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Original Article

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: Molecule 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 65.18-89.67%. 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* drugreleasefindings 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 drugreleasefrom 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, Poly vinyl alcohol, Scanning Electron Microscopy, UV Spectroscopy

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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].

Nanospongesare 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 solutionto form nanosponges [12]. Here, the polyester is commonly biodegradable, so it breaks down in the body decently. When the scaffold of nanospongesbreaks 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 appropriatetablets 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.

Preparationof 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

i) 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 ofcrystals of the compound are put in a slight walledcapillary tube 10-15 cm long, about 1 mm in inside breadth, and shut down towards one side.

iii) Construction of calibration curve of diltiazem HCl

A precisely weighed 100 mg of Diltiazem hydrochloride was dissolved in water and made up to 100 ml in volumetric flask (Stock solution-I 1000µg/ml). From this, 10 ml of solution was pipetted out and made up to 100 ml volumetric flask (Stock solution–II 100µg/ml). From this solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0 ml were pulled back and diluted to 10 ml to give 2, 4, 6, 8, 10, 12, 14,16, 18, 20 µg/ml separately andmeasured the absorbance at 237 nm.

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

Formulationcode	Composition					
	DrugMg	Ethyl cellulosegm	PVAgm	β-cyclodextrin gm	Dichloromethane (ml)	Water(ml)
F1	30	0.3	0.3	-	20	100
F2	30	0.6	0.5	-	20	100
F3	30	0.6	0.7	-	20	100
F4	30	0.9	0.9	-	20	100
F5	30	1.2	1.2	-	20	100
F6	30	-	0.3	0.3	20	100
F7	30	-	0.5	0.6	20	100
F8	30	-	0.7	0.6	20	100
F9	30	-	0.9	0.9	20	100
F10	30	-	1.2	1.2	20	100

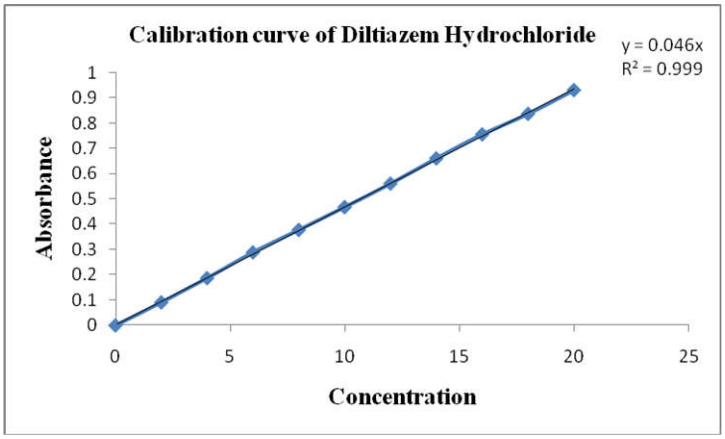

Fig. 1: Calibration curve of diltiazem HCl

Characterization of diltiazem hydrochloride nanosponges

Morpholog

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

Particle size

Average molecule measurement of prepared nanosponge preparations was resolved utilizing dynamic light scattering technique (zeta 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 whatmann 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 40C for 10 min. The supernatant was sifted. The capture efficiencies and the stacking efficiencies of the Diltiazem HCl-stacked formulatins 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 anoperative 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 1037, 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.

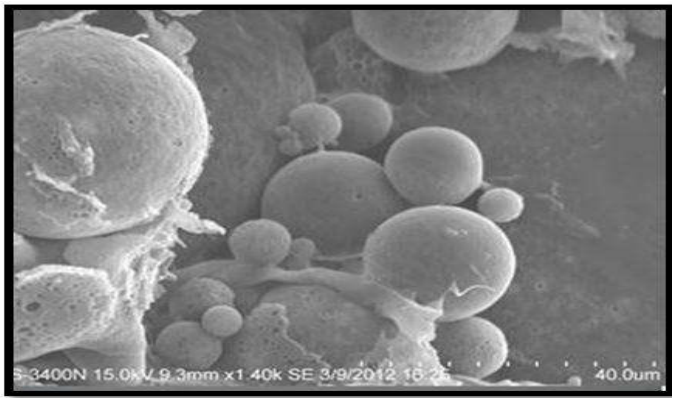

Fig. 2: Sem image of nanosponges

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

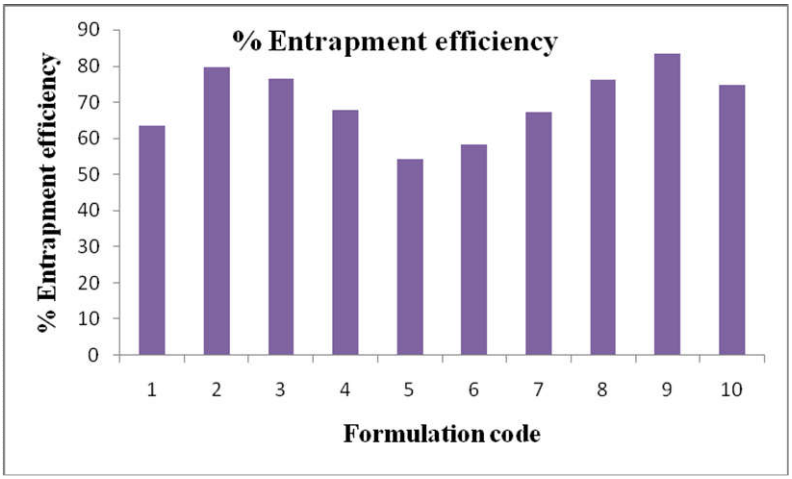

Fig. 3: Entrapment efficiency of F1 to F10 formulations

The molecule size of the nanosponge was governed by optical microscopy and the nanosponges were seen as uniform in size. Particle size of Nanosponges containing ethyl cellulose was found to be in the range of 186 nm to 389 nm. Nanosponges containing β-Cyclodextrinwas found to be in the range of 250 nm to 476 nm respectively. The normalparticle size was significantly influenced by the drug to polymer proportion. The moderately littler 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 nanosponges 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 nanosponges 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 nanosponges was found to increase with growing polymer concentration. This could be due to the expansion of drug capturing limit of nanosponges as the polymer strength rose. Nanosponges 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 invitro 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.

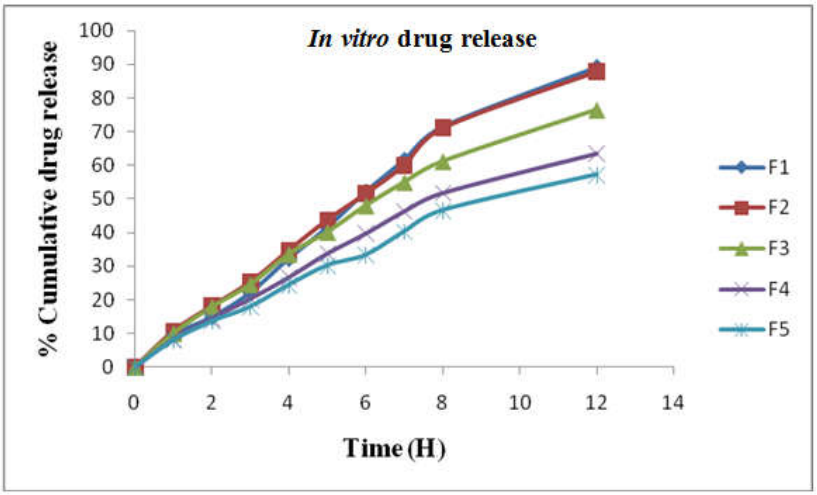

Fig. 4: *In vitro* diffusion studies for F1 to F6

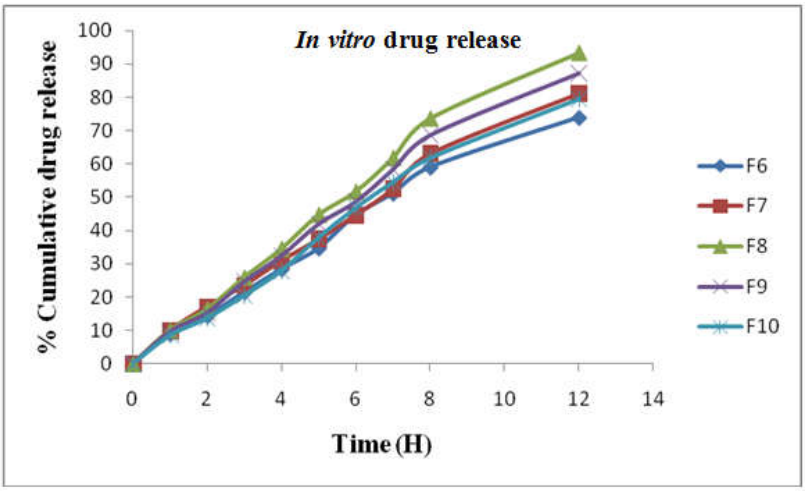

Fig. 5: *In vitro* diffusion studies for F7 to F12

The *in vitro* release information was exposed to zero, first order, Higuchi's and Korsemeyers-Peppas model so as to set up the drug release means and kinetics involved. At the point, when the information was exposed to zero and first kinetics model, a straight relationship was seen with high R^2 value for zero order models when contrasted with first order model and its proposed that the formulations obeyed zero order release. Higuchi's model was applied to the *in vitro* release information, linearity was gotten with

high R^2 values recommended that the drug discharge from the Nanosponges followed by different components. So as to characterize pefect model which will speak to a superior fit for *in vitro* release information, Korsemeyer-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-fickianandiffusion.

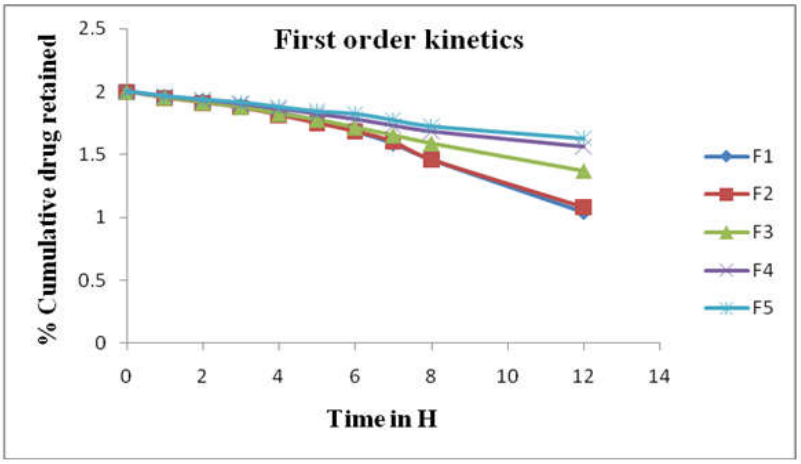

Fig. 6: Time Vs drug retained (First order kinetics) of formulations F1 to F5

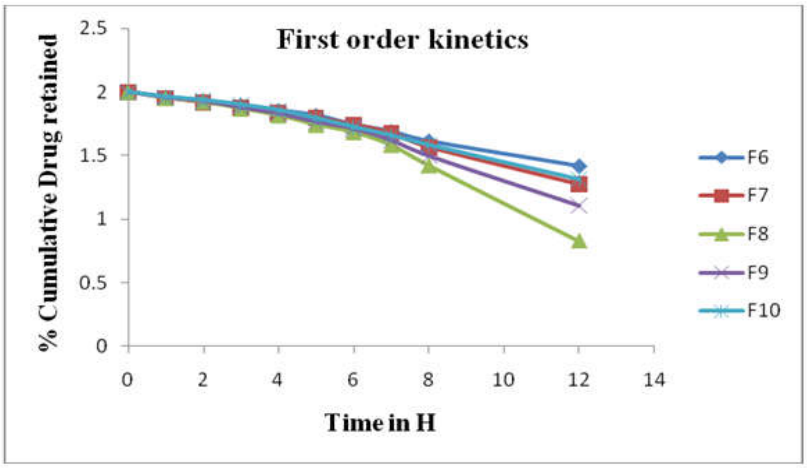

Fig. 7: Time Vs drug retained (First order kinetics) of formulations F6 to F10

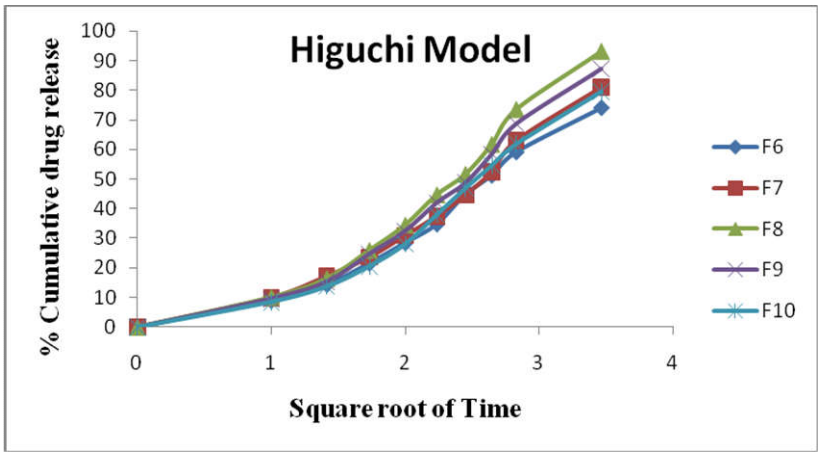

Fig. 8: Square root of time Vs % cumulative drug released (Higuchi release mechanism) of formulation F1 to F5

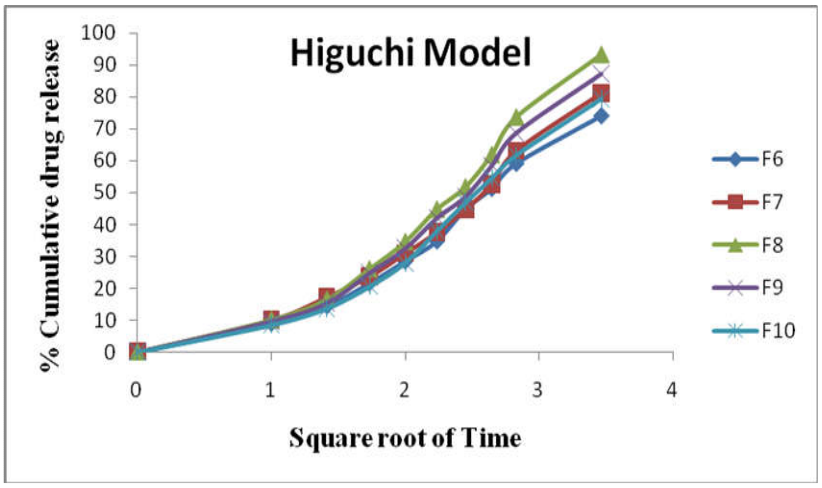

Fig. 9: Square root of time Vs % cumulative drug released (Higuchi release mechanism) of formulation F6 to F10

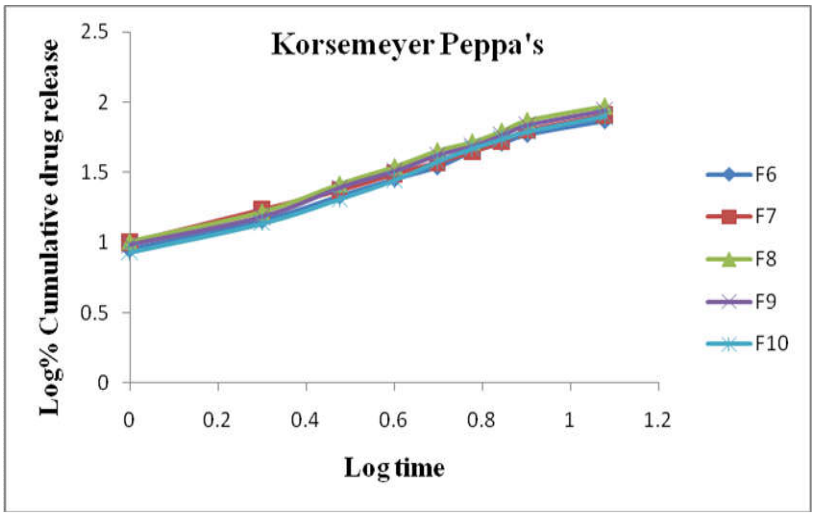

Fig. 10: Log time Vs cumulative % drug released (Korsmeyer-peppas release mechanism) of formulations F1 to F5

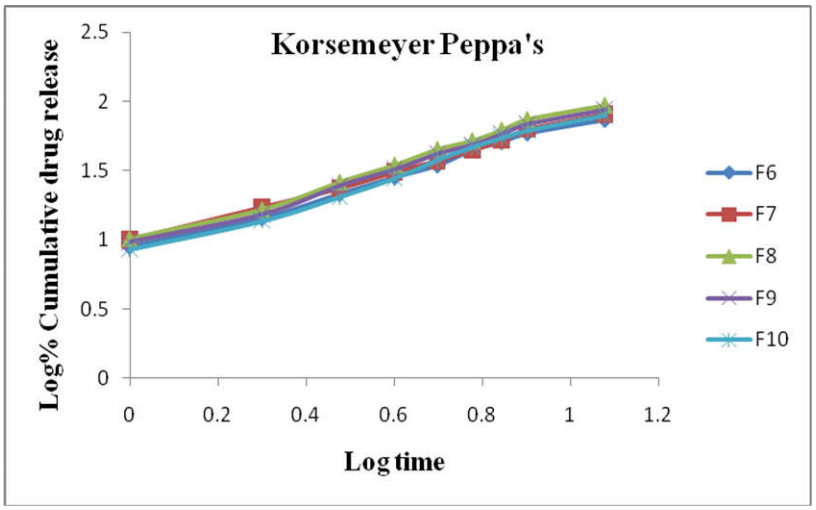

Fig. 11: Log time Vs cumulative % drug released (Korsmeyer-peppas release mechanism) of formulations F6 to F10

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

Formulation code	Zero order R^2	First order R^2	Higuchi's R^2	Korsemeyer peppa's	
				n	R^2
F1	0.980	0.950	0.910	0.977	0.985
F2	0.981	0.960	0.932	0.892	0.993
F3	0.974	0.994	0.952	0.848	0.995
F4	0.972	0.994	0.947	0.861	0.994
F5	0.976	0.993	0.947	0.823	0.994
F6	0.981	0.986	0.928	0.901	0.991
F7	0.990	0.965	0.928	0.864	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

CONCLUSION

Diltiazem Nanospongesmade by solvent evaporation technique utilizing β-cyclodextrin and ethyl cellulose was assessed for its various parameters which uncovered many intriguing outcomes for productive production of the nanosponges. Nanosponges offer a simple and practical approach to achieve increased bioavailability, and modify drug release profiles essential for sustained, site specific and localized drug action. The investigation affirmed that all the readied Nanosponges have permeable structure and the drug content of formulations satisfied uniform distribution of drug within the drug delivery system. *In vitro* drug release studies indicated that,at 12 h, ethyl cellulose containing formulationsreleased the drug in the range of 57.27-89.09% and for the β-cyclodextrin containing formulations drug released in the range of 73.94-93.26%. Drug release is sustained in case of ethyl cellulose formulations compared to formulations containing β-cyclodextrin. Meanwhile, the *in vitro* diffusion obeyed zero order kinetics with mechanism of release zero order followed non fickian diffusion. So, Diltiazem HCl used for the treatment of angina as nonosponges can produce fast absorption. The study conducted so far reveals promising result suggesting scope for pharmacodynamic and pharmacokinetics evaluation. Thus, the developed nanosponges formulation may prove to be a promising carrier for Diltiazem HCl and other drugs, especially due to their simple production and simplistic scale up.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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