AJPRHC

Research Article

DEVELOPMENT AND EVALUATION OF FLOATING-MUCOADHESIVE DIPYRIDAMOLE TABLET

BIRAJDAR SHIVPRASAD M.[1], DARVESHWAR JAGDEEP D.[2]

For Author affiliations see end of the text

This paper is available online at www.jprhc.in

ABSTRACT

The present study was aimed towards development and evaluation of tablet as a floating-Mucoadhesive drug delivery system, which can provide sustained release of the model drug. The work also was aimed to study various parameters affecting the behavior of floating-mucoadhesive tablet in oral dosage form. Formulation of Gastro-Retentive Dosage Forms (GRDFs) containing suitable drug candidate which would remain in stomach and/or upper part of GIT for prolonged period of time thereby is maximizing the drug release at desired site within the time before GRDFs leave the stomach and or upper part of GIT. Dipyridamole is BCS class II drug having low solubility and high permeability. It is soluble at low pH but insoluble in high pH (i.e. alkaline ph of small intestine)its oral bioavailability is 37-66% & biological half life is also short (40 min). In this study the bioavailability of the dipyridamole increase by using various concentration of HPMC, Carbapol and Sodium bicarbonate for swelling, mucoadhesive and floating behavior respectively. Bioadhesive strength depends upon carbapol as concentration of polymer increases bioadhesive strength also increases. HPMC is water Swealable but Carbapol is hydrogel in nature it restricts movement of polymer and affect the swelling index.

KEYWORDS: Mucoadhesive**,** Floating**,** HPMC**,** Dipyridamole**,** Vasodilator agent

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. Oral sustained release drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs.

Floating –Mucoadhesive Drug Delivery System:

A gastro retentive dosage form will release the drug over an extended period in the stomach and upper gastrointestinal tract (GIT) thus enhancing the opportunity for absorption. Various approaches have been proposed to control the gastric residence of drug delivery systems in the upper part of the GIT including floating drug delivery systems (FDDS). High density DDS, bioadhesive systems, swelling and expanding DDS, modified shape systems and other delayed gastric devices. FDDS is a gastro retentive dosage form (GRDF), which can prolong the gastric residence time (GRT) to produce an acceptable drug bioavailability.

FDDS is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs which act locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid FDDS or hydro dynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Based on the mechanism of buoyancy, two distinctly different technologies, *i.e.* non-effervescent and effervescent systems, have been used in the development of FDDS.

The effervescent system uses matrices prepared with swellable polymers and effervescent components *e.g.* sodium bicarbonate and citric acid or stearic acid. In non-effervescent FDDS, the drug mixes with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy on these dosage forms.

AIM AND OBJECTIVE

Need for the Study

Drug absorption in GI tract is highly variable procedure and prolonging gastric retention of dosage form extend the time for drug absorption. Floating Mucoadhesive Drug Delivery System promises to be a potential approach for gastric retention.

It has been suggested for following instances that an active material should be formulated in form of Floating-Mucoadhesive to enhance Bioavailability.

1. Having improper dissolution or stability problem in small intestine.
2. Needs local effect in stomach.
3. Being absorbed only in stomach or upper part of intestine.

Aim

The present study was aimed towards development and evaluation of tablet as a floating-Mucoadhesive drug delivery system, which can provide sustained release of the model drug. The work also was aimed to study various parameters affecting the behavior of floating-mucoadhesive tablet in oral dosage form. Formulation of Gastro-Retentive Dosage Forms (GRDFs) containing suitable drug candidate which would remain in stomach and/or upper part of GIT for prolonged period of time thereby is maximizing the drug release at desired site within the time before GRDFs leave the stomach and or upper part of GIT.

Objective

The Major objectives of the work are:

- To develop an optimized method for floating-Mucoadhesive matrix tablet of Dipyridamole.
- Study the effect of various processing parameters.
- Formulation and evaluation of floating-Mucoadhesive matrix tablet of Dipyridamole.

MATERIAL AND METHOD

The following materials that were Pharma grade or the best possible Laboratory Reagent were used as supplied by the manufacturer without further purification or investigation.

Materials

Table No.1: List of chemicals used with grade and supplier

Sr. No.	Materials Used	Grade	Manufacturer
1.	Dipyridamol	Pharma	Torrent Pharma Ltd., Mumbai
2.	HPMC K4M	LR	Colorcon Asia Pvt.Ltd.
3	Carbopol 934P	LR	Noveon Chemicals, Mumbai
4.	Sodium bicarbonate	LR	S.D. Fine Chem. Ltd
5	Magnesium sterate	LR	S.D. Fine Chem. Ltd
6	Lactose	LR	S.D. Fine Chem. Ltd.
7	Con HCl	LR	Ranbaxy Fine Chemicals Ltd, New Delhi

Preformulation Studies

Identification Tests

a) IR Spectroscopy [41, 42]

The FT-IR spectrum of the obtained sample of drug was compared with the standard FT-IR spectra of the pure drug.

b) Solubility analysis:

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used.

c) Melting Point determination:

Melting point determination of the obtained drug sample was done because it is a good first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range.

Compatibility Studies [43, 44]

a) IR Spectroscopy:

FT-IR spectroscopy was carried out to check the compatibility between drug and polymers. The FT-IR spectra of drug with polymers were compared with the standard FT-IR spectrum of the pure drug.

b) Preparation of o.1 N HCL

8.5 ml of concentrated HCL was taken and diluted with distilled water up to 1000 ml.

c) Preparation of Standard Calibration curve of Dipyridamole

10 mg Dipyridamole was accurately weighed and dissolves in small portion of 0.1N HCL in a 100 ml volumetric flask then volume was made up to 100 ml with 0.1N HCL. This was the primary stock solution of concentration100 µg/ml. From this primary stock solution 20 ml was accurately taken and diluted up to 100ml, this was the second stock solution of concentration 20 µg/ml form second stock solution withdraw 1ml, 2ml up to 10ml & make up 10ml to make resulting solutions of concentration 2,4, up to 20 µg/ml respectively. The absorbance of solution were measured against in 0.1NHCL as a blank at 283 nm the uv spectrophotometer the plot of absorbance vs concentration was plotted and beers rang was determined

Formulation and Preparation of Floating-Mucoadhesive Dipyridamole tablet by direct compression [, 46]

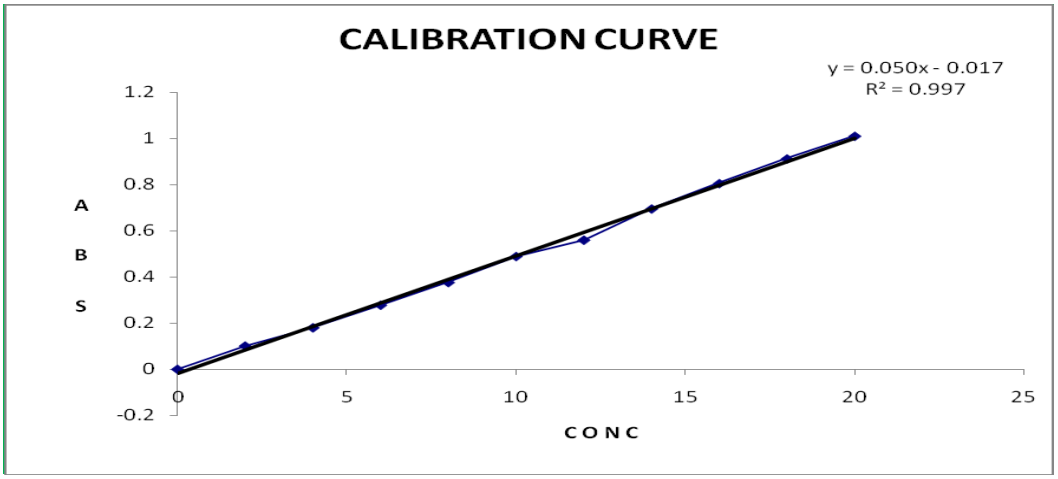
Weight all the ingredient accurately fist add polymer hpmck4m in mortar then carbopol 934p & sodium bi carbonate mix it well for 10 min then add drug &lactose blend for 10 min at the last magnesium stearate 1% add mix all ingredient homogenously to form a tablet mix for direct compression

Table No 2: Formulation Chart of Floating-Mucoadhesive Dipyridamole Tablets

Ingeridents	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**
Diyridamole (mg)	150	150	150	150	150	150	150	150	150
Hpmc k4m (mg)	60	60	60	70	70	70	80	80	80
Carbopol 934 (mg)	15	20	25	15	20	25	15	20	25
$NaHco_3$ (mg)	30	30	30	30	30	30	30	30	30
Mg. St.(mg)	3	3	3	3	3	3	3	3	3
Lactose (mg)	42	37	32	32	27	22	22	17	12
TOTAL WT (mg)	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

RESULT & DISSCUSSION

Preparation of standard calibration curve of Dipyridamole in 0.1 N HCL (λ max 283 nm)



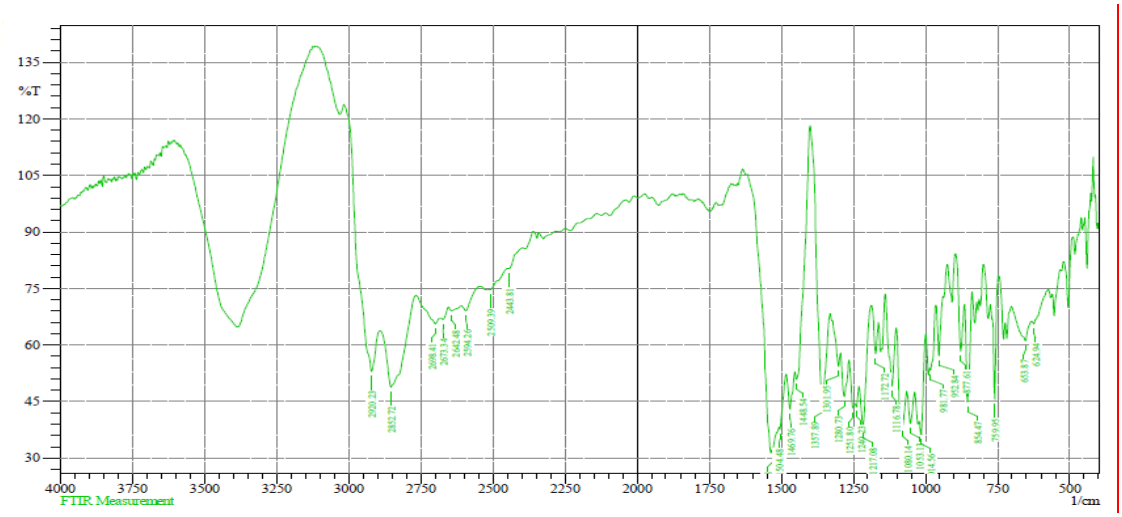
Graph No 1: Standard calibration curve of Dipyridamole at 283nm.

The linear regression analysis was done on Absorbance data points. The results are as follows-

For standard curve in 0.1N HCL

The slope	=	0.050
The intercept	=	0.017
The correlation coefficient (R^2) =		0.997

Compatibility study by IR spectroscopy

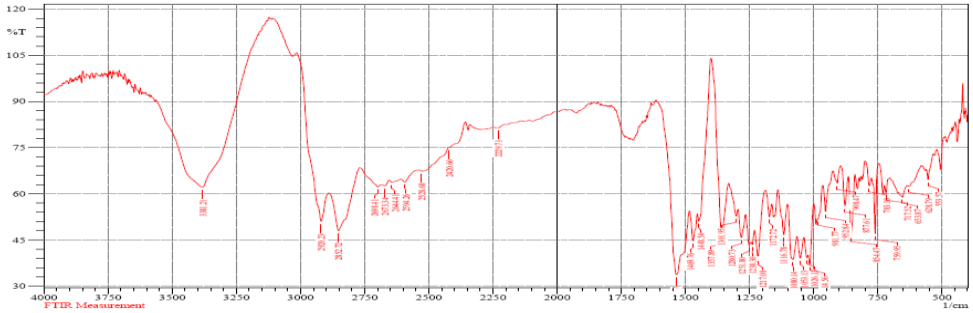


Graph No 2:-IR spectra of pure drug: (Dipyridamole)

The FT-IR spectrum of the Dipyridamole pure drug was found to be similar to the standard spectrum of Dipyridamole. The spectrum of Dipyridamole showed the following functional groups at their frequencies.

Table no 4: IR spectra of pure drug

Group	Wave Number
O-H stretch	3381.21
C-C stretch	2920.23
N-H stretch	3050
N-H bending	1569.73
C-C stretch	759.95



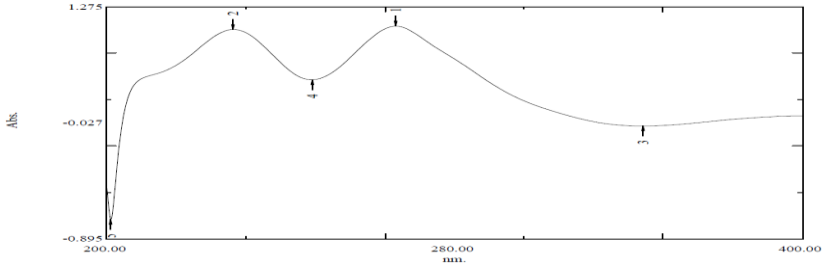
Graph No 3:-IR Spectra of combination of Dipyridamole+all excipients

Table No. 5: Comparison of the peak of functional groups observed in IR spectra of compatibility studies

Functional group	O-H stretch	C-H stretch(in cH2)	N-H stretch	N-H Bending	C-C Stretch
Dipyridamole	3381.21	2920.23	3050	1569.73	759.95
Dipyridamole+all excipients	3381.21	2920.23	30050	1569.73	759.95

Determination of Maximum Absorption Wavelength (λ max)

The ultraviolet spectrum of Dipyridamole is obtained by scanning from 200 to 400 nm at a medium scan rate. The resulting spectrum is qualitatively compared to the spectrum obtained from a Dipyridamole reference standard. The drug substance spectrum is characterized by maxima at 283 nm.



Graph No 4: Maximum Absorption Wavelength (λ max)

Solubility Analysis

Obtained sample was found to be freely soluble in 0.1 n HCL & ethanol practically insoluble in water. . It complies with USP standards[44] thus indicating the purity of the drug sample.

Melting point determination:

The melting point of the obtained drug sample was found to be 163°C which is the reported range of 163-169°C. It complies with USP standards[44] thus indicating the purity of the drug sample

Evaluation physical property of powder

Table No. 6: Flow Properties of Dipyridamol Powder

Batch	Angle of Repose (θ°)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index	Hausner Ratio
F_1	26.3455± 1.65	0.5	0.562	11.481±1.18	1.129±0.46
F_2	28.0529±1.23	0.5	0.569	12.22±1.26	1.139±0.16
F_3	28.4535 ±1.49	0.5	0.575	13.33±0.89	1.153±0.68
F_4	29.6894±2.16	0.5	0.580	13.88±0.82	1.611. ±0.89
F_5	30.9689±2.41	0.5	0.588	15±0.59	1.176±0.56
F_6	30.3222±1.89	0.5	0.596	16.11±0.69	1.192±.0.78
F_7	31.3031±1.28	0.5	0.604	16.66±0.78	1.2±0.86
F_8	32.1329± 1.64	0.5	0.620	19.44±0.84	1.241±0.51
F_9	32.7568 ±1.74	0.5	0.629	20.55±0.78	1.258±0.43

Evaluation of physical properties of tablets

Table No. 7: Evaluation parameters of Tablet formulations

Formulation code	Evaluation parameters			
	Thickness ± S.D. (mm) (n = 3)	Hardness ± S.D. (kg/cm^2) (n = 3)	Friability (%)	Average weight (variation in mg)
F_1	4.554±0.057	3.4±0.12	0.167	301.8±3.12
F_2	4.451±0.052	4±0.17	0.213	301.55±2.41
F_3	4.461±0.064	3.4±0.16	0.189	301±2.59
F_4	4.561±0.053	4.1±0.18	0.198	299.75±2.34
F_5	4.567±0.061	4.1±0.12	0.241	299.7±3.49
F_6	4.545±0.065	3.4±0.13	0.166	300.4±3.32
F_7	4.567±0.067	3.4±0.14	0.184	299.67±2.67
F_8	4.564±0.054	4.1±0.15	0.227	298.78±2.78
F_9	4.565±0.058	4.10.16	0.179	299.87±3.14

Floating property

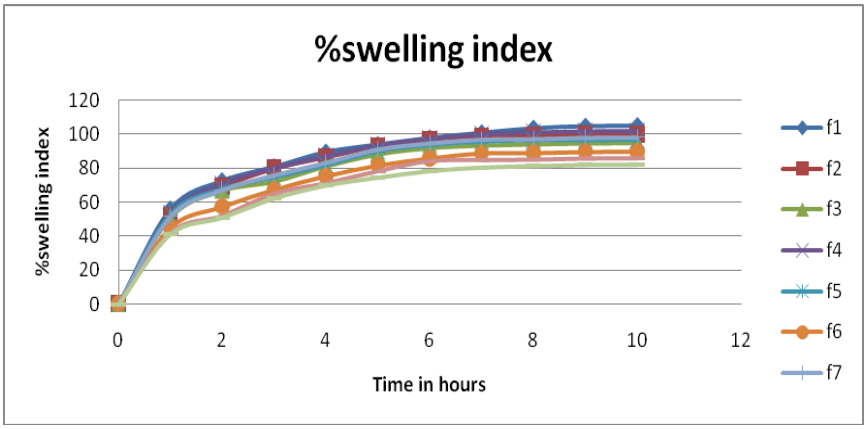
Figure No. 1: Dipyridamole floating tablet buoyancy time study

Table No. 8: Results of floating Lag time of Tablet formulations

Formulation Code	Floating lag time(sec)	Total floating time (hr)
F_1	5±2	>12
F_2	10±1	>12
F_3	14±2	>12
F_4	11±1	>12
F_5	16±3	>12
F_6	20±2	>12
F_7	13±1	>12
F_8	23±3	>12
F_9	26±1	>12

Floating time was observed in all 9 formulations, all the 9 formulations shows the floating time more than >12 hours which is sufficient to achieve sustained release action. It is observe that as polymer conc. increase floating lack time increase

Swelling study

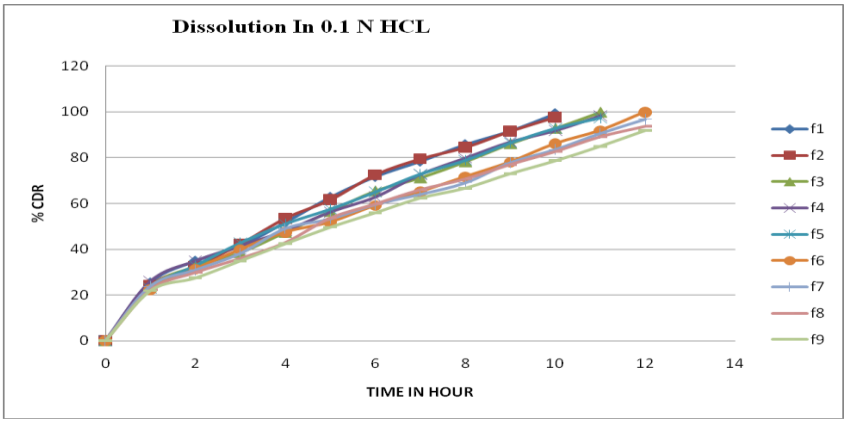


Graph No 5: swelling index V/S Time for formulation f1to f9

As the conc. of polymer higher swelling index decease this is fact as con increase restrict the movement of polymer hpmck4m & carbopol have higher cross linking this indicates that polymers having cross linking constrain and therefore the polymer did not open up easily

Dissolution Study

Graph No. 6: %cumulative drug release



Mucoadhesive strength

Table No. 12: Mucoadhesive strength of tablet

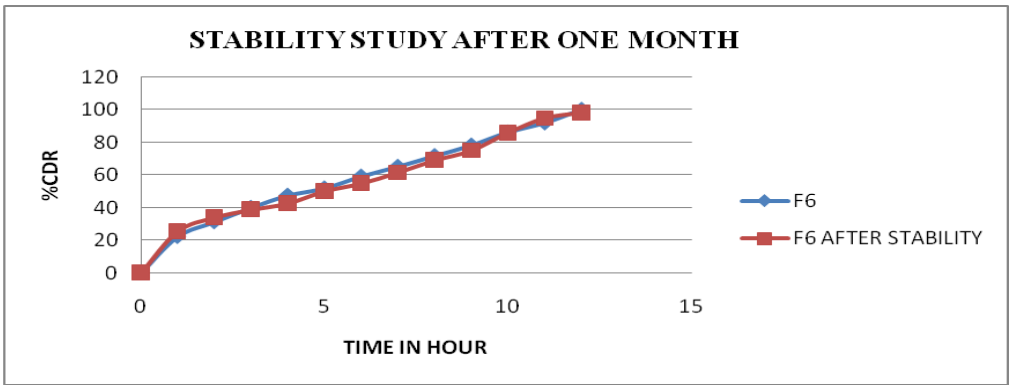
Formulation Code	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Strength in gm	10.14 ±0.6	13.28 ±0.5	17.48 ±0.3	12.41 ±0.1	15.12 ±0.7	18.71 ±0.8	16.84 ±0.32	20.14 ±0.2	22.58 ±0.6
Mucoadhesive force in dyne	0.99	1.30	1.71	1.21	1.48	1.83	1.65	1.97	2.21

Stability study

Table No. 13: Stability study for optimized formulations

Sr No.	Evaluation parameter	Before stability	After stability of 30 days
1	**Hardness (kg/cm^2)**	3.4±0.13	3.4±0.13
2	**Content uniformity**	98.94	98.12
3	**% CDR**	99.92	98.76
4	**Mucoadhesive strength (gm)**	18.71±0.8	17.64±0.2
5	**% Friability**	0.166	0.172
6	**Floating lag time**	20±2	17 ±2

Table No. 14: Release rate profile of formulation F6 after stability



Graph No 7: Comparitive graph for In-vitro cumulative % drug released v/s time for optimized formulation-F6 before and after stability testing

CONCLUSION

Literature survey on bioadhesive-floating drug delivery was carried out. Dipyridamole is BCS class II drug having low solubility and high permeability. It is soluble at low pH but insoluble in high pH (i.e. alkaline ph of small intestine)its oral bioavailability is 37-66% & biological half life is also short (40 min).all the above reason are suitable for gastroretentive drug delivery system .

After procurement of drug sample it was characterized for identification by FT-IR. After identification check compatibility of drug with all excipeint. It was found that it is compatible with all excipeint there is no change in functional group.

Flow property of dipyridamole tablet powder was found within range & or comply with official pharmacopeia. Physical property of dipyridamole tablet Hardness, friability Average weight also complies with standard reference.

Floating lag time of all nine formulation show within 1 min total floating time was more than 12 hrs. Hardness of tablet affect the floating lag time.

The in vitro release profile indicated that Batch (F6) was the most promising formulation as the extent of drug release from this formulation was high as compare to other formulations, which are suitable for sustained release drug delivery system. The in vitro drug release studies in Stomach pH conditions was carried out in pH 1.2 buffer for 12 hrs. The Batch F6 shows 99.92% release in 12 hrs, so we concluded that rate of drug release increases in the Acidic environment of Stomach. Formulation f6 show desirable swelling index and bioadhesive property. Bioadhesive strength depends upon carbapol as concentration of polymer increases bioadhesive strength also increases. HPMC is water Swealable but Carbapol is hydrogel in nature it restricts movement of polymer and affect the swelling index.

Release kinetic data of all the formulation showed that F1-F9 formulation follows korsmeyer-peppas model.

Stability study was conducted on tablets of Batch F6 at 40 ± 2^0C for one months. Tablets were evaluated for drug release pattern, hardness, floating behavior and *in vitr*o bioadhesion. No significant changes were observed in any of the studied parameters during the study period, thus it could be concluded that formulation was stable.

From the discussion it was concluded that the tablets of Batch F6 had considerable bioadhesion along with considerable floating and swelling behaviors with good drug release pattern. Tablets of Batch F6was selected as an optimum batch and evaluated for stability study.

From the discussion it was concluded that the tablets of Batch F6had considerable bioadhesion along with considerable floating and swelling behaviors with good drug release pattern. Tablets of Batch F6 was selected as an optimum batch and evaluated for stability study.

The stability study revealed that there was no significant change in the dissolution profile and bioadhesive strength for a period of 1 month.

ACKNOWLEDGMENT:

The authors are thankful to Torrent Pharma Ltd., Mumbai ; Colorcon Asia Pvt.Ltd.;Noveon Chemicals, Mumbai; S.D. Fine Chem. Ltd & Ranbaxy Fine Chemicals Ltd, New Delhi for providing gift samples of API & other excipients respectively. The authors are also thankful to Management of Maharashtra College of Pharmacy, Nilanga as well as S.R.T.M.U.Nanded for providing necessary facility for the work.

REFERENCES:

1. Amit kumar nayak gastro retentive drug delivery system Asian journal of pharmaceutical and clinical research vol 3 issue 1 2010, 2-10
2. shweta arora floating drug delivery system aaps phamscitech 2005 ;6(3) article 47 page 372-390
3. A V mayavanshi floating drug delivery system to incrses gastric retention of drug www.rjptonline org issn 0974 3618 page345-348
4. Arora S, Ali J, Khar RK, "Floating drug delivery System: A Review", AAPS Pharm SciTech. (2005) 6(3), E372-E390.
5. Ross and Wilson, "Anatomy and Physiology in health and illness" 9th Edition, Churchill Livingstone, USA (1996) 295-297
6. Chawla G, Gupta P, Koradia V, Bansal A K. "Gastroretention a mean to address regional variability in intestinal drug absorption" Pharm tech. (2003) 50-68.
7. Garg, S., Sharma, S. "Gastro-retentive drug delivery system", Pharm. Tech. (2003) 27, 50-68.
8. Wab H, Robinson JR, "Design of oral controlled release drug delivery systems". In: Robinson VR, Lee VHL (editors). Controlled Drug Delivery Fundamentals and Applications, 2nd edition, New York: Marcel Dekker (1987) 418-420.
9. Atyabi F, Sharma HL,. "*In vivo* evaluation of a novel gastroretentive formulation based on ion exchange resins". J. Control. Release, 1996; 42:105-13.
10. Shivakumar HG, Gowda DV,. "Floating controlled drug delivery systems for prolonged gastric residence: a review". Indian J Pharm Edu 2004; 38(4):172-8.
11. ikura h Suzuki y,nagani t,machid y oral sustend release pharmacutiacl preparation us patent 4,777,033(1988)oct 11
12. whitehead l,fell jt collet jh development of a gastroretantive doses form eur. J.pharm.sci.1996;4(suppl):s 182
13. kawashima y, niwa t, takeuchi h,hollow microsphere for use as a floating controlled drug delivery system in stomach j. Pharma sci. 1992,81,135-140
14. babu vbm, khar rk in vivo in vitro in vitro studies of sustained release floating doses form contanig salbutamol sulphatepharmzin 1990;45,268-270
15. S.u. Zategastro retentive bioadhesive drug delivery system international journal of pharmtech research coden (usa): ijprif issn : 0974-4304 vol.2, no.2, pp 1227-1235
16. Flávia Chiva Carvalho Mucoadhesive drug delivery systems Brazilian Journal of Pharmaceutical sciences vol. 46, n. 1, jan./mar., 2010
17. Sachan Nikhil K Basics and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems International Journal of Pharmaceutical and Clinical Research 2009; 1(1): 10-14
18. Shaikh R, Raj Singh TR, Mucoadhesive drug delivery systems. J Pharm Bioall Sci2011;3:89-100
19. SAROJ KUMARROY Bioadhesive polymeric platform for transmucosal drug delivery system areview trop j pharm res feb 2010 ;9,(1)91,104.
20. Abubakar o.nur; Captopril floating and/or bioadhesive tablet: design and relies kinetics. Drug development an industrial pharmacy2000; 26(9):965-969.

21. Girish s.sonar; Bioadhesive-floating matrix tablet of salbutamol sulfate using response surface methodology. Journal of pharmacy research 2009:2(5):908-914.
22. Zawar Laxmikant R;Formulation And Evaluation Of Floating-Mucoadhesive Tablet Of Clarithromucin.International Journal Of Pharma And Bio Science 2010: V1(2):1-10
23. Mukopadhyay s, goswami; Formulation and evaluation of floating bioadhesive tablet of ciprofloxacine hydrochloride by direct compression technique. Ijpps 2010:vol 2,issue3,issn0975-1491:113-115
24. Mahesh d. Chavanpatil; novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin international journal of pharmaceutics, volume 316: 86-92
25. Manoj n.gambhire,kshitij w.ambade; Development and invitro evaluation of an oral floating matrix tablet of diltiazem hydrochloride; AAPS pharmascitecch 2007;8(3)
26. S ramakant; Formulation and characterization of floating tablet of Diltiazem HCl; journal of pharmacy research 2010 3(6) 1263-1267.
27. Jaleh varshosha: formulation and in vitro characterization of Ciprofloxacin floating bioadhesive extended release tablet. Drug delivery: 2006:13; 277-285.
28. H. R. Chueh; H. Zia,C. T. Rhodes :Optimization of Sotalol Floating and Bioadhesive Extended Release Tablet Formulations
29. Bhupinder singh; Formulation optimization of hydrodinamically balance oral control released bioadhesive tablet of tramadol HCl; scientia pharmaceuticals; 2010; 78:303- 323.
30. A.H.E kamel et al preparation and evaluation of Ketoprofen floating oral delivery system international jouranal of pharmaceutics
31. Raymond C.Rowe, Paul J.Sheskey and Sian C Owen, "*Hand book of Pharmaceutical Excipients*", U.S.A, 4th edn, 2000: 737-753
32. Raymond C.Rowe, Paul J.Sheskey and Sian C Owen, "*Hand book of Pharmaceutical Excipients*", U.S.A, 4th edn, 2000; 89-92.
33. C. V. S. Subrahmanyam. "Text Book of Physical Pharmaceutics". 2nd edition. Delhi: Vallabh Prakashan. 2004; 210 – 28.
34. v.f.patel.et al. self correcting monolithic floating matrix tablet of dipyridamol tablet of dipyridamol : influence of formulation variable.ijpsonline .com ip 59,90.142.112 page 219-225
35. viral f. patil statical evaluation of influence of viscosity and content of polymer on dipyridamol release from floating matrix tablet :atechnical note aaps pharmscitech 2007;8(3)article 69
36. Aulton M E. Pharmaceutics: The Science of Dosage Form Design. 2nd edition, Published by Churchill Livingstone, USA (1998) 223-253.
37. Martin A, Swarbrick J, Cammarata A. "Physical Pharmacy", 3rd Ed, Varghese Publishing Company, Bombay, 1991, pp.492-52
38. The United State Pharmacopoeia. United state Pharmacopoeial Covenction, Rockville, MD .Asian Edn, 2000, 1941-3.
39. Banker GS and Anderson NR. Tablets. In: Lachman L, Lieberman H and Kanig JL. (eds.) *The Theory and Practice of Industrial Pharmacy*. Varghese Publishing House, Bombay (1998) 298-301
40. Garima Chawla " 'Gastroretention' A means to address regional variability in intestinal drug absorption" Pharmaceutical Technology, july 2003, p 50-58
41. Dave BS,et al. "Gastroretentive drug delivery system of Ranitidine hydrochloride: Formulation and *in vitro* evaluation" AAPS PharmSciTech 2004; 5 (2) Article 34
42. Uttam Mandal "Formulation and Optimization of SR matrix tablets of metformin Hcl using response surface methodology" the pharmaceutical society of Japan 127 (8) 1281-1290 (2007)

AUTHORS AFFILIATION AND ADDRESS FOR CORRESPONDENCE

1. Department of Quality Assurance, Maharashtra College of Pharmacy, Nilanga-413521, Dist. Latur (Maharashtra) India

2. NRI Institute of Pharmaceutical Science, Bhopal (M.P.), India

For correspondence: birajdar100@gmail.com