaning analytical method and related sampling methodologies for the determination and quantitation of Telmisartan. The challenge was to detect the drug at the low concentration. In addition, the sampling methodologies were a critical aspect of the project. Product contacting surfaces were evaluated to determine whether the API residues could be adequately removed from the surfaces whilst ensuring minimal interferences from the swab and manufacturing equipment surfaces. The results show the development of a relatively rapid and robust UV method for the determination and quantitation of drug substances. The API were efficiently detected and quantitated and the method was found to be both linear (r^2> 0.999) and precise (%RSD < 2.0%). Future work could involve an examination of the removal of problematic API from critical surfaces on the manufacturing equipment trains such as silicone.

References

[1] Smart analysis of a ternary mixture of amlodipine, hydrochlorothiazide and telmisartan by manipulation of UV spectra: Development, validation and application to formulations Author links open overlay panelMaheshAttimarad a, Muhammad ShahzadChohan b, RafeaElaminElgackElgorashe Department of Pharmaceutical Sciences, College of Clinical Pharmacy, King Faisal University, Al Ahsa, 31982, Saudi Arabia Department of Biomedical Sciences, College of Clinical Pharmacy, King Faisal University, Al Ahsa, 31982, Saudi Arabia, Department of Chemistry College of Science, King Faisal University, Al Ahsa, 31982, Saudi Arabia

[2] R. Klinkenberg, B. Streel, A. Ceccato, Development and validation of a liquid chromatographic method for the

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ISSN: 2519-9889
Impact Factor: 5.958

determination of amlodipine residues on manufacturing equipment surfaces, J. Pharm. Biomed. Anal., 32, (2003), 345- 352.

[3] T. Mirza, M.J. Lunn, F.J. Keeley, R.C. George, J.R. Bodenmiller, Cleaning level acceptance criteria and a high pressure liquid chromatography procedure for the assay of meclizine hydrochloride residue in swabs collected from pharmaceutical manufacturing equipment surfaces, J. Pharm. Biomed. Anal., 19, (1999), 747-756.

[4] T.T. Fazio, A.K. Singh, E.R. Kedor-Hackmann, M.I. Santoro, Qualitative determination and sampling of azathioprine residues for cleaning validation in production areas, J. Pharm. Biomed. Anal., 43, (2007), 1495-1498.

[5] M.J. Nozal, J.L. Bernal, J.J. Jimenez, M.T. Martin, F.J. Diez, Development and validation for determination of lacidipine residues on surfaces in the manufacture of pharmaceuticals, J. Chromatogr. A., 1024, (2004), 115-122.

[6] M.J. Nozal, J.L. Bernal, L. Toribio, M.T. Martin, F.J. Diez, Development and validatio of an LC assay for succinate residues on surfaces in the manufacture of pharmaceuticals, J. Pharm. Biomed. Anal., 30, (2002), 285-291.

[7] N. Dubey, M. Mandhanya, D.K. Jain, Cleaning level acceptance criteria and HPLC-DAD method validation for the determination of nabumetone residues on manufacturing equipment surfaces using swab sampling, J. Pharm. Anal., 2 (6), (2012), 478-483.

[8] PDA Technical Report No. 29 (Revised 2012): Points to consider for Cleaning Validation.

[9] Cleaning and Cleaning Validation, Volume 2: Paul L. Pluta, 2013.

[10] P. Yang, K. Burson, D. Feder, F. Macdonald, Swab sampling for cleaning validation of a residual active pharmaceutical ingredient, Pharm. Technol., (2005), 84-95.

[11] Kathy Miscioscio, The Texwipe Company, Choosing the correct swab for cleaning validation, 1997.

[12] S. Fekete, J. Fekete, K. Ganzler, Validated UPLC method for the fast and sensitive determination of steroid residues of cleaning validation in formulation area, J. Pharm. Biomed. Anal., 49, (2009), 833-838.

[13] R.J. Forsyth, J.C. O'Neill, J.L. Hartman, Cleaning Validation: grouping materials of construction based on recovery data, Pharm. Technol., 31 (10), (2007), 104-112.

[14] R.J. Forsyth, Cleaning Validation: factors affecting recovery data and materials of construction grouping, J. Val. Technol., Autumn (2009), 91-96.

[15] M.J. O'Keeffe, S. Martin, L. Regan, Validation of a multiresidue liquid chromatography-tdem mass spectrometric method for the quantitation and confirmation of corticosteroid residues in urine, according to proposed SANCO 1085 criteria for banned substances, Anal. Chim. Acta., 483, (2003),341-350.

[16] Y. Deceuninck, E. Bichon, F. Monteau, G. Dervilly-Pinel, J.P. Antignac, B. Le Bizec, Fast and multi residue determination of twenty glucocorticoids in bovine milk using ultra high performance liquid chromatography-tandem mass spectrometry, J. Chromatogr. A., 1294, (2013), 76-86.

[17] Y. Kitaichi, A. Miyamoto, K. Uchikura, Determination of selected corticosteroids in sewage treatment plant samples by liquid chromatography mass spectrometry, J. Health. Sci., 56, (2010), 547-556.

[18] K. Croes, L. Goeyens, W. Baeyens, J.V. Loco, S. Impens, Optimisation and validation of a liquid chromatography tandem mass spectrometry (LC/MS) method for analysis of corticosteroids in bovine liver, J. Chromatogr. B., 877, (2009), 635-644.

[19] J. Zhang, B. Shao, J. Yin, Y. Wu, H. Duan, Simultaneous detection of residues of β-adrenergic receptor blockers and sedatives in animal tissues by high performance liquid chromatography/tandem mass spectrometry,

[20] J. Chromatogr. B., 877, (2009), 1915-1922.F. Sai, M. Hong, Z. Yunfeng, C. Huijing, W. Yongning, Simultaneous detection of residues of 25 β2-agonists and 23 β-blockers in animal foods by high performance liquid chromatography coupled with linear ion trap mass spectrometry, J. Agric. Food Chem., 60, (2012), 1898-1905.

[21] G.J. Murray, J.P. Danaceau, Simultaneous extraction and screening of diuretics, beta-blockers, selected stimulants and steroids in human urine by HPLC-MS/MS and UPLC-MS/MS, J. Chromatogr. B., 877, (2009), 3857-3864.

[22] R.S. Kadam, U.B. Kompella, Cassette analysis of eight beta-blockers in bovine eye sclera, choroid-RPE, retina, and vitreous by liquid chromatography-tandem mass spectrometry, J. Chromatogr. B., 877, (2009), 253-260.

[23] F. Nasir, Z. Iqbal, A. Khan, L. Ahmad, Y. Shah, A.Z. Khan, J.A. Khan, S. Khan, Simultaneous determination of timolol maleate, rosuvastatin calcium and diclofenac sodium in pharmaceuticals and physiological fluids using

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ISSN: 2519-9889
Impact Factor: 5.958

HPLC- UV, J. Chromatogr. B., 879, (2011), 3434-3443.

[24] F. Tamtan, F. Mercier, J. Eurin, M. Chevreuil, B.L. Bot, Ultra performance liquid chromatography tandem mass spectrometry performance evaluation for analysis of antibiotics in natural waters, Anal. Bioanal. Chem., 393 (2009), 1709-1718.

[25] U. Hubicka, P. Zmudzki, P. Talik, B. Zuromska-Witek, J.K. Rzek, Photodegradation assessment of ciprofloxacin, moxifloxacin, norfloxacin, and ofloxacin in the presence of excipients from tablets by UPLC-MS/MS and DSC, Chemistry Central Journal., 133, (2013), 1-12.

[26] U. Hubicka, P. Zmudzki, B. Zuromska-Witek, P. Zajdel, M. Pawlowski, J. Krzek, Separation and characterization of ciprofloxacin, difloxacin, lomefloxacin, norfloxacin, and ofloxacin oxidation products under potassium permanganate treatment in acidic medium by UPLC-MS/MS, Talanta., 109, (2013), 91-100.

[27] N.K. Karamanos, F. Lamari, J. Katsimpris, S. Gartaganis, Development of an HPLC method for determining the alpha2-adrenic receptor agonist brimonidine in blood serum and aqueous humor of the eye, Biomed. Chromatogr., 13, (1999), 86-88.

[28] S. Jiang, A.K. Chappa, J.W. Proksch, A rapid and sensitive LC/MS/MS assay for the quantitation of brimonidine in ocular fluids and tissues, J. Chromatogr. B, 877 (2009), 107-114.

[29] A. Madhavi, A. Naidu, D.V. Subba Rao, P. Srinivasu, Development and validation of a new LC method for analysis of brimonidine tartrate and related compounds, Chromatograhia., 69 (2009), 1413-1419.

[30] P. Gallo, S. Fabbrocino, G. Dowling, M. Saline, M. Fiori, G. Perretta, L. Serpe, Confirmatory analysis of non-steroidal anti-inflammatory drugs in bovine milk by high performance liquid chromatography with fluorescence detection,

[31] J. Chromatogr. A., 1217, (2010), 2832-2839.H. Shaaban, T. Gorecki, High temperature-high efficiency liquid chromatography using sub-2 µm coupled columns for the analysis of selected non-steroidal anti-inflammatory drugs and veterinary antibiotics in environmental samples, Anal. Chim. Acta., 702 (2011), 136-143.

[32] M. Nawaz, Simultaneous determination of non-steroidal anti-inflammatory drugs in pharmaceutical formulations and human serum by reversed phase high performance liquid chromatography, Quim. Nova., 35 (5), (2012), 939-943.

[33] M.A. Radwan, B.T. AlQuadeib, N.M. Aloudah, H.Y. AboulEnein, Pharmacokinetics of ketorolac loaded to polyethylcyanoacrylate nanoparticles using UPLC MS/MS for its determination in rats, Int. J. Pharm., 397, (2010), 173-178.

[34] S.N. Razzaq, I. Mariam, I.U. Khan, M. Ashfaq, Development and validation of a liquid chromatographic method for gatifloxacin and ketorolac tromethamine in combined dosage form, J. Liq. Chromatogr. Related. Technol., 35, (2012), 651-661.

[35] T. Hu, T. Peng, X.J. Li, D.D. Chen, H.H. Dai, X.J. Deng, Z.F. Yue, G.M.Wang, J.Z. Shen, X. Xia, S.Y. Ding, Y.N. Zhou, A.L. Zhu, H.Y. Jiang, Simultaneous determination of thirty non-steroidal anti-inflammatory drug residues in swine muscle by ultra-high-performance liquid chromatography with tandem mass spectrometry, J. Chromatogr. A, 1219, (2012), 104-113.

[36] L.R. Synder, J.J. Kirkland, J.W. Dolan, Introduction to Modern Liquid Chromatography, 3rd edition Wiley & Sons, Inc., Hoboken, New Jersey, 2010.www.chemaxon.com

[37] C. Hansch, A. Leo, D.H. Hoefman, "Exploring QSAR: Hydrophobic, Electronic and Steric Constants", American Chemical Society, Washington, DC, 1995.

[38] [25] www.chemspider.com

[39] P.C. Iraneta, K.D. Wyndham, D.R. McCabe, T.H. Walter, A review of Waters Hybrid Particle Technology. Part 3: Charged Surface Hybrid (CSH) Technology, Waters Corporation (2011), 1-11.

[40] J.W. Dolan, LC GC Europe, LC Resources Inc., Walnut Creek, California,USA, Retaining polar compounds, 19 (11), (2001), 1132-1135

[41] J. K. Telford, A Brief Introduction to Design of Experiments, APL Technical Digest, 27, (2007), 224-232.

[42] N.M. Richard, How to Use Minitab: Design of Experiments (2014).

[43] Agrawal, U.; Raju, R. and Udwadia, Z.F. (2020). Favipiravir: A new and emerging antiviral option in COVID-19. Medical Journal Armed Forces India, 1(1):1-7. Baokar, S.; Mulgund, S. and Ranpise, N. (2013).

[44] Development and validation of RP-HPLC method for simultaneous estimation of vildagliptin and metformin. Research. J. Pharm. Dos. Forms Technol., 5(2): 95-98. Bharti Mittu, A.C. and Chauhan, P. (2015).

[45] Analytical method development and validation: Aconcise review. J. Anal. Bioanalytical. Tech., 6(1):1-5. Blessy,

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M.R.; Patel, R.D.; Prajapati, P.N. and Agrawal,Y.K. (2014).

[46] Development of forced degradation and stability indicating studies of drugs-A review. J. Pharm. Anal., 4(3):159-165. Bulk,Ý.(2021).

[47] HPLC-UV method for quantification of favipiravir in pharmaceutical formulations. Acta. Chromatographical. 33(3):157- 209. Chen, C. (2020).

[48] Favipiravir versus arbidol for COVID-19. A randomized clinical trial. Med. Rxiv., 3:17-20. Forsyth, R.J. and Haynes, D.C. (1998).

[49] Cleaning validation in pharmaceutical research facility. Pharmaceutical Technology, 22(9):104-112. Ibrahim, Bulduk (2021).

[50] HPLC-UV method for quantification of favipiravir in pharmaceutical formulations ActaChromatographical, 33:209- 215. Jyothi and K avya (2021):

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