DESIGN, DEVELOPMENT AND EVALUATION OF DILTIAZEM HYDROCHLORIDE LOADED NANOSPONGES FOR ORAL DELIVERY

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ABSTRACT

Objective: In the current investigation, nanosponges were set up by emulsion solvent diffusion technique utilizing ethyl cellulose and β-cyclodextrin as polymers.

Methods: Diltiazem hydrochloride is taken as model medication for considering different nanosponge formulations. The similarity of different formulation segments was set up by Fourier Transform Infra-Red (FTIR) spectroscopy. Molecular size, surface morphology, entrapment efficiency and drug content of nanosponges were analyzed. Shape and surface morphology of the nanosponges were inspected utilizing scanning electron microscopy.

Results: Molecular size of formulated nanosponges was seen in the scope of 186 to 476 nm. Scanning electron microscopy uncovered the permeable, round nature of the nanosponges. The drug content of nanosponges for ethyl cellulose containing formulations was seen as in the scope of 62.25 to 85.11% and for the β-cyclodextrin containing details were seen as in the scope of 65.81-89.67%. The percentage entrapment effectiveness of nanosponges for ethyl cellulose containing formulations were seen as in the scope of 54.18 to 79.49% and for the β-cyclodextrin containing details were seen as in the scope of 58.21-83.45%. In vitro drug release findings demonstrated that at 12 h ethyl cellulose containing formulations discharged the drug in the scope of 57.27-89.09% and for the β-cyclodextrin containing formulations discharged in the scope of 73.94-93.26%.

Conclusion: Sustained drug release from formulations is supported if there is an occurrence of ethyl cellulose in the formulations rather with plans containing β-cyclodextrin.

Keywords: Diltiazem hydrochloride, β-Cyclodextrin, Ethyl cellulose, Polyvinyl alcohol, Scanning Electron Microscopy, UV Spectroscopy

INTRODUCTION

The drug delivery technology has unquestionably another concern for drugs by giving them new life through their therapeutic targets. Target oriented drug administration with upgrades in therapeutic efficacy, decrease in side-effects and enhanced dosing routine, will be the main patterns in the region of therapeutics [1]. Targeted drug delivery suggests for specific and compelling confinement of pharmacologically active moiety at pre recognized objective in therapeutic concentration, while limiting its entrance to non-target typical cell linings and in this manner limiting harmful impacts and augmenting therapeutic index of the drug [2-5].

Nanosponges are permeable polymeric delivery systems that are little round particles with enormous permeable surface [6]. Nanosponges (NSs) are a significant part to control the pace of delivery of active agent to the predetermined site by little size and productive carrier attributes. NSs are nonmutagenic, nonallergenic, nonirritant, and nontoxic [7, 8].

The expression "Nanosponge" signifies the nanoparticles with permeable structures. Nanosponges are little sponges almost equal to the size of virus with a normal breadth under 1μm [9]. Owing to their little size and penetrable nature they can tie poorly soluble drugs inside the framework and enhance their bioavailability by altering the pharmacokinetic limits of actives [10, 11].

The nanosponges are a three-dimensional framework (backbone) or system of polyester that are fit for degrading normally. These polyesters are blended in with a crosslinker in a solution into form nanosponges [12]. Here, the polyester is commonly biodegradable, so it breaks down in the body decently. When the scaffold of a nanosponge breaks down, it discharges the medication particles which are stacked, in an injurious fashion [13].

Nanosponges are smaller in nature and are little particles with penetrable surface can be considered as oral, parenteral and topical dosage forms. Nanosponges meant for oral administration, might be scattered in a framework of excipients, diluents, anticaking agents and lubricants to build up appropriate tablets or capsules of them and the significant advantages of these dosage forms are reduced drug dose, decrease in toxicity and improving patient consistence by delayed release [14-16]. For parenteral administration, these can be essentially blended in with sterile water, saline or different watery solutions. Further, nanosponges can be successfully added to topical hydrogel for topical application [17, 18].

MATERIALS AND METHODS

Diltiazem hydrochloride, β-Cyclodextrin and Ethyl cellulose obtained from Yarrow chemicals limited, Mumbai. Polyvinyl alcohol and Dichloromethane procured from SD fine chemicals, India.

Preparation of diltiazem HCl nanosponges

Diltiazem HCl nanosponges were set up by the emulsion solvent diffusion strategy. DTZ and EC/β-Cyclodextrin were disintegrated in DCM (Phase 1), while Phase 2 was set up by adding PVA to refined water. Stage 1 and Phase 2 were put independently on an magnetic stirrer for 15 min. Stage 1 was added gradually to Phase 2 with mixing and afterward left them for 15 min on the stirrer at room temperature. The blend was homogenized at various velocities for 2 h. From that point onward, it was sifted. The shaped nanosponges were dried at 40 °C for 12 h.

Preformulation studies

1) Identification of drug

The got sample drug was inspected by Infrared absorption spectral investigation and was contrasted with the reference standard IR
range of Diltiazem HCl. IR Spectra of medication and mixes were recorded on a FTIR (Bruker, Germany) in the scope of 4000-400 Cm-
1 utilizing potassium bromide discs.

ii) Determination of melting point

Melting point of Diltiazem HCl was found by open capillary technique. Melting-point apparatus is most regularly utilized for the assurance of the melting point of a solid. A couple of crystals of the compound are put in a slight walled capillary tube 10-15 cm long, about 1 mm in inside breadth, and shut down towards one side.

### Table 1: Composition of nanosponges of diltiazem HCl (F1 to F10)

| Formulation code | Composition | DrugMg | Ethyl cellulose gm | PVAgm | β-cyclodextrin gm | Dichloromethane (ml) | Water (ml) |
|------------------|-------------|--------|-------------------|-------|-----------------|---------------------|------------|
| F1               | 30          | 0.6    | 0.3               | -     | 0.3             | 20                  | 100        |
| F2               | 30          | 0.6    | 0.3               | -     | 0.3             | 20                  | 100        |
| F3               | 30          | 0.6    | 0.3               | -     | 0.3             | 20                  | 100        |
| F4               | 30          | 0.9    | 0.3               | -     | 0.3             | 20                  | 100        |
| F5               | 30          | 1.2    | 0.3               | -     | 0.3             | 20                  | 100        |
| F6               | 30          | -      | 0.3               | -     | 0.3             | 20                  | 100        |
| F7               | 30          | -      | 0.3               | -     | 0.3             | 20                  | 100        |
| F8               | 30          | -      | 0.3               | -     | 0.3             | 20                  | 100        |
| F9               | 30          | -      | 0.3               | -     | 0.3             | 20                  | 100        |
| F10              | 30          | -      | 0.3               | -     | 0.3             | 20                  | 100        |

Characterization of diltiazem hydrochloride nanosponges

Morphology

For SEM studies, one drop of nanospone preparation was set on the stub secured with clean glass and covered with gold. It was later seen under the scanning electron magnifying lens at quickening voltage of 20KV and photomicrographs of appropriate amplification was gotten.

Particle size

Average molecule measurement of prepared nanospone preparations was resolved utilizing dynamic light scattering technique (beta sizer; Malvern, ZSP nano) following a previous portrayed technique. Aqueous dispersions of NS were appropriately diluted for scattering force at 25 °C. Tests were kept in expendable cuvette and estimations were made at 372.0 kcps (check rate) for 20s.

Drug content

Drug content consistency was resolved as triplicate by dissolving the Nan sponges in methanol and broke down Nan sponges were experienced centrifugation at 3000rpm for 2 h and separated with whatman channel paper (0.45 µm, Whatman, Maidstone, UK). The solution was diluted to Beer’s range and seen in UV-Spectrophotometer.

Entrapment efficiency

The amount of Diltiazem HCl in the formulation was dictated by UV investigation after disturbance of the vesicles with Triton X-100 (0.5% w/w). The vesicle/Triton X-100 arrangement was centrifuged at 10,000 rpm at 40°C for 10 min. The supernatant was sifited. The capture efficiencies and the stacking efficiencies of the Diltiazem HCl-stacked formulatin were determined by UV.

In vitro drug release studies

The in vitro penetration behavior of Diltiazem HCl from all nanosponges plans were explored utilizing cellophane layer (Molecular weight cut of 12000–14000). The vertical kind of the Franz Diffusion cell was planned, manufactured, and approved preceding the saturation study. The cellophane film was mounted on a diffusion cell assembly with an operative dissemination region of 2.303 cm. The receptor compartment comprised of a 22.5 ml phosphate buffer at pH 6.8, stirred at 100 rpm, and was kept up at 37±0.5 °C all through the analyses. The prepared NS formulation was applied to the layer in the donor compartment. An aliquot of test was pulled back at reasonable time spans and supplanted.
promptly with an equivalent volume of new diffusion medium. The total amount that permeated over the cellophane film was determined and plotted against time.

RESULTS AND DISCUSSION

The IR spectrum of wholesome drug was seen as like that of standard range of Diltiazem HCl. The spectrum of Diltiazem HCl exhibits the accompanying groups at their frequencies appeared at 1637, 1330, 1412, 1586, 2923, 3108 cm$^{-1}$. The melting point of Diltiazem HCl was found to be 212 °C which consented to the BP guidelines. Compatibility investigations of wholesome drug, Diltiazem HCl with polymers were completed past formulation of Nanosponges. All the distinguishing peaks of Diltiazem HCl were available in spectra at particular frequency. Hence, showing similarity among medication and polymers. It illustrates that there was no huge change in the chemical reliability of the drug.

Morphology

The readied Nanosponges were experienced morphological examinations by utilizing optical microscopic technique. Little amount of test was spread over clean slide. The slide was engaged under optical light and pictures were snapped by utilizing optical microscopy joined with Dewinter Microscopic camera programming. As indicated by morphological assessment investigation, all vesicles types appeared to have a circular or oval molded. These oval-molded vesicles may have come about because of the Nanosponges’ distortion, which may happen during the sample readiness.

Table 2: Particle size, entrapment efficiency of F1 to F10 formulations

| S. No. | Formulation code | Particle size (nm) | Drug content (%) | Entrapment efficiency (%) |
|--------|------------------|--------------------|------------------|--------------------------|
| 1      | F1               | 186                | 70.44            | 63.51                    |
| 2      | F2               | 222                | 85.11            | 79.49                    |
| 3      | F3               | 284                | 84.08            | 76.34                    |
| 4      | F4               | 345                | 73.65            | 67.83                    |
| 5      | F5               | 389                | 62.25            | 54.18                    |
| 6      | F6               | 250                | 65.18            | 58.21                    |
| 7      | F7               | 323                | 73.49            | 67.11                    |
| 8      | F8               | 376                | 83.68            | 76.04                    |
| 9      | F9               | 410                | 89.67            | 83.45                    |
| 10     | F10              | 476                | 81.24            | 74.62                    |

Fig. 2: Sem image of nanosponges

Fig. 3: Entrapment efficiency of F1 to F10 formulations
The molecule size of the nanosponge was governed by optical microscopy and the nanospenses were seen as uniform in size. Particle size of Nanospenses containing ethyl cellulose was found to be in the range of 186 nm to 389 nm. Nanospenses containing β-Cyclodextrin was found to be in the range of 250 nm to 476 nm respectively. The normal particle size was significantly influenced by the drug to polymer proportion. The moderately litter molecule size is because of lower strength of polymer giving lesser opportunity to droplet arrangement. Thus, we could see that the particle size increases as the concentration of ethyl cellulose and β-cyclodextrin increases. The drug content of nanospenses for ethyl cellulose containing formulations were found to be in the range of 62.25 to 85.11% and for the β-cyclodextrin containing formulations were found to be in the range of 65.18-89.67%. The percentage Entrapment efficiency of nanospenses for ethyl cellulose containing formulations were found to be in the range of 54.18 to 79.49% and for the β-cyclodextrin containing formulations were found to be in the range of 58.21-83.45%. The entrapment efficiency of the nanospenses was found to increase with growing polymer concentration. This could be due to the expansion of drug capturing limit of nanospenses as the polymer strength rose. Nanospenses with 0.3% EC and β-CD showed 63.51% and 58.21% entrapment efficiency respectively, which improved to 67.83% and 83.45% respectively when the polymer strength rose to 0.9% respectively.

**In vitro drug release studies**

The in vitro drug release of Diltiazem HCl was acted in phosphate buffer pH 7.4. The in vitro discharge profile of Diltiazem HCl was primarily influenced by type and measure of polymer utilized. In vitro drug release investigations demonstrated that at 12 h ethyl cellulose containing formulations discharged the medication in the scope of 57.27-89.09% and for the β-cyclodextrin containing details drug discharged in the scope of 73.94-93.26%. Drug release was sustained in case of ethyl cellulose formulations compared to formulations containing β-cyclodextrin.
high $R^2$ values recommended that the drug discharge from the Nanosponges followed by different components. So as to characterize perfect model which will speak to a superior fit for in vitro release information, Korsmeyer-Peppas model was applied which will characterize the specific system. Great linearity with high $R^2$ values was seen with this model. The estimation of $n$ acquired for all the formulations was $>0.5$ and $<1.0$, recommending that the drug discharged followed non-fickian and diffusion.

**Fig. 6:** Time Vs drug retained (First order kinetics) of formulations F1 to F5

**Fig. 7:** Time Vs drug retained (First order kinetics) of formulations F6 to F10

**Fig. 8:** Square root of time Vs % cumulative drug released (Higuchi release mechanism) of formulation F1 to F5
Fig. 9: Square root of time Vs % cumulative drug released (Higuchi release mechanism) of formulation F6 to F10

Fig. 10: Log time Vs cumulative % drug released (Korsmeyer-peppas release mechanism) of formulations F1 to F5

Fig. 11: Log time Vs cumulative % drug released (Korsmeyer-peppas release mechanism) of formulations F6 to F10
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REFERENCES
1. Vishvakarma A, Nikam P, Mogal R, Talele S. Review on nanosponges: a beneficiation for novel drug delivery. Int J PharmTech Res 2014;6:11-20.
2. Yadav GV, Panchory HP. Nanosponges— a boon to the targeted drug delivery system. J Drug Delivery Ther 2013;3:151-5.
3. Rita L, Amit T, Chandrashekhar G. Current trends in β-cycloexdrin based drug delivery systems. Int J Res Ayurveda Pharm 2011;2:1520-6.
4. Shringirishi M, Prajapati SK, Mohar S, Alok S, Yadav P, Verma A. Nanosponges: a potential nanocarrier for novel drug delivery- a review. Asian J Curr Pharm Res 2014;4:19-26.
5. Susmitha, Charanjit, Reddy VM, Naveena, Gupta VRM. Nanosponges— a concise review of emerging trends. Int J Pharm Res Biomed Anal 2014;3:1-6.
6. Challa R, Ahuja A, Ali J, Khar RK. Cyclodextrins in drug delivery: an updated review. AAPS PharmSciTech 2005;6:E329-57.
7. Khopade AJ, Jain S, Jain NK. The microposome. East Pharm 1996;25:49-53.
8. Silpa JN, Nissankarao SR, Bhimavarapu R, Sreventhi SL, Vinusha K, Renuka K. Nanosponges: a versatile drug delivery system. Int J Pharm Life Sci 2013;4:221-6.
9. Yang CY, Liao TC, Shuai HH, Shen TL, Yeh JA, Cheng CM. Micropatterning of mammalian cells on inorganic-based nanosponges. Biomaterials 2012;33:4988-97.
10. Bolmal U, Manvi FV, Rajkumar P, Palla SS, Paladugu A, Reddy KR. Recent Advances in nanosponges as drug delivery system. Int J Pharm Sci Nanotechnol 2013;6:1934-44.
11. Sharma R, Pathak K. Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation. Pharm Dev Technol 2011;16:367-76.
12. Swaminathan S, Vavia PR, Trotta F, Cavalli R, Tumulsu S, Bertinetti L, et al. Structural evidence of differential forms of nanosponges of beta-cycloextrin and its effect on solubilization of a model drug. J Incl Phenom Macrocycl Chem 2012;76:201-11.
13. Bhowmik H, Venkatesh DN, Kaula A, Kumar KH. Nanosponges: a review. Int J Appl Pharm 2018;10:1-5.
14. Tambe RS, Battase PW, Arane PM, Palve SA, Talele SG, Chaudhari G. Review on nanosponges: as a targeted drug delivery system. Am J PharmTech Res 2015;5:215-24.
15. Subramanian SMK, Anandam S, Kannan KM, Rajappan M. Nanosponges: a novel class of drug delivery system— review. J Pharm Sci 2012;15:103-11.
16. Shankar S, Vavia PR, Francesco T, Satyen B. Formulation of betacyclodextrin based nanosponges of itraconazole. J Incl Phenom Macrocycl Chem 2007;57:89-94.
17. Niles J, Ruchi J, Navaneet T, Bhram P, Gupta, Deepak K, et al. Nanotechnology: a safe and effective drug delivery system. Asian J Pharm Clin Res 2010;3:159-65.
18. Indira B, Bolisetty SS. Nanosponges: a new era in drug delivery. J Pharm Res 2012;5:5293-6.

Table 3: Release kinetics data of the formulations F1 to F10

| Formulation code | Zero order R² | First order R² | Higuchi’s R² | Korsemeyer peppa’s n | R² |
|------------------|---------------|---------------|--------------|----------------------|----|
| F1               | 0.980         | 0.950         | 0.910        | 0.977                | 0.985 |
| F2               | 0.981         | 0.960         | 0.932        | 0.989                | 0.993 |
| F3               | 0.974         | 0.994         | 0.952        | 0.988                | 0.995 |
| F4               | 0.972         | 0.994         | 0.947        | 0.981                | 0.976 |
| F5               | 0.976         | 0.993         | 0.947        | 0.982                | 0.994 |
| F6               | 0.981         | 0.986         | 0.928        | 0.901                | 0.991 |
| F7               | 0.990         | 0.965         | 0.926        | 0.984                | 0.996 |
| F8               | 0.986         | 0.915         | 0.920        | 0.946                | 0.993 |
| F9               | 0.986         | 0.953         | 0.922        | 0.939                | 0.992 |
| F10              | 0.983         | 0.977         | 0.915        | 0.964                | 0.988 |