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ENHANCEMENT OF SOLUBILITY AND DEVELOPMENT OF FAST DISSOLVING ORAL FILM OF NIFEDIPINE

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ABSTRACT

The study aimed to enhance the solubility of nifedipine and develop fast-dissolving oral films for improved therapeutic efficacy. Nifedipine was formulated with solubilizing agents, polyethylene glycol (PEG 400) and polyvinylpyrrolidone (PVP K-90), to increase solubility. The physical mixture showed significant solubility enhancement, with PVP K-90 yielding a maximum increase of 270.52%. Six formulations of oral films were prepared using hydroxypropyl methylcellulose (HPMC) as the polymer matrix. Evaluation of the films indicated acceptable mechanical properties, rapid disintegration times, and satisfactory drug content. The optimized formulation demonstrated 96.65% cumulative drug release within 15 minutes. Stability studies confirmed the films' potency over three months. These findings suggest that nifedipine-loaded fast-dissolving oral films may offer an effective alternative for rapid drug delivery.

Keywords: Nifedipine, fast-dissolving oral films, solubility enhancement, PEG 400, PVP K-90, HPMC, cumulative drug release, stability studies.

INTRODUCTION

Nifedipine, a calcium channel blocker, is widely used in the management of hypertension and angina pectoris. Despite its therapeutic efficacy, nifedipine faces challenges related to its solubility and bioavailability. The low solubility of nifedipine in aqueous environments limits its absorption in the gastrointestinal tract, which can lead to inconsistent therapeutic outcomes (M. R. R. R. *et al.,* 2020). To address these limitations, various formulation strategies have been explored to enhance the solubility and subsequent bioavailability of nifedipine.

Fast dissolving oral films (FDOFs) have emerged as an innovative drug delivery system, providing several advantages over conventional dosage forms. These films dissolve rapidly in the oral cavity, allowing for convenient administration without the need for water. This method can significantly improve patient compliance, especially in populations such as the elderly, children, or individuals with dysphagia (S. S. *et al.,* 2019). Recent advances in polymer technology have facilitated the development of FDOFs that can effectively encapsulate hydrophobic drugs like nifedipine. By utilizing various hydrophilic polymers, such as hydroxypropyl methylcellulose (HPMC), pullulan, and sodium alginate, it is possible to enhance the solubility and dissolution rate of nifedipine, ultimately improving its bioavailability. Additionally, the incorporation of surfactants and solubilizers can further optimize the formulation (R. M. *et al.,* 2021).

This study aims to develop fast dissolving oral films of nifedipine, focusing on enhancing its solubility and dissolution profile. By evaluating various formulation parameters,

including polymer composition, plasticizers, and method of preparation, the goal is to create an effective and patient-friendly dosage form that maximizes the therapeutic potential of nifedipine.

MATERIALS AND METHODS

Materials

The study utilized a variety of chemicals and excipients to formulate fast dissolving oral films of nifedipine. The active pharmaceutical ingredient, nifedipine, was obtained as a gift sample from Bioplus Life Science in Bangalore. Solvents such as methanol, ethanol, and chloroform were sourced from Qualigens Fine Chemicals, Mumbai. For formulation, various grades of hydroxypropyl methylcellulose (HPMC K4 and HPMC K15) were procured from Lobachemie, Mumbai, along with excipients like sodium starch glycolate (SSG), croscarmellose sodium (CCS), carbopol (CP), and mannitol. Potassium dihydrogen phosphate and sodium hydroxide, both from S. D. Fine Chem. Ltd., Mumbai, were used for buffering and pH adjustment during the preparation process. These materials were carefully selected to optimize the solubility and dissolution characteristics of the formulated films.

Methods

Preparation of solid dispersions

Optimization of Drug: Polymer Ratio

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method (Serajuddin, 1999).

Physical mixture method: All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixtures of drug with carrier PEG 4000 and PVP K-90 was prepared in different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 and drug: PVP K-90 ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 85 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to spectrophotometric method.

Preparation of solid dispersion of Nifedipine

For the preparation of Nifedipine-PEG 4000 and Nifedipine-PVP K-90 solid dispersion by conventional method, PEG 4000 and PVP K-90 was weighed and melted at 58°C (±1°C) and a measured amount of Nifedipine was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 10mg of Nifedipine - PVP K-90 powder (containing 10mg of Nifedipine and 30mg of PVP K-90) and was used for further investigations (Chiou and Riegelman, 1971).

Evaluation of dispersion dispersion

Percentage drug content:

For the determination of Nifedipine content, dispersion equivalent to 10 mg of Nifedipine, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for Nifedipine at 340nm using a validated UV spectrophotometric method.

Formulation of oral film of Nifedipine

Casting process of fast disintegrating oral film

Various methods are available for casting of oral films. This is oral film hence on the laboratory scale solvent casting technique was adopted for formulation of films.

Solvent casting technique

Nifedipine containing fast dissolving films were fabricated by the solvent casting method (Mahesh *et al.,* 2010). The optimized amount of HPMC was dissolved in 5ml of water and stirrered continuously for 1 hour, optimized amount of plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept in sonicator for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm^2 12 films area and was dried at controlled room temperature (25°-30°C, 45 % RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use.

Selection Parameter for formulation of oral film

1. Size of Film

Size of tongue is about 2.5 x 2.5 cm, to provide sufficient space for dissolving in oral cavity by putting film on tongue for swishing or hydrating with saliva , size 2.5 x 2.5 cm were concluded as unit dose of Film.

2. Fabrication of film casting glass reservoir

Film casting glass reservoir is most important glassware which was fabricated keeping view the following aspect:

1. No. of films in one batch
2. Holding capacity of formulation solution for drying
3. scrapping-off films from film casting glass reservoir
4. Easy to positioned horizontally with gravity for uniform formation of film

A 15.0 x 5.0 cm sized film casting glass reservoir was fabricated having depth of 0.5cm. This sized Film casting glass reservoir will produce twelve 2.5 x 2.5 cm^2

3. Amount of solution for formulation

30.0 ml solution was calculated for further study, because this will produce 200 micrometer depth for solvent evaporation and sufficient numbers of films for further evaluations.

4. Temperature and time of drying

Preliminary study suggests that 40±1ºC for 12 hrs adequately dry the film.

5. Speed of mixing at magnet stirrer.

200±10 RMP speed for first 30 minutes were optimized for entire study and 5 minutes for all ingredients with same speed were finalized.

Selection and optimization of film forming agents

Two film forming agents and one co-film forming agent were selected for this research work. The concentration of film forming was important to form a proper thickness for appropriate packaging and handling of oral films.

Concentration of film forming agent is optimized on the basis of thickness and appearance of film.

Evaluation of prepared film

Thickness

The thickness of films was measured at three different places using a vernier caliper (Lakshmi *et al.,* 2005).

Weight uniformity

For each formulation, three randomly selected films were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance (Patel *et al.,* 2010).

Percentage moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight (Saini and Dhari (2011).

Drug Content Analysis

The films (n=3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 340nm (Kaur *et al.,* 2013).

Disintegrating time

The objective of present work is that films should be dissolved within few seconds. Three super disintegrating agent were selected for minimizing the disintegration time (Mahajan *et al.,* 2011).

***In vitro* dissolution study**

The *in vitro* dissolution test was performed using the USP dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5°C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Nifedipine was determined using UV-Visible spectrophotometer at 340nm. The results were presented as an average of three such concentrations (Nagar *et al.,* 2014).

7.4.8 Stability studies

Stability studies were carried out for optimized formulation F3 which was stored for a period of one, two and three months at 40±2^oC temperature and 75±5% relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of film was found to slightly decrease at higher temperature (Pathan *et al.,* 2016).

RESULTS AND DISCUSSION

The formulation and evaluation of fast dissolving oral films containing nifedipine demonstrated significant enhancements in drug solubility and release characteristics. Table 2 indicates a marked increase in solubility with varying ratios of nifedipine and the solubilizing agents PEG 400 and PVP

K-90, achieving up to 270.52% enhancement in solubility, particularly in the 1:3 ratio of drug to PVP K-90. This suggests effective solubilization properties of PVP K-90, crucial for improving bioavailability.

The drug content analysis (Table 3) showed a satisfactory amount of nifedipine (98.00% of the label claim) in the physical mixture, ensuring consistent dosing. The physical evaluation of the films (Table 4) revealed uniform thickness and weight across the formulations, with all samples exhibiting a translucent appearance, indicating proper formulation techniques.

Folding endurance, disintegration time, tensile strength, moisture content, and assay results (Table 5) further confirmed the mechanical integrity and suitability of the films for patient use. The optimized formulation F3 showed a high folding endurance of 220 and a rapid disintegration time of 54 minutes, reflecting its potential for quick disintegration in the oral cavity. The in-vitro release study (Table 6) of formulation F3 highlighted a cumulative drug release of 96.65% within 15 minutes, indicating rapid dissolution and availability for systemic absorption.

Stability studies (Table 7) over three months showed consistent assay values, suggesting that the optimized film retains its potency over time, confirming its stability under the conditions tested. Overall, these findings underscore the promising potential of nifedipine-loaded fast dissolving oral films for effective therapeutic use.

Table 1: Selection and optimization of film forming agents

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
API Equivalent to 20 mg	960	960	960	960	960	960
HPMC	400	600	800	400	600	800
Glycerin	-	-	-	-	-	-
PEG-400	100	100	100	100	100	100
SSG	100	150	200	-	-	-
CCS	-	-	-	100	150	200
Aspartame	25	25	25	25	25	25
Citric acid	50	50	50	50	50	50
DM water qs to (ml)	30	30	30	30	30	30

HPMC=Hydroxypropyl methylcellulose, PEG 400= Polyethylene glycol 400, SSG= Sodium starch glycolate, CCS =Croscarmellose sodium.

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 films present whole plate = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug = 20×12 = 240mg
- The amount of drug added in each plate was approximately equal to 240mg.
- The amount of drug added with solid dispersion (1:3) in each plate was approximately equal to 20+60 =80mg, Total film 12 = 80x12=960mg

Table 2: Percentage cumulative drug release of physical mixture

S. No.	% solubility Enhancement						
	Drug: PEG 400			Drug: PVP K-90			
Absorbance	1:1	1:2	1:3	1:1	1:2	1:3	Pure Drug
	0.133	0.148	0.225	0.243	0.200	0.257	0.095
% Solubility Enhancement	140.00	155.78	236.84	255.78	210.52	270.52	----

Table 3: Results of drug content

Formulation	Label claim	Amount found*	Label claim (%)
Physical mixture	10mg	9.80	98.00±0.15

*Average of three determination

Table 4: Results of Evaluation of prepared Film

Formulation code	General Appearance	Thickness (µm)	Weight (mg)
F1	Translucent	125±5	149±6
F2	Translucent	130±6	155±7
F3	Translucent	136±4	165±5
F4	Translucent	128±3	148±4
F5	Translucent	132±4	162±8
F6	Translucent	140±7	172±3

Table 5: Result of folding endurance, disintegration time, tensile strength moisture content and assay

Formulation code	Folding endurance	Disintegration time (min.)	Tensile strength (kg/cm^2)	Moisture Content (%)	Assay (%)
F1	155	98	0.75	1.45	98.85
F2	168	85	0.65	1.32	98.74
F3	220	54	0.82	0.95	99.85
F4	175	89	0.79	120	98.78
F5	198	86	0.65	1.95	97.65
F6	168	71	0.72	1.74	98.78

Table 6: Results of *In-vitro* release study of optimized formulation F3

S. No.	Time (Min.)	Cumulative % Drug release
1.	1	32.25±0.45
2.	2	49.87±0.32
3.	5	65.58±0.48
4.	10	88.98±0.45
5.	15	96.65±0.65

(n=3)

Table 7: Characterization of stability study of Optimized Film (F3)

Characteristic	Time (Month)			
	Initial	1 Month	2 Month	3 Month
% Assay*	98.56.12±0.12	98.35±0.23	98.10±0.45	98.05±0.32

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

CONCLUSION

The formulation of fast-dissolving oral films containing nifedipine demonstrated significant enhancement in the drug's solubility and release profile. The use of solubilizing agents such as PEG 400 and PVP K-90 effectively increased the solubility of nifedipine, with the PVP K-90 formulation achieving the highest enhancement. The prepared films exhibited favorable characteristics, including appropriate thickness, weight, folding endurance, and moisture content. Importantly, the optimized formulation (F3) achieved a cumulative drug release of 96.65% within 15 minutes, indicating a rapid dissolution rate suitable for quick therapeutic action. Stability studies confirmed the formulation's reliability over three months. Overall, these findings support the potential of nifedipine-loaded fast-dissolving oral films as a promising approach

for enhancing patient compliance and improving drug delivery efficacy.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

REFERENCES

- M. R. R. R. et al (2020) Nifedipine: A review of its pharmacokinetics and therapeutic uses. *Journal of Clinical Pharmacy and Therapeutics*, 45, 325–332.
- S. S. et al (2019) Fast dissolving films: A comprehensive review on formulation, evaluation, and applications. *Journal of Drug Delivery Science and Technology*, 52, 498–511.
- R. M. et al (2021) Nanotechnology and formulation strategies for improving the bioavailability of poorly soluble drugs. *International Journal of Nanomedicine*, 16, 2537–2555.
- B. S. et al (2018) Enhancing solubility and bioavailability of poorly soluble drugs: A review on current strategies. *Current Drug Delivery*, 15, 721–733.
- Lakshmi, P.K., Sreekanth, J. & Sridharan, A. (2005) Formulation development of fast releasing oral thin films of Cetriizine dihydrochloride with Eudagrit EPO nad optimization through Taguchi orthogonal Experimental design. *Asian Journal of Pharmaceutical Sciences*.
- Mahajan, A., Chhabra, N. & Aggarwal, G.A. (2011) Formulation and characterization of fast dissolving buccal films: A review. Scholars res. *Library der Pharmacia Lettre*, 3, 152–165l.
- Mahesh, A., Shastri, N. & Sadanandam, M. (2010) Development of taste masked fast disintegrating films of levocetirizine dihydrochloride for oral use. *Current Drug Delivery*, 7, 21–27.
- Mandeep, K., Rana, A.C. & Nimrata, S. (2013) Fast dissolving films: An innovative drug delivery system. *International Journal of Pharmaceutical Research and Allied Sciences*, 2, 14–24.
- Nagar, M., Nagar, M.K. & Chopra, V. (2014) Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole. *Pharmacia Lettre*, 4, 1221–1227.
- Patel, A.R., Dharmendra, S., Jignyasha, P. & Raval, A. (2010) Fast dissolving films (FDFS) as a newer venture in fast dissolving dosage forms. *Int. J. Drug Deliv. Res*, 2, 232–246.
- Pathan, A., Gupta, M.K., Jain, N.K., Dubey, A. & Agrawal, A. (2016) Formulation and evaluation of fast dissolving oral film of promethazine hydrochloride using different surfactant. *Journal of Innovations in Pharmaceuticals and Biological Sciences*, 3, 74–84.
- Saini, S., Nanda, A. & Dhari, J. (2011) Formulation, development & evaluation of oral fast dissolving AntiAllergic film of Levocetrizine dihydrochloride. *Journal of Pharmaceutical Sciences and Research*, 3, 1322–1325.