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Optimization of Biodegradable Polymer-Based Implants for Localized Drug Delivery

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Abstract:

Targeted drug delivery with biodegradable polymer-based implants presents a novel approach to treating a variety of diseases, including cancer, chronic illnesses, and post-operative problems. These implants offer a number of benefits over traditional drug delivery techniques, including the ability to precisely target, regulate, and prolong the release of therapeutic medicines at the site of action. This minimizes side effects, enhances drug absorption and lowers systemic exposure. A full understanding of the interplay between the geometry of the implant, the characteristics of the drug and the polymer is important to optimise these implants. In the present work, Clotrimazole loaded implantable system for localized infections. Chitosan was used as a biodegradable polymer, and sunflower oil worked as an exterior phase. The I-optimal design was employed for optimizing the process parameters. The drug release at 12 h and on the 10th day was picked as a response. At 12 hours and 10 days, the optimized formulation demonstrated 5.531% and 97.99% release, respectively. The particle size of the prepared implantable formulation was found to be $15.35 \pm 6.29 \mu\text{m}$ with a PDI of 2.45. The optimized formulation demonstrated prolonged medication release, it was concluded.

Keywords: Biodegradable, implants, drug delivery, optimisation, targeted release

1. Introduction

The development of biodegradable polymer-based implants for localized drug delivery offers several advantages over conventional drug delivery systems, such as enhanced drug bioavailability, reduced systemic side effects, and controlled and sustained medication release. These implants represent a significant advancement in medical science and have the potential to cure chronic illnesses, cancer, and surgical consequences [1-3].

The concept of localized drug delivery was developed to get around the problems with systemic

medicine administration. Conventional delivery methods, such as oral or intravenous administration, sometimes result in less-than-ideal concentrations of medications at the target region, which decreases therapeutic efficacy and raises side effects. In order for systemic administration to produce the desired benefits, higher dosages of the medication are also required, which could exacerbate side effects. However, localized drug delivery systems are designed to release the therapeutic agent at the site of action in order to limit systemic exposure and maximize local medication concentration. This approach is particularly beneficial for treating localized diseases such as cancer, infections, and inflammatory problems [4–7].

Biodegradable polymers are now a crucial part in the creation of localized drug delivery systems because they can contain a wide range of therapeutic chemicals and have adjustable breakdown rates. These polymers are designed to decompose into readily absorbed or excreted by the body non-toxic byproducts. Examples of these polymers are polyglycolic acid (PGA), polylactic acid (PLA), and their copolymers. As a result, once the medication is discharged, there is no longer a need for surgical implant removal, making implants a desirable long-term therapy option [8–10].

One of the main challenges in designing biodegradable polymer implants is optimizing the drug release profile. The medication's characteristics, the polymer's properties, the implant's geometry, and other factors all influence how quickly the drug releases its effects. To produce a controlled and prolonged release, one must have a solid understanding of these components and how they interact. Numerous characteristics of the polymer, including its hydrophilicity, crystallinity, and molecular weight, might affect the breakdown rate and, consequently, the drug release profile. The stability, solubility, and interaction of the drug with the polymer matrix are significant aspects that influence the rate at which the drug takes effect [11–13].

The size, shape, and surface area of the implant, together with its geometry, all have a significant impact on the drug release rate. Implants with greater surface areas usually release the medication more quickly due to higher rates of polymer degradation and drug diffusion. Optimizing the morphology for continuous release, however, requires careful consideration of the intended usage of the implant [14–15].

Advances in material science and engineering have led to the creation of novel biodegradable polymers with enhanced properties for targeted medication delivery. These consist of polymers with enhanced mechanical strength, adjustable rates of degradation, and sensitivity to pH and temperature fluctuations. By designing these "smart" polymers to release the medication in response to specific physiological conditions, a more tailored and efficient drug delivery system can be produced [16–17].

Making sure that the medication stays stable during the polymer's breakdown and the manufacturing process is one challenge in the optimization of biodegradable polymer-based implants. A few factors that could affect the drug's stability are temperature, pH, and moisture exposure; these should be carefully controlled throughout implant manufacturing and storage. Additionally, careful research must be done on the interaction between the medicine and the polymer matrix to prevent any detrimental effects on the effectiveness of the treatment. [18-19].

In conclusion, optimizing biodegradable polymer-based implants for localized drug delivery holds great promise for improving the treatment of various diseases. By enhancing the control over drug release, reducing systemic side effects, and eliminating the need for surgical removal, these implants have the potential to revolutionize the way medications are delivered. Advances in polymer science, material engineering, and manufacturing techniques are paving the way for the development of more effective and patient-specific drug delivery systems. As research in this field continues to evolve, it is expected that these technologies will become an integral part of modern medicine, offering new hope for patients and clinicians alike. In conclusion, the development of biodegradable polymer-based implants with optimized localized drug delivery has enormous potential to advance the treatment of numerous illnesses. These implants have the potential to completely change how pharmaceuticals are administered by improving control over drug release, decreasing systemic side effects, and doing away with the need for surgical removal. The creation of more efficient and patient-specific drug delivery systems is being made possible by developments in polymer science, material engineering, and manufacturing techniques. These technologies are predicted to play a major role in modern medicine as research in this area develops, providing new hope for both patients and medical professionals [20-23].

2. Materials and Methods

2.1 Materials

All of the chemicals and reagents utilized in the study, including solvents and other materials needed to prepare the formulation, were purchased from several well-known companies.

Selection of Excipients

The selection of oil, which acts as an external phase in ISFM formulation, depended upon its toxicity profile, viscosity, immunogenicity, irritancy, physicochemical stability and

biocompatibility. Suitable quantities of internal and external phases required to form a stable emulsion were determined by trying different ratios of internal phase *w.r.t.* external phase.

Formulation Development:

This study involved the development of chitosan-based Clotrimazole implants for localized infections. Formulations were optimized by I-optimal design of Experimental design.

Preparation of Chitosan Based Clotrimazole Implant:

Membrane filters with a pore size of 0.2 μm were utilized to filter every solvent included in the formulations. A precise weight of chitosan was dissolved in a solvent mixture in a glass vial that had been autoclaved. The mixture was kept at room temperature for 12 hr, mixing it periodically to allow the polymer to dissolve in the solvent system. To create an *in-situ* forming implantable system, a precisely weighed quantity of drug was injected to the clear, transparent polymer solution once it had formed.

The produced solution served as the first internal phase in the Clotrimazole implant preparation process. Plutonic F-127 (1% w/w) was dissolved in phase 1 of the polymer phase. 2% tween 80 and 2% w/w aluminium monostearate were added to phase 2, or the oil phase. Aluminium monostearate and Tween 80 serve as emulsion stabilizers and surfactants, respectively, in Plutonic F-127. Phase 2 (oil containing 2% tween 80 and 2% aluminium monostearate) was continuously stirred while phase 1 (a solution of Clotrimazole, chitosan, and Plutonic F-127 in an appropriate solvent) was added dropwise from a syringe. Emulsification was accomplished by aspirating the mixture back into the syringe that was equipped with a 21-gauge needle and forcing phase 1 into phase 2 drop-wise. At a pace of one cycle every five seconds, the cycle was performed fifty times. After that, the formulations were ultrasonically treated for 30 minutes at room temperature.

Design of Experiment (DoE) for the optimization of Clotrimazole *in situ* forming implantable system

Different *in-situ* implantable system of Clotrimazole were prepared to optimize polymer concentration and oil percentage or ratio of internal phase *w.r.t.* external phase. Amount of drug was kept constant (50 mg) in all formulations. Optimization of formulation was carried out by using Design Expert software (www.statease.com). An I-Optimal Response Surface Design was used to optimize the formulation. It is suitable for investigating the quadratic response surfaces and for constructing a second-order polynomial model, thus enabling

optimization of a process with a small number of experimental runs. The two independent variables studied at different levels were polymer concentration (% w/v) (X1) and oil % (X2) in the formulation. The two variables were studied at three different levels, represented by transformation values of -1 , 0 , and $+1$, respectively. The details of studied factors and levels were shown in Table 1. Response variables investigated were *in-vitro* drug release at 12 h (R1) and 10th day (R2) and were considered for determining final optimized formulation of clotrimazole. According to the RSM I-Optimal experimental design, the sixteen combinations of the different levels of two variables were prepared and these were listed in Table 1.

Table 1: Response surface I-Optimal experimental design matrix

Formulation No.	Polymer concentration, % w/v (X1)	Oil % (X2)
F1	15	35
F2	16.66	20
F3	10	50
F4	17.5	42.5
F5	20	50
F6	15	35
F7	15	35
F8	20	30
F9	20	30
F10	20	50
F11	10	35
F12	15	50
F13	12.5	27.5
F14	10	20
F15	16.66	20
F16	12.5	42.5

Evaluation of Chitosan Based Clotrimazole Implant Formulation:

***In vitro* release studies of implantable formulations**

In-vitro release studies of *in situ* formed microparticles of Clotrimazole was conducted in a

shaking water bath at 37°C and 100 horizontal strokes for entire period of the study, which amounted to 10 days. To make *in-situ* forming microparticles, a conical glass vial containing 100 mL of releasing media was filled with a formulation equal to 50 mg of Clotrimazole using a 21-gauge fitting needle. Glass vials with a conical mouth were covered with aluminium foil to keep the release medium from evaporating. About 100 mL of pH 7.4 phosphate buffer, 70:30 DMF, and 0.05 % w/v sodium azide as a preservative made up the release medium. DMF was added to the release medium to increase the solubility of Clotrimazole. A 5 ml sample aliquot was removed from the vial and replaced with fresh release medium at predefined intervals of 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 48, 96, 192 and 240 h (10th day). The drug concentration of the withdrawn samples was analyzed by U.V. visible spectrophotometer after the proper dilutions had been made.

Statistical analysis

The formulations prepared according to the design were statistically analysed using the Design Expert® ver 11 software package. One-way analysis of variance (ANOVA) and multiple linear response analysis (MLRA) were used to generate the equation for each response parameter.

Validation of optimization results

The formulation predicted to be optimal by optimization methodology was prepared and analyzed to validate the response. The predicted and experimental values of different response variables were compared, and the percent prediction error was calculated.

Evaluation of optimized Clotrimazole Implantable formulation

Rheological studies of optimized formulation:

Using a rheometer, rheological analyses of the optimized formulation were performed. Determining the link between shear stress, stress rate, and viscosity is the primary goal of rheology.

The consistency index determines how the consistency of the excipients affects the drug's release and percutaneous absorption in a gel formulation. Gel's "mobility" or "flowability" from the container is indicated by its flow index. At $25 \pm 2^\circ\text{C}$, the viscosity was determined using the Rheoplus/32, v 3.40 software on a Rheolab QC rheometer.

Particle size, surface morphology and polydispersity index (PDI) of suspended microparticles:

To prepare samples for analysis, the formulation was injected into pH 7.4 phosphate buffer, and the system was then shaken and maintained at 37°C for 24 hours. After being extracted from the medium, the *in situ*-formed microparticles were examined for PDI, surface morphology, and particle size. The samples underwent triplicate analysis. A dynamic light scattering zeta sizer was used to determine the microparticle size distribution. Distilled water was used as the dispersion medium. The volume mean diameter in μm was used to express the average particle size. 50% and 90% of the particle volume mean diameters undersize were noted. Optical microscopy images were used to evaluate optimised in-situ forming microparticles' shape and surface properties. Under an optical light microscope at 10x magnification, the optimal implantable formulation was examined.

***In-vitro* release studies of optimized Implantable formulation:**

A similar method, as stated above, was adopted for the determination of drug release from optimised implantable formulation.

Results and Discussion

The current research work involved designing, developing and evaluating a novel in-situ forming drug delivery system of Clotrimazole for treatment of localized infections. The DoE optimization technique was also applied to determine the most optimal formulation.

Formulation development

Chitosan was mixed with the solvent to create *in-situ* implants. The concentration of the polymer was changed in the formulations while the drug's dosage remained fixed at 50 mg. Various chitosan concentrations were used to monitor implant development. A 5% w/v polymer concentration was first attempted for implant creation; however this low concentration of polymer was insufficient to encapsulate 50 mg of medication and produce an implant. When a 5% w/v chitosan solution containing the medication was put into a phosphate buffer pH 7.4 and DMS mixture, it dispersed right away and produced a hazy solution. After that, the polymer concentration was adjusted to between 10 and 30% w/v for the implant formation; however, concentrations higher than 20% w/v caused the polymer solution to become too viscous to pass through a 21-gauge syringe. These investigations led to the selection of a polymer concentration of between 10 and 20 percent w/v for the development of the Clotrimazole in situ forming implantable. Trials were conducted using ratios of 0.25:1, 0.5:1, 1:1, 1:2, and 1:4.

The amount of oil (sunflower oil) in the final formulation ranged from 20 to 50 percent v/v.

Design of Experiment (DoE) for the optimisation of Clotrimazole Implantable system

With the goal of maintaining a constant amount of medicine, the polymer concentration and oil phase % in the formulation were optimized through the use of experimental design software (Design Expert®, v13, Stat-Ease, USA). 16 distinct formulations were produced using RSM I-optimal design, with two independent variables—the polymer concentration (X1) and the oil phase percentage (X2)—being examined at different levels. % drug release at 12 hours (R1) and 10 days (R2) were among the response/dependent variables that were chosen and analyzed. Table 2 presents results from 16 conducted trials. The response surface quadratic model, which was chosen based on model p-values, lack of fit test, adjusted R², and anticipated R², was used to analyze the design in order to identify the significant design terms, their interactions, and their impact on the response variables R1 and R2. ANOVA produced quadratic polynomial model equations. When there is no lack of fit in the regression, the model is deemed sufficient.

Table 2: Response variables 1 & 2 for different factor combinations of Implantable system

Formulation No.	Polymer concentration, % w/v (X1)	Oil % (X2)	Response 1 (R1), % drug release at 12 h	Response 1 (R2), % drug release at 10 th day
F1	15	35	5.71	98.15
F2	16.66	20	7.98	98.37
F3	10	50	21.56	99.24
F4	17.5	42.5	7.23	96.42
F5	20	50	4.69	72.81
F6	15	35	6.11	97.59
F7	15	35	5.89	97.66
F8	20	30	4.97	79.48
F9	20	30	5.15	80.24
F10	20	50	5.09	75.73
F11	10	35	22.61	99.56
F12	15	50	6.72	97.35
F13	12.5	27.5	20.53	98.47
F14	10	20	25.58	99.79
F15	16.66	20	8.32	98.27
F16	12.5	42.5	19.37	99.13

Table 3: ANOVA for Reduced Cubic model for Response 1: Drug release at 12 h

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	811.50	7	115.93	11.55	0.0013	significant

A-Polymer conc.	237.49	1	237.49	23.66	0.0012	
B-Oil conc.	3.66	1	3.66	0.3649	0.5625	
AB	0.3182	1	0.3182	0.0317	0.8631	
A ²	85.77	1	85.77	8.55	0.0192	
B ²	1.99	1	1.99	0.1983	0.6679	
A ² B	0.1383	1	0.1383	0.0138	0.9094	
AB ²	1.52	1	1.52	0.1512	0.7076	
Residual	80.29	8	10.04			
Lack of Fit	80.05	3	26.68	569.51	< 0.0001	significant
Pure Error	0.2343	5	0.0469			
Cor Total	891.79	15				

The model is deemed significant based on its F-value of 11.55. The probability that an F-value this great may be the result of noise is only 0.13%. P-values below 0.0500 suggest the significance of the model terms. A and A² are important model terms in this instance. The considerable lack of fit is indicated by the F-value of 569.51 for lack of fit. A high Lack of Fit F-value has a 0.01% probability of being caused by noise. Significant misfit is undesirable; we need the model to fit.

Table 4: ANOVA for Cubic model for Response 2: Drug release on 10th day

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1391.17	9	154.57	74.62	< 0.0001	significant
A-Polymer conc.	0.3951	1	0.3951	0.1907	0.6776	
B-Oil conc.	2.47	1	2.47	1.19	0.3163	
AB	8.95	1	8.95	4.32	0.0829	
A ²	176.23	1	176.23	85.08	< 0.0001	
B ²	0.1608	1	0.1608	0.0776	0.7899	
A ² B	1.53	1	1.53	0.7396	0.4228	
AB ²	0.1374	1	0.1374	0.0663	0.8054	
A ³	24.64	1	24.64	11.89	0.0137	
B ³	3.89	1	3.89	1.88	0.2195	
Residual	12.43	6	2.07			
Lack of Fit	7.69	1	7.69	8.10	0.0360	significant
Pure Error	4.74	5	0.9486			
Cor Total	1403.60	15				

The model is significant, according to the model's F-value of 74.62. This kind of huge F-value has a 0.01% probability of being caused by noise. P-values below 0.0500 suggest the

significance of the model terms. A^2 and A^2 are important model terms in this instance. The 8.10 F-value for lack of fit indicates a significant lack of fit. A significant Lack of Fit F-value has a 3.60% probability of being caused by noise. The polynomial equation's terms fitting suggested that the model was significant and would successfully traverse the design space. Below are the final polynomial equations for each response variable expressed in terms of real factors:

$$R1 \text{ (Drug release at 12h)} = 8.45 - 10.32A - 1.28B + 0.3601AB + 5.93A^2 + 0.9113B^2 - 0.4247A^2B + 1.43AB^2$$

$$R2 \text{ (Drug release at 10th Day)} = 98.62 - 1.03A + 2.59B - 1.94AB - 9.07A^2 - 0.2750B^2 - 1.42A^2B - 0.4355AB^2 - 8.98A^3 - 3.58B^3$$

3D charts can be used to show the response surface of the models that have been analyzed. Therefore, the three-dimensional plots for the two response variables—the 12-hour and 10-day release times—were plotted against the factors of chitosan concentration and the proportion of the oil phase in the formulation as a whole in Figures 1 and 2. The three-dimensional plot showed that when the concentration of polymer increases and the percentage of oil in the formulation falls overall, the amount of medication released at 12 hours decreases. On the tenth day, the medication release increases in tandem with a rise in the formulation's oil percentage and a reduction in the polymer concentration.

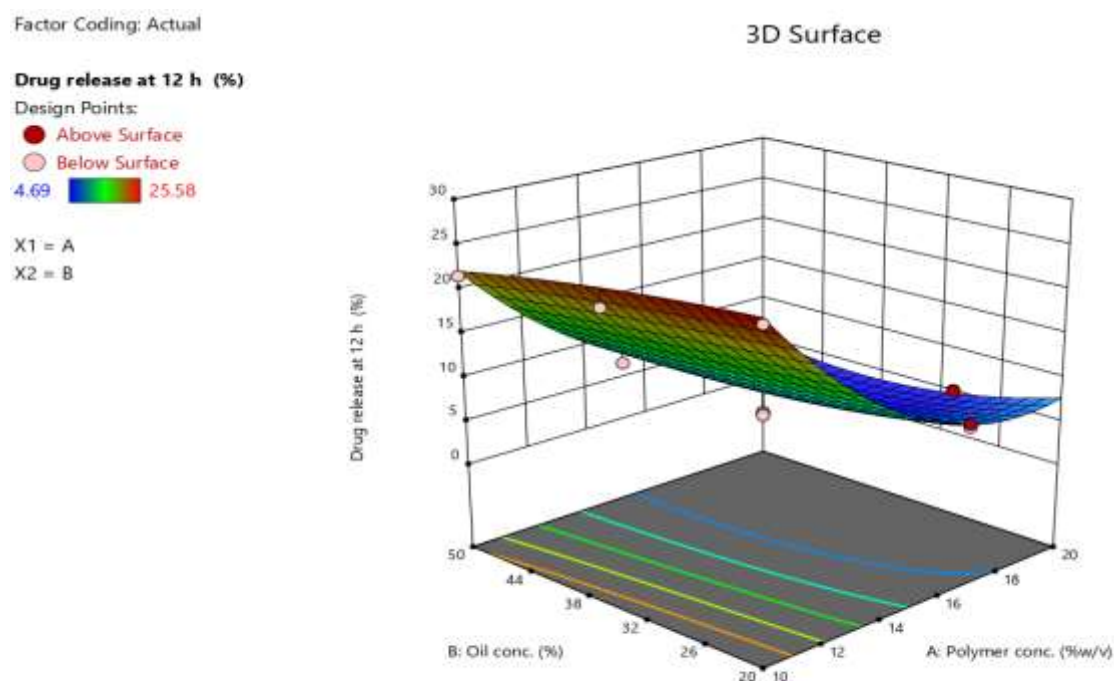


Figure 1: 3D plot for response (R1) % drug release at 12 hr

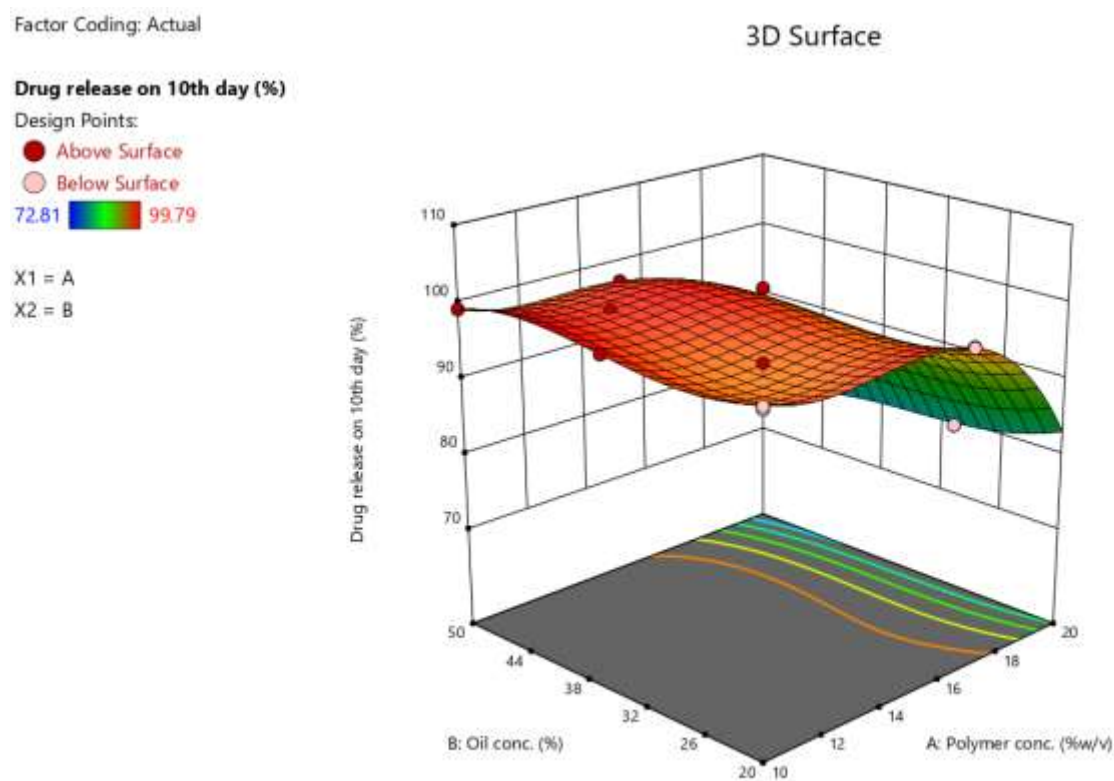


Figure 2: 3D plot for response (R2) % drug release at 10th day

Evaluation of prepared formulations

***In-vitro* drug release behaviour of Clotrimazole Implantable formulation**

The in-vitro drug release profile was used to determine the drug release pattern from the generated in-situ forming microparticle formulations, specifically F1–F16. For the first twelve hours, high burst release of the medication was seen in F3, F11, F13, F14, and F16, according to the cumulative percent release graph. The table illustrates that it was low in other implanted formulations. Increased polymer concentration caused a denser, lower porosity polymer network to form in ISFM, delaying both the water inflow and the pace at which the liquid-liquid phase separated. The system takes longer to pass the physical barrier created by the polymer solidifying and the presence of the oil phase when the water influx rate drops, which slows down the release of the medicine. Implantable formulations with low polymer concentration and an enhanced oil phase have a reduced initial burst release at 12 hours and a maximum drug release on the tenth day, according to the results of in vitro release experiments. This is because an increased proportion of oil phase acts as a barrier to the interchange of solvents between the polymer phase and the aqueous release media by decreasing the rate at which solvent diffuses from the polymer phase to the release media.

Determination of optimal formulation

The next stage was to choose the most effective final formulation after taking into account the pattern and potential mechanism of drug release from several implantable Clotrimazole formulations. A numerical optimization technique was used to look for the best formulation within the investigated experimental domain. The desired aims were established as the constraints, and the full experimental domain was searched for compositions in which the requirements were maximally satisfied. The constraints for numerical optimization, the optimized solutions that were obtained, and the formulation compositions with the related response and desirability values are shown in Table 5 and Figure 3.

The optimal solution is represented by the numerical optimization results (Table 5). The aim requirements of minimum burst release at 12 hours and maximum release on the tenth day are met by the solutions. It was discovered that the attractiveness value for solution 1 was 0.940, which is desirable and closest to 1. For both solutions, the maximum drug release occurred on day ten; however, the formulation for solution 1 was chosen based on the least amount of drug released in a 12-hour period. The formulation had a minimum burst release of 5.86% at 12 hours, a maximum release of 98.05 percent on the tenth day, and an exterior phase consisting of 41.21 percent oil (sunflower oil) and 16.31% polymer (chitosan).

Table 5: Solutions obtained from Numerical optimisation

Number	Polymer conc.	Oil conc.	Drug release at 12 h	Drug release on the 10th day	Desirability	
1	16.315	41.217	5.862	98.057	0.940	Selected

Evaluation of optimised Clotrimazole Implantable formulation

Validation of optimised results

Three replicates were prepared, and their release at 12 hours and 10 days was used to validate the performance of the optimized formulation that was acquired using numerical and graphical optimization. The optimized formulation's composition resembled the amount specified in Table 6. The anticipated outcomes and the actual ones were compared. The response variables R1 (percent release at 12 hours) and R2 (percent release on the tenth day) for the optimized formulation are displayed in Table 6 together with their projected values.

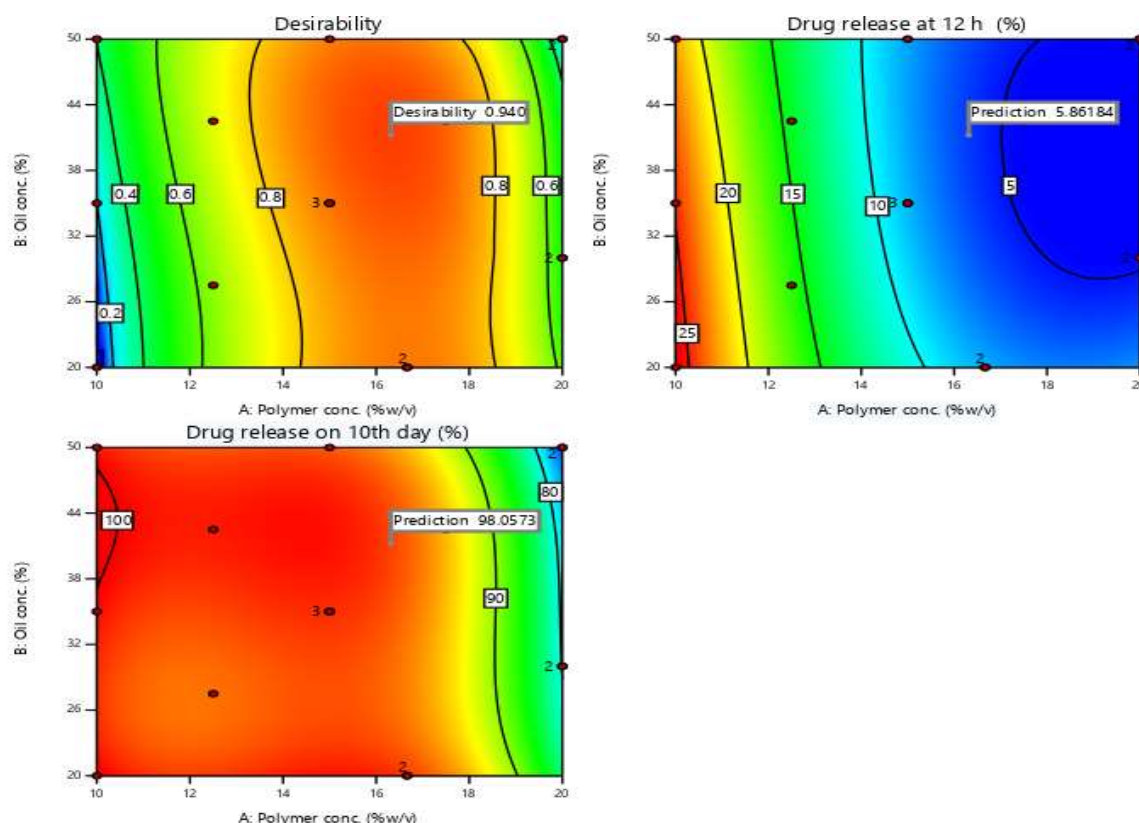


Figure 3: Desirability graph showing the optimised clotrimazole implantable formulation

Table 6: Comparative predicted vs experimental values of different response variables for optimized formulation (OF)

S. No.	Polymer conc.	Oil conc.	Drug release at 12 h	Drug release on the 10th day
1	16.315	41.217	Predicted=5.862% Experimental=5.531%	Predicted=98.057% Experimental=97.99%

Rheology of optimised implantable formulation

As the shear rate was increased from 1 to 100 s⁻¹, the optimized implantable formulation OF's rheological behavior varied from 359 to 109 centipoise [cP], suggesting a decrease in viscosity. It was discovered that the average viscosity was 197.68 ± 25.55 cP.

Particle size, surface morphology and polydispersity index (PDI) of optimised Implantable formulation

Malvern Mastersizer found the optimized Clotrimazole Implantable formulation OF's particle size distribution. It was discovered that the average size of in situ microparticles was 15.35 ± 6.29 μ m. The in situ microparticles' polydispersity index (PDI) was 2.45.

The implanted system's surface morphology was examined using optical microscopy. The

microglobules had a clear boundary dividing the internal phase from the external phase and were spherical and non-aggregated.

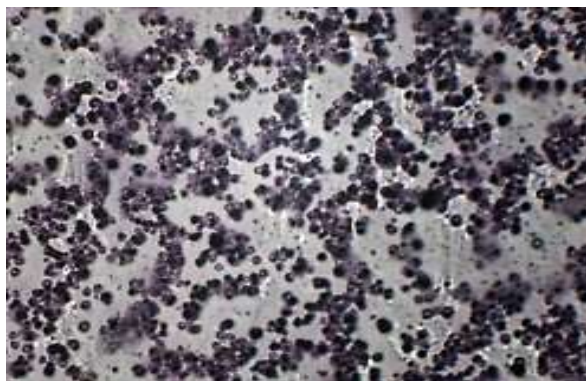


Figure 4: Photomicrograph of optimised batch of Clotrimazole implant taken by optical microscope (10x)

In contrast to the kind of solvent employed in the formulation, the polymer:oil ratio has a significant impact on the surface morphology of in-situ microparticles. Dense and non-porous microparticles were produced by slow polymer precipitation caused by the external oil phase in the implantable system in aqueous media or phosphate buffer. The surface morphology of microparticles yields results that are consistent with in vitro drug release experiments, wherein the dense and non-porous structure of microparticles led to a reduced initial burst release.

***In-vitro* release studies of optimised Implantable formulation:**

The per cent drug release profile of optimised Clotrimazole implantable formulation was presented in Figure 5. Drug release from the formulation was about 97.99% at the end of 240 hr.

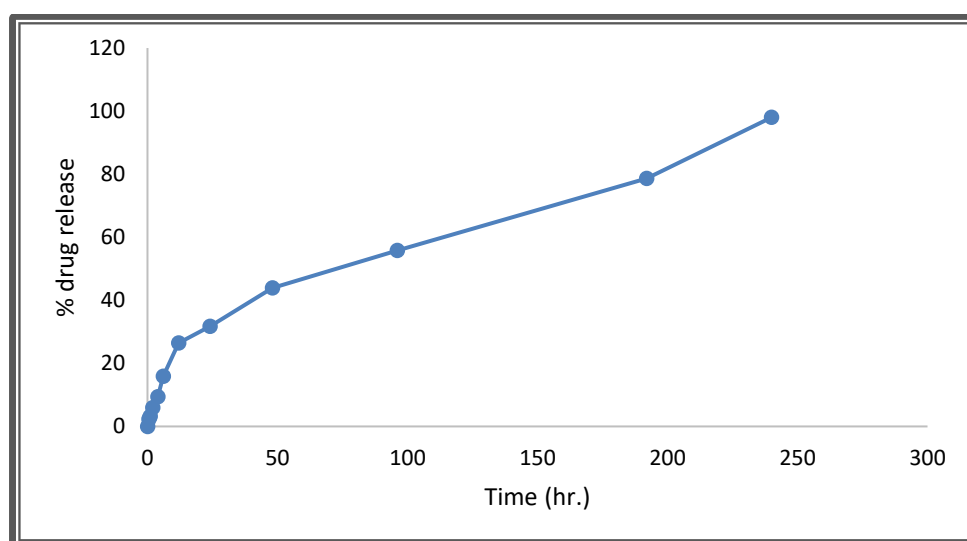


Figure 5: Percent drug release profile of optimised Clotrimazole Implantable formulation (OF)

Conclusion

The current study used DoE and optimization strategies to construct an implanted Clotrimazole device *in-situ*. The choice of biodegradable polymer was chitosan. In order to formulate *in-situ* forming microparticles of Clotrimazole, sunflower oil was selected as the external oil phase, pluronic F-127 as the surfactant, and aluminum monostearate as the emulsion stabiliser. These choices were made based on published literature. For ten days, the Clotrimazole implantable system displayed a longer sustained release profile with a smaller initial burst.

Reference:

1. Sternberg K, Petersen S, Grabow N, Senz V, zu Schwabedissen HM, Kroemer HK, Schmitz KP. Implant-associated local drug delivery systems based on biodegradable polymers: customised designs for different medical applications. Biomedizinische Technik/Biomedical Engineering. 2013 Oct 1;58(5):417-27.
2. Gulati K, Aw MS, Findlay D, Losic D. Local drug delivery to the bone by drug-releasing implants: perspectives of nano-engineered titania nanotube arrays. Therapeutic delivery. 2012 Jul 1;3(7):857-73.
3. Santos A, Aw MS, Bariana M, Kumeria T, Wang Y, Losic D. Drug-releasing implants: current progress, challenges and perspectives. Journal of Materials Chemistry B. 2014;2(37):6157-82.
4. Wen H, Jung H, Li X. Drug delivery approaches in addressing clinical pharmacology-related issues: opportunities and challenges. The AAPS journal. 2015 Nov;17:1327-40.
5. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science. 2004 Mar 19;303(5665):1818-22.
6. Zhang H, Wang G, Yang H. Drug delivery systems for differential release in combination therapy. Expert opinion on drug delivery. 2011 Feb 1;8(2):171-90.
7. Haley RM, von Recum HA. Localised and targeted delivery of NSAIDs for treatment of inflammation: A review. Experimental Biology and Medicine. 2019 Apr;244(6):433-44.
8. Doppalapudi S, Jain A, Domb AJ, Khan W. Biodegradable polymers for targeted delivery of anti-cancer drugs. Expert opinion on drug delivery. 2016 Jun 2;13(6):891-909.
9. Athanasiou KA, Niederauer GG, Agrawal CM. Sterilization, toxicity, biocompatibility and clinical applications of polylactic acid/polyglycolic acid copolymers. Biomaterials.

- 1996 Jan 1;17(2):93-102.
10. Mohtashami Z, Esmaili Z, Vakilinezhad MA, Seyedjafari E, Akbari Javar H. Pharmaceutical implants: Classification, limitations and therapeutic applications. *Pharmaceutical Development and Technology*. 2020 Jan 2;25(1):116-32.
 11. Li C, Guo C, Fitzpatrick V, Ibrahim A, Zwierstra MJ, Hanna P, Lechtig A, Nazarian A, Lin SJ, Kaplan DL. Design of biodegradable, implantable devices towards clinical translation. *Nature Reviews Materials*. 2020 Jan;5(1):61-81.
 12. Danckwerts M, Fassihi A. Implantable controlled release drug delivery systems: a review. *Drug Development and Industrial Pharmacy*. 1991 Jan 1;17(11):1465-502.
 13. Varma MV, Kaushal AM, Garg A, Garg S. Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. *American Journal of drug delivery*. 2004 Mar;2:43-57.
 14. Meredith N. A review of implant design, geometry and placement. *Appl Osseointegr Res*. 2008 Jan 1;6:6-12.
 15. Visan AI, Popescu-Pelin G, Socol G. Degradation behavior of polymers used as coating materials for drug delivery—A basic review. *Polymers*. 2021 Apr 14;13(8):1272.
 16. Sartore L, Vox G, Schettini E. Preparation and performance of novel biodegradable polymeric materials based on hydrolyzed proteins for agricultural application. *Journal of Polymers and the Environment*. 2013 Sep;21:718-25.
 17. James HP, John R, Alex A, Anoop K. Smart polymers for the controlled delivery of drugs—a concise overview. *Acta Pharmaceutica Sinica B*. 2014 Apr 1;4(2):120-7.
 18. Nag S, Banerjee R. Fundamentals of medical implant materials. In *Materials for medical devices* 2012 Jun 1 (pp. 6-17). ASM International.
 19. Johnson AR, Forster SP, White D, Terife G, Lowinger M, Teller RS, Barrett SE. Drug eluting implants in pharmaceutical development and clinical practice. *Expert Opinion on Drug Delivery*. 2021 May 4;18(5):577-93.
 20. Liu Y, Li X, Liang A. Current research progress of local drug delivery systems based on biodegradable polymers in treating chronic osteomyelitis. *Frontiers in Bioengineering and Biotechnology*. 2022 Nov 24;10:1042128.
 21. Quarterman JC, Geary SM, Salem AK. Evolution of drug-eluting biomedical implants for sustained drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics*. 2021 Feb 1;159:21-35.
 22. Lynch C, Kondiah PP, Choonara YE, du Toit LC, Ally N, Pillay V. Advances in biodegradable nano-sized polymer-based ocular drug delivery. *Polymers*. 2019 Aug

20;11(8):1371.

23. Geraili A, Xing M, Mequanint K. Design and fabrication of drug-delivery systems toward adjustable release profiles for personalized treatment. View. 2021 Oct;2(5):20200126.