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FORMULATION AND EVALUATION OF NIFEDIPINE LIPID SEMISOLID MATRIX SYSTEM FILLED IN HARD GELATIN CAPSULES

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ABSTRACT

The objective of present study was to increase the aqueous solubility of poorly soluble nifedipine by inclusion complexation and further to achieve the sustained release. Sustained release was achieved using a relatively new concept of semisolid matrix formulations by liquid filling technology in hard gelatin capsule in which the carriers are melted at elevated temperatures, the drugs are dissolved in molten carriers and the hot solutions are then filled in capsules. Sustained release formulation of nifedipine helps in reducing the dosing frequency of nifedipine. Nifedipine and β- cyclodextrin inclusion complex was prepared by kneading method. The semisolid matrix of nifedepine was prepared using Glyceryl Palmitostearate (compritol 888ATO) and Glyceryl Behenate (precirol ATO5) in varying concentrations and filled with syringe in hard gelatin capsule. Formulations were evaluated for solubility, moisture uptake, percent yield, *in vitro* drug release studies. The optimized formulation showed precirol ATO5 zero order release kinetics followed by Korsenmeyers Peppas model. This technology can make a significantcontribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in - house formulation.

KEYWORDS: Nifedipine, Sustained release, Liquid filling technology, Compritol 888ATO, Precirol ATO5.

INTRODUCTION

Nifedipine is classified as BCS class II compound with poor aqueous solubility. It is in a group of drugs called calcium channel blockers. It works by relaxing the muscles of heart and blood vessels. Nifedipine is used to treat hypertension (high blood pressure) and angina (chest pain).[1]

The objective of present study was to increase the aqueous solubility of nifedipine and to further achieve the sustained release. Inclusion complex with β-cyclodextrin is among the several approaches that have been proposed to improve aqueous solubility of poorly water soluble drugs.[2] In present study, similar approach was used to increase the aqueous solubility. Sustained release dosage form was developed by using a relatively new concept of semisolid matrix formulations and liquid filling technology in hard gelatin capsule. Compritol 888 ATO and Precirol ATO 5 were used as release retarding agents in present work.

MATERIALS AND METHODS

Nifedipine was obtained as a gift sample from Appcure labs, Hyderabad. Compritol 888 ATO and Precirol ATO 5 were received as gift samples from Gattefosse, Mumbai. β-cyclodextrin and Tween 80 were received from Himedia Labs, Mumbai. Size 00 Hard gelatin capsules were provided by ACG Capsules, Mumbai.

Preparation of inclusion complex of Nifedipine

The β-cyclodextrin and nifedipine (in ratios of 1:0.5, 1:1 and 1:2 w/w) were weighed and added in 0.5 mL of solvent. The obtained paste obtained was cold-triturated in a mortar for 30 minutes and dried in the oven at 50°C to a constant mass. After drying, obtained mass was dry-triturated in the mortar, and complexation yields were determined.

Solubility study of Inclusion complex of Nifedipine

Excess amount of pure drug and the prepared complexes were added separately in 25 ml volumetric flask containing 5ml water. All samples were then kept in orbital shaker for 24 hrs. Solutions were filtered and checked for absorbance with λ_{max} of 237 nm.

Preparation of lipid semisolid matrix and filling in HGC

The capsules were kept in upright position in a capsule holder. The cap of the empty capsules was separated from the body. Accurately weighed amount of solid lipids were taken in a beaker & heated to 10°C above their respective melting points using a constant temperature

water bath. To this molten base, measured quantity of drug inclusion complex (1:1 w/w) along with Tween 80 was added with constant stirring for 40 minutes. The semisolid matrix was then filled in hard gelatin capsule using 1ml syringe. The capsule body was left undisturbed until a solid plug was obtained in 2 hours. After solidification of base in cap was fitted on capsule body and the corresponding weight of the filled hard gelatin capsules was noted. The reproducibility of results was confirmed on three different batches for all formulation.[8]

Table 1: Composition of sustained release formulations of Nifedipine.

Ingredients	Quantities (mg)									
	P_1	P_2	P_3	P_4	P_5	C_1	C_2	C_3	C_4	C_5
Nifedipine Complex with β-cyclodextrin	180	180	180	180	180	180	180	180	180	180
Precirol ATO 5	30	60	90	120	150	-	-	-	-	-
Compritol 888 ATO	-	-	-	-	-	30	60	90	120	150
Tween 80	15	15	15	15	15	15	15	15	15	15
Total	225	257	285	315	534	225	257	285	315	534

Weight variation study

Twenty capsules from each formulation were individually weighed in grams using an analytical balance. The average weight and standard deviation were calculated. Individual weight of each capsule was compared with average weight.

Drug content estimation

The cap was separated from the body of capsule and is dropped in a 25ml volumetric flask containing methanol. It was kept in a water bath at 65°C for 40mins. Then it was sonicated for 30 minutes and the solution was filtered using whattman filter paper. Dilutions were prepared from the filtrate in methanol. Further final dilution was prepared in phosphate buffer pH 7.4.

Moisture uptake studies

A moisture uptake study at 75% RH was conducted to have an insight into the stability of the formulation. The moisture uptake should not be more than 2% as the capsules are reported to alter their shape and dimensions and hence were not acceptable.

***In vitro* dissolution studies**

In vitro drug release of the samples was carried out using USP-type II dissolution apparatus (basket type). The volume taken was 900 ml of dissolution medium (2 hrs in 0.1N HCl

followed by phosphate buffer pH 7.4). The temperature of the medium was maintained at 37 ± 0.5°C. The apparatus was allowed to run at 100 rpm. Aliquots of 5 ml samples were withdrawn at various intervals. The samples were filtered through whattman filter. The fresh dissolution medium (0.1 N HCL for first 2 hrs then phosphate buffer pH 7.4) was replaced every time with the same quantity of the sample. Collected samples were analyzed at λ_{max} of drug (237nm). The percentage cumulative drug release (% CDR) was calculaed.

Drug Release data were analyzed as per zero order, first order, Higuchi's and Peppa's equation models to assess the drug release kinetics and mechanism from the matrix tablets prepared.

RESULT AND DISCUSSION

Solubility study of Inclusion complex of Nifedipine

Aqueous solubility of pure drug was found to be 2.1 µg/ml. Among different complexes, 1:1 w/w ratio observed to provide highest aqueous solubility of 8.6±0.01 µg/ml. Solubility of Nifedipine was improved by 4 times by using inclusion complex. This Nifedipine Complex with β-cyclodextrin (1:1 w/w) was further used in sustained release formulation development.

Table 2: Solubility study of inclusion complex of Nifedipine and pure drug.

S. No.	Sample	Solubility (µg/ml)
1	Nifedipine Complex with β-cyclodextrin (1:0.5 w/w)	5.5±0.02
2	Nifedipine Complex with β-cyclodextrin (1:1 w/w)	8.6±0.01
3	Nifedipine Complex with β-cyclodextrin (1:2 w/w)	6.4±0.07
4	Pure drug	2.1±0.01

Drug content, weight variation and moisture uptake results for lipid semisolid matrix filled in HGC

Weight variation and moisture uptake values for formulations containing Compritol 888ATO and Precirol ATO 5 are shown in Table 3. To obtain a stable formulation, moisture uptake should not be more than 2% of the weight of formulation. All formulations were found to be stable at 75% RH as the % moisture uptake was less than 2%.

Table 3: Drug content, weight variation and moisture uptake results for lipid semisolid matrix filled in HGC.

Formulations	%Weight variation	% Moisture Uptake	%Drug content
	(Avg. ± SD)	(Avg. ± SD)	(Avg. ± SD)
P_1	0.61±0.06	0.81±0.02	95.2±0.12

P_2	0.68±0.01	0.78±0.01	96.5±0.52
P_3	0.75±0.02	0.75±0.05	94.6±0.32
P_4	0.67±0.03	0.57±0.04	98.7±0.15
P_5	0.65±0.03	0.35±0.08	90.6±0.52
C_1	0.59±0.02	0.59±0.01	92.0±0.65
C_2	0.64±0.02	0.64±0.08	90.5±0.85
C_3	0.63±0.02	0.23±0.05	94.1±0.98
C_4	0.96±0.21	0.66±0.09	67.2±3.15
C_5	0.99±0.34	0.59±0.07	70.1±5.66

Drug content was above 90% for Precirol ATO 5 based formulations. Compritol 888 ATO formulations at higher level showed slightly lower drug content and high variability. Similar observations were noted for weight variation study.

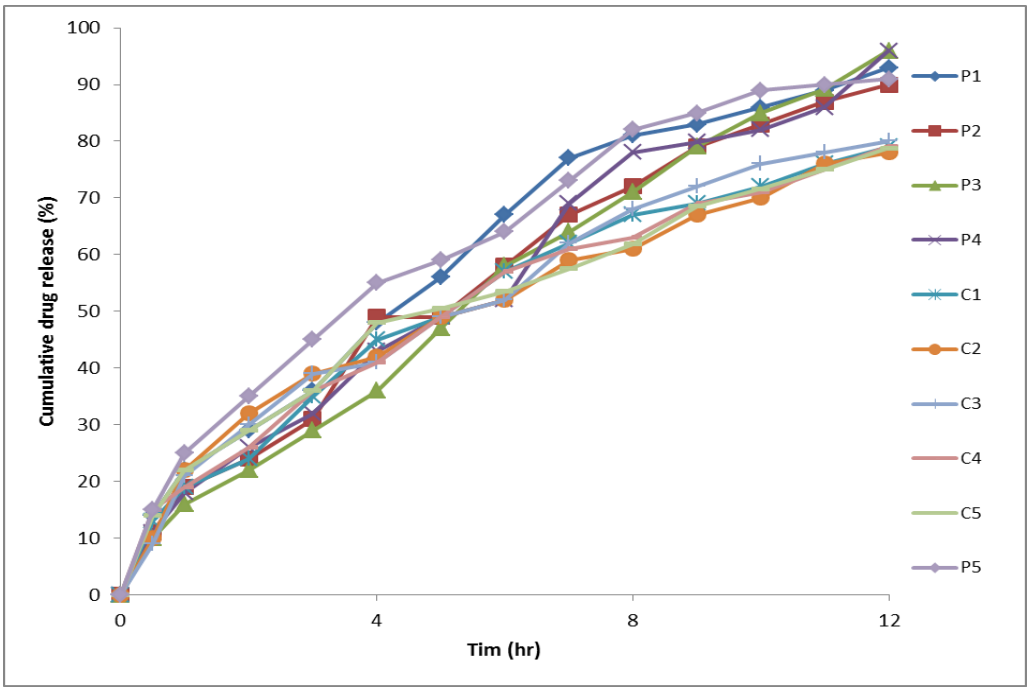
***In vitro* dissolution studies**

In vitro drug releases of the formulations are shown in Fig. 1. Compritol 888 ATO was retarding the release upto12 h. However, the highest cumulative drug release of 77% was noted for C3 formulation (containing 60mg/unit Compritol 888 ATO). Rest all of Compritol 888 ATO batches had a non-acceptable cumulative release lower than 80% in 12 h.

P1 formulation showed complete drug release (77%) in 7 hrs. With increasing Precirol ATO 5 content, rate and extent of drug release was found to decrease. Amongst the tested formulation, P4 was found to have acceptable sustained drug release pattern with 78% and 96% cumulative release achieved in 8, 12 h respectively.

At present, the most common pharmaceutical application of Compritol 888 ATO is in lipid-based colloidal drug delivery system such as solid lipid microparticles, solid lipid nanoparticles and nanostructured lipid carriers.[2] Different lipid classes have been extensively used as pharmaceutical excipients due to their relative low cost, negligible toxicity and biodegradable properties. Glycerides represent a family of lipid molecules that serve as multipurpose excipients in the pharmaceutics field. Among different glycerides, Compritol 888 ATO has attracted particular interest as it has been successfully utilized in diverse pharmaceutical dosage forms. Compritol 888 ATO is used as a lubricating agent in the manufacturing of oral tablets and capsules. It has been extensively employed as a matrix forming agent in the preparation of different sustained-release tablets. It has also been investigated as a hot-melt coating agent for powders or granules for controlled release purposes. As a coating agent, Compritol 888 ATO provides several noteworthy advantages over polymers as it is generally required in less amounts to achieve the desired effect and it

do not crack during tablets compression. Different researches have highlighted the applicability of Compritol 888 ATO in the preparation of aqueous colloidal dispersions such as solid lipid microparticles (SLMs), solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) for entrapment of lipophilic drugs. Compared to homogenous glycerides, Compritol 888 ATO is superior in terms of drug entrapment ability due to its complex nature and lessperfect orientation thus leaving more space for the drug to be loaded. Also, the long chain length of behenic acid in Compritol 888 ATO enhances the intermolecular entrapment of the drug by interchain intercalation. Liquid filling in HGC technology can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in - house formulation. In this technique carriers are melted at elevated temperatures, the drugs are dissolved in molten carriers and the hot solutions are then filled in capsules. Due to the surface activity, drugs dissolve or disperse rapidly once the plugs come in contact with the GI fluid.



Drug release mechanism

A decrease in release kinetics of the drug was observed by increasing the lipid concentration. The *in-vitro* drug release profile was applied in different mathematical models and was interpreted in the form of graphical presentation and evaluated by correlation coefficient (R2) represented in Table 4. The highest degree of correlation coefficient determines the suitable mathematical model that follows drug release kinetics.[9]

From the table, it was concluded that the optimized formulations P4 followed zero order release.

Table 4: Results of Different models in terms of R^2, slope and intercept for P4.

Model name	P4		
	R^2	Slope	Intercept
Zero order model	0.992	8.330	2.557
First order model	0.8132	-0.4206	2.1673
Higuchi model	0.9940	45.823	0.000
Korsmeyer -Peppas model	-4.156	3.0862	0.000
Hixson-Crowell model	0.9578	0.8122	0.0213

CONCLUSION

The resulting outcome indicates that Beta cyclodextrin inclusion complex enhance the aqueous solubility with a simultaneous reduction in drug dosage providing a potential capsule formulation of nefidipine. Semisolid matrix of nefidipine shows sustained drug release upto 12 h. Release kinetics studies stated that optimized formulation P4 exhibited zero order release kinetics and followed Korsemeyers Peppas model. Promising results shown by the nifedipine semisolid lipid dispersion, with its advantage of once daily administration suggest that it is likely to become one of the preferred nifedipine formulations for the treatment of hypertension and the various forms of angina.

REFERENCES

1. Lalitha Y, Lakshmi P K. Enhancement of dissolution of Nifedipine by surface solid dispersion technique. International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3(3): 41-46.
2. Nalluri B, Chowdary K, Murthi K Satyanarayana, V, Hayman A, Becket G. Inclusion complexation and dissolution properties of nimesulide and meloxicam–hydroxypropyl-b-cyclodextrin binary systems. J. Incl. Phen. Macrocyclic Chem, 2005; 53: 103-110.
3. Vijay K Tyagi, Singh D Pathak. Semisolid matrix – filled hard gelatine capsules for rapid dissolution of amlodipine besilate: Development and assessment. Journal of Advanced Pharmaceutical Technology & Research, 2013; 4(1): 42–49.
4. Vijay N, Anusha Reddy R, Liquid filling in hard gelatine capsules: A Review, Journal of Pharmacy, 2013; 1(1): 10-18.

5. Colea E T, Cade D, Challenges and Opportunities in the Encapsulation of Liquid and semisolid Formulations into Capsules for oral administration, Advanced Drug Delivery Reviews, 2008; 60: 747-756.
6. Girija P. P., Novel Approach – Liquid Filled Hard Gelatin Capsules, Pharma Review, 2003; 18: 135-141.
7. Akhelesh T, Formulation and evaluation of nifedipine sustained release pellets, International Research Journal of Pharmacy, 2011; 2(8): 177-180.
8. Rajesh Pavan A, Hindustan A A, Naresh Babu G, Chakrapani B, Sanjay K Mishra. Liquid Filled Hard Gelatine capsules, A Novel Revolution in Delivering Liquid Formulations', International Journal of research in Pharmacy and Life Sciences, 2014; 2(1): 176-181.
9. Kambham Venkateswarlu. Formulation and Evaluation of Sustained Release Matrix Tablets of Repaglinide. Bangladesh Pharmaceutical Journal, 2016; 19: 92-99.
10. Mona H A, Shimaa M. Compritol 888 ATO: a multifunctional lipid excipient in drug delivery systems and nanopharmaceuticals. Expert Opin Drug Deliv, 2014; 11(12): 1865-83.
11. Dredan J, Antal I and Racz I. Evaluation of mathematical models describing drug release from lipophilic matrices. Int J Pharm, 1996; 145(1-2): 61–64.
12. Parida P, Mishra S C, Subha P T. Simple spectrophotometric method validation of nifedipine solid dosage form. Indo American Journal of Pharmaceutical Reasearch, 2014; 4(5): 2307-12.
13. Rahul T, Gupta D G. *In-vitro* study of amlodipine and nifedipine drugs of pulsatile drug delivery system. International Journal of Pharmaceutical Science and Research, 2017; 1820-25.
14. Deepthi Y & Gopalakrishna Murthy. Design and Development and Evaluation of Candesartan Cilexetil Liquid Filling Formulations. International Journal of Pharm Investigation, 2015; 5(2): 81–86.
15. Roopa Rani Balivada. Solubilized Formulation And Evaluation Of Liquid Filled Hard Gelatin Capsules Of Estrogen Receptor Modulator Drug. International Journal of Research in Pharmacy and Chemistry, 2011; 1(4): 89-95.
16. Saly Galal. Formulation of Fast Release Glibenclamide Liquid and Semi Solid Matrix Filled Capsules. Acta pharma, 2003; 53: 57-64.