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PREFACE

The healthcare and pharmaceutical sectors are currently standing at a pivotal crossroads where traditional methodologies meet cutting-edge technological innovations. This book provides a comprehensive exploration of the transformative advancements reshaping drug development and medical education in 2026. As the industry moves toward more personalized and precise solutions, understanding the synergy between sophisticated analytical methods and next-generation manufacturing techniques has become paramount for researchers and practitioners alike.

The following chapters delve into critical areas of modern science, ranging from the rigorous validation of dissolution methods via HPLC to the revolutionary potential of 3D and 4D printing in pharmaceutical technology. Furthermore, this work addresses the evolving landscape of medical pedagogy, specifically examining how the integration of Artificial Intelligence is enhancing the study of anatomy and histology. By bridging the gap between laboratory research and classroom innovation, this publication serves as an essential resource for those dedicated to advancing the frontiers of pharmaceutical sciences and healthcare education.

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April 20, 2026
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CHAPTER 1
A CONCISE REVIEW OF THE DEVELOPMENT AND VALIDATION OF THE DISSOLUTION METHOD FOR IMMEDIATE RELEASE TABLETS BY HPLC

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INTRODUCTION

Tablets with immediate release dosage form without regulating rate features like coating and other methods They show a very high drug release profile and disintegration with time. Immediate-release tablets have gained good marketability due to their simplicity, improved patient compliance, and prompt beginning of treatment. Mehta and coworkers claim that the procedure of the dissolution test helps in establishing the drug's bioavailability and, hence, the determination of pharmaceutical equivalence between different batches of the same drug. Dissolution method development is capable of determining drug release profiles with suitable conditions as per ICH guidelines and solubility as per BCS classification with the use of high-performance liquid chromatography methods. The process through which drugs enter dissolution media under suitable conditions like temperature, time interval, and USP apparatus is called dissolution. In the pharmaceutical industry, particularly in the Quality Control Department or Analytical Department, the dissolution test has an important role in quality control testing to identify the quality of drug products and an important role in drug development. Dissolution testing is performed in industries, followed by different pharmacopoeias for testing the drug release of different types of dosage forms with different time intervals. In recent times, dissolution has become a major tool for testing drug release. Different types of tablets, gums, capsules, transdermal patches, suppositories, semisolid dosage forms, etc. The testing of dissolution has been developed since the 19th century with the help of physical chemists and research scientists. The major aim is to find a complete set for USP testing.

1. THE GENERAL STATE OF DISSOLUTION APPARATUS

- Capacity-1000ml
- The Dissolution medium temperature should be maintained at 37±0.50C.
- The distance of 25±2 mm is kept between the paddle/basket and the inner bottom of the container.
- The pH of media varies from -±0.05 as per available monograph.

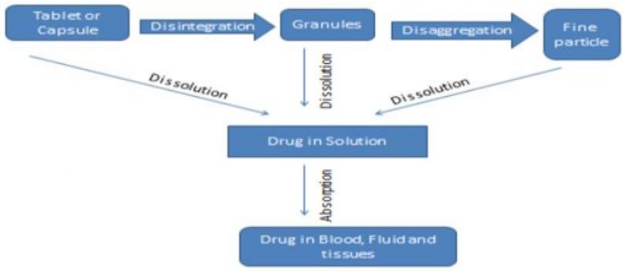

Figure 1. Schematic illustration of the dissolution process

1.1 Dissolution Test Apparatus - Related Factors are the Following:

Agitation

- The agitation speed and thickness of the diffusion layer are inversely correlated, and both parameters can have a significant impact on diffusion- control.
- The intensity of agitation was utilized. The strength of agitation and rate of dissolution are significantly influenced by the system's turbulent flow and level of laminar flow, as well as the design and form of the stirrer.
- The rate through which the agitation flow modifies the solvent-drug interface's liquid or solid state over time.
- Resolution speeds of 50–70 rpm are used for the paddle dissolution method.
- A resolution speed of 100 rpm was used for the basket dissolution method.

Stirring Element Alignment

- According to the USP, the stirring element's axis cannot vary from the vessel by more than 0.2 mm, meaning that the stirring shaft must be centred within ±2 mm.
- A test with paddle equipment indicates that a tilt greater than 1.50 may cause the dissolution rates to rise between 2 and 25 percent.

Positioning of the Filter and Sample Probe

- The hydrodynamics of the system and consequent shift in the dissolution rate can be influenced by the sample probe.
- The USP/NF sample position guidelines specify that the used sample needs to be maintained at 50% or less the distance between the media and basket or paddle.

2. IMMEDIATE RELEASE TABLETS

The main goal of the immediate release dosage form is to decay and release the active pharmaceutical ingredient without controlling rate features like coating or other methods. The term ‘’immediate release’’ refers to tablets that breakdown quickly and release the medication. An immediate-release dosage form helps in market diversification from other dosage forms and provides patients with a practical dosage form.

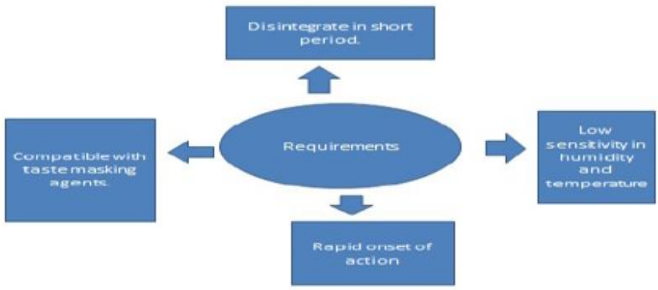

Figure 2. Essential requirements of an immediate release tablet

Advantages of the Immediate Release Dosage Form

- Enhanced solubility, stability, bioavailability, and improved compliance with additional convenience.
- Having the ability to offer the solid preparation benefits of liquid medication.
- Cost- effective.

- Reduced periods of breakdown and disintegration for oral dosage formulations for quick action in immediate release tablets.
- Adaptable and compatible with the processing and packaging equipment already in use.

Disadvantages of the Immediate Release Dosage Form

- A medication with a short half-life requires frequent doses.
- One dose of a drug may cause a high plasma concentration, which could be harmful.

3. CHROMATOGRAPHY

In order to separate a mixture of components between the stationary phase and the mobile phase, the chromatography technique is generally used. The mobile phase may be gas or liquid, and the stationary phase is solid or liquid. When the separation takes place between two immiscible liquid phases, the chromatography is known as liquid-liquid chromatography. When the physical surface is in the stationary phase, the mobile phase helps in movement. This type of chromatography is known as solid-liquid chromatography. The principle of chromatography is adsorption or partition. The molecules having good affinity for the stationary phase and less solubility for the mobile phase will move slower, while the molecules having less affinity for the stationary phase and more solubility in the mobile phase will move faster.

3.1 High Performance Liquid Chromatography

One type of column chromatography is HPLC. HPLC is generally used for the identification, separation, and quantification of mixtures of components. HPLC works on the principle of partition. The compounds get partitioned based on the partition coefficient in the mobile phase, reach the detector, and give area, height, retention time, and tailing factor in the chromatogram. The elute of HPLC depends on the theoretical number of plates. HPLC is a more accurate, sophisticated, advanced, and accurate technique than UV spectroscopy, where it can detect absorptions less than 0.2.

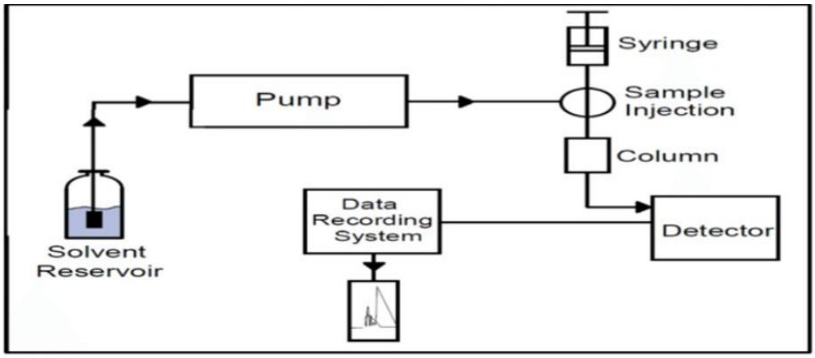

Figure 3. Flow diagram OF HPLC

4. DISSOLUTION METHOD DEVELOPMENT BY HPLC

Dissolution method development is capable of determining the dissolution rate of immediate-release tablets. Capable of selecting the dissolution parameter in the dissolution apparatus and chromatographic conditions used in HPLC. After the sample preparation by dissolution apparatus, the sample reaches vials for HPLC. Both clinical trials and market approval are achievable with the development and validation of new methods. This will help in further analysis and routine work for the dissolution test.

4.1 Dissolution Method Development Procedure

Role of BCS in Dissolution Method Development Before developing dissolution test conditions, we need to know the class of biopharmaceutical classification system of the drug that undergoes method development.

Class-I

These drugs work in vivo, like a quickly dissolved and absorbed oral solution. Bioavailability and bioequivalence are useless for class I drug products because of how quickly these medications dissolve and absorb. In the target regions of the GI tract, class I drug molecules do not have limited solubility or permeability.

Class II

BCS-containing drugs show very poor solubility and a slow dissolution rate because of rate-limiting steps.

Class -III

This family of medications enters the intestinal membrane at the step where the drug's rate is determined. Bioavailability regulates the amount of medicine released from the dosage form on its own because absorption is based on the rate of permeability. For instance, superimposable plasma concentration versus time profiles are produced in vivo by several ranitidine compounds with differing dissolving characteristics. Because of their typically limited bioavailability, this class of medications typically requires permeability enhancement. It is difficult to produce these medications for controlled release.

Class -IV

This class of drugs has inconsistent and low bioavailability. Numerous factors, including rate of dissolution, intestinal permeability, gastric emptying, and others, influence general bioavailability. Oral drug delivery is typically not appropriate for many medications; in such cases, specialised drug delivery technologies such as nanosuspensions may be preferable.

5. SELECTION OF THE DISSOLUTION TEST PARAMETERS

5.1 Selection of Apparatus

Based on the components of dosage form performance in the in vitro test setup and formulation design, the apparatus is chosen. Dissolution testing is done using appropriate equipment, like that listed in the United States Pharmacopoeia (USP) under the Drug Discharge and Dissolution charts.

Table 1. Statements about each class of biopharmaceutical classification system

Class	Solubility	Permeability	Statements
Class-I	High	High	BCS Class-I-containing drugs dissolve rapidly in dissolution media and are absorbed. Drug products with immediate release are not anticipated to have bioavailability issues.
Class -II	Low	High	Dissolution is limited for BCS Class II-containing drugs. Dosage form and the drug substance's rate influence bioavailability.
Class -III	High	Low	Permeability is limited for BCS Class III-containing drugs. If the drug is not delivered and dissolved within the absorption window, bioavailability can be insufficient.
Class -IV	Low	Low	It might be a requirement for a different route of administration in the case of BCS Class IV-containing drugs.

Table 2. List of official Dissolution apparatus with rotating speed and dosage form

Dissolution Apparatus Type (USP)	Dissolution Apparatus Type (USP)	Dissolution Apparatus Type (USP)
TYPE1 (Basket)	Delayed release, Immediate release, ,Extended release	50-120
TYPE 2 (Paddle)	Extended release, Immediate release, Delayed release	25-50
TYPE 3(Reciprocating cylinder)	Immediate release, ,Extended release	6-35
TYPE 4(Flow through cell)	Poorly soluble Active pharmaceutical ingredient, Extended release,	N/A
TYPE 5(Paddle over disk)	Transdermal	25-50
TYPE 6(Rotating Cylinder)	Transdermal	N/A

TYPE 7(Reciprocating Holder)	Extended release	30

5.2 Selection of Dissolution Medium

The Dissolution medium selection for Dissolution depends on physicochemical property of Drug used. Major dissolution media used for dissolution include buffers, acids, surfactants with or without acid, and buffers. Surfactants in dissolution media are used to increase the solubility and wettability of drugs. The use of sodium lauryl sulphate (SLS) can also affect the solubility of mefenamic acid through small changes in the strength of ions, but this is this is not seen with cetyl trimethyl ammonium bromide (CTAB).

Table 3. Use of dissolution media with different drugs

Dissolution medium used	Drugs
Buffer as dissolution medium	Azithromycin Capsule
Simulated gastric fluid as a dissolution medium	Piroxicam Capsule
Water as a dissolution media	Ampicillin Capsule
HCL solution as a dissolution media	Cimetidine Tablet

5.3 Dissolution Media Sink Condition

The minimal quantity of drug that has to dissolve is selected as a dissolving medium. At least three times the volume of medium is needed to make a drug-saturated solution. In the absence of sink conditions, investigate methods to enhance solubility, e.g., the use of a surfactant. If a surfactant is used, its concentration should be properly justified (e.g., typically <2% Sodium Lauryl Sulphate (SLS)). If a medium is proven to be preferable or has other valid reasons, it might be accepted even if it doesn't offer sink conditions.

5.3.1 Selection of Dissolution Media Volume and Sink Condition

Generally, the volume of dissolution media used in dissolution apparatus is 500, 900, 1000, or 1800 ml for acidic media and buffer. In cases where the drug is not well soluble in dissolution media, a large quantity or volume of media is used so that complete dissolution can be achieved.

5.4 Selection of Temperature

Solubility of drugs is temperature-dependent, so temperature should be maintained throughout the dissolution process. Generally, the temperature condition used for dissolution of all oral dosage forms, including immediate-release tablets, is 37±0.5 °C because of human body temperature.

5.5 Selection of RPM

The selection of RPM used in dissolution apparatus depends on the type of formulation, its solubility, the apparatus used, etc. For example, in the case of capsules, USP-1 (basket) is used, and the RPM selection or rotation speed for capsules is 50 to 75 RPM. In the case of tablets, USP-2 (paddle) is used, and the RPM selection or rotation speed for tablets is 75 to 100 RPM. Any changes in apparatus, physicochemical properties of the drug, and RPM are otherwise recommended parameters.

5.6 Selection of the Dissolution Time Interval

The time interval or time point in the dissolution apparatus depends on the type of formulation or dosage form. For the immediate release tablet, they release their dosage of about 80% within 30 to 60 minutes, and sometimes it reaches up to 90 to 120 minutes. So the maximum time interval used in the dissolution apparatus is 2 hours. Modified-release tablets (delayed-release tablets, sustain-release tablets, and enteric-coated tablets) depend on the properties of the drug and the site of action in the human body. The last time point or time interval may be up to 24 hours. for these formulations. Single-time points and two-time points are also used in some dosage forms, except modified-release dosage forms.

5.7 Reagents and Chemicals

There is a need for a working standard for the immediate release tablet for standard preparation. Also, the concentration of the sample drug used for analytical method development should match the concentration of the standard drug.

Different reagents like potassium dihyrogen phosphate, sodium lauryl sulphate, and concentrated hydrochloric acid should be used for dissolution media preparation and HPLC-grade Acetonitrile, methanol, etc. were used for mobile phase preparation in HPLC. Milli-Q water is generally used for HPLC method development.

Selection of HPLC chromatographic conditions: The development of chromatographic conditions is required for the analysis and determination of the drug release percentage of the dissolution sample. Selection of different chromatographic parameters like mobile phase, flow rate, run time, column, etc. is required to perform any dissolution test by HPLC for a particular drug with or without a combination.

5.8 Selection of Column

It is one of the important step during dissolution method development. In stationary, functional groups are attached to silica in RP-HPLC. The popular bonds are alkyl groups like -CH3, -C4H9, -C8H7, and -C18H17, phenyl groups, amino groups, and cyano groups. Generally, C8 and C18 columns are used in RP-HPLC. Less acidic silica is used for basic compound separation.

6. OPTIMISATION OF THE MOBILE PHASE

Buffer Selection

The reversed-phase silica-based packing has a pH range of 2 to 8. In order for buffers to regulate pH at their particular pH, it is crucial that their pKa be near the intended PH.

Guidelines for Buffer Selection

- Certain salt buffers have a tendency towards hygroscopicity, which can cause chromatographic alterations like an increasing tailing factor of basic chemicals but also variations in selectivity.
- Phosphate buffer damage silica-based HPLC column at PH greater than 7. Organic buffer is used in these conditions.
- After buffer preparation, the buffer should be filtered using the filter assembly.

- TFA used for mobile phase preparation degrades with time. So, we cannot use such a mobile phase for a longer time.
- Sonicate should be used for degassing the mobile phase.
- Ammonium salts used for buffer preparation are soluble in organic solvents and water.

Organic Modifier Impact

Generally, methanol and acetonitrile are used in RP-HPLC. Since it's not always possible to extract every component from complex multicomponent samples, gradient elution is typically used.

Selection of Detector and Wavelength

This parameter depends on the characteristics of the sample and the analysis goal. Some common detectors are electrochemical detectors, fluorescence detectors, UV detectors, mass spectroscopy detectors, and refractive index detectors. When we do an analysis of a multicomponent drug, the absorption spectra shift to a shorter or longer wavelength, known as a hypsochromic shift or bathochromic shift. Therefore, UV detectors are used for target analytes and impurities. And wavelength is selected based on response.

Table 4. List of detectors that can detect different compounds

Detectors	The detected compounds
Conductivity detector	Charged compounds like organic acids and inorganic ions
Evaporative light scattering detector and refractive index detector	Substances without properties that can be used by other detectors, such as saccharides, polymers, etc.
Ultraviolet-visible and photodiode array	The compounds that show chromospheres are due to arenes and conjugated double bonds.
Electrochemical detector	Substances that show very easy oxidation, like amines or quinines

Sample Preparation

Transfer six tablets individually into each of the six dissolution vessels containing the respective dissolution media as per the developed method that was previously equilibrated at a temperature of 37 ± 0.5 °C. Withdraw a quantity of sample from the dissolution medium after a certain time interval and collect it at the dissolution apparatus collector. Replenish with a pre-equilibrated medium volume equal to the volume of the aliquot. Use filtration and dilution if required.

Standard Preparation

Accurately weigh and transfer the working standard into the required volumetric flask. Add diluent and sonicate until it dissolves the content property. Keep the volumetric flask at room temperature. Make up the volume with the same or different diluent as per the developed method. Same further dilution and filtration as per the developed method. The final concentration of standard preparation and sample preparation should be the same.

7. SYSTEM SUITABILITY

System suitability is used to check if the system majorly used by the pharmaceutical the pharmaceutical industry on any analytical instrument like HPLC, GC, etc. is working properly before analysis. System suitability is performed each and every time before analysis to avoid failure of analysis at the end of analysis. To check system suitability, there are some system suitability criteria.

- Percentage of Relative Standard Deviation (%RSD).
- Theoretical No. of Plates or Efficiency (N).
- Tailing Factor (T).
- Correlation.
- Resolution.
- Capacity ratio, or capacity factor (k').

7.1 The Percent Relative Standard Deviation (%RSD)

To determine %RSD, first determine the standard deviation of calibration. The RSD can be easily calculated by dividing the standard deviation by the calibration mean.

- If %RSD is less than 2.0%, then 5 replicate injections are used.
- If %RSD is more than 2.0%, then six replicate injections are used.

7.2 Theoretical No. of Plates or Efficiency (N)

Efficiency or theoretical No. of plates is column characteristics. It is defined as the degree of peak dispersion or the estimation of the level of peak scattering. The formula for calculating efficiency is mentioned in figure No. 4.

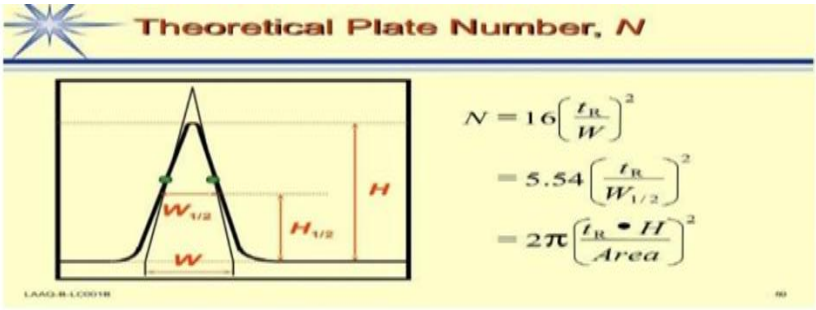

Figure 4. Determination of Efficiency

N = efficiency/theoretical number of plates
TR = retention time
W1/2 = peak width at half-height as a Gaussian function
W = peak width at full height as a Gaussian function
H = height of peal
A = area of the peak

7.3 Tailing Factor (T)

Ideal chromatography refers to accepting the Gaussian shape of the peak in its perfect state. A peak that can deviate shows non-uniform movement becoming asymmetrical, flattening, and becoming broader. Tailing factor: It's commonly used in the pharmaceutical industry.

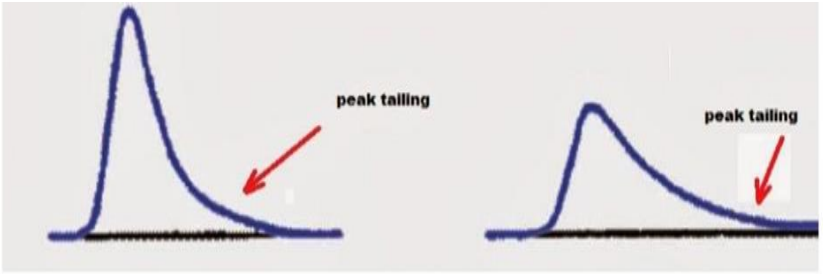

Figure 5. Tailing Factor in chromatogram Peak

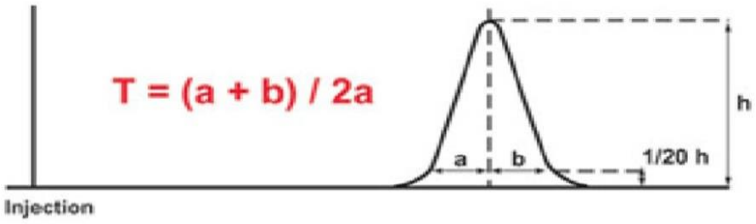

Figure 6. Determination of Tailing Factor in chromatographic Peak

7.4 Correlation

A correlation is a statistical measure of the relationship between two working standards. Correlation is a crucial system appropriateness and suitability criteria before doing analysis on a sample. If the correlation does not lie within the range, we cannot use the working standard for sample preparation.

The correlation between STD A and STD B should lie between 0.98 and 1.02.

$$\text{Correlation} = \frac{\text{average area of STD B x weight of STD A}}{\text{average area of STD A x weight of STD B}}$$

7.5 Resolution

The resolution factor (R) used to check pairs of adjacent peaks are acceptable separated. And used for integration. R can be calculated using the below formula:

$$R = \frac{2[(t_{R2} - (t_{R1}]}{W_{w1} + W_{w2}}$$

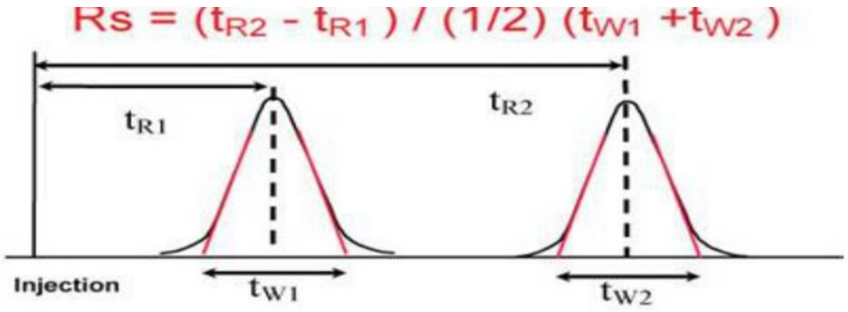

Figure 7. Resolution measurement between two peaks

t_{R2} and t_{R1} = Retention times for two peak components

$W_A + W_B$ = between the angles of tangent towards the peaks edges serves as the baseline.

7.6 Capacity Factor/Capacity Ratio (K')

It is the relationship between the amount (or time) of a substance in the mobile phase and the same substance in the stationary phase. This basically refers to the primary peak's placement in relation to the void volume. There must be no void at all in the summits.

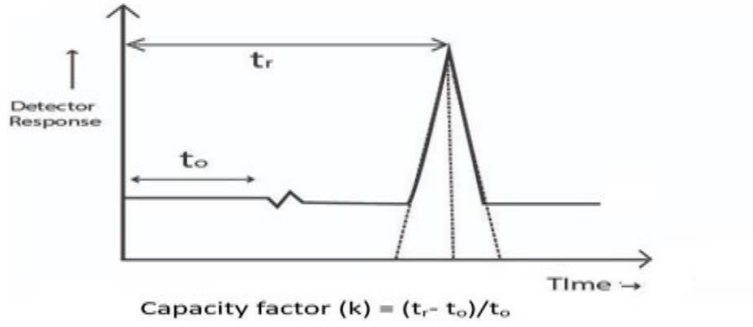

Figure 8. Capacity factor/ Capacity ratio (k') determination

Capacity factor /Capacity ratio (k') = $(t_r - t_0)/t_0$

Where t_r = signifies the T_R of sample main peak.

t_0= signifies T_R of unretained peak.

Calculation Of % Drug Release

% Drug release = $\frac{AT}{} \times \frac{DS}{} \times \frac{P}{} \times \frac{1}{} \times F$

- AT: Area of the test drug peak in the sample chromatogram obtained from SPL SOL.
- AS: Area of STD A peak in the STD chromatogram from STD A
- DS: Dilution of working/reference STD of STD A (mg)
- DT: dilution of the test drug.
- Potency of Reference Standard and Drug.
- LC: Drug label claim (mg/tablet)
- F: Factor

8. ANALYTICAL METHOD VALIDATION

Validating analytical procedures is the process of proving they are appropriate for the purpose for which they are intended. This is known as analytical method validation. It is used to accept or reject the developed test method. It is documented evidence that says a specific method or procedure will provide a consistent result. The developed method should always be valid, transferable, robust, reliable, precise, and accurate for routine activities in any quality control and research and development department.

8.1 Method Validation Parameters

Accuracy and recovery Accuracy was determined by using a placebo spiked with an active pharmaceutical ingredient in dissolution media in a specific volume in different concentrations, like 50%, 100%, and 150%. The amount added of active pharmaceutical ingredient compared with label claim and recovery is calculated.

Table 4. Validation parameter with different Tests

Different validation parameters	Dissolution/ Assay	Specific Tests	Quantitative impurity test	Limits of the impurity test
Accuracy-Parameter	Yes	Yes	Yes	No
Precision-Parameter (Repeatability)	Yes	Yes	Yes	No
Precision-Parameter (Intermediate precision)	Yes	Yes	Yes	No
Linearity-Parameter	Yes	No	Yes	No
Range-Parameter	Yes	No	Yes	No
Limit of detection: Parameter	No	No	Yes	Yes
limit of quantification: Parameter	No	No	Yes	No
Specificity-Parameter	Yes	Yes	No	Yes
Robustness-Parameter	Yes	Yes	Yes	No

Precision

Precision should be checked by several measurements taken from various samplings of an exact sample in given circumstances. It can be determined by calculating the percentage of drug dissolved and the relative standard deviation. Precision can be performed in three states:

- Repeatability
- Intermediate precision
- Reproducibility

Repeatability

Repeatability describes precision over a brief period of time under the same operating conditions. It is sometimes known as intra-assay precision.

Intermediate precision (ruggedness)

Variations within laboratories, such as various days, equipment, and different analysts that perform procedures, can be defined as intermediate precision.

Reproducibility

Laboratory precision can be demonstrated through reproducibility, which is typically used in collaborative examinations for uniform methodology.

Robustness

An analytical procedure's robustness is a measure of how well it tolerates small changes in procedure and shows how reliable it is under typical use. The composition of the mobile phase (±10 absolute or ±30% relative, whichever is lower), pH (±0.2), flow rate (±10%), column temperature (±5%), etc. are to be varied for performing robustness validation parameters.

Results are accurate and precise under a variety of conditions, including different flow rates, column temperatures, etc.

Linearity and Range

The linearity validation parameter is used for the entire range of concentrations to check the result for linearity. The ICH guidelines suggest 20% of the Q value, such as the Q value of an immediate release tablet, is "tablet dissolved 80% in 45 minutes". A linear curve should meet the following results: correlation coefficient, slope of curve, and Y-intercept.

Specificity

Dissolution media contain active pharmaceutical ingredients and placebos that are present in the sample. The specificity validation parameter can be calculated or measured by observing placebo interference or blank interference with the drug. The results will be specific if there is no interference with the drug's main peak. (Used during the identification test, determination of impurities, and assay)

CONCLUSION

The development of the analytical test method of the dissolution test used regarding the percentage of drug release, drug recognition, and purity evaluation has brought a great deal of attention and a lot of interest to the sector of pharmaceuticals over the past few years. This review article for dissolution method development and validation of immediate release tablets using HPLC helps in the selection of various dissolution apparatus parameters and chromatographic conditions. Deep knowledge of the physicochemical properties of the test sample helps during method development. The developed test methods enable the dissolution of immediate-release tablets by HPLC. The validation required to check the assigned test method used in drug development is accurate, precise, reliable, and easy to use. This developed dissolution method is further used for routine work and quality control of sample drugs in the pharmaceutical industry. After this method's development and validation, conducting clinical trials on humans can be possible.

Abbreviations

- HPLC: High Performance Liquid Chromatography
- ICH: International Council for Harmonisation
- BCS: Biopharmaceutical classification system
- USP: United States Pharmacopoeia
- USP-NF: The United States Pharmacopoeia and the National Formulary
- UV: ultraviolet (visible)
- SLS: sodium lauryl sulphate
- RPM: revolutions per minute
- RP-HPLC: Reverse phase High-performance liquid chromatography
- TFA: trifluoroacetic acid
- GC: Gas Chromatography

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CHAPTER 2
INTEGRATION OF ARTIFICIAL INTELLIGENCE IN THE PEDAGOGY OF ANATOMY AND HISTOLOGY

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INTRODUCTION

Anatomy and histology are basic pillars of medical, veterinary and life-sciences education, in term of diagnosis, treatment and practice in the clinical scope. The conventional method of instruction in anatomy and histology has been based upon textbooks, lectures, dissection of cadaver and histological slides in laboratory. Although cadaver dissection is the gold standard, this conventional method has numerous limitations: it is time consuming, logistical and engagement problems reduce with the students (Joseph et al., 2025). Professional clinical practice is based upon anatomy and histology of patients, invasive procedures like surgery, diagnosis and therapeutic approach rely on the precise knowledge of normal and abnormal anatomy. Essentially, these sciences are the foundation of health science, encompassing the basics of clinical science and, therefore, important to the students of these subject (Petra et al., 2023).

In the past decades, there has been a significant change in the field of anatomy and histology. The major issue are the lack of faculty, time spent to teach is high, number of students per faculty is high, and use of older and less interactive teaching method. In many cases, the teaching approaches are unchanged this students find gross anatomy very dull and tedious (Abdellatif et al., 2022). Attempts to add multimodal instructional methods like learning in groups, computer based models and blended instruction has proven fruitful, however, no one model has come out as a best teaching method.

More recently, the adoption of integrated systems and modern technologies has shifted emphasis away from depth-oriented anatomical education in some medical curricula (Singh et al., 2015). In this context, the emerging role of AI(AI) presents a major opportunity: AI-generated learning materials and adaptive virtual platforms offer the potential to address many of the longstanding educational challenges (Moxham and Plaisant, 2007). Initial uses of electronic technology in anatomy education included three-dimensional interactive teaching platforms that enabled image rotation and layered exploration of anatomical structures (Turney, 2007). Today, AI-powered solutions are increasingly available for example, the AI Study Assistant in the 3D Organon platform combines immersive visualization with instant anatomical queries and tailored explanations (Wilson et al., 2018).

Virtual dissection, 3D-printed anatomical models, and body-painting techniques have likewise expanded the pedagogical toolkit (Baratz et al., 2019), allowing for realistic simulation of dissection, demonstration of anatomical anomalies and more effective visualization of small or complex structures (Estai and Bunt, 2016; Martin et al., 2018).

With such developments, the need to come up with new assessment methods which are more holistic, and individualized, to suit the learning difference among students is a continuous and urgent requirement. The integration of AI offers a promising path forward: by providing tailored feedback, adaptive content and scalable resources, AI-enhanced pedagogy could improve student engagement, deepen understanding and better prepare learners for clinical practice. This chapter therefore reviews the evolving landscape of anatomy and histology education, examines the current role of AI integration, and sets out the scope, objectives and relevance of applying AI in the pedagogy of these foundational disciplines as shown in Fig.1.

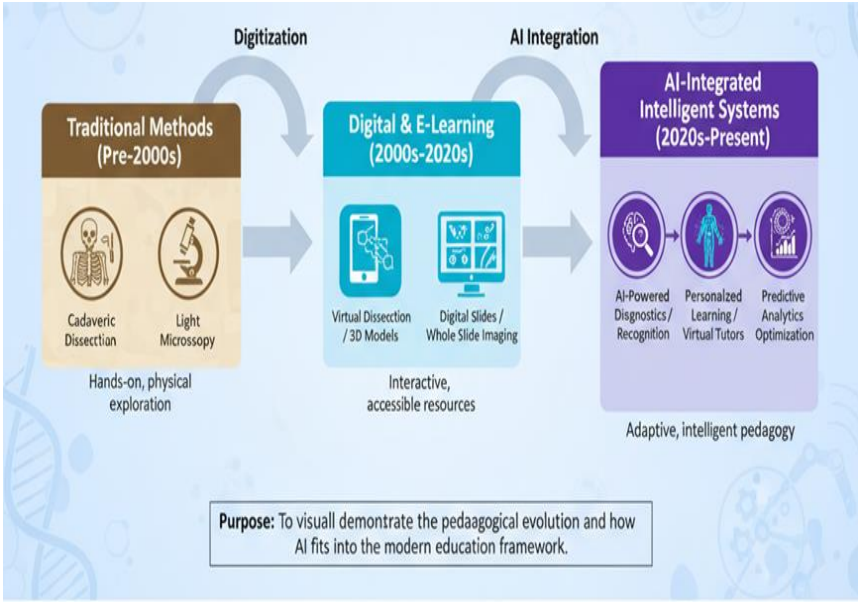

Figure 1. Evolution of Anatomy and Histology Teaching Methods

1. OVERVIEW OF AI IN EDUCATION

AI refers to the ability of machines to perform tasks that normally require human cognitive processes. A key branch of this field is Machine Learning (ML), which enables computer systems to learn from data; other related sub-fields include natural language processing and specialised AI systems. As many foundational AI textbooks note, the discipline places emphasis on learning by machines, in contrast to the natural intelligence found in humans and animals (Chatterjee, 2020). AI research pursues practical goals: for example in natural language processing, planning, decision-making and education. At its core, AI aims to build intelligent agents that can reason, adapt to new situations, and modify their behaviour over time. The advancement of AI has accelerated dramatically in recent years. AI researchers strive to replicate aspects of human thought including creativity in machines (Poole and Mackworth, 2010).

ML is now an essential component of AI-enabled intelligent systems. ML is the ability of systems to autonomously build analytical models as well as to solve problems by learning on the data instead of being programmed directly (Janiesch et al., 2021). ML helps in creating smoother intelligent systems since it does not require human beings to state their knowledge explicably to be used by the machines. In recent years, the sphere of ML provided significant progress in learning algorithms and more effective methods (Miller, 2019). MLcan break a significant part of the limitations of traditional helps systems: as far as performance is concerned, computer programs developed with the help of machine learning have delivered impressive performance. ML is aimed at automating model building so as to accomplish complex, intelligent tasks. This is done by means of strategies that are learned base on specific training data of a problem, and this allows computers to extract complex and knowledge without any programming as such (Jordan & Mitchell, 2015).

The appearance of deep learning (DL) methods in recent years has been the peaks of co-evolution between the approaches to ML and the computational capacities. A key distinction between deep learning techniques and traditional neural networks is the size and depth of the networks. Recent scientific advances in ML are illustrated by deep learning models. Over time, complex task-specific architectures comprising many layers and specialized structures have been developed (Pichler & Hartig, 2023).

The DL research community itself is a deep and dynamic network of researchers whose interactions have complex mutual influences. Researchers in neural networks have applied advanced global search techniques, though not all deep learning studies adequately reference this recent significant work. My own familiarity with DL research collaborators over the past 25 years has undoubtedly introduced a certain bias (Schmidhuber, 2015).

2. CURRENT CHALLENGES IN TEACHING ANATOMY AND HISTOLOGY

The issue of anatomy and histology has been challenging to generation of students who feel that the subject is abstract and conceptually rigorous. The loss of student interest in histology has been revealed over the years. Although central to medical education, the impact of rise in interest in clinical integration has occasionally come at the expense of basic science, creating impact on their perceived relevance (Chapman et al., 2020). Besides, limited access to cadaver availability and ethical limitation in anatomy laboratories has added to limited students access to direct correlation of macro and microscopic observations.

The complexity of histology along with lack of familiarity with the terminology will often present cognitive overload to learners with little experience. Inconsistency is the interpretation of slides by the students particularly in the case where resources are limited affects the confidence and diagnostic accuracy. These are further complicated by lack of access to light microscopes and individualized supervision as student have problems in marking out the boundaries of cell and finding tissue correctly. There is little opportunity to practice intricate structures and stain principles, since time limits inherent in the contemporary integrated curricula produce little time to practice and no time to receive individual feedback (Mohammedsaleh, 2024). Histology courses and virtual slides online have enhanced learning but they seldom offer adaptive and feedback based (Sung et al., 2016). (Eng-Tat et al., 2023). Even a simple adaption technology enhanced teaching to these concern would greatly address learning outcomes and keep student interested in the anatomy sciences. The comparison of traditional vs. AI-assisted pedagogy in Anatomy and Histology is shown in Tab.1.

Table 1. Comparison of Traditional vs. AI-Assisted Pedagogy in Anatomy and Histology

Teaching Aspect	Traditional Method	AI-Assisted Approach	Educational Benefit
Content Delivery	Lectures, static diagrams, and chalkboard teaching	Interactive 3D visualization and virtual dissection	Improves spatial understanding and retention
Microscopy	Manual slide observation using light microscopes	AI-powered digital slides with auto-labeling and pattern recognition	Enhances image interpretation and efficiency
Assessment	Subjective written/oral exams	Automated, adaptive AI-based evaluation tools	Provides real-time feedback and objective grading
Learning Style	One-size-fits-all, instructor-driven	Personalized learning paths guided by AI algorithms	Supports self-paced, student-centered education
Resource Use	Physical cadavers and slides	Virtual resources and simulations	Reduces ethical and logistical constraints
Feedback & Monitoring	Limited to manual observation	Continuous data-driven monitoring	Improves performance tracking and formative feedback

3. APPLICATIONS OF AI IN ANATOMY PEDAGOGY

Anatomy has been essential part of medical education since ancient times and it form a basis of all clinical medical sciences. In order to investigate patients, understand the underlying structures and make correct diagnosis,medical professionals should possess a good knowledge of anatomy. Also, anatomy is vital in performing invasive procedures, which include surgery. It is important to learn how disease change anatomy structure as it affects the diagnosis and treatment as it determines the treatment approaches (Singh et al., 2015).

The field of anatomy education can be transformed by AI in the sphere of teaching, training and assessment as shown in Fig.2. The AI-driven system can be used to represent complex structures and process in the human body and offered personalized learning experience that address the needs of individualized students. In addition, the precision of anatomical test can be enhanced with the help of AIs ability to process large volumes of data and detect any significant patterns.

AI therefore can change practice since it has vast opportunities such as ability to have remote control robotic surgery (Abinaya et al., 2024).

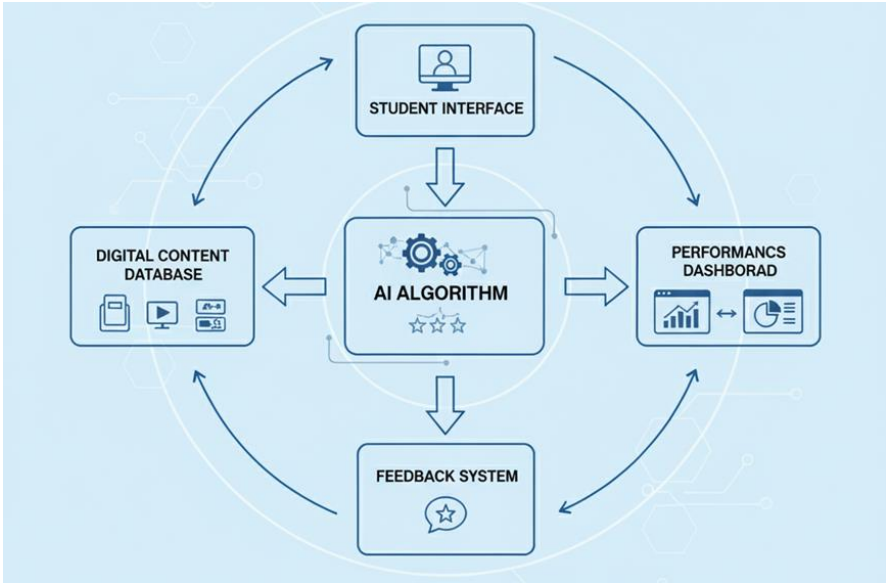

Figure 2. Architecture of an AI-Assisted Learning Ecosystem

3.1 AI-Based 3D Visualization and Virtual Dissection

There are several methods used in traditional anatomy such as lectures, animal dissection, anatomical model and radio-graphic anatomy. Cadaver dissection involves learner studying body organizes by cutting through specimens along various planes to identify various body features. It is a practice of method of teaching that has been essential, ans has been paired with lectures and lab works. It is however has been criticized to be costly and time consuming, in order to curb some of these limitations, student can study, pre-dissected cadaver that will provide a means to view real anatomical structures without the time consuming delays of complete dissection (Azer and Eizenburg, 2007). Example of such specimens are usually found in anatomy museums. Another method that involves the use of chemical process to conserve of cadavers of dissection is called plastination. The technique minimizes the repeating dissection as it yields odorless, and solid specimens that do not necessitate use of traditional chemical preservatives.

Plastination as a handy complement to the conventional approaches provides the possibility of good management and long term preservation of an anatomical specimens (Fruhstorfer et al., 2011).

The invention of digital technology in its early days saw the establishment of three dimensional interactive platforms in anatomy education as shown in Fig.3. With such tools, students are able to see the anatomical structures in different angles and move through stratified structures of the anatomical systems. More, recently, digital dissection, which provide learners with opportunities to visually explore the body by dissecting it has been shown to facilitate a more engaging and accessible learning experience (Pushpa et al., 2022).

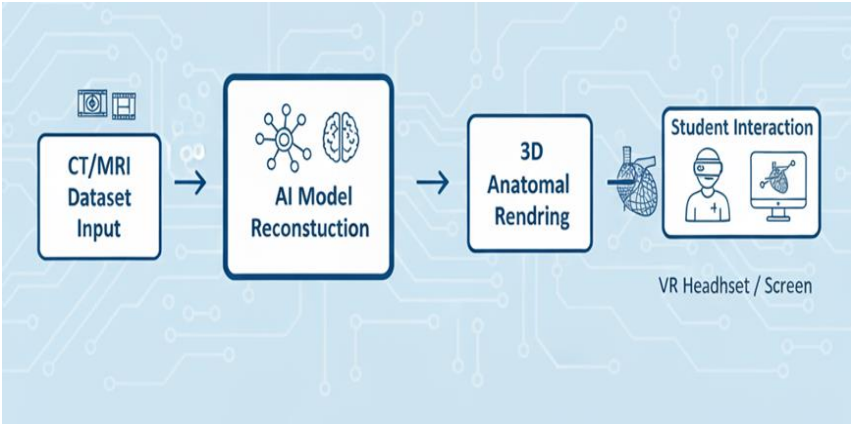

Figure 3. AI-Based 3D Visualization and Virtual Dissection Workflow

3.2 Intelligent Tutoring Systems (ITS)

As technology advances rapidly, machine-learning and artificial-intelligence methods are increasingly used to create more individualized educational programme. These systems are known as intelligent tutoring systems (ITSs). While there is no universally accepted definition of intelligence, it is generally recognized that intelligent tutoring integrates a learner's prior experiences. However, a major challenge in building an ITS lies in how to represent educational knowledge and teaching strategies effectively. Currently, many teaching systems do not yet incorporate dynamically adaptive learner models within their programming (Hui and Ye, 2025).

Moreover, limited effort has been made to model expert-teacher behaviors explicitly when developing instructional modules for ITSs. The classical architecture of ITSs is often described as comprising four modules: first, the domain or expert knowledge module. This module contains the domain knowledge that learners must master (Ma et al., 2014), and supports problem-solving and analytic strategies for the learner's tasks. The second component is the student model (or diagnostic module), which is constructed from elements such as the learner's knowledge gaps, learning styles, activities and other data collected during the system's operation (Carter, 2014). The third module is the pedagogical (or instructional) module. These advances can target important pedagogic aims such as improvement of spatial knowledge, accessibility and personalized learning route; therefore, filling the gap between the traditional approach and the next generation anatomy education. (Hooshyar et al., 2017).The last module is the user interface module that controls the interactions between the learner and system (Mousavinasab et al., 2021).

In anatomy and histology teaching, ITSs can be used to help students close the knowledge gaps through teaching techniques and strategies that adapt content to the progress of the learner, thus offering personalized instruction in complex spatial and microscopic learning. The use of AI based feedback and performance tracking would allow real time evaluation of the misconceptions of students and engage corrective advice (Peters et al., 2017). These systems further engage learners by gamification and adaptive testing, such as moving up the level as anatomical zones are mastered, rewarding learners with identification of muscle structures, (Janseen et al., 2017), and quizzing them with adaptive quizzes that are more challenging where they the learners have the most weakness (Nevin et al., 2014). Although, gamification has a potential, it should be applied judiciously to balance between teacher directed difficulty and learner independence and promote applied knowledge in structure-function interaction (Ang et al., 2018).

3.3 AI in Radiological Anatomy Training

Since the introduction of AI into radiology, radiologists are increasingly required to become familiar with this emerging technology. Several studies report that medical professionals are aware of the significant transformations under way in radiology as AI capabilities expand. A recent study demonstrated that the majority of radiologists believe they should engage immediately in AI-training programme and are keen to learn how to integrate AI into their workplace (Collado-Mesa et al., 2018).

Despite this interest, formal AI training is still not widely embedded in many radiology curricula. Several initiatives have been launched to train radiologists in AI-related areas, yet many training systems remain without the necessary coursework to fulfil guideline recommendations (Schuur et al., 2021). The use of AI is increasingly being adopted in medical imaging and research. These cutting-edge technologies have the potential to perform imaging tasks such as segmentation, detection and recognition of anatomical and pathological structures more rapidly and accurately than humans. AI is particularly well-suited to medical-imaging analysis where tasks include interpreting complex computed tomography (CT), Magnetic Resonance Imaging (MRI), and ultrasound datasets.

In the context of anatomy pedagogy, this offers opportunities to integrate anatomy with clinical imaging: AI-based image-recognition tools can be applied in CT, MRI and ultrasound training, helping students correlate anatomical knowledge with live imaging. Nevertheless, these are still issues on the way: AI training systems require reliable image quality management, pre-processing and and standardization in place, (Komatsu et al., 2021), so that the adaptive learning pathway can be developed between anatomical theory and imaging modalities used in clinical settings, thus, changing the manner in which anatomy and radio-logical anatomy are taught and learn.

4. APPLICATIONS OF AI IN HISTOLOGY PEDAGOGY

However, histology appears to be losing momentum despite its fundamental importance, the continued use of traditional teaching techniques, and the relatively limited application of diverse instructional modalities.

Contemporary medical professionals need not only microscopic expertise, but also an understanding of the genetic and molecular mechanisms underlying tissue development, proliferation and disease as shown in Fig.4. In teaching histology, a combined multi-modal approach rather than reliance on a single or few techniques is recommended (Kristoffersen et al., 2025).

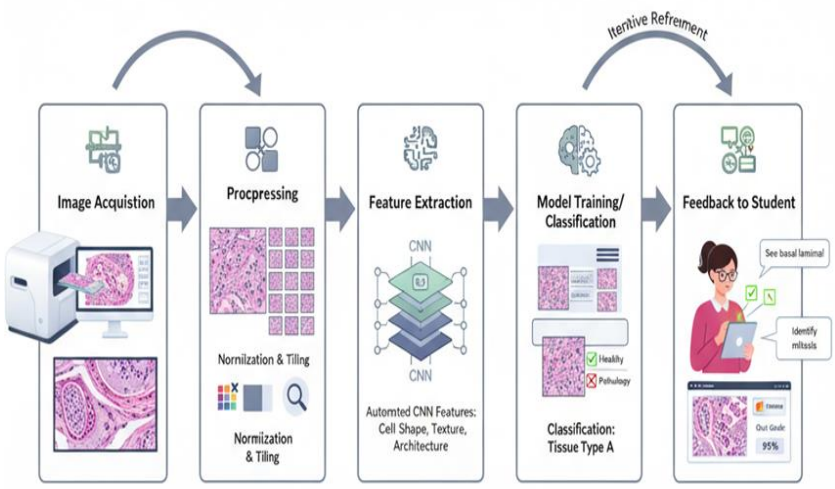

Figure 4. Machine Learning Pipeline for Digital Histology

4.1 Digital Slide Recognition and Annotation

AI algorithms have substantially enhanced visual-recognition capabilities and are increasingly applied to support both radiological and histological diagnosis. A principal aim of computational pathology is to enhance diagnostic precision and efficiency in response to rising workloads and increasing complexity in tissue-based diagnosis. However, computational pathology research has been challenged by limited general-purpose, many studies remain constrained to specific diseases, organs or tissue types and may struggle to detect novel (Komura and Ishikawa 2018).

Annotation practices in many digital-pathology systems remain coarse: slide-level tags or simple outlines offer only minimal spatial precision, whereas whole-slide images present unique challenges such as very high resolution, complex spatial context, and stain/slide preparation variability.

Many existing datasets are limited to broad labels (e.g., "healthy" vs "diseased") and lack rare or emerging disease categories, thus restricting model applicability. Focusing on tissue-type classification may offer a more tractable route, since the number of primary tissue types is finite and well-defined; yet some datasets use only a small number of tissue classes, further limiting general-purpose. The development of clinically relevant computational tools is hampered by the relative scarcity of finely annotated region-level visualization covering a broad spectrum of histological tissue types (Hosseini et al., 2019).

4.2 ML for Pattern Recognition

ML has become a very powerful in the microscopic image analysis. It allows cell and tissue biologists to get pertinent structural information much faster, more accurately and uniformly. ML can be used to predict without explicit programming by analyzing imaging data through the use of algorithms that learn based on the data and identify complex patterns features of data. The use of ML is involved in the analysis of fluorescence microscopy, cell phenotyping and automated cell counting (Durkee et al., 2021).

Also, ML normalizes image assessment and allow more predictable results, overcoming variation caused by the staining procedure, e.g. haemotoxylin & eosin and immunohistochemistry. ML is able to differentiate stromal, epithelial and immune cells in histological specimens by identifying characteristics such as cytoplasmic and nuclear morphology. New imaging technique have also contributed to the AI/ML capacity of analysis microscopic structure. These cutting-edge methods are complementary traditional microscopy, which means they allow the examination of biochemical cellular and tissue alternations (Ali et al., 2025). MLhas assumed a large role of diagnosing abnormalities like tumors or cancer cells and helping to interpret progression of disease treatments. Researchers are able to easily classify tissue or organ by training models on large datasets (Liu et al., 2022).

5. AI-BASED ASSESSMENT AND EVALUATION IN ANATOMY AND HISTOLOGY

Learning platforms being powered by AI have been remarkably promising in personalizing educational process to specific students particularly when learning complex anatomical concepts. These systems integrate the traditional and digital learning with high level algorithms to offer real time and personalized the feedback of student performance. The further expansion of this versatility achieved through intelligent tutoring systems and AI-driven technologies that provide dynamic learning environments (Joseph et al., 2025).

Embalming, dissection, plastination and mounting of anatomical specimens, which are all processes involved in this, traditionally happen occur in well-organized facilities that are associated with anatomy departments. Only non-interpretative AI system could be necessary to facilitate the workflow in such a facility. Artifical intelligence can be used as teaching tool especially in case where cadaver dissection is a part of medical training (Richardson et al., 2021).

With the help of deep learning, AI may become a valuable labour intensive aspect of anatomy studies. It is able to study anatomical structures accurately and recreate them in systematic displays especially when it comes to complex part. As an example, segmentation of CT images of high quality is essential in the study of musculoskeletal anatomy which is currently being used to detect musculoskeletal disease and identify specific muscles within CT scans (Li et al., 2021).

The assessment of learning method is extensively applied in medial education since it promote active and realistic ways of assessment. It has emerged to be among the most effective methods of enhancing learning strategies and drawing desired results. Recent curriculum changes now involve all evaluation strategies that are updated to new anatomy delivery systems, even those that incorporate AI (Choudhury and Freemont, 2017). This means that anatomist need to re-evaluate assessment formats and embrace genuine approaches that can help him or her make good use of knowledge and skills (Samarasekera et al., 2020). The applications of AI techniques in anatomy and histology education as shown in Tab.1.

Table 2. Applications of AI Techniques in Anatomy and Histology Education

AI Technique	Educational Purpose	Example Tool/Platform	Learning Outcome
ML(ML)	Image classification and tissue pattern recognition	TensorFlow, PyTorch	Enhances histological image analysis and accuracy
Deep Learning (CNNs)	Automated detection of histological structures	Google Cloud AutoML, Bioimage.io	Reduces observer bias, supports diagnostic teaching
Natural Language Processing (NLP)	Intelligent tutoring and question answering	ChatGPT, IBM Watson Tutor	Facilitates interactive and personalized learning
Virtual/Augmented Reality (VR/AR)	3D visualization and virtual dissection	Anatomage, Visible Body	Improves anatomical understanding and engagement
AI-Based Assessment Systems	Automated grading and progress tracking	Coursera AI-Quiz, Smart Learning Tools	Enables instant, objective feedback and adaptive tests

6. LIMITATIONS AND CHALLENGES OF AI-BASED PEDAGOGY

The implication of the use of AI in the classroom remains constrained by several technical challenges, through the current advancement in AI technology has improved. Such constrains are caused by aspects like the learning environments, the limitation of language processing and limited field knowledge by AI systems. AI tutors might have difficulties in generalizing the reasoning behind the question or the assumption of a student. These systems are usually performed base on knowledge that is restricted to a particular area. They are able to deliver all encompassing and precise information in those limits. Nevertheless, AI tutor are not as rich and flexible as human instructors when asked questions that are not in the scope of their programming. They would also be giving wrong or inaccurate answers and this may cause misinterpretations.

This shortcoming highlights the need to combine human skills with AI tutoring software, particularly in the area of specialization (Tian, 2023). Despite the fact that AI instructors have achieved a lot in the provision of individualized training, they have still have considerable weakness. A primary issue is that the AI tutor are not able to evaluate the behavioral and cognitive condition of students accurately because of their limited capacity. They might therefore not be able to meet the psychological or affective learning needs of the learners by altering their teaching methods. Although, such limitations exits, AI tutor can take advantage of the opportunities and provide useful guidance and support to the learning process. To address these limitations, continuous research is being done to enhance AI systems functionality in other aspects, including natural language understanding, state of the art MLalgorithms and affecting computing. Further development of this technology in the education infrastructure is largely consuming and thus expensive in term of hardware, software, connectivity and maintenance, which makes it a hindrance to many institutions in resource-starved environments. Education hybrid educational systems, in which AI is used to supplement conventional instructors, might utilize the strengths of each to provide more complex and efficient instruction. Also, it is important that faculty training and adaptation will help to make instructors proficient user of AI tool (Neo, 2025).

7. FUTURE PROSPECTS AND INNOVATIONS

Anatomists believe that the increasing demand is the need to create new AI-powered systems to promote the pedagogy of anatomy and histology. Virtual reality, augmented reality, and mixed reality technologies with the integration of AI can be used to design immersive learning experiences where students can visualize and engage with complex part of anatomy like neuroanatomy and embryology. These AI powered tools create a sense of spatial awareness and deep learning by creating realistic 3D images, making it easier to learn structures that are otherwise hard to dissect. The teaching platforms that are improved and enriched with deep learning can also offer guide demonstration of complex regions such as head, face, and neck that will improve the gap between theoretical and clinical practice.

The anatomy educators should be trained and institutionally supported to incorporate and evaluate AI assisted learning outcomes to enable an effective adoption. Additionally, morphometry and digital pathology research that has been boosted by AI will still transform the integration of teaching as comparable learning datasets will be structured as shown in Fig.5. With the increasing global attention to AI assisted anatomy and histology, standardization of curriculum and ethical standards will play a critical role in enhancing uniformity, fairness, and quality of education in various learning settings (Mezei et al., 2024).

Figure 5. Future Prospects of AI in Anatomical and Histological Pedagogy

CONCLUSION

The integration of intelligent technology in education marks a paradigm shift, offering immense opportunities alongside notable challenges. In anatomy and histology teaching, AI can revolutionize learning through immersive, interactive, and personalized experiences from microscopic tissue study to full-body anatomical visualization. However, its success depends on harmoniously combining AI with traditional methods like cadaver dissection and microscopy.

Ethical use, data privacy, and fairness must guide AI adoption, ensuring educational equity and social responsibility. Collaborative efforts among educators, developers, and policymakers are essential to harness AI's transformative potential and build an inclusive, intelligent, and globally accessible future in anatomical education.

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CHAPTER 3
RECENT ADVANCES IN 3D AND 4D PRINTING IN PHARMACEUTICAL TECHNOLOGY

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INTRODUCTION

There is always a continuous demand for developing advanced drug delivery systems (DDS) to boost the therapeutic effect of pharmaceutically active ingredients, including large biomolecules (e.g., peptides and proteins) suffering from poor bioavailability, hydrophobicity, or narrow therapeutic window. Conventional DDS demonstrate a restricted ability for adapting to patient to-patient pharmacokinetic behaviors variations. Additionally, conventional DDS are more likely to cause undesirable side effects resulting from over- or underdosing. Failure of precisely dose controlling based on individual patient differences can lead to patient incompliance, mainly for pediatrics and geriatrics. More specifically, the use of implantable DDS may rise some safety concerns related to the unfavorable foreign body reactions. Additionally, the presence of different formulations for a certain drug varying the dosage and physical form may affect its in vivo performance. Also, the limitations in size and design of conventional DDS restrict the highest incorporated dosage in a single device, which, in turn, affects the ability and durability for long-term delivery. Accordingly, the need for dosage controlled DDS has attracted the attention of scientists for the last years.

Since the research in the drug delivery field constantly attempts to meet new challenges and hard-to-reach therapeutic objectives, such as enhancing the pharmacokinetic profiles, and improving patient compliance, this attitude entailed to manufacture unusual approaches for advanced fabrication techniques. Additive manufacturing has been developed as a highly auspicious procedure for personalized medicine in the pharmaceutical technology field, to resolve the problems related to current DDS.

Additive manufacturing, also known as 3D printing technology, utilizes a 3D model as a base to superimpose printing materials layer by layer with computer-aided control into a 3D object using a printer. Additive manufacturing offers greater flexibility levels for the creation of sophisticated 3D structures directly based on design requirements. Compared to conventional manufacturing techniques since 1980s, and till now, emerging 3D printing technologies have been developed and applied.

Because of its extremely automated, high efficiency, extraordinary precision, and low cost, this advancing technology plays a significant role in the fields of construction, automotive industry, electrochemical energy storage, aerospace, flexible sensing as well as medical devices. On the other hand, the more advanced four-dimensional (4D) printing, the smart materials are 3D printed to produce items that alter their shape after production, in a programmed manner over time, when exposed to a certain external stimuli. 4D-printed dosage forms differ from 3D ones in that time is considered as the 4th dimension during their performance. The term "4D printing" describes smart materials manufactured by the additive technique to produce easily achieved, complex-shaped, nonstatic objects that are more advanced than 3D objects. 4D-printed objects can be manufactured with 3D printers. Moreover, 3D printing can be exploited in the biomedical research fields represented in regenerative medication, tissue engineering, cancer research, and drug screening. The term "Bioprinting" describes this emerging, potent, and multipurpose biofabrication technique which demonstrated promising applications in this field. In bioprinting process, depositing solutions or hydrogels of cell-laden polymer on a podium constructed using a computer-aided design (CAD) model is performed. Various merits are offered by bioprinting process over other conventional biofabrication techniques, such as the accurate modeling of cells and biologics, permitting coprinting of numerous cells and biomaterials, and assisting the construction process for a tissue or an organ by imitating three-dimensional (3D) model. Commonly adopted bioprinting methods comprise inkjet-based bioprinting, laser-assisted bioprinting, and extrusion-based bioprinting. The former lies bioink picoliter droplets, via a noncontact process, on a substrate. On the other hand, laser-assisted bioprinting utilizes a laser source to deposit biomaterials onto a substrate. While in extrusion-based bioprinting technique, layer-by-layer bioink deposition creates predesigned 3D constructs. Such technique offers an advantage of printing highly viscous ink and high cell density over the other techniques, and thus, it is the mostly adopted bioprinting technique.

This technique was adopted by Joung et al. to fabricate a spinal cord scaffold aiming to construct an in vitro tissue model of complex central nervous system,to fabricate 3D scaffolds intended for bone regeneration by Roque et al. and also employed by Gospodinova et al. to develop hydroxyethylcellulosebased bioink implanted with Hela cells to bioprint a model for cervical tumor . Extrusion-based bioprinting can be further differentiated, based on ink dispensing systems, into the following categories: screw-driven dispensing, piston-driven dispensing, and pneumatic dispensing .

Three dimensional printing 3D printing technology can be defined as a process to construct subjects having a 3D structure applying a computer-aided design (CAD) model. This is performed via layer-by-layer deposition on a built platform. 3D printing was invented based on a stereolithography procedure four decades ago and was primarily used in industrial process optimization and prototyping.3D printing has proved a pronounced potential in interdisciplinary biomedical research field, including pharmaceutical technology and bioengineering. Additionally, 3D printing technology is a required substitute for the traditionally fabricated DDS as it facilitates the efficient and cost-effective preparation of sophisticated customizable creations. Furthermore, polypills fabricated by additive manufacturing technology include multiple pharmaceutically active ingredients and excipients compositions, and demonstrate distinctive drug pharmacokinetics, prompting the pharmaceutical industry revolution.3D-printed DDS also enable drug controlled release for different compounds exerting specific functions in human body.

1. TYPES OF 3D PRINTERS

The 3D printers used in the pharmaceutical field comprise inkjet-based 3D printers, selective laser sintering stereolithography, pressure-assisted microsyringe, and fused-deposition modelling.

1.1 Inkjet Based 3D Printers

Inkjet-based 3D printers spray the liquid in droplets form. This type is classified as drop-on-demand and continuous jet printers. The former type, being more economic, produces an accurate ink amount as demanded for the printing process.

The droplets stream is controlled by piezoelectric nozzle vibration or vapor bubble induction by a thermal nozzle. Whereas, in continuous jet printers, a continuous ink droplets stream is produced from a pressure pump. In 2015, Spritam®, fast-disintegrating levetiracetam tablet was introduced in the market manufactured by the inkjet-based 3D printer solving the problem of swallowing difficulty associated with high drug dose conventional tablets.

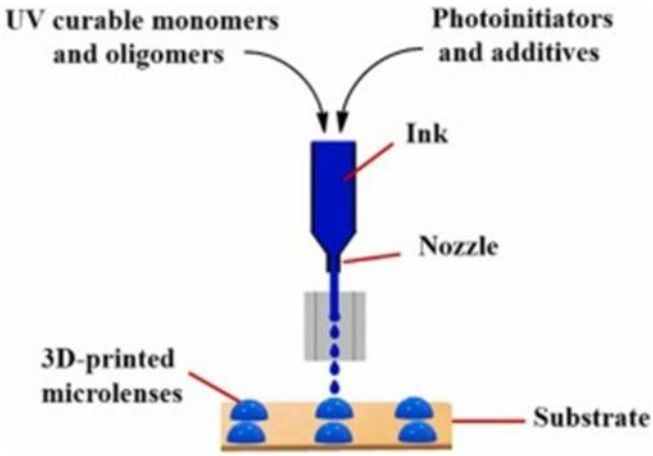

Figure 1. Inkjet-based 3D printers

1.2 Stereolıthography 3D Printers

The principle of stereolithography (SLA) 3D printers is based on exposing a liquid dispersing a mixture of a photosensitive polymer with the drug to ultraviolet light, as a high source of energy, till solidification.The source of ultraviolet light in SLA printers is the laser beam whereas in digital light processing printers, digital light is the source. Briefly, upon exposing photosensitive polymers to the high energy of light, they act as a crosslinker initiating liquid solidification into the intended 3D objects. SLA 3D printers are able to produce high-resolution 3D designs with smooth surfaces. Conversely, the main disadvantage arises from the toxicity endorsed from the photosensitive cross-linkers. Pressure assisted microsyringe 3D printers One type of nozzle-based printers is the pressure-assisted microsyringe 3D printers. A paste, formed from the drug and excipients, is deposited by the pressure force of the piston of the syringe's nozzle to form the designed 3D object.

This process is suitable for thermolabile drugs; however, the produced objects might shrink or got destructed in the post-printing drying step.

1.3 Fused Deposition Modelıng 3D Printers

On the other hand, in the commonly used fused-deposition modeling printers, a hot-melt extruder is used to form filaments from the polymer and drug, which are rolled in a spool to be ready for the printing process. Then, the printer pulls the filament from the spool to move across a preheated nozzle, to deposit the designed 3D object on the printing platform. Fused-deposition modeling printers are rapid and cheap in printing, this merit aided in their widespread use; however, they demonstrate a limited use with thermosensitive drugs owing to the exposure to high temperature. Also, a step of surface smoothing is required to obtain objects with acceptable shape. In this article, demonstration of the applications of 3D printing to develop pharmaceutical dosage forms as well as 3D bioprinting for tissue reconstruction that were recently published is presented.

1.4 Selective Laser Sintering 3D Printers

Selective laser sintering 3D printers point a beam of laser on a powder bed surface containing a mixture of the polymer and drug, the beam raises the powder bed temperature resulting in sudden powder sintering.

Performing this process repeatedly lays new powder layers over the sintered ones, with the aid of a roller till the construction of the intended 3D object.

This type of printers utilizes the powder form of the polymer and drug excluding the use of solvents and without any extrusion process.

The use of this type is limited due to the liability of drug decomposition by the elevated heat; however, this could be overcome by speeding up the laser scanning.

3D printers are industrial additive manufacturing machines that use a high-powered laser to fuse small thermoplastic powder particles (typically Nylon) into solid, functional, and durable parts.

Because the surrounding, unfused powder supports the part during printing, SLS eliminates the need for support structures, allowing for highly complex geometries, interlocking parts, and dense, nested printing for high productivity.

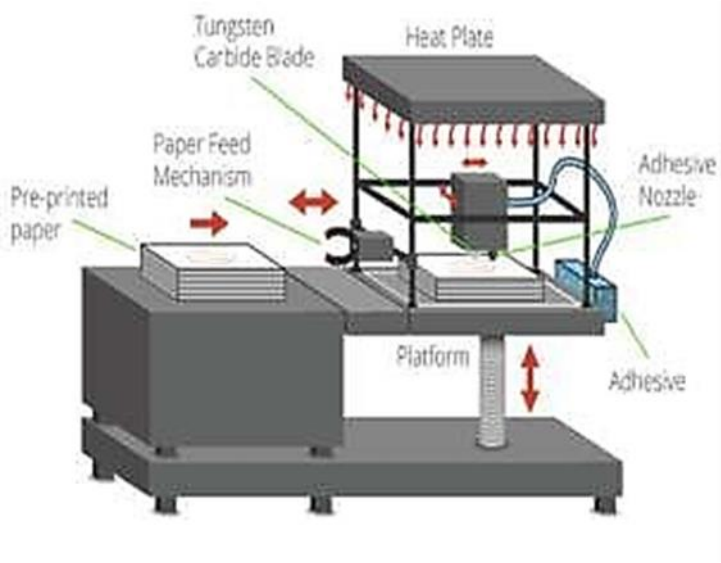

Figure 2. Laser Sintering 3D Printers

2. 3D PRINTING FOR FABRICATING DRUG LOADED OCULAR INSERTS AND PUNCTAL PLUGS

The production of patient-centered, tailored, and complex-shaped ciprofloxacin HCl-loaded ocular insert was facilitated by combining fused-deposition modeling and hot-melt extrusion 3D printing. The biodegradable, biocompatible, and bioadhesive Klucel™ hydroxypropyl cellulose was the polymer of choice for the 3D printing process with the aid of an experimental design approach to attain the intended tailored drug release profile. The authors performed a thorough investigations regarding drug-excipient compatibility, thermal characteristics, drug content, topography, in vitro drug release, antibacterial efficacy, ex vivo transcorneal penetration, as well as a stability study for the prepared ocular inserts.

The optimum design revealed the presence of the drug in an amorphous form and attained an extended drug release profile for 24 h. The optimum formulation also possessed smooth surfaces, good mucoadhesive strength, and absence of chemical or physical incompatibility.

3. FOUR DIMENSIONAL PRINTING

Four-dimensional (4D) printing is an evolving technique in which smart materials are 3D printed to produce items that alter their shape after production, in a programmed manner over time, upon exposure to certain external stimuli (electric or magnetic fields, temperature, moisture, pH, UV, or ion composition). 4D-printed dosage forms differ from 3D ones in that time is considered as the 4th dimension during their performance. The term "4D printing" describes smart materials manufactured by the additive technique to produce easily achieved, complex-shaped, nonstatic objects that are more advanced than 3D objects. 4D-printed objects can be manufactured with 3D printers.4D printing technologies yield high-resolution biostructures in a more advanced manner than the 3D printing biofabrication methods do.The transformation potential of 4D-printed substances has the ability to fabricate either dynamic and controlled structures or unique, hollow structures as well. It also gives the ability of the transformation from 2D patterns to 3D patterns via self-folding abilities.

Shape memory materials are smart materials that gained much interest in different research fields.They dynamically react to an externally applied environmental stimulus, and adapt themselves to perform the required function according to the endured change.The ability of shape memory materials to control the undertaken modification is behind their description as smart materials. By applying an excess stress, a temporary shape is attained from a permanent one. The process can be referred to as a "shape memory creation process" or "programming step." After stress removal, the temporary shape is maintained till the substance is subjected to a specific unmechanical stimulus to recover its original shape. Thus, they are able to temporarily preserve the applied mechanical stress during the programming step and undergo the predefined mechanical actuation.

Remarkably, the restoring happening throughout the recovery alters the mechanical distortion causing the acquired temporary shape. Employment of the shape recovery behavior has many reasons and applications. It may be employed to enable a sustained in situ retention with minimal invasive administration, or to ensure removal from the target site. In addition, it can trigger drug release after reaching drug delivery site.

4. TYPES OF SHAPE MEMORY MATERIALS

Shape memory materials are generally categorized as shape memory polymers, shape memory hydrogels, shape memory ceramics, and shape memory alloys. The first two types being the most important for the pharmaceutical technology field.

4.1 Shape Memory Polymers

Shape memory polymers possess two shapes. Shape "A," created from a mechanical distortion, is a temporary architecture and can be transformed to the permanent structure; shape "B." The transformation from the temporary to the permanent forms depends on the molecular structures, which are not essential to be positioned within the chemical structure and that get the mechanical properties through repeated units, in a manner that precise molecular parameters can be adjusted. In this type of polymers, the net points are linked through chain fragments, which creates the permanent form. Physical interaction takes place in the polymeric units, the morphological framework of which involve amorphous and crystalline phases. The efficient shape transformation requires the net points to be deformed, to elongate the chains and increase chains flexibility. Hence, the permanent form is achieved via recoiling of the chain structures. Shape fixation is completed via extra temporary cross-links, which could be either chemical crosslinks or physical interactions.

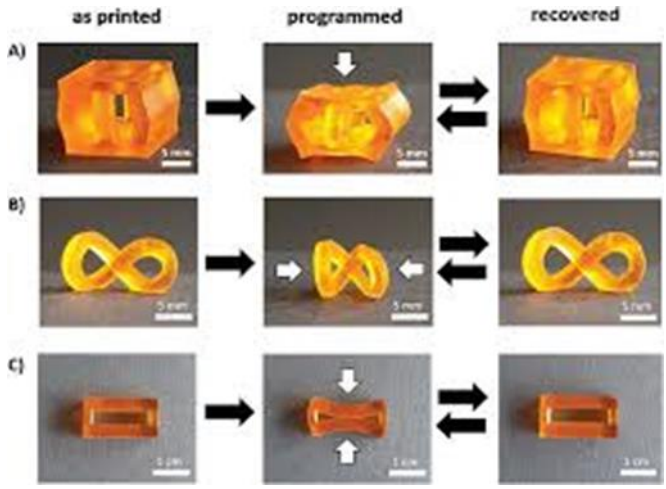

Figure 3. 4D printing of shape memory polymers

4.2 Shape Memory Hydrogels

Hydrogels can also respond to pH, light, or temperature resulting in programmable temporary shape memory hydrogels. The amendment of shape memory polymers arises from changing the network morphology in the polymeric backbone as a consequence of functional chains responding to an effect as temperature or polarity. The first introduction of shape memory hydrogels was performed by copolymerizing acrylic acid and stearyl acrylate with the aid of a cross-linking agent (methylenebisacrylamide) creating a thermosensitive shape memory hydrogel. Molecular switches permit polymer reshaping, by combining with water molecules resulting in architecture alteration.Whereas the temperature-responsive influence of shape memory hydrogels is affected by a thermal stimulation to the cross-linking groups, the breakdown of the weak physical cross-links produces a temporary structure. Consequently, structure is deformed and the materials is softened. When cooled, shattered physical bonds reformed and positional deformation is retained.

Shape memory hydrogel was also effectively exploited for chronic wounds treatment; by responding to a specific temperature, geometrical change of the polymer would result in terminating the need of repeated wound dressing application, resulting in better patient compliance.In another study by Yasin et al., a shape memory hydrogel was developed using the host–guest approach.

A crystalline domain resulted from cross-linking α-cyclodextrins and hydrophobic chains of the polymers with the aid of N,N′-methylenebisacrylamide. The produced crystalline domain can be delineated to temporary forms in response to temperature variation and complete regaining of the deformed shape.

4.3 Shape Memory Polymer Composites

Shape memory composites involve numerous constituents that enhance the matrix material performance or function, together. They are intended to improve the mechanical characteristics and to consolidate more stimulus techniques.Lin et al. designed a composite for photothermal therapy, biomedical use, and tissue engineering. In their study, 3D filaments of polylactic acid and polylactic acid/polybutylene succinate were manufactured by a high-quality fused-deposition modeling printer. The shape memory behavior, tensile strength as well as surface morphology of the produced filaments were examined. Then, the honeycomb-structured carbon compound, graphene oxide that possesses an outstanding photothermal property was functionalized on the prepared filament. This unique design was intended to function as a vascular, tracheal, or intestinal stent. Endoluminal and starfish stents were prepared using the polylactic acid/polybutylene succinate filaments. To assess their shape recovery performance, temporary shapes were placed in a hot water bath, where the starfishshaped stents exhibited a changed recovery time relative to the endoluminal structure. This might be related to the dense wall of starfish stent, taking more time to transfer heat and restore its shape. Furthermore, 4D-printed scaffolds of near-infrared-triggered (graphene oxide/ polylactic acid/polybutylene succinate) composite were applied for bone regeneration. The scaffold had a porous structure, and their transformation was remotely and dynamically controlled by the near-infrared laser. As a conclusion, the prepared polylactic acid/polybutylene succinate scaffolds could be functionalized as various structures based on the required disease to be treated.

5. APPLICATIONS OF 4D PRINTING

4D printing for developing drug-loaded implants for breast cancer treatment, unfolding/expandable dosage forms, drug-loaded stents as well as tablets loaded with anticancer drugs.

5.1 4D Printing For Developing Drug Loaded Implants For Breast Cancer Treatment

Although breast-conserving surgery is performed as a primary approach to treat breast cancer in its early-stage, the chance of recurrence and body image alteration adversely influence patient by the emotional distress. It is advised also to complete the treatment with either radiotherapy or systemic therapies to increase the patient's survival chance, and also to avoid possible recurrence. This leads to longer treatments durations, and undesirable systemic adverse effects. A patient-centered approach is essential to eradicate the heterogeneity between tumors and individuals. To achieve this aim, a multipurpose 4D-printed doxorubicin-loaded implant was developed by Moroni et al. by blending carboxymethyl cellulose sodium salt and cellulose nanocrystals. Full rheological investigation was performed in order to expect the printability accomplishment. Herein, by swelling, the designed smart device was programmed to change size for exact fitting in the intended tissue cavity. This fitting is highly desirable for personalization of treatments and improves the esthetic results. The effect of the printing as well as formulation parameters on shape conversion was tested by conducting a swelling test, to prove the possibility of programming a 4D shape. The assessment of the anticancer efficacy was performed in vitro using MDAMB-231 cells, where the designed 4D-printed implant displayed an excellent anticancer efficacy. The results of the in vitro studies as well as the morpho-transformation suggested the potential of the designed implants as a promising treatment approach for breast cancer after resection, by filling the surgery-left void and providing an anticancer influence to prevent recurrence, as well. The authors suggested performing comprehensive investigations for the technical aspects for the fruitful translation of 4D printing technology into biomedical applications.

This necessitates proficiency regarding material selection, including their availability and smart properties, as well as a thorough understanding of how printing parameters and design could influence responsiveness to specific stimuli. Moreover, exploring other trigger stimuli that could increase other potential applications of 4D printing. However, in spite of these prospects, lack of clear regulatory guidelines for additive manufacturing technologies, and inadequate focus on scalability, hinders further progression from research to clinical use. Therefore, foregrounding regulatory strategies for large-scale production is fundamental.

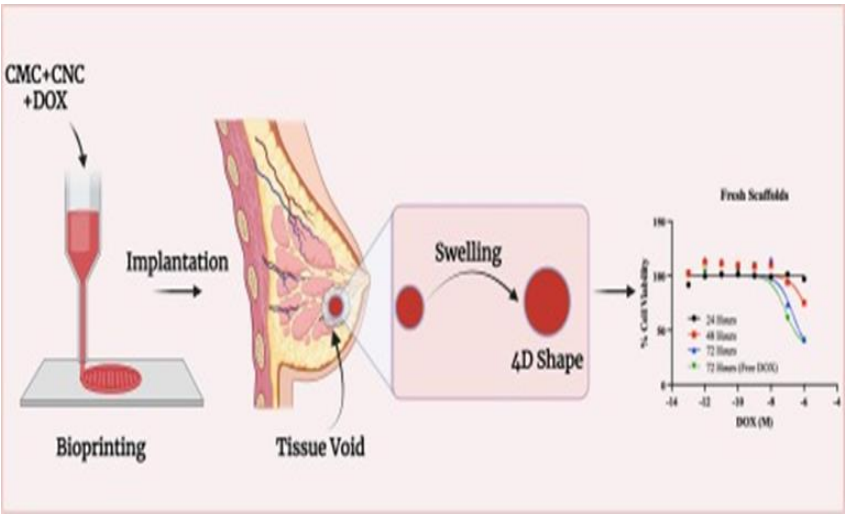

Figure 4. 4D Printed multipurpose Smart Implants for Breast Cancer Management

CONCLUSION

The presented chapter demonstrates the merits achieved upon utilizing the 3D printing technique in the pharmaceutical field. Knowing that this technique is still in the initial stages, but in retrospect, it will enable the manufacture of personalized or customized medications with favorite features that cannot be achieved by the traditional manufacturing technologies. Although, as stated in the above sections, some challenges are facing their large-scale manufacturing, 3D-printed pharmaceuticals will overcome such challenges sooner or later.

In the upcoming future, 3D printing technique will be exploited to develop organ transplantation and tissue repair remedies. On-demand 3D pharmaceutical and medical devices manufacture will be more economical and affordable. Also, the opportunity of manufacturing 3D-printed tablet with multiple drugs "a polypill" will be globalized, enhancing the patient compliance and promoting patient adherence to given medications. 3D printing will be applied to prepare customized drugs, organs as well as nutritional products, after solving the obstacle of integrating 3D printing with tissue engineering. The incorporation of complicated drug delivery systems within smart dosage forms via the 3 D printing technology will enable successful personalized release profiles and targeting, which in turn, enhances the therapeutic outcomes. Also in the future, developing portable compact 3D printers that can be utilized at hospitals or pharmacies. This will enhance the speedy manufacture of personalized treatments, and improve patient access to customized medications. Furthermore, 3D printing can be integrated with other digital health technologies, such as patient monitoring systems and electronic health records to facilitate adaptive dosing based on individual patient requirements, continuous data transfer, and realtime monitoring of patient response to the administered therapy.

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