# COMPARISON OF BATCH VERSUS CONTINUOUS PROCESS IN THE PHARMACEUTICAL INDUSTRY BASED ON SAFETY CONSIDERATION

A Thesis

by

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Submitted to the Office of Graduate and Professional Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

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May 2017

Major Subject: Chemical Engineering

# ABSTRACT

As opposed to the petro-chemical and bulk chemical industry, where continuous processes are widely applied, the pharmaceutical industry still primarily relies on traditional batch process due to the complexity of product, multi-step operation and low-volume production. Considering these conditions, the versatile batch process is more appropriate.

Nowadays, driven by the contradiction between increasing demand for drugs and inefficient batch production mode, there is a trend in pharmaceutical industry, that is the transformation from traditional batch process to novel continuous process. Related projects and research that is aimed at analyzing this transition are conducted in worldwide, and the scale of these studies ranges from lab-scale reactions to overall arrangement of the factories.

Although continuous pharmaceutical process is thriving, the safety issue in this field is not promoted at the same time. Since the continuous pharmaceutical process is a novel technology, little information can be provided to evaluate its safety level. Moreover, process conditions are usually intensified for continuous process comparing to batch process. It also may bring potential risks and make continuous manufacturing inappropriate for some of pharmaceutical productions.

This research provides a comprehensive comparison for batch versus continuous pharmaceutical process by application of Dow's Fire and Explosion Index. In addition to

this conventional safety evaluation, influences from production efficiency and specialties in pharmaceutical production are integrated into the comparison. Production of 2-methyl benzimidazole and peracetic acid via batch and continuous processes are conducted in this research. In these integrative and systematic studies, F&EI values for both cases are higher for continuous processes than batch processes, hence the higher safety level of the continuous process is demonstrated. The ways in which process conditions, production efficiency, and other requirements influence safety level for different production modes are illustrated.

# DEDICATION

*To my mom for her consistent support, understanding and always believing in me as my best friend.*

*To my dad for his pertinent advice, inspiration, solicitude and encouragement as my best spiritual mentor.*

# ACKNOWLEDGEMENTS

I would like to thank my committee chair, Dr. M. Sam Mannan, for his constant support and pertinent advice on my research. I benefited greatly from his devoted service at the Mary Kay O'Connor Process Safety Center, where I began my study in the field of process safety. I would like to thank my committee members, Dr. Mahmoud M. El-Halwagi and Dr. Gerald L. Morrison, for their guidance and support throughout the course of this research. Also, I am grateful to Dr. Charles Glover for his kind support during my defense.

Thanks also go to Dr. Yogesh Koirala for his constant guidance, patience and encouragement in this study. I would also like to thank my friends and colleagues in the Mary Kay O'Connor Process Safety Center who have taught me so much and inspired me, both in academics and life, and made my time here such a rewarding experience.

Finally, I want to thank my mother and father, Hualian Yu and Zhixiong Chen, for their consistent encouragement, patience, and love.

CONTRIBUTORS AND FUNDING SOURCES

## Contributors

This work was supervised by a thesis committee consisting of Professor M. Sam Mannan, my advisor, and Professor Mahmoud M. El-Halwagi of the Department of Chemical Engineering and Professor Gerald L. Morrison of the Department of Mechanical Engineering.

All work for the thesis was completed by the student, under the advisement of Professor M. Sam Mannan of the Department of Chemical Engineering.

## Funding Sources

There are no outside funding contributions to acknowledge related to the research and compilation of this document.

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# 1. INTRODUCTION

Continuous process is widely applied in petro-chemical and bulk chemical industry for its high production rate, automated operation and saving in cost (Plumb, 2005). In contrast, the pharmaceutical industry still primarily relies on traditional batch process. This aspect stems from intrinsic limitations in active pharmaceutical ingredients (APIs) production. Complexity of medical substances means multistep synthesis. An average of 8.1 steps is needed for one API synthesis (Laird, 2006). Another limitation is production volume. Demand for drugs are not comparable with most of the bulk chemicals. These limitations make batch process dominate pharmaceutical industry for a long time.

However, due to the gradual expansion of the pharmaceutical market, batch process is behind the time because of its low production rate caused by low yield and inefficient operation mode. Driven by this contradiction between increasing demand for drugs and inefficient production mode, many pharmaceutical manufacturers are trying to shift from a traditional batch process to a novel continuous process. Experimental and industrial trials that are aimed at this transitioning have been done and exhibit the practicability of this new production mode. Several companies such as Lonza, Phoenix Chemical, and Corning make significant progress in this area (Braune *et al*., 2009; Proctor & Warr, 2002; Dominique *et al.*, 2009). Novel continuous process exhibits great potential for the pharmaceutical industry.

"Which process should be applied?" and "Is there enough benefit to move forward?" are the questions that are raised when an innovative process is introduced. To answer these

questions, comprehensive comparison between batch process and continuous process is required.

This comparison should be specific in the early stages. For example, for a given substance, based on its intrinsic properties and demand in market, reasonable comparison is required to make a selection between batch and continuous process. After composing a conclusive summary that is based on number of different specific cases, the result of these comparisons can be modified and applied to generate a practical process screening methodology.

For the questions mentioned above, economic benefits, safety and environmental impacts should all be considered to get a reliable answer. In the batch versus continuous process comparisons, related economic analysis and environmental analysis have been done by many researchers (Hessel *et al.*, 2012; Jolliffe & Gerogiorgis, 2016; Spencer *et al.*, 2011). However, there remains gaps in research and understanding of safety considerations in comparison of batch versus continuous process. Therefore, the need arises for related comparison within safety consideration and systematic methodology for safety evaluation.

In the following sessions, the development in continuous pharmaceutical process, the previous studies in process screening, selecting and comparing, and concept of inherent safety assessment are discussed. The statement of research objective, the description of methodology and results of case studies are illuminated as well.

# 2. LITERATURE REVIEW

## 2.1. CONTINUOUS PHARMACEUTICAL PROCESS

Continuous process and batch process are two types of production mode in chemical industry in a broad sense. In a batch process, the raw material is charged before the processing and the product is discharged after this period of processing. In a continuous process, the raw material and the product is charged and discharged simultaneously during the period of processing. These definitions can describe either a single unit operation or a integrated manufacturing process.

Compared to the batch process that is widely applied in pharmaceutical industry, continuous process is a more efficient production mode of marked advantages (Gutmann, Cantillo, & Kappe, 2015).

Firstly, continuous unit or process is usually less spacious than batch unit or process. Take batch vs. continuous reactor as an example, by using continuous manufacturing technology, the volume of reactor decreases from at least two cubic meters to at most three liters (Hessel *et al*., 2012). For some industrial chemical production, the volume ratio of batch reactor to continuous reactor can be several thousands (Wakami & Yoshida, 2005). Significant miniaturization in dimension leads to high efficiency in mass and heat transfer: smaller volume means lager heat exchange surface, shorter residence time and much easier control of process. This kind of intensification in continuous unit operation further provides benefits for integrative production: by reducing footprint of equipment, decreasing time between batches and cutting down manual operations between

discontinuous steps within one batch, the factory could be designed and manipulated in a more compact and efficient way.

Secondly, the continuous process allows the use of extreme process conditions which improve yield. In contrast, these conditions are difficult to achieve in the batch process. Most of conventional batch reactors in pharmaceutical facilities do not allow reaction temperature above 200 °C and pressure above 10 bar (Damm, Glasnov, & Kappe, 2009). These limitations impose restrictions on application of more efficient reactions conditions and potential but hazardous synthesis routes. Continuous process, on the other hand, enables reaction under more hazardous conditions (300 °C/30 bar) (Damm *et al*., 2009). This growth in tolerance of high temperature and high pressure considerably intensify the reaction kinetics and therefore increase the yield. Moreover, the application of extreme conditions also provides another approach to speed up the production, that is, the use of supercritical solvents. Some substances have enhanced solubility at the temperature and pressure above its critical point. For example, supercritical carbon dioxide ($scCO_2$) is one of the most frequently used supercritical solvents in the flow chemistry domain. Application of $scCO_2$ is actualized in reactions such as condensation, hydroformylation and hydrogenation (Gutmann *et al*., 2015). Compared to traditional organic solvent, $scCO_2$ is obviously a much safer and eco-friendlier choice for pharmaceutical industry which expends a lot of solvent in organic synthesis.

Thirdly, scaling up for a continuous process is easier, faster and more flexible than for a batch process. Pharmaceutical manufacturing has a significant long life cycle compared to bulk chemical industry. Demand for drug starts from milligrams in discovery

stage and increases to tens of grams even kilogram in the following clinical studies. Once the active pharmaceutical ingredient (API) is permitted for commercialized production, production amount at the scale of hundreds of tons needs to be guaranteed. For batch process, due to its unstable performances in different production scales, significant changes are inevitable in scaling up procedure. Some of processes even cannot be scaled up owing to technical limitations. In contrast, referring to the literature, continuous process in laboratory can be scaled up with less re-optimizations and less changes in synthesis route (Gutmann *et al*., 2015).

## 2.2. PROCESS COMPARISON AND SELECTION

To decide whether to head to novel continuous process or not, evaluations of batch and continuous process are in demand for pharmaceutical companies.

In preliminary stage of the evaluation, fundamental information about reaction kinetics, heat transmission and mass transfer is collected and analyzed. The objective of this investigation is looking into the technical feasibility of chosen reaction. After these basic assessments for intrinsic properties of reaction, far-reaching analyze in economic, environmental and safety aspect can be achieved. In this more comprehensive comparison based on overall picture, more factors such as expenditure, wastewater treatment and loss control measure should be covered. Among these factors, which factor should be selected as criterion, how these factors interact, and what's the correlation between these factors and comparison results are questions require to be answered.

To answer these questions, some researchers put efforts in individual comparisons of manufacturing for specific active pharmaceutical ingredient (API). Most of these studies focus on economic advantage of continuous process. Spencer D. Schaber *et al*.(Schaber *et al*., 2011) estimated the capital, operating and the overall cost for production of a given API from synthesis to tablet formulation by integrated continuous and batch pharmaceutical manufacturing respectively. Based upon the equal annual yield, the result shows that the capital expenditures for continuous production could be markedly lower than those of batch mode. Differences in operating and overall cost are not such significant but potential saving by material handling and labor in continuous process is explicitly illustrated in the study. Hessel, V. *et al*. compared continuous vs. batch pharmaceutical manufacturing for production of ibuprofen and artemisinin on the standpoint of cost and environmental impact. Capital expenditure and operating expenditure savings are up to 57.0% and 51.6% respectively for ibuprofen, while capital expenditure and operating expenditure savings are up to 19.6% and 29.3% respectively for artemisinin (Hessel *et al*., 2012; Jolliffe & Gerogiorgis, 2016). These study shows the potential economic benefits in application of continuous pharmaceutical processes.

In addition to process comparison, some researchers developed general criterions or created systematic methodologies for process selection. Dominique M. Roberge *et al*. (Roberge *et al.*, 2005) classified reactions used in the fine and pharmaceutical industry into 4 categories according to kinetic properties. Based on this classification, the very fast reactions (reactions time less than 1s) and the fast reactions (reactions occurring from 1s to10min) would benefit the most from continuous process. These two types of reactions

occupy 44% of all reactions investigated. Ryan L. Harman and Jonathan P. McMullen (Hartman, McMullen, & Jensen, 2011) developed a decision roadmap of flow process for use in lab-scale. Considering objectives of the study, the intrinsic properties of the chemistry and requirements for mixing, heat transferring, related questions are asked at the various nodes in this flow map to get the final choice. Gary S. Calabrese and Sergio Pissavini (Calabrese & Pissavini, 2011) established an conceptual methodology to evaluate applicability of continuous reactor in the form of reaction properties test. They measured applicability of flow reactor via series of questions. These questions covered issues in reaction properties and some requirements on process. Three "zones" that tagged with different level of applicability are defined. Different questions are included for each "zone". For any given reaction, the more answers with "yes" in the "zone", the higher possibility of this reaction to be at the level of applicability that the "zone" stands for.

## 2.3. INHERENT SAFETY AND SAFETY ASSESSMENT

Inherent safety is a well-known concept that has a history of more than 100 years. This concept is further developed and carried forward by Trevor Kletz, a famous British chemical engineer. He introduced this idea in a 1978 article entitled "What you don't have can't leak" (Kletz, 1978). In contrast to traditional safety study such as incident prevention and mitigation measures, inherent safety emphasizes eliminations of intrinsic hazards in the process, rather than protective activities. There are four main principles to achieve application of inherent safety proposed by Kletz (Kletz, 1991):

- Minimization: decreasing the amount of hazardous materials

- Substitution: Replacing hazardous materials with less hazardous substitutes
- Moderation: Operating the process at less harsh conditions (using dilute reaction, applying low pressure, low temperature, etc.)
- Simplification: Eliminating problems by designing instead of adding protective equipment to deal with them

Compared to conventional approach to control hazard by the protective system, inherent safety approach is usually hard to apply in the early stage of process design, however, once this concept is integrated in process design, intrinsic vulnerability of process could be reduced significantly.

To quantify level of inherent safety in manufacturing facility, many researchers proposed different methodologies for inherent safety assessments. Numerous assessments proposed recently are in the form of indices. Most of indices divide hazards into two types, chemical hazards and process hazards, then discuss specific parameters that influence each kind of hazard separately, and integrate chemical and process factors to get the final result.

According to literature, the first safety index is Dow's Fire & Explosion Index developed by Dow Chemical Company in 1964. Dow's Fire & Explosion Index (F&EI) is a widely used quantification of inherent safety and is one of the leading hazard index recognized by the chemical industry. Another useful tool developed by Dow Company is Dow's Chemical & Exposure Index (C&EI) which considers toxic exposure and is used in conjunction with Dow's F&EI (AIChE, 1994).

The first published index that totally surrounded inherent safety was "quantifying inherent safety of chemical process routes" by Lawrence in 1996(Lawrence, 1996). Based

on Lawrence's work, another index for inherent safety assessment was proposed by Heikkila in 1999 named "inherent safety index" (Heikkilä, 1999). This index introduced the fundamental concept to rank the chemical process on the basis of temperature, pressure, composition in the unit, etc. It is a more specific index that aims at inherent safer design and becomes the prototype for the following development in this field. Besides of this conventional safety indices, there is another type of modified approach of index towards inherent safety, that is the Fuzzy Logic Based Inherent Safety Index developed by Gentile (Gentile, Rogers, & Mannan, 2003). Fuzzy logic accounts for uncertainties in the quantitative hazard and risk assessment. By transform hierarchical ranking into fuzzy ranking, this index successfully combines quantitative modeling and qualitative expert judging.

# 3. PROBLEM STATEMENT

Although advantages of continuous process in pharmaceutical manufacturing are illustrated by many studies, it is still too early to claim that continuous process is the right direction to go forward. Several gaps in the literature survey are required to be focused on.

Firstly, most of process selection methodologies are confined to analyzing separate properties of reaction taken in process, rather than evaluation in a systematic way. For example, small inventory is usually identified as one of significant advantage of continuous process, however, it is possible that to achieve similar yield in the corresponding batch process, the reaction in continuous process requires more intensified conditions like higher temperature, higher pressure, and higher concentration of hazardous chemicals. Selection and comparison by independent and individual parameters without integration is not enough.

Secondly, existing comparisons between batch and continuous processes mainly focus on economic aspect, while lacking combination of safety issue and other important aspects from real production. Although the driving force for the application of this novel process is the economic interests, safety issues directly determine its feasibility. A choice between batch and continuous process needs to be made based on business performance within acceptable safety levels. Those comparisons that merely consider the profits are not enough.

Thirdly, the existing studies are limited to fixed production system. Potential problems in a different scale are not considered. In the pharmaceutical industry, gradually

increasing production scales is required which is different from the bulk chemical industry. Hence, safety of process conditions needs to be guaranteed for all scale production. Comparison only based on fixed scale is not comprehensive.

Therefore, the primary objective of this study is to provide a comprehensive and systematic comparison between batch and continuous process used in pharmaceutical industry. Then on the basis of this analysis, this study will evaluate how main factors considered in Dow F&EI impact the safety level for these two different processes. Finally, this study will provide support to further improve existing methodology for process screening and selection for pharmaceutical industry.

It is worth mentioning that there are other risks such as chemical exposure for pharmaceutical manufacturing, however, this study mainly focuses on potential fire, explosion and reactivity incident. In addition, comparison in this study focuses on intrinsic properties of the reaction and process which are the major hazards of the reaction system. Therefore, other factors like loss control measures and emergency equipment are supposed to be effective for both batch and continuous systems.

# 4. METHODOLOGY

## 4.1. INTRODUCTION

To measure the realistic fire, explosion and reactivity potential of batch and continuous process, Dow's Fire and Explosion Index (F&EI) methodology is applied as hazard index in this study, since it is the most widely used hazard index that recognized by the chemical industry (AIChE, 1994).

From the first edition of Dow's Fire & Explosion Index Hazard Classification Guide in 1964, this index has been continuously improving though the past 50 years. The last version is the seventh edition that published in 1994. The purposes of this index include forecasting quantitative damage of potential explosion, reactivity incidents and fire; determining hazardous equipment which is possible to give rise to incidents in the system; conveying this F&EI risk potential to related managements and organizations. Since the aim of this study is to identify major hazard that affect selection, application of Dow F&EI will be mainly focus on its function of hazard identification.

## 4.2. PROCEDURE FOR HAZARD IDENTIFICATION

Procedure for calculating Dow F&EI is shown in the Figure 1.

The first step, selection of pertinent process unit is usually made considering following factors: chemical energy potential, quantity of hazardous material, capital density, process operation conditions, malfunctions history and special operations. In current study, because the primary difference between continuous and batch systems is

operation of reactor, batch and continuous reactors are defined as research unit in the following calculation.

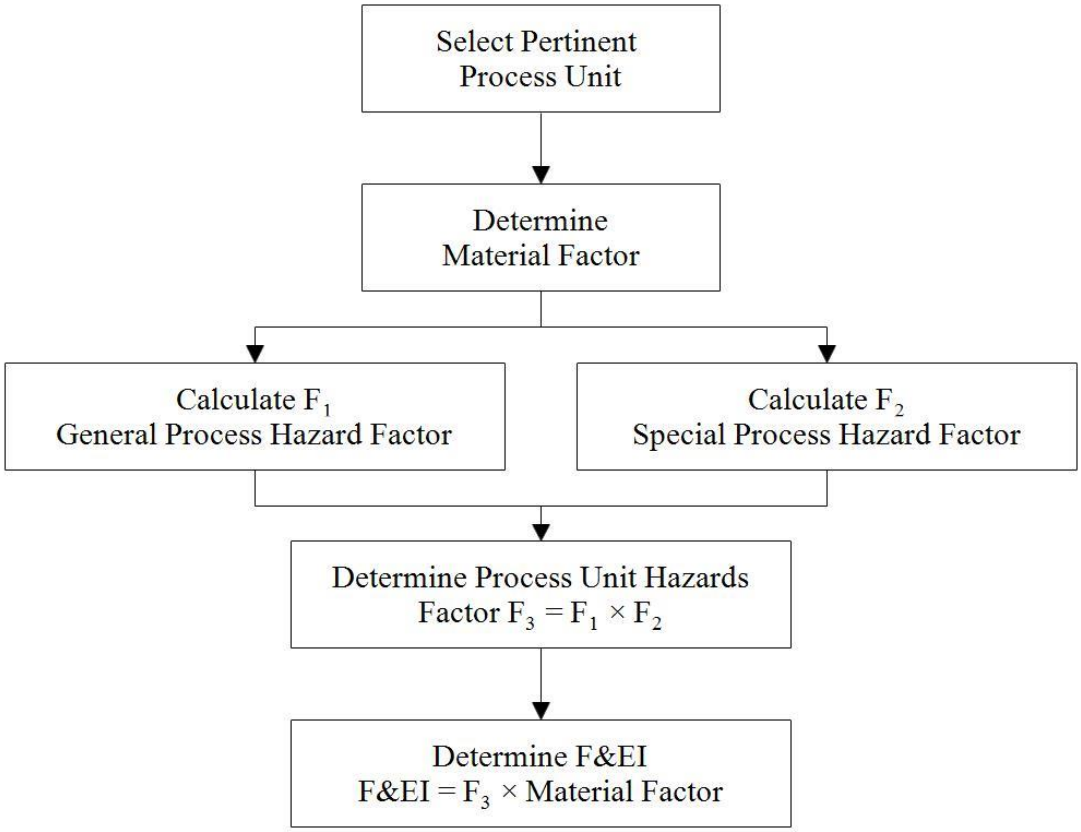


**Figure 1.** Procedure to Calculate Fire & Explosion Index (AIChE, 1994)

The second step is calculation of Material Factor (MF). MF is a measure of inherent potential of energy releasing from fire or explosion due to combustion or chemical reaction. Value of this factor can be obtained from NFPA 325M, NFPA 49, material safety data sheet or calculated manually based on flammability and instability of substances involved.

The third step is determination of the Process Unit Hazard Factor ($F_3$). In Dow's F&EI, the value of the Process Unit Hazard Factor is constituted of the General Process Hazard Factor ($F_1$) and the Special Process Hazard Factor ($F_2$):

The general process hazard factor ($F_1$) considers hazards that take primary roles when evaluating the level of loss in incident. It involves with hazards that are applicable for most of process situation, such as impact of exothermic/endothermic reaction, material handling and transfer, maintenance construction and issues related to emergency equipment. In contrast, the special process hazard factor ($F_2$) represents specific process conditions that exhibited to be primary causes for incidents. Influences of elements like toxicity, operating pressure, flammable conditions, dust explosion, corrosion, leakage and use of special equipment are assessed in the calculation.

The Process Unit Hazard Factor ($F_3$) is product of the General Process Hazard Factor ($F_1$) and the Special Process Hazard Factor ($F_2$). The final result of F&EI is calculated by following formula:

$$\mathrm{F\&EI} = \mathrm{MF} \times \mathrm{F_3}$$

Higher the value of F&EI, larger the magnitude of estimated damage once incident happens. Ranking values of F&EI to measure degree of hazard are given in the Table 1. In addition to F&EI, the Process Unit Hazard and the Material Factor Hazard can indicate severity of secondary events independently.

**Table 1.** List of Degree of Hazard for F&EI (AIChE, 1994)

| Degree of Hazard for F&EI | |
|---|---|
| F&EI Index Range | Degree of Hazard |
| 1-60 | Light |
| 61-96 | Moderate |
| 97-127 | Intermediate |
| 128-158 | Heavy |
| 159-up | Severe |

### 4.3. CORRELATION TO ECONOMIC ANALYSIS

Provided additional information, calculation of Fire & Explosion Index can be used for following risk analysis, such as property damage. The flowsheet for risk analysis is shown in Figure 2.

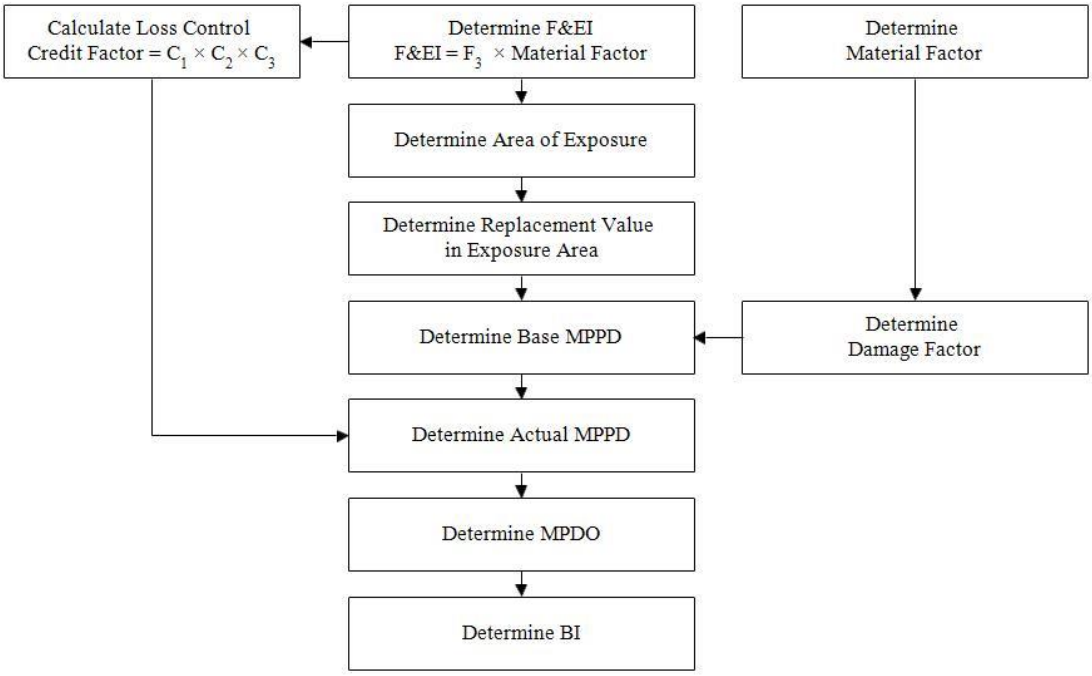


**Figure 2.** Risk Analysis Procedure (AIChE, 1994)

Three basic factors, including F&EI, the Loss Control Credit Factor, and the Damage Factor, provide support for this risk analysis. F&EI can be transformed to Radius of Exposure (R) via multiplying the F&EI factor by a factor of 0.84. Unit of this estimated radius is meter. Then, area of exposure is calculated by the equation: $\text{Area} = \pi R^2$. The Loss Control Credit Factors considers all the loss control properties and preventive measures that refrain system from severe incidents and play a role in weakening the frequency and consequence of specific scenarios. Three types of loss control properties are included in calculation: Process Control (C1), Material Isolation (C2) and Fire Protection (C3). Base on installation of related device and fulfillment of related regulation, penalties is accumulated for factors of each category. The Loss Control Credit Factor is the product of these three factors. The damage factor demonstrates the total impact of fire

and blast damage due to loss of content in a process unit. Determination of the Damage Factor is based on the Process Unit Hazard Factor ($F_3$) and the Material Factor (MF).

Once F&EI, the Loss Control Credit Factor and the Damage Factor are confirmed, provided information about expenditure on equipment, following economic loss risk analysis can be done. The Base Maximum Probable Property Damage (Base MPPD) is the product of Value of Area of Exposure and Damage Factor. This parameter represents economic loss without control feature to mitigate this loss. The Actual Maximum Probable Property Damage (Actual MPPD) is determined by multiplying Base MPPD and the Loss Control Credit Factor. The Actual MPPD represents the economic loss while adequate protective measures functioning in the incident. Another important parameter is the Maximum Probable Days Outage (MPDO) which is a significant factor in evaluating the potential Business Interruption (BI). Usually, the indirect economic loss in BI frequently equal even exceed that of property damage that directly resulted from the incident. The MPDO value is correlated with the Actual MPPD value. BI is calculated by the formula below:

$$\mathrm{BI} = \frac{\mathrm{MPDO}}{30} \times \mathrm{VPM} \times 0.70$$

In this formula, VPM represents the Value of Production for the Month, and 0.70 represents the sum of fixed costs and profits.

From description of procedure aforementioned in the Dow's Fire & Explosion Index Hazard Classification Guide, economic analysis is confined to financial loss after an incident. Correlation between safety and economic gain from production is not built. Actually, this kind of connection could be established via yield of reactions and geometry

and inventory of units, since these factors take important role in both safety assessment and process gain. In the current study, this correlation between safety and profit is constructed on the foundation of Dow's Fire & Explosion Index.

# 5. CASE STUDY I: BENZIMIDAZOLE SYNTHESIS

## 5.1. OVERVIEW

Benzimidazole derivative is an important type of intermediates in pharmaceutical industry. It is widely exhibited in a variety of pharmaceutical substance, such as proton pump inhibitors, antimicrobials, antivirals, anticancer, anti-inflammatory, hormone modulators as well as depressants, antidiabetics and so on (Bansal & Silakari, 2012). Famous drug with benzimidazole nucleus includes Omeprazole and Albendazole. Omeprazole is used to treat gastroesophageal reflux disease and peptic ulcer disease (AHFS Monographs, 2017), and Albendazole is an effective drug in treatment of various parasitic worm infestations(AHFS Monographs, 2017). The molecular structures of benzimidazole, Albendazole, and Omeprazole are shown in Figure 3.

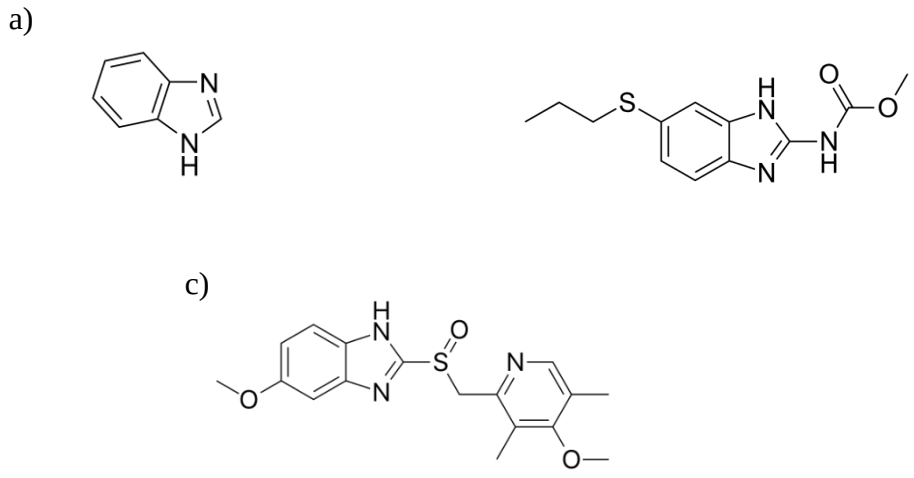


**Figure 3.** a) Molecular Structure of Benzimidazole, b) Molecular Structure of Albendazole, c) Molecular Structure of Omeprazole
(reprinted from Bansal & Silakari, 2012)

2-methyl benzimidazole is a pharmaceutical-potential substance that belongs to this benzomidazole ring system. As presented in Figure 4, the condensation of o-phenylenediamines with carboxylic acids is one of the most common synthesis route for 2-methyl benzimidazole (Patil, Ganguly, & Surana, 2008). Conditions and production comparisons of o-phenylenediamines condensation by batch vs. continuous processes are showed in Table 2 (Damm *et al*., 2009). These fundamental parameters are used for safety evaluation by Dow's F&EI in the following study.

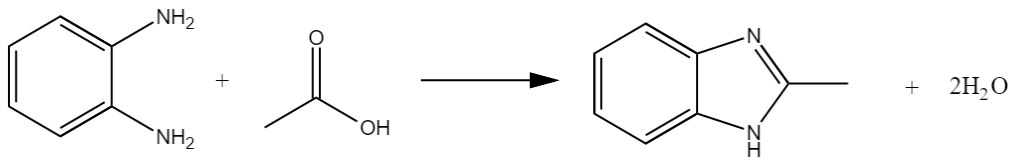


**Figure 4.** Synthesis of 2-methyl Benzimidazole by Condensation of o-phenylenediamine

**Table 2.** Production Conditions of Batch and Continuous Processes for Synthesis of 2-methyl Benzimidazole

| | Batch Process | Continuous Process |
|---|---|---|
| Temperature (°C) | 200 | 270 |
| Pressure (psi) | 145 | 1885 |
| Reaction Time (min) | 5 | 0.5 |
| Yield (%) | 98 | 94 |
| Substrate Concentration (M) | 5 | 1 |
| Reaction Volume (ml) | 1000 | 4 |

In order to concentrate on study in intrinsic differences between two processes, and simplify the hazard identification in F&EI, several assumptions are adopted:

1. The reaction mass is perfect mixed in reactors;
2. Adjunct cooling systems in both processes are in perfect performances;
3. Emergency equipment is same and in perfect performances in both processes;
4. Scalabilities of both processes are good enough that reaction conditions remain same in all scales.

## 5.2. SAFETY COMPARISON RESULT

The comparison is conducted based on material properties and process features. Related explanation is stated below.

### 5.2.1. COMPARISION OF MATERIAL

In this study, impacts from intrinsic properties of reactants are same for both processes. Material factors of all substances are listed in Table 3. According to Dow's Fire and Explosion Index Hazard Classification Guide, impact from the most hazardous material dominates the material factor of the whole process, therefore only impact from acetic acid is considered for both processes. In addition, although temperatures and composition are different in two processes and may lead to different chemical properties, these features are neglected in this part and contained in process comparison.

**Table 3.** Material Factor for Batch and Continuous Reactor

| | Batch Reactor | Continuous Reactor |
|---|---|---|
| o-phenylenediamine | 10 | 10 |
| 2-methyl Benzimidazole | 1 | 1 |
| Acetic Acid | 14 | 14 |

### 5.2.2. COMPARISON OF PROCESS

First of all, it's worth mentioning that albeit lots of distinctions exist between batch and continuous processes (see Figure 5), comparisons in this study are confined to synthesis in reactor on account of its core role in the whole process: operation mode of reactor – continuously or intermittently – determines whether the process is continuous or not from the start (see Figure 6). Therefore, the reactor is selected as the pertinent process unit without conventional unit screening procedure.

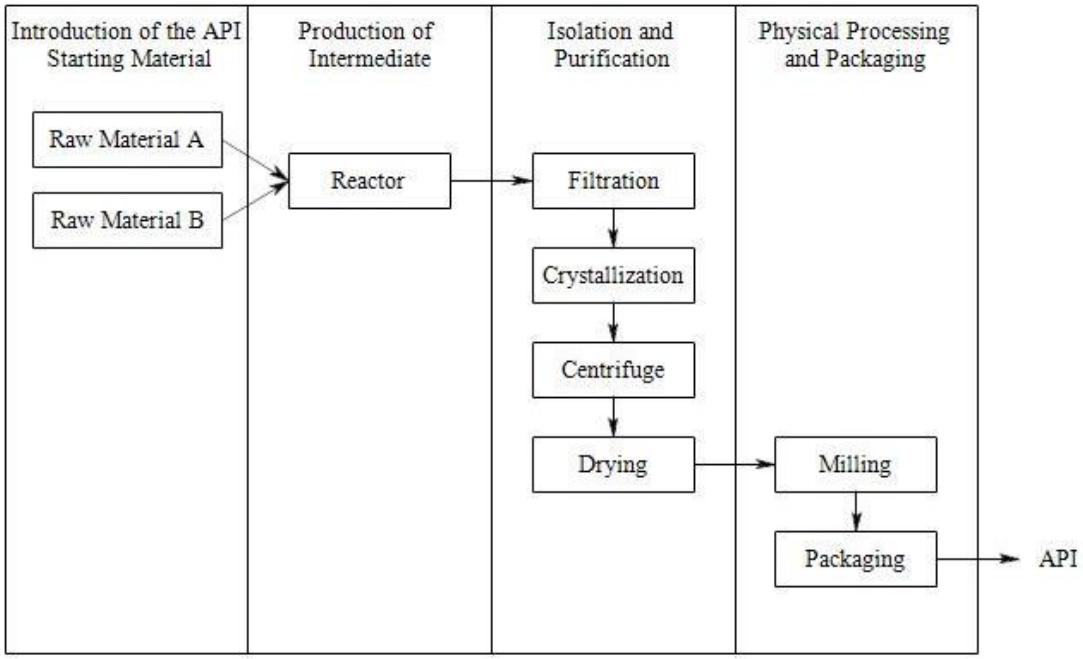


**Figure 5.** Procedure for Pharmaceutical Production (Das, 2012)

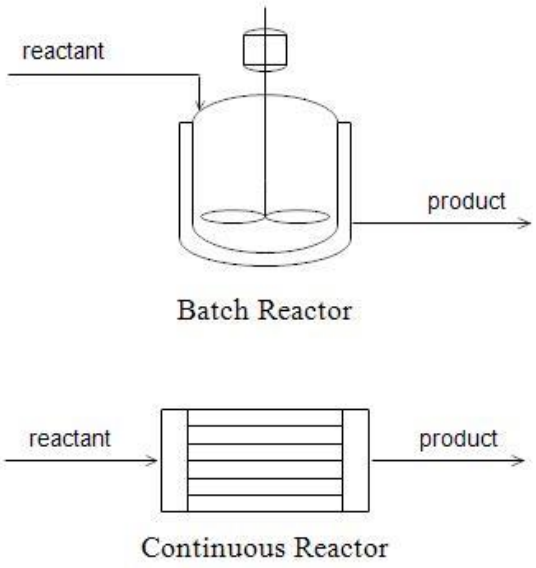


**Figure 6.** Differences in Structure between Batch and Continuous Reactors

On the foundation of safety evaluation by Dow's Fire & Explosion Index, quantitative judges between batch and continuous process are illustrated through comparison in sensitivity and productivity within safety consideration.

#### 5.2.2.1. SENSITIVITY ANALYSIS

This sensitivity analysis focus on correlation between safety level and inventory of reactor. Inventory of unit plays an important role in the safety. In addition, this sensitivity analysis can also provide supportive information for scaling up procedure.

Inventory of unit plays an important part in the safety via quantity of flammable or unstable material. This potential is considered in both the General Process Hazards (F1) and the Special Process Hazards (F2) according to Dow's F&EI Hazard Classification Guide. In general, more the flammable or unstable material, higher the risk of fire and explosion within the process. For different unit (process unit or storage unit) and different phase (liquid, gas or solid), different correlation formula between inventory and penalty is given in the Special Process Hazards (F2) part of the Dow's F&EI Guide. Moreover, other issues such as whether these materials are processed indoor or outdoor, what's the temperature to handle these materials influences the safety level as well. These questions are included in the General Process Hazards (F1) part.

In this sensitivity analysis, F&EI that combines both the general and the special process hazards is expressed as a dependent variable that changes with the variation of total inventory of reactor. Other operation conditions remain the same for different

inventory. Correlations between the F&EI and material inventory for batch and continuous process are shown in the Figure 7.

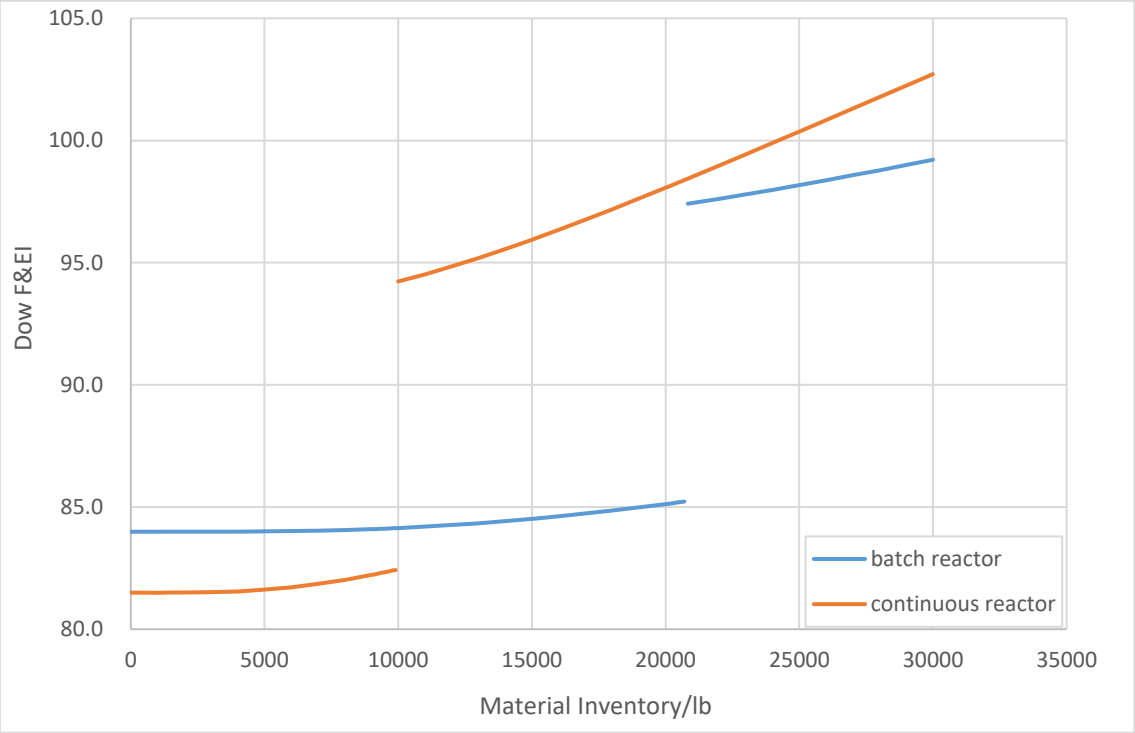


**Figure 7.** Analysis of Sensitivity to Inventory for Batch and Continuous Reactors Based on 2-methyl Benzimidazole Synthesis

Expressions of F&EI as a function of inventory for batch and continuous reactor are shown below:

For batch reactor,

If 0 lb < Inventory < 20833 lb:

$$\text{F\&EI} = 4\times10^{-9}\times(\text{Inventory/lb})^2 - 3\times10^{-5}\times(\text{Inventory/lb}) + 84.003$$

If 20833 lb < Inventory < 30000 lb:

$$F\&EI = 3\times10^{-9}\times(\text{Inventory/lb})^2 - 5\times10^{-5}\times(\text{Inventory/lb}) + 95.108$$

For continuous reactor,

If 0 lb < Inventory < 10000 lb:

$$F\&EI = 1\times10^{-8}\times(\text{Inventory/lb})^2 - 4\times10^{-5}\times(\text{Inventory/lb}) + 81.507$$

If 10000 lb < Inventory < 30000 lb:

$$F\&EI = 4\times10^{-9}\times(\text{Inventory/lb})^2 - 3\times10^{-4}\times(\text{Inventory/lb}) + 90.98$$

These formulas are generated by Microsoft Excel using the 2nd polynomial trend line. R-square values for these formulas are all greater than 0.99.

for 0 lb < Inventory < 10000 lb:

F&EI of batch reactor is slightly greater than continuous reactor. This difference mainly comes from difference in usage of stirrer and reaction pressure. Due to requirement for homogeneous mixture, stirrer is necessary in batch reactor, while such a stirrer is not needed (or not allowed) in a continuous tubular reactor. Thus, stirrer, as a hazardous rotating equipment, adds extra penalty to batch process. As for difference in pressure, higher penalty is given to continuous process for its intensified condition. From the result, influence from rotating equipment is greater than that from pressure in this case.

Another observation is that, the magnitude of the difference in the F&EI between two reactors decreases with the growing inventory. This trend stems from the increasing impact from quantity of hazardous material. When inventory approaches zero, difference in F&EI is mainly caused by stirrer and distinct pressure aforementioned. As inventory increases, influence from unstable material extends. This influence depends on composition of mixture, or more specifically, concentration of acetic acid that defines the

Material Factor (MF). Based on information of reactions, molar concentrations of acetic acid in batch and continuous reactor are 8.31M and 15.66M respectively. Thus, for similar total inventory, penalty from hazardous material in continuous reactor is greater than batch reactor.

when 10000 lb < Inventory < 20833 lb:

F&EI of continuous reactor is signally higher than batch reactor, and this difference grows along with the increasing inventory. In this range, part of influences come from rotating equipment, pressure and increasing inventory that mentioned above. More importantly, quantity of flammable and unstable liquids handled above boiling point exceeds threshold of 10,000lb for continuous reactor, therefore give a vertical rise to F&EI for continuous reactor, as shown in the Figure 7. This threshold is illustrated clearly in Dow's F&EI Hazard Classification Guide: when quantity of flammable and unstable liquids above its boiling point is less than 10,000 lb, a penalty of 0.60 is determined. A penalty of 0.90 is given when this liquids quantity above its boiling point is greater than 10,000 lb. In this case study, operation temperature of continuous reactor (270°C) is higher than boiling point of both o-phenylenediamine (257°C) and acetic acid (118°C), while operation temperature of batch reactor (200°C) merely higher than boiling point of acetic acid (118°C). Therefore, for inventory in the range of 10,000lb to 20833lb, total mass in continuous reactor is defined as unsafe, while merely acetic acid mass is defined as unsafe in the batch reactor. This divergence leads to different penalty in this range of inventory.

when 20833 lb < Inventory < 30000 lb:

F&EI of batch reactor drastically increases. However, F&EI of continuous reactor is still slightly greater than batch reactor, and the magnitude of this difference increases with the growing inventory.

This vertical rise in the F&EI of batch reactor is also caused by critical quantity of material above the boiling point. When total quantity in batch reactor goes beyond 20,833lb, quantity of flammable and unstable substance - acetic acid - also goes beyond threshold of 10,000 lb. Thus, penalty from material above boiling point is similar for both of processes.

The higher F&EI of continuous reactor originated from quantity of flammable and unstable material in this range of inventory. Since higher concentration of acetic acid is applied in continuous reactor, more proportion of substance is identified as unsafe for continuous reactor, thus higher penalty is given. This explanation is similar to that in range of low inventory (< 10,000 lb). However, unlike appearance in the low inventory range, influence from these flammable and unstable materials exceeds impact from pressure and stirrer. Therefore, continuous reactor becomes more dangerous for this range of total inventory.

It's worth mentioning that higher inventory is not considered here. Upper limit of inventory (30,000 lb) is set based on the general highest inventory of reactor used in pharmaceutical manufacturing.

Degree of hazard for batch versus continuous reactor used in this case study is shown in Table 4. In the range of inventory investigated, batch reactor is identified as moderate

hazardous for a broader range of inventory, while continuous reactor is identified as intermediate hazardous for a broader range of inventory. Even so, It's worth mentioning that the F&EI values for both reactors are in a relative safe range (F&EI > 128 indicates heavy even severe hazard).

**Table 4.** Degree of Hazard for Batch and Continuous Reactors

| Material Inventory X | Batch Reactor | Continuous Reactor |
|---|---|---|
| X < 15,152 lb | Moderate | Moderate |
| 15,152 lb < X < 20,833 lb | Moderate | Intermediate |
| 20,833 lb < X < 30,000 lb | Intermediate | Intermediate |

In summary, F&EI for both batch and continuous reactors increase as material inventory increases. Moreover, F&EI of continuous reactor is more sensitive to change of inventory comparing to batch reactor. This higher sensitivity caused by comprehensive influence from higher concentration of unstable and flammable material, higher operation temperature and higher pressure it applied.

#### 5.2.2.2. SAFETY VS. PRODUCTIVITY EVALUATION

Evaluation in this part mainly focuses on safety of batch versus continuous process base on productivity considerations. Emphasis on productivity scale of this study primary comes from flexibility required for pharmaceutical production. Pharmaceutical industry is highly supply driven. Requirement on production rate is changed according to demand of

market all the time. Therefore, better understanding on correlation between safety and productivity provides practicable support for research in process selection.

To approach this target, safety level is evaluated for the process at the same productivity capacity, as shown is Figure 8. In this part, F&EI is regarded as indicator for safety evaluation as above. Annual production is set as indicator for productivity. Related formula is shown below.

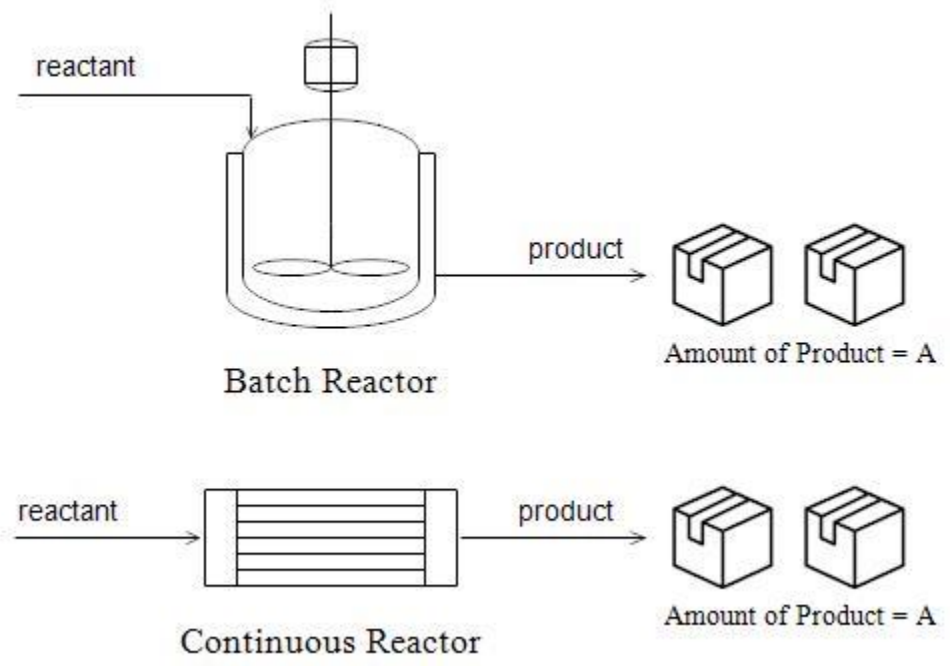


**Figure 8.** Basic Idea for Safety Comparison Based on Productivity

General calculations for productivity capacity are:

$$\text{Annual Production} = \text{Product Yield} \times \text{Annual Operation Time}$$

$$\text{Product Yield} = \text{Mass Flow of Reagent} \times \text{Conversion}$$

Mass flow is supposed to be proportional to reactor volume as set in the laboratory trial.

According to definition of fine chemical, annual production of fine chemical is limited to 1,000 tons per year (Patt *et al*., 2002). Therefore, 1,000 tons per year is set as the upper limit in this evaluation.

As for product yield and annual operation time, the former is provided in Table 3, and expression for the latter is formed referring to the normal operation time (Latexman, 2013).

Annual operation time for batch reactor is:

$$\text{Annual Operaton Time} = 300 \text{ day/yr} \times 24 \text{ hr/day}$$

Annual operation time for continuous reactor is:

$$\text{Annual Operation Time} = 8000 \text{ hr/yr}$$

Normally, in pharmaceutical industry, multi products are produced in one production line. Therefore, the same product cannot occupy the producing line for the whole year. In this study, 2-methyl benzimidazole is assumed to be produced in 2 months of one year.

In addition, circulating time in batch reactor need to be considered. According to the literature (Damm *et al*., 2009), the ratio of reaction time to total operation time for this reaction is shown below. Excepted reaction, other operations include filling, cleaning and cooling and other additional work.

$$\frac{\text{Reaction Time}}{\text{Total Operation Time}} = 0.185$$

Based on these formulas and assumptions, correlation between annual productions and F&EI is shown in the Figure 9.

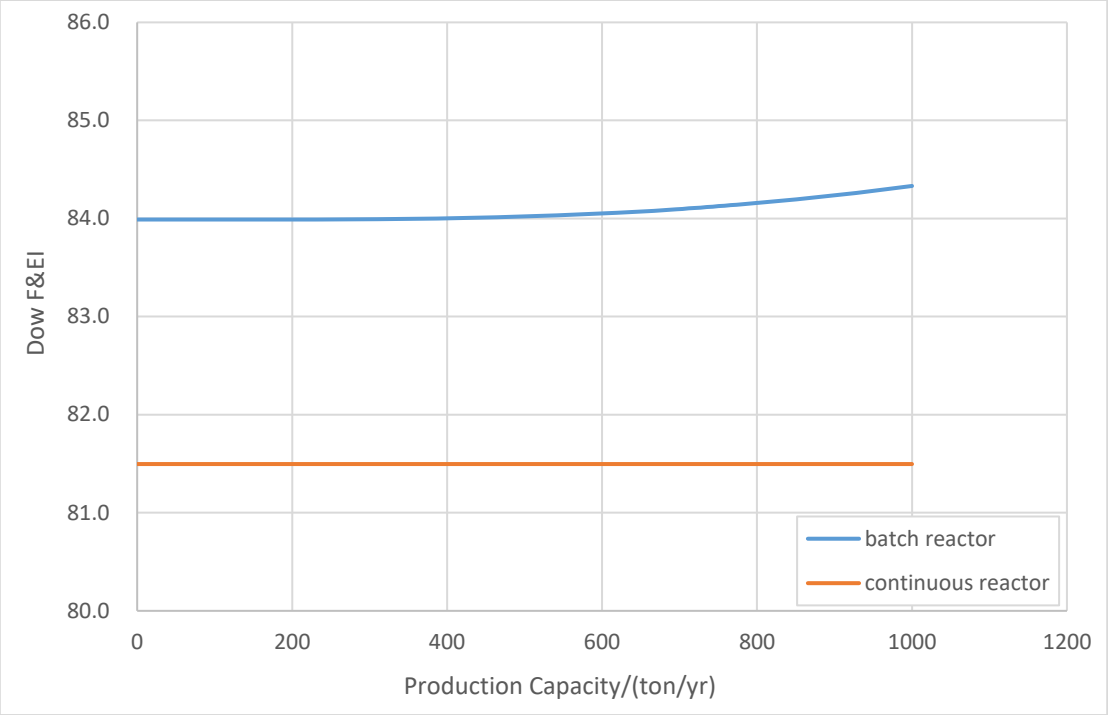


**Figure 9.** Analysis of Safety Based on Production for Batch and Continuous Reactors Based on 2-methyl Benzimidazole Synthesis

According to the Figure 9, F&EI value is constant in the range of practicable annual production (0 ~ 1000 tons per year). Plus, the F&EI for both reactors corresponds to a moderate level of hazard (61 < F&EI < 96).

This low F&EI resulted from relatively low demand for production. According to the sensitivity analysis, F&EI for both batch and continuous reactor increase as material inventory increases. Both processes could be intermediate hazardous once its inventory is higher than a specific value. However, these values are unapproachable in practical pharmaceutical manufacturing. Since demand for fine chemical, always less than 1,000 tons per year, confines scale of production.

Another observation is that, the F&EI of continuous reactor is always lower than that of batch reactor for same production. Plus, slight rise appears for batch reactor when production capacity exceeds 500 tons per year. These appearances predicate consistent superiority in safety for continuous reactor than batch reactor. Explanation is stated below:

Firstly, as stated in the sensitivity analysis, settled elements, such as operation pressure, temperature and use of rotating equipment, take major account for the difference at small-scale production. Advantages of continuous process in these aspects determine its superiority in small-scale pharmaceutical production.

Secondly, continuous reactor possesses higher space-time yield compared to batch reactor. This advantage stems from the intrinsic property of continuous operation mode - the low residence time and high flow throughput. That is to say, it costs fewer time and lower inventory for continuous reactor to produce same amount of product than batch reactor. These benefits in production efficiency influence safety level indirectly but significantly: Smaller inventory means fewer unstable materials in process, and shorter operation time means less chance to fail. This point is not considered in separate safety evaluation, but can be clearly illustrated by correlation between production capacity and F&EI. In this case, when demand on production growing, demand on inventory grows faster for batch reactor than continuous reactor. This faster rise in inventory lead to faster rise in amount of unstable material in process so as to the faster rise in F&EI value. It explains why slight rise appears for batch reactor when production capacity exceeds 500 tons per year.

In fact, the comparable batch and continuous reactor are rarely at the same level of volume. Referring to literature, for commercial production of fine chemical, the volumes of continuous reactor are usually in a range of 0.1 to 3 liter, while the volume of batch reactor is usually around the range of 2 to 10 cubic meters (Hessel *et al*., 2012). For this case, based on assumption of same annual production, as presented in Figure 10, the ratio of batch reactor inventory and continuous reactor inventory is as much as one hundred.

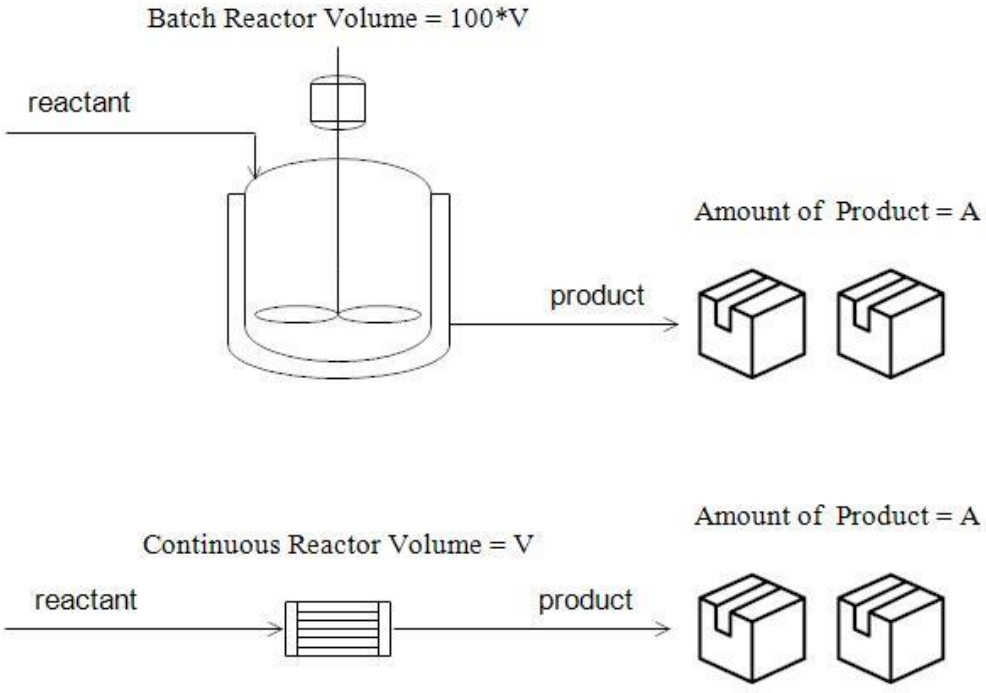


**Figure 10.** Comparison in Reactor Volume between Batch and Continuous Process for Equal Amount in Production

# 6. CASE STUDY II: OXIDATION WITH HYDROGEN PEROXIDE

## 6.1. OVERVIEW

Hydrogen peroxide is one kind of widely used oxidation agent in pharmaceutical production. Typical reaction involving hydrogen peroxide includes Baeyer–Villiger oxidations for synthesis of lactone (Gutmann *et al*., 2015), N-oxidation of alkyl pyridine for synthesis of alkyl pyridine N-oxidant (Pineda-Solano *et al*., 2012) and benzylic hydro-peroxide rearrangement for synthesis of Brivanib alaninate (LaPorte *et al*., 2014).

This common oxidation agent is also used in production of peracetic acid. As shown in Figure 11, peracetic acid is produced via oxidation of acetic acid by hydrogen peroxide with sulfuric acid as the catalyst. Conditions for peracetic acid production by batch vs. continuous process are showed in Table 5 (Fatemeh Ebrahimi, Kolehmainen, & Turunen, 2009).

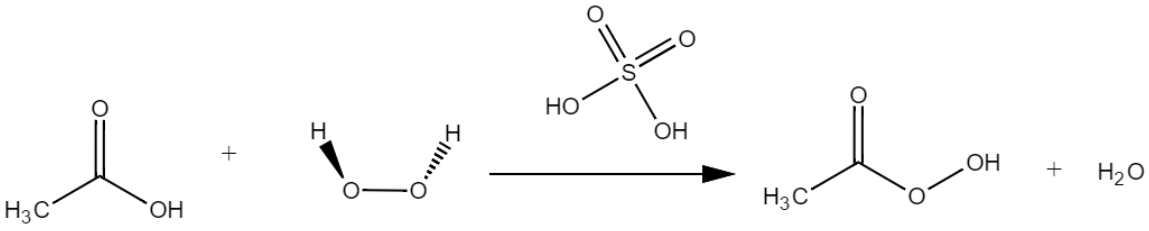


**Figure 11.** Synthesis of Peracetic Acid by Oxidation of Acetic Acid

**Table 5.** Production Conditions of Batch and Continuous Process for Synthesis of Peracetic Acid

| | Batch Process | Continuous Process |
|---|---|---|
| Temperature (°C) | 60 | 80 |
| Pressure (psi) | 14.5 | 14.5 |
| Reaction Time (min) | 30 | 15 |
| Yield (kg/h) | 170 | 20 |
| Acetic Acid Concentration (M) | 7.3 | 7.3 |
| Reaction Volume (L) | 4000 | 10 |

Assumption for this case study is listed below:

1. The reaction mass is perfect mixed in reactors.
2. Since the temperature for decomposition of hydrogen peroxide in peracetic acid synthesis reaction is higher than 120 °C (Kadla & Chang, 2001), which is larger than operation temperature for both processes in the case study, decomposition of hydrogen peroxide is assumed to be inexistent.
3. Sulfuric acid is dissociated completely to $H^+$ and $HSO_4^-$, in addition, concentration of $H^+$ is assumed to be constant of 0.67 mol/L during the reactions for both processes.
4. Influence from sulfuric acid is not considered in safety evaluation.
5. Emergency equipment and cooling system are perfectly performed for both of processes.

6. Scalabilities of both processes are good enough that reaction conditions remain same in all scales.

## 6.2. SAFETY COMPARISON RESULT

The comparison is conducted based on material property and process feature. Related explanations are stated in the following paragraph.

### 6.2.1. COMPARISON OF MATERIAL

In this case, impact from material within the reactor is same for both of processes. Material factors for reactants involved are listed in Table 6. According to Dow's Fire and Explosion Index Hazard Classification Guide, influence from the most hazardous material dominates the material factor. Although material factor values are same for hydrogen peroxide and peracetic acid, since concentration of hydrogen peroxide is higher than peracetic acid, hydrogen peroxide is chosen to be the dominant material. Therefore, only impact from hydrogen peroxide is considered for both processes. Change on substances' property from temperatures are neglected in this part and reconsidered in process comparison.

**Table 6.** Material Factor for Batch and Continuous Reactor

| | Batch Reactor | Continuous Reactor |
|---|---|---|
| Acetic Acid | 14 | 14 |
| Hydrogen Peroxide | 24 | 24 |
| Peracetic Acid | 24 | 24 |

### 6.2.2. COMPARISON OF PROCESS

The major difference between these two production processes come from distinctions in reaction conditions and reactor constructions. These differences are shown in Table 5 and Figure 6. Based on safety evaluation by Dow's Fire & Explosion Index, quantitative judges between batch and continuous process are illustrated through comparison in sensitivity and productivity within safety consideration.

#### 6.2.2.1. SENSITIVITY ANALYSIS

Procedure for sensitivity comparison is the same as the first case study. Correlations between the F&EI and material inventory for batch and continuous process are shown in the Figure 12.

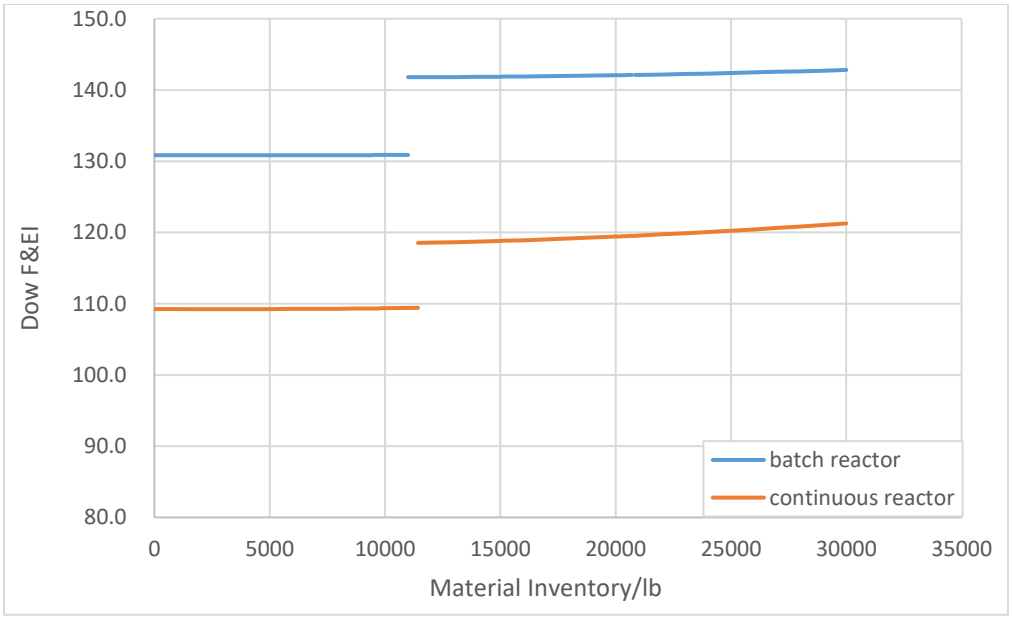


**Figure 12.** Analysis of Sensitivity to Inventory for Batch and Continuous Reactors Based on Peracetic Acid Synthesis

Expressions of F&EI as a function of inventory for batch and continuous reactor are shown below:

For batch reactor,

If 0 lb < Inventory < 11000 lb:

$$\text{F\&EI} = 4\times10^{-10}\times(\text{Inventory/lb})^2 - 2\times10^{-6}\times(\text{Inventory/lb}) + 130.85$$

If 11000 lb < Inventory < 30000 lb:

$$\text{F\&EI} = 2\times10^{-9}\times(\text{Inventory/lb})^2 - 4\times10^{-5}\times(\text{Inventory/lb}) + 141.95$$

For continuous reactor,

If 0 lb < Inventory < 11430 lb:

$$\text{F\&EI} = 2\times10^{-9}\times(\text{Inventory/lb})^2 - 1\times10^{-5}\times(\text{Inventory/lb}) + 109.25$$

If 11430 lb < Inventory < 30000 lb:

$$\text{F\&EI} = 4\times10^{-9}\times(\text{Inventory/lb})^2 - 4\times10^{-5}\times(\text{Inventory/lb}) + 118.35$$

These formulas are generated by Microsoft Excel using the 2nd polynomial trend line. R-square value for these formulas are all greater than 0.99.

for 0 lb < Inventory < 11000 lb:

F&EI of batch reactor is larger than continuous reactor. This difference is almost caused by usage of stirrer in batch reactor. Application of such a rotating equipment increases penalty for batch process.

when 11000 lb < Inventory < 11430 lb:

F&EI of batch reactor is still higher than continuous reactor, but this difference grows drastically due to the sharp transition in F&EI of batch reactor. This transitions is caused

by quantity of flammable liquids that handled above flashing point exceeds threshold of 10,000lb. This threshold is illustrated clearly in Dow's F&EI Hazard Classification Guide: when quantity of flammable liquids above their flashing point is less than 10,000 lb, a penalty of 0.30 is determined. A penalty of 0.45 will be given when this quantity of flammable liquids above their flashing point is larger than 10,000 lb. For peracetic acid production, operation temperature for batch reactor (60°C) and continuous reactor (80°C) is higher than flashing point of both acetic acid (39°C) and peracetic acid(40.5°C). Therefore, the value of inventory for higher penalty is determined by compositions of peracetic acid and acetic acid in reactors. Since concentrations of these two materials is slightly higher for batch comparing to continuous reactor, batch reactor approaches this transition in F&EI at a smaller total inventory.

when 11430 lb < Inventory < 30000 lb:

F&EI of continuous reactor exceed the transition caused by quantity of unsafe material above flashing point. However, it is still lower than F&EI of batch reactor.

Compared to the first case study, value of slope for both processes is similar low. It results in the consistent superiority of continuous reactor in safety level compared to batch reactor. This similarity in slopes comes from similarity in operation conditions. Differences only appear in operation temperature and hydrogen peroxide concentration. These differences are not such significant that lead to huge divergence between slopes. Thus, difference in F&EI value between two reactors does not change along with increasing inventory.

Degree of hazard of this case study is exhibited in Table 7. Although marked transitions appears for both reactor, safety levels for two reactors do not change based on scaling up of reactor size. The safety levels are majorly decided by settled parameters, such as operation pressure and usage of stirrer. These parameters do not change with inventory as variable. Hence, inventory does not play a significant role in judgement on degree of hazard.

**Table 7.** Degree of Hazard for Batch and Continuous Reactors

| Reactor Type | Batch Reactor | Continuous Reactor |
|---|---|---|
| Degree of Hazard | Heavy | Intermediate |

In sum, F&EI for both batch and continuous reactor increase as material inventory increases due to the increases of quantity above flashing point. However, since operation conditions are relatively mild and similar for these two reactors, both reactor do not exhibit high sensitivity when inventory is growing gradually.

#### 6.2.2.2. SAFETY VS. PRODUCTIVITY EVALUATION

For evaluation based upon productivity, assumption for practical production are set as following:

1. Confined by the conversion of this reaction route and volume of reactor, upper limit for annual production is settled to be 580 tons per year.

2. Same as the first case study, referring to normal operation time for this two operation mode(Latexman, 2013), annual operation time for batch reactor is 8760 hour per day, and annual operation time for continuous reactor is 8000 hour per day.
3. Peracetic acid is assumed to be produced for 2 months in one year.
4. According to the literature (Ebrahimi *et al*., 2009, Ebrahimi *et al*., 2011), the ratio of reaction time to total operation time for this reaction is :

$$\frac{\text{Reaction Time}}{\text{Total Operation Time}} = 0.143$$

Based upon these formulas and assumptions, correlation between annual productions and F&EI is shown in the Figure 13.

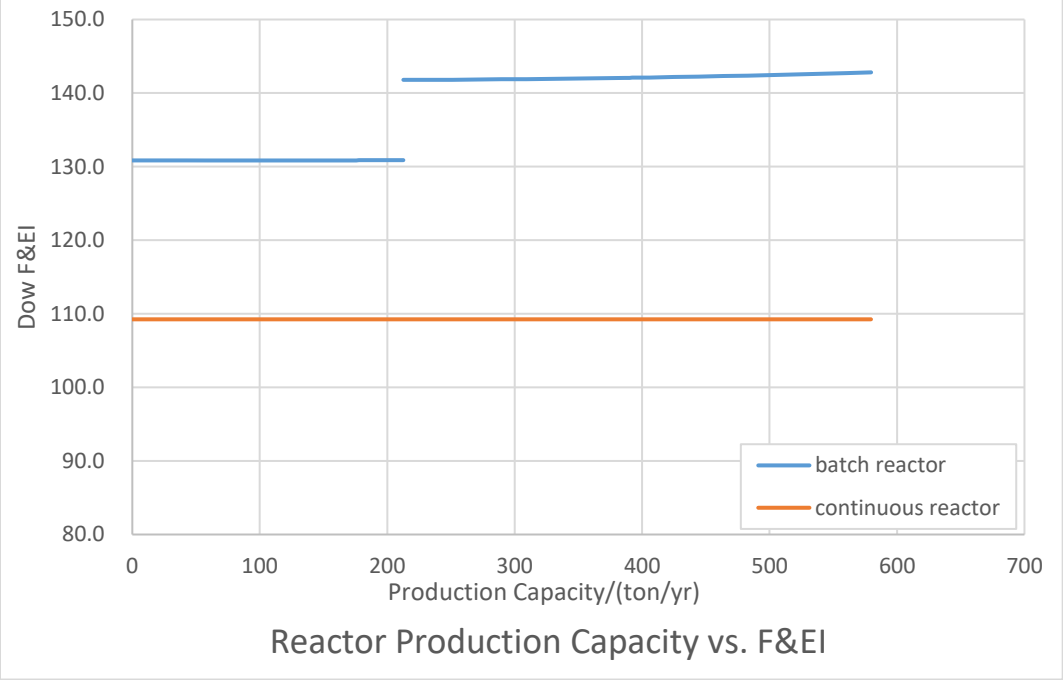


**Figure 13.** Analysis of Safety Based on Production for Batch and Continuous Reactors Based on Peracetic Acid Synthesis

According to the Figure 13, F&EI is stabilized at 109 in the range of practicable annual production for continuous reactor. For batch reactor, the F&EI value rise drastically when the annual production is higher than 220 tons per year.

For the batch production mode, relatively low production efficiency leads to substantial increase in reactor volume when demand on production grows. This increase in reactor volume is so significant that exceed the threshold for large quantity of flammable and unstable material above flashing point. Therefore, the F&EI value jump from 131 to 143 when the annual production is higher than 220 tons per year.

For continuous production mode, high production efficiency causes only a few change in volume hence only few change in F&EI in as well. This difference in F&EI between batch and continuous reactor means that, to produce the same amount of peracetic acid in the given period, the volume of continuous reactor is much smaller than batch reactor.

# 7. RESULT SUMMARY

Figure 14 represents the comparisons of two case studies. The X-axis represents two different case studies, and the Y-axis represents the average Dow's F&EI value which can be used to define the degree of hazard.

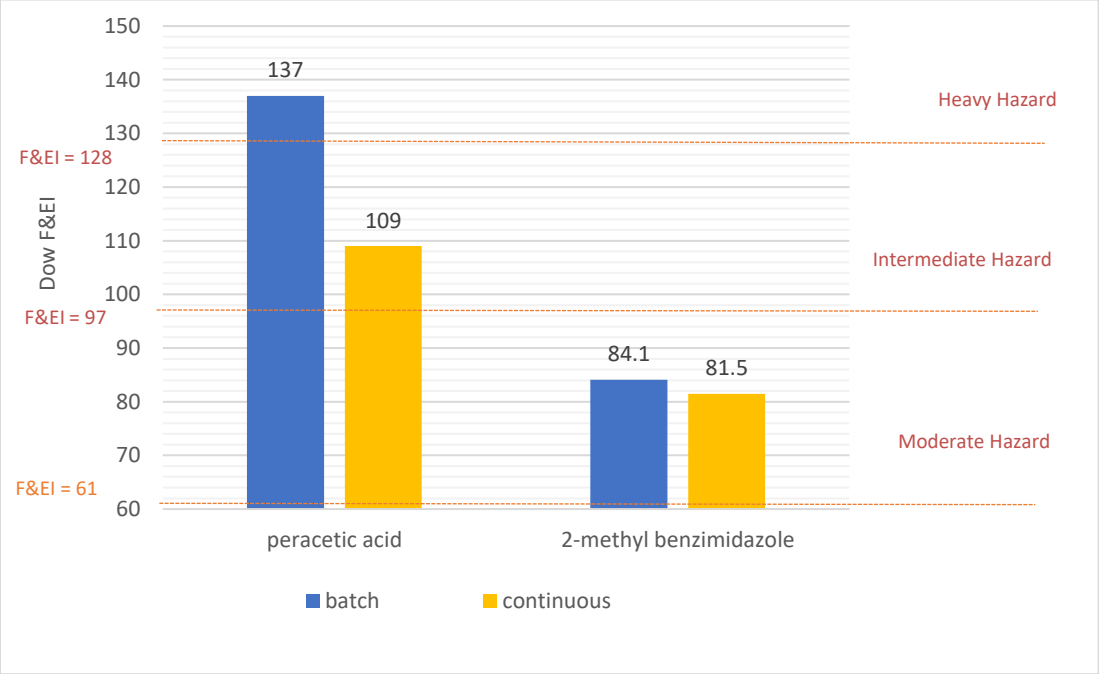


**Figure 14.** Comparison of Safety Level by Batch and Continuous Productions for Two Case Studies

Regardless of the reactor type, the safety level is predetermined by properties of the synthesis reaction. Although distinctions in F&EI appear when using different reactors for both cases, peracetic acid production is generally more hazardous than 2-methyl benzimidazole production, no matter which reactor it uses. This higher level of danger

comes from the intrinsic properties, which consist of the flammability and reactivity of the chemicals involved in the synthesis of peracetic acid.

Taking batch and continuous reactors into consideration, distinction in F&EI comes from the differences in operation conditions and production efficiency. These varying factors such as temperature, pressure, and yield do not influence F&EI as individual factors. Instead, they are correlated and impact the F&EI as an ensemble. Difference in these ensembles decides the variance in F&EI value between reactors, then determines to which extent the selection of reactor can make a difference. For this study, the variance in F&EI value between batch and continuous reactor is greater for peracetic acid production (variance in F&EI = 28) than 2-methyl benzimidazole production (variance in F&EI = 2.6). Therefore, selecting a reactor is more important for peracetic acid comparing to 2-methyl benzimidazole production.

The importance of choosing a reactor is different for the two cases, the F&EI value for a continuous reactor is lower than a batch reactor for both cases. This consistency exhibits the superiority of a continuous reactor in safety.

# 8. CONCLUSION

A comprehensive comparison between the batch and continuous process used in the pharmaceutical industry based upon Dow's F&EI is made in this study. Two typical pharmaceutical productions, the production of 2-methyl benzimidazole and the production of peracetic acid are analyzed. Safety levels for batch and continuous reactors are compared based on both inventory and annual production being used as variables. The conclusions on the foundation of these two case studies are stated below:

1. The comparison of batch versus continuous processes in the pharmaceutical industry is complex. It's determined by reaction properties, operation conditions, structures of equipment, production efficiency, scale of production, and many other factors. To get a conclusive comparison between these two production modes, more systematic studies based on the integrated batch and continuous process need to be conducted for safety consideration.
2. Just focusing on the reactor in which part of API synthesis occurs, the continuous reactor is more sensitive to inventory in general. The magnitude of this sensitivity is determined by operation conditions such as operation temperature, operation pressure and concentration of hazardous material. This sensitivity to inventory might lead to problems for continuous production in a relatively large scale.
3. However, when considering practical pharmaceutical production, which is always in a small scale (no larger than 1000 tons per year), hazardous large-volume continuous reactor is not necessary. In addition, the space time yield of continuous production

mode is usually higher than the batch production mode, application of a continuous reactor is relatively safer when compared to batch reactors.

# 9. FUTURE WORK

This work is a preliminary attempt to use Dow's F&EI in comparative study for pharmaceutical processes. Based on the challenges faced during this study, several opportunities can to be explored to continue the development in comparing the batch and continuous process:

1. This research only studies the separate reactor with potential fire, explosion, and reactivity incidents. To get a more comprehensive comparison, which should be made for the whole process and considers all kinds of potential risks, the hazard and operability studies (HAZOP) are necessary for both batch and continuous pharmaceutical processes.
2. For both case studies, abrupt transitions appear in F&EI that correspond to gradually changing inventory. In fact, these abrupt transitions are not reasonable and cannot be explained by the real production. Therefore, to get a more accurate evaluation in sensitivity, more data surrounding the transition points needs to be collected to understand the real situations at the critical points.
3. Dow's F&EI primarily focuses on the large scale bulk chemical and petrochemical productions. Its objectives determine that this methodology is relatively insusceptible in evaluation of pharmaceutical processes with low scale. For further studies in comparisons between batch and continuous process within the pharmaceutical industry, modifications in judgement of Dow's F&EI are necessary. These adjustments can make the comparison results more accurate and reasonable.

4. The Dow's F&EI evaluation is on the foundation of the most hazardous normal operation state. It attempts to determine the maximum loss for the given process. Therefore, only consequence analysis is covered by this methodology. More information on frequency analysis needs to be combined in the future work for an integrative risk assessment.

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