ejpmr, 2015,2(7), 211-219

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 3294-3211

EJPMR

ATENOLOL AND GLIPIZIDE BILAYER FLOATING TABLETS: FORMULATION AND EVALUATION

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Article Received on 08/10/2015 **Article Revised on 29/10/2015** **Article Accepted on 20/11/2015**

ABSRTACT

The FDDS formulations can be used for the medicaments which are absorbed from the stomach as well as intestine. A bilayer tablets contain two layer immediate release layer which release initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable Colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach. The effervescent systems include use of gas generating agents, carbonates(ex. Sodium bicarbonate) and other organic acid(e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporate at body temperature. The non effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as polycarbonate, polyacrylate, polymethacrylate, polystyrene as well as bioadhesive polymer such as chitosan and carbopol. The Bilayered Floating tablets containing glipizide (anti diabetics) and atenelol (anti hypertensive) were successfully prepared by direct compression method. The physiochemical evaluation results for the powdered blend of all fullfill official limits .The F_7 formulation which releases the glipizide in sustained manner in up to 12 hours and Atenelol immediate release F5 formulation showed 100.6% drug release with in 30min. Dissolution of all the tablets prepared followed zero order kinetics with coefficient of determination (R^2) values above 0.965. Plots of percent release versus square root of time were found to be linear with R^2 0.9877 with all the tablets prepared indicating that the drug release from these tablets was diffusion controlled. FTIR studies were perfmed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India) as a result no interactions were observed drug-excipients.

KEYWORDS: Floating tablets, immediate release, Bilayer tablets, Floating lag time, Dissolution.

INTRODUCTION

Floating drug delivery systems (FDDS), also known as hydro dynamically balanced systems (HBS). These systems have a bulk density lower than gastric fluids, thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time, the drug is released slowly at a desired rate from the system. Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of floating drug delivery system which are effervescent system and non effervescent system.[13,17-20]

Bi layered tablet is a new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bi layered tablet is a suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Several pharmaceutical companies are currently developing, for a variety of reasons; patent extension, therapeutic marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses are used to develop, produce such tablets. In the last decade, interest in developing a combination of two or more active pharmaceutical ingredient (API) in a single dosage form (belayed tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablets can be a primary option to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles(immediate release with extended release).Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, The mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures

as well as patient-friendly administration which pose serious challenges to the pharmaceutical scientists. From various current methods for treating illness and diseases, chemotherapy (treatment with drugs) is the most frequently used technique. It has the broad range of applications over the greatest variety of disease states and is frequently the preferred treatment method. For many decades, treatment of acute disease or chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as drug carriers. However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery system. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms and is the most convenient and preferred route for systemic effects due to its ease of dosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation.[1-12]

Glipizide, is a widely prescribed anti diabetic drugs under BCS class II exhibit low and variable oral bioavailability due to poor aqueous solubility and dissolution rate. It is used with diet to lower blood glucose in patients with diabetes mellitus type II. In human's glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. In man, stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long-term glipizide administration, but the postprandial insulin response continues to be enhanced after at least 6 months of treatment. Some patients fail to respond initially, or gradually lose their responsiveness to sulfonylurea drugs, including glipizide.

Atenolol, is a widely prescribed anti hyper tensive drug under BCS class III exhibit high solubility low permeable exhibit variable oral bioavailability and dissolution rate. Competitive beta (1)-selective adrenergic antagonist, has the lowest lipid solubility of this drug class. Although it is similar to metoprolol, atenolol differs from pindolol and propranolol in that it does not have intrinsic sympathomimetic properties or membrane-stabilizing activity. Atenolol is used alone or with chlorthalidone in the management of hypertension and edema.

EXPERIMENTAL

MATERIALS

Glipizide was a gift sample from Chandra labs, Hyderabad. Atenelol was a gift sample from Chandra labs, Hyderabad HPMC, PVP, Guar gum, Carbopol, MCC, Crospovidone, Ethyl Cellulose were gift samples from Myl chem.., Mumbai. Talc and magnesium stearate were procured from S.D Fine chem. Limited. Mumbai. All other materials used were of pharmacopoeial grade.

METHODS

Estimation of Glipizide: An UV Spectrophotometric method based on the measurement of absorbance at 274 nm in 0.1N hydrochloric acid was used for the estimation of glipizide. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.88 % and 1.28% respectively. No interference by the excipients used in the study was observed.

Estimation of Atenlol

An UV Spectrophotometric method based on the measurement of absorbance at 275nm in 0.1N hydrochloric acid was used for the estimation of atenlol. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beer's law in the concentration range of 0 – 10 µg/ ml. When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variance were found to be 0.77 % and 1.48% respectively. No interference by the excipients used in the study was observed.

Formulation of Floating layer (Glipizide)

Different formulations of glipizide floating layer were designed to prepare by direct compression method using polymers Shown in table. Floating tablets containing glipizide were prepared by direct compression method using varying concentrations of different grades of polymers. All the powders were accurately weighed and passed through sieve no 60 .Then except magnesium stearate and talc. All the ingredients were weighed were dry blended for 20 min followed by addition of magnesium stearate and talc. The mixture was then further blended for 10 min. The blend was compressed in to tablets having weight 300 mg a single punch tablet compression machine (Cadmach machinery) fitted with an 9 mm punch and die to obtain tablets.[21-30]

Formulation of Immediate Release Layer (Atenlol)

Weighed accurately Atenolol and all other ingredients listed in table except magnesium stearate, were passed sieve no 60 to get uniform size particles and weighed accurately. Finally, magnesium stearate (passed through a 60-mesh/250 micron screen) was introduced to the powder mixture. The powder was passed through the hopper of 16 station rotary tableting machine and punched into tablets using 8mm. which are prepared by direct compression technique.[14-16] After formulation of floating layer and immediate layer was compressed into bi layer floating tablet.

Evaluation of Tablets: All the tablets prepared were evaluated for hardness, friability, and disintegration time and dissolution rate as follows.

Hardness: The hardness of prepared tablets was determined by using Monsanto hardness tester and measured in terms of kg/cm^2.

Friability

The friability of the tablets was measured in a Roche friabilator using the formula

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

In vitro Buoyancy studies for floating tablets

The in vitro buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N hydrochloric acid Buffer. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time respectively (TFT).[31-35]

Dissolution Rate Study: Dissolution rate of tablets prepared was studied in 0.1N hydrochloric acid (900 ml) employing eight station dissolution rate test apparatus (LABINDIA, DS 8000) using paddle stirrer at 50 rpm and at a temperature of 37°C ± 1°C. One tablet was used in each test. Samples of dissolution fluid (5 ml) were withdrawn through a filter at different time intervals and assayed for glipizide at 274 nm and atenlol at 275 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh drug free dissolution fluid and a suitable correction was made for the amount of drug present in the samples withdrawn in calculating percent dissolved at various times. Each dissolution experiment was run in triplicate (n=3).

FTIR Studies

FTIR studies were perfmed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}

Analysis of Data

The dissolution data were analyzed as per zero order, first order kinetic, and Higuchi and Pappas models.

RESULTS AND DISCUSSION

Table 1. Flow Properties

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio
F1	24.8	0.3	0.36	16.67	1.20
F2	28.5	0.29	0.34	14.71	1.17
F3	26.4	0.37	0.45	17.78	1.22
F4	27.3	0.34	0.43	20.93	1.26
F5	25.2	0.45	0.52	13.46	1.16
F6	27.5	0.42	0.48	12.50	1.14
F7	25.7	0.34	0.43	20.93	1.26

Table. 2 Formulae for Floating layer Prepared

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Glipizide	10	10	10	10	10	10	10
NaHCO3	45	45	45	45	45	45	45
Guar gum	60	-	-	-	90	-	90
HPMC	-	60	-	-	-	90	-
EC	-	-	60	-	-	-	15
Carbopol	-	-	-	60	-	-	-
PVP K 30	15	15	15	15	15	15	15
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium Stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight (mg)	300	300	300	300	300	300	300

Table 3. Formulae for Immediate release layer Prepared

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F6	F7
Atenelol	50	50	50	50	50	50	50
CP	12.5	-	-	25	-	31.25	-
CCS	-	12.5	-	-	-	-	-
SSG	-	-	12.5	-	25	-	31.25
PVP	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Magnesium stearate	6.25	6.25	6.25	6.25	6.25	6.25	6.25

Talc	6.25	6.25	6.25	6.25	6.25	6.25	6.25
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight (mg)	250	250	250	250	250	250	250

Table. 4 Formulae for Bilayer Floating Tablets Prepared (F_7)

S.N	Floating layer	Weight (mg)
1	Glipizide	10
2	Guar gum	90
3	EC	15
4	MCC	Q.S
5	Magnesium stearate	7.5
6	Sodium bicarbonate	45
7	Talc	7.5
	Immediate release layer	
8	Atenelol	50
9	SSG	25
10	PVP	12.5
11	Talc	6.25
12	Megnesium stearate	6.25
13	MCC	q.s
14	Total weight	250mg
	Total weight of the Bilayered Floating tablet 550mg	

Table 5. Physical Properties of Bilayered Floating Formulations Prepared

Formulations	Weight variation	Hardness Kg/sq.cm	Thickness (mm)	Friability (%)	Lag Time (min)	Floating time
F1	306	4.8	3.41	0.12	6	>12hrs
F2	311	5.6	3.40	0.13	3	>12hrs
F3	304	5.9	3.41	0.09	20	>12hrs
F4	307	5.7	3.42	0.10	7	>3hrs
F5	298	5.5	3.43	0.12	5	>12hrs
F6	300	5.9	3.46	0.09	6	>12hrs
F7	297	5.8	3.41	0.10	5	>12hrs

Table 6. Cumulative Percentage Drug Release from Floating Layer

Time(hrs)	F1	F2	F3	F4	F5	F6	F7
0.5	13.2	17.8	15.8	18.9	20.1	10.1	12.4
1	21.4	26.4	27.3	24.8	29.1	18.2	20.1
2	38.6	40.8	41.9	38.3	40.2	30.6	28.7
3	51.7	60.2	54.2	50.1	53.8	41.8	42.9
4	78.8	79.1	70.4	68.7	66.2	50.2	53.4
6	99.8	98.6	82.8	83.2	85.8	64.9	70.1
8	-	-	99.5	96.4	99.8	76.3	83.1
10	-	-	-	100.1	-	88.5	99.8
12	-	-	-	-	-	99.6	-

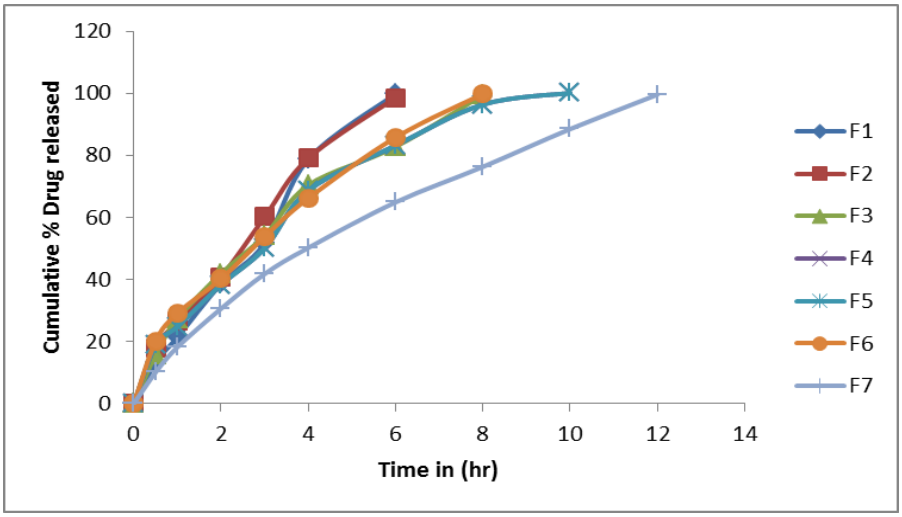

Fig .1 Cumulative Percentage Drug Release from Floating Layer

Table.7 Cumulative Percentage Drug Release from Immediate release Layer

Time in mins	F1	F2	F3	F4	F5	F6	F7
5	6.4	7.2	17.1	20.1	26.8	20.6	30.2
10	14.1	12.4	30.2	31.8	50.4	45.4	49.2
15	24.8	28.1	50.9	50.6	85.7	70.1	71.8
30	38.9	33.4	63.8	76.5	100.6	86.4	99.7
45	50.6	40.6	71.5	89.2	-	99.8	-
60	70.8	50.7	80.1	100.8	-	-	-

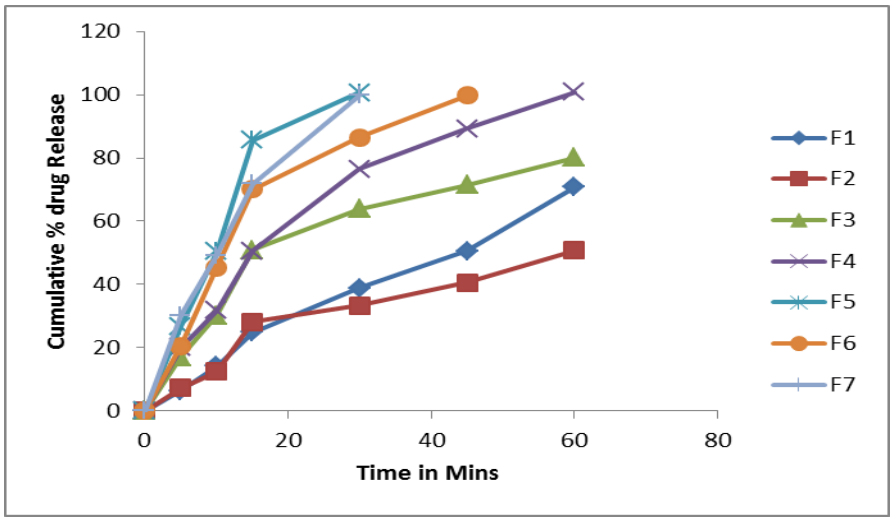

Fig.2 Cumulative Percentage Drug Release From Immediate release Layer

Table.8 Dissolution Profile of Bilayered Floating Formulation F_7

S.No	Time in (hr)	Percentage drug released (%)	
		Atenlol	Glipizide
1	0.15	80.8	3.8
2	0.30	99.5	8.0
5	1	--	29.6
6	2	--	33.9
7	3	--	42.7
8	4	--	55.8
9	5	--	65.8
10	6	--	77.0
11	8	--	89.8
12	12	--	98.9

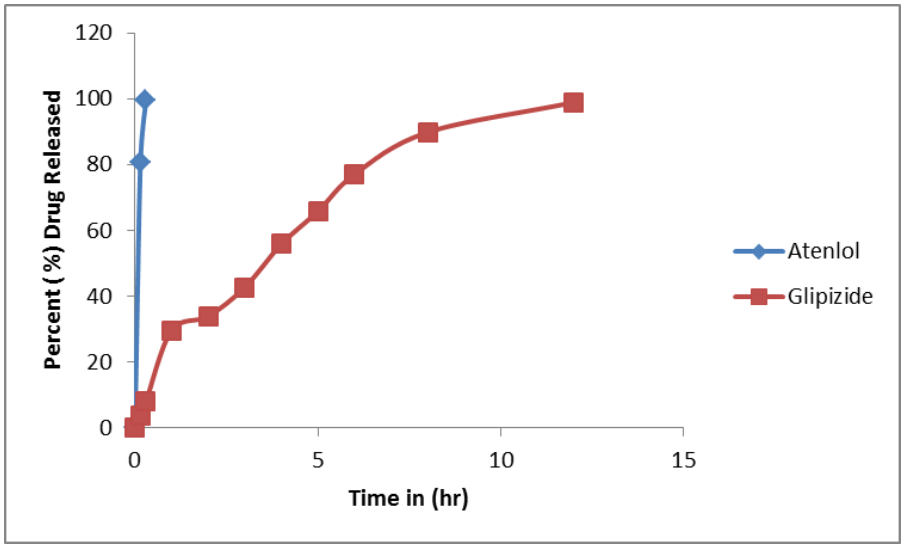

Fig.3 Dissolution Profile of Bilayered Floating Formulation F_7

Table 9. Release kinetics for Bilayer Floatimg Formulation F_7

Coefficient of Determination (R^2)			
Zero Order	**First Order**	**Higuchi Model**	**Peppas Model**
0.96588	0.7722	0.98776	0.62497

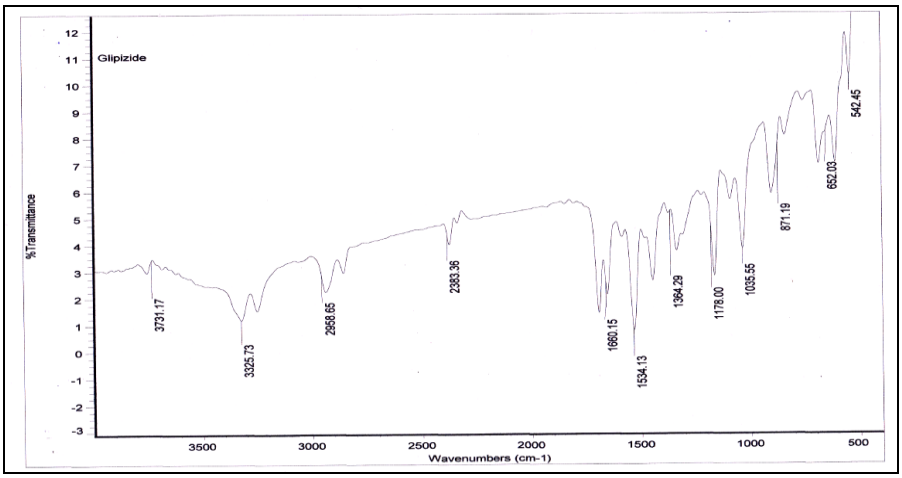

Fig.4 FTIR Spectra of Glipizide pure drug

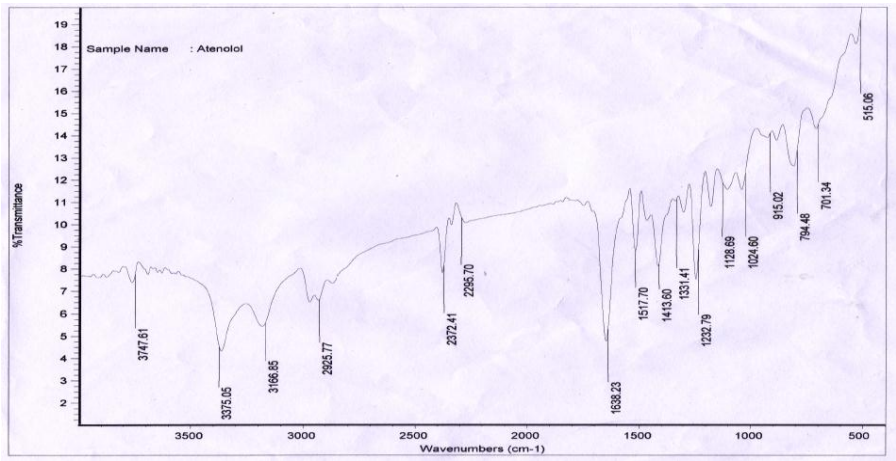

Fig.5 FTIR Spectra of Atenlol Pure drug

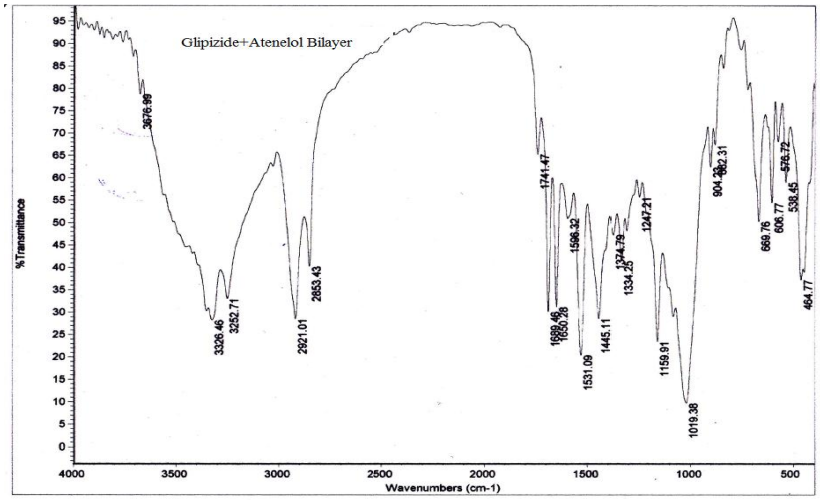

Fig.6 FTIR Spectra of Bilayer Floating Tablet Formulation F_7

The tablets were prepared by direct compression method as per the formulae given in Table 2,3,4. The blends of ingredients of various formulations exhibited angle of repose (θ) values in the range 24.8-28.5^0 and compressibility index values in the range 12.50 – 20.93 % indicating good flow characteristics of the blends suitable for direct compression. The tablets prepared were evaluated for hardness, friability, floating lag time, total floating time, dissolution rate characteristics and drug excipients compatibility studies. The physical parameters of the tablets prepared are given in Table 5. The hardness of the tablets was in the range 4.8-5.9 kg/cm^2. Weight loss in the friability test was less than 0.13% in all the cases. Many variations were observed in the disintegration and dissolution characteristics of the tablets prepared. The Floating lag time was in range 3 min to 20 min and total floating time >12 hrs in all the tablets prepared fulfilled the official requirements.

Dissolution rate of the tablets prepared was studied in 0.1N hydrochloric acid. The dissolution profiles of the floating layer, immediate layer tablets and bilayer floating tablets F_7 are shown in Fig.1,2 and 3. Dissolution of all the tablets prepared followed zero order kinetics with coefficient of determination (R^2) values above 0.965. The Zero order dissolution rate constant (K_1) values were estimated from the slope of the zero order linear plots. Plots of percent release versus square root of time were found to be linear with R^2 0.9877 with all the tablets prepared indicating that the drug release from these tablets was diffusion controlled. When the release data were analyzed as per peppas equation, the release exponent 'n' was 1.010 indicating Super case-II transport diffusion as the release mechanism from all these tablets prepared. The FTIR spectra of atenlol and glipizide pure drug and bilayered floation tablets formulation F_7 are shown in Figs 4,5,6. The FTIR spectras were identical and no interactions were observed.

CONCLUSION

The Bilayered Floating tablets containing glipizide and atenelol were successfully prepared by direct compression method.

The physiochemical evaluation results for the powdered blend of all fullfill official limits The F_7 formulation which releases the glipizide in sustained manner in up to 12 hours and Atenelol immediate release F5 formulation showed 100.6% drug release with in 30min.

Dissolution of all the tablets prepared followed zero order kinetics with coefficient of determination (R^2) values above 0.965.

Plots of percent release versus square root of time were found to be linear with R^2 0.9877 with all the tablets prepared indicating that the drug release from these tablets was diffusion controlled.

FTIR studies were performed as a result no interactions were observed drug-excipients.

REFERENCES

1. Reynolds JEF, In; Martindale; The Extra Pharmacopoeia, 29th Edn., The Royal Pharmaceutical Society of Great Britain, London,1993; 295.
2. Aulton`s Pharmaceutics, The design & manufacture of medicines, Biopharmaceutics and pharmacokinetics, A Treatise, second edition, Valabh Prakashan, 315-384
3. Indian Pharmacopoeia. Vol. II, 4th ed. TheController of Publications, New Delhi, 1996; 736.
4. J Siepmann; H Kranz; R Bodmeier; NA Peppas; Pharm Res., 1999; 16: 1748-1756.
5. Martindale: Thirty first Edition, The Complete Drug Reference. P.102.1
6. Chien YW. Controlled and Modulated Release Drug Delivery System in Swarbrik J, Boylan JC (Eds.).

Encyclopaedia of Pharmaceutical Technology, Marcel Dekker, New York, 1990; 281-313.
7. Ansel .2006. 'Pharmaceutical dosage forms & drug delivery systems-Types of tablets'. 8th Edition, 227-260.
8. Gilbert, S., Banker., Christopher, T. Rhodes. 'A text book of Modern Pharmaceutics- Granulation techniques'. 2nd Edition, 1986; 124-162.
9. E Rippe. Compression of solids and compressed dosage forms. In: Encyclopedia of Pharmaceutical Technology, third Edition, Swarbrick J. Marcel Dekker. Inc. NY, 1990; 149-166.
10. Pharmacopoeia of India, Ministry of Health and Family Welfare, Govt. of India, Controller of Publications, New Delhi. 1996; 2: 736.
11. Talwar N, Sen H, Staniforth JN, inventors. Orally administered controlled drug delivery system providing temporal and spatial control. Jul 2001. US patent 6261 601.
12. Lachman L, Lieberman H, Kanig JL. The theory and practice of industrial pharmacy.3rd edi. 355-59.
13. Garg S, Sharma S. Gastro retentive Drug Delivery Systems, Pharma.tech, 2003; 160-164.
14. Rao MRP, Bachhav D, Gogad V. Formulation and evaluation of Aceclofenac immediate release tablets. The Ind Pharmacist 2007; 6(61): 73-78.
15. Valentina R, Alberto R, Giorgio R, Monica C. Increased absorption rate of Diclofenac from fast acting formulation containing its potassium salt. Arzneimittel-Forschung 2001; 51(11): 885-90.
16. Patel HP, Karwa P, Bukka R, Patel NJ. Formulation and evaluation of immediate release tablets of Zolpidem Tartrate by direct compression. Int J Pharm Sci Review Res 2011; 7(2): 80-85.
17. M.Soumya, M. Saritha developed and optimized bilayered sustained release matrix tablets of Valsartan. International Journal of Pharmaceutical & Biological Archives 2011; 2(3): 914-920.
18. Narendra C, Srinath M, Ganesh B. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. AAPS PharmSciTech. 2006 April 7; 7(2).
19. Girish S. Sonara, Devendra K. Jaina, Dhananjay M. More Preparation and in vitro evaluation of bilayer and fl oating-bioadhesive tablets of rosiglitazone maleate. Bilayer and floating-bioadhesive tablets of rosiglitazone maleate/Asian Journal of Pharmaceutical Sciences 2007; 2(4): 161-169.
20. Upendra Kumar Sharma, Himanshu Pandey and Avinash Chandra Pandey. Controlled Release Of An Anti- Emetic Agent From A Polymeric Matrix: Formulation And In- Vitro Study. Pandey et al., IJPSR, 2011; 2(10): 2746-2749.
21. Shirwaikar A. et al. formulated sustained release of Diltiazem hydrochloride tablets by utilizing the bilayer concept using matrix material rosin and ethyl cellulose.
22. Vishnu M. Patel,1 Bhupendra G. Prajapati,1 and Madhabhai M. Patel Formulation, Evaluation, and Comparison of Bilayered and Multilayered Mucoadhesive Buccal Devices of Propranolol Hydrochloride. AAPS PharmSciTech 2007; 8(1): Article 22.
23. Bhavesh Shiyani, Surendra Gattani, and Sanjay Surana Formulation and Evaluation of Bi-layer Tablet of Metoclopramide Hydrochloride and Ibuprofen. AAPS Pharma Sci Tech. Sep 2008; 9(3): 818-827.
24. Nirmal J, Sasivam S, Peddanna C, Muralidharan S, Kumar SG, Nagarajan M. Formulation and evaluation of bilayer tablets of atorvastatin calcium and nicotinic acid. Chem Pharm Bull (Tokyo) 2008; 56(10): 1455-58.
25. Chinam N, Arethi B,PanditH,singh P,Maeduri V Design and evaluation of sustained release bilayer tablet of propranolol hydrochloride. Acta Pharm. 2007 Aug 20; 57: 479-89.
26. KulKarni A, Bhatia M development and evaluation of regioselective bilayer floating tablets of atenolol and lovastatin to give immediate release of lovastatin and sustained release of atenolol.Iranian journal of Pharm,Research. 2009 June; 8(1): 15-25.
27. Yassin El-Said Hamza and Mona Hassan Aburahma Design and In Vitro Evaluation of Novel Sustained-Release Double-Layer Tablets of Lornoxicam: Utility of Cyclodextrin and Xanthan Gum Combination. AAPS PharmSciTech. 2009 Dec 7; 10(4): 1357-1367.
28. M. C. Gohel, R. K. Parikh, and B. A. Jethwa Fabrication and Evaluation of Bi-layer Tablet Containing Conventional Paracetamol and Modified Release Diclofenac Sodium. Indian J Pharm Sci.2010 Mar-Apr; 72(2): 191-196.
29. Vishnu M Patel., Bhupendra G. et al Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS PharmSciTech. Sep 2007; 8(3): E203–E208.
30. Raghuram RK, Srinivas M, Srinivas R. Once-daily sustained –release matrix tablets of nicorandil formulation and in vitro evaluation. AAPS PharmaSciTech. 2003; 4(4): E61.
31. Raslan HK, Maswadeh. In vitro dissolution kinetic study of theophylline from mixed controlled release matrix tablets containing hydroxypropylmethylcellulose and glycerylbehenate. Indian J Pharm Sci. 2006; 8: 308-311.
32. Ravi PR, Kotreka UK, Saha RN. Controlled release matrix tablets of zidovudine: effect of formulation variables on the in vitro drug release kinetics. AAPS PharmSciTech. 2008; 9(1): 302-313.
33. Salsa T, Veiga F, Pina ME. Oral controlled-release dosage forms. I. Cellulose ether polymers in hydrophilic matrices. Drug Dev Ind Pharm. 1997; 23: 929-938.
34. Sandip BT, Krishna Murthy T, Raveendra Pai M, Pavak RM, Pasula BC. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech. 2003; 4(3): 1-7.

35. Selim R, Mohiuddin AQ, Syed SH. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Pharmaceut Sci. 2003; 6(2): 282-291.