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Design and Development of Solid Self Emulsifying Osmotic Delivery System of Nifedipine

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Abstract

Objectives: In order to enhance solubility and to obtain controlled release characteristics, preparation of nifedipine has been made into a osmotic pump tablet which includes Gelucire 44/14, Lutrol F127, Transcutol P, silicon dioxide, lactose, mannitol, citric acid, and sodium bicarbonate.

Material and methods: The developed dosage form was evaluated for particle size, solid state properties and release profile. Effect of orifice size and amount of plasticizers on drug release was also studied.

Results: The results revealed that Self-emulsifying osmotic pump tablet (SEOPT) has not only provided improvement in solubility of nifedipine by self-emulsifying effect (SEDDS) but also controlled release due to elementary osmotic pump system. The particle size analysis revealed no difference in the droplet size of liquid SEDDS & reconstituted SEDDS.

Conclusion: Release studies revealed that nifedipine followed zero order release profile for 12 h independent of agitational intensity with cumulative release of 83.85%. The *in vitro* release profiles of the optimized system & commercialized conventional tablet (Nicardia ® Retard 20) in different amount of sodium lauryl sulphate (SLS) were also compared.

Key words

Gelucire, Nifedipine, Osmotic tablet, self emulsifying drug delivery system, zero order release

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Introduction

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). In the form of NDDS, an existing drug molecule can get a 'new life,' thereby, increasing its market value, competitiveness, and patent life [1]. The fact that a majority of the newly discovered chemical entities and many existing drug molecules are poorly water soluble, which presents a serious challenge to the formulation development [2]. Several novel drug delivery systems with many advantages have been developed in the recent years. Among these systems, the oral controlled drug delivery has received greater attention since it is the most popular route of drug administration [3,4]. Since pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, there has been increasing interest in the development of osmotic systems in the past two decades [5,6]. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. Osmotic pumps are well known for delivering drug at a zero order rate. The elementary osmotic pump (EOP) consists of an osmotic core with the drug, surrounded by a semipermeable membrane with a delivery orifice. However, poorly soluble drugs are unable to deliver through EOP as it is only suitable for water soluble drugs. To overcome this limitation, a push pull osmotic system was developed and commercialized {Glucotrol XL (Glipizide), Procardia XL (Nifedipine)} [7- 9]. However, this technology is complex comprising of bilayer compression and drug release in suspension form, which has more viscosity and to withstand the effective osmotic pressure within the tablets, the semi permeable membrane must be thicker than that of EOP. One of the formulation factors affecting drug release from oral osmotic pump is the solubility of drug within the core. Many formulation attempts have been made to enhance the solubility of poorly water-soluble drugs eg. Co-

compression of drug with excipients, use of encapsulated excipients, use of solid dispersion, use of swellable polymers and use of cyclodextrin derivatives [10]. In recent years, self-emulsifying and self-microemulsifying drug delivery systems (SEDDS and SMEDDS) [11-17] have shown a reasonable success in improving oral bioavailability of poorly water soluble and lipophilic drugs [13; 14]. SMEDDS are normally prepared either as liquids or encapsulated in soft gelatin capsules, which have some shortcomings especially in the manufacturing process, leading to high production costs [18]. Moreover, these dosage forms may be inconvenient to use and incompatibility problems with the shells of the soft gelatin are usual [19]. Incorporation of a liquid self-emulsifying formulation into a solid dosage form may combine the advantages of SEDDS with those of a solid dosage form and overcome the disadvantages of liquid formulations described above [20].

Nifedipine, a well known vasodilator is practically insoluble in water [21] and exhibits low bioavailability after oral administration. A formulation which could increase bioavailability of nifedipine, through improvement of solubility, and at the same time also release nifedipine for an extended period of time, thereby improving patient compliance will be highly appreciated.

In present work we intend to develop a formulation of Nifedipine in which solid self emulsifying system will solubilize drug and also avoid first pass effect by lymphatic absorption. Moreover combination of this system with osmotic system strategy may provide controlled release of drug and thus provide a new therapeutic dimension to existing drug.

Materials And Methods

Materials:

Nifedipine was generous gift from Torrent Pharmaceutical Ltd, India. Gelucire 44/14 and Transcutol P were supplied by Gattefosse India Pvt. Ltd, Mumbai, India. Lutrol F127, Poly vinyl pyrrolidone (Kollidon® K30) was purchased From BASF, Germany and Colloidal silicon dioxide (Aerosil 200, Degussa, Frankfurt, Germany); lactose was purchased from Meggle Pharma, Germany. Citric acid was procured from Qualigens Fine Chemicals, Mumbai. Sodium bicarbonate was purchased from S.D.Fine chemicals Ltd, Mumbai. Mannitol & Cellulose Acetate CA 398.10 NF was provided by Signet chemical corporation Pvt. Ltd, India.

Methods:

Preparation of liquid SMEDDS:

Gelucire 44/14 and Lutrol F127 were melted above 60°C, and nifedipine was added to the melt under continuous stirring. To aid solubilization of nifedipine, Transcutol P was added to the drug-melt mixture to form a clear solution in form of SMEDDS (Table I). The mixture was self-emulsifying base having a melting point of 44.54°C (obtained using DSC).

Table I. Composition of liquid SEDDS

Ingredients	Amount (mg/tablet)
Nifedipine	20
Gelucire 44/14	30
Lutrol F127	45
Transcutol P	35
Total	**130**

Formulation of self emulsifying osmotic pump tablet:

SEOPT was prepared according to Table II. Silicon dioxide, lactose, mannitol, citric acid, sodium hydrogen carbonate, and polyvinyl pyrrolidone were individually weighed and sifted. All these excipients were then granulated using above mentioned molten self emulsifying base. The obtained granules were passed through # 24 mesh sieve to obtain uniform particle size. Finally the granules were lubricated with 1% (w/w) magnesium stearate and compressed using 12 mm standard concave punch on a single punch tablet compression machine (Cadmach) to obtain a 700 mg tablet with hardness of 2.0–2.5 kg/cm^2. Coating was done with Cellulose Acetate CA 398.10 NF in acetone: methanol (90:10) mixture, with PEG 400 (50% w/w with respect to polymer) as plasticizer. An orifice was created on one face of the tablet through the coating membranes using a sharp needle.

Table II. Formulation composition of Self-emulsifying osmotic pump tablet

Ingredients (SEOPT)	Amount (mg/tablet)
Liquid SEDDS	130
Colloidal silicon dioxide	25
Lactose	209
Mannitol	209
Poly vinyl pyrrolidone	70
Citric acid	20
Sodium bicarbonate	30
Magnesium stearate	7
Membrane Coating	
Cellulose Acetate	14
Polyethylene Glycol 400	14
Total	**728**

Reconstitution properties of solid SMEDDS:

SEOPT was stripped of the semipermeable membrane and the core tablet was placed in volumetric flask containing 100 ml distilled water. After disintegration and dispersion under the effervescent effect, the solution obtained was filtered through a 0.45 µm membrane to remove the insoluble materials. The filtered solution was used for particle size analysis. The z-average diameter and polydispersity index of the solid and liquid SEDDS was recorded using Zeta sizer Nano ZS90. All studies were repeated three times and the average values were used.

Physical Characterization of Nifedipine in SEOPT:

Physical characterization of prepared Solid SEDDS is important parameter. Pure Nifedipine, placebo mixture, physical mixture and solid self emulsifying mixture with nifedipine was used for DSC, and X-ray diffraction experiments. To further substantiate the results, only self emulsifying system containing nifedipine adsorbed on colloidal silicon dioxide was also used.

Differential Scanning Calorimetery (DSC):

DSC was performed using Perkin Elmer 1020 series DSC-7 thermal analysis system. Samples (2-3 mg) were heated in hermetically sealed aluminum pans under nitrogen flow (60 Kg/cm^2) at a scanning rate of 10°C/min from 25ºC to 300 ºC. Empty aluminum pan was used as a reference. The DSC thermograms were obtained for nifedipine, placebo mixture, physical mixture and solid self emulsifying mixture with nifedipine.

X-Ray Powder Diffraction (XRPD):

XRPD patterns of samples were recorded at room temperature on Bruker D8 advance diffractometer (Bruker, Germany) with Cu Kα radiation (1.54 Å), at 40 kV, 40 mA passing through nickel filter. Analysis was performed in a continuous mode with a step size of 0.02° and step time of 1 sec over an angular range of 2-40° 2θ. Obtained diffractograms were analyzed with DIFFRACplus EVA (version 9.0) diffraction software.

In-Vitro Drug Release:

In-Vitro drug release of the formulations was carried out using USP type I dissolution apparatus (100 rpm; 37 ºC ± 0.5 ºC) using 0.5% w/v sodium lauryl sulphate (SLS) as dissolution medium. At predetermined time intervals, 5 ml samples were withdrawn and the drug concentration was determined by UV spectrophotometer at 238 nm. The volume removed was replaced each time with fresh dissolution medium. All experiments were carried out in triplicate and the results presented were the mean values of the three experiments. Effect of different factors like concentration of plasticizer, varying concentration of SLS, weight gain, agitation intensity and pore size on dissolution profile was also evaluated.

Scanning electron microscopy:

Cellulose acetate (CA) membranes containing PEG 400 obtained before and after complete dissolution of core contents were dried at 45ºC for 3 h and then examined for their porous morphology by Scanning Electron Microscope XL 30 ESEM with EDAX (Philips, Netherlands). SEM analysis was carried out to find out microporous nature of coating membrane after dissolution.

Results and Discussion

Reconstitution properties of solid SMEDDS:

The mean droplet size and polydispersity index of the reconstituted microemulsions are presented in Table III. The average droplet sizes of both microemulsions were less than 65 nm. The droplet size of the microemulsions from the solid SMEDDS was slightly increased, compared to the liquid SMEDDS. From these results, adsorbing the liquid SMEDDS on colloidal silicon dioxide did not seem to have a remarkable effect on droplet size. The solid SMEDDS showed to preserve the self-emulsification performance of the liquid SMEDDS.

Table III. Droplet size with polydispersity index (Mean ± SD, n = 3)

Formulation	Z-average diameter (nm)	Polydispersity index (PDI)
Liquid SEDDS	45.23±3.49	0.189±0.026
Solid SEDDS	65.12±2.39	0.170±0.0164

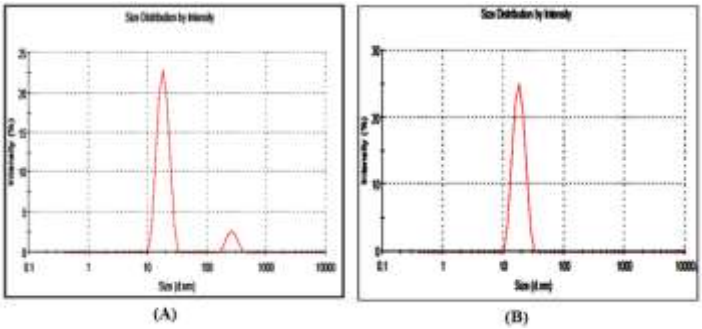

Fig.1. Emulsion droplet size distribution: (A) liquid SEDDS; (B) solid SEDDS

Physical Characterization of nifedipine in SEOPT:

Differential Scanning Calorimetery (DSC):

The DSC thermograms of nifedipine, placebo mixture, physical mixture and solid self emulsifying mixture with nifedipine are shown in fig.2. Nifedipine exhibited a sharp endothermic peak at 174.36°C, which corresponded to its melting point. There were some crystalline structures in the placebo tablet core, but this would not interfere with the results because there were no peaks around 174.36°C [22]. The DSC curve of the physical mixture was the superposition of the fig.2 (a) and (b); only the intensity of the nifedipine peak was reduced because the drug content was low in the physical mixture. No obvious peaks for nifedipine were found in the solid SMEDDS (curve d). In one such study on solubility enhancement of Nifedipine using Vitamin E TPGS or Solutol HS-15, similar such behavior was observed in DSC and it was concluded that the lack of a drug endotherm may suggest its amorphous nature in solid dispersions with this polymer [21, 23].

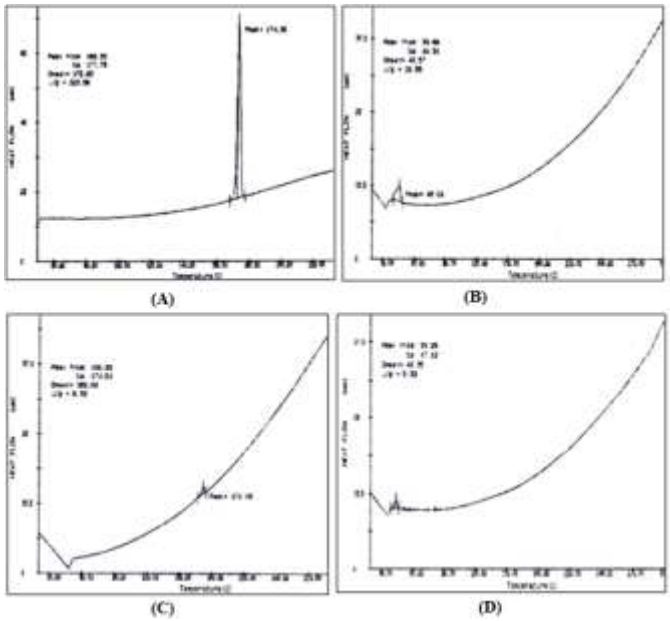

Fig.2. DSC curves of (A) Nifedipine, (B) Placebo mixture, (C) Physical mixture, (D) Self emulsifying mixture containing nifedipine.

X-Ray Powder Diffraction (XRPD)

From X-ray powder diffractograms shown in Fig.3, the internal physical state of nifedipine in the solid SMEDDS was further verified. The X-ray diffractograms of pure nifedipine from 5 to 40° 2θ showed numerous distinctive peaks that indicated a high crystallinity. It can be seen from fig.3, that the characteristic peak at 2θ angle of 8.06, 11.79, 24.45, 27.14º existed in the profile of nifedipine; fig.3 (a) and physical mixture; figure (d), but disappeared in the profile of placebo & solid self emulsifying system. The XRD patterns of self emulsifying mixture containing nifedipine exhibited the absence of characteristic diffraction peaks of nifedipine, indicating that the crystalline characteristic of nifedipine has disappeared in this self emulsifying mixture [24]. Davidson and Sittig [25] have reported in a study on water soluble resins, the lack of peaks characteristic of nifedipine in the diffractograms as an indication of conversion to a metastable form or existence in ultra-crystalline form. The subsequent faster dissolution rates from solid dispersions was attributed to the formation of this high energy metastable state of the drug formed due to the inhibition effect of PEG on drug crystallization. The probability of occurrence of similar such phenomenon cannot be ruled out here.

In-vitro release studies:

During dissolution, water ingress in tablet core through semipermeable coating initiate reaction between citric acid and sodium hydrogen carbonate to generate carbon dioxide (CO_2). This generated CO_2 facilitate formation of microemulsions. Controlled release was achieved through use of mannitol & lactose as an osmotic agent. For most period of dissolution, zero release characteristic was obtained with the average cumulative release of 83.85% at 12 hr (Fig.4.).

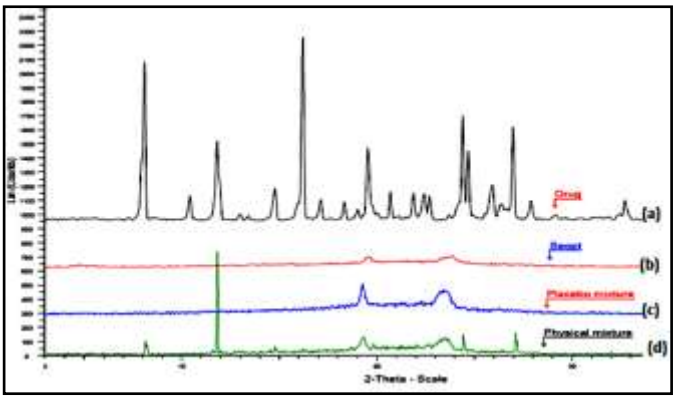

Fig.3. X-ray diffractograms of (a) Nifedipine, (b) Self emulsifying system containing nifedipine. (c) *Placebo mixture, (d) Physical mixture*

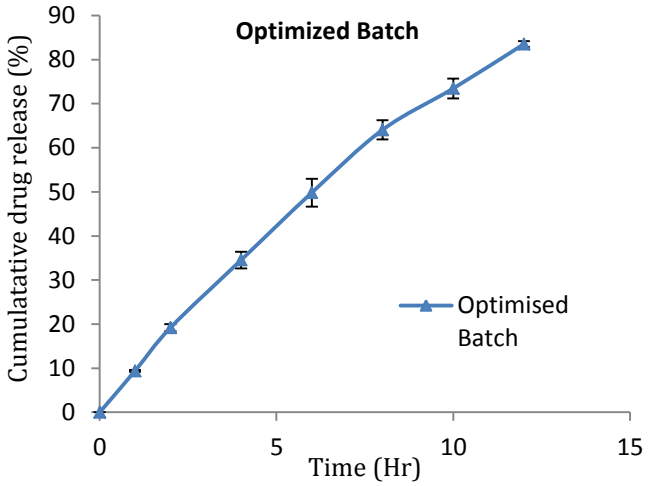

Fig.4. *The in vitro release profile of nifedipine from SEOPT*

Effect of PEG-400 level on drug release profile:

Polyethylene glycols act as inert carriers inhibiting crystal growth and phase transformation along with improving dissolution rate of drug due to their rapidly water soluble nature (26). To study the influence of amount of PEG-400 on the drug release profiles, coating levels were kept at 4% & CA membranes were plasticized with 35%, 50%, 65%, of PEG-400 and dissolution studies were carried out. From fig.5, it is evident that increase in PEG 400 level leads to increase in drug release. As PEG is a hydrophilic plasticizer, it would be leached easily and leave behind a wholly porous structure, which increases membrane permeability and drug release rate [27] with 65% of PEG 400 drug release was somewhat rapid and uncontrolled probably due to this phenomenon.

Effect of membrane thickness:

In order to study the effect of thickness of the coating membrane, PEG 400 level was kept at 50% and coating on the core tablets of nifedipine was continued for sufficient duration so as to get tablets with different weight gains (4, 6, and 8%).

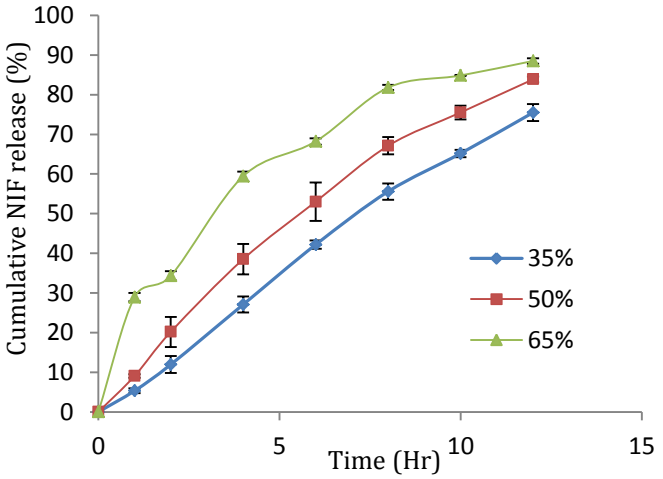

Fig.5. The effect of PEG 400 on release profile of Nifedipine.

The fig. 6 shows that the thickness of the membrane has a profound effect on the drug release from osmotic systems. We can see from equation below that release rate from osmotic system is inversely proportional to membrane thickness: dM/dt = A, hKπC where dM/dt is drug delivery rate, A and h are the membrane area and thickness respectively, C is the concentration of compound in the dispersed fluid (soluble fraction of the drug), π is the osmotic pressure of the system, and K is the equation constant. It is clear from the equation that release rate from osmotic devices is inversely proportional to membrane thickness. As the thickness increased, the resistance of the membrane to water diffusion increased and the rate of imbibing water decreased. In turn, the liquefaction rate of the tablet core decreased, resulting in the drug release rate decreasing. In current study drug release was found to decrease with an increase in the weight gain of the membrane [6]. Release profile of nifedipine as a function of weight gain of the membrane is shown in fig.6.

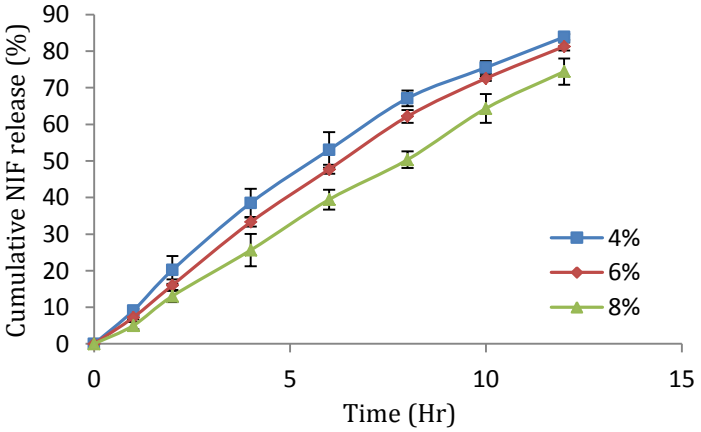

Fig.6. The effect of membrane thickness on release profile of Nifedipine.

Effect of agitational intensity

Release studies of the optimized formulation of SEOPT were carried out in USP dissolution apparatus type I at varying rotational speed (50, 75, and 100 rpm). It is clearly evident from fig.7, that the release of nifedipine is independent of the agitational intensity which was supported with f_2 values of 78.63 (calculated for 100 rpm and 50 rpm) and 91.6 (calculated for 100 rpm and 75 rpm).

Influence of orifice size on drug release profile:

Aperture diameter is one of the critical parameters that greatly influences release rate, lag time and release kinetics of the osmotic drug delivery devices. Thus, the size of delivery orifice must be optimized in order to control the drug release from osmotic systems [28]. In order to evaluate effect of orifice size on drug release, different sizes of orifice (0.2, 0.5, 0.75, 1.0, 2 mm) were created on one side of tablet surface and dissolution studies were carried out. Fig.8 shows the influence of orifice size on release profile. No significant difference existed in the release profiles for orifice diameters ranging from 0.5 mm to 1.0 mm. However, the release was somewhat rapid with an orifice diameter of 2 mm. This may be due to the

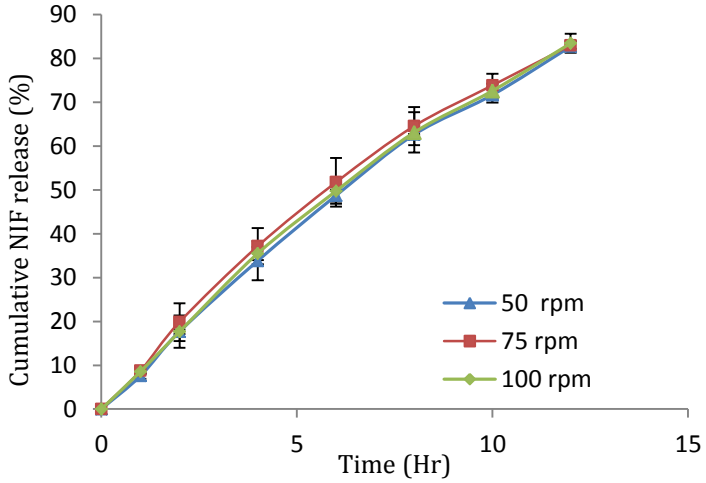

Fig.7. The effect of agitation on release profile Nifedipine.

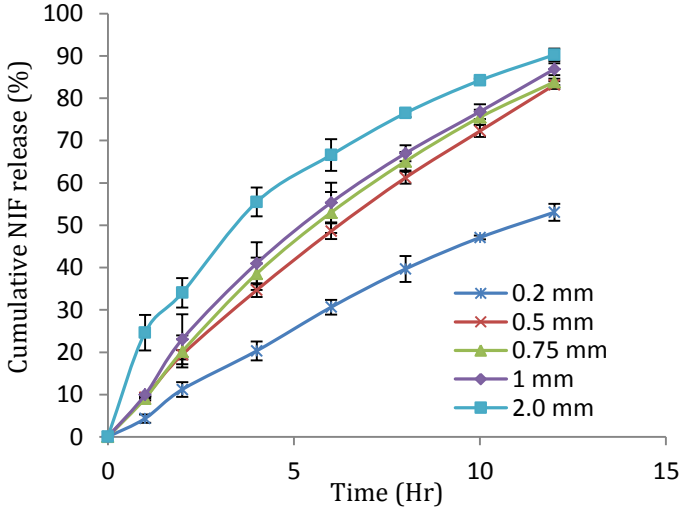

Fig.8. The effect of the size of delivery orifice on the release profile of Nifedipine.

result of solute diffusion from the bigger orifice. On the other hand, a low release rate and anomalous release were exhibited at an orifice diameter of 0.2 mm probably

due to occlusion of such a small orifice with insoluble component of tablet core. This indicates that the size of delivery orifice must be optimized to control the drug release from osmotic devices. If the size of delivery orifice is too small, zero order release will be affected because of development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of delivery system, thereby resulting in unpredictable drug delivery as observed when orifice diameter was 0.2 mm [29]

Influence of different amount of Sodium lauryl sulphate on dissolution profile of marketed formulation & SEOPT:

United State Pharmacopoeia (USP) prescribes 0.5% (w/v) of Sodium lauryl sulphate (SLS) as the dissolution medium for nifedipine tablets. Effect of different amount of SLS (0.1, 0.3, and 0.5%) on release profile of marketed formulation (Nicardia ® Retard 20, J.B.Chemicals & Pharmaceutical Ltd) of nifedipine and SEOPT were checked. This test was carried out to check whether release of drug from marketed nifedipine tablet & SEOPT was dependent of the amount of SLS used in dissolution medium. In this medium, the release of nifedipine from the SEOPT was faster than from the market formulation. When the concentration of SLS in dissolution medium was reduced to 0.1% (w/v), the difference in the release of nifedipine from marketed formulation was more as shown in fig.9. Dissolution from the conventional tablet was improved with increasing amount of SLS in medium .On the other hand, dissolution of nifedipine from the SEOPT was not influenced by concentrations of SLS added which showed similar drug release profile in all the medium. Thus it indicates that release of nifedipine from SEOPT is independent of amount of SLS used, which was not observed in case of, marketed formulation [30].

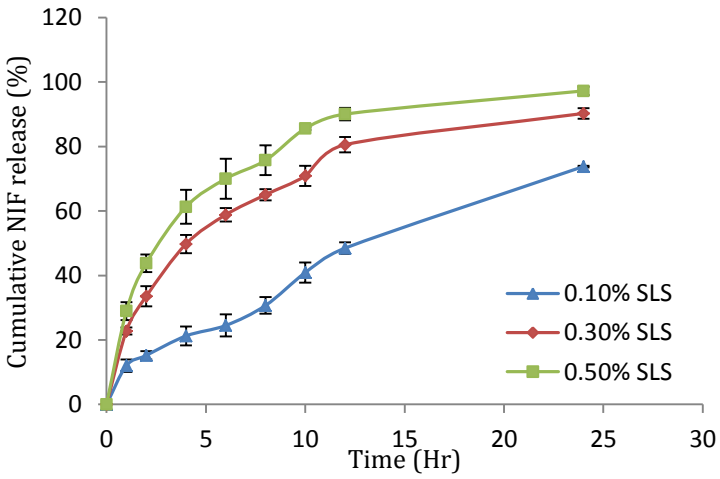

Fig.9. (A)

Scanning Electron Microscopy

Cellulose acetate (CA) membranes containing PEG 400 (50%) obtained before and after complete dissolution were taken for SEM analysis. SEM microphotograph shown in fig.10.

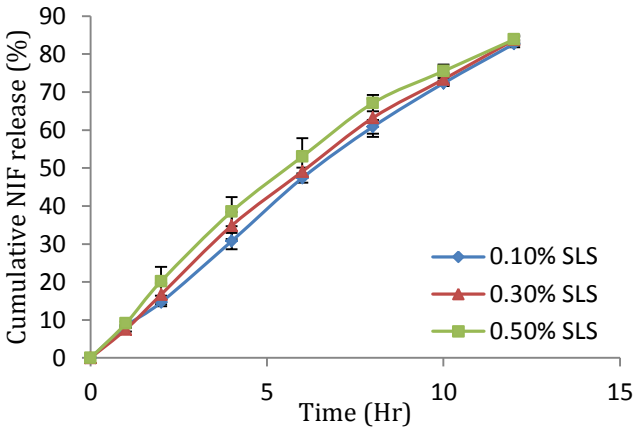

Fig.9. (B)

Fig.9. (A) Dissolution profile of market formulation & (B) SEOPT

Coating membrane contains hydrophilic plasticizer (PEG 400) which leaches out, when it comes in contact with dissolution medium which results in formation of microporous region (fig.10B)

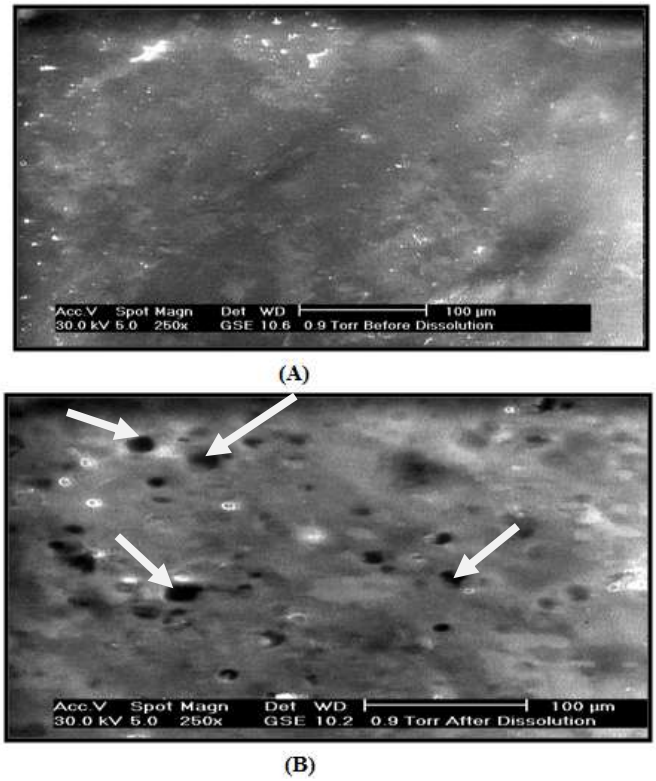

Fig.10. SEM microphotographs of coating membranes containing 50% PEG 400: (A) obtained before dissolution, non-porous region of membrane (250×); (B) obtained after dissolution porous region of membrane (250×). Membrane obtained before dissolution showed non-porous region.

Conclusion

The conventional approaches of drug formulation can

barely meet the challenges presented by the growing number of insoluble/impermeable drugs. In current work SEDDS of nifedipine were successfully formulated, and characterized for physicochemical parameters and release profile. The developed solid SEOPT of nifedipine prepared by adsorbing SEDDS on water-insoluble Aerosil 200 as a solid carrier exhibited zero order dissolution profile for 12 hrs without altering the self-emulsification performance of the liquid SMEDDS. Both DSC measurements and X- ray diffraction analysis confirmed that adsorption of liquid SEDDS containing nifedipine in the amorphous or molecular dispersion state was retained in the same amorphous state upon its adsorption on inert matrix. In Dissolution studies SEOPT exhibited least variation on dissolution profile upon varying the concentration of wetting agent as compared to conventional formulations. In conclusion this approach might be effectively used to develop solid dosage form for similar such oral poorly water-soluble drugs, though *in-vivo* studies for evaluating the escape from lymphatic escape will give true picture.

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Conflict of Interest

The authors declare no conflict of interest

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References

1. Verma, R., Garg, S. Current status of drug delivery technologies and future directions. Pharmaceutical Technology, 2001 ,25. 1–14.
2. Lipinski,C.A., Lombardo, F., Dominy, B.W., Feeney,P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Delivery. 2001, 46. 3–26.
3. Banakar, U.V. Drug delivery systems of the 90's: Innovations in controlled release , Am. Pharm, 1987,9–48.
4. Speers, M., Bonnano, C. In Encyclopedia of Controlled Drug Delivery. Mathiowitz E., Ed.; Wiley: New York. 1999, 341.
5. Santus, G., Baker, WR. Osmotic drug delivery: a review of patent literature. J. Control.Rel. 1995,35. 1-21.
6. Liu, L., Khang G., Rhee, J.M., Lee, H.B. Monolithic osmotic tablet system for nifedipine delivery. J. Contr. 2000,67. 309-322.
7. Swanson, Dr., Barclay, Bl., Wong, Psl., Theeuwes, F. Nifedipine gastrointestinal therapeutic system. Am. J. Med. - 1987. 83 . 3-9.
8. Wong, PSL., Barclay, BL, Deters, JC, Theeuwes F. Osmotic device for administering certain drugs. US Patent 4765, 989. 1988.
9. Grundy, J.S., Foster,R,T. The nifedipine gastrointestinal therapeutic system (GITS). Evaluation of pharmaceutical, pharmacokinetic and pharmacological properties. Clin Pharmacokinet. 1996, 30, 28–51.
10. Verma, R.K., Krishna, D.M., Garg, S. Pharmaceutical Development of Solid Dispersion Based Osmotic Drug Delivery System for Nifedipine. J. Control. Rel., 2002. 79. 7.
11. Lawrence, M.J., Rees, G.D. Microemulsion-based media as novel drug delivery systemAdv. Drug Deliv. Rev. 2000, 45. 89-121.
12. Humberstone, A.J., Charman, W.N., Porter, H., Edwards, G.A., Müllertz, A., Kristensen, H.G., Charman, W.N. Lipid-based vehicles for the oral delivery of poorly water soluble drugsAdv. Drug Deliv. Rev. 1997, 25. 103-128.
13. Holm, R.,. Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in selfmicroemulsifying drug delivery systems containing structured triglycerides. Eur. J. Pharm. Sci. 2003,20. 91-97.
14. Kang, B.K., Lee, J.S., Chon, S.K. , Jeong, S.Y., Yuk, S.H., Khang, G., Lee, H.B., Cho, S.H. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogsInt. J. Pharm. 2004,274. 65–73.
15. Pouton, C.W. Lipid formulations for oral administration of drugs: nonemulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systemsEur. J. Pharm. Sci. 2000,11. S93-S98.
16. Pouton, C.W. Formulation of self-emulsifying drug delivery systems. Adv. Drug Deliv. Rev. 1997,25. 47-58.
17. Charman, W.N., Porter,C.J.H., Mithani,S., Dressman,J.B. Physicochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J. Pharm. Sci. 1997, 86. 269-282.
18. Franceschinis, E., Voinovich,D., Grassi,M, Perissutti,B., Filipovic-Grcic, J., Martinac,A., Meriani-Merlo, F., Self-emulsifying pellets prepared by wet granulation in high-shear mixer: influence of formulation variables and preliminary study on the in vitro absorption Int. J. Pharm. 2005, 29. 87- 97.
19. Tuleu, C., Newton, J.M., Rose, J., Euler, D., Saklatvala, R., Clarke, A., Booth, S., Comparative bioavailability study in dogs of a self-emulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of progesterone. J. Pharm. Sci. 2004, 93. 1495–1502.
20. Nazzal, S., Khan, M.A., Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters Int. J. Pharm. 2006. 315. 110–121.

21. Syed Laik Ali, Florey, K.,. Nifedipine. In: Analytical Profiles of Drug Substances. New York : Academic Press. 1989, 18. 221–289.
22. Datta, A., Ghoshb,N., Ghosh,S., Debnathd,S., kumard,.S., Bhattacharjeed,C.,. Development, characterization and solubility study of solid dispersion of nifedipine hydrochloride by solvent evaporation method using poloxamer 407, International journal of applied biology and pharmaceutical technology, 2011, 2. 1-7.
23. Takeuchi, H., Nagira, S. , Yamamoto, H., Kawashima, Y.,. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spraydrying methodInt. J. Pharm. 2005 293. 155–164.
24. Lanlan Wei Jie Li., Liangran Guo., Shufang Nie., Weisan Pan., Peinan Sun .,Hui Liu.. Investigations of a Novel Self-Emulsifying Osmotic Pump Tablet Containing Carvedilol Drug Development and Industrial Pharmacy, 2007 33. 990–998.
25. Davidson, R .L., Sittig,M., 1962. "Water Soluble Resins".
26. Save.T., Venkkitachalam, P., Studies on solid dispersions,of nifedine Drug Development And Industrial Pharmacy, 1992. 18. 1663-1679.
27. Lu, E.X., Jiang, Z. Q., Zhang, Q. Z., Jiang, X. G.. A water-insoluble drug monolithic osmotic tablet system utilizing gum Arabic as an osmotic, suspending and expanding agent. J. Control. Release 2003 92. 375–382.
28. Shokri, J., Ahmadi, P., Rashidi, P., Shahsavari , M., Rajabi-Siahboomi, A., Nokhodchi, A., Swellable elementary osmotic pump (SEOP): An effective device for delivery of poorly water-soluble drugs European Journal of Pharmaceutics and Biopharmaceutics 2008.68. 289–297.
29. Nokhodchi, A., Momin, M.N., Shokri,J., Shahsavari,M., Rashidi,P.A., Factors Affecting the Release of Nifedipine from a Swellable Elementary Osmotic PumpDrug Delivery, 2008. 15. 43–48.
30. Balakrishnan, P., Beom-Jin Lee., Dong Hoon Oh., Jong Oh Kim ., Myung Ja Hong ., Jun-Pil Jee ., Jung Ae Kim., Bong Kyu Yoo., Jong Soo Woo., Chul Soon Yong., Han-Gon Choi., Enhanced oral bioavailability of dexibuprofen by a novel solid SEDDS formulation. Eur. J. Pharm and Biopharm. 2009.72, 539-545.