CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF SUBLINGUAL STRIPS OF NARATRIPTAN

Naresh Kshirasagar* Sriram Pavani, D Adukondalu, J.Kishan Pavani
Department of Pharmaceutics, Vaagdevi College of Pharmacy.
Ramnagar, Hanamkonda 50600, Telengana, India.

Abstract:
Naratriptan hydrochloride, a piperidine derivatives selective agonist of serotonin, binds with high affinity to 5-HT1B and1D receptor (Hydroxy Tryptamine) has oral bioavailability in men 63% and women 74% due to hepatic first metabolism. The present investigation is to development of naratriptan sublingual films, allowing easy of drug dissolution in oral cavity, thus by passing first pass metabolism and to produce rapid onset of action. Sublingual films were prepared by solvent casting method. Low viscosity grade HPMC E5, HPMC E15, HPMC E50 (Hydroxy Propyl Methyl Cellulose) were used in combination also as film forming polymer with different ratios, PEG 400 (Poly Ethylene Glycol) is used as plasticizer, mannitol and aspartame were used as sweetener, to decrease the disintegrating time of formulation sodium starch glycolate was used as disintegrating agent. Mint is used as cooling agent, all the films formulation (A1-A4, B1-B4, C1-C4, and D1-D4) was evaluated for their thickness weight variation, assay, folding endurance, surface pH, in-vitro disintegration. Disintegration time showed by the formulation was found to be in range of 21-48 sec. B1 showed 99.89% of drug dissolved within 10 sec, the film showed an excellent stability for 1 month when stored at 40ºC and 75% RH (Relative Humidity) in stability chamber.

Key words: *Naratriptan, Sublingual films, solvent casting method, stability chamber*

Corresponding author:
Naresh Kshirasagar,
Department of Pharmaceutics,
Vaagdevi College of Pharmacy.
Ramnagar, Hanamkonda -50600,
Telengana, India.

QR code

Please cite this article in press as Naresh Kshirasagar et al, ***Formulation and Evaluation of Sublingual Strips of Naratriptan****, Indo Am. J. P. Sci, 2016; 3(7).*

INTRODUCTION:

Drugs have been applied to the mucosa for topical application for many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation. The oral route of administration is considered as the most widely accepted route. The unique environment of the oral cavity offers its potential as a site for drug delivery. Because rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver. The continuous secretion of saliva results in rapid removal of released drug and this may desire that the oral cavity be restricted to the delivery of drugs, which have a short systemic circulation. The mucin film, which exists on the surface of the oral mucosa, may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged periods if it is designed to be mucoadhesive. Such system ensures a close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the differential pathway.

The oral mucosa may be potential site for controlled or sustained drug delivery. Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients. About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphasia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance. The target sites for local drug delivery in the oral cavity include buccal, sublingual, periodontal region, tongue, and gum. Other desirable targeting sites adjacent to oral cavity include pharynx, larynx, adenoids and tonsils.

Advantages

- Ease of administration
- Precise dosing as compared to liquid formulations.
- Water is not required for swallowing the dosage form,
- Immediate access to water.
- Good mouth feels
- Rapid, onset of action.
- Pregastric absorption can result in enhanced
- Reduced dosage,
- Enhanced clinical performance
- Decrease unwanted effects.

MATERIALS AND METHODS:

Materials

Naratriptan was received as gift samples from Orchid health care. Chennai, India. HPMC E5, E15, E50 was procured from Qualikems fine chem. Pvt. Ltd. Vadodara. Sodium starch glycolate was obtained from Loba Chem. Mumbai, India. PEG 400 was obtained from S.D. Fine chemicals limited. Mumbai. Mannitol from Merck, Mumbai. Aspartame from Callahan. Mumbai. Vanilla from IFF. Mumbai.

Methods

Formulation design:

Naratriptan sublingual films were prepared using different grades of hydroxyl propyl methyl cellulose like HPMC E5, HPMC E15 and HPMC E50 by solvent casting method. Different formulations of Naratriptan ODFs were prepared using the polymer in different ratios keeping all other ingredients constant. They are assigned with formulation codes shown in table.

Preparation method:

Fast-dissolving sublingual film of naratriptan was prepared by the solvent-casting method. Phase I was prepared by dissolving the polymer in specific proportion of distilled water and was allowed to stir for 4 hours and kept for 1 hour to remove all the entrapped air bubbles. Phase II was prepared by dissolving the Naratriptan, mannitol, PEG400, Aspartame, sodium starch glycolate in specific proportion in distilled water. Both phase I and II were mixed and stirred for 1 hour. Then the mixture solution was casted onto a plastic petri dish and it was dried in the oven at 50^0C for 3 hours.

The film was carefully removed from the petriplate, checked for the imperfections and cut to the required size to deliver the equivalent dose ($2\times2cm^2$) per strip. HPMC E5, HPMC E15 and HPMC E50 formulations resulted in transparent films. Thus, formulations were further evaluated for various parameters.

Drug polymer compatibility studies:

FTIR spectra of pure naratriptan and finalized formulation were recorded on Bruker ALPHA model directly placing on probe analyzing for functional groups. Each spectrum was derived from single average scan collected in the region 400-4000cm^{-1} at spectral resolution of 2 cm^{-2}. The obtained spectrums are allowed for peak picking.

Evaluation of sublingual formulations:

Thickness:

The thickness of the patch was measured using Vernier callipers with a least count of 0.01 mm at

different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated.

Weight variation:

Four centimeter square of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation and SD was calculated.

Folding endurance:

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was counted as the folding endurance value.

Drug Content:

Drug content determination of the film was carried out by dissolving the film of 4 cm^2in 100 ml of pH 6.8 phosphate buffer using stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at 221nm. The determination was carried out in triplicate for all the formulations, average with standard deviation were recorded.

In-vitro dissolution:

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 6.8 phosphate buffer maintained at 37˚C at 50 rpm. 5 ml of aliquots were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37°C. Drug content was estimated spectrophotometrically at 221 nm. The results were expressed as mean and SD was determinations.

In-vitro Disintegration:

In vitro disintegration time was determined visually in a petri dish containing 4 ml of pH 6.8 phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

Stability studies:

The optimized formulation of naratriptan were packed in amber color bottle and aluminum foil laminated on the upper part of the bottle and these packed formulation was stored in stability chamber maintained at 40ºC ± 2ºCand 75%± 5% RH for 1 months.

RESULTS AND DISCUSSIONS:

Naratriptan oral dissolving films were prepared by solvent casting method using HPMC E5, HPMC E15, HPMC E50 and combination of HPMC E15 + HPMC E50 as film forming polymers. The results of the present study indicated that HPMC E15 could be used as a film forming polymer for formulation of fast dissolving film containing naratriptan. Acceptable mechanical properties were obtained for all the batches, FTIR studies revels that there is no interaction between drug and polymer as shown in table 4. On the basis of data obtained from in-vitro dissolution studies that B1 is a promising formulation suitable for the immediate release of naratriptan for the systemic use since they exhibited maximum drug release of 100% in 10 min. The formulation batch B1 was found to be stable for a period of one month at 40°C/75%RH.

Order of Film forming polymer activity is as follows: HPMCE15+HPMCE50+HPMC (E15+E50) +HPMC E5.

Based on disintegration and dissolution results, formulation B1 was the best one from prepared sublingual formulations. Sublingual Films of Naratriptan were found to improve the versatility, convenience, patient compliance leading to an enhanced approach for the administration of drug to the pediatrics and geriatrics.

CONCLUSION:

Sublingual drug delivery has been used for formulation of drug naratriptan, with view of rapid drug release and quick onset of action. The result of the present investigation reveals that HPMC E15 could be best among the other polymers for formulation of fast dissolving film, on the basis of data obtained from *in-vitro* dissolution, that B1 is promising formulation for immediate release of drug. It can be accomplished that sublingual films can be possible novel drug dosage form for pediatric, geriatric and for general people. Hence fast dissolving films of naratriptan were found to be suitable for better therapeutic effect in treatment of migraine.

ACKNOWLEDGEMENT:

The Authors are thankful to Principal Dr Challa Srinivas Reddy, the principal of Vaagdevi College of pharmacy, Warangal for providing necessary facility for research work.

REFERENCES:

1.Y. Shravan Kumar, T. Nagaraju, R. Gowthami, M. Rajashekar. S. Sandeep, M. Mallesham, D. Sathish. Comprehensive Review on Oral Disintegrating Films. Current Drug Delivery,10, 96-108, **2013.**

2.KhanusiyaA.Qadir, Charyulu, RN, Prabhu, P. Bhatt, S. Shastry, CS. Formulation and Evaluation of Fast Dissolving Films of Loratadine for Sublingual Use. International Research Journal Of Pharmacy, 3(7), 157-161, **2012.**

3.BhyanBhupinder, JangraSarita. Formulation and evaluation of fast dissolving sublingual films of

Rizatriptan Benzoate. International Journal of Drug Development Research, 4(1), 133-143, **2012.**
4.Jayashri S. Borse. Atul, A. Shirkhedkar. Estimation of Naratriptan hydro- chloride in Bulk and Formulation by First Order Derivative UV- Spectro-photometric Methods. Journal of Applied Pharmaceutical Science,**2012**, 2(6), 227-229.
5.Kumara Swamy, Kumar, JMR, Sheshagiri Rao, J.V.L.N, U.Ashok Kumar, Vidyasagar. Spectrophotometric determination of Naratriptan hydrochloride in Bulk and Pharmaceutical dosage form, Indo American Journal of Pharmaceutical Reasearch, 1(4), 253-256, **2011**.
6.N.L Prasanthi, C. Sowmya Krishna, M. Eswar Gupta, S.S. Manikiran, N. Rama Rao. Design and Development of Sublingual Fast Dissolving Films for an Antiasthmatic Drug. Scholars Research Library, 3(1), 382-395, **2011**.
7.Kulkarni, A. S. Deokule, H.A. Mane, M.S. Ghadge, D. M. Exploration of Different Polymers for Use in the Formulation of oral fast dissolving strips, Journal of Current Pharmaceutical Research., 2(1), 33-35, **2010**.
8.Alpesh R, Patel. Dharmendra, S. Prajapati, Jignyasha A. Raval, fast dissolving films (fdfs) as a newer venture in fast dissolving dosage forms, Int. J. of drug dev& Research**.,** 2(2), 232-246, 2010**.**
9.Dixit, R.P. Puthli, S.P. Oral strip technology: Overview and future potential. J. Control Release, 139(2), 94-107, **2009.**
10.Bupendra, G Prajapathi, NayanRatnakar. A Review on Recent patents on Fast Dissolving Drug Delivery System. Int. J of Pharm Tech Research, 1(3), 790 – 798, 2009.
11.Barnhart SD, Sloboda MS, Dissolvable films the future of dissolvable films. Drug Dev tech., 1, 34-35, 2007.
12.Barnhart S, Rathborne M, Hadgraft J, Roberts M, Lane M. Thin film oral dosage forms, in: Modified release drug delivery technology, 2nd edition, Drugs & the pharm sciences., 209 - 216.
13.Dixit RP, Puthli SP, Oral strip technology: Overview and future potential. J. Control.Release. 139(2), 94-10, 2009.
14.Frey P, Film Strips and Pharmaceuticals,Pharma. Mfg. &Packag.Sourcer, winter, 92-93, 2006.
15Felton L, Donnell P. O, McGinity J. Mechanical properties of polymeric films prepared from aqueous dispersions, in: Aqueous polymeric coatings for pharmaceutical dosage forms, 3rd edition, McGinity J, Felton L Drugs & the pharm sciences., 108, 2006.
16.Fulzele S.V, Sattuwar P.M and Dorle A.K. Polymerized rosin: novel film forming polymer for drug delivery, Int. J. Pharm., 249, 175 -184, 2002.
17.Hoffmann & baron, llp (6900 jericho turnpike, syosset, ny, 11791, us) United States Patent Application 20080226695.
18.International Conference on Harmonization, ICH topic Q3C (R3) Impurities residual solvents. Note for guidance on Impurities: residual solvents. (CPMP/ICH/283/95), (www.emea.europa.eu/pdfs/human/ich/028395en.pdf).
19.Kuldeepak Sharma, William R. Pfister, and Tapash K. Ghosh, Drug Delivery to the Oral Cavity, Quick – Dispersing Oral Drug Delivery Systems, 261 – 289, 2005.
20.Kuchekar B, S Arumugam V, Ind J. Pharm. Edu. 35, 150, 2001.
21.Manoj Ashok Wagh, KothawadeParagDilip, KishorSahebraoSalunkhe, Nayana Vijay Chavan, VandanaRadheshyamDaga. Techniques used in orally disintegrating drug delivery system. Int. J. Pharm Drug Delivery: 2, 98 – 107, 2010.
22.Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki ,; Sugiyama T, Itoh Y. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film. Int J Pharm., 368 (12), 98-102, 2009.
23.Renuka Mishra and Avani Amin, Formulation and Characterization of Rapidly Dissolving Films of Cetirizine hydrochloride using Pullulan as a Film Forming Agent, Ind J of Pharm Edu. Res., 45(1), 2011.
24.Renuka Mishra, Avaniamin, Pharm Tech, 33(2), 48- 56, 2009.
25.Repka M et al., "Hot melt extrusion", in J. Swarbrick and J. Boylan, Eds., Encyclopedia of Pharmaceutical Technology, Volume 2, 2nd Edition (Marcel Dekker Inc, New York, NY USA., 1488–1504, 2002.
26.Shinde A, J.Garala K.C and More H.N. Development and characterization of transdermal therapeutics system of tramadol hydrochloride, Asian J. Pharm. 4, 265 - 269, 2008.
27.United States Patent No: 5648093; Gole et al; titled ‘Pharmaceutical and other dosage forms’; 1997.
27.Vondrak B, Barnhart S, Dissolvable Films for Flexible Product Format in Drug Delivery, Pharm Tech Suppl., April 2008.
29.Yarwood R, Zydis, A novel, Fast Dissolving Dosage Form. Man. Chem., 61: 36-37, 1990.
30.Zhang H, Zhang J, Streisand J.B. Oral mucosal drug delivery: clinical pharmaco-kinetics and therapeutic applications, Clin. Pharmacokinet., 41 (9), 661-680, 2002.

Table 1: Formulation codes of sublingual films

Polymer used	Drug polymer ratio	Formulation code
HPMC E5 Cps	1:15 1:16 1:17 1:18	A1 A2 A3 A4
HPMC E15 Cps	1:15 1:16 1:17 1:18	B1 B2 B3 B4
HPMC 50 Cps	1:15 1:16 1:17 1:18	C1 C2 C3 C4
HPMCE15+HPMC E50	1:15 1:16 1:17 1:18	D1 D2 D3 D4

Table 2: Formulation details

F-CODE	NAR (mg)	HPMC E5 (mg)	HPMCE 15 (mg)	HPMC E50 (mg)	PEG 400 (µl)	ASP (mg)	FLV (mg)	MNT(mg)	SSG(mg)	Water(ml)
A1	24	360	-	-	0.50	2.00	2.00	5.00	2.00	15.00
A2	24	408	-	-	0.50	2.00	2.00	5.00	2.00	15.00
A3	24	432	-	-	0.50	2.00	2.00	5.00	2.00	15.00
A4	24	456	-	-	0.50	2.00	2.00	5.00	2.00	15.00
B1	24	-	360	-	0.50	2.00	2.00	5.00	2.00	15.00
B2	24	-	408	-	0.50	2.00	2.00	5.00	2.00	15.00
B3	24	-	432	-	0.50	2.00	2.00	5.00	2.00	15.00
B4	24	-	456	-	0.50	2.00	2.00	5.00	2.00	15.00
C1	24	-	-	360	0.50	2.00	2.00	5.00	2.00	15.00
C2	24	-	-	408	0.50	2.00	2.00	5.00	2.00	15.00
C3	24	-	-	432	0.50	2.00	2.00	5.00	2.00	15.00
C4	24	-	-	456	0.50	2.00	2.00	5.00	2.00	15.00
D1	24	-	180	180	0.50	2.00	2.00	5.00	2.00	15.00
D2	24	-	192	192	0.50	2.00	2.00	5.00	2.00	15.00
D3	24	-	204	204	0.50	2.00	2.00	5.00	2.00	15.00
D4	24	-	216	216	0.50	2.00	2.00	5.00	2.00	15.00

NAR: Naratriptan, **HPMC:** Hydroxy propyl methyl cellulose, **PEG:** Poly ethylene glycol, **ASP:** Aspartame, **FLV:** Flavor, **MNT:** Mint, **SSG:** sodium starch glycolate,

Table 3: Evaluations of Sublingual Films

Formulations Code	Color	Weight variation (mg)	Thickness (mm)	Disintegration time (sec)	Assay
A1	Transparent	23.5±1.21	0.04±0.21	21.1±0.2	99.1±0.37
A2	Transparent	25..3±0.32	0.05±0.13	25.4±0.5	98.5±0.13
A3	Transparent	26.2±0.18	0.05±0.11	31.6±0.5	98.8±0.28
A4	Transparent	27.8±0.18	0.05±0.01	33.5±0.5	98.8±0.40
B1	Transparent	23.6±0.53	0.05±0.01	15.3±0.3	99.8±0.08
B2	Transparent	25.5±0.82	0.05±0.22	18.5±0.2	99.7±0.07
B3	Transparent	26.6±0.61	0.05±0.01	25.1±0.8	99.1±0.23
B4	Transparent	28.2±0.23	0.05±0.01	26.1±0.03	98.8±0.22
C1	Transparent	23.8±0.25	0.05±0.14	27.2±0.3	98.7±0.42
C2	Transparent	25.8±0.31	0.05±0.20	32.3±0.5	99.4±0.16
C3	Transparent	27.3±0.22	0.06±0.23	41.6±0.1	99.3±0.08
C4	Transparent	28.6±0.22	0.06±0.01	43.2±0.1	99.1±0.03
D1	Transparent	24.1±0.01	0.05±0.23	42.5±0.02	99.1±0.17
D2	Transparent	25.9±0.01	0.06±0.25	44.2±0.1	98.5±0.13
D3	Transparent	27.8±0.03	0.06±0.80	46.5±0.03	98.8±0.23
D4	Transparent	28.9±0.01	0.07±0.01	48±0.05	98.8±0.30

Table 4: characteristic ftir peaks of pure drug and finalized batch

FTIR Peaks	Naratriptan	Batch B1
Aromatic C-H	**3031.89 cm^{-1}**	**3031.89 cm^{-1}**
Aliphatic C-H Stretching	**2966.31 cm^{-1}**	**2965.25 cm^{-1}**
N-H Stretching 2° amine	**3395.05cm^{-1}**	**3395.05cm^{-1}**

FTIR:

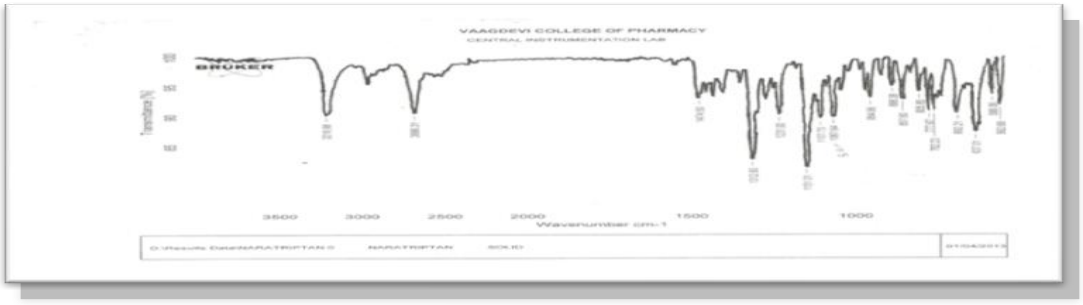

Fig 1: FT IR of Pure Naratriptan

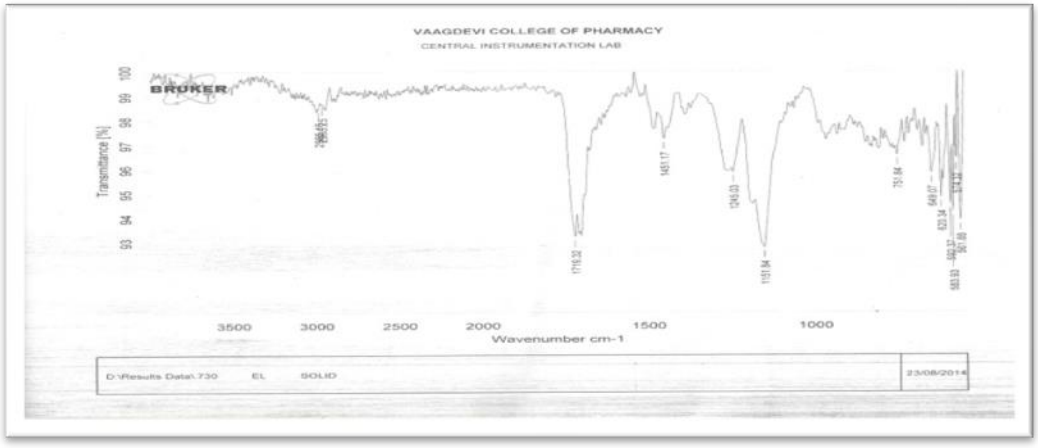

Fig 2 FTIR of Finalized Batch B1

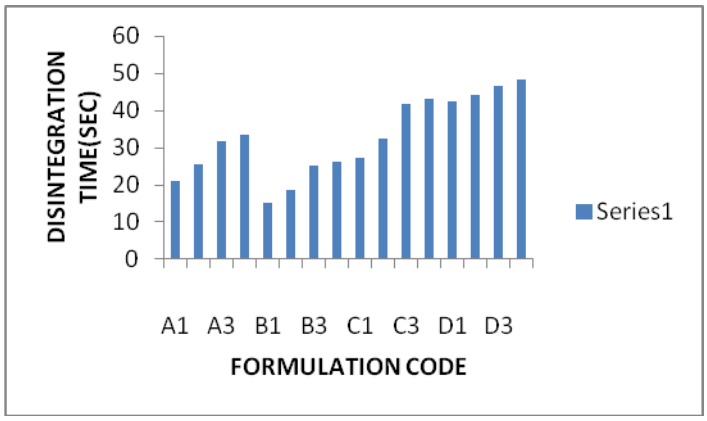

Fig 3: Disintegration times of Naratriptan sublingual films

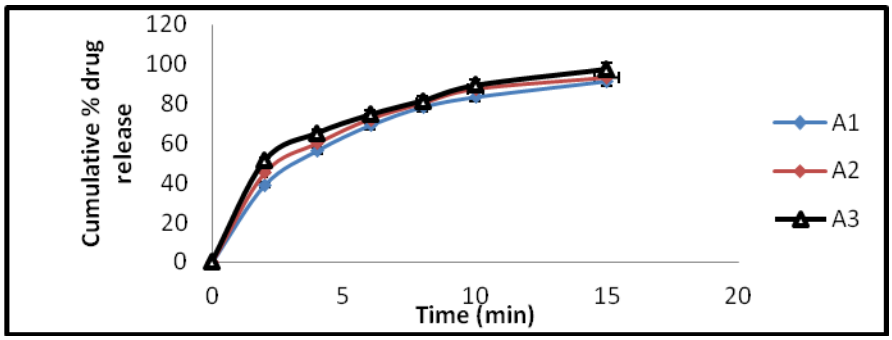

Fig 4: Cumulative % Release of Naratriptan (A1, A2 & A3) formulations

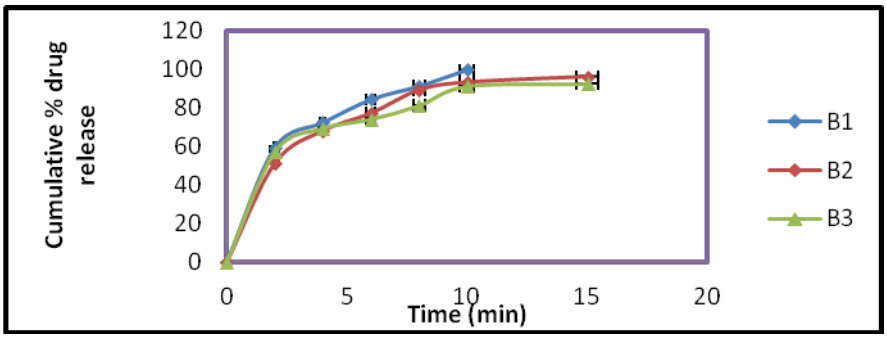

Fig 5: Cumulative % Release of Naratriptan(B1, B2 & B3) formulations

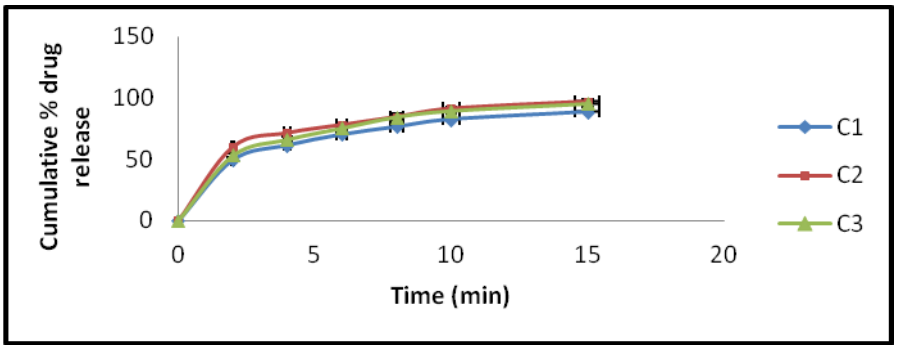

Fig 6: Cumulative % Release of Naratriptan (C1, C2 & C3) formulations

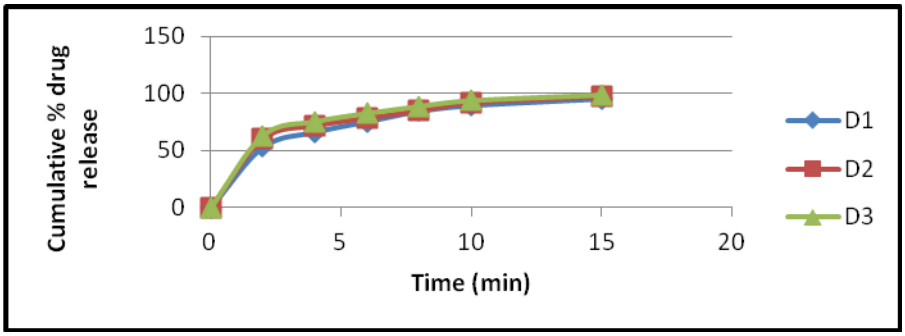

Fig 7: Cumulative % Release of Naratriptan (D1, D2 & D3) formulations