Towards a Machine-Learning-Based Application for Identification of Amorphous Drug Forms

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***Abstract*—The amorphous drug structure represents an important feature to be reached in the pharmaceutical field due to its possibility of increasing drug solubility, considering that at least 40% of commercially available crystalline drugs are poorly soluble in water. However, it is known that the amorphous local structure can vary depending on the amorphization technique used. Therefore, recognizing such variations related to a specific amorphization technique through the pair distribution function (PDF) method, for example, is an important tool for drug characterization concerns. This work presents a method to classify amorphous drugs according to their amorphization techniques and related to the local structure variations using machine learning. We used experimental PDF patterns obtained from low-energy X-rays scattering data to extract information and expanded the data through the Monte Carlo method to create a synthetic dataset. Then, we proposed the evaluation of such a technique using a Deep Neural Network. Based on the results obtained, it is suggested that the proposed technique is suitable for the amorphization technique and local structure recognition task.**

Link to graphical and video abstracts, and to code: https://latamt.ieeer9.org/index.php/transactions/article/view/8988

***Index Terms*—drug amorphization, monte-carlo method, deep neural networks**

I. Introduction

Active Pharmaceutical Ingredients (API) for drug formulations production are usually used in their crystalline states due to the physicochemical stability of these structures [1]. However, a frequently faced issue is the low solubility of many crystalline drugs, which can impair their bioavailability in the body [2]. Therefore, the approach that can be used to overcome this problem is to turn the crystalline structures into their amorphous phases, which have a higher internal energy and can increase the solubility of drugs. The absence of a long-range three-dimensional structural order characterizes the amorphous structure. However, local organizations (short and medium range) may exist [3], which generally results in global structure disorder.

The complexity of such amorphous structures makes their characterization challenging, primarily when the conventional X-ray powder diffraction technique is used due to the broadening peaks and the loss of information about the global molecular packing. Therefore, one way to deal with the limitation of structural analysis related to the conventional technique is to use the pair distribution function (PDF) method. This analysis tool has been used, mainly in the last decade, to describe local ordering in amorphous drug structures. This method allows the identification of distances between atomic pairs (atomic bonds), providing an intra- and intermolecular "fingerprint" of the local structure and can be applied in the characterization of amorphous, nano, and crystalline materials [4]. In a typical PDF pattern, the x-axis represents the distance between atomic pairs in the structure, and the peak integrated intensity can provide information about the coordination of that pair. Fig. 1 displays an example of a PDF for a crystalline drug, wherein correlation distances below 4.5 Å usually represent intramolecular distances, and above this value, the distances represent intra plus inter and intermolecular atomic pairs correlations.

There are several methods to reach the amorphous state from a crystalline drug sample, such as solvent evaporation, melt-cooling, spray drying, and milling, among others, leading to different local structure ordering for the same chemical compound. In a recent work, Martins et al. [5] demonstrated the influence of spray drying, melt-cooling, and mechanical milling processes in obtaining amorphous structures of the drug hydrochlorothiazide. In that case, the authors, in addition to demonstrating the occurrence of local amorphous structure variation, also demonstrated the direct interconversion between amorphous of the aforementioned drug, with different physical and thermal stabilities, as well as their relaxation behaviors. Therefore, advanced methods and features should be developed and applied in order to characterize amorphous drugs, considering their impact on physical and chemical properties.

Herein, a machine-learning-based feature was developed to identify, within a single chemical compound, those that exhibit different structural conformations due to the amortization process. After those processes, PDF patterns are obtained with X-ray total scattering data. It is important to emphasize that the goal of the present work is to use PDF patterns of crystalline and amorphous samples that have already been characterized elsewhere [6], [7], i.e., our focus is the validation of our algorithm on PDF patterns recognition.

II. Related Works

The introductory section of this work highlighted that variations can be present in the local structure of amorphous drugs depending on the amorphization technique used and also the necessity of advanced methods to characterize and identify

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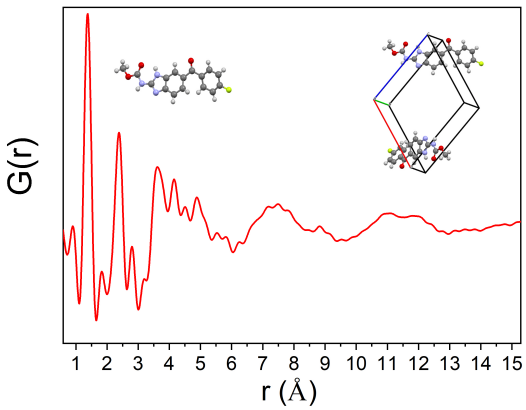

Fig. 1. Pair Distribution Function pattern for a crystalline drug.

such complex structures. In that regard, machine learning features explored in several fields are stated as an important tool that can be used, for example, to recognize the drug amorphization method based on the local structure. In this section, we explore the novel technologies created towards this end. Given their objectives or methods, we explored the literature that describes similar works.

In the work proposed by Jiang et al. [8] they experimented with several machine learning techniques to predict the glass-forming ability (GFA) from 171 drugs. These authors evaluated Support Vector Machines (SVM), XGBoost, and Random Forest (RF) in two different forms to attribute a GFA score to these drugs. Furthermore, they explored which variables contributed the most to this score.

In another work, Jiang et al. [9] used a similar methodology to classify the amorphization and chemical stability of 760 formulations containing 49 APIs using hot-melt extrusion (HME) as the amorphization method. The authors employed models and data of different natures than this work to perform their classification.

In a previous work, Alhalaweh et al. [10] performed the predictions of the glass-forming ability and crystallization tendency of drug molecules. Their approach uses a support vector machine (SVM) to perform both classification methods. The usage of classical machine learning methods differs from our neural network approach, as does the nature of the evaluated data.

Fink et al. [11] evaluated using several classic machine-learning models to predict the formation of co-amorphous systems. They used XGBoost, Random Forest, SVM, and KNN classifiers to evaluate a set of descriptor variables. Therefore, this work uses different methods and data concerning a different nature to evaluate their desired outcome.

Nguyen et al. [12] proposed an arbitrary machine-learning model to predict the solubility of amorphous drugs. They used two variables obtained from their experiments to predict the desired feature. The authors produced a regression model, while this work approaches a classification model. Also, the nature of the input data is very different from the one proposed in this work.

Our work differs from their approach as we study the usage of Neural Networks aiming to identify and classify the amorphization method and the local structure of the amorphous phase among different PDF patterns provided, yielding a type of search-and-match features for classification. This approach displays some related works concerning the usage of machine learning in the context of drug amorphization. The preliminary analysis suggests that this work differs from previously published material in several aspects. This overview suggests the novelty of this work, given the possibility of working with machine learning within the context of drug amorphization and the novel approach herein presented.

III. Materials and Methods

These experiments' availability requires using several PDF patterns for different samples. However, for initial test concerns, we started by evaluating a synthetic dataset generated from three different experimental PDF patterns obtained by us. Initially, as a proof-of-concept, we evaluated the flubendazole (FBZ) drug used to treat gastrointestinal nematode infections [13]. For this purpose, we obtained three PDF patterns of this drug, one for its crystalline form and the other patterns for the amorphized FBZ obtained by ball-milling and evaporation methods.

The ball-milling amorphous sample was characterized in the work proposed by Bezzon and co-workers (2022) [7], wherein PDF and Reverse Monte Carlo (RMC) methods were used to describe the amorphized structure of FBZ fully. In that work, the FBZ crystal structure for the crystalline sample was also analyzed using the PDF method, including the adjustment between the measured and calculated patterns indicating the crystalline nature of the precursor sample.

In the evaporation sample, the FBZ was incorporated in a polymeric matrix, both in the amorphous state, wherein the final sample was obtained through the solvent-evaporation technique. Thus, the PDF from the solvent-evaporation technique represents a more complex case for the identification by our algorithm. This sample that comprises amorphous FBZ in a hydroxypropyl methylcellulose matrix was analyzed in the work proposed by Bezzon et al. (2021) [6] using X-ray total scattering and derivative differential PDF, evidencing the amorphous nature of the sample. The methodologies used to obtain the sample, as well as the PDF patterns, are entirely described in the above-mentioned works.

Fig. 2 shows the experimental PDF patterns for each sample. The blue line is the PDF acquired for the crystalline form, the green line displays the PDF obtained from the ball-milling process (amorphous state), and the red line is the PDF achieved from the evaporation process (amorphous state).

From these data, we created a synthetic dataset using these patterns as baselines. We employed the Monte Carlo method to produce 2000 samples for each class. According to Harrison [14], the monte-carlo simulation has no unique shape but requires a set of steps:

- Defining a probability function;
- Sampling the data;
- Compute the sampling data.

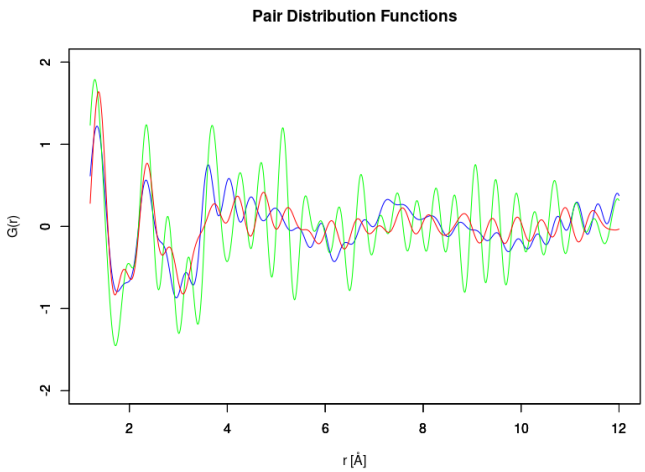

Fig. 2. Pair Distribution Functions patterns for crystalline (blue line), amorphous through ball-milling (green line), and amorphous through evaporation (red line) samples.

A. Synthetic Dataset using Monte-Carlo Method

We developed our work according to the perspective proposed by Harrison [14], which is specified as follow.

- **Defining a probability function:** Our goal was to insert white noise to each distribution, considering that the result may be affected by several aspects during the experimental stage. For this matter, the selected noise is sampled by a *uniform distribution*.
- **Sampling the data:** In this stage, we intended to generate a noised PDF pattern instance resembling the original one. For this matter, each i-th instance of $G(r_i)$ value on the original data, we sampled an uniform distributed factor f_i within the interval $f \in [0.6, 1.4]$.
- **Compute the sampling data:** After sampling the data from the uniform distribution, we employed the sampled factor f_i individually obtained for each i-th value of $G(r_i)$. With this method, we generated a noised instance $\hat{G}(r_i) = f_i \times G(r_i), \forall i \in [0, i_{max}]$. This method describes how to create a single $\hat{G}(r)$ noised distribution from the original sample. We repeated this process 2000 times for each class, generating a balanced synthetic dataset with 6000 samples. Fig. 3 displays the noise distribution obtained for each sample.

The produced dataset contains 6000 samples, where 2000 belong to each class. For training purposes, we separated our dataset among three different sets: training, validation, and test. The separation among the three classes initially shuffled the samples from the dataset. Then, as this approach is novel, we established an initial baseline for separation. Therefore, we separated 70% of the produced samples for training, 15% for validation, and 15% for testing. As the sampling is random, this process was repeated after all testing to ensure the results repeatability.

B. Deep Neural Network (DNN) model

In this approach, we suggested the use of a deep neural network as the model for classifying the sample into three categories: crystalline, amorphized by the ball-milling method, and amorphized by the solvent-evaporation method. We employed the synthesized dataset created using the Monte-Carlo method, according to the aforementioned rules. As stated in Section II, this approach's novelty also comes from the employed techniques.

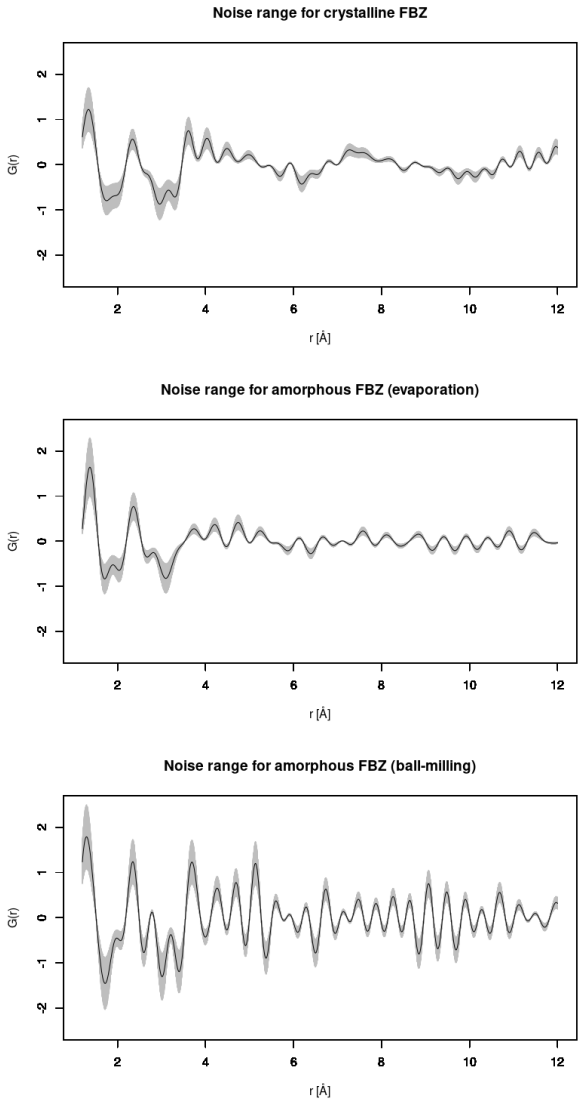

Fig. 3. Noise distribution obtained for each sample. The gray shadow was obtained from the samples of the synthetic dataset. The solid black line represents the original experimental samples. The first subplot displays this data for the crystalline FBZ, the second for the amorphized by evaporation, and the third for the amorphized by ball-milling.

We tackled the issue with a straightforward DNN model, consisting of three hidden layers. The input layer receives the 1081 values from the PDF pattern for each amorphization technique. We then utilized three fully-connected (dense) layers, each with 16 neurons, employing the *ReLu*. The classification is performed using a three-neuron output layer with the *Softmax* activation function. The final output predicts the input sample's category for each of the three presented methods. Figure 4 provides a visual representation of the

proposed architecture.

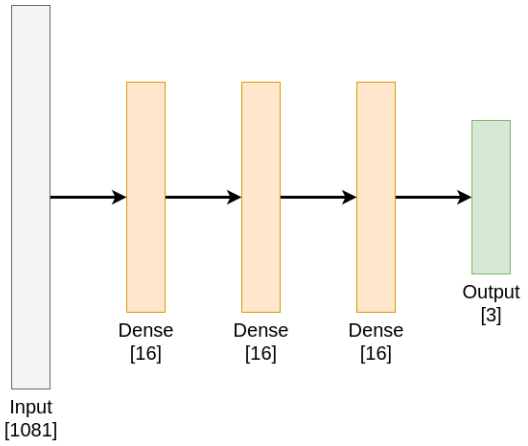

Fig. 4. Illustration of the DNN Architecture.

This architecture was selected for its simplicity and ease of implementation. We utilized the Tensorflow/Keras framework to develop and train the proposed model. The optimizer function employed in this case was ADAM, with a learning rate of 1×10^{-5}. The loss function used in this task is the categorical cross entropy. The learning rate is dynamically adjusted, reducing if the validation loss reaches a plateau for ten epochs. Finally, the training runs for a maximum of 2000 epochs, with an early-stopping mechanism configured for a plateau of 20 epochs, ensuring the model's reliability and accuracy.

C. Evaluation Metrics

The evaluation of a machine-learning model uses a set of known metrics. One of these metrics is global accuracy, which indicates the number of correctly predicted samples. Nevertheless, this evaluation requires further metrics to study the number of false positives and false negatives. Therefore, we use *Precision*, *Recall*, and the *F1-Score* as evaluation methods [15].

$$Precision = \frac{TP}{TP + FP} \tag{1}$$

$$Recall = \frac{TP}{TP + FN} \tag{2}$$

$$F1\text{-}Score = 2 \times \frac{Precision \times Recall}{Precision + Recall} \tag{3}$$

In this context, the term "true positive" (TP) refers to samples successfully classified as belonging to the positive class by the classifier. Similarly, "true negative" (TN) denotes the samples correctly classified as belonging to the negative class. A "false positive" (FP) occurs when the classifier wrongly classifies the model as belonging to the positive class. At the same time, a "false negative" (FN) occurs when the model is incorrectly categorized as belonging to the negative class. Additionally, we employed the confusion matrix as the ultimate evaluation metric on the test dataset. This matrix presents the allocation of accurate and inaccurate categorizations for each class.

IV. Results

The previous section presented the methods used in this work and the evaluation methods produced. This section discusses the obtained results. Initially, we evaluate the model training. Then, we discuss the metrics regarding the classification model.

A. Model Training

We separated our dataset into three different sets: Training, validation, and test. We separated 70% of the produced samples for the training dataset, 15% for validation, and 15% for the test set. Our training happened according to the parameters established in Section III. Initially, we evaluate the evolution of the training and validation loss and accuracy, presented in Fig. 5.

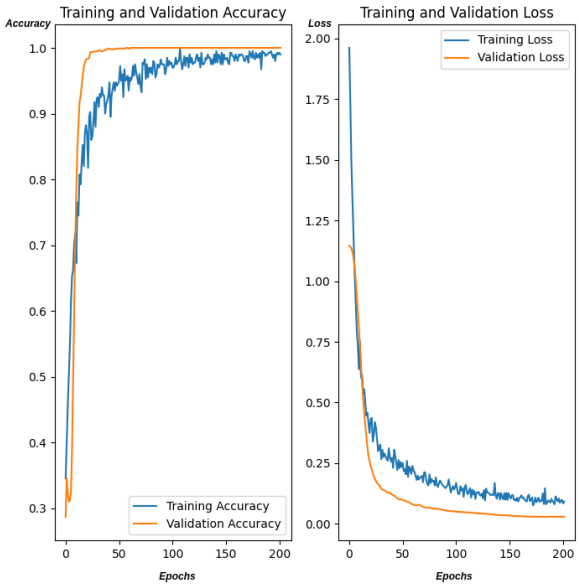

Fig. 5. Training results. The blue line displays the values for training, and the orange line represents the values for validation.

The results from this stage indicate that the solution did not overfit towards the training set, as both the loss and the accuracy evolution lines converge. Nonetheless, the quicker convergence from the validation dataset indicates a slightly biased dataset. This result is not surprising, given the usage of scarce data to produce the given solution.

B. Model Evaluation

After starting with the training analysis, we also need to validate the model according to the proposed metrics. We start by overseeing the confusion matrix produced in evaluating the test dataset. Fig. 6 displays the confusion matrix obtained in this evaluation, presented in percentages. The confusion matrix in untrained data corroborates with the results from the training stage. This model generalized its solution in the context of the given dataset.

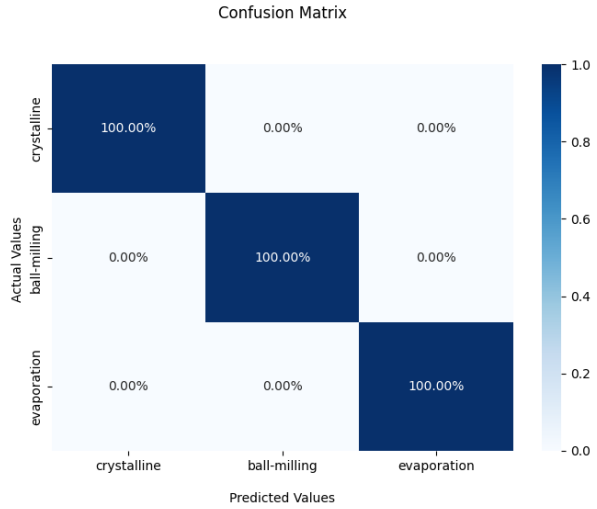

Fig. 6. Confusion Matrix obtained from the Classification Model.

Finally, we present the metrics of *Precision*, *Recall*, and *F1-Score* for each class. The confusion matrix demonstrates that neither false positive nor false negative was produced. The test dataset contains 282 samples of data from crystalline drugs, 322 samples of drug amorphized by ball-milling, and 296 samples of drug amorphized by evaporation. The model was able to classify all samples correctly. Table I individually displays the metrics for each class, the macro average, and the average weighted by the number of samples of each class.

TABLE I
EVALUATION METRICS FOR THE CREATED MODEL

	Precision	Recall	F1-Score	Support
Crystalline	1.00	1.00	1.00	282
Ball-milling	1.00	1.00	1.00	322
Evaporation	1.00	1.00	1.00	296
Accuracy			100%	
Macro Avg.	1.00	1.00	1.00	900
Weighted Avg.	1.00	1.00	1.00	900

The results obtained indicate the initial feasibility of the proposed method. Using a simple deep-learning technique was enough to produce a model that could differentiate all samples from the untrained set. Nevertheless, there are some limitations to this method. Real data is scarce, which favors the creation of a biased dataset. This also limits the reach of this work, as further testing is required to evaluate the generalization of this technique.

V. CONCLUSIONS

In this work, we developed a machine-learning-based method to classify the amorphization technique and, consequently, the drug's local structure using Pair Distribution Function (PDF) patterns obtained from X-ray total scattering diffraction data. We used the Monte Carlo method to produce a synthetic dataset from real samples and trained a deep neural network to perform the classification task.

Drug amorphization is a feature that can be used to solve the issue of low solubility frequently faced in crystalline pharmaceutical formulations that often face low solubility problems. The amorphization reduces the long-range structure ordering, increasing the inner energy and its solubility. Some authors present machine-learning-based methods to assess aspects of amorphous drugs. Nevertheless, these authors employ different approaches, techniques, data nature, and aims, which ensure the novelty of the proposed work.

The available data is scarce. Therefore, we selected the Monte Carlo method to generate a synthetic dataset with more diversity. The data was noised using a uniform distribution to reach a white noise condition. Then, we proposed the architecture of a Deep Neural Network to differentiate the samples between each class. The proposed method was able to differentiate all samples among the three classes. Although the results are promising, the limitations of the proposed experiments require more data, tests, and results to ensure the feasibility of this proposal.

Future works require creating more samples from the same drug to evaluate its diversity. Also, the same technique can be tested with different drugs to expand the comprehension of the proposed technique. It is essential to highlight that our work can also be considered as a promising application for quality control of solid-state batches wherein automatic recognition is desired.

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DATA AVAILABILITY

Our data and codes are publicly available through the url: https://github.com/matcoelhos/flubendazol-recon.

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