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FORMULATION AND IN-VITRO EVALUATION OF TRANSDERMAL PATCHES OF NEVIRAPINE CUBOSOMES

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ABSTRACT

Objective: Nevirapine is a BCS class-II antiretroviral drug used in the treatment of HIV/AIDS, specifically HIV-1 and Half life of Nevirapine is 45 hours. The aim of the present work is to formulate and evaluate a sustained release formulation of Nevirapine in the form of cubosomes and transdermal patches of cubosomes. **Methods**: Cubosomes are prepared by top-down approach employing glyceryl monooleate (GMO) as lipid phase vehicle, Pluronic F127 as a stabilizer and distilled water as aqueous phase and Nevirapine as an API. The formulation is evaluated for drug release by diffusion studies subjected to Zeta sizing and visualized by transmission electron microscopy. Transdermal patches are prepared in a manner similar to cubosomes dispersion employing polymers like sodium alginate, Guar Gum, Xanthan Gum, Carbopol 940 B., HPMC, Gum acacia. **Results**: Cubosomes formulation NVF11 containing 55% GMO showed a maximum drug release of 91.2% within 8 hours, having average particle size of 33.29nm and Zeta potential –7.03mV and pdi was found to be 0.301. The cube-like structure with round vesicles was observed by TEM. Sustained release up to 8 hours was observed in patch formulated by using polymers. In vitro release kinetics exhibited sustained release and followed nonfickian diffusion and zero order kinetics by the optimized formulations. Satisfactory pH, viscositywere obtained. **Conclusion**: cubosomes formulated with GMO serves as Transdermal Drug Delivery vehicles. Further sustained release will be attained when they are formulated as Transdermal patches.

KEYWORDS: Cubosomes, Transdermal patches, Sustained drug release, Transdermal drug delivery, Skin penetration, Systemic circulation, Lyotropic Liquid Crystals (LLC).

INTRODUCTION

Cubosomes are distinct, sub-micron, Nano-organized particles of bicontinuous cubic fluid crystalline stage. Cubosomes contain an interchangeable microstructure from the close relative cubic phase however have bigger particular exterior region and their scatterings have much lower steadiness in contrast with the collection cubic stage. Lipids, surfactants and polymer particles have together polar and non-polar segments, named as amphiphilic. The hydrophobic contact drives amphiphilic particles in polar solvents to without delay self collecting in to a mixture of thermodynamically steady fluid crystalline stages with lengths on nanometer scale. A container is the bicontinuous cubic fluid crystalline stage. Bicontinuous cubic stages are optically isotropic, tremendously viscous and strapping like fluid crystalline matter having cubic crystallographic equilibrium.

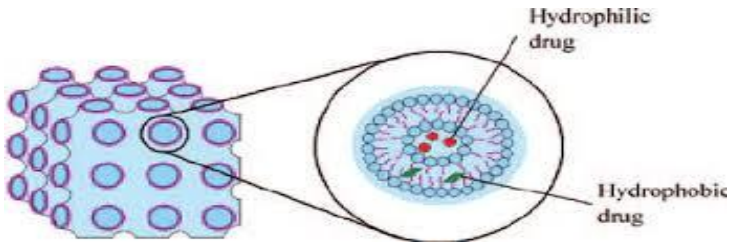


Figure 1: Cubosomes exhibiting its spacious interior and cubic arrangement and its covering opus with dissimilar drug loading modalities.

STRUCTURE OF CUBIC PHASE: Cubosomes contain honeycombed (vast) structures whose dimension range from 10–500 nm in space crossways. They appear like spots, which are fairly spherical in structure. Each fragment relates to the occurrence of hole containing fluid cubic phase in lipid water arrangement. The vital structure of cubosomes incorporates honeycombed structures dividing the two within watery channels beside vast interfacial zone. Cubosomes are nanoparticles, all the additional accurately nanostructure particles of a fluid crystalline phase with cubic crystallographic regularity shaped by the personality get mutually of amphiphilic or surfactant similar to molecules. The cubosomes having elevated innermost surface region beside cubic crystalline structures. The cubic stages have a tall strong like width, which is an unexpected belonging in light of their attractive bicontinuous structures which sheath two exacting districts of water isolated by a prohibited bilayer of surfactant. Amphiphilic atoms border bicontinuous water and oil channels, wherever "bicontinuous" alludes to two instantly recognizable (consistent, however non-converging) hydrophilic locales isolated by the bilayer. The interconnectedness of the arrangement brings on a sensible sticky gel analogous in look and rheology to cross-connected polymer

hydrogels. Be that as it might, monoglyceride-based cubic gels contain overall extra-long-run assemble than hydrogels and, on description of their creation (icelid and water), implausible biocompatibility. At show cubic mesophases set by unsaturated monoglycerides (glyceryl monooleate (GMO) or phytosterol (PT) are the majority every now and yet again explored fluid crystalline structures for medicate delivery.

ADAVANTAGES OF CUBOSOMES

cubosomes are excellent solubilizers.

It has continued and targeted release profiles for drugs.

It can entrap equally lipophilic and hydrophilic drugs.

It has tremendous bio adhesive properties.

Due to elevated internal surface area and cubic crystalline structures there is high drug loading.

It can be easily incorporated into product formulations.

It is non-toxic and biocompatible.

It has skin permeation enhancement

MATERIALS AND METHODS

Material: Glyceryl monooleate (GMO) was purchased from Finar Chemicals (LR), Pluronic's F127 was gifted from Natco Pharma, Irbesartan gifted from Hetero, dialysis membrane 110 was purchased from HIMEDIA laboratories, Hyderabad, sodium alginate, HPMC, Gumacacia, Guargum, gum Tragacanth, Carbopol 940 B.P was brought from Finar chemicals (LR), Water used is Millipore water and media used 0.1N HCl with pH 1.2.

Equipment's: Bruker FTIR spectrometer shimadzu UV spectrophotometer, electronic water bath Bio technics; Mumbai, zetasizer Malvern zeta sizer ZS90, transmission electron microscope (JEOL, Japan) diffusion cell (Locally Fabricated), ultrasonic bath sonicator (REMI); magnetic stirrer (REMI), pH meter Systronics 361, light microscope (Edition instruments).

PREPARATION OF CUBOSOME DISPERSIONS

Varying concentration of Glyceryl monooleate (5-75%) is heated along with Pluronic F127(5% weight corresponding to GMO) on an electric water bath at temperature of 42-45^{o}C until Pluronic F127 completely dissolves in GMO. To the above solution Nevirapine is added and mixed well. This clear lipid solution obtained is added drop by drop to distilled water and

subjected to bath sonication for period of 15 to 45 minutes with intermittent shaking and stirring to disperse and breakdown lipid aggregates. The end result will be white opaque dispersion without presence of any aggregates. Formulations are prepared in such a manner that each 5ml contains 72mg (on drug entrapment efficiency basis) of drug. For placebo formulations addition of Nevirapine is skipped. The prepared dispersions are stored in closed glass vials at room temperature for 72 hours in a dark place and later subjected to evaluation parameters.

FORMULATION OF TRANSDERMAL PATCHES

Drug loaded matrix type transdermal patches of nevirapine cubosomes were prepared by using solvent casting method. In this method polymers are accurately weighed and dissolved in water or chloroform, methanol (1:1) ratios of solution and kept a side to form clearsolution was obtained. Drug dispersion was dissolved in the above solution and mixed until clear solution was obtained. polyethylene glycol 400 was used as plasticizer and propyleneglycol was used as permeation enhancer. Glycerin was used as lubricant. The resulted uniform solution was cast on the Petri dish, which was lubricated with glycerin and dried at room temperature for 24 hours.

METHODS FOR CHARACTERIZATION AND EVALUATION OF CUBOSOMES

Transmission electron microscopy: Transmission electron microscopy can be utilized to observe the condition of the cubosomes. Kim et al. portrayed that the suspensions of cubic phase nanoparticles were contrarily recolored with naturally set phosphotungstic corrosive arrangement (2%, pH 6.8) and were exchanged onto a formvar/carbon covered framework (200 work), air dried at room temperature. The electron microphotographs were gone up next to an electron magnifying instrument.[28] SEM investigation may not be performed on cubosomes or several vesicular frameworks since the respectability and power of the detailing might be lost amid the plan while presenting to electron show.

Photon correlation spectroscopy: particle estimate appropriations of cubosomes are fundamentally dictated by dynamic laser light diffusing utilizing Zeta sizer (Photon connection spectroscopy). The sample diluted with a suitable dissolvable is changed in accordance with light dissipating force of around 300 Hz and measured at 25°C in triplicate. The information can be gathered and for the most part appeared by utilizing normal volume weight estimate. The zeta potential and polydispersity catalog can likewise be recorded.

Polarized light microscopy: Polarized light microscopy can be utilized expose the optically birefringent (potentially vesicular) surface casing of the cubosomes and furthermore can be familiar with anisotropic and isotropic substances.

Zeta sizing: The optimized formulation obtained from the above study is diluted 1:100 with Millipore water and subjected to Zeta sizing using Malvern zeta sizer ZS90 for determining the average particle size and Zeta potential employing laser scattering with an angle of 180^{o}.

CUBOSOMES APPLICATIONS

Oral drug delivery systems: Cubosomes speak to the stimulated difficulties in oral transport of dissimilar promising blends counting poor liquid dissolvability, poor osmosis, and incredible sub-nuclear size. These are both liquid and fine particles in the event that thing including our self emulsifying liquid crystalline nanoparticles development (LCNP). In an alternative submission far reaching proteins have been exemplified for adjoining activity in the gastrointestinal tract. Liquid crystalline nanoparticles development bearers can be joined with controlled discharge and concentrating on functionalities. The particles are planned to outline in situ in a controlled rate, which engages a convincing in vivo distribution of the solution. Liquid crystalline nanoparticles development bearers can furthermore be released at dissimilar maintenance goals, for example in the upper or lower stomach related tract, which is basic for the pharmaceuticals that have restrict area ingestion casement.

Melanoma treatment: Starting late pair of anticancer meds have been sufficiently exemplified in cubosomes and depicted physiochemically. The extraordinary arrangement of this promising nanocarrier suggests its appliance in melanoma treatment.

Topical drug delivery systems: Cubic stages are more bio adhesive in nature, so they can attentively use in topical and mucosal oaths and transport of dissimilar meds. Topical transport systems rely upon the mishandle of single properties of liquid valuable stone (LC) and liquid diamond nanoparticle (LCNP) advancements. Topical medicine transport structures are significant in situ forming bio adhesive LC systems invigorate controlled and intense pharmaceutical association to mucosal surfaces (buccal, ophthalmic, vaginal and others). This amiable structure shapes a thin surface film at mucosal surfaces containing a liquid diamond cross segment which nanostructure can be controlled for achieving an ideal transport outline and gives amazing temporary verification of painful and perceptive skin.

Intravenous drug delivery systems: Lipid nanoparticles having within liquid expensive stone structures of twisted lipid layers are used to solubilize demonstrate and pass on answers for illness goes within the body. whereas emulsions and liposome's contain originate use as intravenous bearers in sedate belongings, liquid gemstone nanoparticle structures absolute payloads of peptides, proteins and various impenetrable small particles, and are ideal transporters for combination or implantation of different actives.

CHARACTERIZATION OF TRANSDERMAL PATCHES

Diffusion studies: Optimization is complete by watching drug release by leading dispersion investigations of set details with help of locally fabricated diffusion cell. The Franz Cell machine comprises of two vital chambers isolated by a film, a contributor compartment and receptor compartment with sampling port. A dialysis film of grade 110 with atomic weight cutoff of 12000 Dalton and test volume limit of 3.63 ml/cm3 is utilized for this study.1cm2 bit of layer are cut and absorbed overnight in buffer of pH 1.2 and are used the following day The receptor compartment is loaded with buffer and layer is attach onto its outside to such an extent that it covers the opening of compartment and touches the buffer solution. At that point contributor compartment is set above and clasped took after by test expansion, the whole get together is set on a magnetic stirrer, temperature is then set to 37^0C with speed of 30 rpm. Intermittently 1ml samples are pulled back and supplanted with determine up to volume of support for consistently. With drawn samples are drawn and afterward analyzed spectrometrically in U.V spectrophotometer at a wavelength of 313 nm and computed for Cumulative drug release.

pH: pH of strategy is dictated by a computerized pH meter by immersing the electrode in gel definition and examination the pH.

Light microscope: A light magnifying device (Edison Optics) is used to observe minutely the difference between cubosome scattering and drifting patchat an amplification of 450X.

Weight variation: 10 patches are weighed and average weight was calculated andeach patches wereweighed individually and %deviation from average weight was calculatedfor each patch. It should not exceed + or – 5+.

Thickness test: Measured by using Vernier calipers by using formula. MSR+(VSR*0.01) MSR-meter scale reading, VSR-Vernier scale reading.

Folding endurance test: Determined folding capacity of film subjected to frequent extreme conditions of folding. Repeatedly folding film at same place until it breaks. The number of times the film could be folded at same place without breaking is folding endurance value.

Weight uniformity test: The Prepared Patches Are to Be Dried At 60 Degree Centigrade For 4 Hours Before Testing. Individually Weighing 10 Randomly Selected Patches Is to Be Cut In Different Parts of The Patch and Weighing in Digital balance.

Drug content determination: Accurately Weighed Portion of Film (About 100mg) is Dissolved In 100ml Of Suitable Solvent and Shaken Continuously For 24 H Then Sonicated. After Sonication and Subsequent Filtration, Drug in Sonication Is Estimated Spectrophotometrically.

Accelerated stability studies: According to ICH rules at 40oC±2oC/75%±5% RH for upgraded Patch formulation at examining intervals of 0, 30, 60 and 90 days separately. The medication material, consistency and pH are resolved intermittently.

RESULTS

The main objective of the study is to develop Transdermal patches of Nevirapine in form of cubosomes and Transdermal patches using various concentrations of GMO, distilled water and polymers (Sodium alginate, HPMC, Gumacacia, Gum Tragacanth, Guar Gum, Carbopol 940 B.P) employing Pluronic F127 as a stabilizer using Top Down Approach. Advantages of the method is simple technique and easy availability of raw materials.

FTIR Studies: The interface examines between the medication and excipients and in addition improved detailing was assessed using IR spectrophotometer. Nevirapine has characteristic absorption peaks at 3295.3cm-1, 2920.7cm-1, 1657.6cm-1, 1110.2cm-1, 1046.5cm-1, 3190.6cm-1 and 1024.4cm-1 individually. similar peaks were seen in spectra of various combinations of excipients and in improved plan (Cubosomes and patch), alongside nonattendance of interfering peaks showing there is no disagreeable response between Nevirapine and different excipients used as a part of the study.

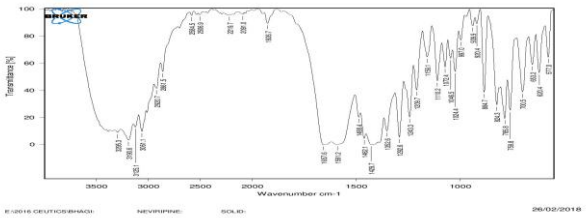


Figure 2: FTIR of Nevirapine

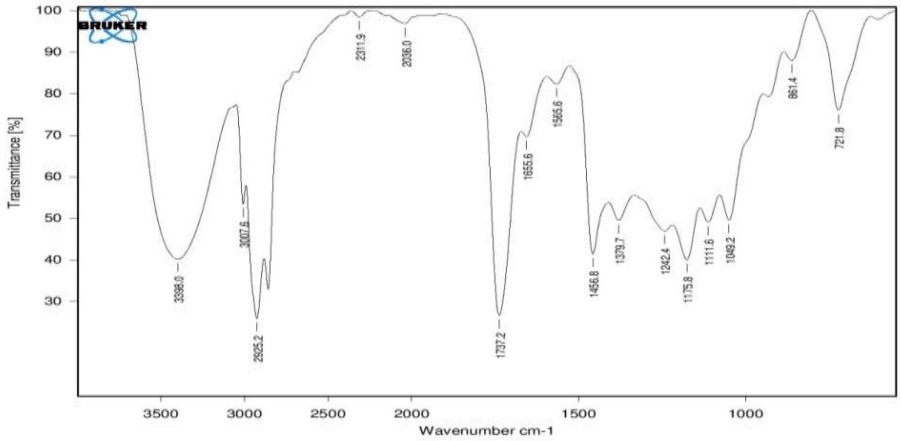


Figure 3: FTIR of Nevirapine&GMO.

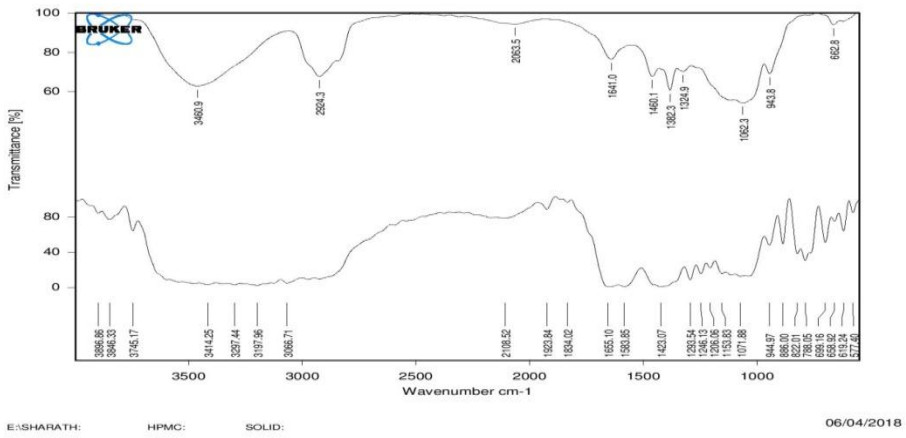


Figure 4: Overlay of a) nevirapine+HPMC& b) HPMC

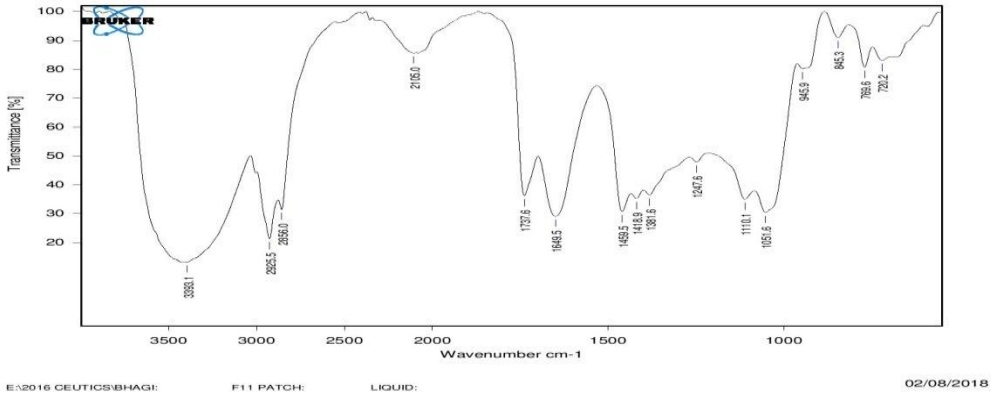


Figure 5: FTIR of optimized patch formulation.

Cubosomes Formulations

Formulation code	Glycerol monooleate(%v/v)		Distilled water		Stabilizer (in mg) (poloxamer 407)
	(%v/v)	(in ml)	(%v/v)	(in ml)	
NVF 1	5	0.25	95	4.75	7.5
NVF 2	10	0.5	90	4.5	15
NVF 3	15	0.75	85	4.25	22.5
NVF 4	20	1.00	80	4.00	30
NVF 5	25	1.25	75	3.75	37.5
NVF 6	30	1.50	70	3.5.	45
NVF 7	35	1.75	65	3.25	52.5
NVF 8	40	2.00	60	3.00	45
NVF 9	45	2.25	55	2.75	52.5
NVF 10	50	2.50	50	2.50	60
NVF 11	55	2.75	45	2.25	67.5
NVF 12	60	3.00	40	2.00	75
NVF 13	65	3.25	35	1.75	82.5
NVF 14	70	3.50	30	1.50	90
NVF 15	75	3.75	25	1.25	102.5

Formulation of transdermal patches

formulation code	GMO (mg)	polymers(mg)						drug (mg)	Peg (mg)	propylene glycol (mg)	Glycerin (mg)	Stabilizer (mg)
		HP MC	Carbopol	sodium alginate	guar gum	traga canth	Aca cia					
NVFHC1	2.75	150	150	_	_	_	_	100	0.25	0.25	0.5	82.5
NVFHC2	2.75	225	225	_	_	_	_	100	0.25	0.25	0.5	82.5
NVFAG1	3.25	_	_	_	150	_	150	100	0.25	0.25	0.5	97.5
NVFAG2	3.25	_	_	_	225	_	225	100	0.25	0.25	0.5	97.5
NVFTN1	3.50	_	_	150		150	_	100	0.25	0.25	0.5	105
NVFTN2	3.50	_	_	225		225	_	100	0.25	0.25	0.5	105

PHYSICAL CHARACTERIZATION OF API'S

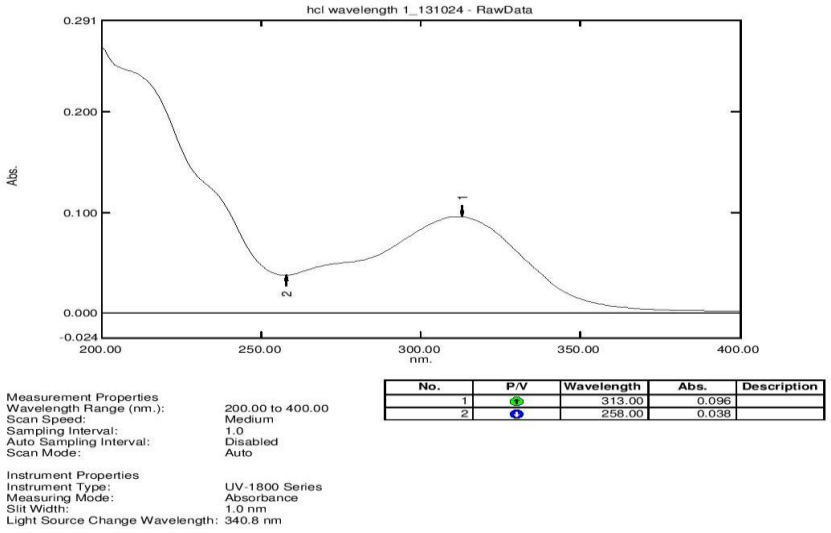
DESCRIPTION	NEVIRAPINE
COLOR	WHITE
MORPHOLOGY	AMORPHOUS
TASTE	METALLIC

THE SOLUBILITY STUDIES OF API'S

SOLVENT	NEVIRAPINE
WATER	IN-SOLUBLE
O.1N HCL	SOLUBLE
METHANOL	SOLUBLE
ETHANOL	SOLUBLE

Determination of λmax of Nevirapine in 0.1N HCL

The spectrum shows maximum absorption UV absorption spectrum of Nevirapine in 0.1N HCI,



Nevirapine standard graph in 0.1N HCL

Absorption and Concentration Are Plotted to Obtain A Standard Graph with Regression Co-efficient 0.999.

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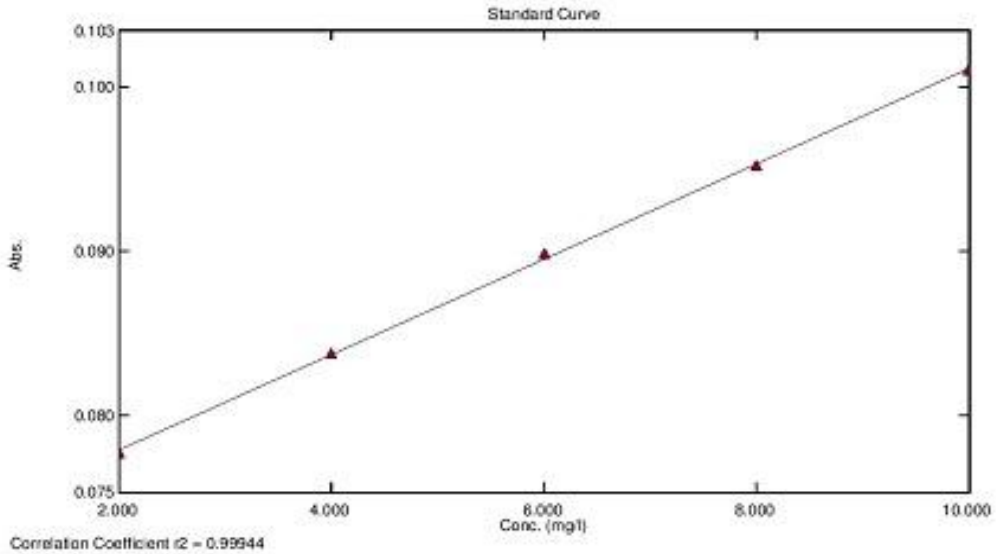


Correlation Coefficient r2 = 0.99944

Standard Table

	Sample ID	Type	Ex	Conc	WL343.0	Wgt.Factor	Comments
1	NEVI 1	Standard		2.000	0.078	1.000	
2	NEVI 2	Standard		4.000	0.084	1.000	
3	NEVI 3	Standard		6.000	0.090	1.000	
4	NEVI 4	Standard		8.000	0.095	1.000	
5	NEVI 5	Standard		10.000	0.101	1.000	
6							

40

Nevirapine Standard graph in 0.1N HCI

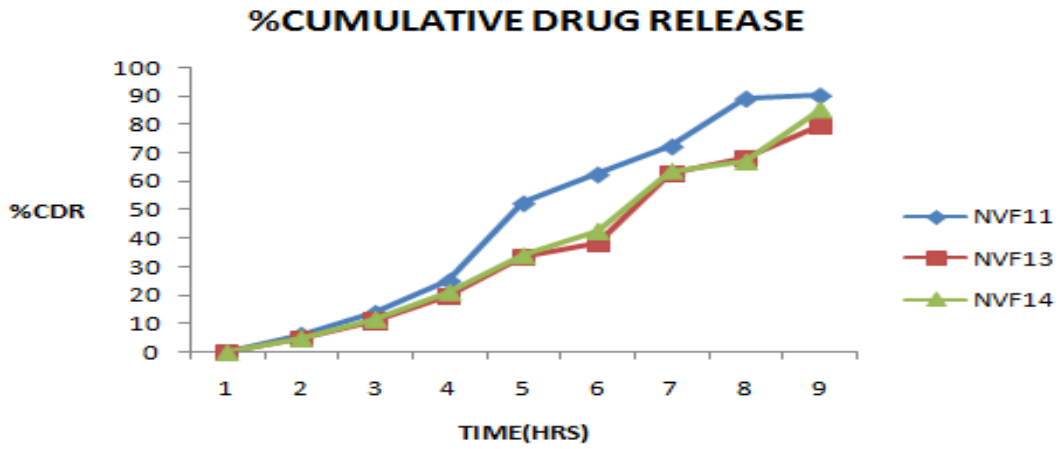
CUBOSOMES DIFFUSION STUDIES

Diffusion studies are conducted for different formulations containing unstable concentrations of GMO (5 to 50%) andwater (95% to 50%) in 0.1 N HCl (buffer of pH1.2). In case of cubosomes dispersions sustained release, action was observed up to 8 hours. The various formulation codes along with cumulative drug discharge values are given in table and fig below.

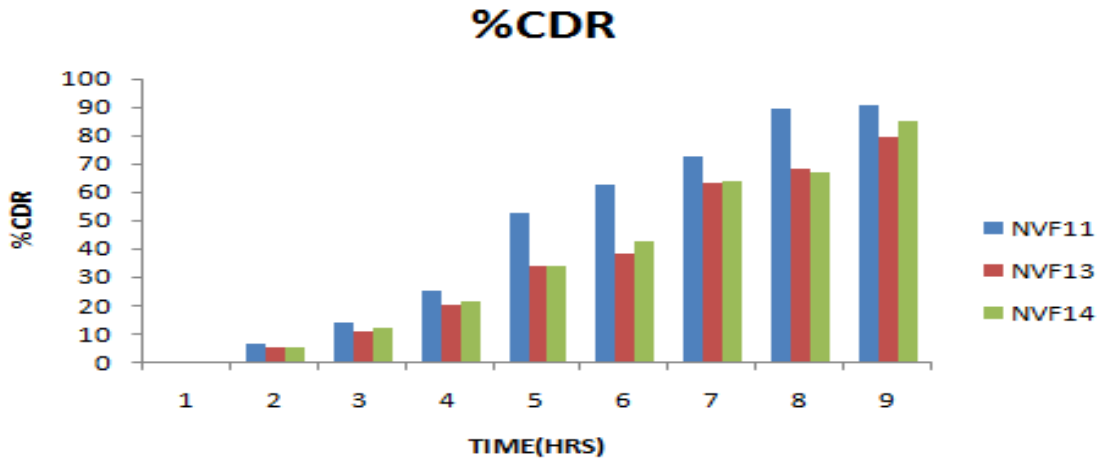
Cumulative drug % of different formulations

Time(hrs.)	%Cumulative drug release		
	NVF11	NVF13	NVF14
0	0	0	0
1	6.1±0.26	4.77±0.58	4.86±051
2	13.78±0.57	10.9±0.69	11.64±0.74
3	25.04±0.43	19.80±0.61	21.18±1.21
4	52.41±0.44	33.56±4.97	33.89±5.32
5	62.57±0.70	38.4±3.68	42.52±2.60
6	72.4±0.45	62.99±7.56	63.61±6.1
7	89.25±0.99	68.39±11.47	66.92±1.24
8	90.34±0.89	79.49±12.08	85.17±2.06

**Values in mean of cumulative % drug release ±standard deviation (n=3).*



Cumulative%drug release of different formulation

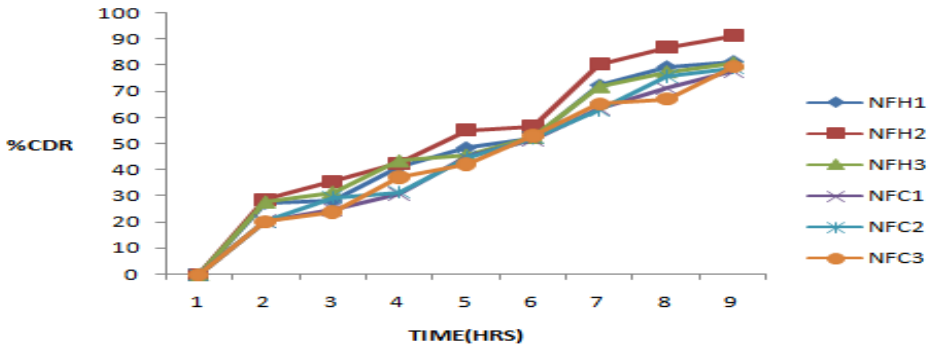


Cumulative % drug release of formulations

TRANSDERMAL PATCHES DIFFUSION STUDIES: cumulative drug release NFH1-3 and NFC1-3.

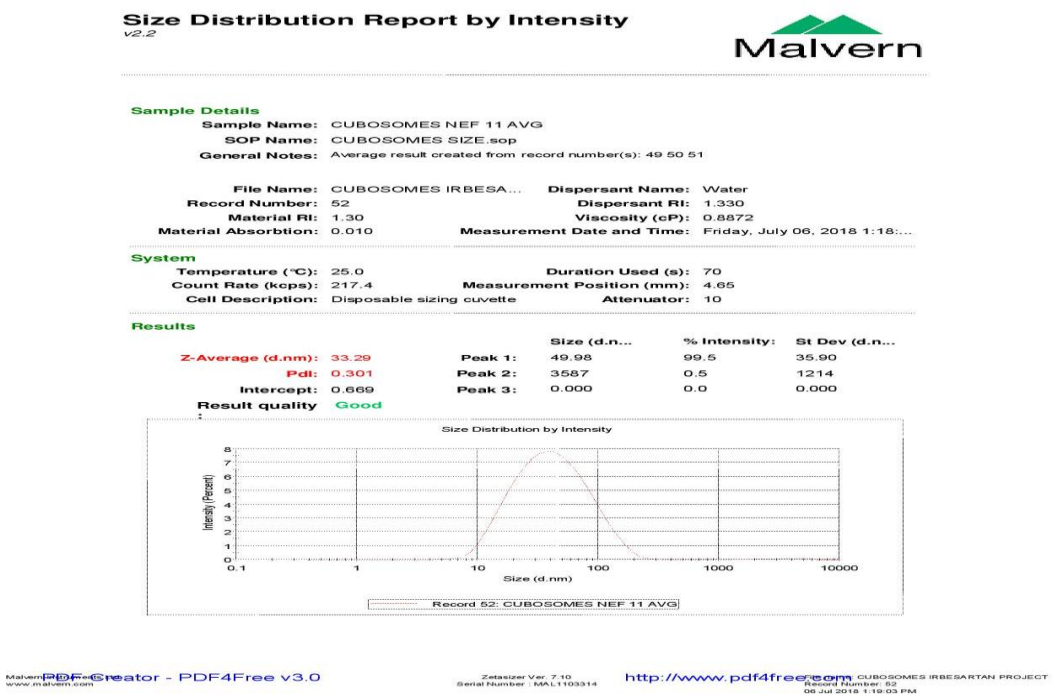
Time in (hrs)	% cumulative drug release					
	NFH1	NFH2	NFH3	NFC1	NFC2	NFC3
0	0	0	0	0	0	0
1	27.4±0.53	28.6±0.27	27.8±0.33	20.5±0.84	20.2±0.22	20.1±0.98
2	28.2±0.62	35.6±0.42	31.5±0.68	24.9±0.73	29.51±0.43	23.8±0.78
3	41.3±0.78	42.5±0.99	43.5±0.87	30.8±0.65	31.5±0.56	37.1±0.46
4	48.5±0.93	55.2±0.87	45.7±0.25	45.1±0.44	44.9±0.79	42.2±0.33
5	52.3±0.21	56.5±0.48	52.5±0.79	51.6±0.75	52.2±0.65	52.9±0.72
6	72.5±0.43	80.5±0.55	71.9±0.21	63.5±0.43	62.8±0.53	65.2±0.19
7	79.5±0.12	86.8±0.98	77.5±0.75	71.4±0.57	75.7±0.61	66.9±0.61
8	81.5±0.34	91.2±0.55	80.9±0.89	77.6±0.71	78.9±0.12	79.3±0.35

Values in mean of cumulative % drug release ± standard deviation (n=3)



Cumulative Drug Release NFH1-3 and NFC1-3.

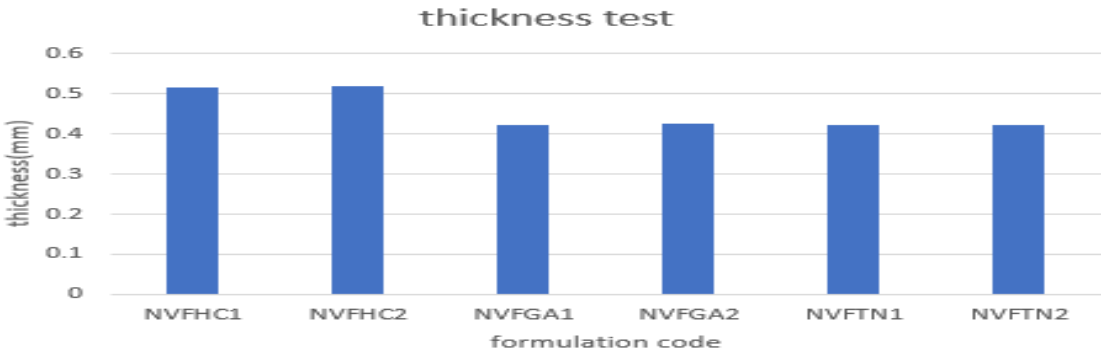
Droplet size and zeta potential determination: From the diffusion study it was finished that the formulation NVF11 showed more drug release % than other formulation. So, it is selected as the finest formulation. Size and potential values are determined for the formulation. Size of the particles was found to be 33.29nm and pdi value was found to be 0.301 and its zeta potential was found to be -7.03mv.



Distribution of size NVF11 Formulation

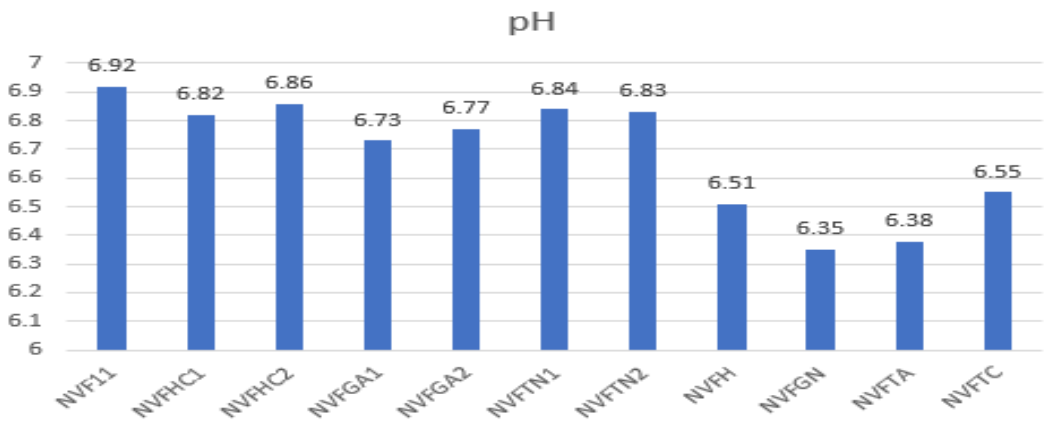
Evaluation of Transdermal patches

Formulation code	Thickness (mm)	Folding endurance	Weight uniformity(gm)	Drug content(mg)
NVFHC1	0.517	120	0.420	80.64
NVFHC2	0.519	116	0.455	81.18
NVFGA1	0.422	122	0.402	68.43
NVFGA2	0.425	126	0.395	77.25
NVFTN1	0.421	112	0.412	71.9
NVFTN2	0.423	114	0.419	72.6



Thickness of Patch Formulation

pH: pH values of selected formulations are given below



pH of selected patch formulations

All values possess same values closer to neutral pH favoring suitability for oral administration.

Release kinetics: Based on drug release values of cubosomes dispersions and patch formulations (NVFHC2) are studied for release kinetics inference is drawn from below values.

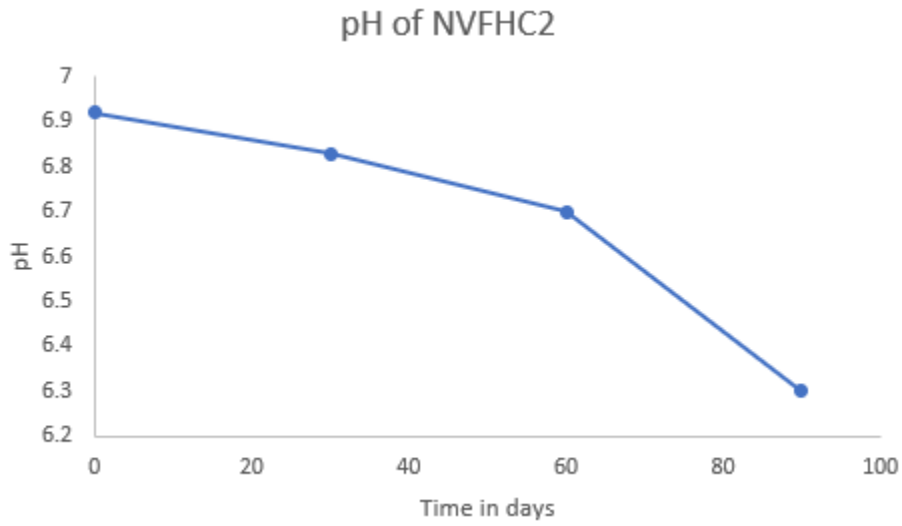
STABILIY STUDIES

KINETIC MODELS	r^2 values
ZERO ORDER	0.958
FIRST ORDER	0.923
KORSMAEYER-PEPPAS	0.95
HICKSON CROWEL	0.885
HIGUCHI	0.845

pH

pH of optimized formulation NVF11

Time in days	pH of NVFHC2
0	6.92
30	6.83
60	6.7
90	6.3



pH of optimized formulation NVFHC2

Stability studies of optimized formulation NVFHC2

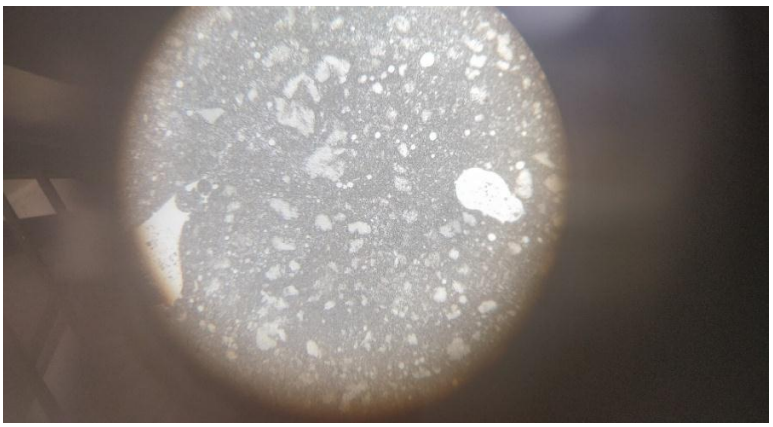
%drug release	**Time in days**			
	1	**30**	**60**	**90**
ACFCNG2	93.5±0.42	92.9±0.62	91.8±0.32	90.6±0.28

**Values in mean of cumulative % drug release ± standard deviation (n=3).*

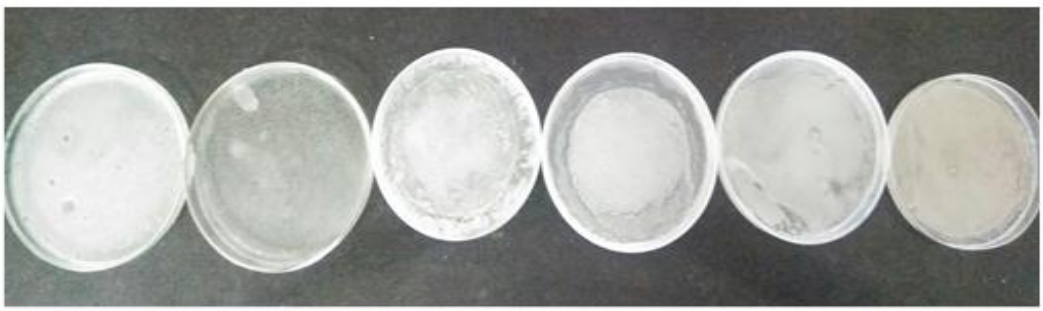
Slight changes in parameters are observed conforming the stability of selected optimized formulations.

SUMMERY AND CONCLUSION: The main aim behind the study is sustained release of drug.Even though many sustained release formulations are developed till date this preparation deserves attention due to its single liquid crystalline structure and ease of preparation. Auspicious conditions, for example, high level of biocompatibility controlled by GMO, capacity of helpful different medications regardless of hydrophilic or hydrophobic nature, maintained release activity prompt examination in detailing of fluid crystalline medication transportation vehicles through different courses of organization. Cubosomes are one such dose forms framed by GMO when added to water. Since it is a lipid and tends to separate in aqueous phase Pluronic F127 is used as a stabilizer to stop aggregation. The model drug Nevirapine is a non-nucleoside reverse transcriptase inhibitors. Cubosomes formulation NVF11 shows satisfactory drug release patterns in 0.1N HCl up to 8 hours following first order kinetics and shows maximum drug release of 90.34%. The persistence of evaluation of cubosomes is to optimize the concentration of GMO showing maximum drug release An alternative is to retard the enzyme attack maintaining the cubosomes structure and extending

the drug release. The innovative plan is to formulate cubosomes in form of Transdermal patches. Polymers like HPMC, Tragacanth, Sodium alginate, Xanthan gum, Guar gum and Carbopol 940 B.P are used in this preparation to make patches. GMO concentration is kept constant and concentration of polymers are varied and optimized by conducting diffusion studies. Among all formulations, NVFHC2 showed maximum sustained drug release of 91.2% after 8 hours following zero order Kinetics. The formulations possess a l0g time in fraction of seconds i.e. they form Transdermal patches immediately after contact with glycerin and PEG. The probable mechanism of formation of Transdermal patches is pH dependent cross linking of polymers surrounding the cubosomes. Dealing with other features, formulations containing Carbopol 940 and HPMC show higher viscosity and stability than other formulations. The microscopic reflection also displays that the addition of Polymers doesn't affect cubosomes structure. The viscosity, pH and drug release values designate that this formulation is suitable for transdermal administration. The cubosomes dispersion and transdermal patches are observed under microscopically. The ordinary cubosomes dispersion comprises individual objects, where as in case of patch formulation the polymers used forms like a matrixlike structure around cubosomes units that acts as a prolonging drug release.



Transdermal patches are observed under microscopically



Transdermal patches formulation

REFERENCES

1. Sai Santosh Bolisetti*, 2M.Sunitha Reddy: Formulation and In-vitro Evaluation of Gastro retentive In-situ Floating gels of Repaglinide Cubosomes, JPR: Bio Med Rx: An International Journal, Vol.1 Issue 8. August 2013.
2. *R. Swathi and M. Sunitha Reddy: UV-Visible Spectrometric Method and Validation, Compatibility Studies of Nevirapine Cubosomes Formulation, World Journal of Pharmacy and Pharmaceutical Sciences, Volume 6, Issue 01, 1111-1121.
3. Chenyu Guo, Jun Wang, Fegliang Cao, Robert J.Lee and Zhai: Volume 15, Numbers 23/24. (2010) 1032 to 1040.
4. JayminC.Shah, Yogesh Sadhale, Dakshina Murthy Chilukuri: Cubic phase gels as drug delivery systems, Advanced Drug Delivery Reviews, 2001; 47: 229-250.
5. Tri-Hung Ngugen, Tracey Hanley, Christopher J.H.porter, BenJ. Boyd.
6. Al- Sayedsallam Enam Khalil, Hussain Ibrahim, Ibtisam Freij: European journal of pharmaceutics and Bio pharmaceutics, 2002; 53: 343-352. Indian Pharmacopeia.
7. Ben J. Boyd, Darryl V. Whittaker, Shui-Mei khoo, Greg Davey: International journal of pharmaceutics, 2006; 309: 218-226.
8. Dasharath M. Patel,*Divyesh K. Patel, and Chhagan N. Patel.
9. R. Burrows, J.H. Collett, D.Attwood. Monoglyceride water liquid crystalline phases drug release. Int. J. Pharm, 1994; 111: 283-293.
10. Bharadwaj T.R., Kanwar M. and Gupta A. sustained release carriers of natural gums and modified gums Drug Devel. Ind. Pharm, 2000; 26: 1025-1038.
11. Formulation and Evaluation of pH-triggered in situ Gelling System of Levofloxacin, Indian Journal of Pharmaceutical Education and Research, 2011; 45(1): 58-64.
12. An overview of a transdermal drug delivery system, Drug delivery system/Asian Journal of Pharmaceutical Sciences, 2009; 4(1): 65-80.
13. Raymond C Rowe, Paul J Sheskey and Marian E Quinn, (2005) editors. Handbook of Pharmaceutical excipients. 6th ed. London: Pharmaceutical Press. Vol I II&III.
14. Kumar M, Pandey P, Dureja H. Box-Behnken designed cubosomes of famotidine. Drug Development and Delivery, 2015; 15(3): 62-7.
15. Geraghaty P. and Attwood D. An investigation of parameters influencing the bio adhesive properties of myverol 18-99/water gels. Biomaterials, 1997; 18: 63-70.
16. Costa P, Ferreria DC, Morgado R, Sousa Lobo JM lorazepam transdermal drug delivery system designed and evaluated. Drug Dev Ind Pharm, 1997; 23: 939-944.

17. Dimas DA, DallesPP, Rekkas dd, Choulis NH. Effect of several factors on the mechanical properties of pressure sensitive adhesive used in transdermal therapeutics systems, AAP Spharm Sci Tech, 2000; 1: E16.
18. V.N.L.Sirisha*, P.Kirankumar, M.ChinnaEswaiah. Propranolol Hydrochloride transdermal patches are formulated and evaluated. IOSR Journal of Pharmacy, Sep-Oct 2012; 2(5): 2250-3013.
19. Md. Intakhab Alam, Nawazish Alam*, Vikramjit Singh, Md. Sarfaraz Alam, Md. Sajid Ali, Tarique Anwer, Mohammed M. Safhi. World Journal of Pharmacy and Pharmaceutical Sciences, 2(4): 2199-2233.
20. Deepak N.Kapoor,*Ruchisharma, Gurvinder Kaur. Fluconazole Loaded Cubosomal Vesicles for Topical Delivery. International Journal of Drug Development and Research. Sep 18, 2015.
21. Tri-Hung Ngugen, Tracey Hanley, Christopher, BenJ. boyd. Phytantriol And Glycerol Monooleate Cubic Liquid Crystalline Phases as Sustained Release Oral Drug Delivery.
22. Chenyuguo, et al. Lyotropic Liquid Crystal Systems in Drug Delivery. Volume 15, numbers 23/24. (2010) 1032 to 1040.
23. Gabiga H, Cal K, Janicki S. Effect of penetration enhancers on isosorbide dinitrate penetration through eat skin from a transdermal therapeutic system, Int J Pharm, 2000; 199: 1-6.
24. Corrigen, O.I., Transdermal drug delivery systems, Department of pharmaceutics, University of Dublin, Ireland.
25. Gottipati Dinesh babu, Kantipotu Chaitanya Sagar, Mitesh R. Boot, Adhikarla Prem Swaroop. Design and evaluation of valsartan transdermal patches. Gottipati Dinesh babu, Mitesh R. Boot et al / IJRAP 3(3): May-Jun 2012.
26. Chenyu Guo, Jun Wang, Fegliang Cao, Robert J. Lee and Zhai: Volume 15, Numbers 23/24. (2O1O) 1O32 to 1O4O.
27. Jaymin.C.Shah, Yogesh Sadhale, Dakshina Murthy Chilukuri: "Cubic phase gels as drug delivery systems, Advanced Drug Delivery Reviews", 47(2OO1) 229-25O.