Safety-Critical Model for Process Validation in Paracetamol 500mg Tablet Manufacturing

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ABSTRACT

Analyses show that processes at critical levels could easily result in process drifts. Process validation however ensures that critical parameters are under a state of control, and that the outcome of the process is proper, correct, and acceptable. In drug manufacturing, process validation relies on sampling of at least three consecutive batches to confirm if the process meets current good manufacturing practice. Drifts in process parameter values can introduce hazard in the quality of the product.

This paper presents synthesis and analysis of critical process parameters for monitoring process validation in Paracetamol 500mg tablet manufacturing that ensures that safety-critical systems for process validation in Paracetamol 500mg tablet manufacturing are better controlled. A framework is proposed for the design of a safety critical system for Paracetamol drug manufacturing processes and simulated using Yunzhong model for fuzzy pattern recognition.

Analyses show that processes at critical value-set (i.e. at maximum and minimum datasets) and optimum dataset exhibit exclusivity properties with safety score set of (0, 0.75). While process at critical dataset yields Highly Unacceptable outcome, that at optimum yields Highly Acceptable outcomes. Processes at varying random datasets yield generally acceptable outcomes with least Poor quality, whereas the outcome is Bad with higher degree of Poor quality. It is therefore concluded that critical systems performance is best at optimal levels and generally yield average results at values varying within the peaks. Results of the simulation show that the framework is feasible and could be quite efficient.

(Keywords: safety, Paracetamol, fuzzy pattern recognition, performance, quality, simulation)

INTRODUCTION

Safety is the property of a system that it will not endanger human life of the environment (Herttua, 2006). Safety is the ultimate concern of everyone. As computer systems become instrumental in providing for the safety of regulated products, the regulations must verify that proper controls are employed to assure that accurate, consistent, and reliable results are obtained from computer control systems.

Critical systems are software systems (Reza and Grant, 2006) that demand ultra-safety, because failures in these kinds of systems may result in loss of lives or cost a great deal of money. A central characteristic of critical systems is dependability, which is a collective property that combines different but related system level properties, such as availability, reliability, safety, and security. The safety and reliability properties of dependable systems leave no provision for any kind of risk or errors, because even a minor error or susceptibility to risk may result in a major problem (Reza and Grant, 2006).

According to Sommerville (2008), the three types of critical systems include:

- ***Safety-critical systems –*** A system whose failure may result in injury, loss of life or serious environmental damage, such as in a control system for a chemical manufacturing plant.

- ***Mission-critical systems*** – A system whose failure may result in the failure of some goal-directed activity, such as in navigational system for a spacecraft.

- ***Business-critical systems*** – A system whose failure may result in very high costs for the business using that system, such as in the customer accounting system in a bank.

A system could be said to be safety-critical if it is intended to achieve, on its own, the necessary level of safety integrity for the implementation of the required safety functions. Figure 1 shows the context of safety, and the elements that are involved.

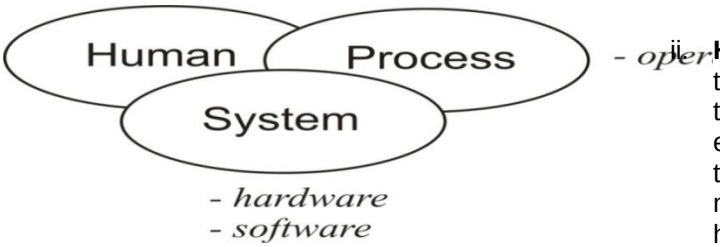


Figure 1: Safety Context Diagram (Herttua, 2006).

Safety-critical software has become a key component of systems, both in terms of contribution to the safety-criticality of the system and in terms of cost. Studies have shown that 70% of faults are introduced early in the life cycle of the system, while 80% of them are caught until integration test or later with a repair cost of 10x or higher (Feiler, 2009). If portions of faults can be discovered earlier in the life cycle of the development, we have the potential of leveraged cost savings.

Process validation is an early fault discovery activity in a critical process (Feiler, 2009). To explicate the risks in process validation of critical systems and the reliability requirements of safety systems, this paper evaluates safety descriptions for critical system variables in process validation and establish a framework for monitoring process validation in Paracetamol 500mg tablet manufacturing using Yunzhong model for fuzzy pattern recognition which by implication is applicable to other related processes with a view to making recommendations for critical systems framework for pharmaceutical and other related processes.

DESIGN APPROACHES FOR A SAFETY-CRITICAL COMPUTER SYSTEM

The basic approach in designing a safety-critical computer system is to identify hazards and to mitigate them to an acceptable level of achievable mishap risk. Three key design steps are:

i. **System Definition**: this involves a general understanding of the people, procedures, facilities, and environment that will be involved in the system. It includes both hardware and software.

ii. **Hazard identification and analysis**: After the system is defined, identifying hazards is the next step based on a systematic examination of the sources of energy and toxicity in an application. This stage calls for multidisciplinary involvement, consisting of: hardware and software design engineers, test engineers, reliability and risk analysts, operating engineers, maintenance engineers, technicians, along with anyone or persons who manage these professionals. After identifying probable hazards, causes are to be determined and analyses modeling carried out using: Fault Tree Analysis, and Failure Mode Effects Analysis.

iii. **System Safety and Safety Standards:** System safety comprises of all coordinated activities taken to guarantee that a final product will be safe. This employs a distinct set of engineering and management principles aimed at helping define safety requirements along with how the design process should be structured and conducted to ensure a safe system. Four key noteworthy concerns about system safety are that: it addresses the system life cycle, it requires a distinct management effort, it is a multidisciplinary effort and it is built around safety standards

To achieve safety in a safety-related system, the key considerations are: *safety requirements*, which include avoidance of hazards and risks, *quality management*, which includes follow up processes, *design/ system architecture*, which involves system reliability, *defined design/ manufacture processes*, *known behavior of the system* in all conditions.

Effective management effort includes systems engineering orientation with the following stakes: design and documentation standards and practices, system configuration management and tracking system verifying all safety issues are resolved.

VALIDATION IN PHARMACEUTICAL PROCESSES

Validation involves establishing documentary evidence demonstrating that a procedure, process, or activity carried out in production or testing maintains the desired level of compliance at all stages (Mubangizi, 2007). Validations in Pharmaceutical Processes undergo three stages (Gupta et al., 2012):

- **Stage 1–Process Design or process pre-qualification:** The process is defined based on knowledge gained through development and scale-up activities which includes performing process understanding studies to establish all process parameters, determining which parameters are critical, and executing supporting validation studies. Pre-qualification activities involve the evaluation of process parameters and their ranges. The key to meaningful pre-qualification studies is a process pre-qualification plan that is based on a well-defined manufacturing process. Each parameter is assessed for its potential to affect (positively or negatively) the applicable process controls or quality attributes.

- **Stage 2–Process Qualification:** This process includes the performance of three consecutive runs at the intended commercial scale. The manufacturing process qualification is performed under a prospective protocol using the appropriate output and results from the stage1 studies (i.e., critical parameters), in process controls and specifications, and any additional criteria specific to the process.

- **Stage 3–Continued Process Verification:** This process includes ongoing assurance assessment through life cycle qualification and management of process changes. Critical process parameters are monitored routinely during batch release. After validation, all changes made to manufacturing procedures are assessed for impact to the validated process, and revalidation is performed as needed.

The regulatory aspects of process validation requires that products are associated with current good manufacturing practice regulations and the application thereof to various analytical, quality assurance, pilot plant, production and sterile product and solid dosage forms considerations. Figure 2 is a flowchart of the process validation process.

TABLET PARACETAMOL AND MANUFACTURING

In MHRA (n.d), Paracetamol is a mild analgesic and antipyretic. The tablets are recommended for relief of mild to moderate pain, including headache, migraine, tension headache, neuralgia, backache, toothache, sore throat, period pain, symptomatic relief of sprains, strains, rheumatic pain, sciatica, lumbago, fibrositis, muscular aches and pains, joint swelling and stiffness, influenza, nerve pains, and for relieving the fever, aches and pains of colds and flu.

Side effects of Paracetamol include:

i. **Liver damage**: Acute overdoses of paracetamol can cause potentially fatal liver damage. Paracetamol toxicity is the foremost cause of acute liver failure in the Western world, and accounts for most drug overdoses in the United States, the United Kingdom, Australia and New Zealand (Wikipedia).

ii. **Skin reactions**: Paracetamol could cause rare, and possibly fatal, skin reactions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis

iii. **Asthma**: There is an association between paracetamol over-use and asthma.

iv. **Overdose:** Untreated overdose can lead to liver failure and death within days.It also results in a lengthy, painful illness.

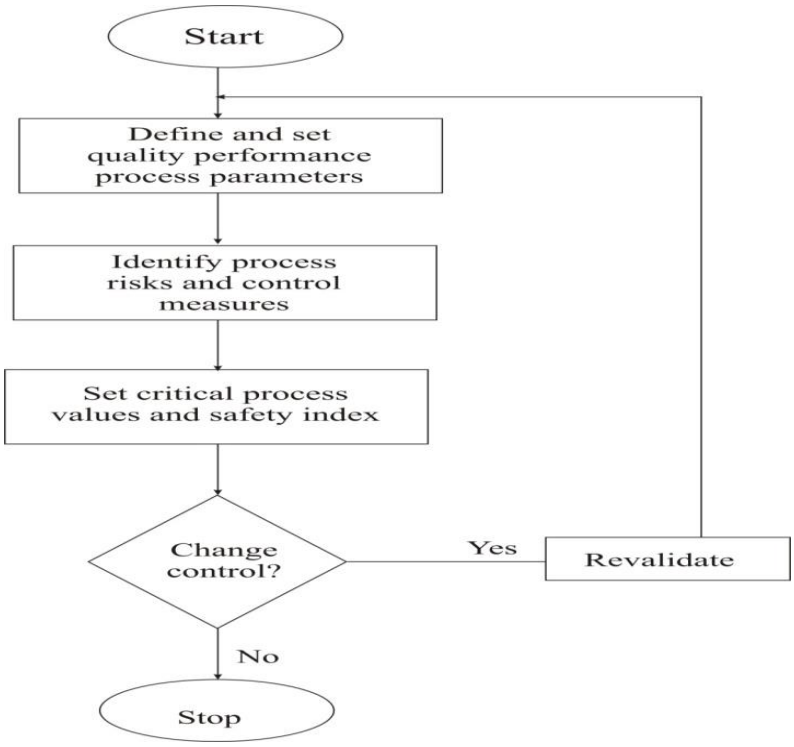


Figure 2: Flowchart of the Process Validation Process.

Symptoms of over dose range from pallor, nausea, vomiting, anorexia and abdominal pain. In severe cases, hepatic failure may progress to encephalopathy, hemorrhage, hypoglycemia, cerebral edema, and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, hematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmia and pancreatitis are also reported.

Management includes immediate treatment with activated charcoal, N-acetylcystein or oral methionine, depending on the severity of the ingestion. Effects of Process Drift includes: Clinical failures, Regulatory infractions, Batch delays, Lot failures, Rejected components, containers, API's, Cost of investigations and Cost of recalls. All aspects of manufacture and control of paracetamol are supported by an EDQM Certificate of Suitability. This certificate is accepted as a confirmation of the suitability of paracetamol for inclusion as medicinal product.

Paracetamol comes in different dose forms, which include tablet, oral granules, capsule, capsule liquid filled, elixir, liquid, powder, powder for solution, solution, suppository, suspension, syrup, tablet, tablet chewable, tablet disintegrating, tablet effervescent and tablet extended release. Tablet paracetamol comes in white, round, flat, beveled edge with the markings Para 500 on one side and M+ on the other side. It is administered orally. Figure 3 shows the stages in the manufacture of tablet Paracetamol 500mg.

CRITICAL PARAMETERS IN TABLET PARACETAMOL TABLET PRODUCTION

Table 1 shows the steps and process parameters in paracetamol tablet production (Gupta et al, 2012)**.** The critical process parameters in tablet production include: Mixing time (min), Moisture (w/w), Impeller speed (rpm), Weight (g or mg), Mixing temperature (^{o}C), Size of granules (mm), Spray rate (cpm) and Compression force or pressure (N of kg/cm^{-3}).

The critical process variables (CPV) for each of the stages are shown in Figure 4.

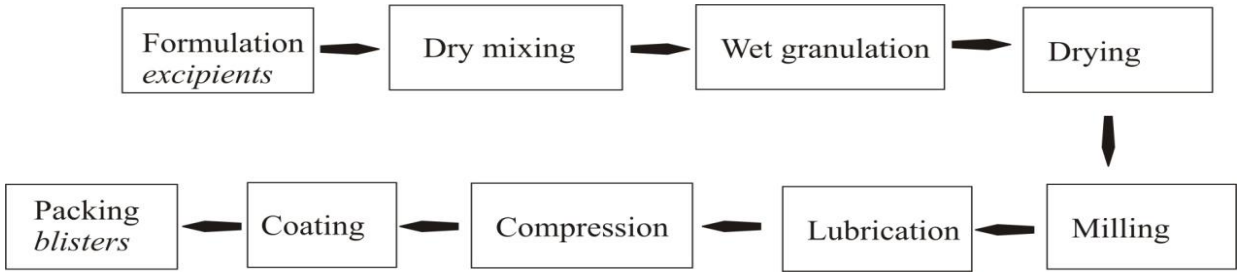


Figure 3: Stages in Tablet Paracetamol 500mg Manufacture.

Table 1: Critical Parameters In Paracetamol Tablet Manufacturing Process (Gupta *et al* , 2012).

Steps	Purpose	Control variable	Test Parameters	Acceptance Criteria
Dry mixing	Homogenous mixture	Mixing time Impeller speed	Mixing time and speed	Mixing time: ……min. Impeller speed: (slow/medium/high)±5RPM. Content uniformity :90%-110% RSD : ±5%
Wet granulation	Convert powder to granules	Time Temperature Ø Solvent used	Mode and time of addition	Depending up on the formulation
Drying	Reduce moisture content to proper level for compression	Inlet temperature Outlet temperature Drying time	Inlet/outlet temperature and drying time	Initial drying: ……..°C Drying time: ……min. Final drying: …….°C±5°C Loss on drying : ……% below 3% or
Milling	Reduce particle size of dried granulation	Mill speed Feed rate	Milling speed	Impeller speed : (slow/medium/high) Chopper speed: (slow/medium/high)
Lubrication	Provide granules suitable flow and	Time Blender/granulator speed	Mixing time and speed	Mixing time: ……min. Speed: ……..rpm. Content uniformity :
Tablet compression	Manufacture of compressed tablets	Compression speed Compression force	Machine speed and compression force	Average weight: ……mg Uniformity of weight mg : Thickness : ……mm Hardness : ……..N or Kp Disintegration time: NMT…min. Friability : NMT……w/w Assay : Dissolution:……%
Tablet coating	Coating of tablet	Pan speed Spray rate	Pan speed, inlet/outlet temperature, spray rate	Average weight : …..mg Weight of 20 tablets : ..mg Thickness : ……mm Disintegration time: NMT…..min. Assay : Dissolution: ……..%

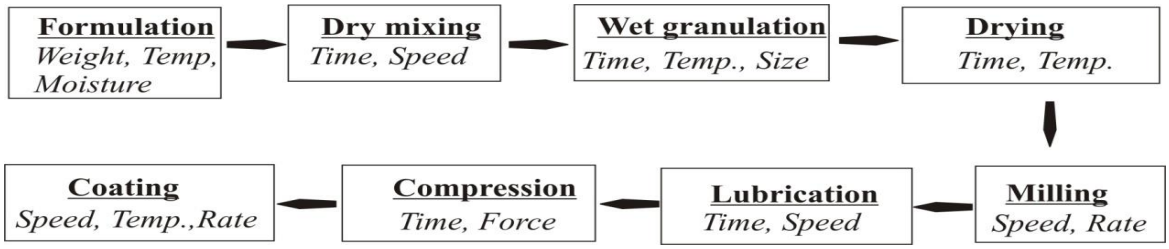


Figure 4: Tablet Paracetamol 500mg Production Stages showing CPVs.

ALGORITHM AND DESIGN FOR SAFETY USING FUZZY SET EVALUATION

The following algorithm depicts the operation of the safety system:

1. Instantiate component
2. Set Mode to process
3. For *n* number sensor_units
4. Select Critical_variables
5. Set T_f← Refresh Time
6. Set Label ←Device_port_id
7. Set Value←Sensor_meter_value
8. Start:
9. Dim dataset As Array{Label:Value}
10. Dim Fuzzy_index As Index
11. Do While Not Value is Null
12. Fuzzy{dataset}
13. If Fuzzy_index is optimum
14. Display "Operating within safety range"
15. Else:
16. Set System Alarm
17. Display "Operating outside safety range"
18. Wait on Decision
19. End if
20. Refresh
21. **Module Refresh**
22. Set dataset = Null
23. Initialize Label
24. Get value
25. **Module Decision**
26. Set option to index
27. Set index as case:
28. 1: Continue
29. 2: Terminate
30. 3: Change control
31. End case
32. Resume

Yunzhong (2001) model based on fuzzy pattern recognition is used to realize the monitoring of the safety process. The Yunzhong model was initially applied in monitoring of goodness of crop working condition of plant agriculture due to effects of weather conditions of sunlight, moisture and temperature. Let U be the whole of the objects (parameters) to be recognized, and each object has *p* characteristic indexes, labeled as $u_1, u_2, \ldots, u_p$. Each characteristic index describes certain aspect of the object *u*. Therefore:

$$u = (u_1, \ldots, u_k, \ldots, u_p) \quad \textbf{(1)}$$

This is named the eigenvector *u*. Yunzhong model is stated for the k[th] variable by the semi-circle defined as:

$$u_i = f(k) = \sqrt{1 - \left(\frac{v_k - \gamma_k}{\gamma_k - \rho_k} \right)^2} \quad \textbf{(2)}$$

Where *f(k)* is the transformation function of critical variable k; v_k is the detected sensor value at time t; $\gamma_k$is the optimum operating value and $\rho_k$is the minimum operating value. These values are required for system performance monitoring at a given time t. Assuming γ_k is the arithmetic mean of the values of the k[th] variable and σ_k is the maximum operating (peak) value (see Equations 3 to 9), we have:

$$u_i = f(k) = \sqrt{1 - \left(\frac{v_k - \gamma_k}{\sigma_k - \gamma_k} \right)^2} \quad \textbf{(3)}$$

where,

$$\sigma_k = 2\gamma_k - \rho_k \quad \textbf{(4)}$$

If *U* is classified into *n* kinds, and every kind can be taken as a fuzzy set of *U*, marked as $A_1, A_2, \ldots, A_n$, then pattern A_i has its eigenvector as:

$$a = (a_{i1}, a_{i2}, \ldots, a_{ip}) \text{ for } i = 1, 2, \ldots, n \quad \textbf{(5)}$$

If the influence of a_{ij} on A_i is presumed to be β_{ij}, then when normalized:

$$\sum_{j=1}^{p} \beta_{ij} = 1 \quad \textbf{(6)}$$

The Euclidean distance between object *u* and eigenvector component a_i is expressed as:

$$d_i(u, a_i) = \sqrt{\sum_{j=1}^{p} \beta_{ij} \left\{ \left(u_j - a_{ij} \right) \right\}^2}, i = 1, 2, \ldots, n \quad \textbf{(7)}$$

The membership of the fuzzy pattern is then defined by the relation:

$$\mu_{Ai}(u) = 1 - \frac{d_i(u, a_i)}{D} \quad \textbf{(8)}$$

where

$D = max(d_i(u,a_i))$ **(9)**

If the threshold value λ is set such that λϵ[0,1], and,

$Max\{\mu_{A1}(u), \mu_{A2}(u),\ldots, \mu_{An}(u)\} < \lambda$, **(10)**

then u is not among the any kind of the pattern of $A_1, A_2, \ldots, A_n$.

If

$Max\{\mu_{A1}(u), \mu_{A2}(u),\ldots, \mu_{An}(u)\} \geq \lambda$, **(11)**

then we draw the conclusion that $u \epsilon A_i$ i.e the object u is most appropriate to the pattern A_i.

PROPOSED FRAMEWORK FOR PARACETAMOL DRUG MANUFACTURING PROCESSES

The proposed framework is depicted in Figure 5 and it is a condensed layout of the stages for process validation proposed by Gupta, et al. (2012).

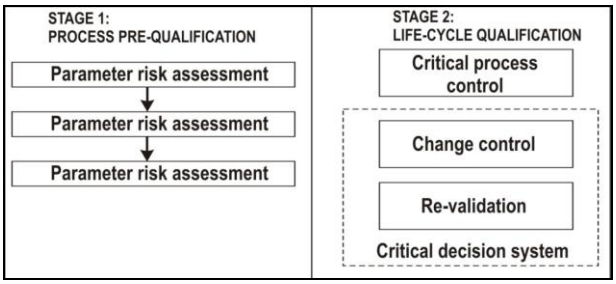


Figure 5: Two Stages of Process Validation.

SYSTEM ARCHITECTURE

The system architecture, as depicted in Figure 6, consists of the unit components or equipment in the production line whose performance is being monitored. These equipment are indicated as Component 1 through Component n (where n is any number of components). Onto each of the device is attached sensing device, which transmits sensor values to the Aggregator Module in the critical monitoring system. The Aggregator Module lays out the values in matrix format, which is then read by the Analysis Module of the system (software program) at specific time interval.

These unit features are discussed as follows:

i. The component level – made up of the components and devices that perform the actual process operations in drug manufacturing. The devices control the critical variables.

ii. The sensor level – made up of sensors attached to each of the components, to sense the performance level of the component and return discrete values to the critical system. Each device with its sensor is connected to the system via a port which serves as the identifier for the component.

iii. The critical system – which monitors the overall performance of the process components and consists of the critical software and visual display unit.

The critical software consists of the following the aggregator module, analysis module and decision module.

The Working Principle of the System

- As the system instantiates on activation, it initializes the current state of the components (devices), setting the values of the CPVs to zero. This is so because any of the variables that may not be required would not have any significant effect on the process. The sensors are also instantiated.
- Thereafter, it sets to a specific operating mode, which is selection of one of the stages of the production processes.
- Having set mode, it determines the defined critical process variables (CPVs) and their acceptable performance ranges for each of the components or devices.
- A refresh time interval between in-process is set by operator or pre-defined in the system.

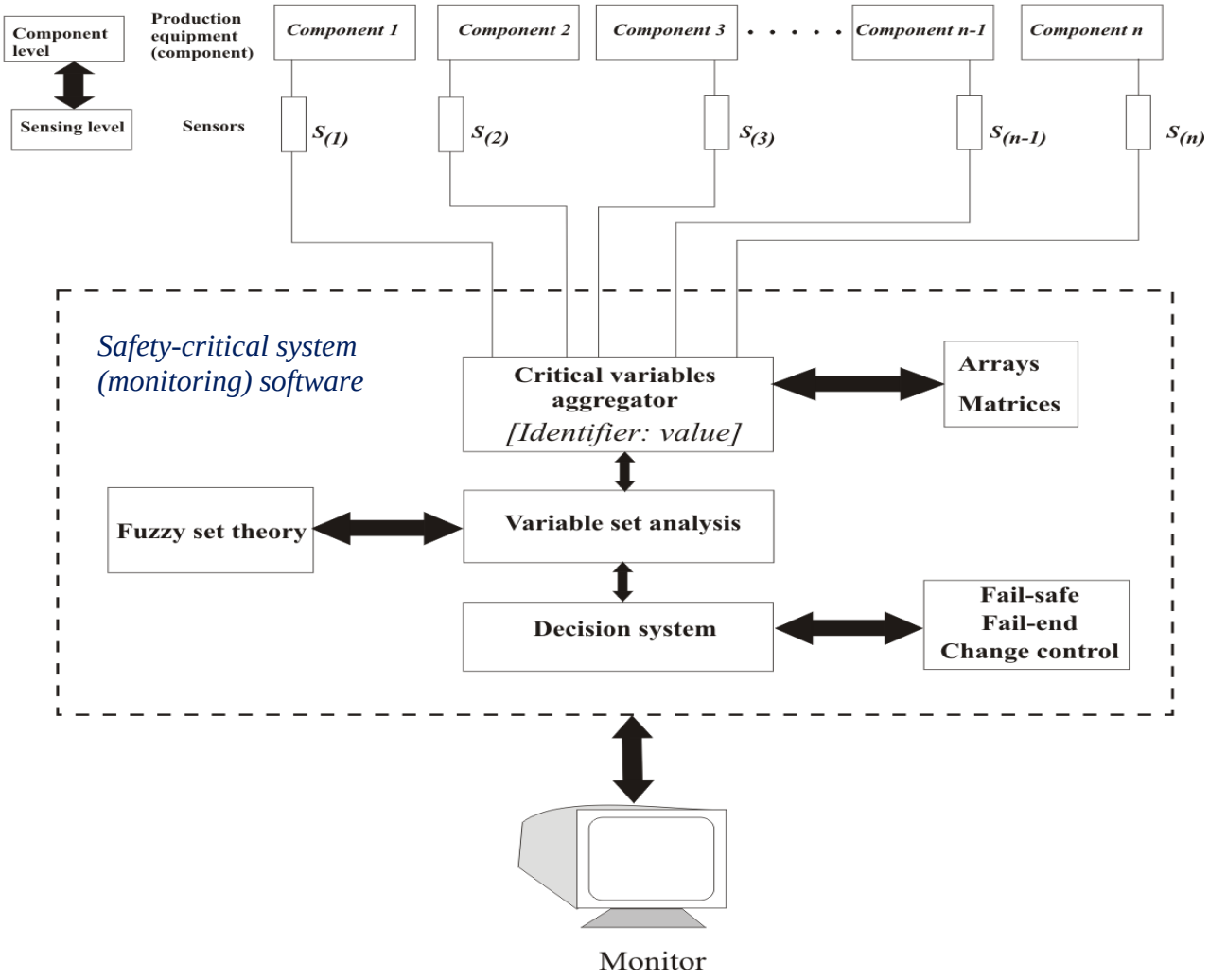


Figure 6: Architecture of the Proposed System Under Study.

- As the process commences, the sensors send signals (values of the CPVs) to the system at every refresh interval.
- The Aggregator module arranges the values and headers in matrix or array form. The module activates the Analysis module.
- The Analysis Module refreshes each time the Aggregator Module sends a request signal analysis of the data set in the aggregate buffer.
- The Analysis Module performs fuzzy operation on the data set to obtain a fuzzy index of the variables. Then it activates the Decision Module.
- The Decision Module sets Alert system if a critical condition has occurred. It also prompts the operator (human or embedded decision function) to make a decision to continue process.

The system can be connected to a visual display unit (VDU) or monitor to visualize the outcome of the operations of the system, with control buttons to effect decisions. Some decisions that could be taken include:

i. Fail-safe: to ignore the failure alert and continue process. It could be that the failure mode is insignificant

Table 2: Specimen Critical Process Variables for Acetaminophen Manufacturing.

Steps	Control variable	Operating range of values		
		Minimum	Maximum	Optimum
Dry mixing	Mixing time Impeller speed	10min Slow	20min High	15min Medium
Wet granulation	Time Temperature Granule size	20min 20^0C 0.9mm	25min 30^0C 1.5mm	22.5min 25^0C 1.2mm
Drying	Inlet temperature Outlet temperature Drying time	40^0C 28^0C 12min	50^0C 30^0C 18min	45^0C 29^0C 15min
Milling	Milling speed Feed rate	Slow Slow	High High	Medium Medium
Lubrication	Time Blender/granulator speed	4min 2rpm	6min 45rpm	5min 23.5rpm
Tablet compression	Compression speed Compression force	25rpm 3N	35rpm 5N	30rpm 4N
Tablet coating	Pan speed Sprayrate	40rpm 30cpm	44rpm 50cpm	42rpm 40cpm

Table 3: Fuzzy Membership Mapping.

Quantifier	Score	Criterion
Very Good	μ_{A1}*(excellent)*	If *critically* or *highly acceptable*
Good	μ_{A2}*(good)*	If *acceptable*
Fair	μ_{A3}*(average)*	If *fairly acceptable* or *fairly unacceptable*
Bad	μ_{A4}*(poor)*	If *highly unacceptable*
Very Bad	μ_{A4}*(poor)*	If *critically unacceptable*

ii. Fail-end: to abort or terminate the process as a result of the failure mode

iii. Change control: to re-input or adjust the CPVs in order to meet expected result.

Simulation of Paracetamol Tablet 500mg Process Monitoring

In-process conditions in Paracetamol 500mg Tablet (Acetaminophen) manufacturing involve different steps and variables. Table 2 shows the critical process variables and associated values.in the manufacturing of Paracetamol Tablet 500mg. These values are extracted from Yadav et al (2012) and from the relation in Equation 4.

For the purpose of ease, let the fuzzy patterns be defined as:

$$a_1 = (a_{11},a_{12},a_{13}) = (0.8,0.8,0.8)$$
$$a_2 = (a_{21},a_{22},a_{23}) = (0.6,0.6,0.6)$$
$$a_3 = (a_{31},a_{32},a_{33}) = (0.4,0.4,0.4)$$
$$a_4 = (a_{41},a_{42},a_{43}) = (0.2,0.2,0.2)$$

The normalized weighting factors are also taken as:

$$\beta_{11} = 0.2\ ,\ \beta_{12} = 0.5,\ \beta_{13} = 0.3$$

for Time, Temperature and Granule size respectively. This indicates that Temperature contributes more effect to the process.

The fuzzy membership scores are defined as:

μ_{A1} = *Excellent,*
μ_{A2} = *Good,*
μ_{A3} = *Average,*
and μ_{A4} = *Poor*

and the threshold $\lambda = 0.6$, for the fuzzy rules defined as:

$$\forall \mu_{A_i} = \begin{cases} critically\ acceptable:\ 0.75 < \mu_{A_1} \le 1.0\ and\ \mu_{A_4} = 0 \\ highly\ acceptable:\ 0.60 \le \mu_{A_1} \le 0.75\ and\ \mu_{A_4} = 0 \\ acceptable: 0 < \mu_{A_i} \le 0.6\big|_{i=1,2,3}\ and\ \mu_{A_4} = 0 \\ fairly\ acceptable: \mu_{A_4} \ne 0\ and\ max(\mu_{A_i})\big|_{i=1,2,3,4} \ne \mu_{A_4} \\ fairly\ unacceptable: \mu_{A_1} \ne 0\ and\ max(\mu_{A_i})\big|_{i=1,2,3,4} = \mu_{A_4} \\ unacceptable: 0 < \mu_{A_i} \le 0.6\big|_{i=2,3,4}\ and\ \mu_{A_1} = 0 \\ highly\ unacceptable:\ 0.60 \le \mu_{A_4} \le 0.75\ and\ \mu_{A_1} = 0 \\ critically\ unacceptable:\ 0.75 < \mu_{A_4} \le 1.0\ and\ \mu_{A_1} = 0 \end{cases}$$

Table 3 contains the fuzzy membership score and mapping.

Simulation of Wet Granulation Process

Simulating the datasets of maximum values, minimum values, optimum values, and randomly selected values, we have the following results:

i. The Process at set of Maximum-Value Dataset

Assume detected values are 25min, 30°C, and 1.5mm at an instance, then:

$$u_1 = f(Time) = \sqrt{1-\left(\frac{25-22.5}{22.5-20}\right)^2} = 0$$

$$u_2 = f(Temp) = \sqrt{1-\left(\frac{30-25}{25-20}\right)^2} = 0$$

$$u_3 = f(Size) = \sqrt{1-\left(\frac{1.5-1.2}{1.2-0.9}\right)^2} = 0$$

$$\therefore u = (0,0,0)$$

$$d_1(u,a_1) = \sqrt{\beta_{11}(u_1-a_{11})^2 + \beta_{12}(u_2-a_{12})^2 + \beta_{13}(u_3-a_{13})^2}$$
$$= \sqrt{0.2(0-0.8)^2 + 0.5(0-0.8)^2 + 0.3(0-0.8)^2} = 0.8$$

$$d_2(u,a_2) = \sqrt{\beta_{11}(u_1-a_{21})^2 + \beta_{12}(u_2-a_{22})^2 + \beta_{13}(u_3-a_{23})^2}$$
$$= \sqrt{0.2(0-0.6)^2 + 0.5(0-0.6)^2 + 0.3(0-0.6)^2} = 0.6$$

$$d_3(u,a_3) = \sqrt{\beta_{11}(u_1-a_{31})^2 + \beta_{12}(u_2-a_{32})^2 + \beta_{13}(u_3-a_{33})^2}$$
$$= \sqrt{0.2(0-0.4)^2 + 0.5(0-0.4)^2 + 0.3(0-0.4)^2} = 0.4$$

$$d_4(u,a_4) = \sqrt{\beta_{11}(u_1-a_{41})^2 + \beta_{12}(u_2-a_{42})^2 + \beta_{13}(u_3-a_{43})^2}$$
$$= \sqrt{0.2(0-0.2)^2 + 0.5(0-0.2)^2 + 0.3(0-0.2)^2} = 0.2$$

D = 0.8

$$\mu_{A1} = 1 - d_1(u,a_1)/D = 1 - 0.8/0.8 = 0$$
$$\mu_{A2} = 1 - d_1(u,a_2)/D = 1 - 0.6/0.8 = 0.25$$
$$\mu_{A3} = 1 - d_1(u,a_3)/D = 1 - 0.4/0.8 = 0.50$$
$$\mu_{A4} = 1 - d_1(u,a_4)/D = 1 - 0.2/0.8 = 0.75$$

Since max{$\mu_{Ai}(u)$=0.75} then $u \epsilon A_4$, we can easily conclude that the outcome would be *Bad* and *Highly Unacceptable.*

ii. The process at set of Minimum-Value Dataset

Assume detected values are 20min, 20°C, and 0.9mm at an instance, then:

$$u_1 = f(Time) = \sqrt{1-\left(\frac{20-22.5}{22.5-20}\right)^2} = 0$$

$$u_2 = f(Temp) = \sqrt{1-\left(\frac{20-25}{25-20}\right)^2} = 0$$

$$u_3 = f(Size) = \sqrt{1-\left(\frac{0.9-1.2}{1.2-0.9}\right)^2} = 0$$

$$\therefore u = (0,0,0)$$

$$d_1(u,a_1) = \sqrt{\beta_{11}(u_1-a_{11})^2 + \beta_{12}(u_2-a_{12})^2 + \beta_{13}(u_3-a_{13})^2}$$
$$= \sqrt{0.2(0-0.8)^2 + 0.5(0-0.8)^2 + 0.3(0-0.8)^2} = 0.8$$

$$d_2(u,a_2) = \sqrt{\beta_{11}(u_1-a_{21})^2 + \beta_{12}(u_2-a_{22})^2 + \beta_{13}(u_3-a_{23})^2}$$
$$= \sqrt{0.2(0-0.6)^2 + 0.5(0-0.6)^2 + 0.3(0-0.6)^2} = 0.6$$

$$d_3(u,a_3) = \sqrt{\beta_{11}(u_1-a_{31})^2 + \beta_{12}(u_2-a_{32})^2 + \beta_{13}(u_3-a_{33})^2}$$
$$= \sqrt{0.2(0-0.4)^2 + 0.5(0-0.4)^2 + 0.3(0-0.4)^2} = 0.4$$

$$d_4(u,a_4)=\sqrt{\beta_{11}(u_1-a_{41})^2+\beta_{12}(u_2-a_{42})^2+\beta_{13}(u_3-a_{43})^2}$$
$$=\sqrt{0.2(0-0.2)^2+0.5(0-0.2)^2+0.3(0-0.2)^2}=0.2$$

D = 0.8

$$\mu_{A1}=1-d_1(u,a_1)/D=1-0.8/0.8=0$$
$$\mu_{A2}=1-d_1(u,a_2)/D=1-0.6/0.8=0.25$$
$$\mu_{A3}=1-d_1(u,a_3)/D=1-0.4/0.8=0.50$$
$$\mu_{A4}=1-d_1(u,a_4)/D=1-0.2/0.8=0.75$$

Since max{$\mu_{A4}(u)$=0.75},then$u\epsilon A_4$,we conclude that the outcome would be *Bad* and *Highly Unacceptable.*

iii. The Process at set of Optimum-Value Dataset

Assume detected values are 22.5min, 25^{o}C, and 1.2mm at an instance, then:

$$u_1=f(Time)=\sqrt{1-\left(\frac{22.5-22.5}{22.5-20}\right)^2}=1$$

$$u_2=f(Temp)=\sqrt{1-\left(\frac{25-25}{25-20}\right)^2}=1$$

$$u_3=f(Size)=\sqrt{1-\left(\frac{1.2-1.2}{1.2-0.9}\right)^2}=1$$

$$\therefore u=(1,1,1)$$

$$d_1(u,a_1)=\sqrt{\beta_{11}(u_1-a_{11})^2+\beta_{12}(u_2-a_{12})^2+\beta_{13}(u_3-a_{13})^2}$$
$$=\sqrt{0.2(1-0.8)^2+0.5(1-0.8)^2+0.3(1-0.8)^2}=0.2$$

$$d_2(u,a_2)=\sqrt{\beta_{11}(u_1-a_{21})^2+\beta_{12}(u_2-a_{22})^2+\beta_{13}(u_3-a_{23})^2}$$
$$=\sqrt{0.2(1-0.6)^2+0.5(1-0.6)^2+0.3(1-0.6)^2}=0.4$$

$$d_3(u,a_3)=\sqrt{\beta_{11}(u_1-a_{31})^2+\beta_{12}(u_2-a_{32})^2+\beta_{13}(u_3-a_{33})^2}$$
$$=\sqrt{0.2(1-0.4)^2+0.5(1-0.4)^2+0.3(1-0.4)^2}=0.6$$

$$d_4(u,a_4)=\sqrt{\beta_{11}(u_1-a_{41})^2+\beta_{12}(u_2-a_{42})^2+\beta_{13}(u_3-a_{43})^2}$$
$$=\sqrt{0.2(1-0.2)^2+0.5(1-0.2)^2+0.3(1-0.2)^2}=0.8$$

D = 0.8

$$\mu_{A1}=1-d_1(u,a_1)/D=1-0.2/0.8=0.75$$
$$\mu_{A2}=1-d_1(u,a_2)/D=1-0.4/0.8=0.50$$
$$\mu_{A3}=1-d_1(u,a_3)/D=1-0.2/0.8=0.25$$
$$\mu_{A4}=1-d_1(u,a_4)/D=1-0.8/0.8=0$$

Since max{$\mu_{A1}(u)$=0.75} then $u\epsilon A_1$,so we conclude that the outcome would be *Very Good* and *Highly Acceptable.*

iv. The Process at set of Varying Random-Value Dataset

Assume detected values are 25min, 22^{o}C, and 1.1mm at an instance, then:

$$u_1=f(Time)=\sqrt{1-\left(\frac{25-22.5}{22.5-20}\right)^2}=0$$

$$u_2=f(Temp)=\sqrt{1-\left(\frac{22-25}{25-20}\right)^2}=0.80$$

$$u_3=f(Size)=\sqrt{1-\left(\frac{1.1-1.2}{1.2-0.9}\right)^2}=0.9428$$

$$\therefore u=(0,0.80,0.9428)$$

$$d_1(u,a_1)=\sqrt{\beta_{11}(u_1-a_{11})^2+\beta_{12}(u_2-a_{12})^2+\beta_{13}(u_3-a_{13})^2}$$
$$=\sqrt{0.2(0-0.8)^2+0.5(0.8-0.8)^2+0.3(0.9428-0.8)^2}=0.3662$$

$$d_2(u,a_2)=\sqrt{\beta_{11}(u_1-a_{21})^2+\beta_{12}(u_2-a_{22})^2+\beta_{13}(u_3-a_{23})^2}$$
$$=\sqrt{0.2(0-0.6)^2+0.5(0.8-0.6)^2+0.3(0.9428-0.6)^2}=0.3567$$

$$d_3(u,a_3)=\sqrt{\beta_{11}(u_1-a_{31})^2+\beta_{12}(u_2-a_{32})^2+\beta_{13}(u_3-a_{33})^2}$$
$$=\sqrt{0.2(0-0.4)^2+0.5(0.8-0.4)^2+0.3(0.9428-0.4)^2}=0.4475$$

$$d_4(u,a_4)=\sqrt{\beta_{11}(u_1-a_{41})^2+\beta_{12}(u_2-a_{42})^2+\beta_{13}(u_3-a_{43})^2}$$
$$=\sqrt{0.2(0-0.2)^2+0.5(0.8-0.2)^2+0.3(0.9428-0.2)^2}=0.5946$$

D = 0.5946

$$\mu_{A1}=1-d_1(u,a_1)/D=1-0.3662/0.5946=0.3841$$
$$\mu_{A2}=1-d_1(u,a_2)/D=1-0.3567/0.5946=0.4001$$
$$\mu_{A3}=1-d_1(u,a_3)/D=1-0.4475/0.5946=0.2474$$
$$\mu_{A4}=1-d_1(u,a_4)/D=1-0.5946/0.5946=0$$

Since max(μ_{Ai}<λ) for i=1,2,3 and μ_4 = 0,we conclude that the outcome would be *Good* and *Acceptable*.

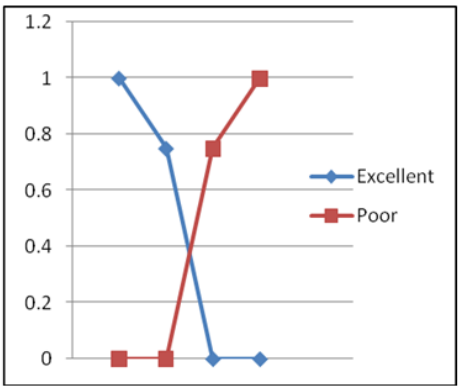


Figure 7: Pattern Characteristic.

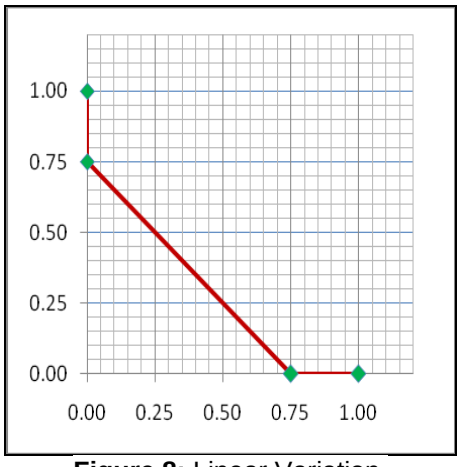


Figure 8: Linear Variation.

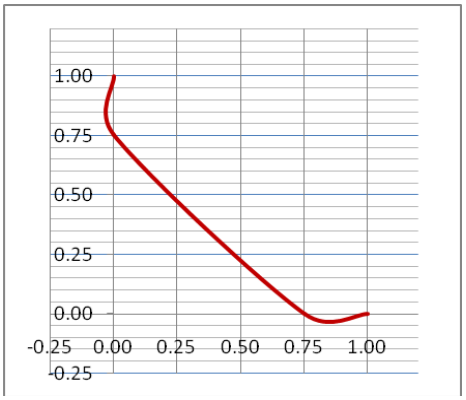


Figure 9: Process Behavior in the Free Space.

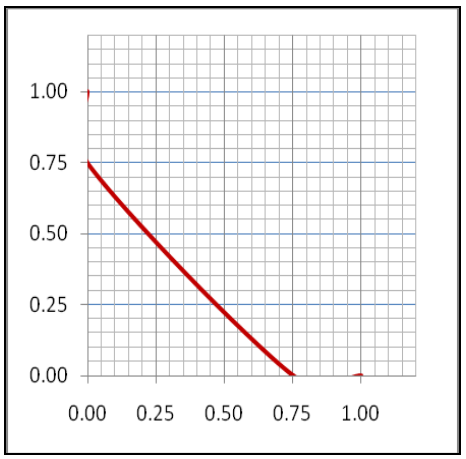


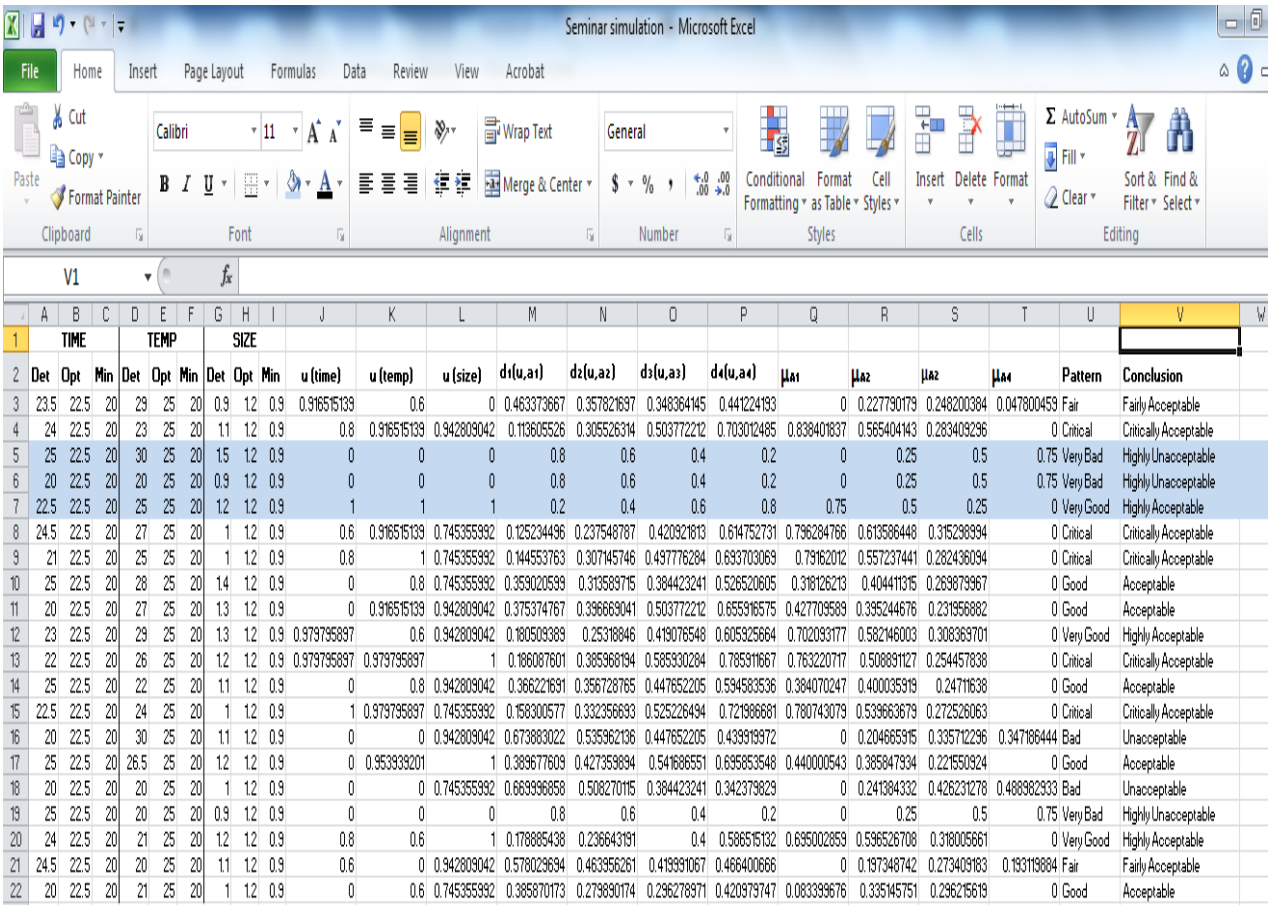
Figure 10: Marginal Cut-Off in the Half Plane.

RESULTS AND DISCUSSION

Figure 7 shows the pattern characteristic of the process evaluation in which the critical value-set and optimum value-set exhibit exclusivity property. The Excellent property lies between the marginal line (i.e., between 0.75 and 1.0), the Poor property lies on axis line. As the Excellent quality begins to decline further from 0.75, the Poor quality begins to rise until 0.75 point where Excellent drops to 0.

It remains at the level while Poor rises to 1. This shows that at the maximum and minimum (peak) values, the process exhibits similar characteristics.

Figure 8 shows the characteristic behavior of the process in a linear relationship showing cut-off values and marginal phases. It shows that 0.75 marks a cut-off value and values higher than this lie marginally on the axis.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V
1		TIME			TEMP			SIZE															
2	Det	Opt	Min	Det	Opt	Min	Det	Opt	Min	u (time)	u (temp)	u (size)	d1(u,a1)	d2(u,a2)	d3(u,a3)	d4(u,a4)	μA1	μA2	μA2	μA4	Pattern	Conclusion
3	23.5	22.5	20	29	25	20	0.9	1.2	0.9	0.916515139	0.6	0	0.463373667	0.357821637	0.348364145	0.441224193	0	0.227790179	0.248200384	0.047800459	Fair	Fairly Acceptable
4	24	22.5	20	23	25	20	1.1	1.2	0.9	0.8	0.916515139	0.942809042	0.113605526	0.305526314	0.503772212	0.703012485	0.838401837	0.565404143	0.283409296	0	Critical	Critically Acceptable
5	25	22.5	20	30	25	20	1.5	1.2	0.9	0	0	0	0.8	0.6	0.4	0.2	0	0.25	0.5	0.75	Very Bad	Highly Unacceptable
6	20	22.5	20	20	25	20	0.9	1.2	0.9	0	0	0	0.8	0.6	0.4	0.2	0	0.25	0.5	0.75	Very Bad	Highly Unacceptable
7	22.5	22.5	20	25	25	20	1.2	1.2	0.9	1	1	1	0.2	0.4	0.6	0.8	0.75	0.5	0.25	0	Very Good	Highly Acceptable
8	24.5	22.5	20	27	25	20	1	1.2	0.9	0.6	0.916515139	0.745355992	0.125234496	0.237548787	0.420921813	0.614752731	0.796284766	0.613586448	0.315298394	0	Critical	Critically Acceptable
9	21	22.5	20	25	25	20	1	1.2	0.9	0.8	1	0.745355992	0.144553763	0.307145746	0.497776284	0.693703069	0.79162012	0.557237441	0.282436094	0	Critical	Critically Acceptable
10	25	22.5	20	28	25	20	1.4	1.2	0.9	0	0.8	0.745355992	0.359020599	0.313589715	0.384423241	0.526520605	0.318126213	0.404411315	0.269879967	0	Good	Acceptable
11	20	22.5	20	27	25	20	1.3	1.2	0.9	0	0.916515139	0.942809042	0.375374767	0.396669041	0.503772212	0.655916575	0.427709589	0.395244676	0.231956882	0	Good	Acceptable
12	23	22.5	20	29	25	20	1.3	1.2	0.9	0.979795897	0.6	0.942809042	0.180509389	0.25318846	0.419076548	0.605925664	0.702093177	0.582146003	0.308369701	0	Very Good	Highly Acceptable
13	22	22.5	20	26	25	20	1.2	1.2	0.9	0.979795897	0.979795897	1	0.186087601	0.385968194	0.585330284	0.785911667	0.763220717	0.508891127	0.254457838	0	Critical	Critically Acceptable
14	25	22.5	20	22	25	20	1.1	1.2	0.9	0	0.8	0.942809042	0.366221691	0.356728765	0.447652205	0.594583536	0.384070247	0.400035919	0.24711638	0	Good	Acceptable
15	22.5	22.5	20	24	25	20	1	1.2	0.9	1	0.979795897	0.745355992	0.158300577	0.332356693	0.525226494	0.721986681	0.780743079	0.539663679	0.272526063	0	Critical	Critically Acceptable
16	20	22.5	20	30	25	20	1.1	1.2	0.9	0	0	0.942809042	0.673883022	0.535962136	0.447652205	0.439919972	0	0.204665915	0.335712296	0.347186444	Bad	Unacceptable
17	25	22.5	20	26.5	25	20	1.2	1.2	0.9	0	0.953939201	1	0.389677609	0.427359894	0.541686551	0.635853548	0.440000543	0.385847934	0.221550924	0	Good	Acceptable
18	20	22.5	20	20	25	20	1	1.2	0.9	0	0	0.745355992	0.669996858	0.508270115	0.384423241	0.342379629	0	0.241384332	0.426231278	0.488982333	Bad	Unacceptable
19	25	22.5	20	20	25	20	0.9	1.2	0.9	0	0	0	0.8	0.6	0.4	0.2	0	0.25	0.5	0.75	Very Bad	Highly Unacceptable
20	24	22.5	20	21	25	20	1.2	1.2	0.9	0.8	0.6	1	0.178885438	0.236643191	0.4	0.586515132	0.695002859	0.596526708	0.318005661	0	Very Good	Highly Acceptable
21	24.5	22.5	20	20	25	20	1.1	1.2	0.9	0.6	0	0.942809042	0.578029694	0.463956261	0.419931067	0.466400666	0	0.197348742	0.273409183	0.193119884	Fair	Fairly Acceptable
22	20	22.5	20	21	25	20	1	1.2	0.9	0	0.6	0.745355992	0.385870173	0.279890174	0.296278971	0.420979747	0.083399676	0.335145751	0.296215619	0	Good	Acceptable

Figure 11: Computer Generated CPVs with MS Excel Functions.

These are critical-point characteristics further which could result in process drifts. On the vertical, it could represent region of hyper-dosage or over-dosage while on the horizontal, it could represent hypo-dosage or under-dosage.

Figure 9 shows the Smoothened variation showing the process behavior in the free space. The process has some degree of abnormalities occasioned by the drift into the negative plane. This could result in uncertainties in the outcome of the process or better referred to as therapeutic failures.

Figure 10 shows the smoothened variation of the marginal cut-off in the positive half plane. It is evident that as the process is adjusted to the positive half-plane, there is a cut-off along the marginal line. This shows there is a point where the process attains a cut-off value, which in this case is 0.75.

Simulation with different values of mixing time, temperature and granule size is presented in Figure 11 showing detected, optimum and minimum values respectively. The results for the maximum, minimum and optimum datasets are indicated with the blue shading.

CONCLUSION

Safety is the major concern of everyone. As processes shift from traditional human methods to computer-based systems, the safety of the system should be of highest priority during design. However, the development of safety critical software systems requires the introduction of mature development process into the organization as well as the use of acknowledged standards. For process activities, key process variables can be identified and their acceptance criteria established.

This research work has highlighted the need for analysis of safety functions in critical systems for the monitoring of pharmaceutical process validation, which is tenable in almost every stage of the production cycle.

Analyses showed that processes at critical levels could easily result in process drifts. Critical systems are better controlled within acceptable range of operating values of the set of critical variables. Therefore, a critical process should be avoided from operating at the critical values to ensure good quality outcome. This paper presented an innovative framework for research in design of safety critical systems for drug manufacturing processes, which by implication is applicable to other related processes.

FUTURE WORK

Areas of further work include:

- Development of algorithms for the implementation of the safety critical system for drug manufacturing processes.
- Creating a relationship model for the overall safety of a system.
- Development of incident response techniques to collect, analyze and respond to safety incident reports in order to lessen the likelihood of accidents.
- Integrated analyses of safety functions for all failure modes in the entire process line.
- Embedding safety variables and decision rules in the critical system.

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SUGGESTED CITATION

Egwali, A.O. and K.C. Nwaekwu. 2018. "Safety-Critical Model for Process Validation in Paracetamol 500mg Tablet Manufacturing". *Pacific Journal of Science and Technology*. 19(2):103-117.

Pacific Journal of Science and Technology