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Novel verdicts of nifedipine encapsulated with cyclodextrin in new-fangled form of microsponges

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ABSTRACT

The fundamental approach for the microsponge technologies arises in solid dosage forms because they showing a promising technology for nifedipine drug in hypertension control. As nifedipine drug is chosen due to its hydrophobic nature second short half-life, third low remark in plasma concentration. Cyclodextrin-based microsponges with different polymer are novel finding in the microsphere technology, the crosslinking of polymers blends with respect to cyclodextrin will enhance the entrapment of nifedipine drug in the new-fangled form by emulsification solvent method and futher Lyophilization. The different microsponges batches are formulated the optimize batch was MN3 with angle of repose; 21.80 ± 0.63., Hausner ratio 1.132, Carrs index 0.132 and higher % drug content (80.5 ± 0.97 %). showed 99.41 ± 1.05 % drug release during 36 hr in vitro release . After that the stability data disclose superior drug retention of loaded nifedipine, besides consistent in vitro release pattern over a period of 90 days.

Keywords: Microsponges, Cyclodextrin, Polymers, Nifedipine

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1. INTRODUCTION

Cross-linking of the polymer sphere are dressed up in new-fangled form of delivery known as microsponges. They are spherical, uniform polymer particle having a capacity to absorb or to load high degree of active constituents in their body or surface due to a larger size and surface area as compared to nano bioactive substance (nanospheres and nanoshells). The entrapment of drug in microsponge is high as compared to other controlled dosage forms that's why we prefer such formulation. Microsponges are a sanctified therapeutic system for a transdermal system but recently it also shows second-hand practice in oral drug delivery system. A calcium channel blocker Nifedipine is used in the treatment of angina pectoris and hypertension. The complications of hypertension are said to be end-organ damage because damage to these organs is the end result of chronic high blood pressure. That's why the diagnosis of high blood pressure is important so efforts made to prevent complications and normalize blood pressure. It was previously thought that rise in diastolic blood pressure was a more important risk factor than systolic elevations, but it is now known that in people 50 years or older systolic hypertension represents a greater risk. If we give the impression on patient compliance a once- or twice-daily administration of the antihypertensive agent is known to increased in dosing scheme if we develop controlled or sustainable system for poor half-life drug the frequency of drug will be reduced so the side-effects reduce parallel which is the need of study. Furthermore, although a blood pressure reduction lasting for 24 hrs has never been proven to be a precondition for the avoidance of cardiovascular complications; it is over and over again browbeaten as an argument to support antihypertensive drugs[1]. For together reasons, the pharmaceutical industry is intensively probing for longer-acting antihypertensive drugs, either by the development of novel agents with a longer eradication of half-life problem, or by the upgrading of the galenic form of existing shorter-acting compounds, accordingly that plasma concentrations well-matched with a blood-pressure-lowering activity are maintained during the whole phase of the day. Many figures of antihypertensive drugs have been permitted by the regulatory bodies for once-daily administration[2,3]. On the other hand, no uniform set of scientific substantiation present that would be uniformly required to obtain approval for a once-daily dosing scheme.

Nifedipine microsponges get surplus advantage when we incorporate β-cyclodextrin, in them the member of cyclic oligosaccharides composed of α-(1, 4) linked glucopyranose subunits give us promising tools for the sustainability and it act as molecular hosts toward various, poorly water-soluble drugs, ranging from ion, very polar molecules to non-polar molecules, affecting advantageously their physicochemical properties[4].

The target of the research work is to achieve the desired in-vitro sustainable release activity of prepared nifedipine loaded β-cyclodextrin microsponges with different polymer ratio the study is focused on the exploring the microsponges technology[5-8] to load nifedipine inside them and found the release rate through the prepared system. Another reason why nifedipine has been chosen is its hydrophobic nature, From the literature studies, it is found that it has a short half-life too and if a drug is used in oral dosage form need for higher stability in the stomach[9-13]. The drug leading low remark in plasma concentration curve when trace by conventional capsule form of nifedipine. In case of increasing its therapeutic efficacy of drug several dosage forms with novel approaches are available in literature alginate gel beads, chitosan microparticles, poly [DL-lactide-co-glycolide] [PLGA] microsphere, Eudragit microparticles and albumin microspheres[14-19].

2. MATERIAL AND METHOD

Nifedipine drug was obtained as a gift sample from Lupin Ltd. Mandideep, Bhopal (MP) India. β-cyclodextrin, Ethylcellulose, acetone, sodium lauryl sulfate, Tween was purchased from Sigma Aldrich, USA. Polyvinyl alcohol, poly (D, L-lactic-co-glycolic acid)PLGA, starch, talc and Magnesium stearate, Dichloromethane was purchased from S.D. Fine chemicals, Indore (MP), India. All the ingredients were of analytical grade.

2.1. Formulation of Microsponges

The microsphere was prepared by emulsification-solvent evaporation method by preparing multiple emulsion water in oil in water (w/o/w). The inner aqueous phase was composed of Nifedipine β -CD complex solution (β-CD show increasing the aqueous solubility of Nifedipine so β-CD was chosen). The organic phase was composed of varying amounts of PLGA in 30 ml of dichloromethane(DCM). The inner aqueous phase was emulsified in organic phase forming the primary emulsion (w/o), using homogenizer (Polytron® PT 10/35 GT) at 21000 rpm for 5 min. Three different polymer ratios were used (1:5, 1:10 and 1:20) with a drug. The w/o/w multiple emulsion was acquired by addition the primary emulsion in 100 ml of PVA(1%). The resultant mutiple emulsion was continuously blended to allow solvent evaporation. The solid microspheres obtained were isolated by centrifuge (Jouan, KR22i, France) at 15000 rpm for 15 min, washed several times with distilled water, and finally, lyophilized. The whole procedure was repeated in triplicates.

2.2 Incoporation of Microsponges in Tablet Formulation

The directly compressible tablet was prepared by using prepared microsponges of nifedipine. The tablets were prepared with the use of two mainly used directly compressible ingredient, starch and microcrystalline cellulose (Avicel PH 101). Tablets were prepared from microsponge formulation MN-3. Batches prepared were denoted as TMN3-1, TMN3-2, TMN3-3 based on the results obtained using drug content determination. Tablets of weight 30 mg equivalent microsponges were compressed by direct mixing of ingredients on the multistation compression machine (Secor, India).

2.3. Experimental Work

2.3.1. TLC Retention factor (Rf) determination for drug excipient interaction:

Rf value of the nifedipine at room temperature and elevated temperature 50˚C was determined using established thin layer chromatographic (TLC) method as described away [17] and found to be between the range 0.67-0.69. If Rf value found in this range indicates that there was no interaction between the nifedipine and excipients and we can be selected for the further use.

2.3.2. Drug Content

30 mg of microsponge was dissolved in 30 ml of chloroform, filtered through Whatman filter paper, then 0.2 ml filtrate was diluted to 10 ml Chloroform and analyzed spectrometrically using at 244.5 nm. Further, the drug content was determined by using calibration curve prepared in chloroform. The study was done in triplicate. The drug content (Production Yield PY) was determined using the formulae:

$$PY\ [\%] = \frac{\text{Practical mass [microsponges]}}{\text{Theoretical mass [polymer + drug]}} \times 100$$

2.3.3. Morphology of nifedipine microsponges

The shape and surface characteristics of microspheres were examined by an optical microscope (Labtech, India) and scanning electron microscopy (SEM) (LEO, 1450 VP, England), respectively. Samples were prepared on stubs and coated by Gold. Zeta potential was determined by using Zetasizer (3000HSA, Malvern, UK) after suitable dilution with double distilled water. Results were reported as Means±SD.

2.3.4. Flow Property of nifedipine microsponges

The microsponges are evaluated for tapped density bulk density by measurement of graduated cylinder and angle of repose by funnel method.

2.3.5. Evaluation of tablet incorporated nifedipine microsponges

Weight variation test was performed on 20 tablets of each tablet batch TMN3-1, TMN3-2, TMN3-3. The hardness of prepared tablets was calculated by Monsanto hardness tester. The experiment was performed in triplicate. Drug content was determined on average 5 tablets by dissolving the whole tablet in chloroform and by its filtration. The final amount was determined by plotting a calibration curve of nifedipine in chloroform. This is the main In-vitro evaluation parameter for testing the sustained release activity of the tablets prepared. In vitro dissolution of prepared microsponges, tablets were carried out by USP XXXIII apparatus paddle type by using distilled water with 0.5% w/v Sodium Lauryl Sulphate (SLS) as dissolution media.

3. RESULTS AND DISCUSSION

3.1 Results

The nifedipine sustainability is the basic need to prepare microsponges, the technology in the sustainable pharmaceutical dosage form. Therefore we have tried to formulate sustained releases microsponges tablets of nifedipine for effective clinical applications. Preparations of microsponges were carried out at different percentage of drug and polymer. These batches are designated as MN-1, MN-2, and MN-3. (Table 1). The drug excipient interaction studies was carried by the Rf value of the nifedipine at room temperature and elevated temperature 50˚C was found to be

between the range 0.67-0.69. Nifedipine and β-CD are found to be 0.068±0.002 and α-CD shows 0.065±0.031 Rf value This indicates that there was no interaction between the nifedipine and CD but the Rf value of β-CD shows better result that's why preferred over α-CD. The electron microscopy firgure revealed the sponges like structure of the prepared nifedipine microsponges. The image (Fig 1) clearly reflecting the surface properties of prepared microsponges The batch is accelearated at the voltage of 10KV and magnification scale at 2000X and 8000X the average size range was found to be 0.93µm. Drug content was tested in 30 mg each of microsponges from each batch. It was found that MN-3 batch was highest dug content whereas MN-1 was found to lowest the variation lies between the 97.68% to 99.41% (Table 1).

Further the tablet was punched successfully white in color, round flat surfaces.The weight variation test was performed on 20 tablets of each tablet batch. The prepared microsponges tablet batches were found to be within limits. All the batches act in accordance with the weight variation test as per I.P. data is shown in Table 2. The hardness of prepared tablets was calculated by Monsanto hardness tester, average hardness was found to be under 5kg/cm^2 and found to be of good quality, the obtained result is mentioned in Table 2.

Drug content was determined on average 5 tablets by dissolving the whole tablet in chloroform and by its filtration amount was determined by calibration curve of the drug in chloroform. (Table 2). As the important In-vitro evaluation parameter for testing the controlled release activity of the tablets prepared the dissolution of prepared microsponges tablets were carried out by using USP XXXIII apparatus paddle type by using distilled water with 0.5% w/v Sodium Lauryl Sulphate (SLS) as dissolution media. The formulation TMN-3 was found to be the better formulation with just 89.55±0.76 % drug release in 24 h. (Table 3; Fig 2).

Table 1: Representing nifidipine polymer ratio, Bulk density, Tapped density, angle of repose, production yield and drug content of different formulations with deviation in polymer ratio(Results are expressed as mean values±SD (n=3)

S. No	Formulation Code	CD:Drug: Polymer ratio	Carr's Index	Hausner Ratio	Angle of Repose (Type of Flow) (% w/w)	Production yield (% w/w)	% Drug content	Zeta potential
1	MN-1	1:1:5	0.1135	1.1135	(36.32 ±0.96) Poor flow	50.21%	39%	-23.3
2	MN-2	1:1:10	0.1454	1.1454	(25.30±1.09) Free flowing	63.23%	63%	-34.3
3	MN-3	1:1:20	0.1325	1.1325	(21.80±0.63) Free flowing	72.31%	80.5%	-34.2

Table 2: The table containing different evaluation parameters for microsponge tablets after direct compression Hardness, Avg. weight and % drug content of different formulations TMN3-I, TMN3-II, TMN3-III. (Results are expressed as mean values±SD (n=3)

Sr. No	Formulation code	Avg. Hardness kg/cm^2	Average Weight (mg)	Average Drug content per tablet in mg	% Drug content
1	TMN3-I	4.3±0.31	100±0.34	29.3042	97.68±1.02
2	TMN3-II	4.3±1.07	101±0.89	29.3361	98.45±0.62
3	TMN3-III	4.4±0.16	100±0.96	29.6241	99.41±1.05

Table 3: In vitro dissolution study of directly compressible nifedipine microsponges tablets. (Results are expressed as mean values±SD (n=3)

FORMULATION		TMN-I	TMN-II	TMN-III
S.No.	Time (hours)	% Cumulative Release		
1	0	0	0	0
2	2	8.37±0.16	8.47±1.33	10.54±0.36
3	4	15.55±0.86	17.36±1.41	13.21±0.98
4	6	53.14±1.25	29.32±0.89	20.96±0.91
5	8	55.98±0.96	42.11±0.84	37.31±0.45
6	10	87.12±0.11	60.86±0.75	65.44±0.57
7	12	92.26±0.34	84.54±0.37	75.86±0.69
8	16	98.32±0.75	88.6±0.66	78.44±0.46
9	24	98.36±0.68	98.14±0.36	79.35±0.73
10	30		98.11±0.47	85.49±0.16
11	36			89.55±0.76

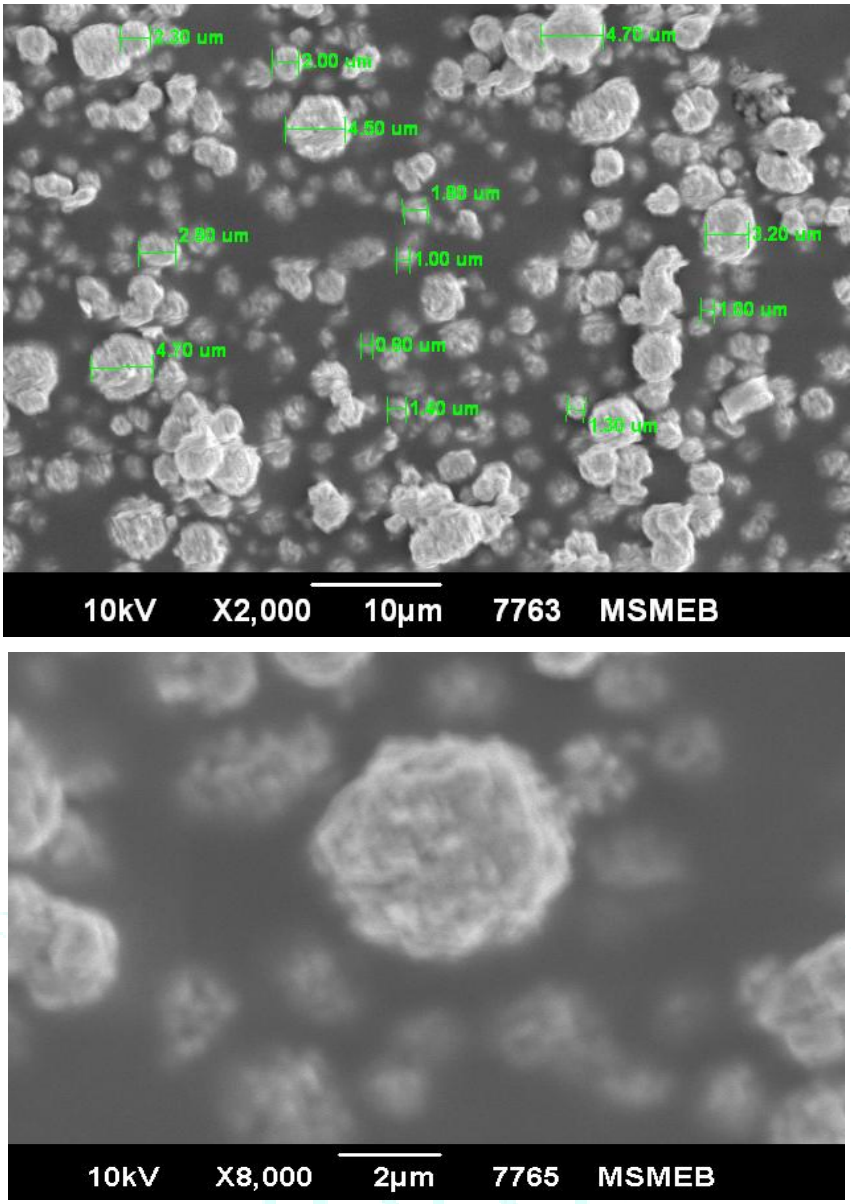

Figure 1:The SEM prediction of MN-3 Batch is shown at different magnification scale first image shows at 2000X and second image is at 8000X focusing on the single microsponges the surface is rigid and containing uneven surface with the different porous shell . SEM image was captured at an acceleration voltage of 10 KV.

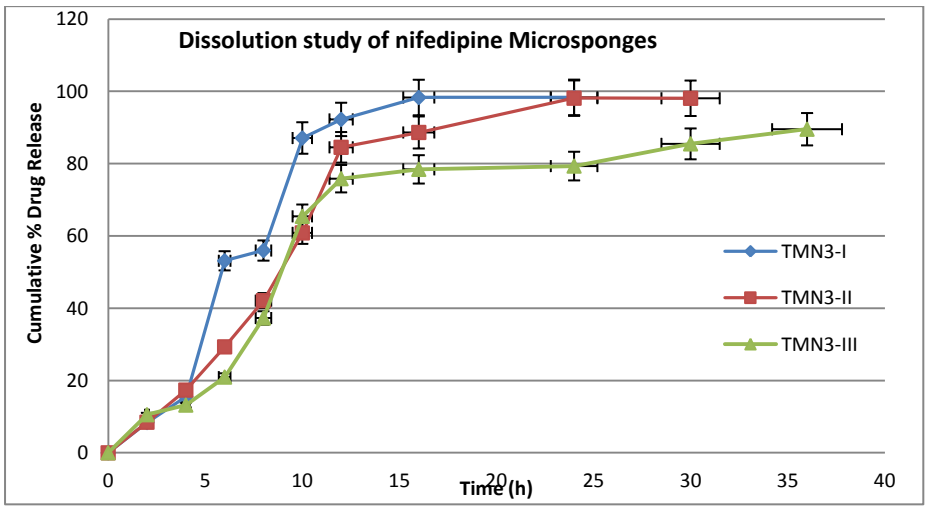

Figure 2: The graph is showing cumulative % drug release from different batches of Microsponges containing CD and PLGA which is formulated in tablet form. Nifidipine drug release from tablet was quantitatively measured by decisive the absorbance in UV-visible spectrophotometer at 244.5 nm. Results are articulated as mean values±SD (n=3)

3.2 Discussion

The selection of materials fis critical process in formulation, being researcher it is very important to choose the excipient as per the experimental condition, the better outcomes always replace the second choice same condition occur with α and β-CD. As we know in between α and β-CD, α-CD was more effective than a β-CD but when we incorporate both materials with nifedipine α-CD shows 0.065±0.031 Rf value and β-CD exhbits 0.068±0.002 retention factor, so we incorporate β-Cyclo dextrin in our preparation instead of another one.

Morphologically sponges are prepared with porous in nature in SEM results it reveals the dimension of microsponges ranged in 1.00 µm to 4.00 µm, as the microsponges were prepared by lyophilization technique no crystallization of drug is seen on the surface of sponges all the drugs was entrapped inside the porous space provided on microsponges. The structural formulation is found to be a spherical shape which is shown in figure 2 (b) at a zoom of 8000X the porosity of the sphere showing that the drug is entrapped inside the small pores, the inert matrices of spherical shape with the higher concentration of polymer firmly load nifedipine inside them.

The PLGA that we used in the formulation has the uniqueness with amphiphile polymer and capsule of self-assembling into the polymeric microsponges formulation which shows high binding with nifedipine results in the high entrapment efficiency. The inert matrices prepared will be fabricated so we can see stiffness and resourcefulness in the wide range of feat which is a benchmark in pharmaceutical companies in casting, molding, extrusion, for catching with any sense of biocompatible product formulations.

In probationary microsponges production initially, we tried for series of an organic solvent which includes ethanol, methanol, acetone, dichloromethane. The resultant higher solubility of PLGA is found in dichloromethane, so we prefer it. Manufacturing of microsponges was done by solvent will give better results compared to another solvent.

The selection of polymer ratio is for the increase in production yield, the PLGA polymer is biodegradable in nature so there is no harm to use this polymer inside body by oral route they undergo there hydrolysis of their ester linkage in presence of water to produce their monomers, lactic acid, glycolic acid which are byproducts of various metabolite activity, second advantage is retention effect which is shown in figure 2 in sense of drug release. The compressibility of microsponges did not give hardness and friability for direct compression so to convert into tablet form we will add direct compression (Avicel 101PH) so to convert into tablet form we will add directly compressible material in it to attain a good tensile strength.

Now on the matter with of drug release, the biggest question will arise in how much time or of how much time we have to control blood pressure, because as a person during a course of a day do different activities to alter their blood pressure. This could be not answered by a physician also how much pressure should be reduced by the mean of medication with effective time, therefore, hypertension disease gives a wide area of research and still projects going on. As demonstrated in the graph three different polymer ratio is given with release rate. The polymer ratio is given with release rate, the release rate of batch TMN3-I shows curve lag followed by sudden burst effect may be due to less concentration of the polymer the achievement which is our target may not be achieved. TMN3-II and TMN3-III ideally follow zero order (linear release) but the time period for both the drug is different this I was shown by two reasons: first, the retention time of PLGA is increased by the increase in the polymer ratio. Second, the releasing rate of increasing or retarding effect of CD, incorporation of a higher amount of CD into the microsponges improves the hydration of microsponges. The addition of CD in this research shows that it enhances the nifedipine release by acting as channeling or wicking agents or by promoting erosion of the matrix. In the phase between 60 to 90hrs the constant effect may be seen because when microsponges reaches in the aqueous medium water penetrate towards the centre of dimension then the diffusion in the porous network is highly limited due to cramped space and get slow until pores grow in size then only they will be able to release drug by polymer erosion.

4. CONCLUSION

Microsponges set their own standards in the solid dosage form drug delivery in relative dosage form they show there touchstones in floating drug delivery, effervescent technology, sustain release, control release, fluctuation release system, osmotic regulation etc through such system incalculably primitive dosage form get advantage appearance, facilitates accurate delivery of small quantities of potent drugs, improve drug integrity, protection of API, taste masking, sustain release, reduce gastric irritation, separation of incompatibility, reduction of volatility (vitamins), stabilization.

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CONFLICT OF INTEREST

There is no conflict of Interest between author.

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