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Formulation and invitro evaluation of diazepam microbeads

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ABSTRACT
The present study is used to prepare Diazepam floating microsphere and control the drug release. HPMC, Ethyl cellulose Eudragit, S100 are the polymers used for the preparation of floating microspheres. Floating microsphere stable at the room temperature and humidity for 90 days. The formulated floating microspheres seem to be potential candidate as an oral gastro retentive controlled drug delivery system in prolonging the drug retention stomach and increasing the bioavailability of drug.

I. INTRODUCTION

1. ORAL CONTROL DRUG DELIVERY SYSTEM

It is a type of drug delivery system which continuously release the drug by oral route. The system reaches the target either local or systemic way. The formulated drug will be administrated through oral or systemic route. The main areas of development of oral controlled drug delivery system.

SCOPE

Oral control dosage forms suffer from two adversities they are short gastric retention time (GRT) and gastric emptying time (GET). Altering the gastric emptying can over helm problems and can also produce side effects.
Extended release dosage form with prolonged residence time in stomach are highly desirable for drugs.

- ❖ They are locally active in stomach.
- ❖ They have an absorption window in the stomach.
- ❖ They are unstable in the intestinal or colonic environment.

They have low solubility at high PH values. Oral route is consider most natural, uncomplicated convenient and safe due to ease of administration.

AIM AND OBJECTIVE OF THE WORK

The aim of the study is to formulate and evaluate diazepam floating microspheres using different polymers i.e. Xanthan gum and Guar gum in different ratios.

PLAN OF WORK

- Preformulation studies.

1. Identification of drug
2. Drug–Excipients compatibility studies by FTIR spectrophotometry

- Formulation of microspheres for controlled drug delivery of diazepam
- Evaluation studies.

1. Entrapment efficacy.
2. Drug loading.
3. Scanning electron microscopy.
4. Buoyancy time.
5. Swelling index.
6. In vitro drug release.
7. In vitro release kinetics.

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FORMULATION DESIGN

Formulation of Diazepam Floating Microspheres

Ingredients(mg/Dose)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diazepam	10	10	10	10	10	10	10	10	10
HPMC	10	20	30	-	-	-	-	-	-
EudragitS100	-	-	-	10	20	30	-	-	-
Ethyl cellulose	-	-	-	-	-	-	10	20	30
$NaHCO_3$	10	20	30	10	20	30	10	20	30
Water(ml)	q.s	q.s	q.s	-	-	-	-	-	-
Dichloro methane:Ethanol (2:1)(ml)	-	-	-	q.s	q.s	q.s	-	-	-
Ethanol(ml)	-	-	-	-	-	-	q.s	q.s	q.s

Table 1Results

Microparticulate Analysis

Formulationcode	Bulk density(g/cc)	Tapped density(g/cc)	Carr'sIndex	HausnerRatio	Angle ofrepose(θ)
F1	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02	28.06 0.31
F2	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04	27.58 0.15
F3	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08	28.44 0.11
F4	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06	28.36 0.13
F5	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08	28.52 0.19
F6	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09	29.32 0.19
F7	0.51±0.045	0.59 ± 0.04	14.48±0.8	1.15±0.09	29.69 0.19
F8	0.45±0.041	0.52 ± 0.10	15.60±0.21	1.15±0.04	28.06 0.41
F9	0.44±0.041	0.52± 0.11	15.48±0.54	1.18±0.12	28.52 0.15

Table2

All the formulations were evaluated for bulk density, tapped density, %compressibility, hausner's ratio and angle of repose. The results of %compressibility, hausner's ratio and angle of repose were found to be <16, <1.25 and <30 respectively. These results show that the formulations have very good flow properties

EVALUATION AND CHARACTERISATION OF MICROSPHERES PERCENTAGE YIELD

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug- polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield of the prepared microspheres is recorded in Table14 and displayed in Figure16.

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DRUG ENTRAPMENT EFFICIENCY

S.No.	Formulationcode	%Yield	%Buoyancy	% Drug entrapment efficiency	%SwellingIndex
1	**F1**	80	63	62.66	33.32
2	**F2**	83.33	67	72	35.66
3	**F3**	85	75	89	30.91
4	**F4**	86	79	56	32.33
5	**F5**	87.22	89	92	38.11
6	**F6**	80	85	72	38.18
7	**F7**	88	70	80	36.55
8	**F8**	82	76	82	37.32
9	**F9**	80	84	67	35.66

Table 3

DRUGENTRAPMENT EFFICIENCY

Percentage Drug entrapment efficiency of Diazepam arranged from 56 to 92% for microspheres. The drug entrapment efficiency of the prepared microspheres incrased progressively with an increase in proportion of the respective polymers Increase in the polymer concentration increase the viscosity of the dispersed phase . The partical size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expectedto decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency The % drug entrapment efficiency of the prepared microsphere displayed in table 1

Percentage yield and percentage drug entrapment efficiency of prepared microspheres

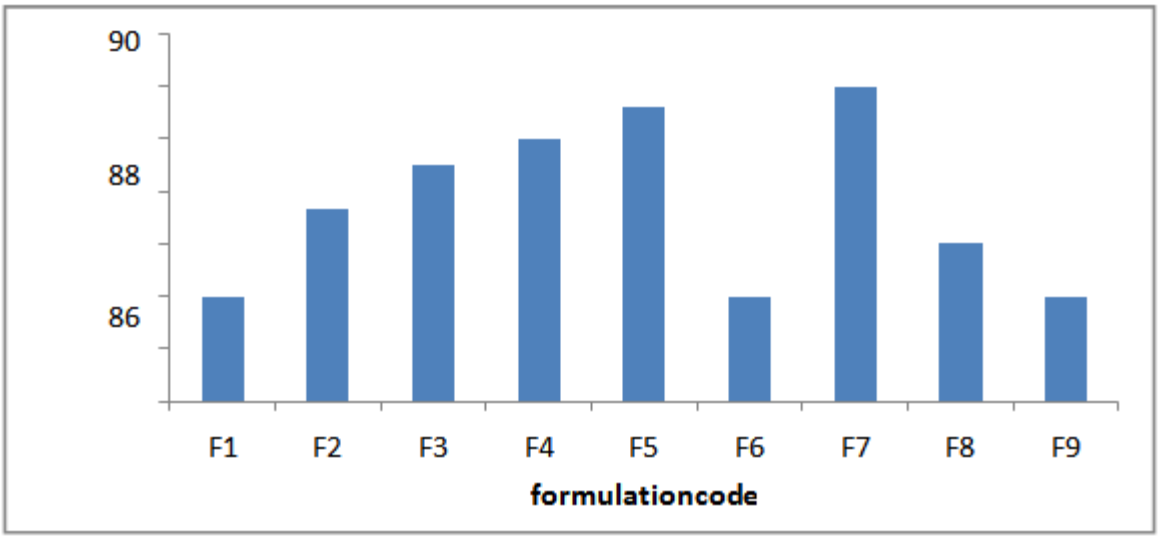

Fig 1

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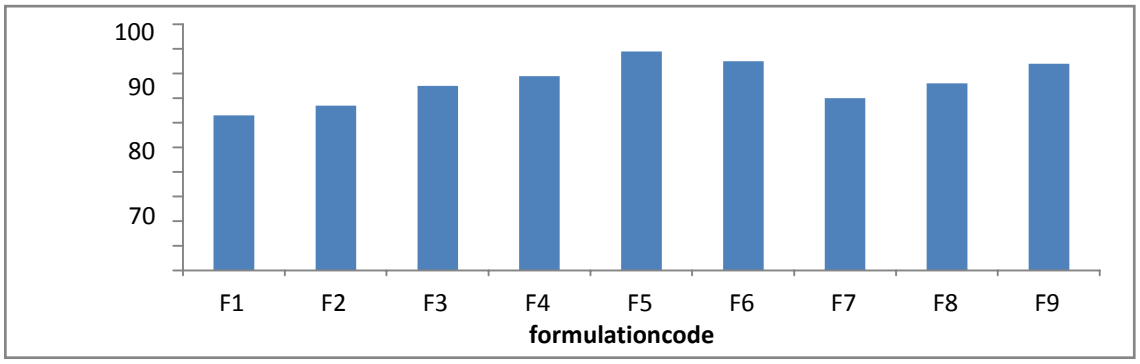

Fig 2

Graph for % buoyancy vs formulation

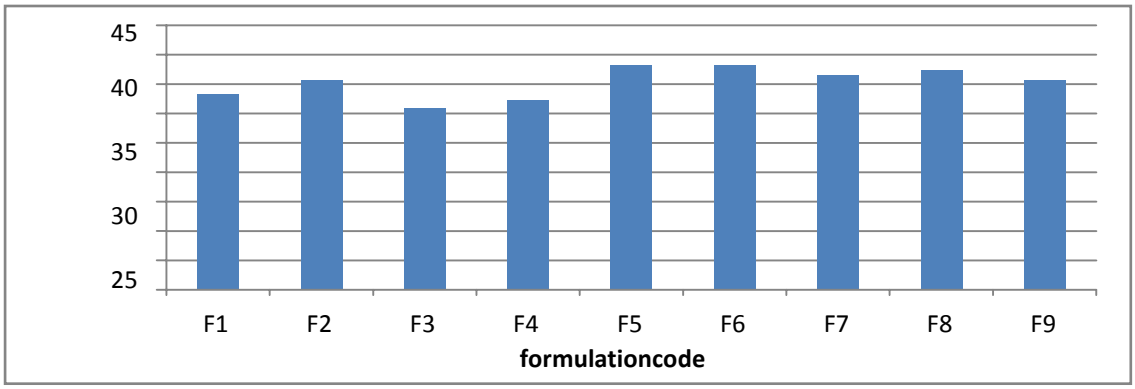

Fig 3

Mean Particle Size

Graph for % swelling index vs formulation code

Mean particle size was determined by optical microscopy and the average particle size was calculated. The results were shown in table-

PARTICLESIZE RANGE (µm)	MIDPOINTSIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE(µm)
400-600	500	80	40000	540µm
600-800	700	20	14000	
		∑n=100	∑nd=54000	

Table 4

Particle size data of F_2

PARTICLESIZE RANGE (µm)	MIDPOINTSIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE(µm)

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400-600	500	49	24500	602µm
600-800	700	51	35700	
		∑n=100	∑nd=60200	

Table 5

Particle size data of F3

PARTICLE SIZE RANGE (µm)	**MIDPOINT SIZE RANGE (d)**	**FREQUENCY (n)**	**nd**	**AVERAGE PARTICLE SIZE(µm)**
400-600	**500**	**28**	**14000**	**644µm**
600-800	**700**	**72**	**50400**	
		∑n=100	∑nd=64400	

Table 6

Particle size data of F4

PARTICLESI ZE RANGE (µm)	**MIDPOINTSIZE RANGE (d)**	**FREQUENCY (n)**	**nd**	**AVERAGE PARTICLE SIZE(µm)**
400-600	500	44	22000	612µm
600-800	700	56	39200	
		∑n=100	∑nd=61200	

Table 7

Particle size data of F5

PARTICLESI ZE RANGE (µm)	**MIDPOINTSIZE RANGE (d)**	**FREQUENCY (n)**	**nd**	**AVERAGE PARTICLE SIZE(µm)**
400-600	500	86	43000	528µm
600-800	700	14	9800	

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	e∑n=100	∑nd=52800	

Table 8

Particle size data of F6

PARTICLESI ZE RANGE (µm)	MIDPOINTSIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE(µm)
400-600	500	38	19000	624µm
600-800	700	62	43400	
		∑n=100	∑nd=62400	

Table 9

Particle size data of F7

PARTICLESIZE RANGE (µm)	MIDPOINTSIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE(µm)
400-600	500	56	28000	588µm
600-800	700	44	30800	
		∑n=100	∑nd=58800	

Table 10

Particle size data of F8

PARTICLESI ZE RANGE (µm)	MIDPOINTSIZE RANGE (d)	FREQUENCY (n)	nd	AVERAGE PARTICLE SIZE(µm)
400-600	500	54	27500	598µm
600-800	700	46	32200	
		∑n=100	∑nd=59800	

Table 11

Particle size data of F9

PARTICLESI ZE RANGE (µm)	MIDPOINTSIZ E RANGE (d)	FREQUENCY(n)	nd	AVERAGE PARTICLE SIZE(µm)

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400-600	500	37	18500	626µm
600-800	700	63	44100	
		∑n=100	∑nd=62600	

Table 12

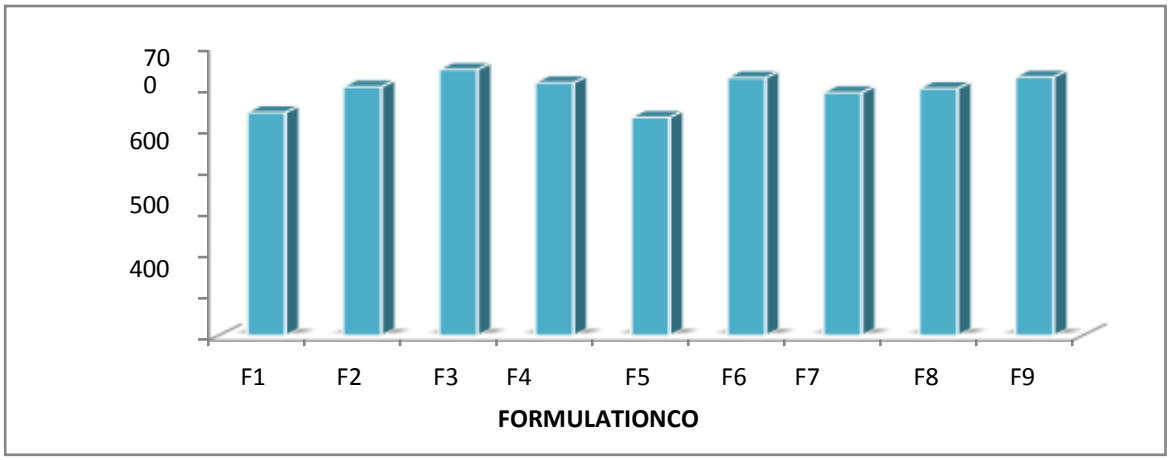

Fig 4

Average particle size of microspheres from formulations F1 to F9.

S.No	Batches	Mean ParticleSize(µm)
1	F1	540µm
2	F2	602µm
3	F3	644µm
4	F4	612µm
5	F5	528µm
6	F6	624µm
7	F7	588µm
8	F8	598µm
9	F9	626µm

Table 13
Average particle size of Diazepam microspheres

IN-VITRO DRUG RELEASE STUDIES

Dissolution studies of all the formulations were carried out using dissolution apparatus USP typeI. The dissolution studies were conducted by using dissolution media, pH 1.2.The results of the in- vitro dissolution studies of formulations F1 to F9areshown in table no.25The plots of Cumulative percentage drug release Vs Time. Figure shows the comparison of %CDR for formulations F1 to F3, figure for formulations F4 to F6 and figure for formulations F7 to F9.

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Percentage cumulative drug release for all formulations

TIME(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	23	18	16	28.4	16.25	14	25.3	23	11.30
2	32	27.2	24	40.3	21.3	20	37.2	38	19.6
3	41.5	36	31	49.7	28.6	26	44.3	45	25.4
4	57.6	45	42	55.3	30.4	28	52.4	50	28.2
5	68.2	53	49	62.4	38.2	38	57.8	54	36.3
6	79.7	67	54	68.3	44.3	42	65.2	63	40.4
7	86.4	72	58.7	76.9	51.6	48	70.8	69	46.8
8	-	84	70.4	83.2	57.2	54	79.2	78	59.3
10	-	-	-	**86.9**	**78.3**	**63**	**85.2**	**83**	**62.4**
12	-	-	-	-	**86.2**	**76**	-	-	**71.2**

Table 14

Dissolution graph for formulation F1 F3

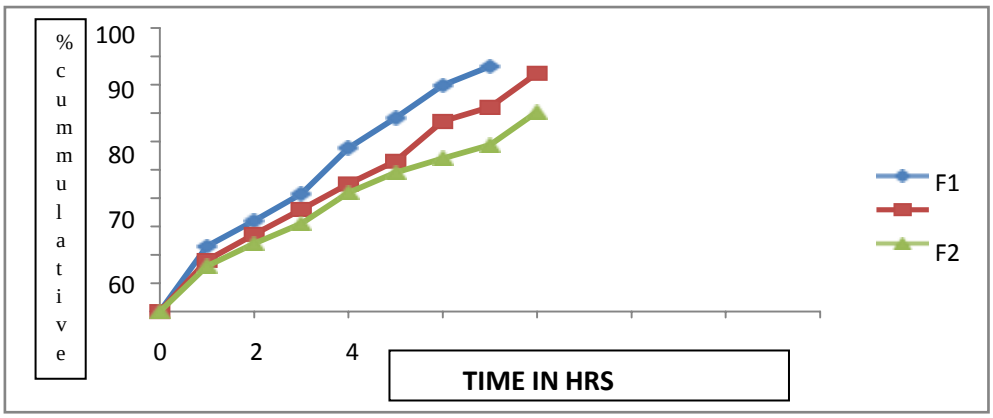

Fig 5

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Dissolution graph for formulation F4–F6

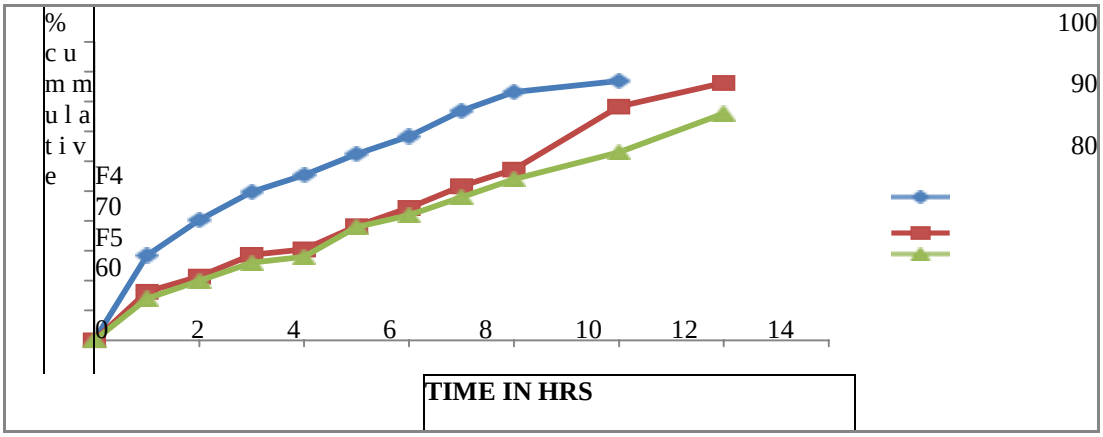

Fig 6

Dissolution graph for formulation F7–F9

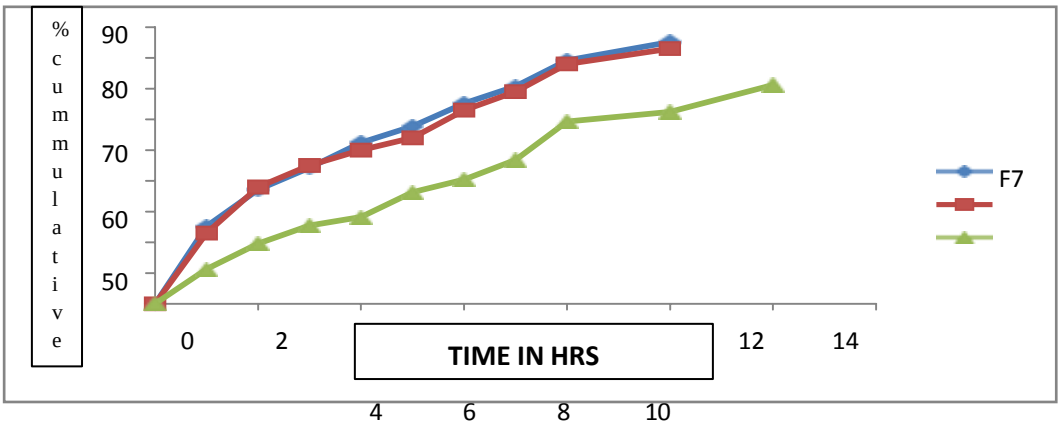

Fig 7

IN-VITRO DRUG RELEASE KINETICS

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled inTable26,27 .The coefficient of determination(R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Zero order (R^2 = 0.985). From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

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In-vitro drug release kinetics data for Formulation F5

Zero order		First order		Higuchi's data		Korsmeyer-Peppasdata	
Time(h)	%CDR	Time(h)	Log % CD Remaining	SQR Time	%CDR	LogT ime	Log%CDR
1	16.25	1	1.922	1	16.25	0	1.21
2	21.3	2	1.895	1.414	21.3	0.301	1.328
3	28.6	3	1.853	1.732	28.6	0.477	1.456
4	30.4	4	1.842	2	30.4	0.602	1.482
5	38.2	5	1.790	2.236	38.2	0.698	1.582
6	44.3	6	1.745	2.449	44.3	0.778	1.646
7	51.6	7	1.684	2.645	51.6	0.845	1.712
8	57.2	8	1.631	2.828	57.2	0.903	1.752
9	78.3	10	1.336	3.162	78.3	1	1.893
10	86.2	12	1.139	3.464	86.2	1.079	1.935

Table15

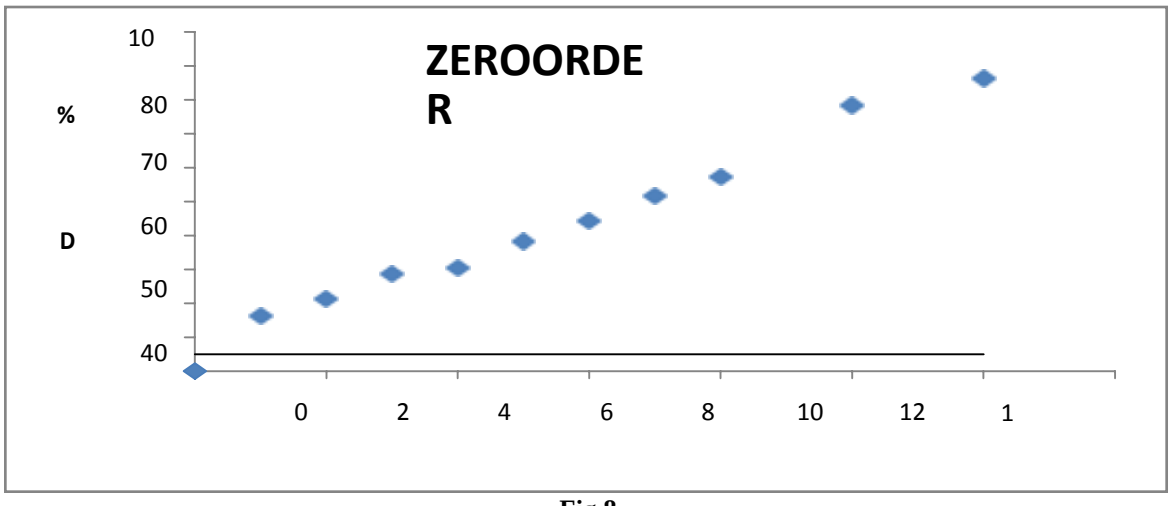

Fig 8

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Zero order kinetic graph for F5 batch

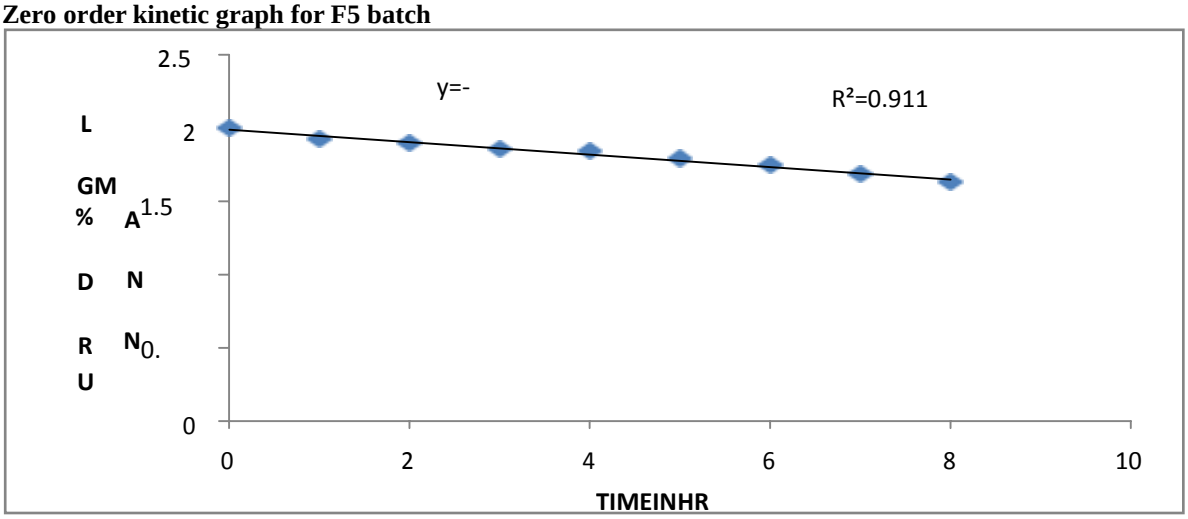

Fig 9 First order kinetic graph for F5 batch

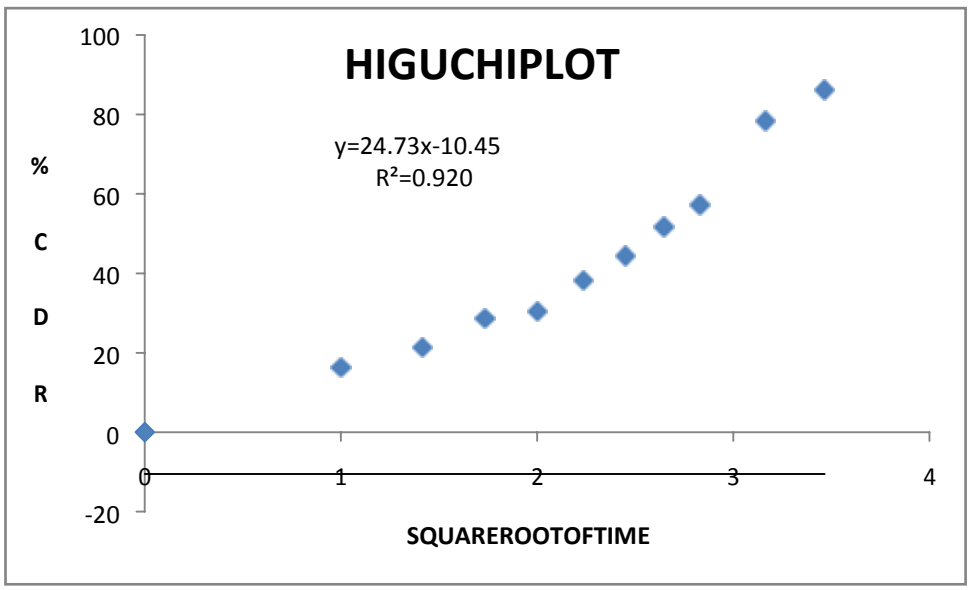

Fig 10

Higuchis model kinetic graph for F5 batch

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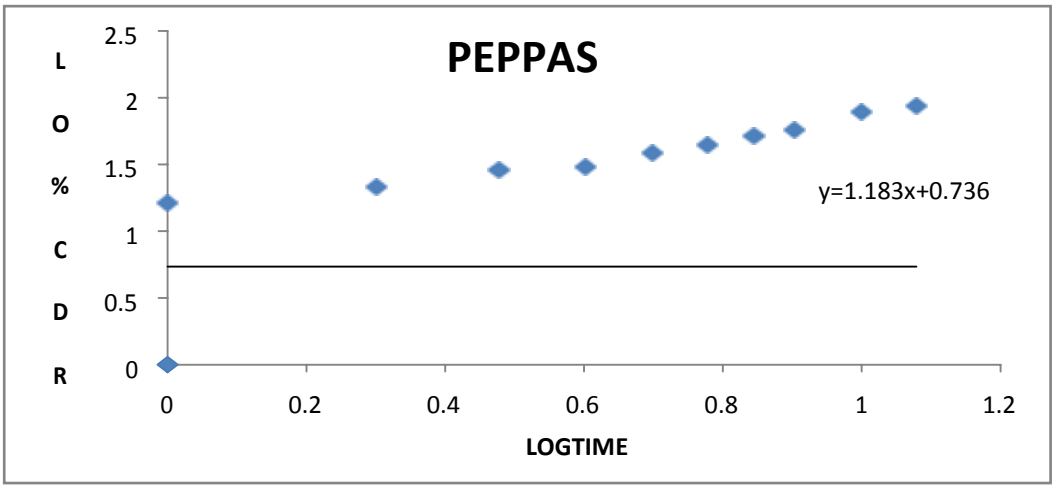

Fig 11

Peppas model kinetic graph for F5

RELEASEKINEITCS				
	ZERO	HIGUCHI	PEPPAS	FIRST
	1	2	3	4
	QVs T	QVs√T	LogC Vs Log T	Log%RemainVs T
Slope	6.85	24.73	1.18	-0.06
Intercept	4.99	10.45	0.73	2.06
Correlation	0.99	0.95	0.83	-0.95
R2	0.9850	0.9365	0.69	0.91

Table16

STABILITY STUDIES OF DIAZEPAM OPTIMIZED FORMULATION:
The optimized formulation of Diazepam (F5) was subjected to short-term stability testingby storing the microspheres at room temperature 25°C /60% RH.

Table: 28 Stability studies of optimized formulation at room temperature

Drug entrapment efficiency±release **ime**	**Colour**	**St.D.at Room Temperature**	**Cumulative% drug ±St.D.**
Firstday	White	92.00±0.91	86.20±0.55

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30days	White	91.84±0.23	86.01±0.72
60days	White	91.06±0.62	85.62±0.65

Results from stability studies indicate that the formulated microspheres are stable for a period of3 months under room temperature i.e., 30˚C temp and 65±5% RH. There were no remarkable changes were observed during the period of storage.

The optimized formulation of Diazepam (F5) was subjected to accelerated stability testingby storing the microspheres at accelerated temperature 40°C/70% RH.

II. SUMMARY

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired plasma concentration of the drug for a particular period of time. However, in complete release of the drug, shorter residence times of dosage forms in the upper GIT leads to lower oral bioavailability. Such limitations of the conventional dosage forms have paved way to an era of controlled and novel drug delivery systems. Diazepam , a benzodiazepine drug used to treat anxiety, panic attacks, insomnia, seizures (including status epilepticus), muscle spasms (such as in tetanus cases), restless legs syndrome, alcohol withdrawal, benzodiazepine withdrawal, opiate withdrawal syndrome and Ménière's disease.. A floating drug delivery system was planned for Diazepam as such system when administered would remain buoyant on the gastric fluids for a prolonged period of time and drug would be available in the dissolved form. In this way it stands an advantage over conventional dosage form Percentage Drug entrapment efficiency of F1 to F3 ranges from 62 to 89% form microspheres containing HPMC as polymer, formulations F4 to F6 ranges from 56 to 92% for microspheres containing Eudragit S 100 as polymer and formulations F7 to F9 ranges from67 to 82% for microspheres containing Ethyl cellulose as polymer. Almost all the formulations showed fairly acceptable values for all the parameters evaluated. The average particle size of floating microspheres was in the range of 528 µm- 644 µm and improved drug entrapment efficiency could be depending upon the type and ratio of polymer used. Among all formulations F5 formulation with drug: polymer (1:2) was found to be satisfactory in terms of excellent micromeritic properties, percent yield (87.22%), drug entrapment efficiency (92%), percent buoyancy (89%),and highest in vitro drug releaseof86.2%in sustained manner over an extended period of timefor12 hrs. Thus, the prepared microspheres proved to be a potential candidate as a microparticulate controlled release drug delivery device in this era of patenting novel and controlled release formulations

III. CONCLUSION

The present study has been a satisfactory attempt to formulate a floating Microspheres of Diazepam with a view to control the release of the drug. From the experimental results it can be concluded that, Biocompatible polymers like can be HPMC, Ethyl cellulose and Eudragit used to formulate a floating Microspheres. Good percentage drug entrapment and practical yields were obtained with the polymers. The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules. The floating microspheres of drug with HPMC and Ethyl cellulose were buoyant while those with Eudragit S100 showed greater buoyancy. Cumulative percentage drug release significantly decreased with increase in polymer concentration. Formulated microspheres were stable and compatible at the room and accelerated temperature and humidity in storage for 90days.Thus, the formulated floating microspheres seem to be a potential candidate as an oral gastro retentive controlled drug delivery system in prolonging the drug retention stomach and increasing the bioavailability of drug. Formulated microspheres were stable and compatible at the room and accelerated temperature and humidity in storage for 90days. Thus, the formulated floating microspheres seem to be a potential candidate as an oral gastro retentive controlled drug delivery system in prolonging the drug retention stomach and increasing the Bioavailability of drug.

Future Scope:

- Further detailed stability studies and in vivo bioavailability studies are to bedone to establish the efficacy of these formulations.

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In vitro–in vivo correlation study is to be done to establish the guarantee of efficacy and bioavailability of the formulation.

REFERENCE

- Hong SI, Oh SY. Dissolution kinetics and physical characterization of three-layered tablet with (polyethyleneoxide) core matrix capped by Carbopol. Int JPharm 2008;356:121-9.
- McGinity JW, Koleng JJ, Repka MA, Zhang F. Hot melt extrusion technology. In:Swarbrik J, editor. Encylopedia of Pharmaceutical Technology. 3 rd ed. New York: Informa Healthcare USA, Inc; 2005. p. 2004-20.
- Trotta M, Gasco MR, Morel S. Release of drugs from oil-water micro emulsions. JControlRelease1989;10:237-43.
- C.Narendra, M.S. Srinathand G.Babu, Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention, AAPSPharmSciTech. 7 (2006)23- 29; DOI: 10.1208/pt070234.
- H.Ravishankar, P.Patil, A.Samel, H-U. Petereit, R.Lizioand J. Iyer-Chavan, Modulated release metoprolol succinate formulation based on ionic interactions: in-vivo proof of concept,J. Control. Rel.111 (2006) 65-72.
- United States Pharmacopoeia 30, National Formulary 25, USP Convention, Rockville2007, p.2648. USP26 /NF21 2003, Asianedition, 1220-1221.
- Hamid AM, Harris MS, Jaweria T, and Rabia IY. Oncedaily tablet formulation and invitroreleaseevaluationofcefpodoximeusing hydroxypropylmethylcellulose:atechnicalnot e.AAPSPharmSciTech. 2006; 7: Article78
- Atsuko F, Ryuta F, Yorinobu Y, and HisakazuS.Analysis of the release process ofphenylpropanolaminehydrochloridefrom ethylcellulosematrixgranulesiv.
- Evaluationofthecontrolledreleasepropertiesfo rinvivoandinvitroreleasesystems. Chem.Pharm. Bull.2007;55: 1569—1573.
- Narendra C, Srinath M, Ganesh B, Optimization ofbilayer floating tablets containingMetoprolol tartrate as a model drug for gastric retention, AAPS Pharm Sci.Tech 2006;7;E1-E7.
- AmidonLG,LobenbergR,kimJS,pharmacoki neticsofanimmediaterelease,acontrolled Release and a two pulse dosage form in dogs. Eur.j.pharm.Bio pharm 2005;60; 17-23.
- B.N. SinghandK. H.Kim,Floating drug delivery systems:anapproachtooralcontrolleddrugdeli veryvia gastric retention, J. Control. Rel. 63 (2000)235–259.
- S. Arora, J. Ali, A. Ahuja, R. K. Khar and S. Baboota, Floating drug delivery systems: areview,AAPSPharmSciTech 6 (2005)372–390.
- R. Bomma, R. A. S. Naidu, M. R. Yamsani and K. Veerabrahma, Development andevaluation of gastroretentive norfloxacin floating tablets, Acta Pharm. 59 (2009) 211–221;DOI: 10.2478/v10007-009Indian Pharmacopoeia,4th edition, Ministryof
- HealthandFamilyWelfare,Govt.ofIndia.Thec ontrollerofpublications,NewDelhi.1996, A-54.Ajit Kulkarni and Manish Bhatia Development and evaluation ofregioselective bilayer floating tablets of Atenolol and Lovastatin for biphasic releaseprofile Iranian Journalof Pharmaceutical Research(2009), 8(1):15-25
- BelgamwarV.S.,SuranaS.J.;Floatingbioadhes ivedrugdeliveryusingnoveleffervescent agents;AsianJournalof Pharmaceutics;AprilJune2009,156-160-0019-6.
- BrahmaN.SinghKwonH.Kim.Drugdelivery-oralroute.In:SwarbrrickJ,ed.Encyclopediaofp harmaceuticaltechnology.NewYork,Marcel Decker.2002 Bhise SD, Aloorkar NH: Formulation and Invitro evaluation of floatingcapsules ofTheophylline.Ind JPharm Sci. 2008; 70(2):88-93.
- FerdousK,MohammedSMI,Razzak,Moham medZRK,KaziRA,SamsMAS,MohammedS R:P reparationandinvitroevaluationofTheophyllin eloadedgastroretentivefloatingtablet of MethocelK4 M. JPharmSci. 2008; 7(1): 184-189.
- Timmermans J, Moes AJ. How Well Floating Dosage Form Float? .Int J Pharm 1990; 62:2076.
- HoffmanBB.Catecholamines,sympathomime ticsdrugs,and

adrenergicreceptorantagonists.In:HardmanJ G,LimbirdLE, eds.GoodmanandGilman'sThePharmacologi calBasisof Therapeutics.10th Edn. NewYork, NY:McGraw- Hill;2001:255Y256.

- TakaraK,KakumotoM,TanigawaraY,Funakos hiJ,SakaedaT,OkumuraK:Interactionofdigoxi nwithantihypertensivedrugsviaMDR1.LifeSc i.2002Feb15;70(13):1491-500.Pubmed.
- Doppenschmitt S, Langguth P, Regardh CG, Andersson TB, Hilgendorf C, Spahn-LangguthH:Characterizationofbindingproper tiestohumanP-glycoprotein:development of a [3H]verapamil radioligand-binding assay. J Pharmacol Exp Ther.1999 Jan;288(1):348-57. Pubmed.