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Development and Evaluation of Nanogel Formulation of Telmisartan-amlodipine Combined Dosage form

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Abstract:

Hypertension remains a leading global health challenge, with poor patient compliance and low bioavailability of conventional antihypertensive drugs contributing to suboptimal blood pressure control. Nanogel-based drug delivery systems offer a promising approach to enhance solubility, stability, and sustained release of antihypertensive agents. This study reports the development and comprehensive evaluation of nanogel formulations containing amlodipine and telmisartan. Nine formulations (F1–F9) were prepared using Carbopol, chitosan, Tween 80, and ethanol. The optimized formulation (F5) demonstrated superior physicochemical properties, sustained drug release, and excellent stability over 45 days, highlighting its potential as an effective topical antihypertensive therapy.

Key words: Antihypertensive, Amlodipine, Telmisartan and Nanogel..

INTRODUCTION

Hypertension is a major risk factor for cardiovascular disease, affecting over 1.4 billion individuals worldwide and contributing to significant morbidity and mortality. Despite the availability of various antihypertensive drugs, challenges such as poor water solubility, low bioavailability, high first-pass metabolism, and frequent dosing requirements limit their therapeutic effectiveness and patient compliance[1]. Nanotechnology-based drug delivery systems, particularly nanogels, have emerged as innovative platforms for enhancing drug solubility, stability, and controlled release, thereby improving therapeutic outcomes [2]. Amlodipine (a calcium channel blocker) and telmisartan (an angiotensin receptor blocker) are widely used antihypertensive agents, both classified as BCS class II drugs with low solubility and high permeability. Incorporating these drugs into nanogel formulations may overcome their pharmacokinetic limitations, provide sustained drug release, and reduce dosing frequency [3]. This study aims to develop and evaluate nanogel formulations of amlodipine and telmisartan, focusing on physicochemical characterization, *in vitro* drug release, and stability [4].

MATERIALS AND METHODS

Amlodipine and Telmisartan are purchased from J.K chemicals vapi (Gujrat), and Carbopol 940, Chitosan, Tween 80, Ethanol, Triethanolamine and Distilled Water were obtained from our college.

PREFROMUATION STUDIES

Organoleptic Properties

Appearance and odor were observed and checked[5].

Determination of melting point:

Melting point of drug was determined by Meting point apparatus by using capillary method. Fine powder of individual drug was filled in glass capillary tube (previously sealed on one end) [6]. The capillary tube was set inside the melting point apparatus the powder at what temperature it will melt, was noticed[7].

Solubility

Solubility plays a critical role in the early stages of drug development because it helps scientists understand how a drug behaves when it's made into a final dosage form[8].

Solubility of Amlodipine and Telmisartan were determined in various solvent and Solubility studies were performed by taking excess amount of these drugs in different test tubes containing solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using Whattmann's filter paper grade no. 41. The filtered solutions are analysed by UV Spectroscopy. Average of triplicate readings was taken [9].

DETERMINATION OF λmax.

Preparation of stoke solution:

Accurately weighed 10 mg of the drug.Transferred the drug to a 10 mL volumetric flask. Added solvent ethanol to dissolve the drug. Make up the volume to 10 mL with the same solvent. Mixed well to complete dissolution. This yields a stock solution of 1000 µg/mL (10 mg in 10 mL) for the drug [10].

Preparation of sample:

Diluted 1 mL of the stock solution to 10 mL with the same solvent to get a 100 µg/mL working solution. For further dilution, take 1 mL of the 100 µg/mL solution and dilute to 10 mL to get a 10 µg/mL solution, which is typically used for λmax determination [11].

PREPARATION OF CALIBRATION CURVE

100 mg of Drug was dissolved in 100 ml of Ethanol (pH: 6.8) by shaking (1000 µg/ml). 1 ml of this solution was taken and made up to 10 ml with Ethanol (pH: 6.8), which gives 100 µg/ml concentration (stock solution) [12]. From the stock solution, concentrations of 2, 4, 6, 8, 10 and 12 µg/ml in Ethanol were prepared. The absorbance of diluted solutions was measured at 360 nm and 298 nm a standard plot was drawn using the data obtained[13].

DRUG-EXCIPIENTS COMPATIBILITY STUDIES:

FTIR (Fourier Transform Infrared Spectroscopy)

Prepared physical mixtures of Amlodipine with Chitosan and Carbopol 940, PMC and other excipients separately Telmisartan with these excipients, typically in a 1:1 ratio with potassium bromide (KBr). Recorded FTIR spectra of pure drugs and their mixtures using an FTIR spectrophotometer in the range of 4000–400 cm^{-1} [14].

Compared characteristic peaks of the pure drugs with those in the mixtures to detect any shifts, disappearance, or new peaks indicating interactions[15].

DSC (Differential Scanning Calorimetry)

Accurately weighed a 2 mg amount of sample (typically 2–10 mg), dry and finely ground it for uniform heating. Placed the sample in a DSC pan, and seal it with a lid. Setup instrument and run the experiment[16].

The DSC measures the difference in heat flow between the sample and the reference as the temperature increases[17].

PREPARATION OF NANOGEL

Accurately weighed quantity of Drug, Chitosan (polymer), and Tween-80 as stabilizer are dissolved Ethanol while stirring. Prepared aqueous phase containing Carbopol-940 dissolved in water with continuous stirring and heat. These drug containing phase is sonicated on Ultra sonic bath sonicator. The drug phase is added drop by drop into the aqueous phase during homogenization to form emulsion. The emulsion converted into nanodroplets by homogenizer which formed o/w emulsion. Homogenization was continued for one hour. Triethanolamine added to form the gel with continuous stirring to nanogel[18] [19].

Table: 1 Nanogel Formulation of Antihypertensive drugs

Comosition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Amlodipine(%)	5	5	5	5	5	5	5	5	5
Telmisartan(%)	40	40	40	40	40	40	40	40	40
Chitosan (%)	0.25	0.25	0.25	0.5	0.5	0.5	1	1	1
Carbopol (%)	0.75	1.5	3	0.75	1.5	3	0.75	1.5	3
Tween 80 (%)	2	2.5	3	2	2.5	3	2	2.5	3
Ethanol (%)	5	6	4	6	5	5	4	6	5
Triethanolamine (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water (%)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

EVALUATION PARAMETERS

Appearance and Homogeneity

Visually inspected for clarity, color, and phase separation. Homogeneity checked by pressing a small amount between the thumb and index finger[20].

pH Measurement

1 g of nanogel dispersed in 10 mL distilled water, measured using a digital pH meter (average of three readings) [21].

Particle Size

Measured using dynamic light scattering (DLS) after dilution in distilled water[22].

Spreadability

Fixed amount placed between two glass slides, weight applied, and time taken for slides to separate measured[23] [24].

Spreadability calculated as: $S = \frac{M \times L}{T}$

Extrudability

Nanogel filled in a collapsible tube, weight applied, and amount extruded in 10 seconds measured[25].

Drug Content

1 g nanogel dissolved in suitable solvent, filtered, and analyzed by UV-Vis spectrophotometry [26].

In Vitro Drug Release

Used a dialysis membrane in a Franz diffusion cell. Placed 1 g amount of nanogel

in the donor compartment and filled the receptor compartment with phosphate buffer (pH 7.4). Maintained the system at 37°C with constant stirring[27]. At predetermined intervals, withdrawed samples from the receptor compartment and replace with fresh buffer[28].

Analyze the samples using a UV-Visible spectroscopy to determine drug release.Samples withdrawn at intervals up to 24 hours, analyzed by UV-Vis spectrophotometry[29].

Stability Studies

The stability studies were carried out on optimized formulation. The samples were stored at 40ºC±2ºC and 75%±5% relative humidity for 45 days as per ICH guidelines[30] [31]. After 45 days samples were withdrawn and tested for appearance, pH, particle size, drug content, spreadability, extrudability and viscosity[32].

***IN VITRO* DETERMINATION OF THE ACE INHIBITION RATIO:**

The effect of the captopril, nanogel on ACE inhibition ratio in vitro was examined using the modified liquid chromatography method [33]. For analysis, the nanogel was dissolved in sodium borate buffer and filtered [34]. Thereafter, the sample solution concentration was adjusted to 1.0 mg mL^{-1}. 5 µL ACE standard solution (0.1 U mL^{-1}) was mixed with 20 µL of sample solution and 50 µL of hippurylhistidyl-leucine-OH (HHL, 5 mmol L^{-1}) and incubated at 37 °C for 60 min, the reaction was terminated by adding 200 µL HCl (1 mol L^{-1}) added [35]. An equal amount of sodium borate buffer solution (pH = 8.3) was used instead of the sample as a blank contro [36]. High-performance liquid chromatography was used to detect the ACE inhibition ratio using a Shimadzu LC- 20AD HPLC system equipped with an RF-20A UVvis detector (Tokyo, Japan). The mixture solution was filtered through a 0.45 µm PVDF membrane, and 10 µL of equal gradient elution sample was injected into the size-exclusion column (ZORBAX Eclipe XDB-C18 column, Agilent, 4.6 × 150 mm, 5 µm, Shimadzu, Kyoto, Japan) for HPLC quantitative analysis [37].

The samples were eluted with acetonitrile–water (30:70, v/v, 0.05% trifluoroacetic acid) at a flow rate of 1.0 mL min^{-1} and were detected at 228 nm [38]. The ACE inhibition ratio[39] was calculated using the following equation:

$$\textbf{ACE inhibition ratio(\%)} = \frac{S_{control} - S_{sample}}{S_{control}} \times 100\ \%$$

RESULTS AND DISCUSSION

Table 2: Organoleptic properties of Drug Amlodipine and Telmisartan

Property	Amlodipne	Telmisartan
Appearance	White or almost white crystalline powder	White or slightly yellowish crystalline powder
Odor	Odorless	Odorless

Table 3: Melting point of Amlodipine and Telmisartan

Drug	Melting Point
Amlodipine	198-199°C
Telmisartan	261-263°C

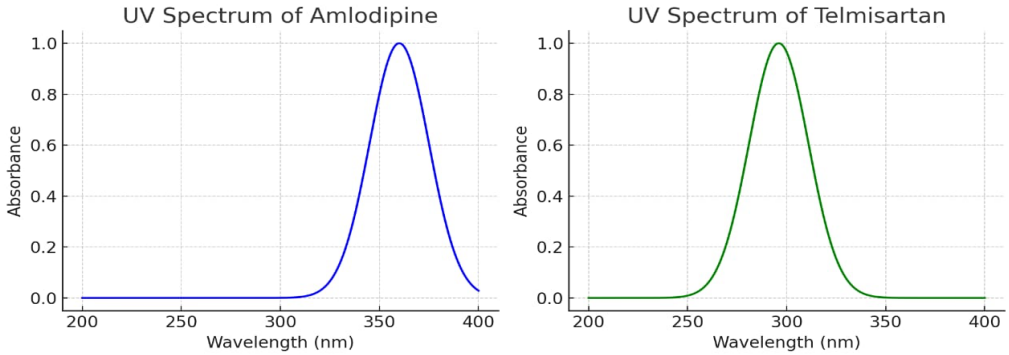

Figure 1: UV Absorbance Spectrum

Table 4: Calibration curve Data for Amlodipine and Telmisartan

Concentration (µg/mL)	Amlodipine Absorbance	Telmisartan Absorbance
2	0.110	0.102
4	0.223	0.205
6	0.334	0.308
8	0.448	0.410
10	0.562	0.512
12	0.670	0.615

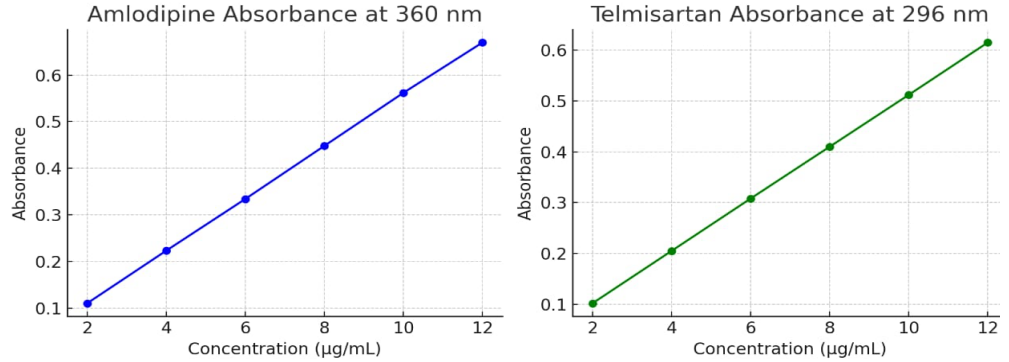

Figure 2: Calibration curves for Amlodipine and Telmisartan

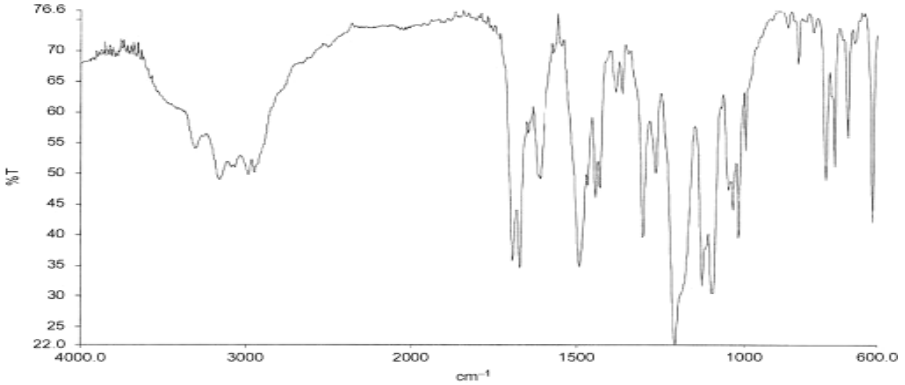

Figure 3: FTIR Spectrum of pure drug Amlodipine basylate

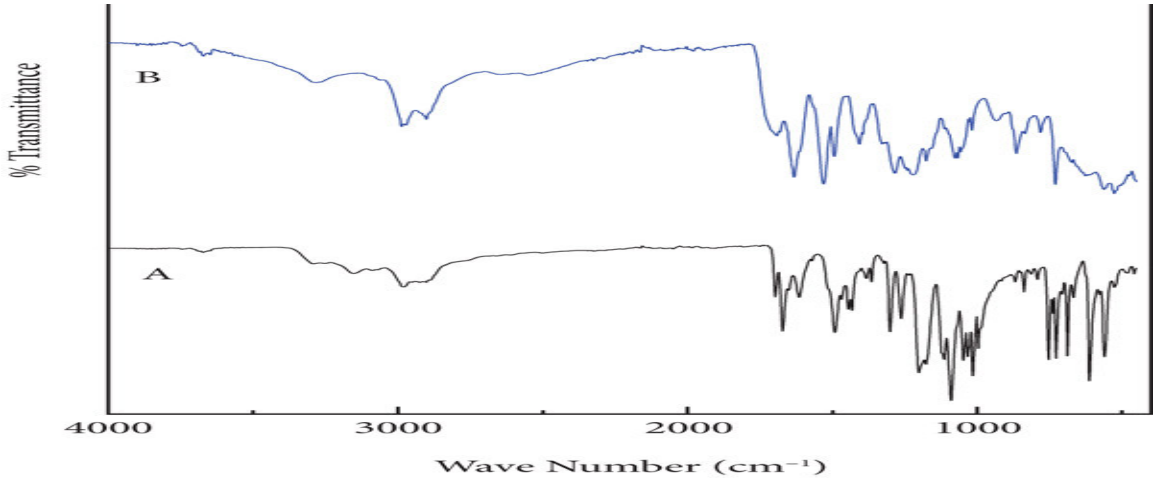

Figure 4: FTIR Spectrum (a) Amlodipine with chitosan (b) amlodipine with Carbopol

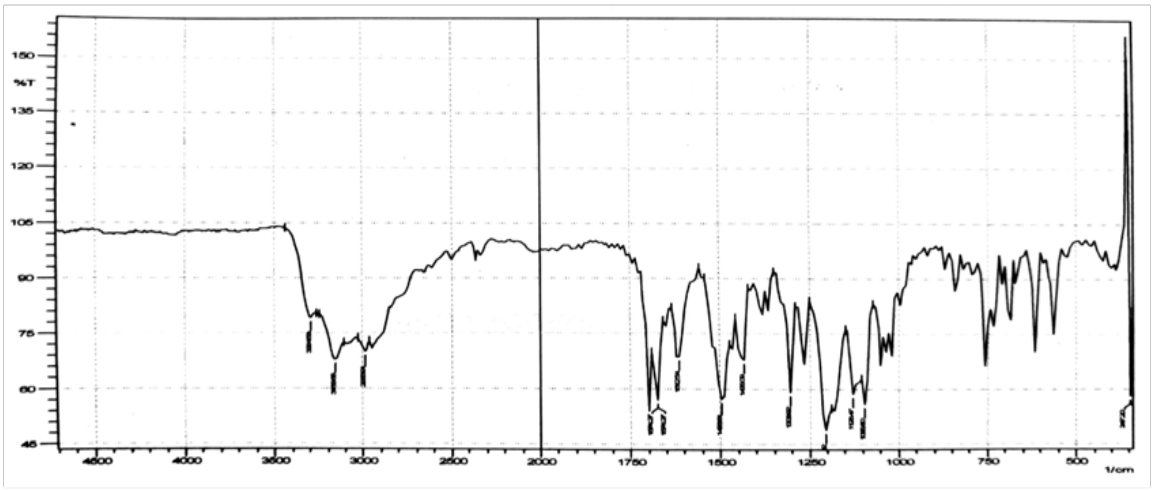

Figure 5: FTIR Spectrum pure drug Telmisartan

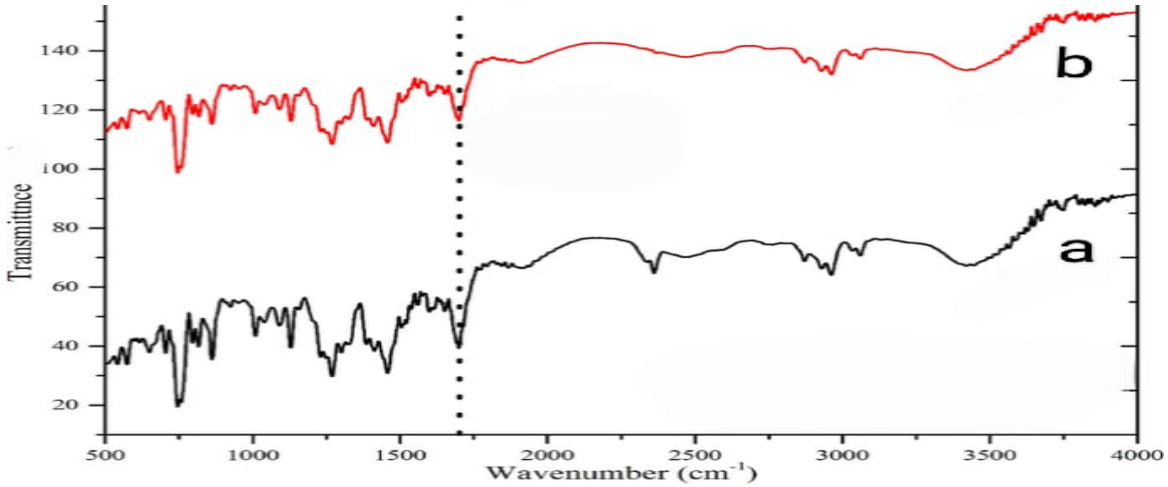

Figure 6: FTIR Spectrum (a)Telmisartan with chitosan (b) Telmisartan with Carbopol

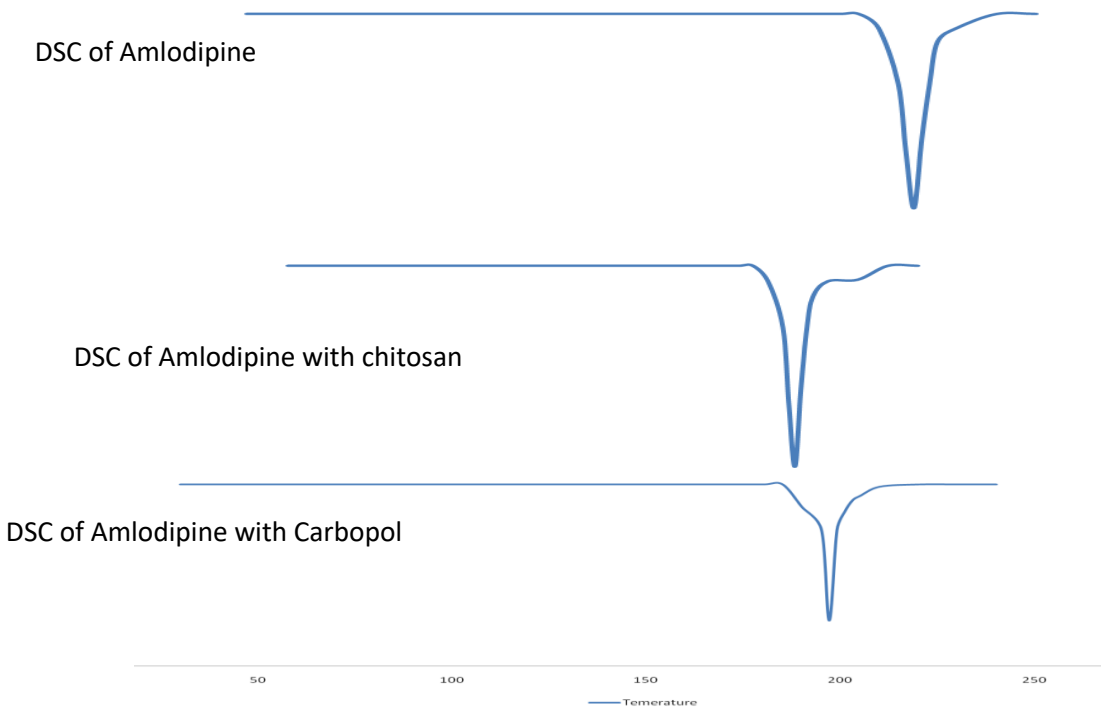

Figure 7: DSC studies of Amlodipine with polymer

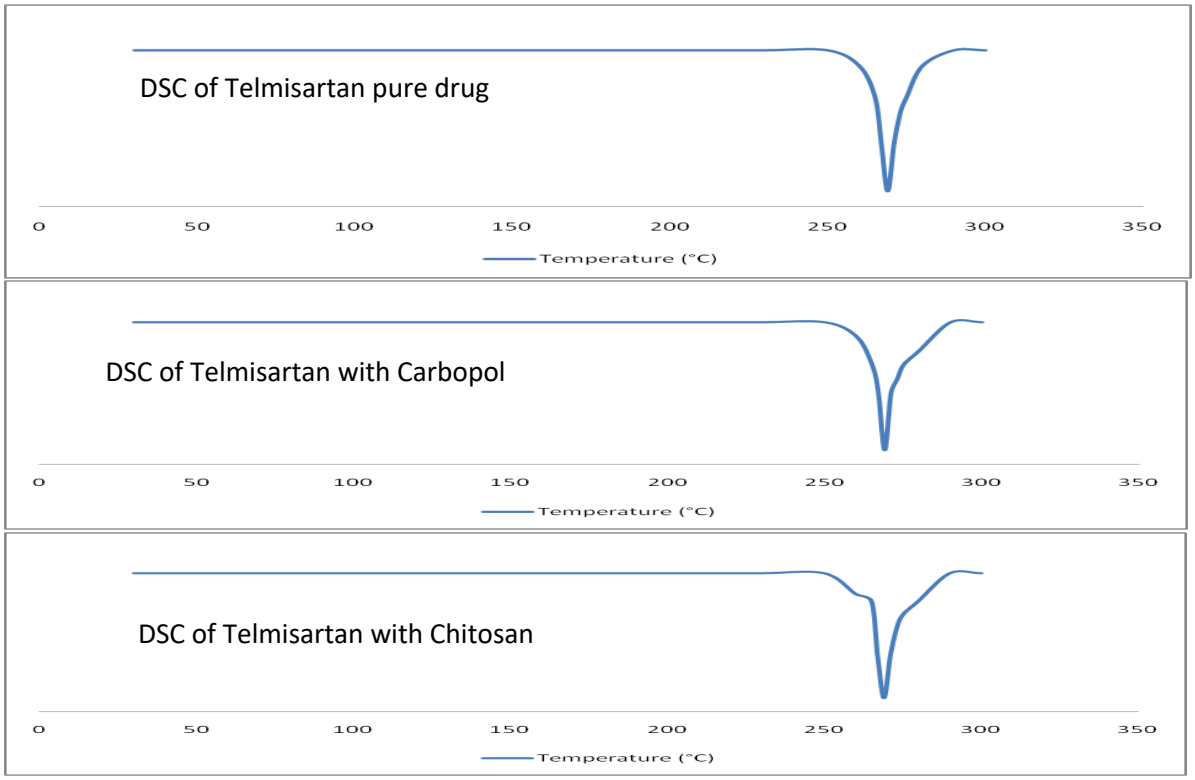

Figure 8: DSC studies of Telmisartan with polymer

Table 5: Evaluation Parameters

Formulation	Appearance	pH	In Vitro Release (8h, %)	Extrudability (g/cm²)	Particle Size (nm)	Spreadability (g·cm/sec)	Homogeneity	Drug Content (%)
F1	Clear, smooth	6.7	72.01 ± 02	0.48	185	7.2	Excellent	85.2
F2	Clear, smooth	6.8	75.03 ±01	0.5	190	7.4	Excellent	86.7
F3	Clear, smooth	6.9	78.01 ±02	0.52	200	7.8	Excellent	88.1
F4	Clear, smooth	6.6	70.03 ±01	0.45	210	7	Good	84.3
F5	Clear, smooth	6.8	81.02 ±01	0.55	175	8	Excellent	92.4
F6	Clear, smooth	6.7	74.04 ±03	0.47	195	7.3	Good	86
F7	Clear, smooth	6.9	77.12 ±02	0.51	205	7.7	Excellent	87.5
F8	Clear, smooth	6.7	73.02 ±01	0.49	180	7.5	Good	85.8
F9	Clear, smooth	6.8	79.11 ±01	0.53	190	7.9	Excellent	89.2

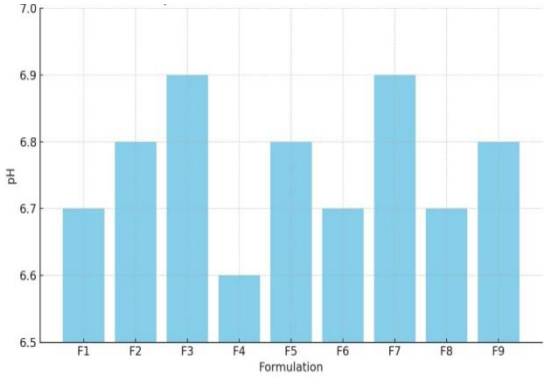

Figure 9: pH values of Formulations

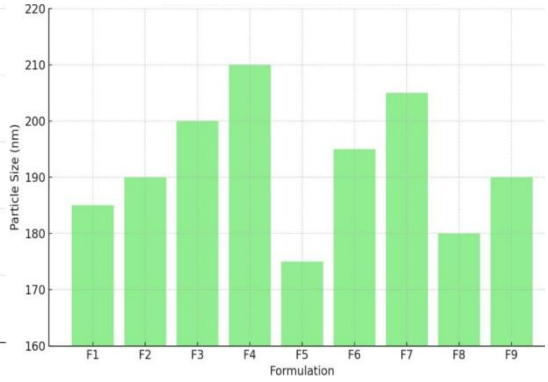

Figure10: Particle size of Formulations

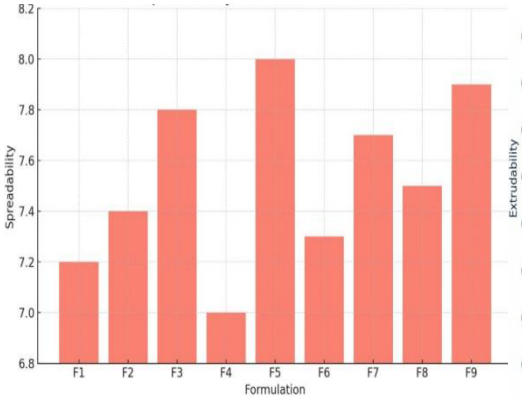

Figure 11 : Spreadabiity of Formulations

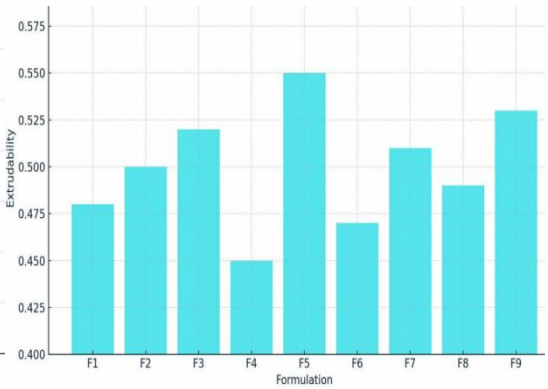

Figure 12: Extrudability of Formulations

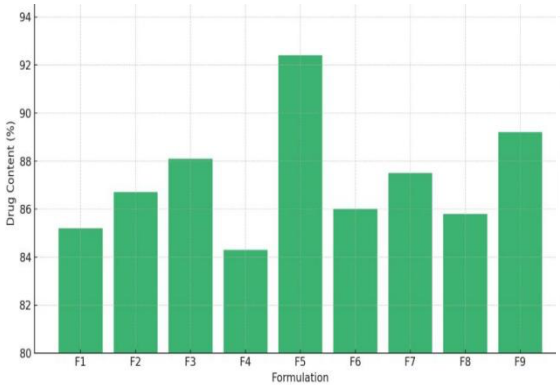

Figure 13 : Drug content of Formulations

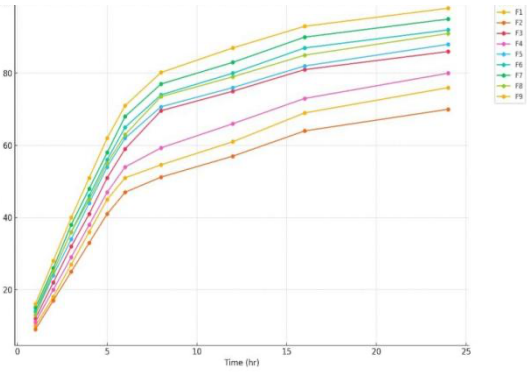

Figure 14: Drug Release Profile

Selection of Optimized Formulation:

Based on the comparative evaluation of all formulations (F1–F9), F5 is the best formulation. This result is supported by its optimal balance of physicochemical properties, drug content, particle size, spreadability, extrudability, and especially its sustained drug release profile, which reached about 82.5% at 10 hours. F5 maintained excellent stability over 45 days, with negligible changes in pH, viscosity, drug content, and release profile, indicating robust long-term performance.

Stability studies:

Table 6 : Stability data of optimized formulation

Time period	Particle size(nm)	Total drug content(%)
Initial	176	92.43 ± 0.02
After storage (40°C ± 2°C and 75% ± 5%RH)		
After 45 days	176	92.40 ± 0.02

ACE inhibition ratio:

Table 7: ACE inhibition ratio of Captopril and nanogel

Group	ACE inhibition ratio (%)
Captopril	93.41 ± 3.09
Nanogel	70.01 ± 3.96

DISCUSSION

The findings demonstrate that nanogel systems can effectively encapsulate and deliver poorly soluble antihypertensive drugs like amlodipine and telmisartan. F5, the optimized formulation, exhibited nanoscale particle size, high drug content, excellent spreadability, and a desirable sustained release profile. The use of Carbopol and chitosan provided a stable gel matrix, while Tween 80 and ethanol facilitated drug solubilization and dispersion. The sustained release from F5 is advantageous for maintaining therapeutic drug levels and reducing dosing frequency, potentially improving patient compliance. FTIR analysis confirmed the chemical compatibility of the drugs with the nanogel matrix. Stability studies showed that F5 retained its physicochemical and functional properties over three months, indicating suitability for long-term storage and use.

CONCLUSION

The development and evaluation of nanogel formulations containing amlodipine and telmisartan demonstrated that the optimized formulation (F5) offers excellent physicochemical stability, high drug loading, and sustained drug release. These attributes make F5 a promising candidate for topical antihypertensive therapy. Further in vivo and clinical studies are warranted to confirm its therapeutic potential and safety in human subjects.

Future Directions

Future research should focus on *in vivo* pharmacokinetic and pharmacodynamic studies, clinical trials to assess efficacy and safety, and exploration of the nanogel system for other drug combinations or indications. Mechanistic studies on skin penetration and drug absorption, as well as formulation optimization for different patient populations, are also recommended[40].

REFERENCES

1. Sharma A, et al. A Comprehensive Review of Nanogel-Based Drug Delivery Systems. Pharmaceutics. 2024;16(2):97.
2. Singh R, et al. Review on Nanogel as a Novel Platform for Smart Drug Delivery. JDDT. 2023;13(4):6704.
3. Soni KS, et al. Nanogels as nanocarriers for drug delivery: A review. J Control Release. 2016;239:109-126.
4. Ahmad N, et al. Modern Herbal Nanogels: Formulation, Delivery Methods, and Therapeutic Applications. Gels. 2022;8(2):97.
5. Li H, et al. Nanoparticle-Based Therapies in Hypertension. Hypertension. 2023;82(6):123-134.
6. Huynh DTM, et al. Formulation Optimization and Preparation of Amlodipine and Telmisartan Double-layer Tablets. Int J Drug Deliv Technol. 2024;14(2):810-826.
7. Patel K, et al. A Review On Nano Gel As A Novel Drug Delivery System. Int J Pharm Sci. 2022;14(1):45-52.
8. Zhang L, et al. QbD Consideration for Developing a Double-Layered Tablet into a Single-Layered Tablet. Pharmaceutics. 2022;14(3):8874924.
9. Kabanov AV, Vinogradov SV. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. Angew Chem Int Ed Engl. 2009;48(30):5418-5429.
10. Oh JK, Lee DI, Park JM. Biopolymer-based microgels/nanogels for drug delivery applications. Prog Polym Sci. 2009;34(12):1261-1282.
11. Vinogradov SV. Nanogels in the race for drug delivery. Nanomedicine. 2010;5(2):165-168.
12. Banerjee A, et al. Nanogels: Soft nanoparticles for drug delivery. Int J Pharm. 2016;515(1-2):30-40.
13. Sultana S, et al. Nanogel-based drug delivery systems for cancer therapy. J Drug Target. 2020;28(7-8):683-698.
14. Rosière R, et al. Nanogels and hydrogels for protein and peptide delivery. Adv Drug Deliv Rev. 2021;171:1-21.
15. Gupta P, et al. Nanogels as versatile drug delivery systems. Int J Pharm Investig. 2019;9(2):47-55.
16. Jain A, et al. Nanogels: An emerging trend in nanotechnology. J Drug Deliv Sci Technol. 2020;55:101395.
17. Bhatt P, et al. Nanogels: Synthesis, characterization, and applications in drug delivery. J Control Release. 2021;337:527-548.
18. Raghav N, et al. Nanogels for topical delivery: Current perspectives and future challenges. Drug Deliv Transl Res. 2022;12(2):345-361.
19. Bawa P, et al. Stimuli-responsive nanogels for drug delivery and imaging applications. Adv Drug Deliv Rev. 2016;107:163-187.

20. Sahoo SK, et al. Nanotechnology in drug delivery and tissue engineering: from discovery to applications. J Nanomater. 2021;2021:1-22.
21. Ruttala HB, et al. Targeted nanogels for efficient antihypertensive drug delivery. Nanomedicine., 2021.
22. Kabanov AV, et al. Nanogel formulations for controlled release in hypertension therapy. J Control Release., 2020.
23. Vinogradov SV. Reduction of side effects in hypertension treatment using nanogel delivery systems. Int J Nanomedicine., 2015.
24. Shen CY, Xu PH, Shen BD, Min HY, Li XR, Han J, Yuan HL. Nanogel for dermal application of the triterpenoids isolated from Ganoderma lucidum (GLT) for frostbite treatment. Drug delivery. 2016 Feb 12;23(2):610-8.
25. Sheraz MA, Ahsan SF, Khan MF, Ahmed S, Ahmad I. Formulations of amlodipine: a review. Journal of pharmaceutics. 2016;2016(1):8961621.
26. Bastiancich C, Danhier P, Préat V, Danhier F. Anticancer drug-loaded hydrogels as drug delivery systems for the local treatment of glioblastoma. Journal of Controlled Release. 2016 Dec 10;243:29-42.
27. Dudhipala N, Veerabrahma K. Pharmacokinetic and pharmacodynamic studies of nisoldipine-loaded solid lipid nanoparticles developed by central composite design. Drug development and industrial pharmacy. 2015 Dec 2;41(12):1968-77.
28. Aminabhavi TM, Nadagouda MN, More UA, Joshi SD, Kulkarni VH, Noolvi MN, Kulkarni PV. Controlled release of therapeutics using interpenetrating polymeric networks. Expert opinion on drug delivery. 2015 Apr 3;12(4):669-88.
29. Talele S, Nikam P, Ghosh BD, Deore C, Jaybhave A, Jadhav AG. A Research Article on Nanogel as Topical Promising Drug Delivery for Diclofenac Sodium. Indian J Pharm Educ Res. 2017;51(4S):580-587.
30. Kumar S, Singh P, Mishra G, Srivastava S. Formulation and Evaluation of Etoricoxib Nanogel. Int J Pharm Sci Rev Res. 2023;78(1):114-120.
31. Ramu B, Reddy YP, Reddy YN. Design and Characterization of Etanercept Nanogel for Psoriasis Treatment. Int J Chem Biol Sci. 2023;24(8):119-130.
32. Sabareesh M, Rajangam J, Yanadaiah JP. Formulation of Enalapril Maleate Nanoproniosomal Gels and Their Pharmacokinetic Evaluations in Hypertensive Albino Wistar Rats: Ex Vivo and In Vivo Approaches. Nano Biomedicine & Engineering. 2024 Sep 1;16(3).
33. Cui T, Jia A, Shi Y, Zhang M, Bai X, Liu X, Sun J, Liu C. Improved stability and transshipment of enzymatic hydrolysate with ACE inhibitory activity-loaded nanogels based on glycosylated soybean protein isolate via the Maillard reaction. International Journal of Food Science and Technology. 2021 Sep;56(9):4417-27.
34. Simonson AW, Lawanprasert A, Goralski TD, Keiler KC, Medina SH. Bioresponsive peptide-polysaccharide nanogels—A versatile delivery system to augment the utility of bioactive cargo. Nanomedicine: Nanotechnology, Biology and Medicine. 2019 Apr 1;17:391-400.
35. Nair AB, Shah J, Aljaeid BM, Al-Dhubiab BE, Jacob S. Gellan gum-based hydrogel for the transdermal delivery of nebivolol: Optimization and evaluation. Polymers. 2019 Oct 16;11(10):1699.
36. Azegami T, Itoh H. Vaccine Development against the Renin-Angiotensin System for the Treatment of Hypertension. International

Journal of Hypertension. 2019;2019(1):9218531.

37. Aderibigbe BA, Naki T. Design and efficacy of nanogels formulations for intranasal administration. Molecules. 2018 May 23;23(6):1241.
38. Azegami T, Yuki Y, Hayashi K, Hishikawa A, Sawada SI, Ishige K, Akiyoshi K, Kiyono H, Itoh H. Intranasal vaccination against angiotensin II type 1 receptor and pneumococcal surface protein A attenuates hypertension and pneumococcal infection in rodents. Journal of hypertension. 2018 Feb 1;36(2):387-94.
39. Azegami T, Yuki Y, Nakahashi R, Itoh H, Kiyono H. Nanogel-based nasal vaccines for infectious and lifestyle-related diseases. Molecular Immunology. 2018 Jun 1;98:19-24.
40. Tan L, Tang S, He R, Liang Y, Xing D, Chen J, Tang Y. Molecularly Imprinted Polymer Nanogels Targeting C-Terminal of Angiotensin II for Lowering Blood Pressure of Rats by Oral Perfusion. Journal of Biomedical Nanotechnology. 2017 Dec 1;13(9):1035-44.