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www.mcmed.us/journal/abs **Research Article**

DEVELOPMENT AND EVALUATION OF NANOSPONGES DRUG DELIVERY SYSTEM OF CARVEDILOL BY USING SOLVENT EVAPORATION METHOD

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ABSTRACT

The Aim of this work is to the development and evaluation of Nanosponges drug delivery system of Carvedilol by using solvent evaporation method. Carvedilol is a BCS classII drug, having an half life of 7 hours, which wasn't suitable for maintaining constant plasma concentrations. So Carvedilol was formulated as a nanosponge formulation for effective drug release. FTIR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in these nanosponge. SEM photographs revealed the spherical nature of the nanosponge in all variations. The formulation F11 has better results than remaining formulations. F11 formulation shows entrapment efficiency 98.64%, drug release release 97.24 % in 12 hour, and follows zero order with supercase II transport mechanism.

Keywords :- Carvedilol, Nanosponges, FTIR, SEM.

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INTRODUCTION

Nanosponges are novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized cavities. They enhance stability, reduce side effects and modify drug release. The outer surface is typically porous, allowing sustain release of drug. They are mostly use for topical drug delivery. Size range of nanosponge is 50nm-100nm [1]. This technology is being used in cosmetics, over-the-counter skin care, sunscreens and prescribed drugs. Conventional formulation of topical drugs accumulates excessively in epidermis and dermis. Nanosponge prevents the accumulation of active ingredient in dermis and epidermis. Nanosponge system reduce the irritation of effective drug without reduce their efficacy [2].

They can be used for targeting drugs to specific sites, prevent drug and protein degradation. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and began to release the drug in a controlled and predictable manner [3]. It is possible to control the size of nanosponge. To varying the portion of cross-linkers and polymers, the nanosponge particles can be made larger or smaller [4]. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules [5]. Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. Nanosponges are non-irritating, non-mutagenic, nonallergenic and non-toxic [6].

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Nanosponges are tiny mesh-like structures that used for the treatment of many diseases and this technology is five times more effective at delivering drugs for breast cancer than conventional methods. The nanosponges are solid in nature and can be formulated as oral, parenteral, topical or inhalational dosage forms.

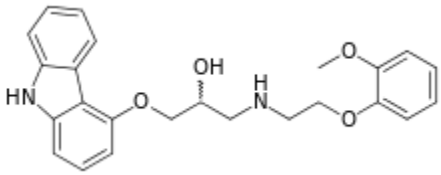
Drug Profile

Carvedilol

Description

Carvedilol is a racemic mixture where the S(-) enantiomer is a beta adrenoceptor blocker and the R(+) enantiomer is both a beta and alpha-1 adrenoceptor blocker. It is currently used to treat heart failure, left ventricular dysfunction, and hypertension. The dual action of carvedilol is advantageous in combination therapies as moderate doses of 2 drugs have a decreased incidence of adverse effects compared to high dose monotherapy in the treatment of moderate hypertension.

Structure



Synonyms: Carvédilol, Carvedilol, Carvedilolum,

Categories: Adrenergic Agents, Antiarrhythmic agents, Antihypertensive Agents, Blockers, Inhibitors

CAS number: 72956-09-3

Weight: Average: 406.4742; **Monoisotopic:** 406.18925733

Chemical Formula: $C_{24}H_{26}N_2O_4$

IUPAC Name: 1-(9H-carbazol-4-yloxy)-3-{[2-(2-methoxyphenoxy)ethyl]amino}propan-2-ol

Pharmacodynamics

Carvedilol reduces tachycardia through beta adrenergic antagonism and lowers blood pressure through alpha-1 adrenergic antagonism. It has a long duration of action as it is generally taken once daily and has a broad therapeutic index as patients generally take 10-80mg daily.

Mechanism of action

Carvedilol inhibits exercise induce tachycardia through its inhibition of beta adrenoceptors. Carvedilol's action on alpha-1 adrenergic receptors relaxes smooth muscle in vasculature, leading to reduced peripheral vascular resistance and an overall reduction in blood pressure. At higher doses, calcium channel blocking and antioxidant activity can also be seen. The antioxidant activity of carvedilol prevents oxidation of low density lipoprotein and its uptake into coronary circulation.

Absorption: Carvedilol has a bioavailability of 25-35%. Carvedilol has a Tmax of 1 to 2 hours. Taking carvedilol with a meal increases Tmax without increasing AUC.

Volume of distribution: Carvedilol has a volume of distribution of 1.5-2L/kg or 115L.

Protein binding: Carvedilol is 98% protein bound in plasma. 95% of carvedilol is bound to serum albumin.

Half life: The half life of carvedilol is between 7-10 hours, though significantly shorter half lives have also been reported.

Excipients Profile

β –Cyclodextrin

Synonyms: β-Cyclodextrin, β-Cycloamylose, β-Dextrin, Cycloheptaamylose; Cycloheptaglucan, Cyclomaltoheptose.

Nonproprietary names: BP: Betadex PhEur: Betadexum USPNF: Betadex

Chemical name and CAS registry number: β-Cyclodextrin [7585-39-9]

Empirical formula and molecular weight: β-Cyclodextrin $C_{42}H_{70}O_{35}$ = 1135

Description: Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

Typical properties

Compressibility: 21.0–44.0% Density (bulk): 0.523 g/cm^3

Density (tapped): 0.754 g/cm^3

Melting point**:** 255–265°C

Solubility: It is soluble 1 in 200 parts of propylene glycol, 1 in 50 parts of water at 20°C, 1 in 20 parts of water at 50°C. It is practically insoluble in acetone, ethanol (95% v/v), and methylene chloride.

Functional category: Solubilizing agent; stabilizing agent.

Incompatibilities: The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of hydroxypropyl-β- cyclodextrin.

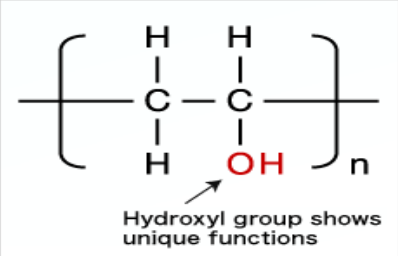
Safety: β- Cyclodextrins are considered to be nontoxic when administered orally.

Polyvinyl alcohol (PVA)

Polyvinyl Alcohol (PVA) is an environmental friendly and water soluble synthetic polymer with excellent film forming property, and emulsifying properties and outstanding resistance to oil, grease, and solvents. It has been extensively used in adhesive, in textile warp sizing and finishing, in paper size and coating, in the manufacturing of PVAc emulsion, in the suspension polymerization of PVC, and as binder for ceramics, foundry cores and various of pigment.

Polyvinyl alcohol (PVOH, PVA, or PVAl) is a water-soluble synthetic polymer. It has the idealized

formula [CH2CH(OH)]n. It is used in papermaking, textiles, and a variety of coatings. It is white (colourless) and odorless. It is sometimes supplied as beads or as solutions in water.



Structure of PVA

Uses: Polyvinyl alcohol is used as an emulsion polymerization aid, as protective colloid, to make polyvinyl acetate dispersions. This is the largest market application in China. In Japan its major use is vinylon fiber production.

HP β-Cyclodextrins

Chemical Names: Hydroxypropyl beta-cyclodextrin; 2-Hydroxypropy-.beta.-cyclodextrin; 2-Hydroxypropylether-b-cyclodextrin; AKOS015901120; AN-13194 More...

Molecular Formula: $C_{54}H_{102}O_{39}$

Molecular Weight: 1375.371 g/mol

General description: Cyclodextrins are cyclic oligosaccharides consisting of 6, 7, or 8 glucopyranose units, usually referred to as α-, β-, or γ-cyclodextrins, respectively. These compounds have rigid doughnut-shaped structures making them natural complexing agents. The unique structures of these compounds owe their stability to intramolecular hydrogen bonding between the C2- and C3-hydroxyl groups of neighboring glucopyranose units.

Dichloromethane

Molecular weight: 84.9
Specific gravity: 1.3255 20°C/4°C
Melting point: –95°C
Boiling point: 39.75°C at 760 mm Hg
Log Kow: 1.25
Water solubility: 13.0 g/L at 25°C
Vapor pressure: 435 mm Hg at 25°C
Vapor density relative to air: 2.93

Dichloromethane is a chlorinated hydrocarbon that has been used as an inhalation anesthetic and acts as a narcotic in high concentrations. Its primary use is as a solvent in manufacturing and food technology. Dichloromethane is used as an extraction solvent in the preparation of decaffeinated coffee, hop extracts and spice oleoresins. Diluent for colour additives and inks for marking fruit and vegetables. The output of these processes is a mixture of methyl chloride, dichloromethane, chloroform, and carbon tetrachloride.

Ethyl Cellulose

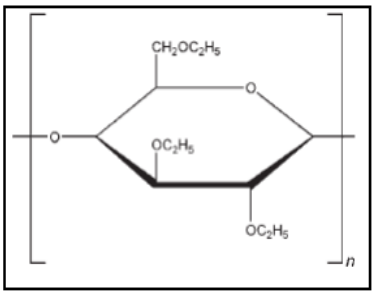
Nonproprietary Names: BP: Ethylcellulose; PhEur: Ethylcellulose; USP-NF: Ethylcellulose

Synonyms: Aquacoat ECD; Aqualon; Ashacel; E462; Ethocel; ethylcellulosum; Surelease.

Chemical name and CAS registry number: Cellulose ethyl ether [9004-57-3]

Empirical formula and molecular weight: Ethylcellulose is partially ethoxylated. Ethylcellulose with complete ethoxyl substitution (DS = 3) is $C_{12}H_{23}O_6(C_{12}H_{22}O_5)nC_{12}H_{23}O_5$ where n can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of banhydroglucose units joined together by acetal linkages.

Structural formula



Functional category: It is used as coating and flavoring agent; tablet binder; tablet filler; viscosity increasing agent.

Applications

Ethylcellulose is widely used in oral and topical pharmaceutical Formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets andgranules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation. Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films.

Related substances: Hydroxyethyl cellulose; hydroxyethylmethyl cellulose; methylcellulose.

Pre-formulation studies

Prior to the development of nanosponge dosage form, it is essential that certain fundamental physical and chemical properties of the drug molecule alone and when combined with excipients are determined. This first learning phase is known as pre-formulation. The overall objective of the pre-formulation is to generate information

useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced.
The goals of pre-formulation studies are:

- To evaluate the drug substance analytically and determine its necessary characteristics, and
- To establish its compatibility with different excipients.

Spectroscopic study
Identification of pure drug
Solubility studies

Solubility of Carvedilol was carried out in different solvents like- distilled 0.1N HCL, 7.4pH buffer and 6.8 pH buffer, and also in organic solvents like Ethanol, Methanol and Dichloromethane. Solubility studies were performed by taking excess amount of drug in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically.

Determination of absorption maximum (λ_{max})

The wavelength at which maximum absorption of radiation takes place is called as λ_{max}. This λ_{max} is characteristic or unique for every substance and useful in identifying the substance. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Most drugs absorb radiation in ultraviolet region (190-390nm), as they are aromatic or contain double bonds.

Accurately weighed 10mg Carvedilol separately was dissolved in 10 ml of methanol in a clean 10ml volumetric flask. The volume was made up to 10ml with the same which will give stock solution-I with concentration 1000µg/ml. From the stock solution-I, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using 6.8pH buffer to obtain stock solution-II with a concentration 100µg/ml. From stock solution-II, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using 6.8pH buffer to get a concentration of 10µg/ml. This solution was then scanned at 200-400nm in UV-Visible double beam spectrophotometer to attain the absorption maximum (λ-max).

Construction of calibration curve using 6.8pH buffer

Accurately weighed 10mg Carvedilol was dissolved in methanol taken in a clean 10ml volumetric flask. The volume was made up to 10ml with 6.8 pH buffer which gives a concentration of 1000µg/ml. From this standard solution, 1ml was pipette out in 10ml volumetric flask and volume was made up to 10ml using 6.8 pH buffer to obtain a concentration of 100µg/ml. From the above stock solution, aliquots of 0.2, 0.4, 0.6, 0.8 , 1.0 and 1.2 ml each was transferred to a separate 10ml volumetric flask and solution was made up to 10ml using 6.8 pH buffer to obtain a concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. The absorbance of each solution was measured at 240nm.

Construction of calibration curve using 0.1N HCL

Accurately weighed 10mg Carvedilol was dissolved in methanol taken in a clean 10ml volumetric flask. The volume was made up to 10ml with 0.1N HCl which gives a concentration of 1000µg/ml. From this standard solution, 1ml was pipette out in 10ml volumetric flask and volume was made up to 10ml using 0.1N HCl to obtain a concentration of 100µg/ml. From the above stock solution, aliquots of 0.2, 0.4, 0.6, 0.8 , 1.0 and 1.2 ml each was transferred to a separate 10ml volumetric flask and solution was made up to 10ml using 0.1N HCl to obtain a concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. The absorbance of each solution was measured at 240nm. Same procedure was repeated by using 6.8pH phosphate buffer.

Drug excipient compatibility study

The drug and excipient compatibility was observed using Fourier Transform – Infra Red spectroscopy (FT-IR). The FT-IR spectra obtained from Bruker FT-IR Germany (Alpha T) was utilized in determining any possible interaction between the pure drug and the excipients in the solid state. The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 4000 to 400cm^{-1}.

Method of Preparation of Nanosponges by solvent Evaporation method

Nanosponges using different proportions of β-cyclodextrin, HP β-cyclodextrin, as rate retarding polymer and co-polymers like polyvinyl alcohol were prepared by solvent evaporation method. Disperse phase consisting of Carvedilol (500mg) and requisite quantity of PVA dissolved in 10 ml solvent (Dichloromethane) was slowly added to a definite amount of PVA in 100ml of aqueous continuous phase, prepared by using magnetic stirrer. The reaction mixture was stirred at 1000 RPM on a magnetic stirrer for 2hours and kept on hot plate upto complete removal of organic solvent from the formulation. The nanosponges formed were collected by filtration through whatman filter paper and dried in oven at 50^{o}C for 2 hours. The dried nanosponges were stored in vaccum desicator to ensure the removal of residual solvent.

Evaluation parameters of Nanosponges

The Nanosponges was evaluated for various parameters:-

Entrapment efficiency
Scanning electron microscopy
Particles size and shape
In-vitro drug release studies
Drug release kinetics studies

Entrapment efficiency

The 10mg of the Carvedilol weight equivalent nanosponge suspension was analyzed by dissolving the sample in 10ml of distilled water. After the drug was dissolved 10ml of clear layer of dissolved drug is taken. Thereafter the amount of drug in the water phase was detected by a UV-Spectrophotometric method at 240nm (U.V Spectrophotometer). The test was repeated with another nanoparticulate sample. The amount of the drug in the suspension was analyzed by centrifugation at 500 RPM for 5 mins and by measuring the concentration of the drug in the clear supernatant layer by the UV-spectrophotometric method. The concentration of the drug is determined with the help of calibration curve. The amount of drug inside the particles was calculated by subtracting the amount of drug in the aqueous phase of the suspension from the total amount of the drug in the nanoparticle suspension. The entrapment efficiency (%) of drug was calculated by the following equation.

$$\% \text{ of Drug entrapment} = \frac{\text{Mass of drug in nanosponge}}{\text{Mass of drug used in formulation}} \times 100$$

Scanning electron microscopy

The morphological features of prepared nanospongess are observed by scanning electron microscopy at different magnifications.

Dissolution study

Dissolution Parameters

Medium : 900ml, 0.1N HCL for 2hrs and 6.8pH buffer for 10hrs.
Apparatus : Basket (USP-I)
RPM : 50
Temperature : 37^{o} C±0.5
Time Points : 1,2, 3,4,5,6,7,8,9,10,11,12, hr

Procedure:

For the oral dosage forms the in vitro dissolution study must be conducted in the dissolution medium which simulate the in-vivo conditions (actual physiological conditions). The in vitro drug release studies for the prepared formulation were conducted for a period of 12 hrs using an Electro lab model dissolution tester USP Type-1 apparatus (rotating basket) set at 50 RPM and a temperature of 37± 0.5°C weight equivalent to 10mg of Carvedilol nanosponge was filled in capsule and kept in basket apparatus and placed in the 900ml of the medium. At specified intervals 5ml samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analyzed at 240nm for the presence of model drug, using a UV-visible spectrophotometer.

Modelling of Dissolution Profile

In the present study, data of the in vitro release were fitted to different equations and kinetic models to explain the release kinetics of Carvedilol from the matrix tablets. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models [7].

Kinetic Studies: Mathematical models

Different release kinetic equations (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) were applied to interpret the release rate of the drug from matrix systems for the optimized formulation. The best fit with higher correlation (r2) was calculated.

Zero-order model

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be representedby the equation

$$\mathbf{Qt = Q0 + K0t}$$

Where Qt is the amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and K0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtainedfrom in vitro drug release studies were plotted as cumulative amount of drug released versustime [8]. Application: It is used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as tablets with low soluble drugs in coated forms, osmotic systems, etc.

First Order Model

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behavior generally follows the following first order equation:

$$\mathbf{Log\ C = Log\ C_o - kt/2.303}$$

Where C is the amount of drug dissolved at time t,
C_o is the amount of drug dissolved at t=0 and
k is the first order rate constant.
A graph of log cumulative of % drug remaining vs time yields a straight line [9].

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drugs in a way that is proportional to the amount of drug remaining in its

interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

The first example of a mathematical model aimed to describe drug release from a system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then sustained to different geometrics and porous systems. This model is based on the hypothesis that

- initial drug concentration in the is much higher than drug solubility;
- drug diffusion takes place only in one dimension (edge effect must be negligible);
- drug particles are much smaller than system thickness;
- swelling and dissolution are negligible;
- drug diffusivity is constant; and
- Perfect sink conditions are always attained in the release environment.

In a general way the Higuchi model is simply expressed by following equation

$$Q = K_H - t^{1/2}$$

Where, K_H is the Higuchi dissolution constant.

The data obtained were plotted as cumulative percentage drug release versus square root of time.

Application: This relationship can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and tablets with water soluble drugs.

Korsmeyer-Peppas model

Korsmeyer et al.(1983) derived a simple relationshipwhich described drug release from a polymeric system equation. To find out the mechanism of drug release, first60% drug release data were fitted in Korsmeyer-Peppas model,

$$Mt / M\infty = Kt^n$$

where Mt / M∞ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices.

Table 1. Formulation table of Carvedilol loaded nanosponges using solvent evaporation method

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Carvedilol (mg)	500	500	500	500	500	500	500	500	500	500	500	500
β-cyclodextrin (mg)	500	1000	1500	2000	--	--	--	--	--	--	--	--
HP-β Cyclodextrin(mg)	--	--	--	--	500	1000	1500	2000	--	--	--	--
Ethyl Cellulose(mg)	--	--	--	--	--	--	--	--	500	1000	1500	2000
PVA (gm)	2	2	2	2	2	2	2	2	2	2	2	2
Dichloromethane	10	10	10	10	10	10	10	10	10	10	10	10
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 2. Drug transport mechanisms suggested based on 'n' value.

S. No	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	$t^{-0.5}$
2	0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
3	0.89	Case II transport	Zero order release
4	Higher than 0.89	Super case II transport	t^{n-1}

RESULTS & DISCUSSIONS

Table 3. Solubility Studies of Carvedilol

Buffer	Solubility (mg/ml)
0.1 N HCL	6.95
6.8 pH buffer	5.04
7.4pH buffer	5.92
Ethanol	26.54
Methanol	34.05
dichloromethane	56.94

T**able 4. Calibration curve data of Carvedilol in 0.1N HCL**

Concentration(µg/ml)	Absorbance
0	0
2	0.116

4	0.219
6	0.337
8	0.439
10	0.537
12	0.647

Table 5. Calibration curve of Carvedilol in 6.8 pH buffer

Concentration(µg/ml)	Absorbance
0	0
2	0.106
4	0.188
6	0.276
8	0.361
10	0.446
12	0.539

Table 6. Entrapment Efficiency F1-F12

Formulation code	% Entrapment Efficiency
F1	93.56
F2	86.59
F3	99.52
F4	101.26
F5	100.64
F6	93.76
F7	95.46
F8	95.61
F9	95.02
F10	97.06
F11	98.64
F12	97.16

Table 7. Percentage of drug release of Nanosponges (F1-F8)

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	28.65	27.64	18.02	12.42	26.45	20.59	16.52	10.36
2	46.21	45.2	28.76	17.26	29.76	29.36	29.52	16.52
3	68.28	58.34	37.02	20.94	37.46	39.16	35.96	21.94
4	76.25	66.15	44.72	27.64	52.65	49.79	44.53	36.49
5	88.94	72.42	51.14	34.33	64.21	50.95	56.28	46.24
6	98.61	80.94	60.63	42.02	78.28	62.59	57.83	50.64
7		89.26	69.4	49.71	86.25	72.36	65.06	57.64
8		95.12	75.42	57.40	92.51	85.19	68.03	60.09
9			82.14	65.09		95.36	76.46	65.34
10			86.46	72.78			86.94	70.64
11			97.22	80.47			96.24	76.49
12				85.64				80.36

Table 8. Percentage of drug release of Nanosponges (F9-F12)

Time	F9	F10	F11	F12
0	0	0	0	0
1	20.49	17.84	16.59	15.64
2	27.49	25.63	22.64	19.46

3	36.45	39.42	29.63	23.49
4	42.79	48.22	36.49	29.75
5	50.64	57.24	49.25	33.46
6	60.63	62.84	56.19	41.52
7	70.16	70.16	62.45	46.19
8	79.27	77.24	72.61	53.61
9	84.36	82.28	79.35	59.42
10	95.24	90.52	88.24	62.79
11		99.64	91.52	72.69
12			97.24	82.64

Table 9. Regression values

Formulation Code	Zero order	First order	Higuchi	Peppas	Peppas
	R^2	R^2	R^2	R^2	n
F12	0.991	0.873	0.950	0.741	1.228

Fig. 1. Solubility Studies of Carvedilol

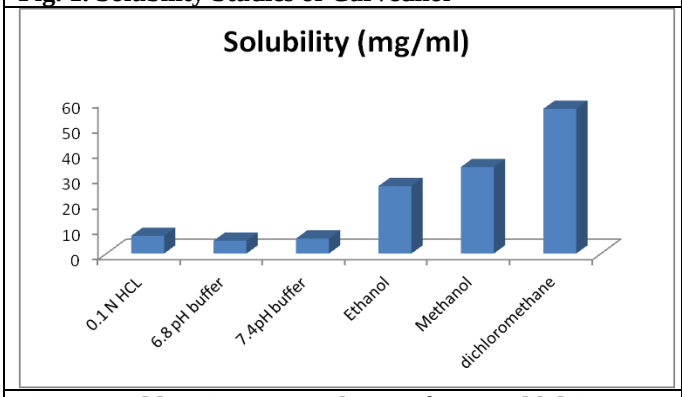


Fig. 2. λ-max in 6.8 phosphate buffer

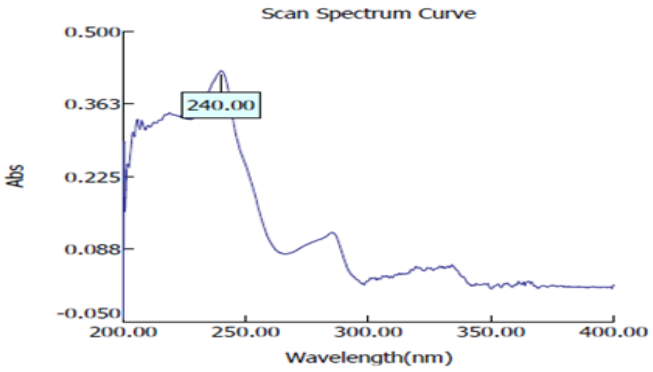


Fig. 3. Calibration curve data of Carvedilol in 0.1N HCL

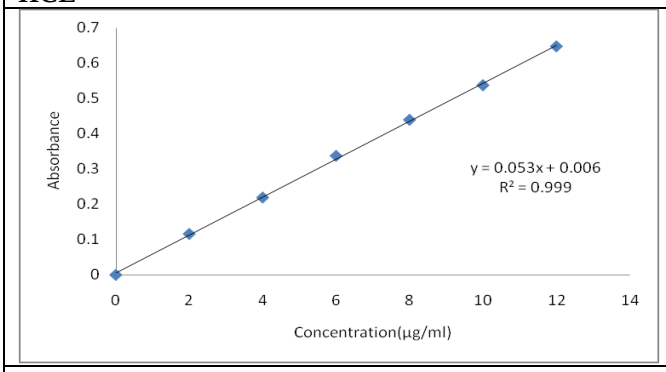


Fig. 4. Calibration curve of Carvedilol in 6.8 pH buffer

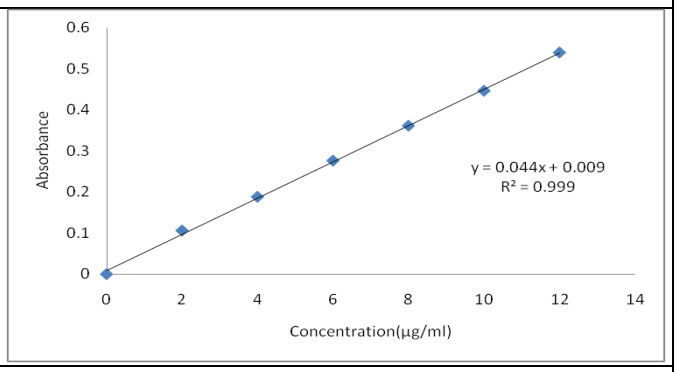


Fig. 5. Percentage of drug release graph F1-F12

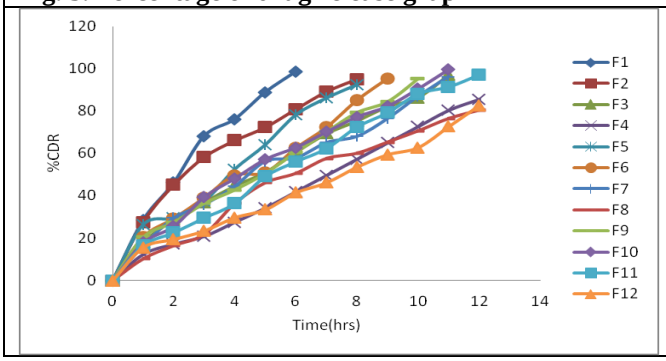


Fig. 6. Percentage of drug release graph F1-F4

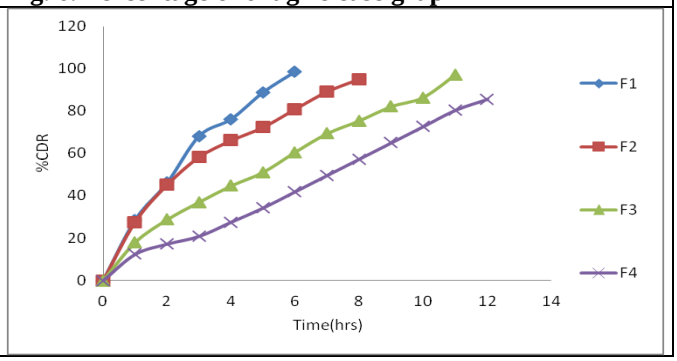


Fig. 7. FTIR Spectra of Pure Drug

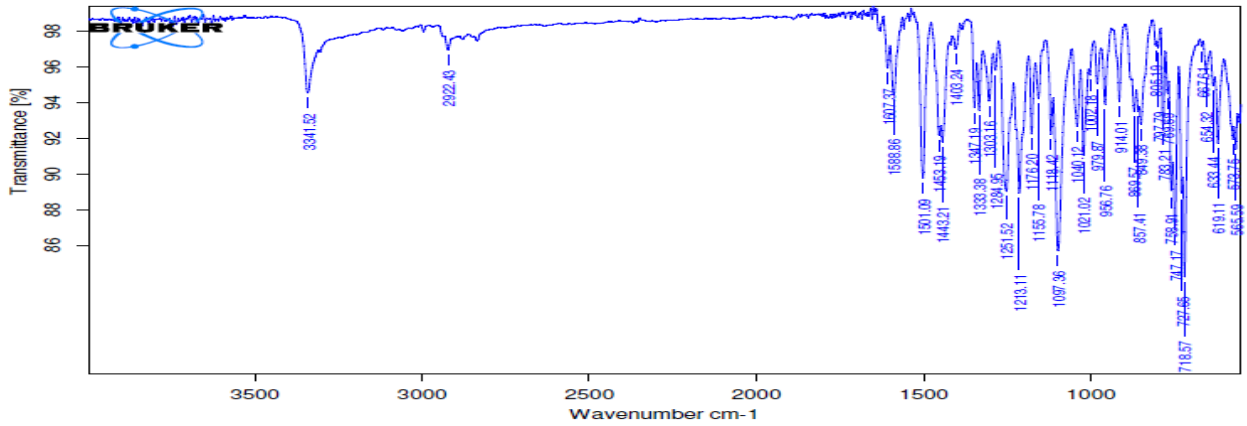


Fig. 8. FTIR Spectra of Optimized Formulaton

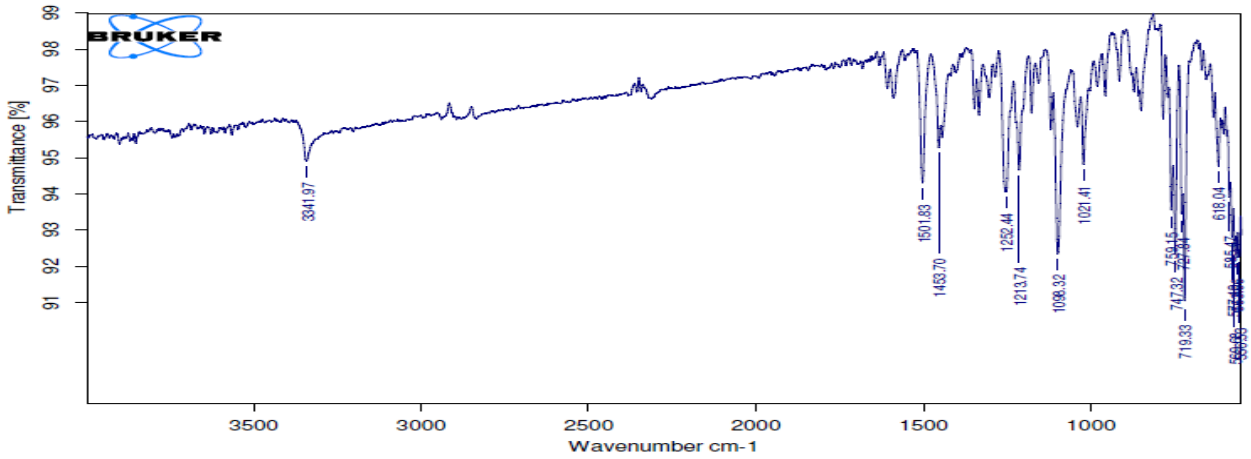
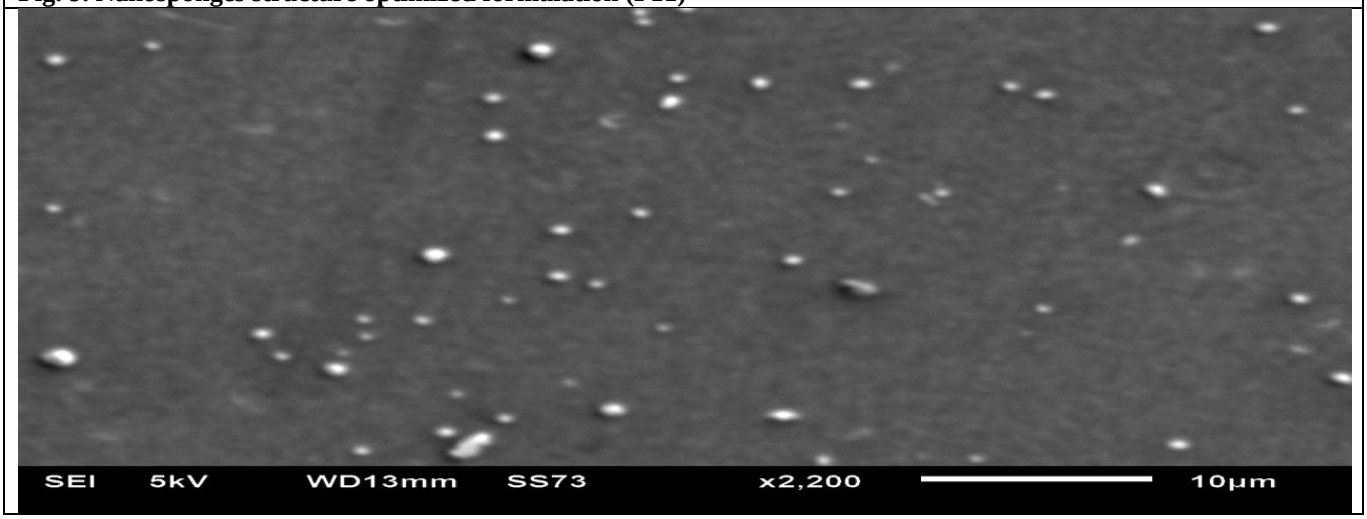


Fig. 9. Nanosponges structure optimized formulation (F11)



Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of Pure drug with that of various excipients used in the formulation.

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption peaks of drug and excipients

were obtained as shown above and as they were in official limits (±100 cm^{-1}) the drug is compatible with excipients.

Determination of absorption maximum (λmax)

Determination of Carvedilol λ-max was done in 6.8 pH phosphate buffer for accurate quantitative assessment of drug dissolution rate.

The linearity was found to be in the range of 2-12µg/ml in 0.1N HCL and 6.8 phosphate buffer. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

A) Particle size analysis of Nanosponges

The particle size of the nanosponge was determined by optical microscopy and the nanosponges were found to be uniform in size. The average particle size of all formulations ranges from 316.4 nm to 454.8 nm which is in increasing order due to the increase in the concentration of polymer but after certain concentration it was observed that as the ratio of drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high drug to polymer ratio, the amount of polymer available per nanosponge was comparatively less. Probably in high drug-polymer ratios less polymer amounts surround the drug and reducing the thickness of polymer wall and nanosponges with smaller size were obtained. By performing the particle size analysis, it is concluded that the formulation has the particle size varies with the concentration of polymer drug ratio.

B) Morphology determination by scanning electron microscopy (SEM):

Scanning electron microscopy (SEM) was used to determine the Morphology of the prepared nanosponges. SEM is useful for characterizing the morphology and size of microscopic specimens with particle size as low as 10 -10 to 10 -12 grams. The sample was placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. Interaction of the electron beam with the specimen produces a variety of physical phenomena that, when detected, are used to form images and provide elemental information about the specimens.

The morphology of the nanosponges prepared by emulsion solvent evaporation method were investigated by SEM. The representative SEM photographs of the nanosponges are shown in Fig.6.7. It was observed that the nanosponges were spherical, and uniform with no drug crystals on the surface. The shape of the nanosponges affects the surface area and surface area per unit weight of spherical nanosponges. The irregular shape of the particles may affect dissolution rate present in dissolution environment.The spongy and porous nature of the nanosponges can be seen in figures.

Entrapment efficiency

It is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production. After the preparation of formulations the Practical yield was calculated as Nanosponges recovered from each preparation in relation to the sum of starting material (Theoretical yield). It can be calculated using following formula.

$$\text{Entrapment efficiency} = \frac{\text{Practical yield}}{\text{Theoretical yield (drug + polymer)}} \times 100$$

The entrapment efficiency of formulation F1-F12 was found to be in the range of 86.59 to 101.26%.

***In vitro* dissolution studies of prepared nanosponges**

In vitro release studies were performed in triplicate using USP basket method at 50 rpm and 37±0.2°C in 900ml of 0.1N HCl for 2hrs and remaining hours in phosphate buffer (pH 6.8). 10 mg of the formulated nanosponges is used for each experiment. Samples were taken at appropriate time intervals for 1,2,3,4,5,6,7,8,9,10,11, & 12 hour. The samples were measured spectrophotometrically at 240nm. Fresh dissolution medium was replenished each time when sample is withdrawn to compensate the volume.

From the *in vitro* dissolution studies it was observed that the formulations containing β cyclodextrin with PVA using solvent evaporation method with drug in (1:1, 1:2, 1:3, 1:4). F1 Formulations shows maximum drug release of 98.61% at the end of 6th hour. Whereas F2 formulation shows maximum drug release of 95.12% at the end of 8hr. while F3 formulation shows maximum drug release of 97.22% at the end of 11hr and F4 formulation shows maximum drug release of 85.64% at the end of 12hrs. It was observed that the formulations containing HP-β cyclodextrin with PVA using solvent evaporation method with drug in (1:1, 1:2, 1:3, 1:4). F5 Formulations shows maximum drug release of 92.51% at the end of 8 hour. Whereas F6 formulation shows maximum drug release of 95.36% at the end of 9hr. while F7 formulation shows maximum drug release of 96.24% at the end of 11hr and F8 formulation shows maximum drug release of 80.36% at the end of 12hrs. The formulations containing Ethyl cellulose with PVA using solvent evaporation method with drug in (1:1, 1:2, 1:3, 1:4). F9 Formulations shows maximum drug release of 95.24% at the end of 10 hour. Whereas F10 formulation shows maximum drug release of 99.645% at the end of 11hr. while F11 formulation shows maximum drug release of 97.24% at the end of 12hr and F12 formulation shows maximum drug release of 82.64% at the end of 12hrs. By comparing the above dissolution studies of formulations F1-F12. Maximum drug release (97.24%)

was found in F11 formulation containing Drug: Ethyl cellulose in 1:3 ratio. So F11 formulation was taken as the optimized formulation, and drug release kinetics were performed for F11 formulation.

The optimized formulation F11 has coefficient of determination (R^2) values of 0.991, 0.873, 0.950, 0.741 for Zero order, First order, Higuchi, Korsmeyer Peppas respectively. A good linearity was observed with the Zero order, the slope of the regression line from the Higuchi plot indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the Korsmeyer Peppas equation which showed linearity with n value of 1.228 for optimized formulation. Thus n value indicates the supercase II transport mechanism.

CONCLUSSION

The Nanosponge was prepared by solvent evaporation method using ethyl cellulose, βcyclodextrin and HP- β cyclodextrin, as rate retarding polymers, PVA and dichloromethane as crosslinking agents. The prepared nanosponges were evaluated for its different parameters which revealed many interesting results for efficient preparation of the nanosponge. FTIR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in these nanosponge. SEM photographs revealed the spherical nature of the nanosponge in all variations. With the revealed results by different evaluation parameters, it is concluded that nanosponge drug delivery system has become highly competitive and rapidly evolving technology and more and more research are carrying out to optimize cost-effectiveness and efficacy of the therapy. The formulation F11 has better results than other 11 formulations. F11 have its particle size 350nm, entrapment efficiency 98.64%, drug release 97.24 % in 12 hour, The optimized formulation F11 has coefficient of determination (R^2) values of 0.991, 0.873, 0.950, 0.741 for Zero order, First order, Higuchi, Korsmeyer Peppas respectively. A good linearity was observed with the Zero order, the slope of the regression line from the Higuchi plot indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the Korsmeyer Peppas equation which showed linearity with n value of 1.228 for optimized formulation. Thus n value indicates the supercase II transport mechanism.

REFERENCES

1. Sharma R, Roderick B and Pathak K. (2011). Evaluation of kinetics and mechanism of drug release from Econazole nitrate Nanosponges loaded carbopol Hydrogel. *Indian J. of Pharma Edu and research*, 45(1), 25-31.
2. Rana Z, Gunjan, Patil and Zahid Z. (2012). Nanosponge – a completely new nano- horizon: pharmaceutical applications and recent advances. *Drug Dev Ind Pharm*, PMID 22681585.
3. Zuruzi S, MacDonald NC, Moskovits M, Kolmakov A. (2007). Metal oxide nanosponges as chemical sensors: Highly sensitive detection of hydrogen using nanosponge titania. *Angewandte Chemie International Edition*, 46(23), 4298-4301.
4. Nacht S, Kantz M. (1992). The Microsponge: A Novel Topical Programmable Delivery System, In: Topical Drug Delivery Systems. David WO, Anfon H A editors. New York: Marcel Dekker, 42, 299-325.
5. Kilicarslan M and Baykara T. (2003). The effect of the drug/polymer ratio on the properties of Verapamil HCl loaded microspheres. *Int J Pharm*., 252, 99-109.
6. Meena KP, Dang JS, Samal PK, Namedo KP. (2011). Recent advances in microsphere manufacturing technology. *International Journal of Pharmacy and Technology*, 2011, 3(1), 854-855.
7. Mishra MK, Shikhri M, Sharma R, Goojar MP. (2011). Optimization, formulation, development and characterization of Eudragit RS 100 loaded microsponges and subsequent colonic delivery. *Int J of Drug Discovery And herbal Research*, 1(1), 8-13.
8. Ramnik S, Nitin B, Jyotsana M, Horemat S. (2010). Characterization of Cyclodextrin Inclusion complexes –A Review. *J Pharm Sci Tech*, 2(3), 171-183.
9. Rao MR, Bajaj AN, Pardeshi AA, Aghav SS. (2012). Investigation of Nanoporous colloidal carrier for solubility enhancement of Cefpodoxime proxetil. *Journal of pharmacy research*, 5(5), 2496-2499.

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