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A BRIEF REVIEW ON PROCESS ANALYTICAL TECHNOLOGY

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ABSTRACT
Process analytical technology (PAT) has been defined as a mechanism to design, analyze and control pharmaceutical manufacturing processes through measurement of critical process parameters which affect critical quality attributes. PAT checks the quality of raw material attributes both off-line, on-line & in-line.The main principle of PAT is the use of different technologies and tools to build quality into the products. Effective implementation of PAT comprise of science-based understanding of the physical, chemical and mechanical properties of all elements of the proposed drug product. The application of early PAT devices, increase safety & process efficiency by acting on data in real time and by eliminating sampling. PAT applies it gives brief knowledge of processes, leading to increased robustness and greater processing opportunities. chemical reactions and process monitoring such as drying, distillations, crystallizations, hydrogenations, and others provided by Modern developments in analytical technologies. while implementing PAT into their new and pre-existing manufacturing processes many pharmaceutical companies face many challenges and problems. In this paper, we will start with brief PAT concepts, Introduction, How PAT works, Importance of PAT tools, PAT implementation steps and a review of their application in the wider pharmaceutical industry.

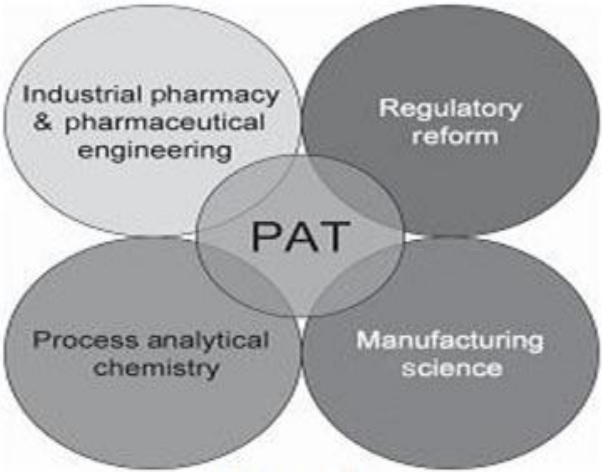
KEYWORDS: PAT, Hyphenated techniques, Critical Process parameters (CPP), ICHQ10.

FDA defines Process Analytical Technology is a system for designing, analyzing and controlling manufacturing processes through timely measurement of critical quality and performance attributes of raw materials, in-process materials and processes with the goal of ensuring final product quality. Food and Drug Administration (FDA) launched PAT in 2001 to reduce the risk of making a poor product. With the help of PAT, pharmaceutical companies are now better equipped to increase process efficiencies and design quality product With the goal of ensuring final quality of product. The concept actually aims at understand the processes then define their CPP's, and accordingly monitoring them in a timely manner (preferably in-line or on-line) and thus being more efficient in testing at the same time reducing over-processing, enhancing consistency and minimizing rejects. The Food and Drug Administration (FDA) is inviting discussions throughout the pharmaceutical industry concerning a new mode of operation. Process analytical technology (PAT) is heart of the Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century - a Risk Based Approach announced by the FDA in August 2002 to improve and modernize pharmaceutical manufacturing. PAT is not a product or service. It is a concept, a working principle for operating, depending on you to implement it. The. It helps real time information to reduce process variation and manufacturing capability. The PAT increases quality and reduces the number of costs in areas such as the chemical and pharmaceutical.

How PAT Works

In successfully implement PAT, a combination of sequential steps is very important First, a unit operation or process must be defined as requiring PAT or being amenable to PAT Deployment. In many cases, a thorough lab-scale feasibility evaluation of analytical methods is conducted to determine which techniques may have adequate sensitivity and selectivity. Most important, PAT goes through extensive cost-benefit analysis as to which approach may reach the production floor. Second, a suitable PAT technique require to be chosen which would allow for measurement of the critical process parameter (CPP), preferably in an in-line or at-line manner. The first step away from off-line laboratory testing would be at-line testing, which moves process dedicated testing equipment to the production line. One approach of PAT is on-line testing, which draws samples and monitors periodically. other mode is in-line testing, which places probes in constantly contact

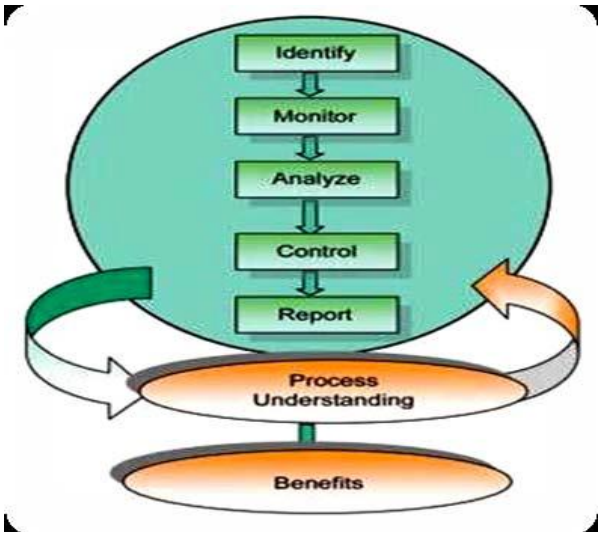
with the drug product. The advantage of on- or in-line testing is good control because it provides the most up-to-date snapshot of the process.



When to Introduce Process Analytical Technology (PAT).

Building quality into a pharmaceutical product has to be considered from the very beginning of the product's life. Essential preconditions are the equal involvement of and seamless communication between R & D and manufacturing. One purpose of PAT is bring quality into a product from the outset. If product Quality requirements are understood and implemented from the beginning root - cause analysis of quality or process failure after scale - up to commercial manufacturing will be much easier. This is why PAT could play an even more important role in the design and analysis of manufacturing processes, enabling performance control to be based on timely measurement of well -described critical processing data. Data processing needs should also be considered in the context of overall process Analysis strategy to meet emerging requirements for the speed and volume of data Collection.

Thus, a PAT data management strategy based on online process analysis can be set up long before generating large sets of measurement data. Changing Current Practice Using PAT. An approach integrating R & D and manufacturing will enhance process understanding and make acceptable risk management possible. A typical illustration of a PAT approach to quality improvement is the use of Near Infrared Spectroscopy (NIRS) to qualify excipients and active pharmaceutical ingredients just before they enter the production process, e.g.in dispensing. Near - infrared (NIR) spectra are give information about product structure and overall quality. Because with substances such as excipients the quality range was investigated at some time in the past and fixed into a calibration, NIR Measurement can provide simultaneous non-destructive confirmation of the predominant physical and chemical parameters. This is an effective method of reducing uncertainties & failure or poor quality or product in production. Each time a given excipient fails its quality requirements at the moment of use, immediate action can be taken.



Proposed steps to a PAT implementation

Identify

This step includes the process of identifying an opportunity that would benefit from the PAT, as well as identifying the critical quality attributes that need to be monitored and controlled in the process.

Monitor

The next step after identifying the critical quality attributes would be to monitor them. Monitoring is usually achieved using on-line instruments. Recent advances in on-line analytical instrumentation have encouraged more online monitoring of parameters of interest. The simple premise is that we cannot control something we cannot monitor. The monitoring step allows us to collect data for the CQA of interest and then evaluate the overall effect of adjusting the CQA on the process efficacy.

Analyze

The analysis step ensures that once we have identified our critical quality points and monitored them, we apply statistical analysis to determine how the critical quality attribute is related to the overall process efficacy. This step includes the development, verification, and validation of any statistical models that could define the process. Experimental studies, engineering test plans and retrospective analysis are methods that we are applied to analyze the CQA relationship to the overall process.

Control

After we have analyzed the relationship between the CQA and overall process efficacy and developed any statistical models, the next step in the PAT effort would be to control the process to confirm that the CQA is within specified limits at all times. This is the more critical step of the PAT roadmap that essentially ensures that "real-time quality assurance is meet.

Report

The reporting elements encompasses any tools that aid in assuring that the process was in fact in control throughout the processing period. Reporting tools serve two purposes-they allow for data to be reported in a fashion that aids in developing process understanding and that allow for any exception from the ideal state to be documented in final release report.

Types of Process Measurement

1. Off-line testing.
2. On-line testing.
3. At-line testing.
4. In-line testing.

Off-Line Testing

Transport of sample from the chemical plant to a laboratory for measurement. It has the advantage of the availability of sophisticated measurement system and trained laboratory personnel. But the transport and measurement are generally slow, requiring hours to days, yielding historical data rather than data that can be used for immediate process adjustment. Hence Off-line measurements are really quality control measurement. i.e. they are used to determine whether the product meets certain specification of purity, quantity etc.

On-Line Testing

This either draws samples or monitors periodically. On line testing used to monitoring of residual water content during drying, by use of moisture sensors that measure water vapor pressure, has been used to predict sublimation end point.

At-Line Testing

In which the instrument is brought into the plant, are more efficient, but still require trained personnel. They are also subjected to the harsh environment to the plant, and still may not provide sufficiently rapid measurements. The instrumentation requirements will differ from those of laboratory instrumentation.

In-Line Testing

In which places probes in constant contact with drug product. The advantage of on/in line testing is better control of the process.

Importance of PAT

Cost control, by efficient production processes, and partly through the minimization of theor reprocessing at the QA final test point, is an important justification for exploring PAT. In a world in which financial issues have entered a triage of decisions, cost control has become tightly entangled with patient treatment and cure, PAT brings other important advantages, however. Even the most rigorous military sampling of end product has a statistical chance of missing a problematic situation. In fact, in the most dangerous of circumstances – human blood processing. However, the addition of monitoring during production as well as at end stage, even if redundant, can only enhance the likelihood of catching aberrant situations and increasing patient safety. In vaccine production and protein separation technologies PAT play important role by continuous monitoring it could potentially enhance the speed and quality of end-product development.

Pat Tools

Analytical tools

The PAT document considers analysis as a method not just for the chemical analysis of a substance but for physical, microbiological, statistical, and risk analysis as well. Analytical pharmaceutical testing has traditionally occurred either off-line in a test laboratory or at-line in the production area. for supplement to these methods, the PAT document suggest the use of other sampling methods.

These include

- On-line methods, where sample is diverted from the main product stream and can be returned after measurement;
- In-line methods, where a probe is inserted into the process stream; and.
- Noninvasive methods, where a sensor (e.g., a Raman detector) is used that never physically contacts the material, and the process stream remains undisturbed.

Titrimetric techniques

In PAT there is application of titrimetric methods to (very) weak acids and bases as well as potentiometric end point detection improving the precision of the methods. They have lot of advantages associated with these methods which include saving time and labor, high precision and the fact that there is no need of using reference standards.

Chromatographic Techniques

Thin layer Chromatography (TLC)

Chromatography is the separation of two or more compounds or ions by the distribution two phases, one which is moving and the other which is stationary. These two phases can be liquid-liquid, liquid-solid or gas-liquid. Although there are many different variations of chromatography, the principles are essentially the same. The cellulose paper was the stationary o phase and the 1-propanol/water mixture was the mobile or liquid phase. Thin-layer chromatography is a liquid-solid form of chromatography where the stationary phase is normally a polar absorbent and the mobile phase can be a single solvent or combination of solvents. TLC is a fast, inexpensive micro scale technique that can be used to:

- Selection of number of components in a mixture.
- Verify a substance‟ s identity.
- Monitor the progress of a reaction.
- Determine appropriate conditions for column chromatography.
- Analyze the fractions obtained from column chromatography.

High performance thin layer chromatography (HPTLC)

The HPTLC is very useful qualitative analysis method. Its combine arts of chromatography with quickness at moderate cost. Its major advance to TLC principle shorten time duration & better resolution. HPTLC is playing an important role in today analytical world, not in competition to HPLC but as complementary method. Unlike other methods, HPTLC produces visible chromatograms complex information about the entire sample is available at a glance. Similarities and differences are immediately apparent and with the help of the image comparison. They can be evaluated either by scanning densitometry with TLC Scanner, measuring the absorption and/or fluorescence of the substances on the plate. TLC is an technique in which subsequent steps are relatively independent, allowing parallel treatment of multiple samples during chromatography.

High-performance liquid chromatography (HPLC)

High-performance liquid chromatography or High pressure liquid chromatography, HPLC is a Type of column chromatography mainly used in biochemistry and analysis to separate identify, and quantify the active compounds. HPLC mainly used a column that holds p stationary phase, a pump that moves the mobile phase(s) through the column, and a detector that shows the retention times of the molecules. Retention time varies depending on the interactions between the stationary phase, the molecules being analyzed, and the solvent(s) used. The sample to be analyzed is by specific chemical or physical interactions with the stationary phase. The amount of retardation depends on the nature of the analyst and composition of both stationary and mobile phase. The time at which a specific analyst elutes (comes out of the end of the column) is called the retention time .mostly used solvents used include any miscible combinations of water or organic liquids. Separation has been done to vary the mobile phase composition during the analysis; this is known as gradient elution. The gradient separates the analyst mixtures as a function of the affinity of the analyst for the current mobile phase. The choice of solvents, additives and gradient depend on the nature of the stationary phase and the analyst.

Spectroscopic Techniques

Spectrophotometry

spectrophotometric methods depend on natural UV absorption and chemical reactions. Spectrophotometry is the quantitative measurement of the transmission or reflection properties of a material as a function of wavelength.uv rays having wavelengths less than 200 nm is very difficult to handle, and is rare used as a routine tool for structural analysis. The energie excite a molecular electron to a higher energy orbital. Consequently, absorption spectroscopy.

Observe in this region is sometimes called "electronic spectroscopy". When sample molecules are interact to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed electron & then promoted to a higher energy orbital. when absorption occur wavelengths is recorded by optical spectrometer & together with the degree of absorption at each wavelength. Then spectrum is presented as a wavelength versus graph of absorbance. Absorbance usually ranges from 0 it means no absorbance to 2 (99% absorption).

Raman Spectroscopy

Raman spectroscopy is used for quantitative analysis of pharmaceutical product because of the relationship between signal intensity and API concentration. Raman spectroscopy has been evaluated for identification and quantification of active ingredients in granulation, compression, drug pellet and both off-line and at-line. Raman spectroscopy has also been used to monitor hydration states of API.

Near infrared spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) is a rapid and non-destructive analytical method. it becomes a very important & powerful tool for the pharmaceutical industry. Indeed, NIRS is suitable for analysis of biotechnological pharmaceutical forms & solid, liquid. NIRS is generally chosen for its speed, its low cost and its nondestructive characteristic towards the analyzed sample. Now days the interest in NIR has increased thanks to the instrument improvements and the development of fiber optics that allow the delocalization of the measurements. Another reason it has increased because of the computer progresses and the development of new mathematical methods allowing data treatment. Whilemid-IR spectra and especially the absorbance bands are directly interpretable due to chemical peak specificity, NIR spectra are difficult to interpret.

Nuclear magnetic resonance spectroscopy (NMR)

NMR spectra have been a major tool for the study of both newly synthesized and natural products isolated from plants, bacteria etc. The introduction of reliable superconducting magnets combined with newly developed, highly sophisticated pulse techniques and the associated Fourier transformation provided the chemist with a method suitable to determine the 3-dimensional structure of very large molecules. NMR spectroscopy has important role in the elucidation and confirmation of structures. For the last decade, NMR methods have been introduced to quantitative analysis in order to determine the impurity profile of a drug, to characterize the composition of drug products, and to investigate metabolites of drugs in body fluids. study the dissolution of tablets, and whole-body imaging is a powerful tool in clinical diagnostics which is done by micro-imaging. Taken together, this review will cover applications of NMR spectroscopy in drug analysis, in particular methods of international pharmacopoeia, pharmaceutics and pharmacokinetics.

Electrophoretic Methods

Capillary electrophoresis

Capillary electrophoresis (CE) is also useful tool pharma industry. Capillary electrophoresis in its different versions represents a powerful separation technique which proved sufficiently competitive /complementary to high performance liquid chromatography. Based on the simultaneous action of electro migration and electro osmotic flow this approach offers a wide range of conditions under which successful separations and quantitation can be obtained. While the „„classical"" version is limited to charged water soluble analysts only, who introduced micellar systems offered the possibility of separating uncharged analysts on the basis of their partition between a micellar phase and the aqueous background electrolyte. Consequently the potentials of this methodology have spread to all kinds of non-polar solutes.

Hyphenated Techniques

Chromatography – Produces complete pure or nearly pure fractions of chemical components in a Mixture and Spectroscopy Produces selective information for identification using standards or library spectra. "The coupling of a separation technique and an on-line spectroscopic detection technology will lead to hyphenated technique." A Hyphenated technique is combination or coupling of two different analytical techniques with the help of proper interface hyphenated techniques ranges from the combination of separation-separation, separation-identification & identification-identification techniques. The term "hyphenation" was first adapted by Hirschfield in 1980 to describe a possible combination of two or more instrumental analytical methods in a single run. The aim of this coupling is obviously to obtain an information-rich detection for both identification and quantification compared to that with a single analytical technique

Examples of Application of Process Analytical Technology

Particle Size

The particle sizes of active pharmaceutical ingredients (APIs) and excipients are of significant importance in most solid dosage products and are traditionally monitored by thief sampling followed by laboratory analysis. Suppose any systems where particle size is critical, this method of control suffers from several limitations. A small part of sample is not be representative of bulk product. Time is required for sampling, transporting, measuring, and report results. There is chances of exposure to operators and lab personnel. The cost of rejected lots can be high. PAT approaches to particle size measurement sample larger, more representative portions of bulk product and offer rapid analysis with immediate feedback directly into the control system. Because PAT is a closed system hence is no exposure to personnel.

Content Uniformity

The main purpose of blending is production of a uniform mixture of API and excipients in the final dosage form. Incomplete mixing is difficult to detect in the final dosage form because measurements of component identity and concentration are often not specific to distribution. Typically blend uniformity is assumed by blending for a set time and is actually monitored by release testing. This approach having several limitations: Release testing on limited samples may not be representative of bulk. Blending for longer than necessary increases cycle time. Variations in feed materials may changes blend time from batch to batch. Excessive blending may lead to 'demixing. 'Failed release tests jeopardize the entire batch. A PAT approach in blending help process understanding and give feedback to more precisely control blending.

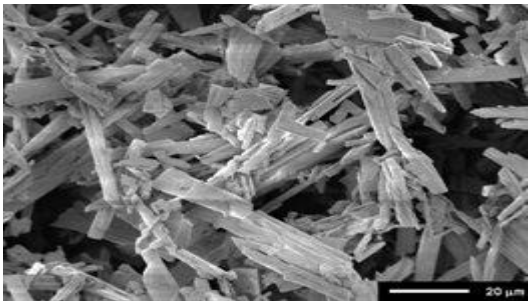


Figure 1: Without particle size control.

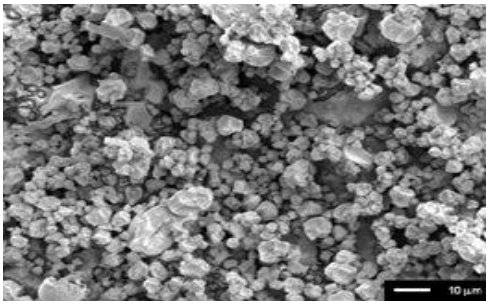


Figure 2: Tight particle size control.

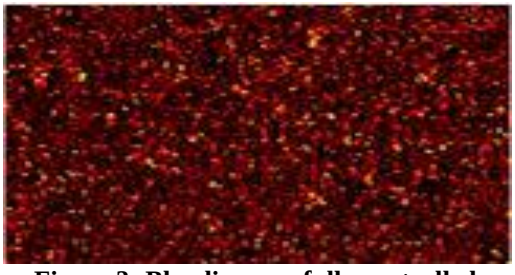


Figure 3: Blending carefully controlled.

Figure 3 shows a Raman microspectroscopic map of a tablet surface where blending was carefully controlled. The uniform distribution of API (red and yellow dots) gives idea that blending was optimized for distribution. By measuring to an endpoint, blending could be discontinued when a goal of distribution was achieved, thereby minimizing cycle time.

Drying

Product drying, after synthesis or during processing, is a necessary step that can have a Sudden impact upon the solid form of the final product. A drying step may be designed to simply remove excess solvent for subsequent processing, or it may be an integral part of solidstate form manipulation through dehydration or desolvation. Under most scenarios, drying is carried out for a set amount of time, which can lead to excessive cycle time and/or undesirable form change if drying continues beyond the endpoint. A PAT approach provides the process understanding and measurement strategies to carefully control drying. By monitoring the product or the effluent, it is possible to determine the endpoint based either upon the rate of solvent removal or the amount of residual solvent in the product.

Crystallization

A recent review of the study of crystallization process using Process analytical technology method notes that the sensor of such process involves the molecule Spectroscopic method of Raman, NIR, ATR, FT-IR spectroscopy. The use of Raman spectroscopy in combination with chemo metric data analysis was used to identify & quantity the amount of several polymorphic forms present in Ranitidine HCL Tablet. Protein crystallization is of some interest for PAT applications, because of the increase in structure-based drug design fuelled by the recent developments in genomics and proteomics.

Pellet manufacturing by Extrusion-Spheronization

An at-line process analytical technology (PAT) main purpose to increase the understanding of the states (solid,liquid) behavior of the active pharmaceutical ingredients (APIs) during pelletization. near-infrared (NIR) spectroscopy, and X-ray powder diffraction (XRPD) & Raman spectroscopy is very useful in the characterization of polymorphic changes during the process. Samples is collected at the end of each processing stage (blending, granulation, extrusion, spheronization, and drying). Batches were dried at 3 temperature levels (60˚C, 100˚C, and 135˚C). Water induced a hydrate formation in both model formulations during processing. NIR spectroscopy gave important real-time data about the state of water in the system, but it was not able to detect the hydrate formation in the theophylline and nitrofurantoin formulations during the granulation, extrusion, and spheronization stages because of the saturation of the water signal. Raman and XRPD measurement results confirmed the expected pseudopolymorphic changes of the APIs in the wet process stages. Generally low level of Raman signal with the theophylline formulation complicated the interpretation. The drying temperature had a significant effect on dehydration. To reach an understanding of the process and to find the critical process parameters, the use of complementary analytical techniques are absolutely necessary when signals from APIs and different excipients overlap each other. determination of active content ranging from 80-120% of the usual active content of the uncoated pharmaceutical pellets by NIR methods.

Benefits and Challenges of Pat

Most industry representatives that either were involved in discussions regarding the feasibility of PAT. Positive perceived benefits of PAT include;

- Decrease in cycle times.
- Lower costs.
- Increased efficiency and batch-to-batch consistency.
- Process fingerprinting (signature) that would be useful for validation, scale-up, and confirming acceptable handling of changes.
- Increased process understanding and a decrease in variability, rejects, and lot failures.
- Conversely, the most-common perceived or actual challenges include:
- Less availability of a written PAT guidance document from FDA.
- Increased pressures to meet aggressive filing timelines, added costs to make changes, lack of senior management support, and resource constraints.

Pat Applications in the Pharmaceutical Industry

Innovations in the process analytical chemistry and in our ability to capture and analyze large amounts of data have served as the key drivers for adoption of PAT in the pharmaceutical industry. The key feature of PAT is that quality is built into the product, rather than being tested before release of product. The PAT framework comprises risk management, at/online sensors that assist in monitoring/controlling/designing of the process and prediction of process performance. A variety of analytical techniques have been used in the pharmaceutical industry, including Fourier transform infra-red spectroscopy (FTIR), UV-Vis spectroscopy, gas chromatography, high performance liquid chromatography (HPLC), X-ray diffraction spectroscopy, and NIR spectroscopy.

PAT application at following sites

- RM Testing (warehouse based)
- Packaging Components
- Crystallization
- Blending (at- line or on- line)
- Drying
- Tableting
- Encapsulation (Coating thickness)
- Biopharmaceuticals

- Packaged product
- Equipment cleaning

CONCLUSION

The use of Process Analytical Technology can provide huge benefit to the pharmaceutical industry by increasing product quality while delivering superior asset utilization and financial value. PAT gives proper knowledge of raw materials by characterizing it both physically and chemically understanding of manufacturing parameters all which is having the impact on the final product quality. This review is aimed at focusing the role of various analytical instruments in the assay of pharmaceuticals and giving a thorough literature survey of the instrumentation involved in pharmaceutical analysis.

REFERENCES

1. Mali AS, Jagtap M, Karekar P: a brief review on process analytical technology (pat**):** 1. International Journal of Current Pharmaceutical Research, 2016; 8(1): 10-15.
2. Thumar RV, Kalola VN, Nadpara NP, Patel PB. A complete review of process analytical technology. International Journal Pharmaceutical Science and Research, 2012; 17: 57-65.
3. Bakeev KA. Near-infrared spectroscopy as a process analytical tool. Part II. At line and online applications and implementation strategies. Spectroscopy, 2004; 19: 39–42.
4. Kamble SM, S. B. Gholve, Ali SS: Process Analytical Techniques: World Journal of Pharmaceutical Research, 2015; 4(12): 852-853.
5. http://www.particlesciences.com/news/technical-briefs/.
6. PAT Initiative Expected to Invigorate Pharmaceutical industry with Improved Quality.
7. Better Efficiency and Improved Profits, White paper, 1-8.
8. Siddiqui R, Rehman N: Analytical Techniques in Pharmaceutical Analysis: A Review: Arebian Journal Of Chemistry, 2013; 3.
9. Dr Nagham MA: Review in(NMR and UV-VIS)Spectra: International Journal Of Medical Research and Pharmaceutical Sciences, 2015; 2(1): 28.
10. Kumar V, Kamle P, Mithal A: High Performance Thin Layer chromatography (HPTLC):A Review: International Journal Of Analytical Bio analytical Chemistry, 2014; 4.
11. Abidi SL, High-performance liquid chromatography of phosphatidic acids and related polar lipids. Journal Chromatography, 1991; 587: 193-203.
12. Haginaka J, Yasuda H, Uno T, Nkagawa T. Alkaline degradation and determination by high-performance by high-performance liquid chromatography. Chemistry Pharmaceutical Bull, 1984; 32: 2752-2758.
13. Malviya R, Bansal V, Pal OP: High Performance Liquid Chromatography: A short Review: Journal of Global Pharma Technology, 2010; 2(5): 22.
14. Phalke P, Kawade S: Review on Hyphenated Techniques: International Journal Of Chemical Studies, 2013; 1(3): 157.
15. Londhe SV, Mulgund SV, Chitre TS, Mallade PS., Barival JB, Jain K.S. Hyphenated techniques in analytical world, Indian Journal Pharmaceutical educational Research Dec., 2008; 42: 4.
16. Roggo Y, Chalus P, Maurer L: A review of near infrared spectroscopy and chemo metrics in pharmaceutical technologies: Journal of Pharmaceutical and Biomedical Analysis, 2007; 44: 683-684.
17. Deyl Z, Miksik I, Taliaro F: Advances in capillary electrophoresis: Forensic Science International, 1998; 92(89).
18. Holzgrabe U, Bernd W, Diehl K: Review NMR Spectroscopy in Pharmacy: Journal of Pharmaceutical & Biomedical Analysis, 1998; 17: 557.
19. http://www.google.co.in/search?ie=ISO-8859-1&q=TLC+review+pdf+8btnG=search.
20. http://www.google.co.in/search?ie=ISO-88591&q=process+Analytical+Technology++ randall+e.Willis=&btnG=Search.
21. Kamble R, Sharma S, Mahadik KR: Process Analytical Technology (PAT) In Pharmaceutical Development and its Application: Int. J. Pharm. Sci. Res., 2013; 23(2): 221.
22. Rathore, AS, Bhambure R, Ghare V, Process analytical technology (PAT) for biopharmaceutical products, Analytical Bioanaiytical Chemistry, 2010; 398: 137–154.
23. Rathore AS, Process analytical technology (PAT), Trends Biotechnology, 2009; 27(12): 698-705.
24. Bradley D, Bronwyn G, NIR Spectroscopy - Just One of Many Analytical Tools for PAT.