

Formulation and Performance Evaluation of Eco-Friendly Smart Blister Packaging with a Colorimetric Expiry Indicator for Temperature-Sensitive Drugs

Irshad Ullah

Department of Pharmacy, University of Swabi, Swabi KPK Pakistan.
Email: hafiz.irshad@ferozsons-labs.com

Syed Sohail Ahmad

Department of Pharmacy, University of Swabi, Swabi KPK, Pakistan

Asnaf Gohar

Department of Pharmacy, Abdul Wali Khan University Mardan.
Email: asnafgohar@gmail.com

Mian Inaam Zeb*

Department of Pharmacy, Bacha Khan University, Charsadda, Pakistan.
Corresponding Author Email: Inaamzeb@gmail.com

Salar Muhammad

Assistant professor Department of Pharmacy Abdul Wali Khan University Mardan. Email : salar_pharmacist@awkum.edu.pk.

Author Details

Keywords:

Smart Blister Packaging, Colorimetric Expiry Indicator, Biodegradable Polymers, Temperature-Sensitive Drugs

Received on 02 May 2025

Accepted on 15 May 2025

Published on 20 May 2025

Corresponding E-mail & Author*:

Mian Inaam Zeb
inaamzeb@gmail.com

Abstract

Pharmaceuticals and vaccines are sensitive to temperatures and other bio-pharmaceuticals and thermolabile oral drugs are also very susceptible to a drop in their strength once exposed to conditions beyond the recommended storage conditions. Traditional PVC-aluminum blister does not offer real-time numerical repulsive exposure of thermal fluctuation and also adds to the pharmaceutical plastic waste. The objective of the present study was to design and test a smart blister packaging system,

which is eco-friendly and consists of biodegradable cavity films and an irreversible natural-dye suffered colorimetric expiry indicator that is able to signal runaway degradation by temperature. Melt-casting and thermoforming were used to prepare two bio-polymer matrices PLA-nanoclay composite and

starch-cellulose to produce structurally stable blister films. One of the bio-pigment colorimetric sensors was imprinted on a cellulose substrate and stickered with non-toxic binders to avoid movement into any drug cavity. Mechanical strength, barrier to moisture and oxygen, indicator functionality, environmental safety and biodegradability were thoroughly evaluated. It was found that both biodegradable films complied with pharmaceutical requirements of tensile strength, puncture resistance, elongation and seal integrity, with PLA composites films exhibiting barrier properties comparable to PVC. The colorimetric indicator was capable of responding to an irreversible high-contrast change of color within minutes at 32–35D, which is exactly the behavior of irreversible degradation of thermolabile drugs. Both films were tested by soil-burial and composting tests as being safely and non-toxicly biodegraded with no pigment or chemical migration. The aggregate results support the possibility of the sustainability and intelligent expiry communication integration, on the unit-dose level. The suggested system, the smart biodegradable blister, is a low-cost, scalable, and easy-readable system, which will be beneficial to patient safety, reduce medication errors, and promote environmentally conscious pharmaceutical packaging practices, especially in the low-resource healthcare environment.

Introduction

Pharmaceuticals that are sensitive to temperatures, like vaccines, biologics, insulin, and some antibiotics, are susceptible to chemical degradation (Khan, A. 2024). when subjected to changes in temperature during storage and distribution. Intermittent exposure to unregulated temperatures in the supply chain can decrease the drug potency, interfere with safety, and cause therapeutic failures. The World Health Organization estimates close to a quarter of vaccines in the world are exposed to accidental temperature spikes

in the supply chain due to lack of real-time measurements and exposed product stability in real-time exposure history. The smart packaging technologies combine environmental monitoring indicators allowing drugs to be linked to their exposure history, which would otherwise be assessed by the automatically picked date based on ideal environmental conditions.

Colorimetric indicators The most recent analysis is on pharmaceutical packaging colorimetric indicators. Colorimetric indicators are under investigation as an option to pharmaceutical medication packaging in unit-dose blister packages due to low cost, facile interpretation, rapid optical response, and the capacity to operate without electronic power sources, unlike electronic expiry indicators. Although in their early stages of development, colorimetric indicators have a clear benefit over electronic expiry indicators in that they provide actual feedback on the integrity of the product, as opposed to an estimated expiry date. Colorimetric indicators are not

At the same time, the environmental pressure, accumulation of plastic waste and sustainability requirements are shifting pharmaceutical industries to environmentally friendly and biodegradable packaging materials (Peeriga et.al,2025). Conventional blister packs are based on polyvinyl chloride (PVC) and multilayers with aluminum, which is challenging to recycle and difficult to dispose of environmentally. Sustainable materials such as polylactic acid (PLA), starch-based polymers, cellulose films, chitosan coatings and bio-nanocom.

Thus, it is extremely necessary to develop smart biodegradable, drug-safe, user-readable, and supply-chain-relevant blister packaging. Incorporation of a non-electronic, biodegradable, colorimetric expiry indicator within a blister pack can assist pharmacists, manufacturers, distributors and patients to recognize at a glance the degraded medicines, to reduce medication error as well as to prevent clinical failure associated with the

undetected cold-chain violation. Also, a printed or laminated indicator on a blister package with non-toxic pigments or natural dye systems (rather than standard heavy-metal or synthetic inks) gives extra form of sustainability and compliance to human safety (Randhawa, K. S. 2024).

The paper will seek to design and analyze a green smart blister pack system that includes a colorimetric expiry mark (Sikaria et.al, 2025) that will be used specifically in temperature sensitive oral drugs to identify thermal excursions. The paper addresses the creation of biodegradable blister cavity films, the choice of the thermochromic or color-responsive dye systems, the confirmation of the optical change based on the temperature, and the evaluation of the packaging parameters such as mechanical strength, barrier, environmental safety, and functional reliability. The innovation of this product is that it is not only (1) environmentally friendly but also (2) thermally smart and can provide not only a visual warning to the final user on the actual use of the product, due to its exposure to elements like temperature and (3) a projected expiry date of the product on the packaging itself, which would be shown as a calendar.

Literature Review

Smart & Intelligent Pharmaceutical Packaging for Temperature-Sensitive Drugs

Passive containment systems have developed into active and responsive to the environment intelligent packaging to monitor and report product condition. Temperature-sensitive drugs like vaccines, insulin, hormones, probiotics, and heat labile antibiotics are likely to denaturing, oxidizing, hydrolyzing, polymorphic transition, and lose therapeutic effects at temperatures that do not match recommended storage limits. Commonly used blister packaging merely puts a print of the expiry date, which is

calculated under presumed ideal conditions, and does not provide information about the history of exposure, and thus cannot be used to assure the quality of thermolabile drugs, particularly in large-scale cold-chain logistics.

Smart pharmaceutical packaging incorporates non-electronic or electronic sensing systems to ensure that the users of the product can see the extent of environmental stress so that they can establish the real use of the product. Optical indicators are regarded as some of the most viable intelligent communication methods because they do not require any power, read instantly by a human, the minimal calibration parameters, lack the digital infrastructure, and can be printed in vast amounts using mass-printing technologies (Chen et.al,2025). Visual smart indicators have a reliability that is based on irreversible response behavior as opposed to reversible thermochromic response where it can revert to original color after normalization of temperature, (Supian et.al,2024) since only irreversible systems can be accurate in reflecting cumulative temperature abuse within supply chain.

Colorimetric smart indicators can be based on molecular structural change, reconfiguring of metal-ligand interactions, protonation states of dyes, redox-mediated pigment dismantling, or bio-dye conformational changes, changing visible absorbance spectra. Such systems are used to support a significant pharmaceutical packaging requirement which includes constant surveillance, dose-unit warning, tamper-proof reading, and quick distinction between viable and inoperable medicines. Smart packaging of thermolabile drugs has been studied using printed inks on secondary cartons, sensor tags, vial labels and paper-based monitoring strips, but integration at the primary

level of the blister strip dosage, is relatively little used although this method is commonly used worldwide with solid oral dosage products.

The regulatory bodies and the pharmaceutical supply-chain systems emphasize the significance of stability monitoring (Ogbuagu et.al,2023) and quality assurance prior to dispensing but real-time monitoring at consumer-level formats is yet to be widely used in commercial blisters. This establishes a gap in the area of innovation in which smart indicator integration needs to be reduced to a standard platform that does not interfere with drugs chemically and physically, is low-cost, to be adopted on a large scale, and is biologically stable to survive long-term storage and accelerated stress testing.

Colorimetric Expiry & Thermochromic Indicator Technologies in Drug Packaging

Colorimetric expiry indicators are developed to generate a visible color change to environmental stimulus. (Peleg, M., & Saguy, I. S. 2024). In the case of temperature-sensitive drugs, colorimetric thermal indicators are divided into two broad categories, namely, reversible thermochromic indicators and irreversible thermo-responsive indicators. Reversible systems are based on leuco dyes, liquid crystals, or changes in polymer matrix color which varies with changes in temperature, and are applicable to momentary temperature display, but not to expiry and drug degradation warnings where the history of exposure has to be stored permanently. Irreversible temperature indicators are permanent changes in molecular or chemical structure which occur once triggered. These modifications are commonly caused either by thermal degradation of dye complexes, diffusion-limited loss of reactant, catalytically activated pigment conversion, catalytically fixed reaction states or organic decay of dyes that causes long lasting changes in chromatic absorbance. The

systems find use in pharmaceuticals in preference as they are closer to the actual behavior of drug degradation, which is irreversible as well.

Recent trends focus on natural and non-toxic systems of dyes, which replace synthetic pigments that could be hazardous to the health or environment. Pharmaceutical applications of natural colorimetric systems 5 are plant-derived anthocyanins, curcumin-based systems, chlorophyll-conjugated pigments, betalains, carotenoid-based mixtures, and hybrid bio-dyes that are stabilised with polymer binders. Although natural dyes are safe and environmentally friendly, they are usually more unstable than synthetic dyes and must be stabilized by using methods like polymer encapsulation, cross-binding binders, UV-blocking overlays, antioxidant film layers, humidity-regulated laminating layers, nanoparticles anchoring, and composite immobilization in order to stop premature fading or premature triggering during normal storage.

A smart blister indicator should fulfill various performance criteria: it should be visible in high contrast in color, it should not be affected by the ambient humidity environment, it should strongly adhere to the backing substrate which could be a cellulose or a biopolymer laminate film, it should be stable in normal storage conditions, it should just change color permanently upon threshold violation, it should be optically clear when printed on small surfaces, and it should be correlated with stability curves of drugs. Accelerated storage tests are performed under worst-case thermal conditions to make sure that optical shift is not induced under conditional tolerable variations of temperature. Another important factor is manufacturability; that indicator should be printable with scalable industrial (Matoc et.al,2024) coating strategies (rotogravure printing, flexographic ink dispersions, spray-coating, lamination integration, or embedment in the back

of the cavity without obstruction by thickness that would allow sealing to fail or endanger safety of the patient. The significant performance issues noted in colorimetric primary drug packaging are false reversibility indicators, dye degradation with time, weak adhesion, oxygen or moisture sensitivity despite the absence of temperature limitations and inadequate color differences following polymer immobilization. Nevertheless, the majority of the business or research is still concentrated on secondary packaging layers other than single dose primary blister cavities. Blister indicator systems should also be sensitive to the issue of migration in case of temperature-sensitive drugs in solid formulation such that the reactive dye components are not leached out of a tablet to affect the performance of aluminum or bio-film coatings.

Sustainable & Biodegradable Polymer Innovations in Blister Packaging Systems

Traditionally, pharmaceutical blister packaging is done with multilayer PVC cavity films (thermoformed) with the backing foils of aluminum. Although PVC offers the desired level of clarity and resistance to moisture, the recyclability of the plastic after usage has been appallingly low owing to chlorine concentration, toxic fumes during combustion, slow decomposition rate and difficulty in removal when mixed with aluminums layers. This poses a bottleneck in sustainability of pharmaceutical packaging, particularly in those nations in which the rate of medicine use is high but recycling facilities of pharmaceutical plastics are scarce. The sustainable blister packaging study examines the use of biodegradable cavity films, recyclable backings. Such classes of polymers as PLAs (Polylactic Acid), PHAs (Polyhydroxyalkanoates), thermoplastic starch, cellulose nanofiber composites, chitosan-biopolymer blends, alginate coatings, bio-nanocomposites reinforced with polymers, polybutylene adipate terephthalate blends, plant-fiber reinforced

biodegradable laminates, and hybrid polymer matrices targeted for thermoform compatibility have been studied. These biopolymers are optimized to give required blister pack characteristics: formable at heat (thermoforming window), tensile strength, impact strength, puncture strength, clarity when needed, moisture permeability, oxygen permeability, controlled degradation characteristics, and compatibility with heat-sealing layers.

Although the use of PLA has been extensively studied because of its clarity and scalability in the commercial sphere, starch-cellulose composite blisters are also receiving interest because of non-petroleum source, safety in medicine storage, and effectiveness in decomposition mechanisms in natural conditions. Nevertheless, bare biopolymers may not comply with the pharmaceutical barrier needs, and thus, advanced composite fortification with nanoclays, graphene derivatives, silicate platelets, zinc oxide dispersions, cellulose nanocrystals, and seal-layer alterations is needed to enhance vapor protection without biodegradability decrease. Some of the methods of sustainability evaluation are soil-burial degradation, enzymatic degradation behavior, (Singh et.al,2022) compostability, water uptake percent stability curve, puncture survival threshold, migration analysis to ensure non-interference with drugs, regulated dye non-toxicity confirmation, film elasticity retention upon molding, and comparison with conventional PVC blister performance criteria.

The future temperature-sensitive drug blister system should provide a combination of two functions: biodegradable material structure and stability smartness. (Jha, A., Rama et.al 2021) The trend is consistent with the pharmaceutical packaging innovation objectives that focus on decreasing the environmental load without undermining the security of drugs, child-resistance functionality, seal integrity, sterility where necessary, and ease of

use by the consumer. Nevertheless, there are only a few studies that have successfully achieved the co-integration of biodegradable thermoformed blister films and a printed colorimetric expiry label at the primary dosage level, which is a research opportunity that is also significant in that sustainability and intelligent pharmaceutical stability communication can be achieved on mass-manufactured blister packages.

Methodology

This paper used an experimental formulation and evaluation approach to design an environmentally-friendly smart blister package system combined with colorimetric expiry sensor with the temperature sensitive drugs. This was done in three stages (1) The choice of material and the preparation of the biopolymer film was done, (2) The colorimetric thermal indicator was developed and laminated, and (3) The final smart blister system was evaluated in terms of its performance. Two polymeric matrices, which consist of PLA-based composite film and starch–cellulose blended biopolymer film, were used in the formulation stage to prepare biodegradable blister cavity films. In case of the starch-cellulose framework, pharmaceutical grade corn starch and microcrystalline cellulose were chosen as the main biodegradable components to be plasticized by glycerol to enhance its flexibility and thermoforming capacity. In the case of the PLA composites, the pellets of polylactic acid were melted and strengthened with organically modified nanoclay to improve the moisture-barrier activities and maintain biodegradability. A melt-casting and hot-press film formation technique was used to form each polymer mixture under controlled temperature and pressure to provide a uniform consistent thickness needed to thermoform a blister. In order to achieve favorable sealing and cavity formation, film thickness was kept according to the range of

pharmaceutical blister film standard. Formulations were all de gassed, homogenized and stabilised and then moulded in to blister films.

In case of the colorimetric expiry, a bio-pigment complex was synthesized into a natural-dye based irreversible thermo-responsive ink system, which could be permanently chromatically changed to the post-drug-safe temperature. The dye system was embedded into a non-toxic polymer binder to stop their migration towards the tablet cavity coupled onto a biodegradable backing sheet of cellulose that substituted the traditional secondary labels. A lamination process is done to the indicator sheet by means of thin-layered laminate with an adhesive that does not interfere with the integrity of heat-seal. The lamination construction was done to withstand the humidity and oxygen in normal storing and offer sensitivity in threshold violation. The activation temperature on indicators was adjusted to recreate common cold-chain failure temperature of thermolabile oral medicines. Testing and evaluation entailed thorough mechanical, barrier, environmental safety, functional reliability and biodegradability tests. Mechanical strength measurements were done on blister films tensile strength, elongation at break, puncture and surviving seal were done to verify that the films resist the packaging, transport, and handling stress. Barrier performance analysis has evaluated water vapor transmission rate (WVTR) and oxygen permeability which is needed to guarantee the protection of drugs under ambient conditions before expiry. Environmental safety assessment involved migration/leachate analysis by placing films in simulated storage conditions and ensuring that no diffusion of chemicals into drug cavities occurred. The safety of dye migration was directly observed by placing active indicator sheets in the close proximity of the inert tablet simulants and evaluating the potential of color/mass transfer.

The functional performance of the colorimetric indicators was tested by controlled temperature exposure cycles. Blister strips were subjected to dry-heat incubators with incremental temperatures above safe-store temperatures to test the clarity of the color transition, contrast and irreversibility. The time and temperature at which visible change was obtained were noted so that the response is only obtained when there have been harmful thermal changes. Blister sheet accrued indicator readability and contrast were further checked using the conditions of accelerated stability that simulated worst-case supply-chain storage hazards. To determine biodegradability, a soil-bury degradation test, which took weeks, was carried out in which developed blister films were incorporated into organic soil under regulated moisture and microbial activity and evaluated the rate of decomposition, loss in mass, physical integrity fragmentation, and relative environmental degradation capacity. Photographically and quantitatively, compostability and the process of degradation were recorded. Also, the eco-compatibility tests ensured the by-products of degradation were non-toxic, and in line with the sustainable pharmaceutical packaging standards.

All the obtained findings were compared to the standard performance of conventional PVC-aluminum blister packaging to ascertain sustainability viability and did not affect the safety of the drug or its ability to perform the required functionality. The optical color transition outcomes were plotted as anticipated thermolabile degradation behavior, where there is a correlation between indicator change and irreversible pharmaceutical stability failure responses. The identified methodology allowed developing a prototype of a dual-function blister package, which is environmentally friendly and temperature-sensitive and confirmed its structural strength, readability by users, safety standards, reliability, and biodegradation performance.

Results

The formulated biopolymer blister films and colorimetric indicator sheets were analyzed across physicochemical, mechanical, environmental safety, functional reliability, and biodegradation parameters. The results are summarized in four evaluation tables followed by interpretation.

Table 1: *Mechanical Strength Evaluation of Developed Blister Films*

Test Parameter	PLA-Composite Film	Starch-Cellulose Film	Standard Requirement for Blister*
Tensile Strength (MPa)	48.6	32.4	≥ 30 MPa
Elongation at Break (%)	6.8	15.5	5–20%
Puncture Resistance (N)	18.7	12.3	≥ 10 N
Seal Integrity Survival	Passed	Passed	Must Pass

Both film versions qualified as the minimum mechanical performance in the pharmaceutical blister thermoforming applications. Nanoclay reinforced PLA-composite film was found to be stronger in tensile and puncture resistance, and starch-cellulose was more flexible, which is an advantage when creating a cavity. Notably, seal integrity stress was also successfully overcome in both movies, which proved that the structure of biopolymers did not affect the integrity of sealing the packs.

Table 2: *Moisture & Oxygen Barrier Performance*

Barrier Property	PLA–Composite Film	Starch–Cellulose Film	Conventional Blister Reference	PVC
WVTR (g/m ² /day) ↓	2.18	5.72	1.80	
Oxygen Transmission (cc/m ² /day) ↓	18.4	34.7	22.5	

PLA composite exhibited moisture-barrier response near to commercial PVC blisters, which means that vapour protection of thermolabile pills is delivery and activation on expiry. Starch cellulose, although biodegradable indicated higher values of WVTR, which is a property of semi-barrier film, but the values did not exceed the acceptable ranges of safe-drug stability, because of lamination overlay, added during the manufacturing process. PLA was also seen to have better oxygen protection as compared to conventional PVC reference and inhibition of oxidative degradation of the PLA during storage.

(↓ = Lower is better)

Table 3: *Colorimetric Expiry Indicator Thermal Activation & Irreversibility*

Indicator Property	Observation	Performance Outcome
Activation Temperature Threshold	32–35 °C	Correctly Calibrated
Visible Color Shift Time at 35 °C	8.5 minutes	Rapid & Readable
Color Change Behavior	Irreversible	100% non-reversible
Accuracy Correlation with Film Stress Cycles	Consistent linear color degradation response	High Reliability

The indicators only generated a high-contrast irreversible color change above the safe threshold. There was no color reversal observed when the pack temperature was normalized indicating successful locking chemistry. Response time was rapid implying real-time detection capability which is in consistency with behavior of drug degradation. The stability of the indicators under stress-mimicking thermal cycles was also stable, which demonstrated that the change was not falsely induced when the conditions were safe.

Table 4: Biodegradability & Environmental Safety Testing

Degradation & Safety Test	PLA-Composite Starch-Cellulose		Environmental Suitability
	PLA-Composite	Starch-Cellulose	
Soil Burial Mass Loss (%)	61.2%	84.5%	Suitable, Non-toxic breakdown
Compostability Progression	High	Very High	Excellent Bio-Decomposition
Migration/Leachate Transfer	None detected	None detected	Safe – No drug contamination
Dye Pigment Migration to Tablet Simulant	No transfer	No transfer	Fully safe integration

The decomposition rate of starch-cellulose film was also higher than that of PLA composites and this confirms that the latter has high biodegradation capacity. PLA-composite also exhibited progressive loss of mass that revealed great environmental friendliness and slow complete decomposing caused by nanocomposite reinforcement. None of the toxic by-products, film extract leakage or color pigment migration were observed close to pill cavities. Indicators and biopolymer films had a resultant zero contamination risk of the pill, which confirmed the compliance of pharmaceutical safety.

Discussions

This study aimed at creating a smart pharmaceutical blister system that is eco-friendly as well as incorporates an irreversible colorimetric expiry detector on temperature-sensitive solid oral drugs. The results confirm that both the intelligent and structural elements of the system passed the necessary performance criteria and at the same time reached a considerable environmental compliance.

The mechanical property exhibited showed that the tensile and puncture resistance of PLA-composite film was better than the starch-cellulose matrix as expected due to the nanoclay reinforcement of the polymer, which enhances the density, molecular bonding, and sturdiness of the polymer. Although both pure biopolymers often do not match the strength profile of PVC, both films developed still met the minimum mechanical demands of pharmaceutical blister thermoforming and could still remain sealed following simulated transport stress. The greater percent of elongation found in the starch cellulose film confirms that it is more elastic and this is a desirable characteristic when forming cavities and push through of tablets. This finding confirms the direction taken in the design strategy wherein the thermoforming feasibility was also taken into account besides the sustainability, to make sure that the packs are not fragile at end-use. The ability of the two films to pass seal survival stressed tests validates that there is no effect of biopolymer substitution to the blister pack safety and functionality- one of the most important issues in pharmaceutical packaging innovation.

The comparison of the two barrier performance also aids the packaging reliability. The lower rate of transmission of oxygen in PLA composites when compared to PVC means that the material is more resistant to oxidative

degradation increasing product stability before activation of a given indicator. WVTR behavior of PLA was also observed to be equivalent of the PVC reference, which proved that the vapor sensitivity of biodegradable polymers was countered by engineered structuring of composite. Though exhibiting greater WVTR, the starch cellulose matrix was within acceptable ranges due to layered lamination approach that was adopted during the pack construction. This result highlights the fact that biodegradability and barrier protection should be designed together since augmentation of biodegradation activity usually augments vapor permeability. The experiment has managed to cope with this trade-off through composite structuring, instead of chemical over-treatment, which did not compromise the protection of the drugs, and which was environmentally viable.

The greatest contribution of the research is the functional performance of the colorimetric indicator. The indicator was activated at 32-35 o C, which is consistent with typical excursion failures of thermolabile medicines in pharmaceutical storage commonly observed at 32-35 o C. Importantly, this indicator demonstrated irreversible chromatic change, which is evidence of locked-state dye chemistry and not of a thermochromic behavior. Reversible systems, which are frequently used as commercial temperature-labels, are not able to serve in expiry communication when used in pharmaceuticals since drugs that have been damaged by high temperature cannot recover their stability once normal conditions are restored. The permanent transition behavior of your indicator is thus a replication of actual drug degradation pathways, and this makes it more reliable as a true expiry confirmation device as opposed to a temperature display tag. The transformation time of 8.5 minutes at threshold breach observed supports the fact that real-time visibility can be obtained rapidly to allow pharmacists and patients to properly detect

loss of stability of the product in last-mile storage or transportation without the use of digital instruments.

Findings of biodegradation showed that starch-cellulose films (84.5) have a better mass-loss compared to PLA composites (61.2), which degrades slowly by slowly (longer) because of polymer reinforcement. High composting and soil-burial degradation progression, which resulted in non-toxic decomposition was documented in both films, and confirmed that the attainment of sustainability did not lead to any hazardous environmental by-products. Notably, the migration analysis revealed no chemical or pigment leakage to the simulants of the tablet cavity, which validated the compliance of pharmaceutical safety of the two blister material and the laminated indicator ink. It has been known that natural dye systems are sensitive to the environment but in this case, the study managed this risk by immobilizing the polymer binder and applying lamination and succeeded in avoiding premature fading or diffusion misbehavior during the safe storage conditions. The two-fold system proposed here has significant benefits to the pharmaceutical supply chains. To start with, visual intelligence at the primary level of the blister allows assessment of drug reliability at the level of unit dose, as opposed to most commercial indicators that measure the temperature on secondary cartons or the logistics containers, and the inner dosage is not affected by monitoring cues. Second, compatibility of sustainability implies that the pharmaceutical blister waste, which is currently one of the least recycled medicine packaging materials in the world, can be substituted with biodegradable or compost-compatible materials that will not compromise the safety of drugs. Finally, the article shows that supply-chain thermal failure visibility is not reliant on costly digital sensors and, therefore, can be adopted in low-resource pharmaceutical markets and public health

systems that are not feasible due to irregular electricity, IoT infrastructure, or continuous electronic package monitoring.

Overall, the results demonstrate that the innovation of the smart blister pack met the criteria of structural endurance, drug-protection capacity, environmental breakdown performance, migration safety, and irreversible colorimetric alert intelligence, which all collectively proves that with environmentally-friendly drug-safe blister technologies, eco-intelligent blisters can actually be used to print the true expiry date, depending on the history of temperature exposure, and no longer need to be intuitively labeled with calendar information. This will provide a sustainable solution to a safer pharmacy dispensing system, fewer medication errors, less therapeutic failure as a result of cold-chain damages, and an environmentally responsible disposal impact of temperature-sensitive pharmaceutical blister packaging.

Limitations

Even though this study was able to develop and test a prototype of a biodegradable smart blister packaging with an irreversible colorimetric expiry sensor, there were various limitations. First, the study was performed in controlled laboratory conditions (i.e., dry-heat incubators, standardized soil-burial conditions) which might not fully recreate the conditions of a real pharmaceutical supply-chain (i.e., varying humidity, mechanical impact of distribution vehicles, or exposure to the environment). Second, the number of tested biopolymer matrices (PLA-composite and starch-cellulose blend) was too small to generalize to other biodegradable thermoform films that may be better in terms of transparency, sealing capability, or degradation rates. Third, drug stability correlation was based on accelerated thermal activation standards as opposed to actual chemical degradation testing of actual temperature-sensitive pills in the blisters, which limits confirmatory capacity

on precise medicine-degree degradation synchronization. Fourth, optical response validation involved more color difference, irreversibility, and activation time than spectral resolution further analysis using sophisticated color quantification tools (e.g., CIE Lab or absorbance curve mapping), which, perhaps, can enhance accuracy in matching indicators and drug degradation. Fifth, mass loss and visual breakdown were used in assessing biodegradation, but polymer micro-fragmentation behavior, long-term ecological toxicity of nanocomposites residues and multi-environment comparative decomposition databases (marine, landfill, hospital incineration, high-rain conditions) were not done. Lastly, consumer-level analysis of usability was strictly to simple color shift readability with no comprehensive human-factor test to be conducted on pharmacists and patients of different literacy levels, including color-blind accessibility considerations and interpretation error-rate measures.

Future Directions

This prototype should be converted into a real-world validation in the active pharmaceutical storage and distribution channels in the future to ensure that the working robustness with respect to other environmental stressors that are not under control. Direct stability tests would need actual thermolabile pills put inside the biodegradable blister cavities, and then chemical potency assessed following periodical exposure to temperature excision to make sure that the indicator transition and medicine degradation curves can be accurately synchronized. The study must go beyond the two systems of biopolymers to other bio-nanocomposites and bio-recyclable back-sheet laminates so that the optimization of the materials can be studied to analyze the transparency, heat-seal bonding, child-resistance durability, and localized sustainable disposal capabilities. Quantitative optical profiling on non-color-assigning analytical color space characterization (CIE Lab ΔE stability changes,

pigment absorbance wavelength drift, threshold locking kinetic modeling) should be used in future research to enhance indicator precision and reproducibility in production on a large scale. Multi-environment biodegradation experiments can be applied to test decomposition activity of humid tropical soil, hospital waste streams, water immersion, oxidative aging in outdoor pharmacy racks, compost chambers and long duration of microbial exposure systems to guarantee wider environmental compliance certification. The research in human-factors must assess the accuracy of pharmacist and patient interpretation, color-blind accessibility overlay patterns, the rate of perceptual expiry alert errors and label to unit-dose recognition reliability to ensure safe dispensing acceptance. Finally, the work in the future must involve scale-up feasibility of industry and indicator printing thickness minimisation studies in order to maintain the uniformity of blister sealing pressure, non-toxicity-based stabilization of regulatory advisory, mapping regulatory advisory compliance to sustainable medicinal packaging framework, and commercial certification of sterility of thermolabile medicine blister packs.

Conclusion

This paper finds that the constructed eco-friendly smart blister packaging solution has reached its desired two-fold aim of both environmental sustainability and primary level temperature excursions based expiry communication in thermolabile solid oral medicines. The experimental results proved that both designed biopolymer films PLA-composite and starch-cellulose blends met all the necessary pharmaceutical blister packaging criteria in mechanical stability, elasticity, puncture resistance, and seal integrity, indicating that the biodegradable polymer replacement did not affect structural integrity during handling and transport. The results of the barrier evaluation further confirmed that the PLA-composite film offered oxygen and

moisture protection, which was very similar to the conventional PVC reference, and that the starch-cellulose matrix, although possessing higher inherent permeability, was still acceptable with regards to safety limits, because of the designed lamination design.

The colorimetric expiry indicator with integrated natural-dye based colorimetric optical transition was shown to exhibit a not only obvious but also prompt and irreversible optical change at elevated temperatures (above the safe-storage range (32–35 °C)) and thus is capable of fulfilling an authentic expiry alerting role instead of a temperature display role. The aspect of this non-reversible degradation of pharmaceuticals by temperature is consistent with the fact that temperature degradation of pharmaceuticals is irreversible, which allows human interpretation of integrity at the unit-dose level of the blister strip, with no electrical input, IoT connection, or digital measurement equipment. Migration and leachate analysis was used to verify the absence of transfer of dye or chemical to the tablet cavities, which confirmed drug safety compliance of the indicator integration.

The biodegradation test confirmed that the starch-cellulose film had a very high level of environmental decomposition, then disintegrated gradually into PLA composite, which is all matters of confirming the non-toxic, soil-disposable and compost-disposable materials, which reduces the environmental burden due to the non-recyclable conventional blister waste. The general findings supply good confirmative data that biodegradable blister systems can be upgraded to irreversible colorimetric intelligence in order to indicate actual expiry in accordance with temperature exposure background rather than presumed ideal-condition calendar dating.

This innovation provides a low-cost, scalable, pharmacy-relevant, environmentally responsible, safe-to-patients, and temperature-sensitive

packaging option to temperature-sensitive medicines particularly in low-resource health systems where electronic labelling deployment is costly or logistically infeasible. The research will be a verified basis on which pharmaceutical adoption will be carried out in the future, safer dispensing, lesser medication error, better visibility of quality of drugs in the last-mile, and modernization of the packaging life-cycle.

References

- Bumbudsanpharoke, N., Harnkarnsujarit, N., Gilchrist, J. F., Ko, S., & Keawpetch, T. (2025). The Rise of Nanotechnology in Pharmaceutical and Healthcare Packaging: Applications and Future Prospective. *Packaging Technology and Science*, 38(1), 3-31.
- Chen, J., Jastrzebska-Perfect, P., Chai, P., Say, M. G., Tu, J., Gao, W., ... & Traverso, G. (2025). Barriers to translating continuous monitoring technologies for preventative medicine. *Nature biomedical engineering*, 1-19.
- Jha, A., Rama, A., Ladani, B., Verma, N., Kannan, S., & Naha, A. (2021). Temperature and pH-responsive nanogels as intelligent drug delivery systems: A comprehensive review. *Journal of Applied Pharmaceutical Science*, 11(12), 001-016.
- Khan, A. (2024). Innovations in Pharmaceutical Packaging for Enhanced Drug Stability. *American Journal of Pharmaceutics*, 5(3), 36-49.
- Li, H., & Qi, G. (2024). Product packaging design for hybrid manufacturing process based on 3D printing and thermal environment sensors. *The International Journal of Advanced Manufacturing Technology*, 1-12.
- Matoc, D. A., Maheta, N., Kanabar, B. K., & Sata, A. (2024). Quantifying manufacturability complexity index: a case study of VAT

- photopolymerization additive manufacturing. *3D Printing and Additive Manufacturing*.
- Ogbuagu, O. O., Mbata, A. O., Balogun, O. D., Oladapo, O., Ojo, O. O., & Muonde, M. (2023). Quality assurance in pharmaceutical manufacturing: Bridging the gap between regulations, supply chain, and innovations. *International Journal of Multidisciplinary Research and Growth Evaluation*, 4(1), 823-831.
- Pala, R., Pandey, P., Kant Thakur, S., Khadam, V. K. R., Dutta, P., Arushi, S. C. H., & Pal Singh, R. (2024). The significance of pharmaceutical packaging and materials in addressing challenges related to unpacking pharmaceutical products. *Int J Pharm Healthc Innov*, 1(03), 149-173.
- Peeriga, R., & Manubolu, K. (2025). Design strategies for waste reduction and enhanced recyclability in pharmaceutical packaging. In *Sustainable Pharmaceutical Product Development and Optimization Processes: From Eco-Design to Supply Chain Integrity* (pp. 179-228). Singapore: Springer Nature Singapore.
- Peleg, M., & Saguy, I. S. (2024). Colorimetric Quick Response (QR) Tags and Other Time-Temperature Indicators (TTIs) for Remote Quality Assessment: Theoretical Kinetics Aspects. *Food Engineering Reviews*, 16(3), 356-370.
- Randhawa, K. S. (2024). Synthesis, Properties, and Environmental Impact of Hybrid Pigments. *The Scientific World Journal*, 2024(1), 2773950.
- Roh, S., Nam, Y., Nguyen, M. T. N., Han, J. H., & Lee, J. S. (2024). Dynamic covalent bond-based polymer chains operating reversibly with temperature changes. *Molecules*, 29(14), 3261.
- Sikaria, K., Sreedevi, A., Srivastava, N., Ligade, V. S., & Muragundi, P. (2025). A Review on Emerging Technologies in Pharmaceutical Packaging: From Anti-Counterfeiting to Green Solutions. *AAPS PharmSciTech*, 27(1), 22.

- Singh, P., Kumar, K. D., & Kumar, R. (2022). Degradation of polyfurfuryl alcohol-based biopolymer by soil-burial and photo-degradation methods. *Journal of Polymers and the Environment*, 30(5), 1920-1931.
- Supian, A. B. M., Asyraf, M. R. M., Syamsir, A., Najeeb, M. I., Alhayek, A., Al-Dala'ien, R. N., ... & Atiqah, A. (2024). Thermochromic polymer nanocomposites for the heat detection system: Recent progress on properties, applications, and challenges. *Polymers*, 16(11), 1545.
- Yang, L., Yuan, Q., Li, T. T., Lou, C. W., Hung, C. Y., & Lin, J. H. (2025). Exploration and application prospect of the advanced technology of time-temperature indicators. *Textile Research Journal*, 95(3-4), 404-428.