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DESIGN AND PREPARE AND CHARECTERIZATION OF THE RAMIPRIL LOADED SOLID LIPID NANO PARTICLES

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Abstract:

The aim of the study was Design and prepare and characterization of the ramipril loaded solid lipid nano particles. Structure and plan and portrayal of the ramipril stacked strong lipid nano particles The chitosan is utilized as polymer. The nano particles is planned by applying by nano precipitation technique. After definition improvement the assessment boundaries played out totally went under the scope of limits. The medication discharge the advanced detailing F8 was seen as 99.76%.The motor profile performed for streamlined plan they follow the zero request and higuchi condition. The security reads did for 90 days there is no corruption in streamlined definition in tranquilize delivery and medication content examinations.

Keywords: *Design, Charecterization, Ramipril, Solid Lipid Nano Particles*

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INTRODUCTION:

In the recent years, with the advent of Nanomedicine, engineered tunable devices with the size in the order of billions of meters have been proposed as an intriguing tool potentially able to solve the unmet problem of enhancing drug transport across the BBB [1]. Amongst different devices, nanoparticles (NPs) technology is rapidly advancing. Nanotechnology refers to structures with a size range of 1–100 nm in at least one dimension [2]. Nanotechnology is the application of science and technology to control matter at the molecular level. At the nanoscale level, the properties of matter are significantly different from their macroscopic bulk properties [3]. Nanotechnology also refers to the ability for designing, characterization, production and application of structures, devices and systems by controlling shape and size at the nanometer scale. One area where nanotechnology has the potential to make a significant impact is drug [4]. This impact has already been felt with the translation of several nanoscale drug delivery systems into the clinic, although the full potential of these systems is only starting to be explored. Nanoscale drug delivery vehicles have shown the ability to encapsulate a variety of therapeutic agents such as small molecules (hydrophilic and/or hydrophobic), peptides, protein-based drugs, and nucleic acids [5]. Because of their unique size range, nanoparticles exhibit "enhanced permeability and retention effect" (EPR) which confirm their potential in specific targeting so as to maximize the therapeutic effects and minimize the undesirable effects [6]. Amongst various nanoparticles, solid lipid nanoparticles (SLNs), introduced in 1991 represent an alternative carrier system to traditional colloidal carriers, such as emulsions, liposomes and polymeric nanoparticles [7]. SLNs are small sized lipid nanoparticles composed of biocompatible and biodegradable solid lipids. Their matrix is composed of physiological lipids which reduce the danger of acute and chronic toxicity [8]. Irrespective of their small size (10-1000nm), they offer a high drug loading capacity, larger surface area and thus enhanced bioavailability. These characteristics make SLNs an interesting drug delivery system [9].

Ramipril is an ACE inhibitor used for the management of hypertension and the reduction of cardiovascular mortality following myocardial infarction in hemodynamically stable patients with clinical signs of congestive heart failure.

Ramipril inhibits the RAAS system by binding to and inhibiting ACE thereby preventing the conversion of angiotensin I to angiotensin II. 5 As plasma levels of angiotensin II fall, less activation of the G-protein coupled receptors angiotensin receptor I (AT1R) and angiotensin receptor II (AT2R) occurs. AT1R mediates vasoconstriction, inflammation, fibrosis, and oxidative stress through a variety of signaling pathways. [10] These include Gq coupling to the inositol triphosphate pathway, activation of phospholipases C, A2, and D which contribute to eicosanoid production, activation of Ca2+-dependent and MAP kinases, Gi and G12/13, and eventual activation of the Jak/STAT pathway leading to cell growth and production of extracellular matrix components. AT1R activation also leads to increased activity of membrane-bound NADH/NADPH oxidase which contributes to production of reactive oxygen species. Decreased activation of this receptor mediates the renoprotective, antihypertensive, and cardioprotective effects of ramipril by reducing inflammation and vasoconstriction.

The aim of the study was Design and prepare and characterization of the ramipril loaded solid lipid nano particles.

MATERIALS:

Ramipril Purchased from Sun pharma. Chitosan and chloroform from Colorcon Asia Pvt. Ltd.

METHODOLOGY:

Preformulation studies:

Organoleptic characters: It is one of the important prerequisite in development of any drug delivery system. Pre-formulation studies were performed on the drug, which included organoleptic characters, determination, solubility and compatibility studies

Solubility: solubility of the Ramipril was determined in water, acetone, methanol, practically insoluble in ethanol (95%), chloroform and ether.

Compatibility Studies: Compatibility with excipients was conformed by carried out I R studies. The pure drug and polymer formulations along with excipients were subjected to IR studies

Preparation of Standard Calibration Curve of Ramipril:

METHOD:

10mg Ramipril was precisely gauged and moved into 10ml volumetric carafe. It was broken down and weakened to volume with CH3)2CO to give stock arrangement containing 1000µg/ml The standard stock arrangement was then sequentially taken 1ml of arrangement from first stock arrangement weakened with CH3)2CO to get 1 to 100µg/ml or auxiliary stock arrangement. From optional stock arrangement take 1ml of the answer for get 10µg/ml or tertiary stock arrangement. The absorbances of the

arrangement were estimated against CH3)2CO as clear at 210 nm utilizing UV spectrophotometer. The absorbance esteems were plotted against fixation (µg/ml) to acquire the standard adjustment bend.

Arrangement of Nanoparticles of Ramipril by Nanoprecipitation Method.

Nanoparticles containing Ramipril were readied utilizing nanoprecipitation technique. Nanoparticles were set up by utilizing distinctive medication to polymer proportion. Medication was broken up in 3 ml of refined water, at that point cosolvent (CH3)2CO 1 mL) was included into this arrangement. A cosolvent was required so as to make the inward stage more homogeneous. At that point polymer were broken up in 4 ml of chloroform, and this arrangement was added to the medication answer for structure scattering. The scattering was added to 10 ml of fluid ethanol arrangement (70%). Following 5 minutes of blending, the natural solvents were expelled by vanishing at 35°C under ordinary tension, nanoparticles were isolated by utilizing cooling axis (10000 rpm for 20 min), supernatant were evacuated and nanoparticles washed with water and dried at room temperature in a desicator. The different groups of nanoparticles were set up as follows

Formulation of the nanoparticles prepared:
Table 1:

S.no	Formulation code	Drug (mg) Ramipril	chloroform	acetone	Polymer (mg) Chitosan
1.	FN1	100	4ml	1ml	50
2.	FN2	100	4ml	1ml	50
3.	FN3	100	4ml	1ml	50
4.	FN4	100	4ml	1ml	50
5.	FN5	100	4ml	1ml	50
6.	FN6	100	4ml	1ml	100
7.	FN7	100	4ml	1ml	150
8.	FN8	100	4ml	1ml	200
9.	FN9	100	4ml	1ml	250

EVALUATION OF NANOPARTICLES:

Particle Size Analysis and Surface Morphology:
Particle size of nanoparticles is very important characteristic. The surface morphology (roundness, smoothness, and formation of aggregates) and the size distribution of nanoparticles were studied by scanning electron microscopy (SEM).

Percentage Yield
The percentage yield of different formulations was determined by weighing the nanoparticles after drying. The percentage yield was calculated as follows Each determination was made in triplicate.

Percentage yield = Total weight of nanoparticles × 100
Total weight of drug & polymer

Drug Entrapment Efficiency
The various formulations of the nanoparticles were subjected for drug content. 50 mg of nanoparticle from all batches were accurately weighted Dissolve the sample in 5 mL of chloroform. 20 mL of phosphate buffer 6.8 was added and the mixture was mixed carefully in a separation funnel. Thereafter, after appropriate dilution the amount of drug in the aqueous phase was detected by a UV-spectrophotometric method at 210 nm . The test was repeated with another nanoparticulate sample The entrapment efficiency (%) of drug was calculated by the following equation: Each determination was made in triplicate.

Entrapement Efficacy = Mass of drug in nanoparticles × 100
Mass of drug in formulation

***In-vitro* Drug Release Studies** : In-vitro dissolution studies carried out by using A modified Franz diffusion cell was used for Ramipril nano particles. The dissolution medium is 6.8 ph phosphate buffer. In franz diffusion cell the medium was poured about 10ml the semipermeable membrane kept around the franz diffusion cell. The dissolution studies kept for 9 hours. The time intervels mainted for 1hr.The 1ml of aloquote was withdrawn and same amount of sample replaced in diffusion cell. The withdrawn aliquote was diluted with 6.8 ph phosphate buffer .The absorbance anlaysed under U.V visible spectroscopy at the 210nm.

Kinetic modeling:
In order to understand the kinetic and mechanism of drug release, the result of *in vitro* drug release study of nanoparticles were fitted with various kinetic equation like zero order (equation 1) as cumulative % release vs. time, Higuchi's model (equation 2) as cumulative % drug release vs. square root of time. r2 and k values were calculated for the linear curve obtained by regression analysis of the above plots.
C = k0t …….. (1)
Where k0 is the zero order rate constant expressed in units of concentration / time and
t is time in hours.
Q = kHt1/2 …….. (2)
Where kH is higuchi's square root of time kinetic drug release constant.
To understand the release mechanism *in-vitro* data was analyzed by peppas model (equation 3) as log cumulative drug release vs. log time and the exponent n was calculated through the slope of the straight line.

Mt / M∞ = btn
Where Mt is amount of drug release at time t, M∞ is the overall amount of the drug, b is constant, and n is the release exponent indicative of the drug release mechanism. If the exponent n = 0.5 or near, then the drug release mechanism is Fickian diffusion, and if n have value near 1.0 then it is non-Fickian diffusion.

Stability Study:
From the prepared nanoparticles formulation FN8 which showed appropriate balance between the buoyancy and percentage release was selected for stability studies. The prepared nanoparticles were placed in borosilicate screw capped glass containers and stored in refrigeration (5-80C), room temperature (27+20C), and in oven temperature (40+20C) for a period of 3 months. The samples were assayed for drug content at regular intervals of two week.

$$\textbf{Amount of drug remain (\%)} = \frac{\textbf{Amount drug recovered}}{\textbf{Amount drug used for test}} \times 100$$

RESULTS:

Preformulation parameters

Table 2: Micromeritic properties of Active Pharmaceutical Ingredient

S.NO	API CHARACTERISATION	RESULTS
1	PHYSICAL APPEARANCE	A WHITE, CRYSTALLINE POWDER
2	MELTING POINT	256-257°C
3	COLOR	WHITE
4	ODOR	ODORLESS
5	TASTE	TASTELESS

Conclusion: based on the above pre-formulation results it was observed that the flow is good.

Solubility Profile

Table 3: Solubility studies

Solvent	Solubility properties of drug (1gm)
Ethanol	Soluble
DMSO	Soluble
Methanol	Soluble
Water	Sparingly soluble

Discussion: Ramipril was found to be sparingly soluble in water , soluble in methanol and freely soluble in ethanol.

Fourier Transformation Infra-red (FTIR) analysis

Calibration curve in Ethanol

Table 4: Calibration curve values of the in Ethanol

S.NO	Concentration (µg/ml)	Absorbance(nm)
1	0	0
2	10	0.18
3	20	0.35
4	30	0.51
5	40	0.69
6	50	0.89

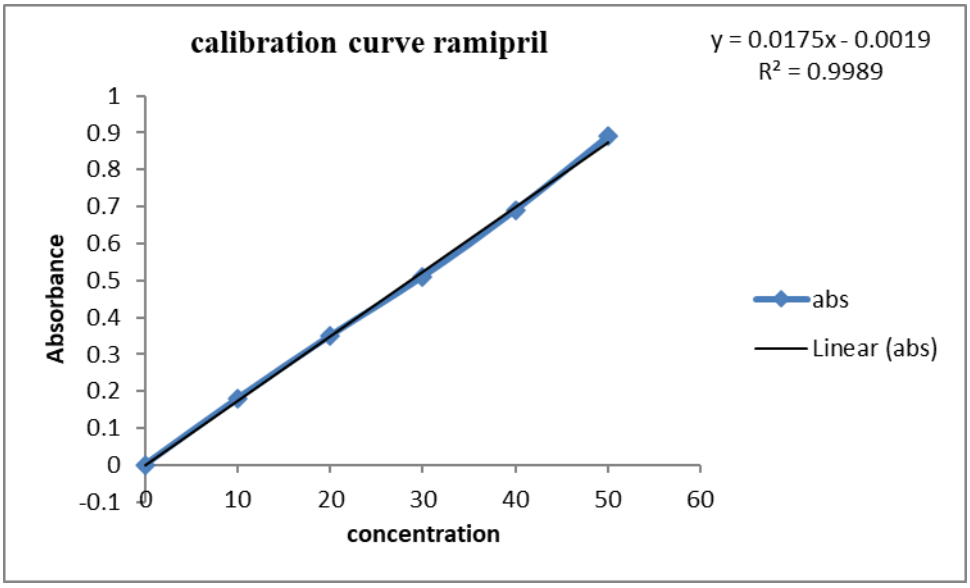

Fig 1: Calibration curve in ethanol

Table 5: Standard graph of Ramipril in DMSO

S. no.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.130
3	4	0.250
4	6	0.380
5	8	0.510
6	10	0.640

Figure 6: Standard graph of ramipril

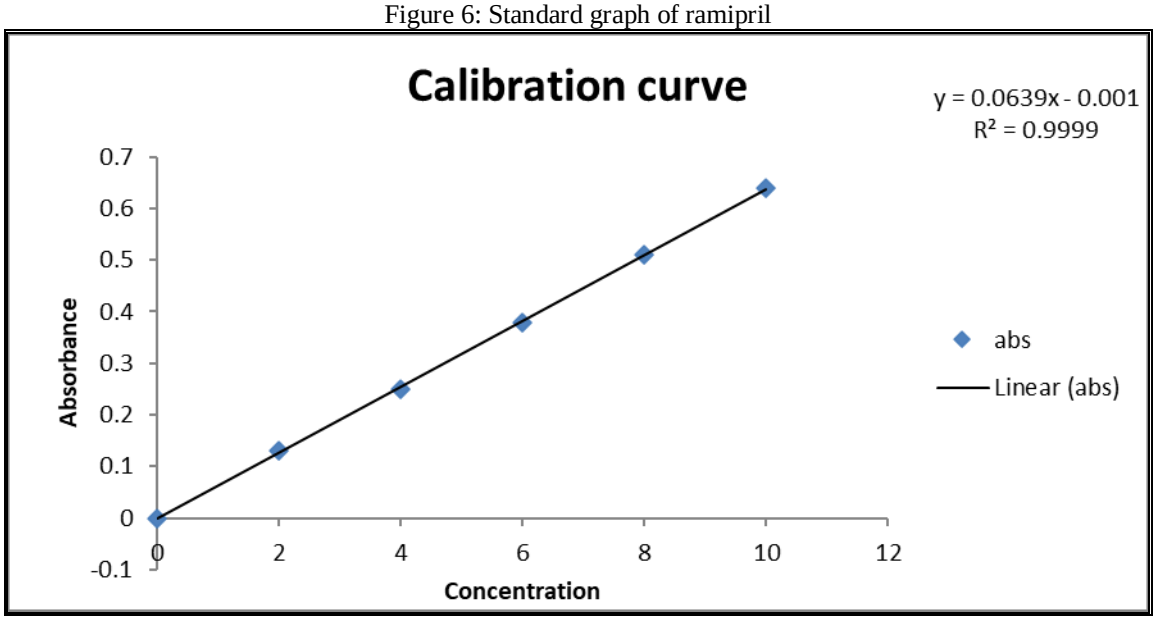

Fig 2: picture showing calibration curve in DMSO

FTIR Studies

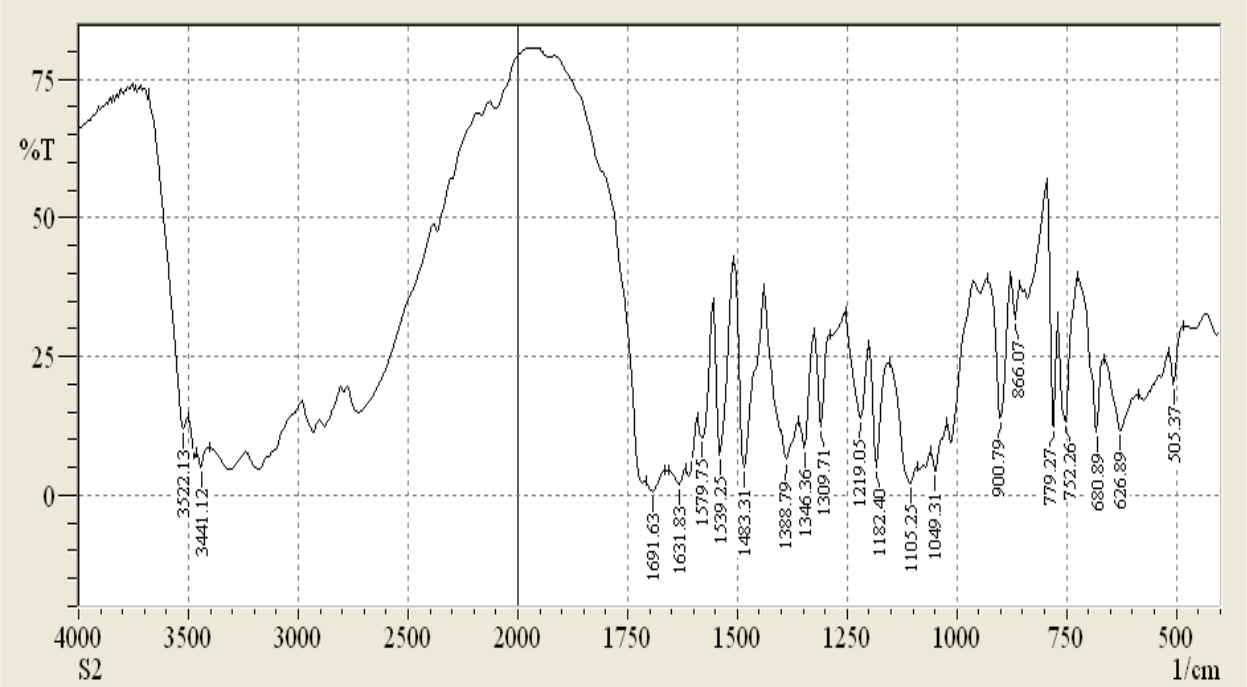

Fig 3: FTIR for drug

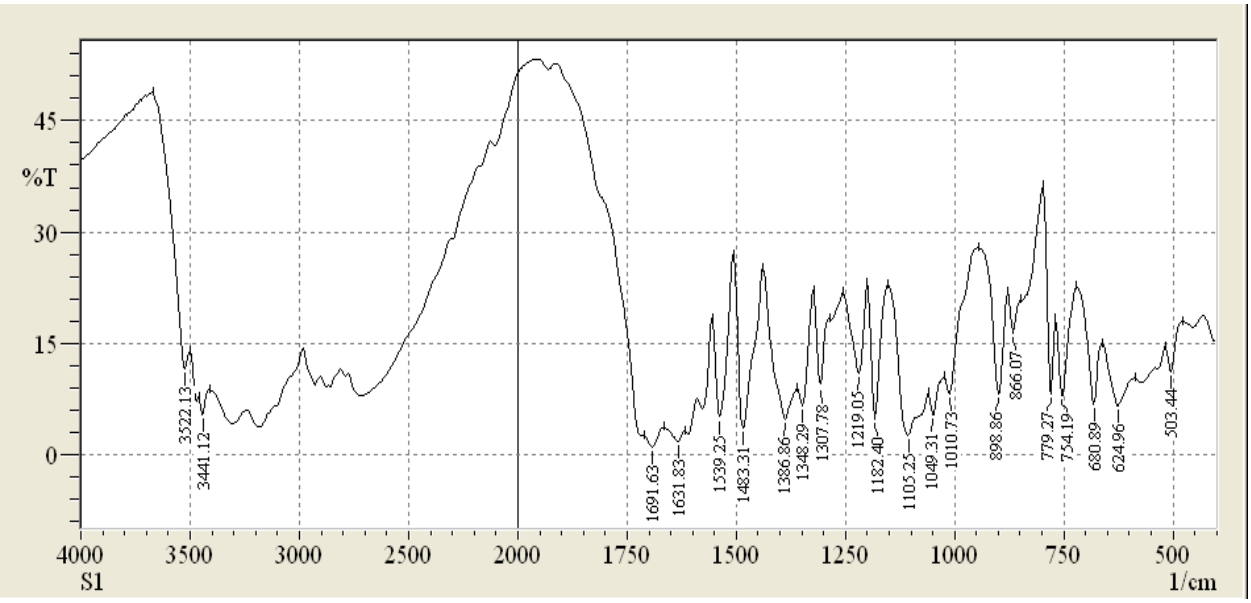

Fig 4: FTIR for drug and polymer

Discussion:

Similarity contemplates were performed utilizing FTIR spectrophotometer. The FTIR range of Pure medication and physical blend of medication and polymers were examined. The trademark ingestion tops were seen at 1691.57cm-1,1632.98 cm-1, cm-1,779cm-1,1010cm-1for the unadulterated ramipril and assimilation tops were seen at 1689.650 cm-1,1630cm-1,776 cm-1 ,1000 cm-1,680 cm-1 for medication and polymer blend show that how they were in authentic cutoff points (±100 cm-1) the medication is good with excepients.

SEM studies

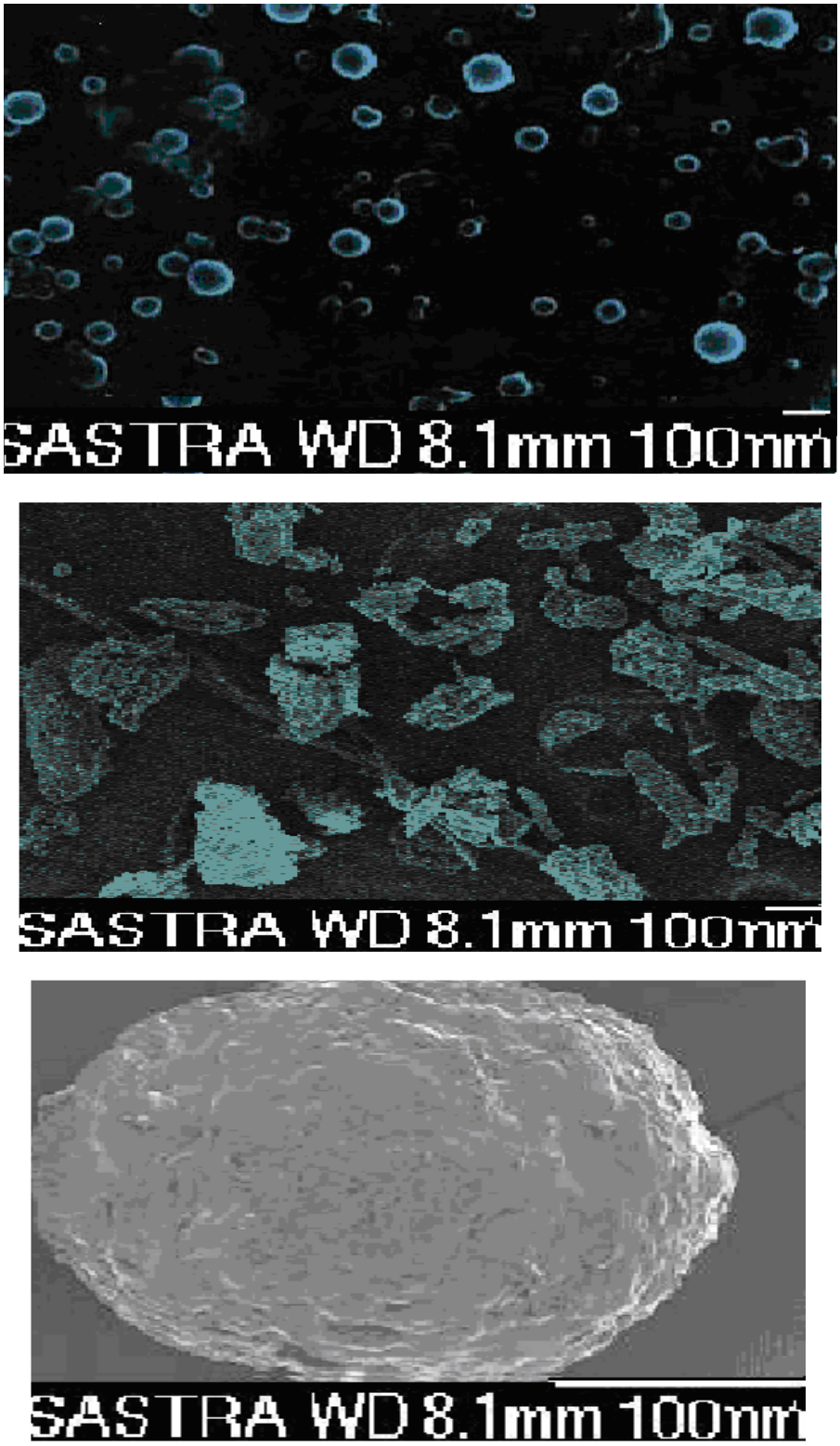

Fig 5: SEM studies

Table 7: Percentage Yield of Different Formulation of Nanoparticles

S.NO	Formulation code	Percentage yield
1	RN1	54.29 + 0.02
2	RN2	53.81 + 0.04
3	RN3	53.09 + 0.05
4	RN4	52.32 + 0.02
5	RN5	51.8 + 0.03
6	RN6	54.92 + 0.04
7	RN7	56.71 + 0.05
8	RN 8	69.13 + 0.04
9	RN9	61.42 + 0.02

Table 8: Entrapment Efficiency of Different Formulations of Nanoparticles

S.NO	Formulation code	Entrapement efficacy
1	RN1	48.32 + 0.02
2	RN2	39.18 + 0.03
3	RN3	23.39 + 0.05
4	RN4	19.09 + 0.05
5	RN5	15.92 + 0.06
6	RN6	56.43 + 0.03
7	RN7	64.13 + 0.08
8	RN 8	82.83 + 0.03
9	RN9	74.62 + 0.02

In vitro drug release studies of all formulations F1-F9

Table 9: showing table *In-vitro* drug release values of the Ramipril

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	10.52	15.22	18.5	19.65	18.65	15.82	16.11	16.2	15.86
2	39.53	24.53	22.65	26.44	29.65	30.56	32.45	31.56	38.75
3	59.6	34.40	37.65	38.67	41.65	47.78	50.42	53.43	49.85
4	74.5	56.52	48.90	44.90	49.67	55.54	63.12	58.60	66.22
5	79.6	76.75	58.75	58.12	64.16	69.80	72.18	67.27	75.65
6	90.56	85.52	66.89	63.20	71.71	74.60	88.78	77.28	89.83
7	99.67	105.85	79.45	74.40	79.76	85.78	91.12	89.98	89.85
8	-	-	81.86	87.65	90.54	92.87	96.34	99.76	95.87

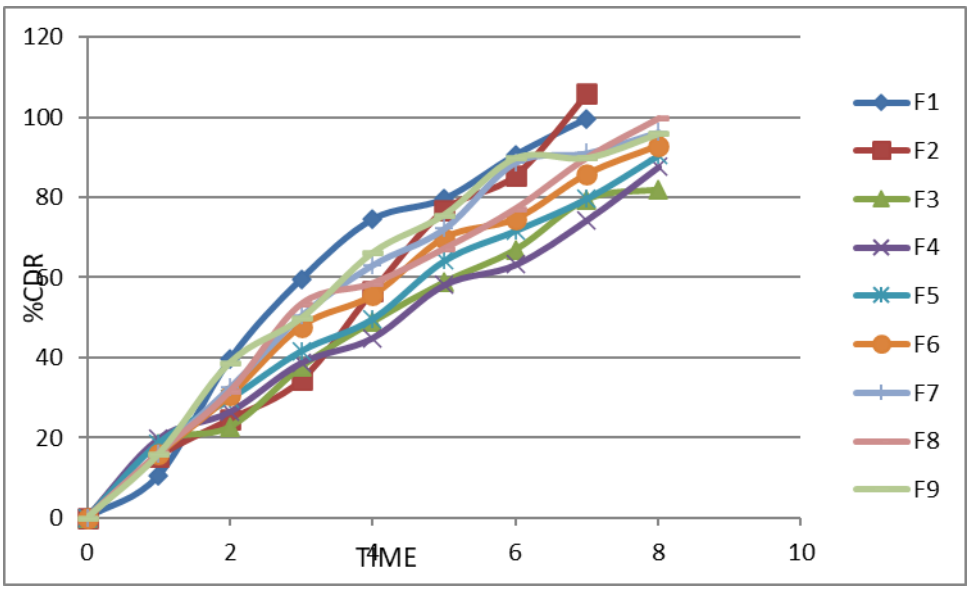

Fig 6: In vitro drug release studies of all formulations Graph F1-F9

Comparative drug release profile of graph F1-F3

Table 10: Comparative *In-vitro* values of the Ramipril nano particles F1-F3

Time	F1	F2	F3
0	0	0	0
1	10.52	15.22	18.5
2	39.53	24.53	22.65
3	59.6	34.40	37.65
4	74.5	56.52	48.90
5	79.6	76.75	58.75
6	90.56	85.52	66.89
7	99.67	105.85	79.45
8	-	-	81.86

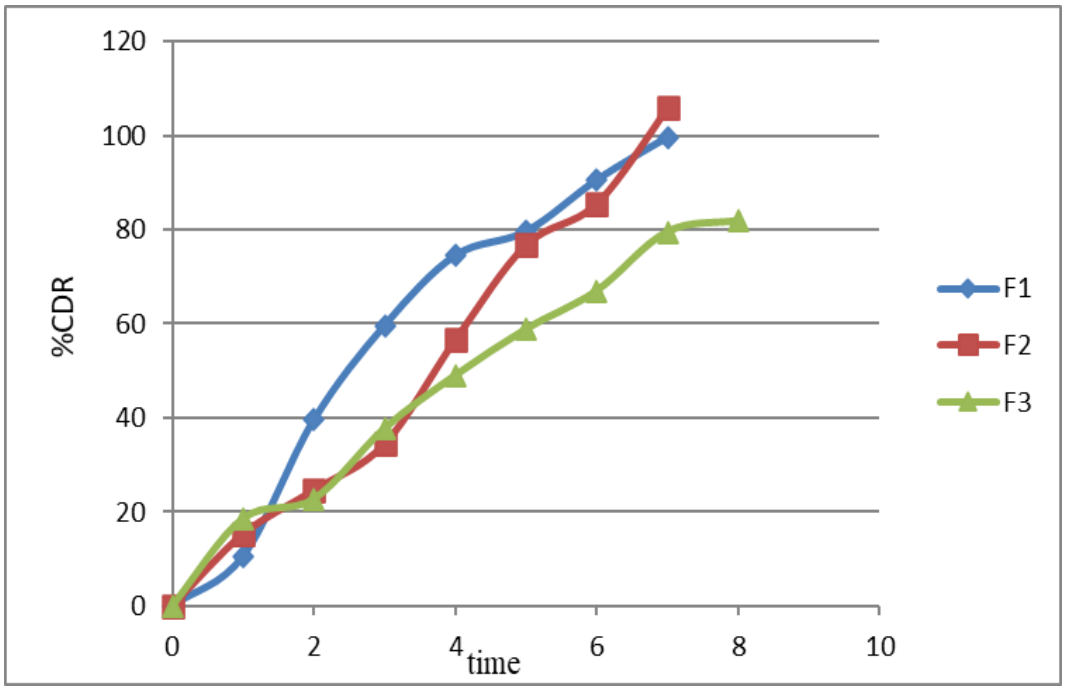

Fig 7: Comparative drug release profile of graph F1-F3

Comparative drug release profile of graph F4-F6

Table 11: Comparative *In-vitro* values of the Ramipril nano particles F4-F6

Time	F4	F5	F6
0	0	0	0
1	19.65	18.65	15.82
2	26.44	29.65	30.56
3	38.67	41.65	47.78
4	44.90	49.67	55.54
5	58.12	64.16	69.80
6	63.20	71.71	74.60
7	74.40	79.76	85.78
8	87.65	90.54	92.87

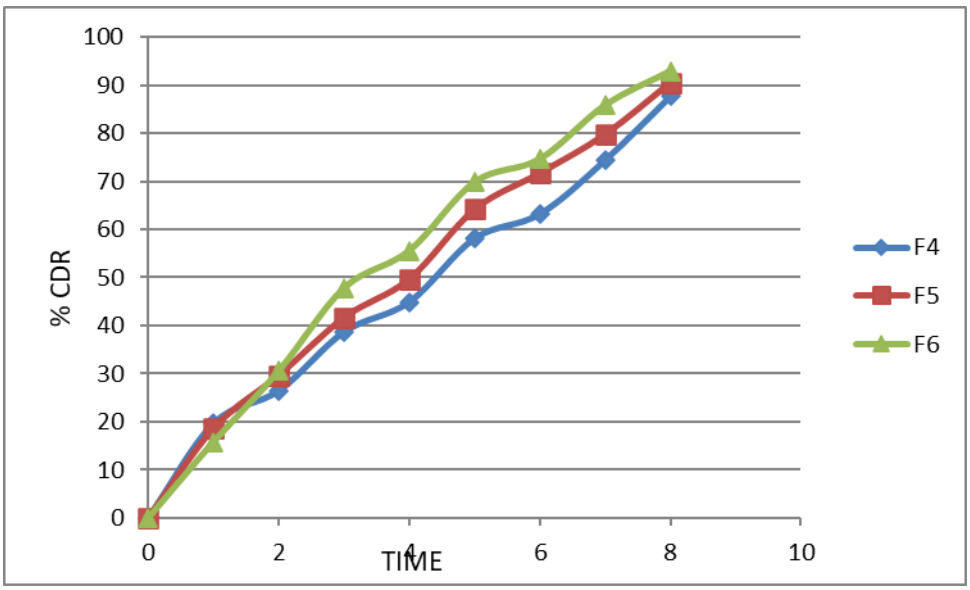

Fig 7: Comparative drug release profile of graph F4-F6

Comparative drug release profile of graph F7-F9

Table 12: Comparative *In-vitro* values of the Ramipril nano particles F7-F9

Time	F7	F8	F9
0	0	0	0
1	16.11	16.2	15.86
2	32.45	31.56	38.75
3	50.42	53.43	49.85
4	63.12	58.60	66.22
5	72.18	67.27	75.65
6	88.78	77.28	89.83
7	91.12	89.98	89.85
8	96.34	99.76	95.87

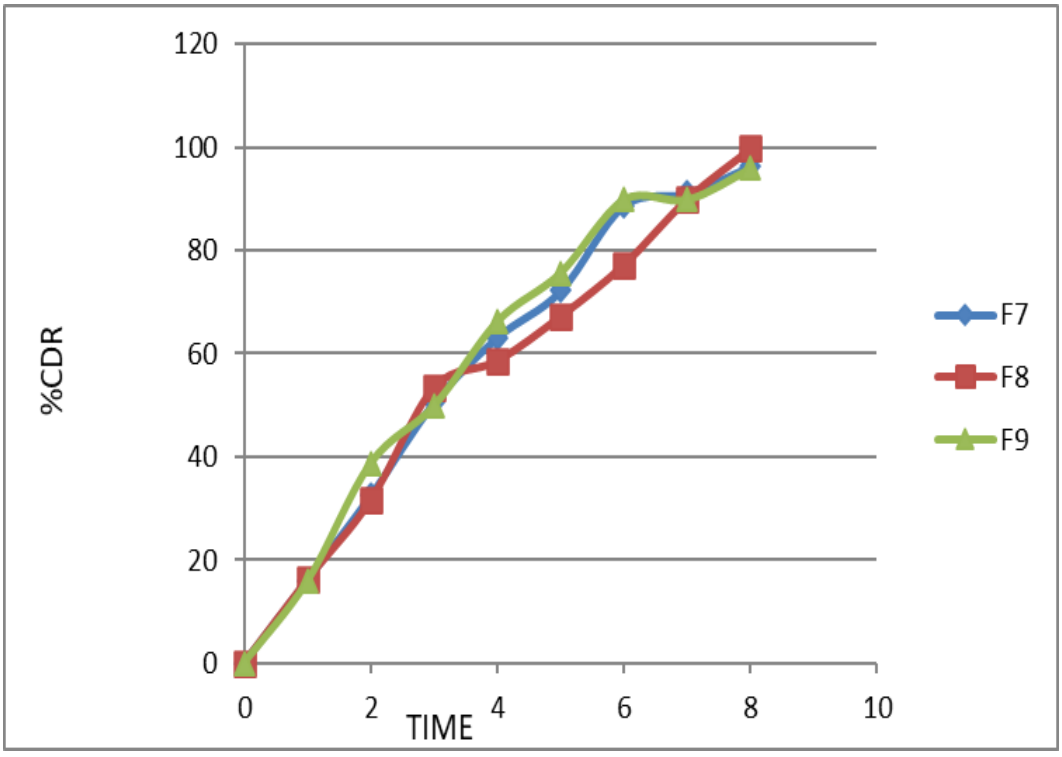

Fig 8: Comparative drug release profile of graph F7-F9

Kinetic study for the optimized formulation(F8)

Table 12: kinetic values of the Ramipril nanoparticles optimized F8

Time	%cdr	logt	√t	log%cdr	ARA	LOG%ARA
0	0	1	0	1	100	2
1	16.2	0	1	1.209515	83.8	1.923244
2	31.56	0.30103	1.414214	1.499137	68.44	1.83531
3	53.43	0.477121	1.732051	1.727785	46.57	1.668106
4	58.6	0.60206	2	1.767898	41.4	1.617
5	67.27	0.69897	2.236068	1.827821	32.73	1.514946
6	77.28	0.778151	2.44949	1.888067	22.72	1.356408
7	89.98	0.845098	2.645751	1.954146	10.02	1.000868
8	99.76	0.90309	2.828427	1.998956	0.24	-0.61979

ZERO ORDER REACTION

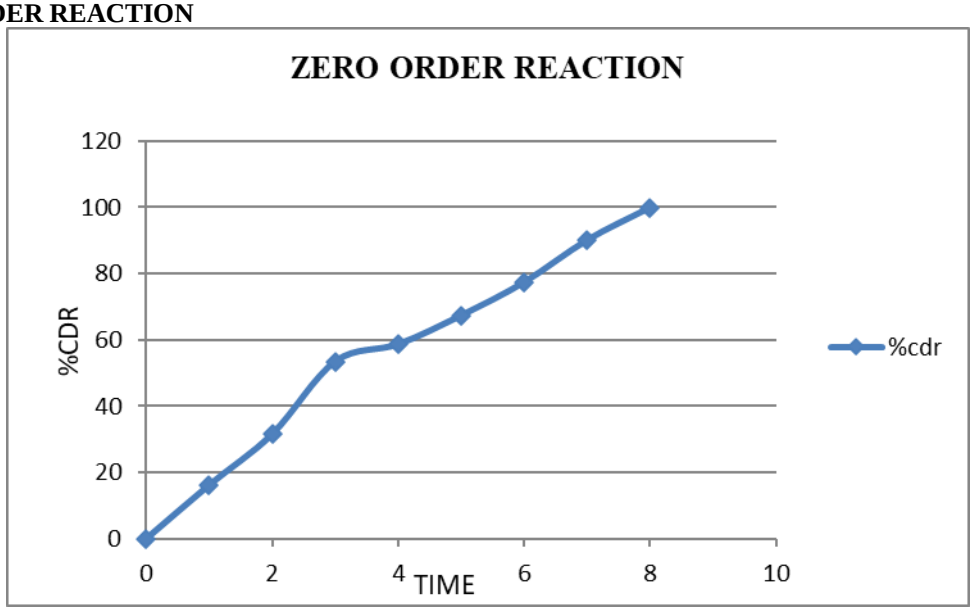

Fig 8: zero order reaction

FIRST ORDER REACTION

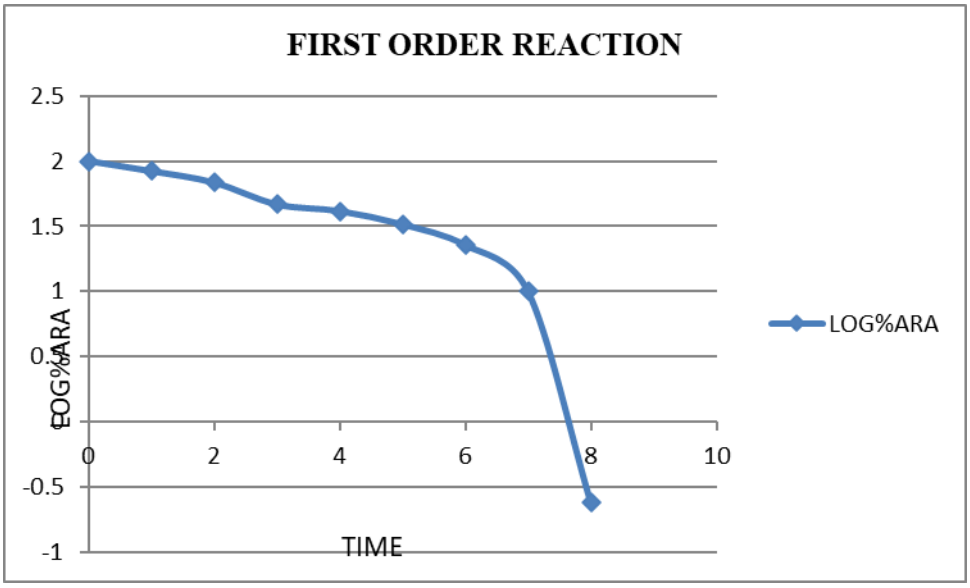

Fig 9: First order reaction

HIGUCHI EQUATION

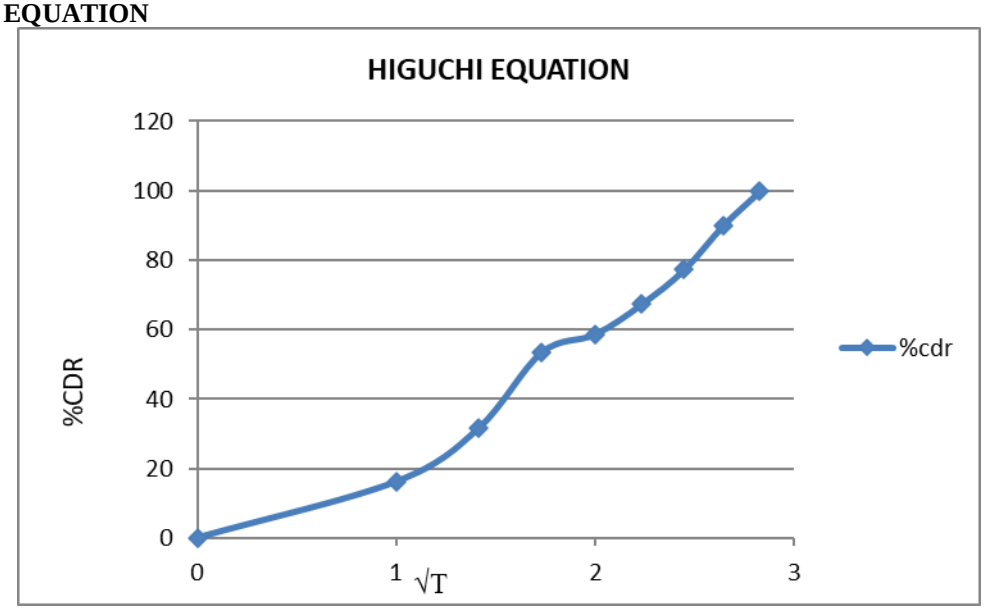

Fig 10: Higuchi equation

KROSS MAYER PEPPAS

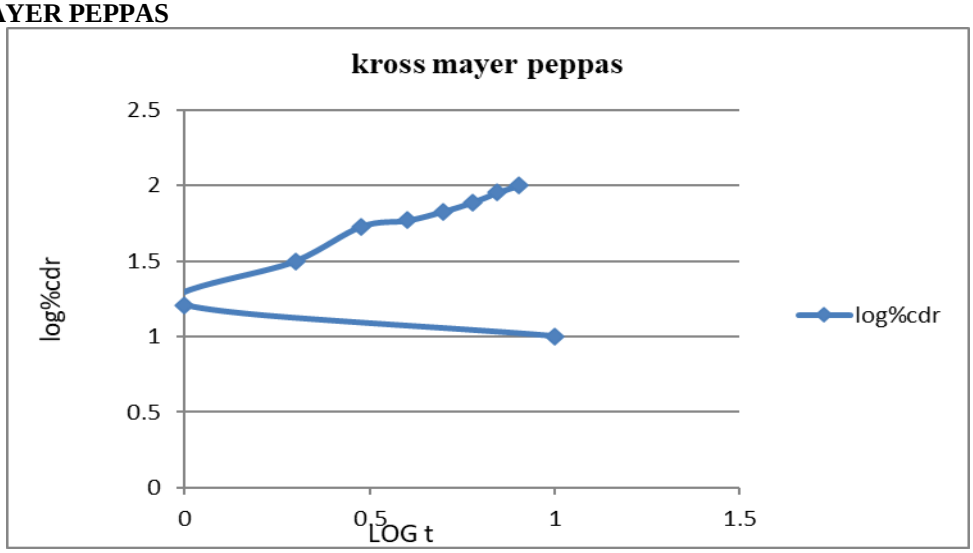

Fig 11: Kross mayer peppas

Table 13: showing table kinetic values of the Atenalol patch optimized F8

S.no	**Zero oreder**	**First order**	**Higuchi**	**Krossmayer peppas**
Code	R^2	R^2	R^2	R^2
F8	0.970	0.826	0.974	0.118

CONCLUSION:

It was concluded that the optimized formulation F8, followed zero order release where the regression value was found to be 0.970 It was also found that the drug was released by diffusion as the regression in Higuchi's plot was 0.974.

Stability studies:

There was no significant change in physical and chemical properties of the Ramipril of Optimized formulation F-8 after 3 Months of stability studies. Parameters quantified at various time intervals were shown;

Table 14: Results of stability studies of optimized formulation F-8

Formulation Code	**Parameters**	**Initial**	**1st Month**	**2nd Month**	**3rd Month**	**Limits as per Specifications**
F-8	**25^0C/60%RH % Release**	**99.76**	**98.23**	**99.57**	**98.53**	**Not less than 85 %**

Table 15: Stability dissolution profile of F-6 for 1st, 2nd & 3rd months

S.NO.	**TIME(Hrs)**	**intial**	**F-7 1M**	**F-7 2M**	**F7 3M**
1	0	0	0	0	0
2	1	16.2	17.50	15.26	14.50
3	2	31.56	35.50	25.20	26.30
4	3	53.43	51.48	43.45	43.75
5	4	58.60	61.60	56.65	57.46
6	5	67.27	75.17	72.24	78.32
7	6	77.28	79.16	86.52	83.82
8	7	89.98	91.58	95.55	91.47
9	8	99.76	96.12	96.57	97.18

Stability dissolution profile of F-7for 1st, 2nd & 3rd months

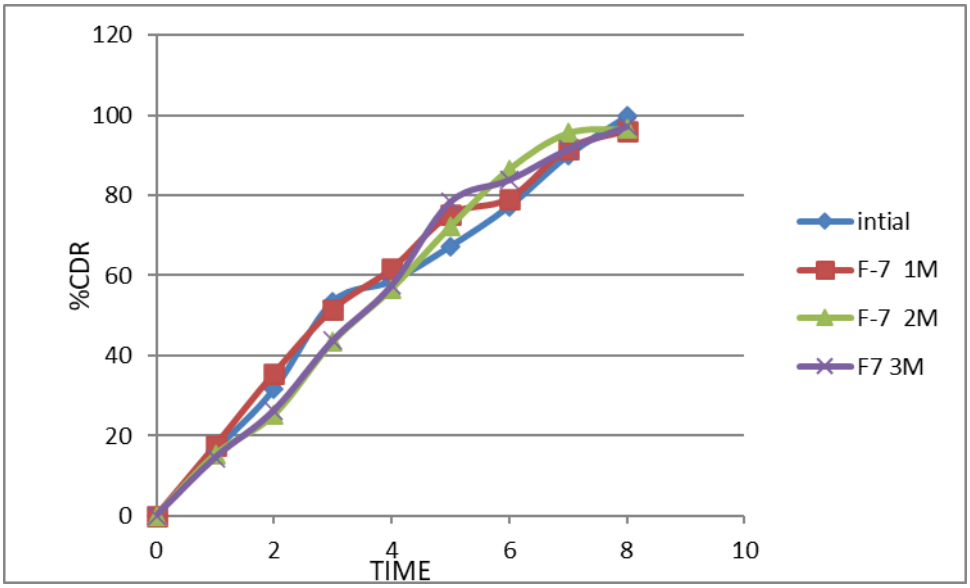

Fig 12: dissolution profile of F-7for 1st, 2nd & 3rd months

SUMMARY:

Plan and get ready and portrayal of the ramipril stacked strong lipid nano particles The Ramipril nano particles is planned by utilizing various polymers and various solvents are utilized in the definition. First the audit writing is completed for the determination of medication and choice of polymers and all excipients.

Before going to build up the detailing the pre definition contemplates are done. They are appearance, shading, smell. The compatability contemplates did, for example, FTIR examines the medication and excipient compatability study did they are compatable with one another.

The plan created by utilizing polymers, for example, chitosan polymer are utilized in various path in various amount is utilized. The Ramipril nano particles are detailed by applying strategy is nanoprecipitation technique. The plan s F1-F9 are defined. After consummation of detailing the assessment boundaries are performed.

The assessment boundaries esteems for upgraded detailing, for example, The medication content examination was seen as, 82.83% %Of yeild was found to be,69.13% The In-vitro tranquilize discharge considers found to be,99.76% The all performed assessment boundaries are seen as qualities inside the restrictions of range. After consummation of medication discharge considers the dynamic information was determined for streamlined detailing it fallows the zero request and fallows higuchi condition. The strength reads are performed for upgraded plan for 90days at quickened security examines. There is no debasement in medicate delivery and medication content investigations.

CONCLUSION:

Structure and plan and portrayal of the ramipril stacked strong lipid nano particles The chitosan is utilized as polymer. The nano particles is planned by applying by nano precipitation technique. After definition improvement the assessment boundaries played out totally went under the scope of limits. The medication discharge the advanced detailing F8 was seen as 99.76%.The motor profile performed for streamlined plan they follow the zero request and higuchi condition. The security reads did for 90 days there is no corruption in streamlined definition in tranquilize delivery and medication content examinations.

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