RESEARCH PAPER

Development and Evaluation of Tizanidine Hydrochloride-Loaded Nano-structured Lipid Carriers in Mucoadhesive Buccal Films for Enhanced Permeation

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Abstract

The present study aimed to formulate and evaluate Tizanidine Hydrochloride-loaded nanostructured lipid carriers (NLCs) incorporated into mucoadhesive buccal films for sustained drug delivery. Tizanidine Hydrochloride is a centrally acting muscle relaxant with a short half-life and extensive first-pass metabolism. Nanostructured lipid carriers were prepared using glyceryl monostearate as the solid lipid, Capryol® 90 as the liquid lipid, Tween® 80 as the surfactant, and Poloxamer 188 as the co-surfactant. The optimized NLC formulation, TF4, showed a particle size of 182.3 ± 2.9 nm, a polydispersity index of 0.214 ± 0.012, a zeta potential of −31.6 ± 1.4 mV, entrapment efficiency of 89.6 ± 0.9%, and drug loading of 7.52 ± 0.09%. The optimized NLCs were incorporated into mucoadhesive buccal films using hydroxypropyl methylcellulose E15 and Carbopol 934P. Among the prepared films, BF5 exhibited satisfactory physicochemical and mechanical properties, including a thickness of 0.138 ± 0.004 mm, folding endurance of 174 ± 5 folds, surface pH of 6.18 ± 0.05, and drug content of 98.64 ± 0.72%. The formulation achieved 91.4% cumulative drug release over 8 hours. Release kinetic analysis showed the best fit with the Higuchi model ((R^2 = 0.9982)), suggesting diffusion-controlled release. Three-month stability studies showed that the optimized film retained satisfactory physical and physicochemical characteristics. These findings indicate that NLC-based mucoadhesive buccal films may offer a promising approach for the sustained delivery of Tizanidine Hydrochloride. Further permeation and in-vivo studies are required to establish their therapeutic performance.

Keywords: Tizanidine Hydrochloride, Nanostructured Lipid Carriers, Mucoadhesive Buccal Films, Sustained Drug Release, Drug Delivery.

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Introduction

Tizanidine Hydrochloride is a centrally acting skeletal muscle relaxant used for the management of muscle spasticity associated with neurological disorders such as multiple sclerosis and spinal cord injury. It acts as an α_2-adrenergic receptor agonist and reduces the release of excitatory neurotransmitters at the spinal cord level, thereby decreasing excessive muscle tone. Despite its therapeutic usefulness, Tizanidine Hydrochloride has a relatively short elimination half-life and undergoes extensive hepatic first-pass metabolism. These properties may limit its systemic availability and duration of action, making the development of alternative drug delivery systems an important area of pharmaceutical research.

Buccal drug delivery is a promising alternative to conventional oral administration. The buccal mucosa is well vascularized and provides an accessible route for drug absorption. Drug delivery through this route can reduce exposure to gastrointestinal conditions and may partially bypass hepatic first-pass metabolism. Mucoadhesive buccal films are thin, flexible dosage forms designed to remain attached to the inner surface of the cheek. Their prolonged contact with the mucosa may support controlled drug release and improve convenience of administration. However, the performance of buccal films depends on their adhesion, mechanical strength, surface pH, drug content, hydration and drug permeation characteristics.

Nanostructured lipid carriers (NLCs) are lipid-based nanocarriers composed of solid and liquid lipids stabilized by suitable surfactants. The combination of these lipids creates a less ordered matrix that may improve drug incorporation and reduce drug expulsion during storage. NLCs can also provide controlled drug release and protect the incorporated drug from environmental degradation. Their incorporation into mucoadhesive buccal films combines the drug-carrying properties of lipid nanoparticles with the prolonged mucosal residence provided by the polymeric film. This approach may

improve drug retention at the administration site and support sustained delivery.

The selection of suitable lipids, surfactants and film-forming polymers is essential for developing an effective formulation. Glyceryl monostearate can serve as the solid lipid, while Capryol® 90 acts as the liquid lipid. Tween® 80 and Poloxamer 188 can support the formation and stabilization of the NLC dispersion. Hydroxypropyl methylcellulose E15 and Carbopol 934P can provide film formation and mucoadhesive properties. The prepared formulation must be evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency, drug loading, film thickness, folding endurance, surface pH, drug content, mucoadhesive strength, in-vitro drug release and stability.

The present study focuses on the formulation, development and evaluation of Tizanidine Hydrochloride-loaded nanostructured lipid carriers incorporated into mucoadhesive buccal films. The optimized formulation is assessed for its physicochemical properties, mechanical characteristics, drug-release behaviour and stability. The study aims to determine whether combining NLCs with a mucoadhesive film can provide satisfactory formulation characteristics and sustained in-vitro drug release. Further permeation, pharmacokinetic and in-vivo studies would be required to establish its clinical relevance.

Methods

4.1 Materials

Tizanidine Hydrochloride was used as the model drug. Glyceryl monostearate (GMS), Capryol® 90, Tween® 80, and Poloxamer 188 were used for nanostructured lipid carrier (NLC) preparation. Hydroxypropyl methylcellulose E15 (HPMC E15) and Carbopol® 934P were used as film-forming and mucoadhesive polymers, respectively. Other excipients included polyethylene glycol 400, glycerol, and mannitol.

Preparation of Nanostructured Lipid Carriers

Tizanidine Hydrochloride-loaded NLCs were prepared using the hot homogenization–ultrasonication method. GMS and Capryol® 90 were heated to 70 ± 2°C until the lipid phase melted, and the drug was added with continuous stirring. An aqueous phase containing Tween® 80 and Poloxamer 188 was heated to the same temperature. The aqueous phase was added to the lipid phase and homogenized at 12,000–15,000 rpm for 10 minutes, followed by probe sonication for 5–10 minutes using alternating 30-second on/off cycles. The resulting dispersion was cooled and stored at 4 ± 2°C. The formulations were evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency, and drug loading.

Preparation of Mucoadhesive Buccal Films

The optimized NLC formulation was incorporated into mucoadhesive buccal films using the solvent-casting method. HPMC E15 and Carbopol® 934P were dispersed in the suitable aqueous medium and allowed to hydrate. The optimized NLC dispersion, plasticizer, and other required excipients were incorporated with continuous stirring to obtain a uniform casting mixture. The mixture was poured into suitable moulds and dried under controlled conditions. The dried films were carefully removed and stored in airtight containers until evaluation.

Evaluation of Buccal Films

The prepared films were evaluated for thickness, folding endurance, surface pH, drug content, tensile strength, percentage elongation, and mucoadhesive strength. In-vitro drug release was studied using a suitable dissolution setup, and the release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models. The optimized formulation was subjected to stability studies under the selected storage conditions for three months, with changes in drug content, folding endurance, and mucoadhesive strength recorded.

Results and Discussion

The results of the preformulation studies, optimization of Tizanidine Hydrochloride-loaded nanostructured lipid carriers (NLCs), preparation of mucoadhesive buccal films, in-vitro drug release, release kinetics, and stability evaluation are summarized below. Numerical results and embedded figures are reproduced from the supplied thesis chapter; they have not been independently re-analysed.

Preformulation and Drug–Excipient Compatibility

Tizanidine Hydrochloride was reported as a white to slightly yellowish-white crystalline powder. Its melting point was 289.5 ± 0.5°C, maximum ultraviolet absorption was observed at 230 nm, and the calibration curve was linear over 2–20 µg/mL (R^2 = 0.9998). FTIR and DSC results reported in the thesis indicated no major incompatibility with the selected excipients**.**

Table 1. Organoleptic properties of Tizanidine Hydrochloride

S. No.	Parameter	Observation
1	Colour	White to slightly yellowish-white
2	Appearance	Fine crystalline powder
3	Odour	Odourless
4	Physical state	Solid
5	Texture	Fine, smooth and crystalline
6	General observation	Uniform powder without visible foreign particles

Table 2. Solubility of Tizanidine Hydrochloride in solvents and selected excipients

S. No.	Solvent/Excipient	Solubility (mg/mL)	Solubility Character
1	Distilled water	0.92 ± 0.03	Freely soluble
2	Methanol	1.68 ± 0.04	Freely soluble
3	Ethanol	0.38 ± 0.02	Slightly soluble
4	Phosphate buffer pH 6.8	2.04 ± 0.05	Freely soluble
5	Glyceryl Monostearate (GMS)	0.31 ± 0.02	Slightly soluble
6	Capryol® 90	5.82 ± 0.08	Highly soluble
7	Tween® 80	8.64 ± 0.11	Highly soluble
8	Poloxamer 188	6.27 ± 0.09	Highly soluble

Table 3. Calibration data for Tizanidine Hydrochloride

S. No.	Concentration (µg/mL)	Absorbance
1	2	0.147
2	4	0.294
3	6	0.438
4	8	0.586
5	10	0.731
6	12	0.877
7	14	1.024
8	16	1.168
9	18	1.316
10	20	1.459

Table 4. Summary of ultraviolet spectrophotometric analysis

Parameter	Result
Wavelength	230 nm
Linearity range	2–20 µg/mL
Regression equation	Y = 0.0731X + 0.0017
Slope	0.0731
Intercept	0.0017
Correlation coefficient (R^2)	0.9998

Table 5. FTIR compatibility observations

S. No.	Characteristic peak of drug (cm^{-1})	Physical mixture peak (cm^{-1})	Observation
1	3310	3305	No significant change
2	3060	3056	No significant change
3	2925	2922	No significant change
4	1610	1607	No significant change
5	1545	1542	No significant change
6	1320	1317	No significant change
7	760	758	No significant change
8	690	688	No significant change

Preliminary Screening and Optimization of NLCs

Five preliminary formulations (TF1–TF5) were screened. Particle size ranged from 182.3 ± 2.9 to 286.4 ± 4.8 nm, while entrapment efficiency ranged from 72.6 ± 1.4% to 89.6 ± 0.9%. TF4 showed the smallest particle size and highest entrapment efficiency among the preliminary batches and was selected for further characterization.

Table 6. Preliminary NLC appearance and physical stability

Formulation	Appearance	Homogeneity	Phase Separation	Physical Stability
TF1	Milky dispersion	Moderate	Slight	Moderate
TF2	Uniform milky dispersion	Good	Not observed	Good
TF3	Uniform milky dispersion	Good	Not observed	Good

TF4	Smooth, uniform dispersion	Very good	Not observed	Very good
TF5	Slightly viscous dispersion	Good	Slight	Good

Table 7. Particle size of preliminary NLC formulations

Formulation	Particle Size (nm)
TF1	286.4 ± 4.8
TF2	238.7 ± 3.9
TF3	214.6 ± 3.5
TF4	182.3 ± 2.9
TF5	205.8 ± 3.7

Table 8. Entrapment efficiency of preliminary NLC formulations

Formulation	Entrapment Efficiency (%)
TF1	72.6 ± 1.4
TF2	78.9 ± 1.2
TF3	83.7 ± 1.1
TF4	89.6 ± 0.9
TF5	86.8 ± 1.0

Table 9. Comparative selection of preliminary NLC formulations

Formulation	Particle Size (nm)	Entrapment Efficiency (%)	Physical Stability	Overall Evaluation
TF1	286.4 ± 4.8	72.6 ± 1.4	Moderate	Unsuitable
TF2	238.7 ± 3.9	78.9 ± 1.2	Good	Suitable
TF3	214.6 ± 3.5	83.7 ± 1.1	Good	Suitable
TF4	182.3 ± 2.9	89.6 ± 0.9	Very good	Selected
TF5	205.8 ± 3.7	86.8 ± 1.0	Good	Suitable

Characterization of Optimized NLC Formulation (TF4)

The optimized TF4 formulation showed a mean particle size of 182.3 ± 2.9 nm, PDI of 0.214 ± 0.012, zeta potential of −31.6 ± 1.4 mV, entrapment efficiency of 89.6 ± 0.9%, and drug loading of 7.52 ± 0.09%. Transmission electron microscopy described predominantly spherical to slightly oval particles with smooth surfaces and no significant aggregation.

Table 10. Particle size of optimized TF4

Parameter	Result
Mean particle size	182.3 ± 2.9 nm
Number of measurements	3
Measurement technique	Dynamic Light Scattering
Temperature	25 ± 1°C

Table 11. Polydispersity index of optimized TF4

Parameter	Result
PDI	0.214 ± 0.012
Number of measurements	3
Interpretation	Narrow and relatively uniform particle-size distribution

Table 12. Zeta potential of optimized TF4

Parameter	Result
Zeta potential	−31.6 ± 1.4 mV
Number of measurements	3
Surface charge	Negative
Interpretation	Good physical stability

Table 13. Entrapment efficiency of optimized TF4

Parameter	Result
Entrapment efficiency	89.6 ± 0.9%
Number of measurements	3
Interpretation	High drug entrapment

Table 14. Drug loading of optimized TF4

Parameter	Result
Drug loading	7.52 ± 0.09%
Number of measurements	3
Interpretation	Good drug incorporation

Table 15. Morphological observations of optimized TF4

Parameter	Observation
Particle shape	Spherical to slightly oval
Surface characteristics	Smooth
Particle distribution	Relatively uniform
Aggregation	Not prominently observed
Overall morphology	Satisfactory

Table 16. Stability observations for optimized NLC at refrigerated conditions

Parameter	0 Month	1 Month	2 Months	3 Months
Appearance	Uniform	Uniform	Uniform	Uniform
Particle size (nm)	182.3 ± 2.9	183.1 ± 3.0	184.0 ± 3.2	185.2 ± 3.4
PDI	0.214 ± 0.012	0.216 ± 0.013	0.218 ± 0.014	0.221 ± 0.015
Zeta potential	−31.6 ± 1.4	−31.2 ± 1.4	−30.9 ± 1.5	−30.6 ± 1.5

(mV)				
Entrapment efficiency	89.6 ± 0.9	89.2 ± 0.9	88.9 ± 1.0	88.5 ± 1.1

Table 17. Stability observations for optimized NLC at room temperature

Parameter	0 Month	1 Month	2 Months	3 Months
Appearance	Uniform	Uniform	Uniform	Uniform
Particle size (nm)	182.3 ± 2.9	184.0 ± 3.1	186.2 ± 3.3	188.5 ± 3.6
PDI	0.214 ± 0.012	0.219 ± 0.013	0.224 ± 0.014	0.231 ± 0.016
Zeta potential (mV)	−31.6 ± 1.4	−31.0 ± 1.4	−30.5 ± 1.5	−29.8 ± 1.6
Entrapment efficiency (%)	89.6 ± 0.9	89.0 ± 1.0	88.4 ± 1.0	87.8 ± 1.1

Preparation and Evaluation of Mucoadhesive Buccal Films

Nine NLC-loaded films (BF1–BF9) were prepared using HPMC E15 and Carbopol 934P. The films were evaluated for appearance, thickness, weight variation, folding endurance, surface pH, drug content, moisture content, moisture uptake, swelling, tensile strength, elongation, and mucoadhesive strength. BF5 showed the most balanced overall characteristics, including thickness of 0.138 ± 0.004 mm, folding endurance of 174 ± 5 folds, surface pH of 6.18 ± 0.05, drug content of 98.64 ± 0.72%, tensile strength of 2.31 ± 0.07 N/mm², and elongation of 59.7 ± 2.3%.

Table 18. Physical appearance of BF1–BF9

Formulation	Colour	Transparency	Smoothness	Flexibility	Uniformity	Air bubbles	Cracks
BF1	Pale white	Slightly translucent	Smooth	Good	Uniform	Absent	Absent
BF2	Pale white	Slightly translucent	Smooth	Good	Uniform	Absent	Absent
BF3	Pale white	Translucent	Smooth	Good	Uniform	Absent	Absent
BF4	Pale white	Translucent	Very smooth	Very good	Uniform	Absent	Absent
BF5	Pale white	Translucent	Very smooth	Very good	Uniform	Absent	Absent
BF6	Pale white	Slightly translucent	Smooth	Good	Uniform	Absent	Absent
BF7	Pale white	Slightly opaque	Smooth	Good	Uniform	Absent	Absent
BF8	Pale white	Slightly opaque	Smooth	Good	Uniform	Absent	Absent
BF9	Pale white	Slightly opaque	Smooth	Moderate	Uniform	Absent	Slight

Table 19. Thickness of BF1–BF9

Formulation	Thickness (mm)
BF1	0.118 ± 0.004
BF2	0.123 ± 0.003
BF3	0.128 ± 0.004
BF4	0.132 ± 0.003
BF5	0.138 ± 0.004
BF6	0.144 ± 0.003
BF7	0.147 ± 0.004
BF8	0.153 ± 0.003
BF9	0.159 ± 0.004

Table 20. Weight variation of BF1–BF9

Formulation	Average Weight (mg)	Weight Variation (%)
BF1	48.6 ± 1.2	2.47
BF2	49.8 ± 1.1	2.21
BF3	51.2 ± 1.3	2.54
BF4	53.6 ± 1.1	2.05
BF5	55.1 ± 1.2	2.18
BF6	56.8 ± 1.3	2.29
BF7	58.7 ± 1.4	2.39
BF8	60.4 ± 1.3	2.15

BF9	62.1 ± 1.5	2.42

Table 21. Folding endurance of BF1–BF9

Formulation	Folding Endurance (folds)
BF1	142 ± 5
BF2	151 ± 4
BF3	158 ± 5
BF4	166 ± 4
BF5	174 ± 5
BF6	169 ± 4
BF7	161 ± 5
BF8	154 ± 4
BF9	146 ± 5

Table 22. Surface pH of BF1–BF9

Formulation	Surface pH
BF1	6.32 ± 0.05
BF2	6.28 ± 0.04
BF3	6.24 ± 0.05
BF4	6.20 ± 0.04
BF5	6.18 ± 0.05
BF6	6.15 ± 0.04
BF7	6.12 ± 0.05
BF8	6.08 ± 0.04
BF9	6.05 ± 0.05

Table 23. Drug content of BF1–BF9

Formulation	Drug Content (%)
BF1	96.42 ± 1.18
BF2	97.15 ± 1.06
BF3	97.63 ± 0.94
BF4	98.12 ± 0.86
BF5	98.64 ± 0.72
BF6	98.31 ± 0.81
BF7	97.86 ± 0.89
BF8	97.42 ± 0.97
BF9	96.94 ± 1.05

Table 24. Moisture content of BF1–BF9

Formulation	Moisture Content (%)
BF1	3.42 ± 0.18
BF2	3.58 ± 0.16
BF3	3.71 ± 0.17
BF4	3.84 ± 0.15
BF5	4.02 ± 0.16
BF6	4.18 ± 0.17
BF7	4.31 ± 0.18
BF8	4.45 ± 0.16
BF9	4.62 ± 0.19

Table 25. Moisture uptake of BF1–BF9

Formulation	Moisture Uptake (%)
BF1	7.82 ± 0.31
BF2	8.16 ± 0.29
BF3	8.54 ± 0.33
BF4	8.91 ± 0.30
BF5	9.28 ± 0.32
BF6	9.64 ± 0.35
BF7	10.02 ± 0.34
BF8	10.38 ± 0.36
BF9	10.76 ± 0.38

Table 26. Swelling index of BF1–BF9

Formulation	30 min	60 min	90 min	120 min
BF1	42.6 ± 1.2	61.8 ± 1.5	74.2 ± 1.7	82.5 ± 1.9
BF2	45.3 ± 1.3	65.4 ± 1.6	78.6 ± 1.8	87.2 ± 2.0
BF3	48.1 ± 1.4	69.7 ± 1.7	82.4 ± 1.9	91.5 ± 2.1
BF4	51.8 ± 1.5	73.6 ± 1.8	87.3 ± 2.0	96.4 ± 2.2
BF5	55.2 ± 1.6	77.9 ± 1.9	92.1 ± 2.1	101.8 ± 2.4
BF6	57.1 ± 1.5	79.8 ± 1.8	94.5 ± 2.0	105.2 ± 2.3
BF7	59.4 ± 1.6	82.6 ± 1.9	97.8 ± 2.2	109.6 ± 2.5
BF8	61.7 ± 1.7	85.4 ± 2.0	101.3 ± 2.3	113.8 ± 2.6
BF9	63.2 ± 1.8	87.1 ± 2.1	104.6 ± 2.4	117.5 ± 2.7

Table 27. Tensile strength of BF1–BF9

Formulation	Tensile Strength (N/mm²)
BF1	1.82 ± 0.08
BF2	1.94 ± 0.07
BF3	2.06 ± 0.09
BF4	2.18 ± 0.08
BF5	2.31 ± 0.07
BF6	2.45 ± 0.08
BF7	2.58 ± 0.09
BF8	2.71 ± 0.08
BF9	2.84 ± 0.10

Table 28. Percentage elongation of BF1–BF9

Formulation	Percentage Elongation (%)
BF1	48.6 ± 2.1
BF2	51.2 ± 2.0
BF3	53.8 ± 2.2
BF4	56.4 ± 2.1

BF5	**59.7 ± 2.3**
BF6	**57.8 ± 2.0**
BF7	**55.1 ± 2.2**
BF8	**52.6 ± 2.1**
BF9	**49.8 ± 2.4**

Table 29. Overall evaluation of BF1–BF9

Formulation	Thickness (mm)	Folding Endurance (folds)	Surface pH	Drug Content (%)	Tensile Strength (N/mm²)	Elongation (%)
BF1	**0.118**	**142**	**6.32**	**96.42**	**1.82**	**48.6**
BF2	**0.123**	**151**	**6.28**	**97.15**	**1.94**	**51.2**
BF3	**0.128**	**158**	**6.24**	**97.63**	**2.06**	**53.8**
BF4	**0.132**	**166**	**6.20**	**98.12**	**2.18**	**56.4**
BF5	**0.138**	**174**	**6.18**	**98.64**	**2.31**	**59.7**
BF6	**0.144**	**169**	**6.15**	**98.31**	**2.45**	**57.8**
BF7	**0.147**	**161**	**6.12**	**97.86**	**2.58**	**55.1**
BF8	**0.153**	**154**	**6.08**	**97.42**	**2.71**	**52.6**
BF9	**0.159**	**146**	**6.05**	**96.94**	**2.84**	**49.8**

In-vitro Drug Release

In-vitro release was evaluated up to 8 hours using phosphate buffer pH 6.8 in a Franz diffusion cell, as described in the thesis. Cumulative release from BF1–BF9 at 8 hours ranged from 87.8% to 91.4%; BF5 showed 91.4% release at 8 hours. The release profile indicates gradual drug release over the test period under the reported in-vitro conditions.

Table 30. Cumulative percentage drug release of BF1–BF9

Formulation	0.5 h	1 h	2 h	3 h	4 h	5 h	6 h	7 h	8 h
BF1	**12.4**	**23.8**	**38.6**	**51.2**	**62.7**	**71.8**	**79.6**	**85.3**	**89.2**
BF2	**11.8**	**22.9**	**37.4**	**50.6**	**62.1**	**71.5**	**79.8**	**85.9**	**90.1**
BF3	**11.2**	**21.8**	**36.2**	**49.5**	**61.4**	**70.9**	**79.4**	**86.2**	**90.8**
BF4	**10.6**	**20.9**	**34.8**	**47.8**	**59.8**	**69.5**	**78.3**	**85.4**	**90.6**
BF5	**10.1**	**20.2**	**33.9**	**46.9**	**58.7**	**68.6**	**77.5**	**84.9**	**91.4**
BF6	**9.7**	**19.4**	**32.8**	**45.5**	**57.1**	**67.2**	**76.4**	**84.1**	**90.8**
BF7	**9.3**	**18.7**	**31.6**	**44.1**	**55.8**	**65.8**	**75.2**	**83.0**	**89.7**
BF8	**8.9**	**17.9**	**30.5**	**42.8**	**54.3**	**64.2**	**73.8**	**81.8**	**88.9**
BF9	**8.5**	**17.2**	**29.4**	**41.6**	**52.9**	**62.7**	**72.4**	**80.6**	**87.8**

Drug Release Kinetics

The reported regression coefficients were 0.9803 for zero-order, 0.9699 for first-order, 0.9982 for Higuchi, and 0.9963 for Korsmeyer–Peppas. The Higuchi model provided the highest R^2 value. The Korsmeyer–Peppas diffusion exponent was n = 0.8344, which the thesis interpreted as anomalous (non-Fickian) transport.

Table 31. Comparison of drug release kinetic models

Kinetic Model	Regression Coefficient (R^2)	Interpretation
Zero-order	**0.9803**	**Good fit**
First-order	**0.9699**	**Comparatively lower fit**
Higuchi	**0.9982**	**Best fit**
Korsmeyer–Peppas	**0.9963**	**Very good fit**

Stability of Optimized Buccal Film

During the three-month stability assessment, BF5 drug content changed from 98.64% initially to 97.96% under long-term conditions (25 ± 2°C/60 ± 5% RH) and 96.94% under accelerated conditions (40 ± 2°C/75 ± 5% RH). Folding endurance changed from 174 folds to 171 and 165 folds, respectively, while mucoadhesive strength changed from 28.6 g to 27.9 g and 26.7 g. These results indicate some changes during storage; longer-term studies would be needed to establish shelf life.

Table 32. Comparative stability results for optimized BF5

Parameter	Initial	3 Months	3 Months

	Value	at 25 ± 2°C / 60 ± 5% RH	at 40 ± 2°C / 75 ± 5% RH
Physical appearance	**Smooth, uniform**	**Smooth, uniform**	**Smooth, slight change**
Thickness (mm)	**0.138**	**0.140**	**0.144**
Folding endurance (folds)	**174**	**171**	**165**
Surface pH	**6.18**	**6.15**	**6.10**
Drug content (%)	**98.64**	**97.96**	**96.94**
Mucoadhesive strength (g)	**28.6**	**27.9**	**26.7**

Figures

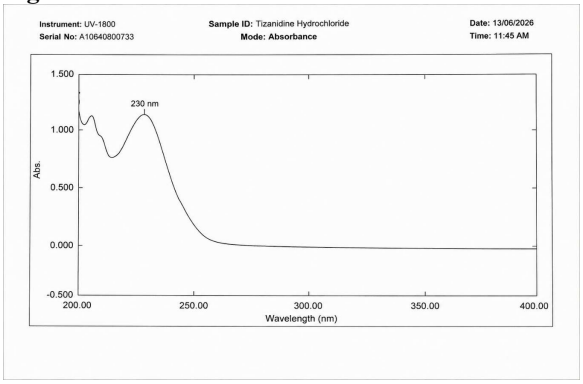


Figure 1. Original embedded figure/image from the thesis chapter

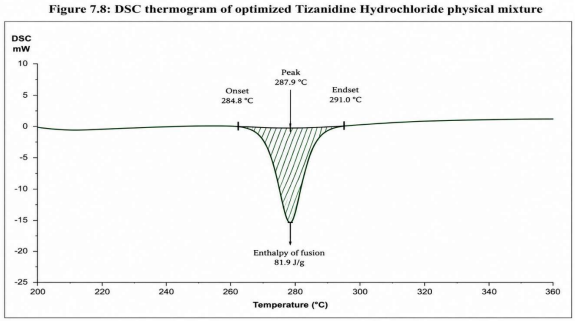


Figure 2. Original embedded figure/image from the thesis chapter

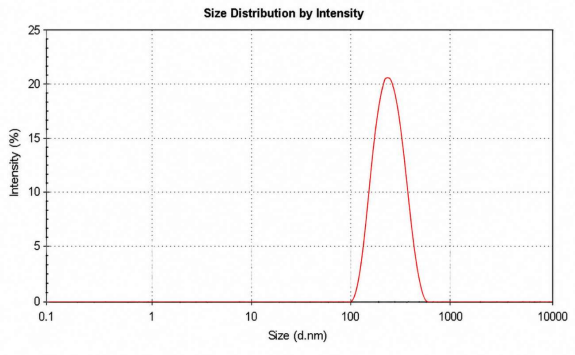


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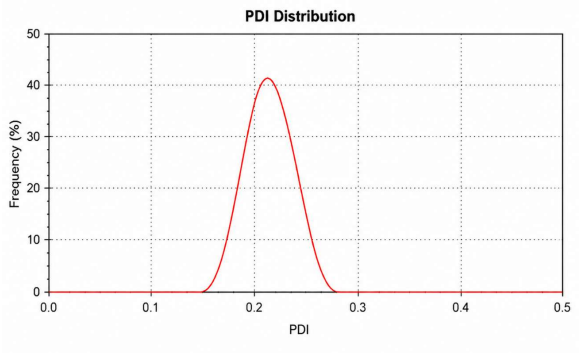


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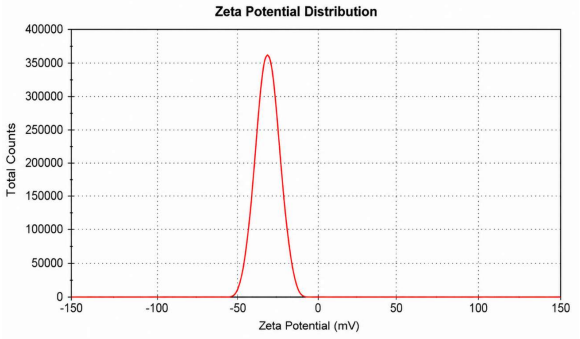


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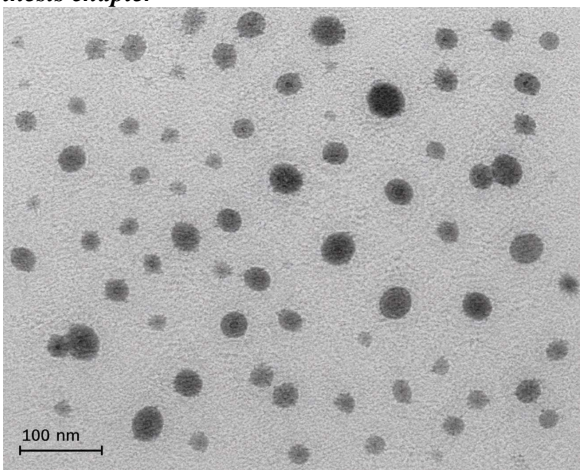


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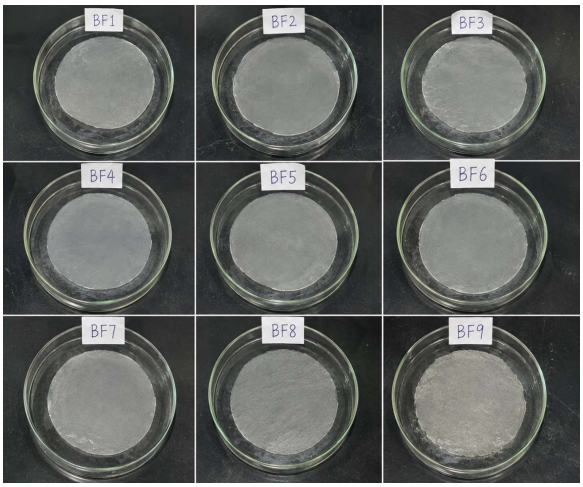


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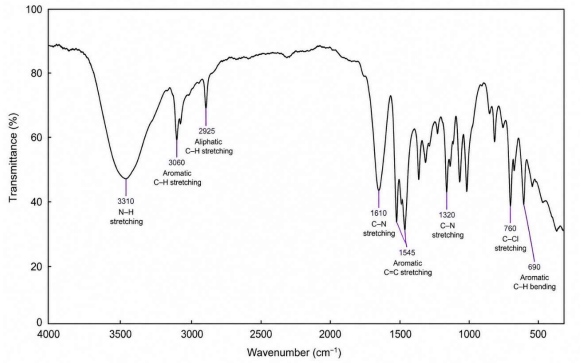


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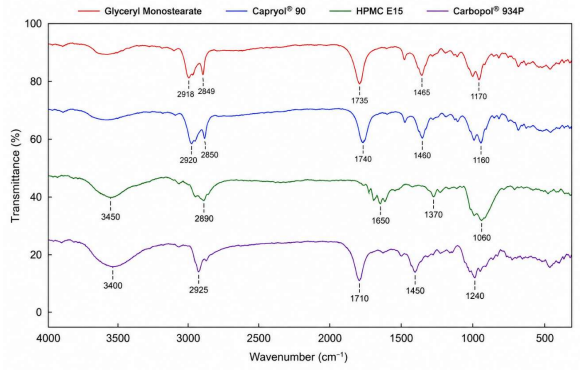


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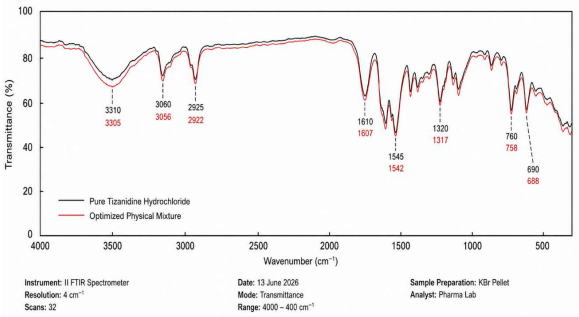


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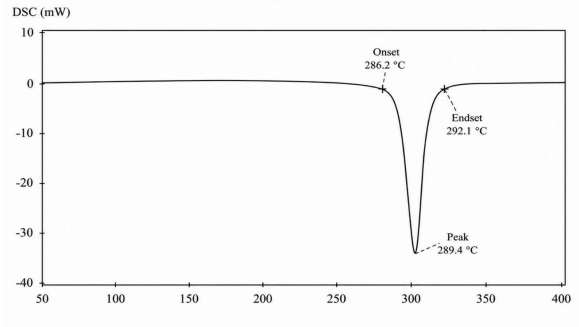


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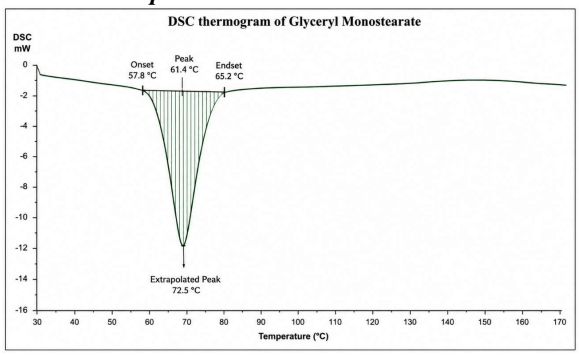


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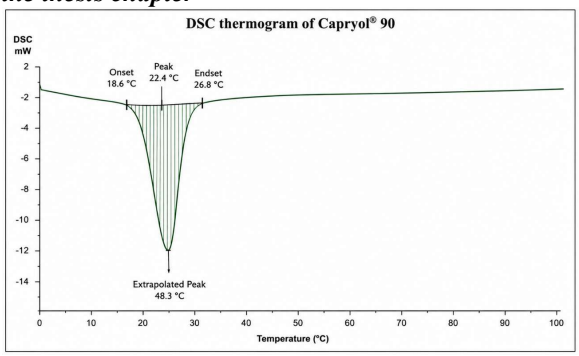


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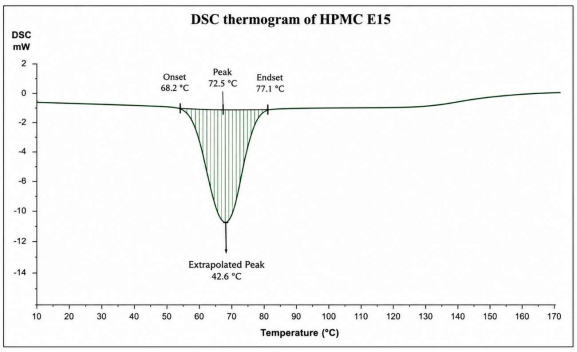


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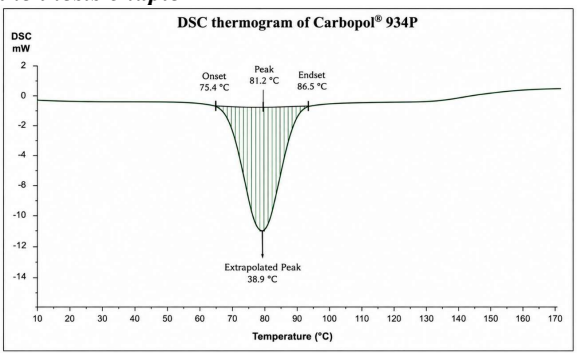


Figure 15. Original embedded figure/image from the thesis chapter (image9.png).

Summary and Conclusion

The present study focused on the formulation and evaluation of Tizanidine Hydrochloride-loaded nanostructured lipid carriers (NLCs) incorporated into mucoadhesive buccal films for sustained drug delivery. The NLCs were prepared using glyceryl monostearate as the solid lipid, Capryol® 90 as the liquid lipid, Tween® 80 as the surfactant, and Poloxamer 188 as the co-surfactant.

The optimized NLC formulation, TF4, showed a particle size of 182.3 ± 2.9 nm, a polydispersity index of 0.214 ± 0.012, a zeta potential of −31.6 ± 1.4 mV, an entrapment efficiency of 89.6 ± 0.9%, and drug loading of 7.52 ± 0.09%. The NLCs were subsequently incorporated into mucoadhesive buccal films prepared using HPMC E15 and Carbopol 934P.

Among the nine film formulations (BF1–BF9), BF5 showed the most suitable overall physicochemical and mechanical properties. It exhibited a thickness of 0.138 ± 0.004 mm, folding endurance of 174 ± 5 folds, surface pH of 6.18 ± 0.05, drug content of 98.64 ± 0.72%, tensile strength of 2.31 ± 0.07 N/mm², and percentage elongation of 59.7 ± 2.3%. The optimized film achieved 91.4% cumulative drug release over 8 hours. Release kinetic analysis showed the highest coefficient of determination for the Higuchi model (R^2 = 0.9982). The Korsmeyer–Peppas model gave an exponent of 0.8344, suggesting anomalous or non-Fickian release behaviour.

Three-month stability studies showed that the optimized film retained satisfactory characteristics, although some changes in drug content, folding endurance, and mucoadhesive strength were observed under the tested storage conditions.

The study demonstrated the feasibility of developing Tizanidine Hydrochloride-loaded NLCs and incorporating them into mucoadhesive buccal films. The optimized NLC formulation showed nanosized particles, good entrapment efficiency, and suitable physicochemical characteristics. Among the prepared films, BF5 exhibited satisfactory mechanical properties, drug content, mucoadhesive strength, and sustained in-vitro drug release over 8 hours.

The findings suggest that NLC-based mucoadhesive buccal films may be a promising formulation approach for the delivery of Tizanidine Hydrochloride. However, further ex-vivo permeation, pharmacokinetic, and in-vivo studies are necessary to establish its actual absorption, bioavailability, safety, and therapeutic effectiveness.

References

1. Shanker G, Kumar CK, Gonugunta CSR, Kumar BV, Veerareddy PR. Formulation and evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets. AAPS PharmSciTech. 2009;10(2):530-539. doi:10.1208/s12249-009-9241-2.
2. Zaman M, Hanif M, Shaheryar ZA. Development of tizanidine HCl-meloxicam loaded mucoadhesive buccal films: in-vitro and in-vivo evaluation. PLoS One. 2018;13(3). doi:10.1371/journal.pone.0194410.
3. Arpa MD, Üstündağ Okur N, Gök MK, Özgümüş S, Cevher E. Chitosan-based buccal mucoadhesive patches to enhance the systemic bioavailability of tizanidine. Int J Pharm. 2023;642:123168. doi:10.1016/j.ijpharm.2023.123168.
4. Arpa MD, Üstündağ Okur N, Gök MK, Cevher E. Chitosan-based buccal mucoadhesive bilayer tablets enhance the bioavailability of tizanidine hydrochloride by bypassing the first-pass metabolism. J Drug Deliv Sci Technol. 2024;97:105739. doi:10.1016/j.jddst.2024.105739.
5. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. Int J Pharm. 2002;242(1-2):121-128. doi:10.1016/S0378-5173(02)00180-1.
6. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and

nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 2002;54 Suppl 1. doi:10.1016/S0169-409X(02)00118-7.
7. Müller RH, Petersen RD, Hommoss A, Pardeike J. Nanostructured lipid carriers (NLC) in cosmetic dermal products. Adv Drug Deliv Rev. 2007;59(6):522-530. doi:10.1016/j.addr.2007.04.012.
8. Souto EB, Müller RH. Cosmetic features and applications of lipid nanoparticles (SLN®, NLC®). Int J Cosmet Sci. 2008;30(3):157-165. doi:10.1111/j.1468-2494.2008.00433.x.
9. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm. 2009;366(1-2):170-184. doi:10.1016/j.ijpharm.2008.10.003.
10. Beloqui A, Solinís MÁ, Rodríguez-Gascón A, Almeida AJ, Préat V. Nanostructured lipid carriers: promising drug delivery systems for future clinics. Nanomedicine. 2016;12(1):143-161. doi:10.1016/j.nano.2015.09.004.
11. Gordillo-Galeano A, Mora-Huertas CE. Solid lipid nanoparticles and nanostructured lipid carriers: a review emphasizing on particle structure and drug release. Eur J Pharm Biopharm. 2018;133:285-308. doi:10.1016/j.ejpb.2018.10.017.
12. Khosa A, Reddi S, Saha RN. Nanostructured lipid carriers for site-specific drug delivery. Biomed Pharmacother. 2018;103:598-613. doi:10.1016/j.biopha.2018.04.055.
13. Haider M, Abdin SM, Kamal L, Orive G. Nanostructured lipid carriers for delivery of chemotherapeutics: a review. Pharmaceutics. 2020;12(3):288. doi:10.3390/pharmaceutics12030288.
14. Salvi VR, Pawar P. Nanostructured lipid carriers (NLC) system: a novel drug targeting carrier. J Drug Deliv Sci Technol. 2019;51:255-267.
15. Fang CL, Al-Suwayeh SA, Fang JY. Nanostructured lipid carriers (NLCs) for drug delivery and targeting. Recent Pat Nanotechnol. 2013;7(1):41-55. doi:10.2174/187221013804484827.
16. Mehnert W, Mäder K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001;47(2-3):165-196. doi:10.1016/S0169-409X(01)00105-3.
17. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Deliv Rev. 2005;57(11):1666-1691. doi:10.1016/j.addr.2005.07.003.
18. Shojaei AH. Buccal mucosa as a route for systemic drug delivery: a review. J Pharm Pharm Sci. 1998;1(1):15-30.
19. Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Deliv Rev. 2005;57(11):1556-1568.
20. Shinkar DM, Dhake AS, Setty CM. Drug delivery from the oral cavity: a focus on mucoadhesive buccal drug delivery systems. PDA J Pharm Sci Technol. 2012;66(5):466-500. doi:10.5731/pdajpst.2012.00877.
21. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. J Control Release. 2011;153(2):106-116.
22. Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Kerr AR, et al. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. Adv Drug Deliv Rev. 2012;64(1):16-28.
23. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. J Biomed Res. 2014;28(2):81-97.
24. Semalty A, Semalty M, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. Indian J Pharm Sci. 2008;70(1):43-48. doi:10.4103/0250-474X.40330.
25. Remuñán-López C, Portero A, Vila-Jato JL, Alonso MJ. Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. J Control Release. 1998;55(2-3):143-152. doi:10.1016/S0168-3659(98)00044-3.
26. Shipp L, Liu F, Kerai-Varsani L, Okwuosa TC. Buccal films: a review of therapeutic opportunities, formulations and relevant evaluation approaches. J Control Release. 2022;352:1071-1092. doi:10.1016/j.jconrel.2022.10.058.
27. Nair VV, Cabrera P, Ramírez-Lecaros C, Jara MO, Brayden DJ, Morales JO. Buccal delivery of small molecules and biologics: of mucoadhesive polymers, films, and nanoparticles—an update. Int J Pharm. 2023;636:122789. doi:10.1016/j.ijpharm.2023.122789.
28. Jiménez-Castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1993;19(1-2):143-194.

29. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm. 1992;78(1-3):43-48.
30. Solomonidou D, Cremer K, Krumme M, Kreuter J. Effect of carbomer concentration and degree of neutralization on the mucoadhesive properties of polymer films. J Biomater Sci Polym Ed. 2001;12(11):1191-1205. doi:10.1163/156856201753395743.
31. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J Control Release. 1985;2(4):257-275.
32. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci. 1961;50(10):874-875.
33. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15(1):25-35.
34. Ritger PL, Peppas NA. A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J Control Release. 1987;5(1):23-36.
35. Ritger PL, Peppas NA. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Control Release. 1987;5(1):37-42.
36. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001;13(2):123-133.
37. Siepmann J, Peppas NA. Higuchi equation: derivation, applications, use and misuse. Int J Pharm. 2011;418(1):6-12.
38. Higuchi WI. Diffusional models useful in biopharmacy: drug release from ointments. J Pharm Sci. 1962;51(8):802-804.
39. Boddupalli BM, Mohammed ZNK, Nath RA, Banji D. Mucoadhesive drug delivery system: an overview. J Adv Pharm Technol Res. 2010;1(4):381-387.
40. Müller RH, Shegokar R, Keck CM. 20 years of lipid nanoparticles (SLN and NLC): present state of development and industrial applications. Curr Drug Discov Technol. 2011;8(3):207-227.