FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF VARENICLINE BY DIRECT COMPRESSION TECHNIQUE

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Abstract
In the present study, mouth dissolving tablets (MDTs) of Varenicline were formulated and evaluated through the direct compression technique for improving the patient's compliance and to achieve quick drug release. MDTs with six different formulations (F1-F6) were prepared by using different levels of superdisintegrants, namely sodium starch glycolate, crospovidone, and croscarmellose sodium. Pre-compression evaluation was carried out for the prepared blends, whereas hardness, friability, weight variation, thickness, drug content, disintegration time, in vitro drug release rate, release kinetics, and stability testing were conducted on the compressed tablets. All formulations possessed acceptable pre- and post-compression characteristics. Out of all the formulations prepared, F3, which comprised of sodium starch glycolate (20 mg) and crospovidone (20mg) had a minimum disintegration time (45±3 s), drug content of 99.12% and drug release of 98.12% within 15 min. From drug release kinetics data, the optimized formulation showed Higuchi model of drug release (R^2= 0.988) indicating that the drug release is controlled by the diffusion process. Stability studies at accelerated condition proved that the optimized formulation is stable up to three months.

Keywords: Varenicline, Mouth dissolving tablets, Direct compression, Superdisintegrants, Sodium starch glycolate, Crospovidone, Higuchi model, In vitro drug release, Stability studies.

Introduction

Varenicline is a selective partial agonist of the α4β2 nicotinic acetylcholine receptor that is extensively used as the primary pharmacotherapy for smoking cessation (Jorenby et al., 2006). Partial stimulation of the nicotinic receptors along with the inhibition of nicotine binding results in reduced cravings and withdrawal symptoms and helps increase the rate of smoking cessation. However, due to its proven efficacy, conventional oral tablets might cause difficulties in swallowing, especially in elderly, pediatric, and dysphagic patients, thus negatively impacting patient compliance (Ebbert et al., 2010).

Oral mouth dissolving tablets (MDTs) are the novel drug delivery system that quickly disintegrates in the mouth due to saliva and without the use of water, making the treatment convenient, easy to administer and increasing the patient compliance (Parkash et al., 2011). Not only does it increase patient compliance, but MDTs provide the fast onset of drug action and can potentially improve the therapeutic effect. The effectiveness of MDTs mainly depends on the proper selection and concentration of superdisintegrants, which help achieve quick disintegration and dissolution of the drug (Al-Khattawi and Mohammed, 2013).

Some of the most popular superdisintegrants are sodium starch glycolate, crospovidone, and croscarmellose sodium, which have great swelling and wicking capabilities resulting in faster disintegration of the tablet

(Sharma and Sonawane, 2017). It becomes important to optimize such excipients to get a formulation having good mechanical strength, disintegration, and drug release rate (Agrawal et al., 2016).

This research work is an attempt to formulate and characterize mouth dissolving tablets of Varenicline by direct compression method using different concentrations of sodium starch glycolate, crospovidone, and croscarmellose sodium. The formulations were studied for their pre-compression and post-compression parameters, disintegration time, in vitro drug release, release kinetics, and stability under accelerated conditions.

Material and Methods

Material

The materials used in the investigation were analytical grade reagents and chemicals. Varenicline was received as a gift sample from a pharmaceutical company. Excipients like sodium starch glycolate, croscarmellose sodium, talc, and lactose were bought from Loba Chemie Pvt. Ltd., Mumbai. Disodium hydrogen phosphate, sodium hydroxide, and hydrochloric acid were received from S. D. Fine Chem. Ltd., Mumbai. Methanol, ethanol, chloroform, and citric acid were bought from Qualigens Fine Chemicals, Mumbai, while magnesium stearate was purchased from Jiangsu Huaxi International, Mumbai.

Methods

Formulation of Mouth dissolving tablets of Varenicline

Tablet forms of Varenicline were prepared using the direct compression method employing different types of super disintegrants in various amounts. The super disintegrants used in the preparation of MDTs include Sodium Starch Glycolate (SSG), Crospovidone, and Croscarmellose Sodium (Mohapatra et al., 2013). Total six formulations (F1 to F6) were developed as per Table 1.

The appropriate amount of Varenicline, Sodium Starch Glycolate, Crospovidone, Croscarmellose Sodium, and Microcrystalline Cellulose (MCC) were carefully weighed and uniformly mixed with the help of geometric dilution in a dry and clean mortar. The powder mixture obtained was passed through sieve No. 60 to make sure of even particle size distribution. To the resulting powder, Talc (5 mg) as a glidant and Magnesium Stearate (6 mg) as a lubricant were added and blended carefully for 3 to 5 minutes.

These prepared blends of powders were studied for pre-compression properties such as angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio to check the flowability and compression nature of these blends.

Finally, these blends were compressed using 8 mm flat-faced punches by using Rimek Mini Press 16 stations rotary compression machine. A total of six formulations (F1-F6) were prepared. Formulations F1-F3 had Sodium Starch Glycolate and Crospovidone in the concentration of 10, 15, and 20 mg, respectively, and formulations F4-F6 had Croscarmellose Sodium and Crospovidone in the concentration of 10, 15, and 20 mg, respectively. Each tablet had 1 mg of Varenicline with a weight of 150 mg.

Table 1: Composition of mouth dissolving tablets of Varenicline

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Varenicline	1	1	1	1	1	1
Sodium Starch glycolate	10	15	20	-	-	-
Crospovidone	10	15	20	10	15	20
Croscarmellose sodium	-	-		10	15	20

Microcrystalline cellulose	118	108	98	118	108	98
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	150	150	150	150	150	150

Evaluation of Precompression Parameter

Angle of repose (θ): The frictional forces for a loose powder or granules can be obtained from the angle of repose. The angle of repose refers to the largest possible angle that the surface of a pile of powder or granules forms with the horizontal plane (Carr et al., 1965).

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to fall through a funnel mounted on a stand at a certain height. The angle of repose was determined by measuring the height and radius of the pile of granules formed.

Bulk density: The both loose bulk density (LBD) and tapped bulk density (TBD) were measured. The accurately weighed quantity of granules in a measuring cylinder of 50 ml was tapped 100 times on a hard wooden surface and the values of LBD and TBD were obtained through the below mentioned formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index (Ansel *et al.*, 1999), calculated by using following formula:-

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Hausner's ratio value <1.25 shows better flow properties

Evaluation of post compression Parameter

Thickness Test

Three tablets were chosen randomly from each formulation and thickness was measured individually. Thickness is measured in mm and standard deviation was calculated. Thickness test was done using dial-caliper (Mitutoyo, Japan).

Weight Variation Test

Twenty tablets were chosen randomly from each formulation and their average weight was calculated. Weight of each individual tablet was taken and compared to the average weight. There is some permissible variation allowed for weight of the tablet as per U.S Pharmacopoeia. Percentage deviation of the weight variation allowed is:

Hardness test

Tablet hardness was measured using Pfizer hardness tester and results are in Kg/cm2 (Abdelbary et al., 2004).

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated (Kuchekar *et al.*, 2004). The friability was determined as mass loss in percent according to Equation:-

$$\%\text{Friability} = (\text{Loss in weight}/\text{Initial weight}) \times 100$$

The test complies if tablets not loss more than 1% of their weight.

Uniformity of drug content

Ten tablets from each formulation (F1 to F6) were grounded finely, and the drug equivalent to 10 mg of the drug was dissolved in 10 ml of phosphate buffer of pH 6.8) was sonicated for 20 min till the drug was completely leached out from the complex, and the solution was filtered through whatman filter paper no. 41. Then, 1 ml from the above solution was diluted to 100 ml with 0.1N HCl. (Deepak *et al.*, 2012).

***In-vitro* dissolution rate studies**

The drug release studies from the prepared tablets were conducted by the in vitro method (Deepak et al., 2012). The drug release studies were done with the help of the USP XXII Paddle type Dissolution test apparatus. For the dissolution studies, 900 ml dissolution medium was used which was agitated at 75 rpm under 37±0.2°C temperature. The process of conducting experiments with the use of simulated fluids was performed in the following manner: A tablet was kept in dissolution medium (900 ml) at 37±0.2°C. Samples were withdrawn at various intervals and replenished with equal volume of fresh dissolution medium. The volume of withdrawn samples was brought up to 10ml 0.1 N HCl.

Mathematical treatment of in vitro drug release data

The in vitro drug release profile of the Varenicline loaded tablets was studied using the calibration curve of Varenicline. The in vitro drug release profiles were analyzed according to several kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. In zero-order release, there is a constant rate of drug release whereas in the case of first-order release, the release occurs in a concentration-dependent manner. The Higuchi model gives an understanding about the drug release due to diffusion from matrix systems and the Korsmeyer-Peppas model was used to establish the mechanism of release depending upon the diffusion exponent (n).

Stability study of optimized formulation

Stability studies of optimized formulation (F3) of Varenicline mouth dissolving tablets were performed following ICH guidelines to examine the impact of storage conditions on the formulation. The tablets were packed in air-tight packaging and stored at 40 ± 2°C temperature and 75 ± 5% Relative Humidity (RH) in a stability chamber for a duration of three months.

Samples were taken at pre-determined intervals of 0, 1, 2, and 3 months and assessed for various parameters such as physical characteristics, hardness, friability, drug content, disintegration time, and in vitro drug release (Patel et al., 2009). The data collected from storage was compared with the initial data to identify any change in the formulation.

Results and Discussion

The present study was undertaken to formulate and evaluate mouth dissolving tablets (MDTs) of Varenicline using different superdisintegrants, namely sodium starch glycolate (SSG), crospovidone, and croscarmellose sodium, to achieve rapid tablet disintegration and drug release. Six formulations (F1–F6) were prepared by

direct compression and evaluated for pre-compression characteristics, post-compression quality attributes, in vitro disintegration, dissolution behavior, release kinetics, and stability.

The flow properties of the powder blends were evaluated before compression. As presented in Table 2, the loose bulk density ranged from 0.335 to 0.345 g/mL, while the tapped bulk density varied between 0.443 and 0.458 g/mL. Carr's index values ranged from 22.646 to 25.885%, and Hausner's ratio ranged from 1.293 to 1.349, indicating acceptable flowability and compressibility of the powder blends. These results confirmed that all formulations possessed suitable flow characteristics for direct compression and ensured uniform die filling during tablet manufacture.

Post-compression evaluation demonstrated that all formulations complied with pharmacopeial quality requirements. As shown in Figure 1 and Table 3, tablet hardness ranged from 3.2 ± 0.3 to 3.5 ± 0.2 kg/cm², providing adequate mechanical strength while maintaining rapid disintegration. Friability values varied between 0.635 ± 0.006% and 0.745 ± 0.006%, remaining well below the acceptable limit of 1%, indicating satisfactory resistance to abrasion during handling. Tablet thickness ranged from 1.12 ± 0.05 to 1.18 ± 0.02 mm, demonstrating uniform compression, while weight variation remained within pharmacopeial limits. Drug content varied from 96.65 ± 0.25% to 99.12 ± 0.45%, indicating uniform distribution of varenicline throughout the tablets (Figure 2, Table 3).

Rapid tablet disintegration is one of the most important characteristics of mouth dissolving tablets. The disintegration study (Table 4 and Figure 3) showed that the disintegration time decreased with increasing concentration of superdisintegrants. Formulation F3, containing 20 mg crospovidone, exhibited the shortest disintegration time (45 ± 3 seconds), whereas F1 showed the longest disintegration time (85 ± 6 seconds). The superior performance of crospovidone may be attributed to its rapid capillary action and swelling behavior, which promotes quick tablet breakup upon contact with saliva. Although croscarmellose sodium also reduced disintegration time, its effect was comparatively less pronounced than that of crospovidone.

The optimized formulation F3 was further evaluated for dissolution behavior. As illustrated in Table 5 and Figure 4a–c, the formulation released 55.45% of the drug within 1 minute, 69.98% within 5 minutes, 88.45% within 10 minutes, and 98.12% within 15 minutes. The rapid dissolution profile is mainly attributed to the fast disintegration of the tablet and the efficient wicking action of crospovidone, which facilitated immediate penetration of dissolution medium into the tablet matrix. Such rapid drug release is expected to improve patient compliance and may enhance the onset of therapeutic action.

Drug release kinetics were analyzed using different mathematical models. The regression coefficients presented in Table 6 showed values of 0.9811 for the zero-order model, 0.9377 for the first-order model, and 0.9880 for the Higuchi model. Since the Higuchi model exhibited the highest correlation coefficient, it indicated that drug release from formulation F3 predominantly followed diffusion-controlled release. The close agreement with the zero-order model also suggests that the formulation maintained a nearly uniform release pattern during the dissolution period.

The stability of the optimized formulation F3 was evaluated for three months under accelerated storage conditions. The results summarized in Table 7 demonstrated that no significant changes occurred in the physical appearance of the tablets throughout the study period. Tablet hardness showed only a slight decrease from 3.3 ± 0.1 to 3.2 ± 0.1 kg/cm², while friability increased marginally from 0.712 ± 0.02% to 0.731 ± 0.03%, remaining well within acceptable limits. Drug content remained above 98%, indicating excellent chemical stability. The disintegration time increased only slightly from 45 ± 3 seconds to 48 ± 2 seconds, and drug release at 15 minutes decreased marginally from 98.12 ± 0.35% to 97.23 ± 0.46%, demonstrating that the optimized formulation retained its pharmaceutical performance during storage.

Table 2: Results of pre-compression parameters of Varenicline

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.335	0.452	25.885	1.349
F2	0.345	0.446	22.646	1.293
F3	0.338	0.443	23.702	1.311
F4	0.341	0.458	25.546	1.343
F5	0.344	0.452	23.894	1.314
F6	0.337	0.448	24.777	1.329

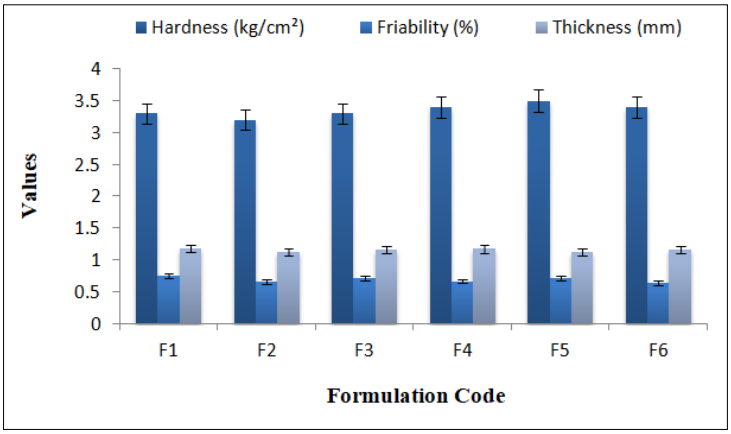


Figure 1: Results of post-compression parameters of Hardness, Friability and Thickness

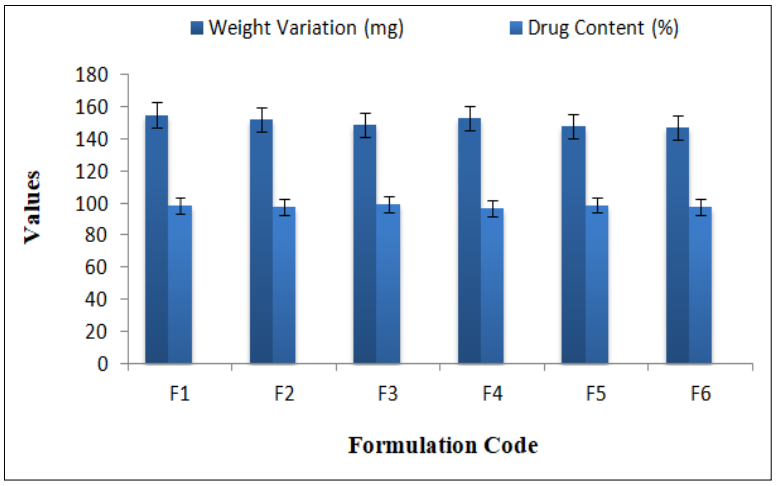


Figure 2: Results of post-compression parameters of Weight variation and Drug content

Table 3: Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.3±0.2	0.745±0.006	155±3	1.18±0.02	98.45±0.15
F2	3.2±0.3	0.658±0.008	152±4	1.12±0.05	97.65±0.32
F3	3.3±0.5	0.712±0.003	149±3	1.16±0.03	99.12±0.45
F4	3.4±0.1	0.663±0.005	153±5	1.17±0.04	96.65±0.25

F5	3.5±0.2	0.712±0.007	148±2	1.13±0.03	98.74±0.36
F6	3.4±0.2	0.635±0.006	147±3	1.16±0.04	97.32±0.41

Table 4: Results of disintegration time parameters of all formulations

Formulation code	Disintegration Time (Sec.) Mean ± SD
F1	85±6
F2	65±4
F3	45±3
F4	74±2
F5	63±5
F6	50±3

***Average of three determinations (n=3)**

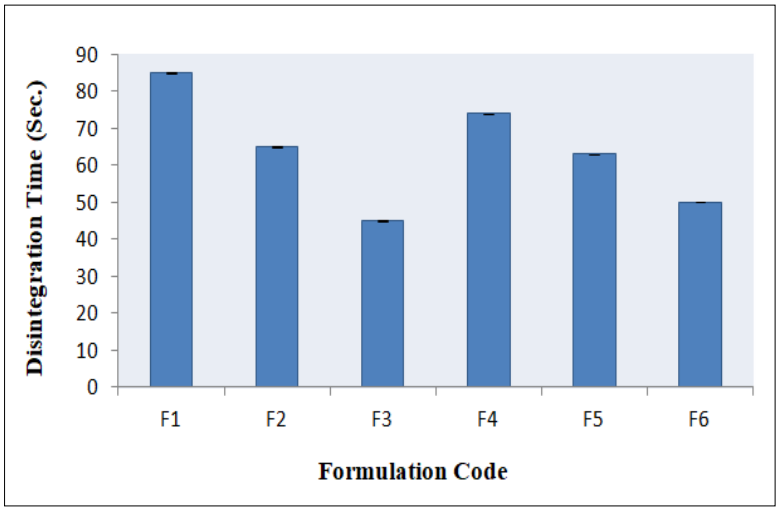
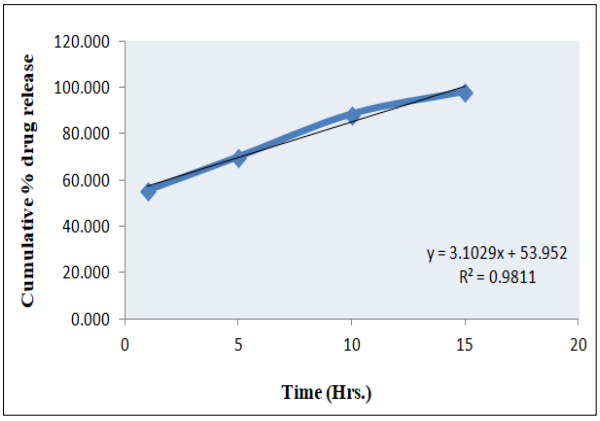


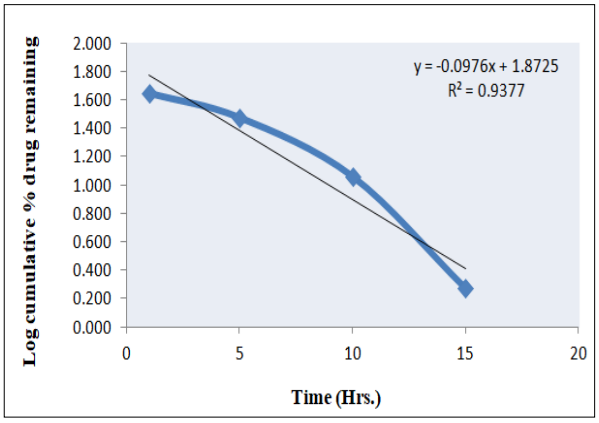
Figure 3: Results of disintegration time parameters of all formulations

Table 5: *In-vitro* drug release data for optimized formulation F3

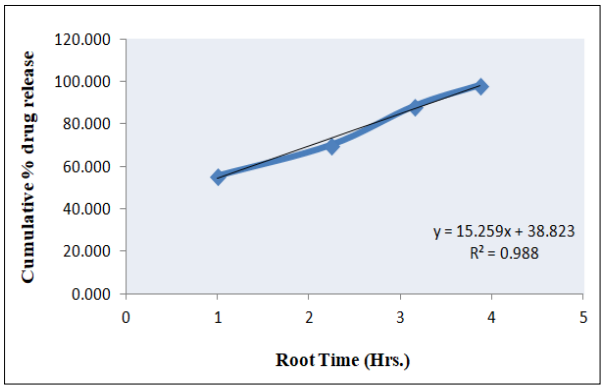
Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	55.45	1.744	44.55	1.649
5	2.24	0.698	69.98	1.845	30.02	1.477
10	3.16	1	88.45	1.947	11.55	1.063
15	3.87	1.176	98.12	1.992	1.88	0.274



a)



b)



c)

Figure 4a-c: Graph of a) zero order release Kinetics, b) First zero order release Kinetics c) Higuchi release Kinetics of formulation F3

Table 6: Regression analysis data

Batch	Zero Order	First Order	Higuchi
	r^2		
F3	0.9811	0.9377	0.988

Table 7: Stability Study Data of Optimized Formulation F3

Parameter	Initial	After 1 Month	After 2 Months	After 3 Months
Appearance	White, intact tablets	No change	No change	No change
Hardness (kg/cm²)	3.3 ± 0.1	3.3 ± 0.1	3.2 ± 0.1	3.2 ± 0.1
Friability (%)	0.712 ± 0.02	0.718 ± 0.03	0.724 ± 0.02	0.731 ± 0.03
Drug Content (%)	99.12 ± 0.24	98.94 ± 0.31	98.76 ± 0.28	98.51 ± 0.35
Disintegration Time (sec)	45 ± 3	46 ± 2	47 ± 3	48 ± 2
Drug Release at 15 min (%)	98.12 ± 0.35	97.84 ± 0.42	97.55 ± 0.38	97.23 ± 0.46

Conclusion

The current research work was able to formulate mouth dissolving tablets of Varenicline using the direct compression technique employing various superdisintegrating agents. Out of all six formulations prepared, the F3 formulation exhibited the best performance in terms of pharmaceutical properties, good characteristics both before and after compression, rapid disintegration (within 45 ± 3 seconds), and the maximum percent drug dissolution (98.12% in 15 minutes). Dissolution profile of the optimized formulation was found to follow

Higuchi kinetics, which shows diffusion-controlled dissolution of the drug. Formulation F3 was also found to be stable up to three months under accelerated conditions.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this research.

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Author Contributions

All authors contributed to the conception and design of the study, formulation development, experimental work, data analysis, manuscript preparation, and approved the final version of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

Not applicable, as this study involved formulation development and in vitro evaluation only.

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